ABSTRACT

TESKE, JESSE ALEXANDER. Natural Product Synthesis via [2+2+2] Cyclotrimerization Reactions. (Under the direction of Dr. Alex Deiters).

The transition metal mediated [2+2+2] cyclotrimerization reaction of alkynes is a highly convergent approach to the synthesis of polysubstituted carbo- and heterocyclic aromatic ring systems. However, few examples of the application of cyclotrimerization reactions in natural product synthesis have been reported. In order to supplement the understanding of various aspects of the cyclotrimerization chemistry such as reactivity, regioselectivity, and chemoselectivity of advanced diyne intermediates, we explored the development of the [2+2+2] cyclotrimerization reaction towards benzene and pyridine derivatives as well as its application to the total synthesis of natural products.

As an approach to solve the chemoselectivity issues associated with the cyclotrimerization reaction, a solid supported cyclotrimerization reaction was utilized as the key step in the regioselective synthesis of an indanone natural product in only 11 steps. The development of microwave assisted nickel catalyzed cyclotrimerization reactions allowed for the rapid synthesis of fused benzene ring systems and led to the total synthesis of the isoquinoline natural product illudinine in only eight steps. Several strategies towards the synthesis of anthraquinone and anthracycline natural products were investigated. The efficiency of these reactions was sensitive to both the electronic and steric properties of the investigated diynes. A novel approach to the tricyclic cannabinoid ring structure via the cyclotrimerization reaction was developed and led to the total synthesis of three cannabinoid natural products all in >20% overall yield. Furthermore, easy access to cannabinoid analogues is possible with this strategy. Initial investigations into the synthesis of four

neolignan natural products from a common precursor were accomplished. The cyclotrimerization reaction successfully provided the core structures; however, subsequent steps to yield the natural products are needed.

With respect to pyridine derivatives, the syntheses of the *Streptomyces* anticancer natural products streptonigrin and lavendamycin were explored. Several model routes, including the use of ynamides, were initiated to access the core structures, and further examination into the substitution of the diynes is necessary to realize the total synthesis of these two natural products. Attempts to synthesize two lycopodium alkaloids, lycopladine A and lycodine, via the cyclotrimerization reaction of alkyne-nitriles have been studied. However, access to the requisite alkyne-nitriles for the cyclotrimerization reaction has been problematic.

Natural Product Synthesis via [2+2+2] Cyclotrimerization Reactions

by
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DEDICATION

To my father, for nourishing my interest in science…

To my mother, for support and encouragement…

And to my wife, for unfailing love and understanding…

BIOGRAPHY

The author, Jesse Alexander Teske, was born in Monterey, CA on November 18, 1982 to Dewey and Dori Teske. After living briefly in Connecticut and Virginia, he moved to Charleston, SC at the age of three and stayed through high school. After high school, Jesse attended the University of Georgia and graduated magna cum laude with honors with a BSCHEM degree in Chemistry and a BS degree in Biochemistry and Molecular Biology. During his undergraduate research under the direction of Professor George Majetich, his passion for Organic Chemistry developed and inspired him to pursue graduate studies in that discipline.

In 2004, Jesse began his graduate career at North Carolina State University under the supervision of Professor Alex Deiters. In July of 2005, Jesse married his high school sweetheart, Amber Mincey. Upon completion of his Ph.D. in 2009, he began a postdoctoral research position at Vanderbilt University under the direction of Professor Gary Sulikowski.

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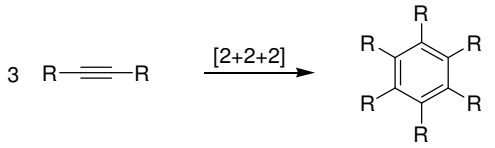
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CHAPTER 1: The Transition Metal Catalyzed [2+2+2] Cyclotrimerization Reaction

1.1 [2+2+2] Cyclotrimerization Reactions Towards Benzene Derivatives

1.1.1 Background and Mechanism

The [2π + 2π + 2π]-electron cyclotrimerization of alkynes into benzene derivatives is a powerful tool for the construction of polysubstituted aromatic compounds (Scheme 1.1). Compared with traditional methods for preparing substituted benzenes, e.g. electrophilic aromatic substitution or *ortho*-metallation, the [2+2+2] cyclotrimerization can offer a more flexible approach limited solely by alkyne synthesis. In a single operation multiple rings and three new carbon-carbon bonds can be formed.[1-9]

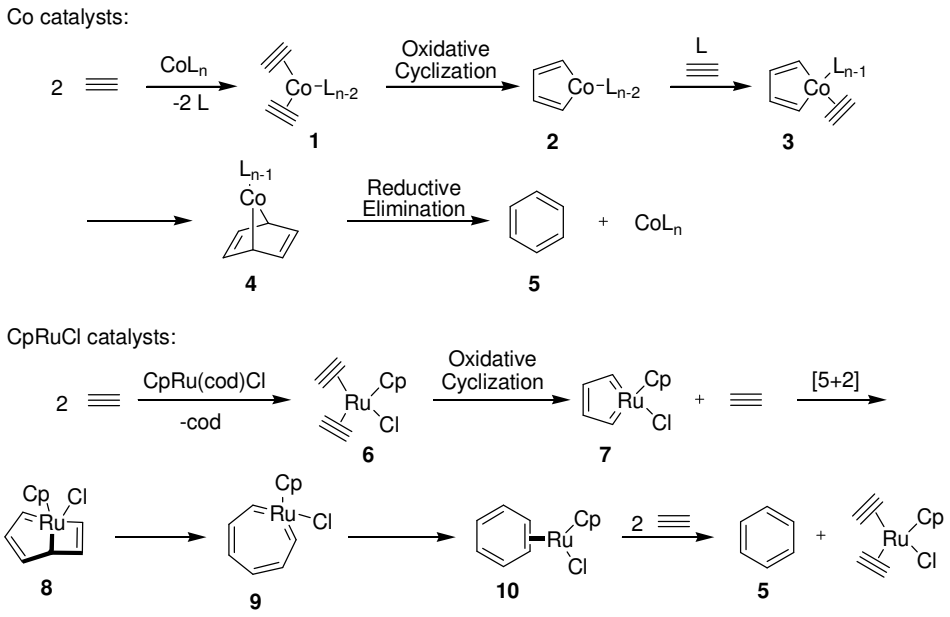


Scheme 1.1. General [2+2+2] cyclotrimerization reaction.

Discovered by Berthelot in 1866, the first known cyclotrimerization reaction produced benzene from acetylene at ~400 °C (without the need of any metal catalyst).[10] Such high temperatures essentially preclude the thermal [2+2+2] cyclotrimerization from synthetic utility despite the reaction being exothermic in nature.[11] A major advance came in the late 1940's when Reppe et al. reported the first transition metal catalyzed [2+2+2] cyclotrimerization reaction in which acetylene was converted into benzene in the presence of $(PPh_3)_2Ni(CO)_2$.[12] Despite the formation of cyclooctatetraene as the major product, the discovery that under certain conditions transition metals could mediate the [2+2+2] cyclotrimerization of alkynes opened the door for the reaction to become synthetically useful.

Following this seminal finding, many other transition metals besides Ni have been identified as catalysts for the cyclotrimerization of alkynes including Co,[13] Ru,[14] Rh,[15-17] and Pd.[18]

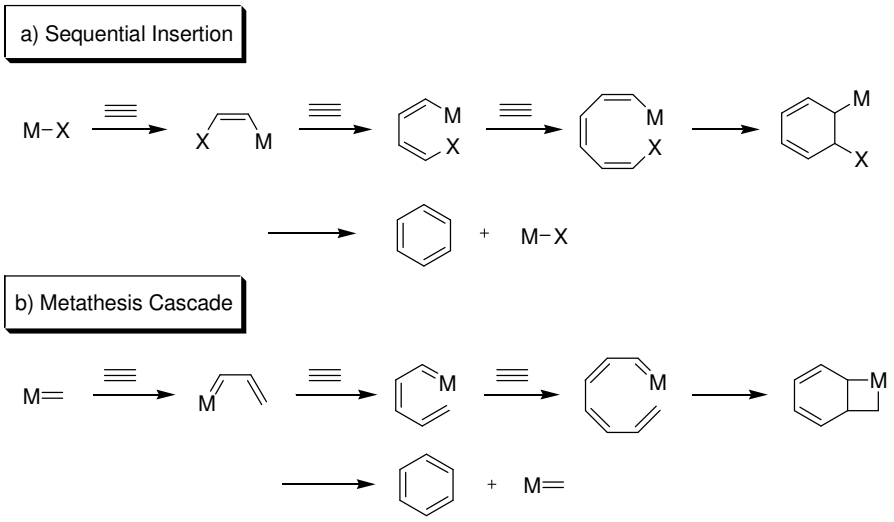
Depending upon the metal catalyst used, the reaction course can proceed by one of several mechanisms.[19] With cobalt based catalysts, the most common mechanism involves the metallacyclopentadiene intermediate **2** formed by the coordination of two alkyne molecules to the metal surface as in **1** followed by oxidative cyclization (Scheme 1.2).[1, 20] Once coordinated to the metal center as in **3**, the third alkyne is added via a Diels-Alder type [4+2] cycloaddition to give the cobaltanorbornadiene intermediate **4**. The final benzene product **5** is released after reductive elimination that also regenerates the catalyst.



Scheme 1.2. Possible [2+2+2] cyclotrimerization mechanisms. L = ligand.

When CpRuCl catalyst systems are employed, insertion of the third alkyne proceeds via a formal [5+2] cycloaddition between ruthenacycle **7** and the alkyne to first give the ruthenabicyclo[3.2.0]heptadiene complex **8** then the metallacycle **9** through cleavage of the

central Ru-C bond (Scheme 1.2).[7, 21] Reductive elimination to the η^2-benzene complex **10** and replacement of the arene with two additional alkynes complete the catalytic cycle. When transition metal hydrides or halides are employed, a sequential insertion mechanism has been postulated (Scheme 1.3a).[22, 23] Each alkyne unit is incorporated by a *cis*-addition of the metal-halide or metal-carbon bond across the triple bond. Finally, a metathesis cascade is proposed using Grubbs' catalyst where each alkyne is added in a series of [2+2] cycloadditions and cycloreversions (Scheme 1.3b).[24] A ring closing metathesis reaction yields the benzene product.

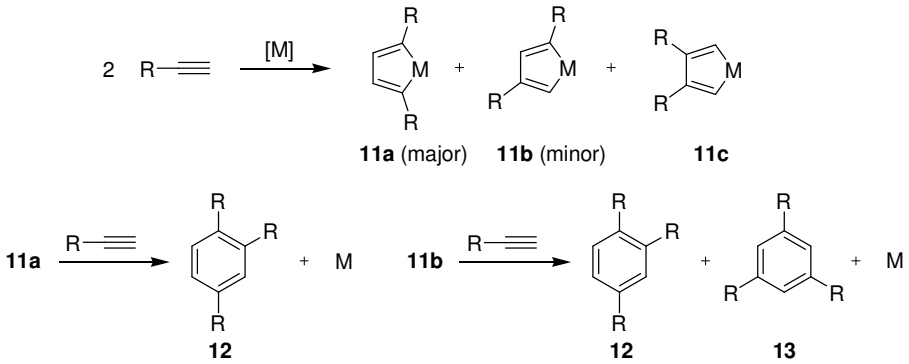


Scheme 1.3. Sequential insertion and metathesis cascade reaction mechanisms. M = metal center, X = halide.

1.1.2 Regioselectivity of the Cyclotrimerization Reaction

Using the first mechanism as a model, the regiochemical outcome of the intermolecular reaction is influenced by two steps: metallacycle formation and insertion of the third alkyne. The oxidative cyclization step can produce three isomeric metallacyclopentadienes **11a**, **11b**, and **11c** (Scheme 1.4). Only **11a** and **11b** need to be

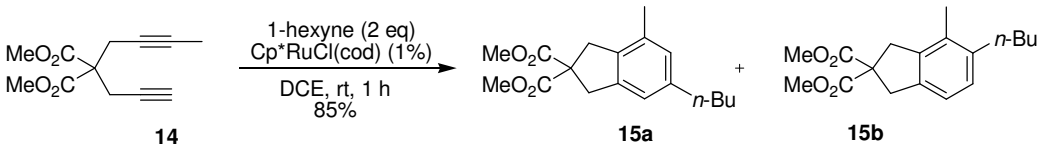
considered, as **11c** can be precluded from forming based on steric arguments. Experimental observation has shown that metallacycle **11a** is preferred where the bulky substituents are placed in an α-position to the metal center.[25] Only the 1,2,4-trisubstituted benzene **12** can form from this metallacycle irrespective of the orientation of insertion of the third alkyne. The minor metallacycle **11b** can form the 1,2,4-isomer **12** as well as the 1,3,5-isomer **13** depending upon the third alkyne's orientation. When two or three different alkynes are used, the product mixture can become quite complex.



Scheme 1.4. Regiochemical possibilities of [2+2+2] cyclotrimerization reactions.

A partially intramolecular cyclotrimerization reaction[2] (one diyne and one monoyne) provides a means of overcoming the regiochemistry issues as the orientation of two of the three alkynes is predetermined. In these cases, high degrees of '*meta* selectivity' can be obtained when using Ru[7] and Rh[26] based catalysts with nonsymmetrical diynes 1**4** and **16** being cyclotrimerized into fused bicycles **15a** and **17a**, respectively, as opposed to **15b** and **17b** (Schemes (1.5).

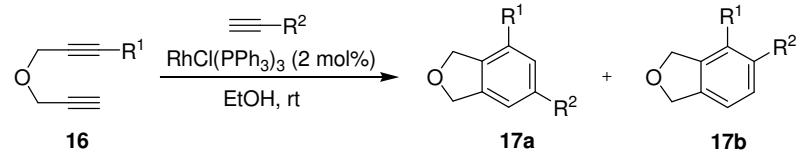
a)



14 **15a** : **15b**

93 : 7

b)

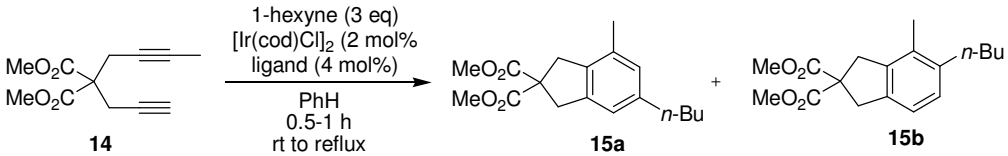


16 **17a** **17b**

R^1	R^2	Yield (%)	ratio (**17a**:**17b**)
CH_3	*n*-Bu	35	1.7:1
CH_3	$C(CH_3)_2OH$	54	**17a** only
CH_3	CH_2OH	53	1.8:1
$C(CH_3)_2OH$	*n*-Bu	36	**17a** only

Scheme 1.5. Partially intramolecular version of the [2+2+2] cyclotrimerization reaction enabling regiocontrol.

The regioselectivity of partially intramolecular cyclotrimerization reactions can be subject to ligand choice as well. For instance, Kezuka et al. obtained the *meta*-regioisomer **15a** preferentially using an Ir precatalyst with 1,2-bis(diphenylphosphino)ethane (DPPE) as the phosphine ligand, however, when the ligand was changed to 1,1′-bis(diphenylphosphino)ferrocene (DPPF), a reversal in the regiochemistry resulted and *ortho*-isomer **15b** was the major product (Scheme 1.6).[27]

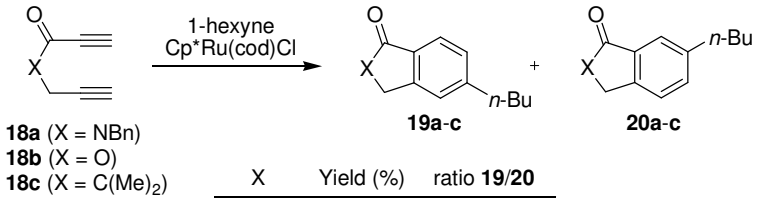


14 **15a** **15b**

ligand	Yield (%)	ratio **15a**/**15b**
DPPE	93	80/20
DPPF	84	12/88

Scheme 1.6. Ligand control of regioselectivity in cyclotrimerization reactions.

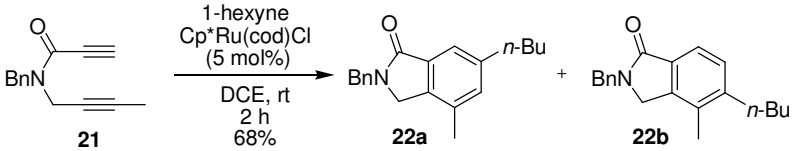
Instances where the electronic nature of the diyne exerts regiocontrol are also known. Yamamoto found that an electron-poor triple bond in the diynes **18a-c** preferentially furnished the benzene products **19a-c** where the substituent was oriented *para* to the carbonyl rather than **20a-c** (Scheme 1.7).[28] Furthermore, the higher the electron withdrawing ability of the carbonyl group (ketone > ester > amide) directly correlated with the degree of regioselectivity.



X	Yield (%)	ratio **19**/**20**
NBn	76	63/37
O	93	70/30
$C(Me)_2$	70	78/22

Scheme 1.7. Electronic effect on regioselectivity.

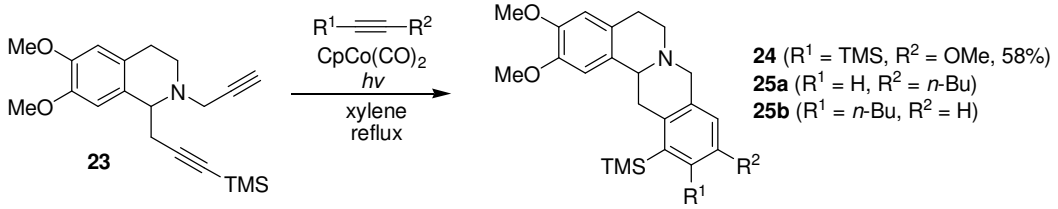
This electronic effect could be overcome, however, with the introduction of a steric control element such as a methyl substituent in **21** yielding **22a** as the major regioisomer (Scheme 1.8).



Scheme 1.8. Electronic versus steric influences on regioselectivity.

The degree of regioselectivity obtained under $CpCo(CO)_2$ catalysis varies by substrate. While exclusive regioselectivity is obtained between the cyclotrimerization reaction of **23** with trimethylsilylmethoxyethyne to give **24** in 58% yield, the similar cyclotrimerization reaction with 1-hexyne gives only a 5% combined yield of a 1:1 mixture

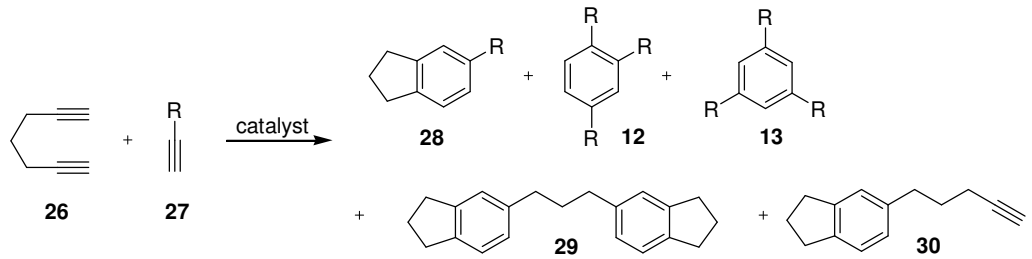
of **25a** and **25b** (Scheme 1.9). Due to the low yield, however, no mechanistic significance can be placed on the lack of selectivity.[29]



Scheme 1.9. Regiocontrol under $CpCo(CO)_2$ catalysis.

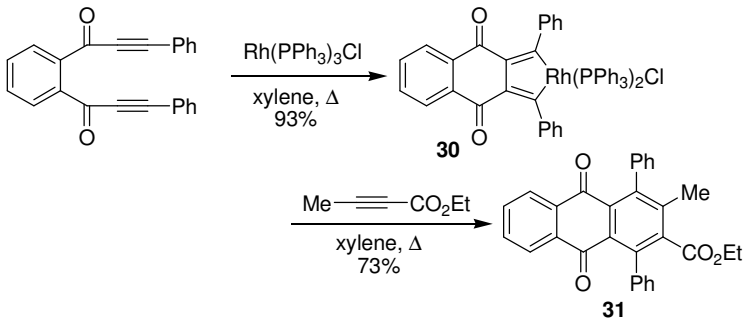
1.1.3 Chemoselectivity in Cyclotrimerization Reactions

Besides the regioselectivity issues associated with the [2+2+2] cyclotrimerization reaction, chemoselectivity problems must be addressed with both inter- and intramolecular reactions. Mixtures of cyclotrimerization products will undoubtedly occur when alkynes of similar steric and electronic properties are involved due to their similar reactivities.[2] The partially intramolecular version of the cyclotrimerization reaction is not void of chemoselectivity issues either. For example, the cyclotrimerization reaction between the diyne **26** and a generic monoyne **27** can furnish multiple products including the desired fused benzene product **28**, dimer and trimer of the diyne (**29** and **30**), as well as trimers from the monoyne reacting with itself (**12** and **13**, Scheme 1.10).



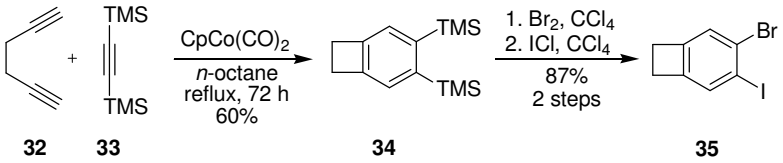
Scheme 1.10. Chemoselectivity issues in the partially intramolecular cyclotrimerization reaction.

Müller et al. successfully used a partially intramolecular approach with the stoichiometrically preformed rhodacycle **31** to provide various anthraquinone derivatives **32** as one solution to the chemoselectivity challenge (Scheme 1.11).[15, 16]



Scheme 1.11. Preformed metallacycle in [2+2+2] cyclotrimerization reaction.

Even with preformed metallacycles, the released metal is catalytically active and can cyclotrimerize the "third" alkyne resulting in by-products.[30] To circumvent this issue, Vollhardt et al. has made use of a "third" alkyne that is incapable of cyclotrimerizing with itself, such as bis(trimethylsilylacetylene) (BTMSA, **33**), providing access to a number of useful intermediates such as **34** and **35** from a cyclotrimerization reaction with **32** (Scheme 1.12).[13]

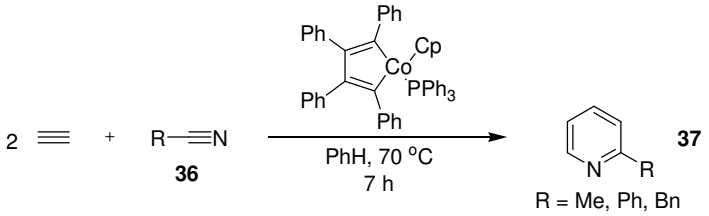


Scheme 1.12. Utility of BTMSA as cyclotrimerization partner.

1.2 [2+2+2] Cyclotrimerization Reactions Towards Pyridine Derivatives

1.2.1 Background and Mechanism

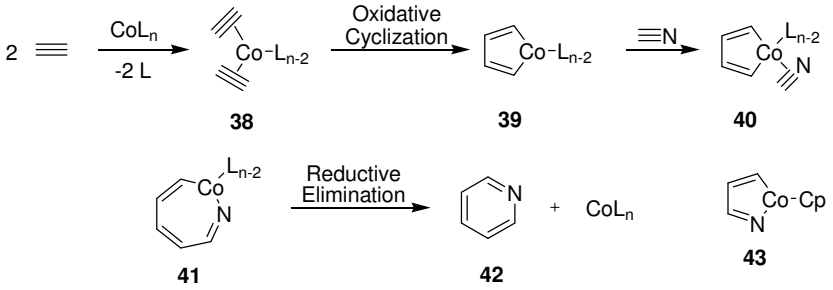
The synthesis of pyridine derivatives has received much interest from both academic and industrial laboratories owing to their wide dissemination in biologically active molecules.[1, 31-34] In the early 1970's, Wakatsuki and Yamazaki first showed the synthesis of pyridines **37** via a [2+2+2] cyclotrimerization reaction by replacing one alkyne unit with a nitrile **36** (Scheme 1.13). The earliest report utilized a stoichiometric amount of cobalt complex; however, it was found that the metal-complex could be used catalytically as well.[35, 36]



Scheme 1.13. Catalytic synthesis of pyridine derivatives.

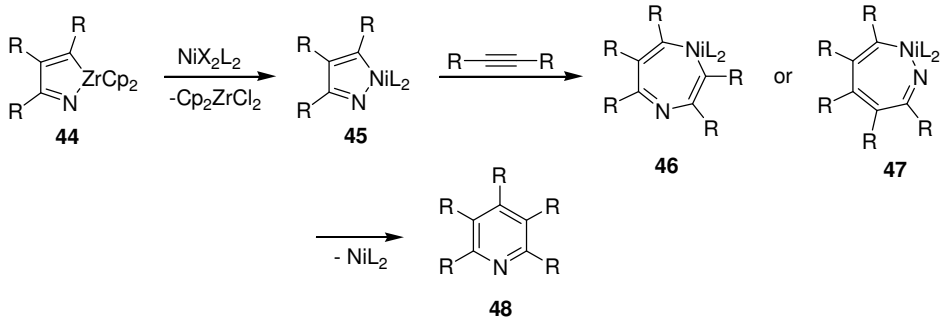
While most catalyst systems are based on Co^{I} complexes, other metals such as Rh,[37, 38] Ni,[39] and Ru[40] have been shown to produce pyridine derivatives from alkynes and nitriles.[1-3, 8, 41-43]

The mechanism of the [2+2+2] cyclotrimerization reaction towards pyridines proceeds in a similar fashion as towards benzenes.[2, 41, 44] Coordination of the two alkynes to the metal complex as in **38** is followed by oxidative cyclization giving the common metallacyclopentadiene intermediate **39** (Scheme 1.14).



Scheme 1.14. Mechanism of the [2+2+2] cyclotrimerization reaction towards pyridines.

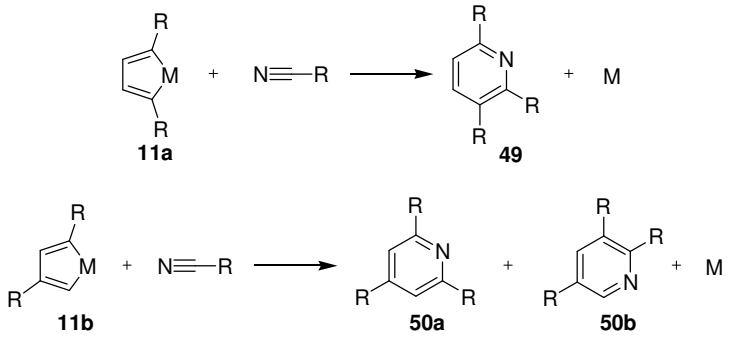
Next, coordination of the nitrile to the metallacycle giving **40** leads to insertion and the formation of the azametallacycloheptatriene **41**. Finally, reductive elimination furnishes the pyridine product **42** and the active metal species. Species where one alkyne and one nitrile undergo oxidative cyclization at the metal center (as in **43**) have been ruled out based on kinetic studies.[41] With Zr/Ni catalyst systems, however, the formation of the analogous azametallacyclopentadiene **45** is postulated from **44** (Scheme 1.15).[45, 46] Two possible azametallacycloheptatrienes (**46** or **47**) can form upon insertion of the second alkyne, and reductive elimination furnishes the pyridine product **48**.



Scheme 1.15. Zr/Ni mechanism for pyridine formation.

1.2.2 Regioselectivity of the Cyclotrimerization Reaction

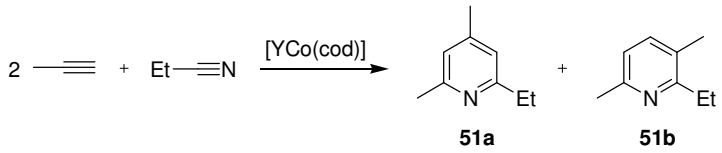
The regiochemical outcome of the cyclotrimerization reaction towards pyridines mirrors the outcome towards benzenes. When terminal acetylenes are employed, only metallacycles **11a** and **11b** are formed in the oxidative cyclization step, as shown previously (Scheme 1.16). Insertion of the nitrile, however, can occur in two fashions. With the symmetrical metallacycle **11a**, insertion can only produce the 2,3,6-trisubstituted pyridine derivative **49**.



Scheme 1.16. Regiochemical outcome of the [2+2+2] cyclotrimerization reaction towards pyridines.

However, with the nonsymmetrical metallacycle **11b**, two modes of insertion are possible leading to the 2,4,6- and 2,3,6-trisubstituted pyridine derivatives **50a** and **50b**, respectively. Experimentally, though, only the 2,4,6-trisubstituted pyridine derivative **50a** is formed where the nitrogen atom is placed next to the higher substituted (sterically more hindered) carbon center. Therefore, the completely intermolecular reaction yields both 2,3,6- and 2,4,6-trisubstituted pyridine derivatives. This ratio can be tuned depending upon the electronic nature of the cobalt catalyst. However, in the case of two different alkynes, three additional metallacycles can be formed, none of which is symmetrical, leading to the potential formation of six different pyridine regioisomers.

Table 1.1. Ligand effect on regiochemistry.

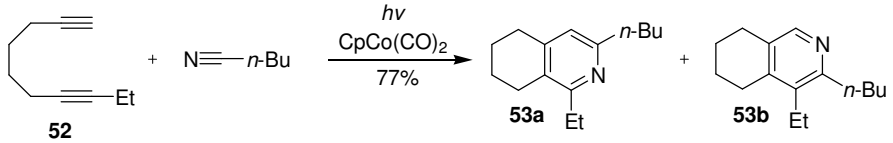


51a **51b**

Entry	Y	**51a/51b**
1	$CH_3COC_5H_4$	1.46
2	$(CH_3)_5C_5$	3.51
3	Bicyclo[3.3.0]octadienyl	2.50
4	$CH_3C_5H_4$	2.02
5	$TMSC_5H_4$	1.67
6	C_5H_5	1.71
7	Indenyl	1.48

The use of electron-poor cobalt catalysts (e.g. $CH_3COC_5H_4Co(cod)$) gives a regioselectivity ratio of 1.46:1 favoring the 2,4,6-trisubstituted regioisomer **51a** compared to the 2,3,6-trisubstituted regioisomer **51b** while electron-rich catalysts (e.g. $(CH_3)_5C_5Co(cod)$) can increase the ratio to 3.51:1.(Entries 1-2, Table 1.1)[42, 47, 48] The relative degree of activity of the catalysts however, is reversed with the electron-poor catalyst ($CH_3COC_5H_4Co(cod)$) being the most active. The steric environment of the cobalt-catalyst due to the ligands can also influence the regioselectivity of the intermolecular cyclotrimerization reaction (Entries 3-7).[42, 43]

As with the benzene syntheses, the partially intramolecular cyclotrimerization reaction (one diyne and one nitrile or a tethered alkyne-nitrile and one alkyne) towards fused pyridines can be used to exert regioselectivity. Vollhardt successfully cyclotrimerized the non-symmetrical 1,7-diyne **52** in a highly regioselective fashion towards the tetrahydroisoquinoline derivative **53a** (Scheme 1.17).[49]

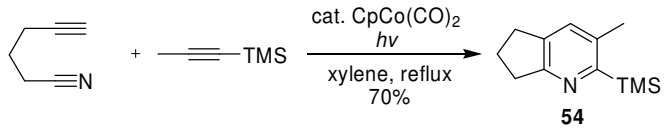


52 **53a** **53b**

18.3 : 1

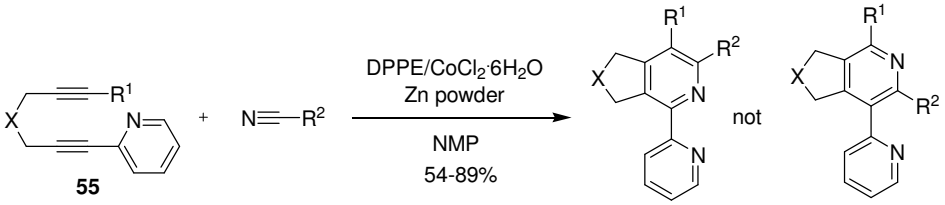
Scheme 1.17. Regioselective partially intramolecular pyridine synthesis.

The cyclotrimerization reaction of alkyne-nitriles can produce fused pyridines such as **54** with high regioselectivity as the initial metallacyclopentadiene formation sets the orientation of the alkynes (Scheme 1.18).[50]



Scheme 1.18. Regioselective alkyne-nitrile cyclotrimerization.

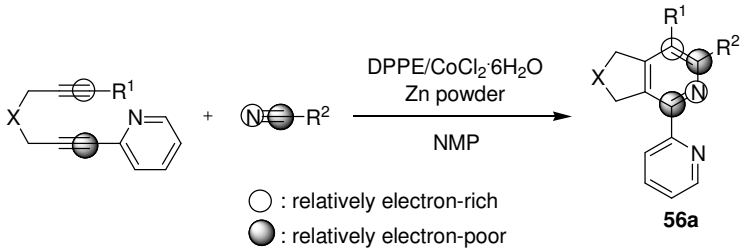
The electronic nature of the diyne may also influence the regiochemical outcome of the cyclotrimerization. Okamoto and coworkers obtained regioselectivity ratios of >99:1 when cyclotrimerizing the non-symmetrical diynes of type **55** with nitriles towards the bipyridines **56a** and **56b** (Scheme 1.19).[51]



Scheme 1.19. Regiocontrolled synthesis of 2,2'-bipyridines.

Based on the selective formation of the 2,2'-bipyridines **56a** over the 2,3'-bipyridines **56b**, the authors suggest the regiocontrol is due to the different electronic nature of the alkyne carbons with one being electron-rich (H or Me substituted) and the other electron-poor (pyridyl substituted). Lining up the electron-rich alkyne carbon with the electron-poor carbon from the nitrile and the electron-poor alkyne carbon with the electron rich nitrogen produces the observed regioisomer (Scheme 1.20).

However, the general applicability of this concept is questionable, and it is surprising that the authors did not employ a stronger electron-withdrawing group. It is not clear why a pyridyl and not a more defined electron-withdrawing substituent, e.g. carbonyl or carboxyl, was used.



Scheme 1.20. Potential electronic control of regioselectivity.

1.2.3 Chemoselectivity of the Cyclotrimerization Reaction

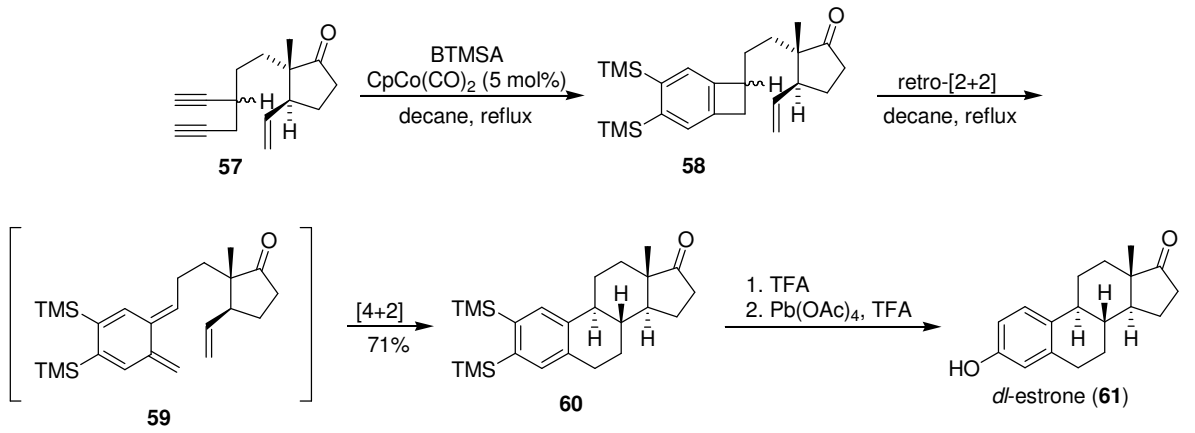
The chemoselectivity of the [2+2+2] cyclotrimerization reaction towards pyridines is determined when either a "third" alkyne or the nitrile is incorporated into the metallacyclopentadiene. Being better σ-donors than alkynes, nitriles coordinate to Co(III) species more readily. As a result, nitriles are preferentially inserted into the metallacyclopentadiene with chemoselectivity ratios for intermolecular reactions on the order of 2:1 pyridine to benzene product.[43, 52] Experimentally, using an excess of nitrile can enhance this selectivity.

1.3 Natural Product Synthesis via [2+2+2] Cyclotrimerization Reactions

1.3.1 Synthesis of Benzene Containing Natural Products

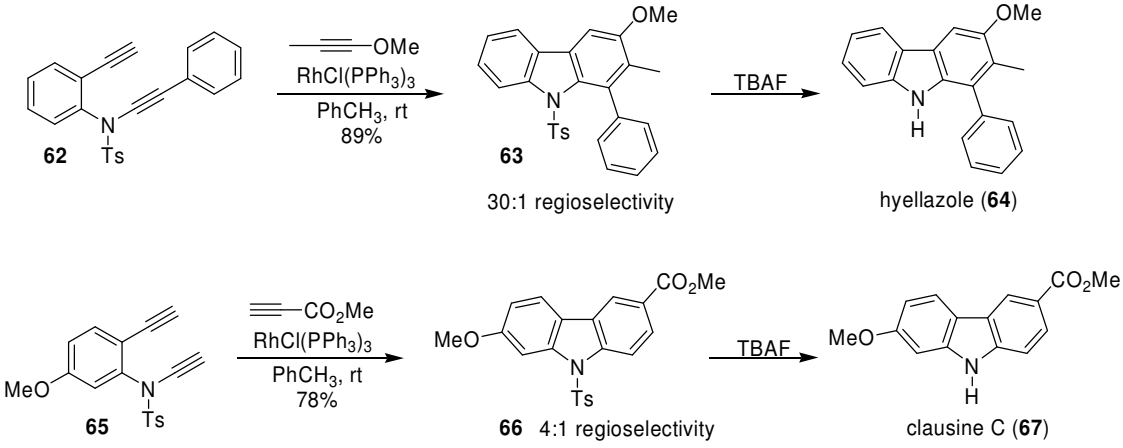
With the ability to produce fused ring systems and three carbon-carbon bonds in a single step, the [2+2+2] cyclotrimerization reaction has been the foundation of multiple total syntheses towards benzene natural products. Due to potential issues in controlling the regio- and chemoselectivity, the [2+2+2] cyclotrimerization reaction towards natural products has relied upon either partially or completely intramolecular cyclotrimerization events. A variety of natural products have been synthesized with the [2+2+2] cyclotrimerization reaction pointing to the reaction's broad applicability as well as the creativity of the practitioners of total synthesis.

As mentioned previously, the partially intramolecular variation of the [2+2+2] cyclotrimerization reaction provides one means to control the chemo- and regioselectivity as the orientation of two of the alkynes is predetermined, and this form of cyclotrimerization has been used in several total syntheses of benzene based natural products. The lab of K.P.C. Vollhardt has contributed much to the understanding of the cobalt-catalyzed [2+2+2] cyclotrimerization reaction, and it produced the first total synthesis of a natural product, *dl*-estrone (**61**), using this reaction.[53] The tetracyclic core of estrone was produced in a single step from the [2+2+2] cyclotrimerization reaction of the 1,5-hexadiyne **57** and BTMSA via the benzocyclobutene intermediate **58** and the *o*-quinodimethane **59** furnishing **60** in 71% yield (Scheme 1.21). Further elaboration of the aromatic ring produced *dl*-estrone in only six steps and 15% overall yield.



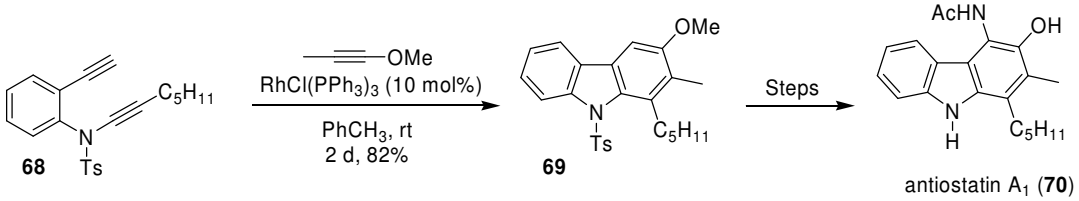
Scheme 1.21. Total synthesis of *dl*-estrone (**61**).

Interestingly, between 1980 and 2000 no total syntheses employing partially intramolecular cyclotrimerization reactions were reported (however, selected completely intramolecular reactions are discussed below). In 2002, Witulski et al. reported the use of ynamides towards the synthesis of carbazoles under rhodium catalysis.[54] The authors succeeded in synthesizing two naturally occurring carbazoles, hyellazole (**64**) and clausine C (**67**), in six and seven steps, respectively, with good regioselectivity from the diynes **62** and **65** and their cyclotrimerization reaction products **63** and **66** (Scheme 1.22).



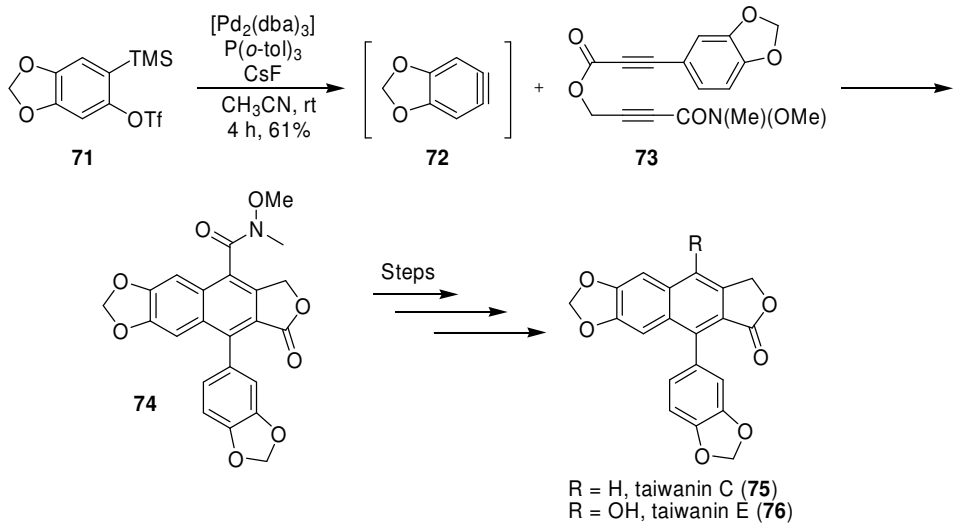
Scheme 1.22. Witulski's synthesis of hyellazole (**64**) and clausine C (**67**).

Similarly, antiostatin A_1 (**70**), a natural antioxidant, was recently synthesized by Witulski utilizing the diyne **68** via **69** (Scheme 1.23).[55]



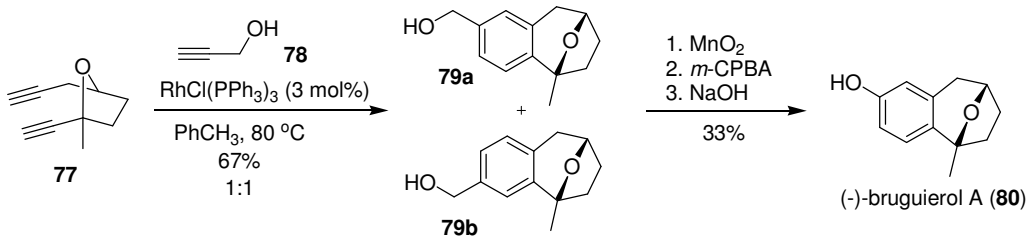
Scheme 1.23. Synthesis of antiostatin A_1 (**70**).

Making use of *in situ* formed aryne intermediates (**72**), Sato and Mori synthesized a common precursor (**74**) to taiwanins C and E (**75** and **76**) via a Pd-catalyzed [2+2+2] cyclotrimerization reaction of the diyne **73** and aryne precursor **71** (Scheme 1.24).[56]



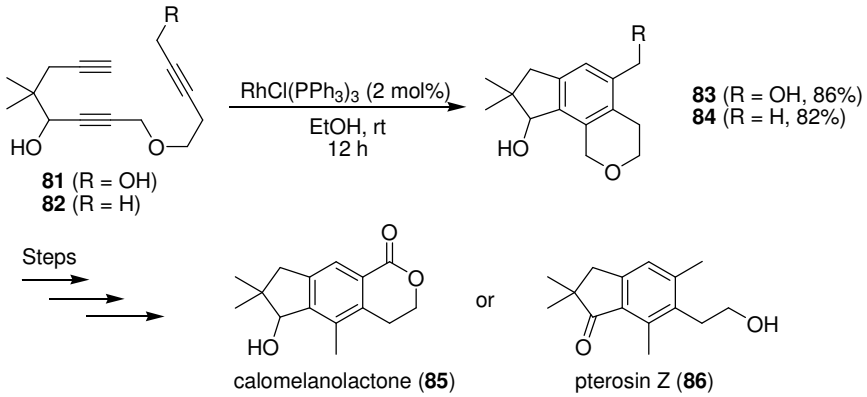
Scheme 1.24. Aryne [2+2+2] route to taiwanins C (**75**) and E (**76**).

Bridged natural products have also been accessed using the [2+2+2] cyclotrimerization reaction. The diyne **77**, synthesized from geraniol acetate, was reacted with propargyl alcohol (**78**) to furnish a 1:1 regioisomeric mixture of 3,4-benzannulated-8-oxabicyclo[3.2.1]octanes **79a** and **79b** in 67% yield using Wilkinson's catalyst (Scheme 1.25).[57] The mixture was then taken forward to (−)-bruguierol A (**80**).



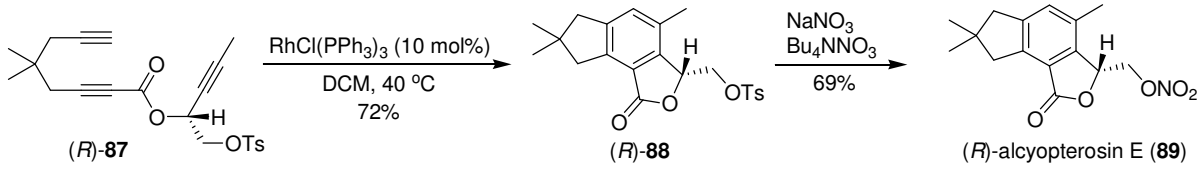
Scheme 1.25. Total synthesis of (–)-bruguierol A (**80**).

The completely intramolecular variation of the [2+2+2] cyclotrimerization has also produced several expedient syntheses of complex benzene natural products. In these cases, complete control of the regiochemistry is possible. For example, Neeson and Stevenson used the triynes **81** and **82** towards the illudalane sesquiterpenes calomelanolactone (**85**) and pterosin Z (**86**), respectively, from intermediates **83** and **84** (Scheme 1.26).[58, 59]



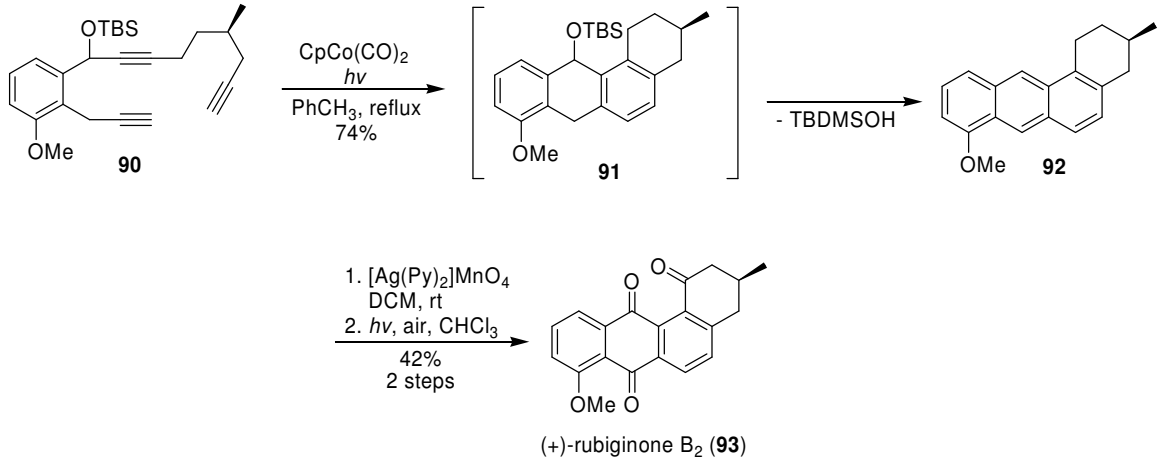
Scheme 1.26. Intramolecular cyclotrimerization reactions towards calomelanolactone (**85**) and pterosin Z (**86**).

Another illudalane sesquiterpene, (*R*)-alcyopterosin E (**89**), was synthesized in similar fashion by Witulski.[60] In this synthesis, the triyne **87** is prepared from L-ascorbic acid and readily undergoes a cyclotrimerization reaction upon treatment with Wilkinson's catalyst in 72% yield to give **88** (Scheme 1.27).



Scheme 1.27. Synthesis of (*R*)-alcyopterosin E (**89**).

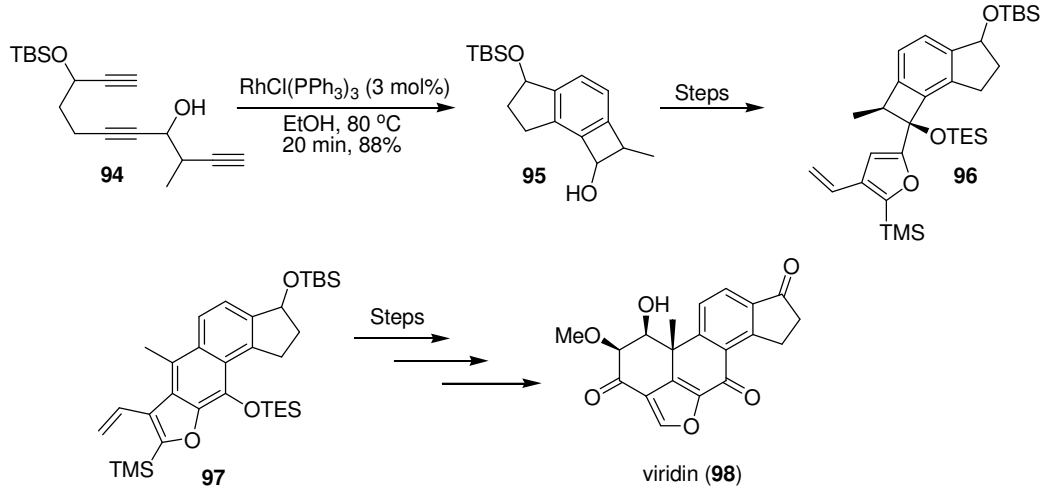
Recently, a synthesis of the tetracyclic angucyclinone (+)-rubiginone B_2 (**93**) employing a cobalt catalyst was reported.[61, 62] Irradiation of the triyne **90** in the presence of $CpCo(CO)_2$ furnished a 74% yield of the anthracene derivative **92** via the intermediate dihydroanthracene **91** (Scheme 1.28). A subsequent oxidation step provided the natural product.



Scheme 1.28. Synthesis of (+)-rubiginone B_2 (**93**).

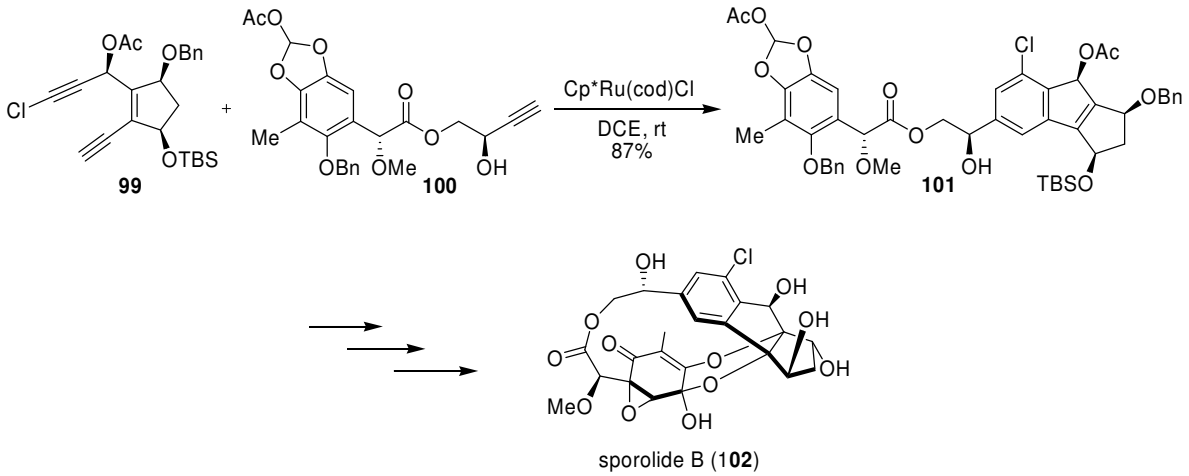
Taking a page from Vollhardt's synthesis of *dl*-estrone, Sorensen et al. exploited the generation of a benzocyclobutene intermediate in the first total synthesis of (±)-viridin (**98**).[63] The triyne **94** undergoes efficient intramolecular cyclotrimerization under rhodium catalysis to give the benzocyclobutene **95** (Scheme 1.29). Installation of the furan moiety to give **96** was followed by tandem electrocyclic ring-opening and 6π-electrocyclization to provide the

tetracyclic intermediate **97** after oxidation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). Subsequent formation and elaboration of the fifth ring provided (±)-viridin (**98**).



Scheme 1.29. Sorenson's synthesis of racemic viridin (**98**).

The regiocontrol exerted by halo-alkynes in the [2+2+2] cyclotrimerization was recently exploited by Nicolaou et al. towards the synthesis of sporolide B (**102**).[64] The monoyne **100** and the diyne **99** undergo smooth cyclotrimerization in the presence of Cp*Ru(cod)Cl to furnish an 87% yield of the advanced intermediate **101** (Scheme 1.30). Complete regiocontrol was realized due to the sterical hindrance imposed by the chlorine atom compared to a hydrogen atom. Several more steps were required to transform **101** into sporolide B.



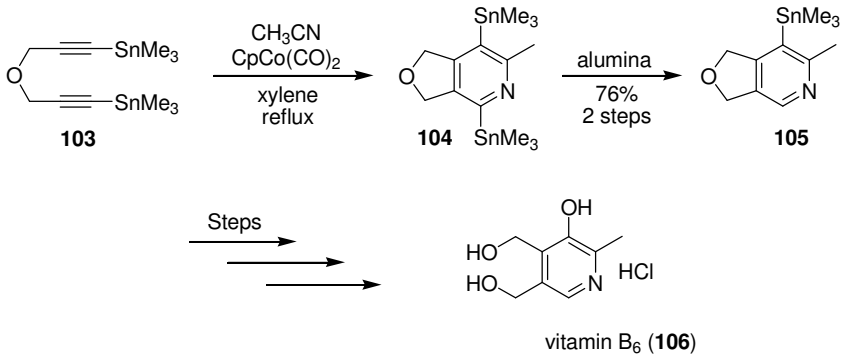
Scheme 1.30. Synthesis of the advanced intermediate **101** towards sporolide B via [2+2+2] cyclotrimerization.

As these examples show, the [2+2+2] cyclotrimerization reaction has been invaluable to the synthesis of a wide variety of natural products. In addition to these syntheses, the [2+2+2] cyclotrimerization reaction has been utilized in approaches to many classes of natural products including taxanes,[65] protoberberines,[29] phyllocladanes,[66] and kauranes.[67, 68] Another variation of the [2+2+2] cyclotrimerization reaction where one alkene is employed in the place of one alkyne has been used in approaches to terpenes,[69, 70] steroids,[71] and alkaloids such as strychnine[72] and morphine.[73]

1.3.2 Synthesis of Pyridine Containing Natural Products

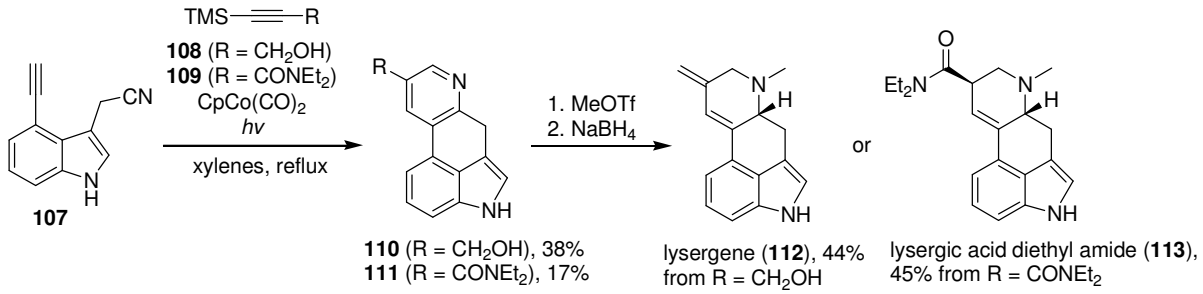
While the use of the [2+2+2] cyclotrimerization reaction towards benzene natural products is quite diverse, its use towards pyridine containing natural products is less developed. As with the synthesis of benzene natural products, the lab of K.P.C. Vollhardt has made seminal contributions in this area as well. For example, cyclotrimerization reaction of the bis(trimethylstannyl)-diyne **103** with acetonitrile under cobalt catalysis gives the fused

pyridine **104** (Scheme 1.31).[74] This pyridine is selectively monodestannylated with alumina to provide the pyridine product **105** in 76% yield over the two steps. Further manipulation of **105** provides vitamin B_6 (**106**).



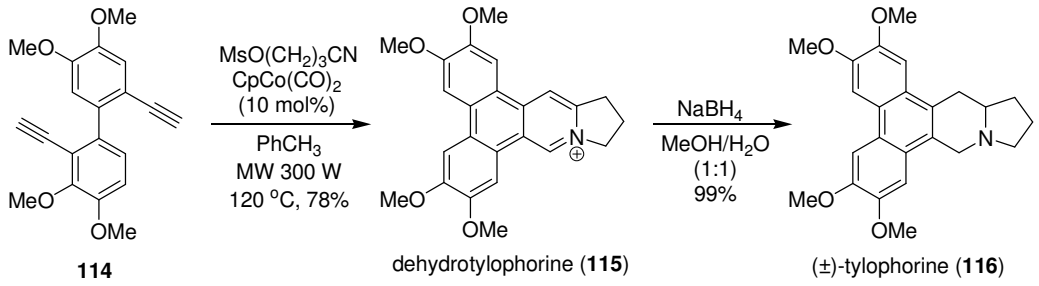
Scheme 1.31. Vollhardt's synthesis of vitamin B_6.

The synthesis of ergot alkaloids has also been examined using the [2+2+2] cyclotrimerization reaction. The alkyne-nitrile **107** reacts with the monoalkyne **108** in low yield to give the tetracyclic structure **110** (Scheme 1.32).[75] Lysergene (**112**) is obtained in 44% yield after methylation and reduction of the resulting pyridinium ion. Lysergic acid diethyl amide (**113**, LSD) is similarly synthesized using monoalkyne **109** via the cyclotrimerization product **111**.



Scheme 1.32. Synthesis of ergot alkaloids.

Most recently, concise syntheses of the alkaloids dehydrotylophorine (**115**) and (±)-tylophorine (**116**) have been accomplished utilizing a convergent [2+2+2] cyclotrimerization/ring closure strategy from the diyne **114** (Scheme 1.33).[76] Only five and six steps, respectively, were needed to produce the natural products in excellent yield.



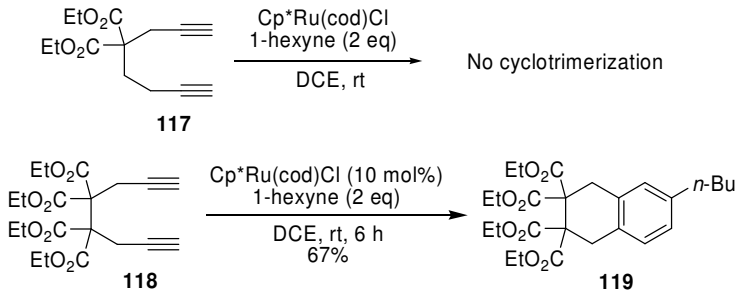
114 dehydrotylophorine (**115**) (±)-tylophorine (**116**)

Scheme 1.33. Total synthesis of dehydrotylophorine (**115**) and (±)-tylophorine (**116**).

1.4 General Cyclotrimerization Considerations

When planning a [2+2+2] cyclotrimerization reaction one must consider many factors including the nature of the metal catalyst and the steric and electronic properties of the three alkynes. In general, terminal alkynes are more active substrates and, consequently, react at faster rates than disubstituted alkynes.[4] Specifically, cobalt-based catalyst systems, such as $CpCoL_2$, have been examined the most and show a broad scope in reactivity with various alkynes.[1, 2] Electron deficient alkynes cyclotrimerize extremely efficiently with Cp*Ru(cod)Cl[7] as catalyst, as well as Pd[77] based catalyst systems. The same Ru catalyst and Grubbs' catalyst have recently been employed in reactions involving electronically neutral alkynes with good to excellent yields.[14, 24] For partially intramolecular reactions, the length and substitution of the tether must also be taken into account. Formation of 5,6-fused carbo- and heterocyclic ring systems is facile with most catalysts including Co,[78] Ni,[79] Ru,[7] Rh,[17]

and Ir.[27] 6,6-fused ring systems have also been prepared with varying degrees of success. Most systems require the assistance of the kinetic Thorpe-Ingold effect[80] as shown by the failure of diyne **117** to cyclotrimerize and the successful cyclotrimerization reaction of the diyne **118** into the 6-6-fused product **119** (Scheme 1.34).[7]

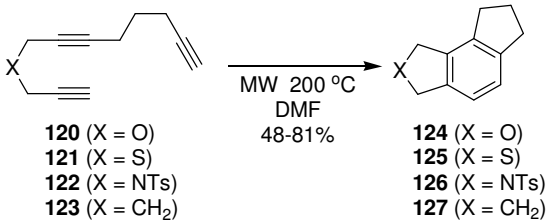


Scheme 1.34. Effect of alkyne tether on cyclization.

Larger fused ring systems (e.g. benzo-oxepins) are limited to completely intramolecular cases.[81, 82] Vollhardt et al. made use of 1,5-diynes to generate benzocyclobutenes that could be further elaborated through the subsequent *o*-quinodimethanes generated *in situ*.[53] Despite these selectivity hurdles, with adequate planning and detailed study of the reaction mechanisms, most substrates can be cyclized in preparatively useful yields.

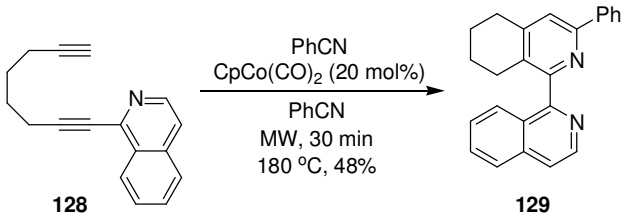
1.5 Microwave-assisted Cyclotrimerization Reactions

Following recent trends in organic chemistry, several groups have begun utilizing microwave irradiation to promote [2+2+2] cyclotrimerization reactions (For a more detailed discussion on the use of microwave irradiation in organic synthesis see Chapter 3). In 2005, the Ley group successfully employed microwave irradiation to promote the purely thermal cyclotrimerization of the triynes **120**-**123** yielding the tricyclic arenes **124**-**127** in good yield (Scheme 1.35).[83]



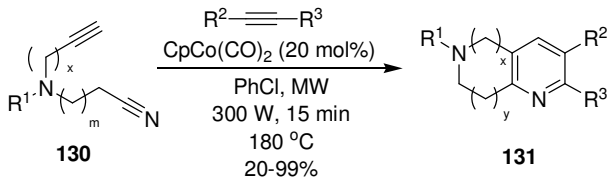
Scheme 1.35. Purely thermal microwave mediated cyclotrimerization reaction.

More importantly, the transition metal catalyzed [2+2+2] cyclotrimerization reaction is also promoted by microwave irradiation. Hrdina et al. accessed bipyridines such as **129** via a $CpCo(CO)_2$ catalyzed cyclotrimerization reaction of diynes (such as **128**) with nitriles under microwave irradiation (Scheme 1.36).[84] This report represents the first transition metal catalyzed microwave mediated [2+2+2] cyclotrimerization reaction.



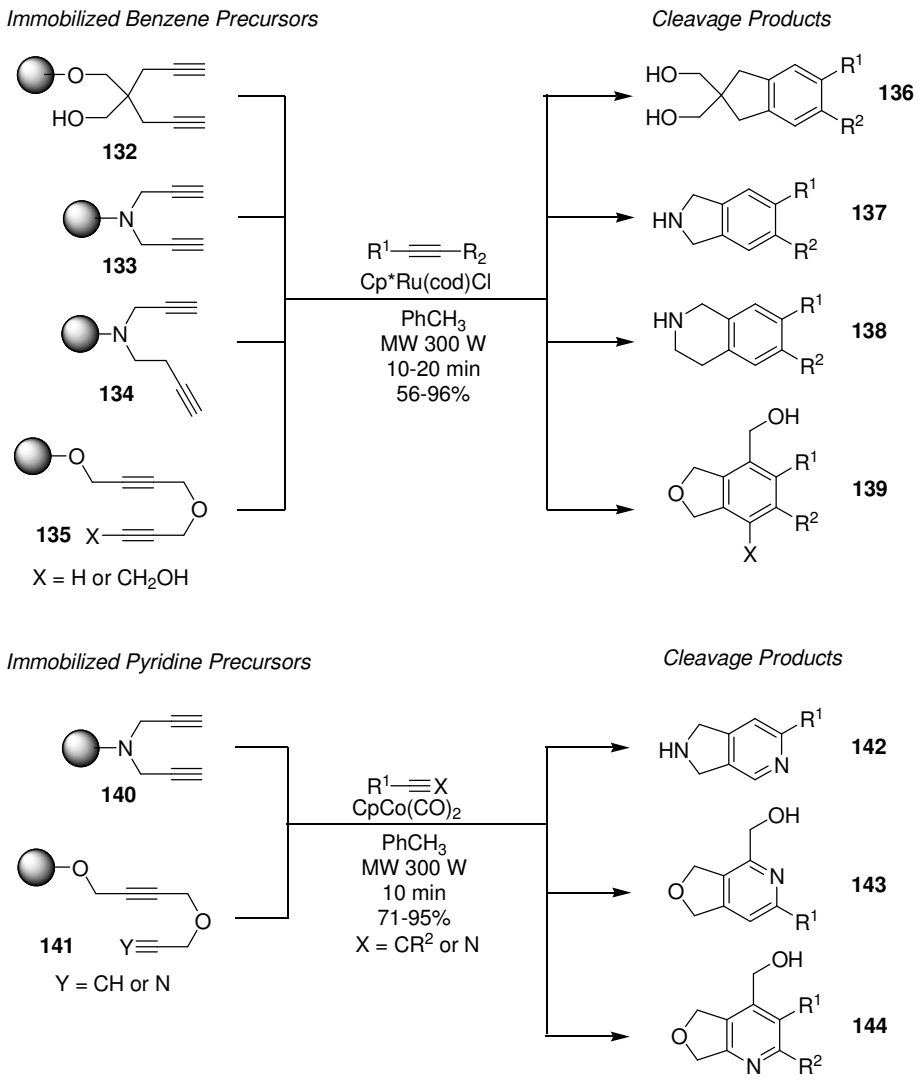
Scheme 1.36. The first transition metal catalyzed microwave mediated cyclotrimerization reaction.

Other examples of the use of microwave irradiation followed shortly thereafter. For example, Zhou et al. synthesized 5,6,7,8-tetrahydro-1,6-naphthyridines (**131**) in good yield from tethered alkynylnitriles (**130**) under $CpCo(CO)_2$ catalysis (Scheme 1.37).[85]



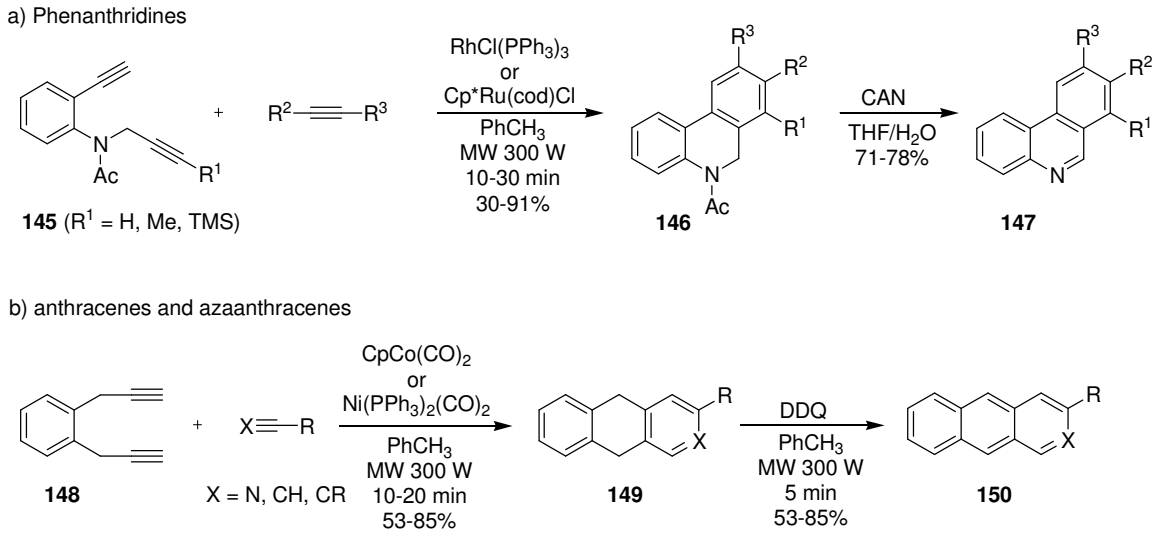
Scheme 1.37. Synthesis of 5,6,7,8-tetrahydro-1,6-naphthyridines.

In 2007, the Deiters group produced several accounts of the application of microwave irradiation with cyclotrimerization reactions. The solid-phase synthesis of benzenes **136**-**139** and pyridines **142-144** from the immobilized substrates **132**-**135** and **140**-**141** allows for the rapid synthesis of an array of carbo- and heterocyclic ring structures in a combinatorial fashion (Scheme 1.38)[86, 87] The microwave irradiation does not alter the regioselectivity of the cyclotrimerization reactions. In order to achieve a high chemoselectivity, it was necessary to utilize the pseudo high-dilution conditions of the solid-support.



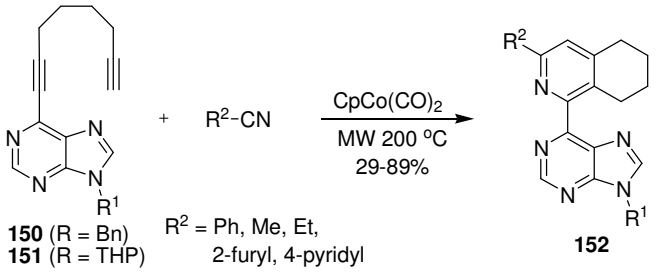
Scheme 1.38. Solid-phase synthesis of benzenes and pyridines under microwave irradiation.

The convergent synthesis of phenanthridine derivatives **147** was also achieved via the dihydrophanthridines **146** constructed by microwave mediated cyclotrimerization reactions of several diynes **145** with monoynes (Scheme 1.39)[88] Furthermore, the synthesis of the anthracene and azaanthracene analogues **150** with applications as fluorescent probes was accomplished starting with dipropargylbenzene **148** via the cyclotrimerization product **149** (Scheme 1.39).[89]



Scheme 1.39. Synthesis of phenanthridines, anthracenes, and azaanthracenes.

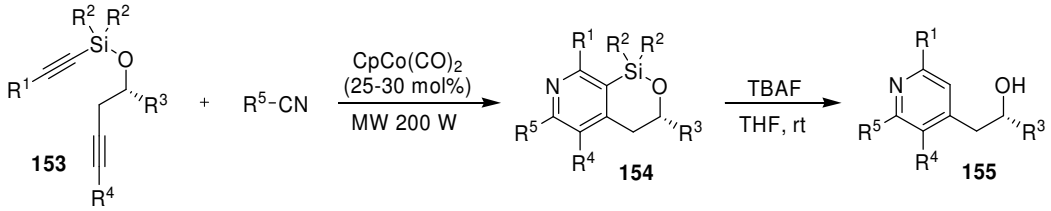
Other groups have also employed microwave promoted cyclotrimerization reactions in the synthesis of various benzene and pyridine derivatives of pharmaceutical interest. Turek et al. produce an array of 6-pyridylpurines (**152**) via $CpCo(CO)_2$ catalysis under microwave irradiation from the diynes **150** and **151** (Scheme 1.40).[90] The authors note that several cyclotrimerization reactions were only possible under microwave irradiation.



Scheme 1.40. Synthesis of 6-pyridylpurines.

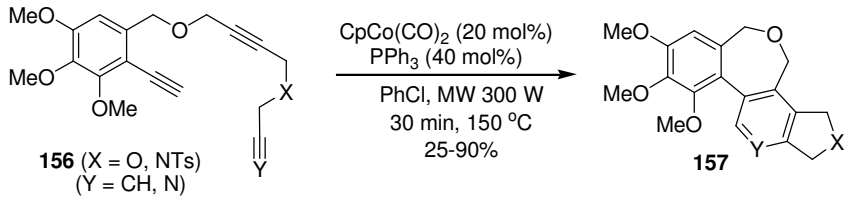
Silyl-tethered diynes **153** were exploited in a cyclotrimerization reaction towards fused pyridine derivatives **154** capable of inhibiting neuregulin-induced neurite growth (Scheme 1.41).[91] The tethers can then be cleaved under to provide the substituted pyridines

155. Similar tethering approaches have recently been realized for the synthesis of small molecule modifiers of developmental pathways (McIver & Deiters, unpublished results).



Scheme 1.41. Utilizing silyl-tethered diynes for pyridine synthesis.

Derivatives of 6-oxa-allocolchicinoids (**157**) have been accessed using microwave promoted cyclotrimerization reactions of triynes and alkynylnitriles (**156**, Scheme 1.42).[92] Several derivatives displayed selective apoptosis-inducing activity against BJAB tumor cells.



Scheme 1.42. Synthesis of 6-oxa-allocolchicinoid derivatives.

Even though the [2+2+2] cyclotrimerization reaction is very capable of generating highly functionalized benzene and pyridine derivatives, the reaction has been underutilized in the area of natural product synthesis with relatively few examples in the literature.[2] We aim to further explore the microwave-mediated [2+2+2] cyclotrimerization reaction in the context of the total synthesis of several benzene containing natural products, such as an indanone natural product (Chapter 2), the sesquiterpene alkaloid illudinine (Chapter 3), anthraquinone based natural products (Chapter 4), cannabinoid natural products (Chapter 5), and neolignans (Chapter 6). Furthermore, we wish to investigate the [2+2+2] cyclotrimerization reaction towards pyridine natural products such as streptonigrin, lavendamycin, lycopladine, and

lycodine (Chapters 7 and 8). These explorations will not only provide routes to the natural products themselves, but will also supplement the understanding of various aspects of the cyclotrimerization chemistry such as reactivity, regioselectivity, and chemoselectivity of advanced diyne intermediates.

CHAPTER 2: Total Synthesis of an Indanone Natural Product

2.1 Background

As an extension of our approach to the regio- and chemoselective synthesis of benzene and pyridine derivatives via solid-supported [2+2+2] cyclotrimerization reactions, [93, 94] we sought to apply this methodology to the synthesis of biologically active structures. Natural products based upon the indanone core structure e.g. pterosin P (**158**), mukagolactone (**159**), and monachosorin A (**160**) display various biological activities including smooth muscle relaxant activity,[95] inhibition of cyclooxygenase 2,[96] and mast cell stabilization (Figure 2.1).[97]

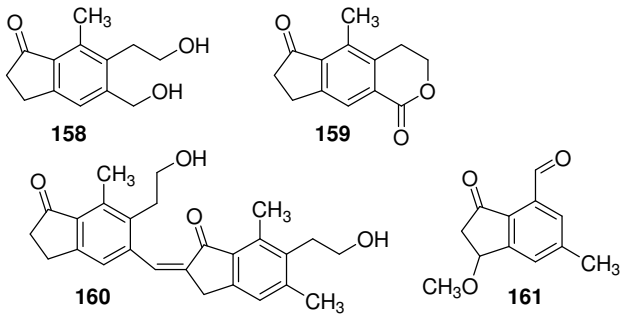
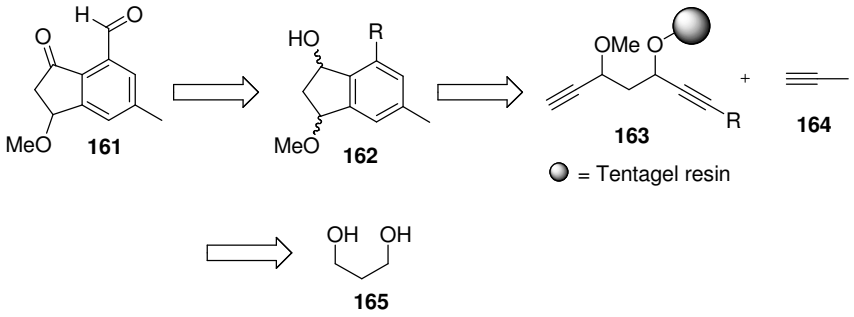


Figure 2.1. Representative indanone natural products **158**-**161**.

Due to the interesting biological activities as well as the multitude of diverse indanone natural products[98, 99] efficient and selective synthetic routes to indanones are desirable.[100] Recently, the indanone natural product **161** has been isolated from the marine cyanobacterium *Lyngbya majuscula* and was found to inhibit hypoxia-induced activation of the vascular endothelial growth factor (VEGF) *in vitro*.[101] Tumor cells express VEGF in response to their low oxygen environment in order to stimulate blood vessel formation (angiogenesis), therefore, inhibitors of this step in tumor development are important

regulators of cancer growth. Cell culture studies with indanone **161**, however, showed no inhibition of secretion of the human bioactive VEGF isoform. Further improvements to the biological activity would require structural modifications, thus providing an impetus to synthesize indanone **161** in a fashion amenable to analogue development.

Retrosynthetically, we envision obtaining indanone **161** from oxidation of the alcohol in **162** with simultaneous conversion of an R group into the aldehyde functionality (Scheme 2.1). The 5,6-fused ring system of the alcohol **162** would arise from a solid-supported [2+2+2] cyclotrimerization reaction between immobilized 1,6-diyne **163** and propyne (**164**). By conducting the key cyclotrimerization step on the solid-support unwanted byproducts, e.g. diyne dimer **166** or trimer **167**, can be eliminated (Figure 2.2).



Scheme 2.1. Retrosynthetic analysis of indanone **161**.

Synthesis of the 1,6-diyne **163** can be traced to 1,3-propanediol (**165**) through a series of protecting group manipulations and 1,2-additions of acetylides into aldehydes. No attempts to synthesize the optically active 1,6-diyne **175** were pursued as, although the isolated indanone rotates polarized light ($[\alpha]_D$ = +1.3°), the angle of rotation was far different than that of the standard (–)-(3*R*)-3-hydroxyindan-1-one ($[\alpha]_D$ = -101°) causing speculation that the isolated product is nearly racemic.[101]

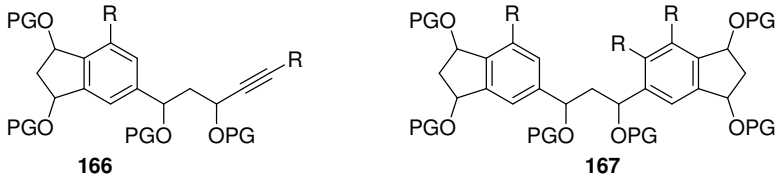
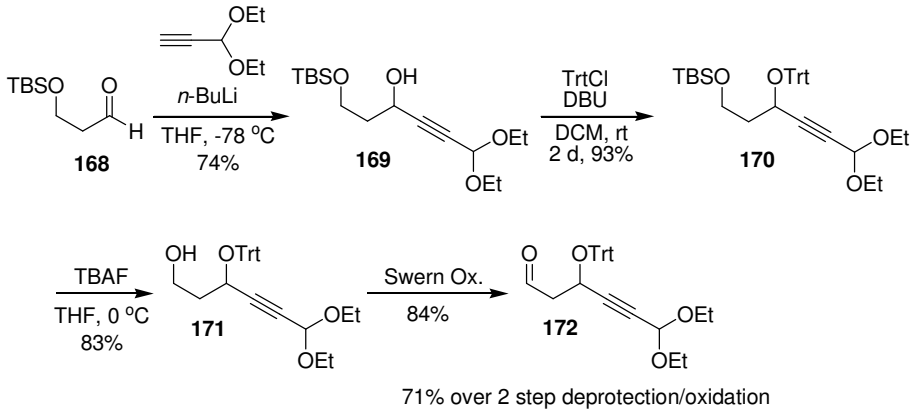


Figure 2.2. Dimer **166** and trimer **167** by-products. PG = protecting group.

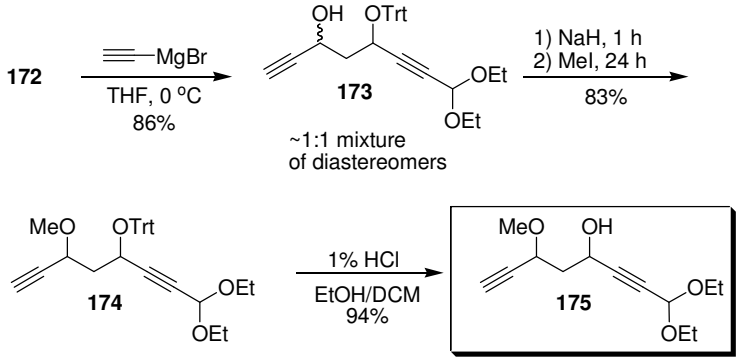
2.2 Diyne Synthesis

Synthesis of the 1,6-diyne **175** began with the 1,2-addition of the Li-acetylide of propargyl aldehyde diethyl acetal into the known aldehyde **168**,[102, 103] prepared in two steps from 1,3-propanediol, to give the propargyl alcohol **169** in 74% yield (Scheme 2.2). Protection of the secondary alcohol as the triphenylmethyl ether **170** was accomplished using trityl chloride with DBU over two days in 93% yield.[104] More classical conditions (TrtCl, TEA, 40 °C) gave the triphenylmethyl ether in only 24% yield. Two equivalents of trityl chloride were necessary to drive the reaction to completion as fewer equivalents gave lower yields (50% with 1.2 eq., 69% with 1.5 eq.). Removal of the TBS group with TBAF as the fluoride source furnished the primary alcohol **171** in an 83% yield.



Scheme 2.2. Synthesis of the aldehyde **172**.

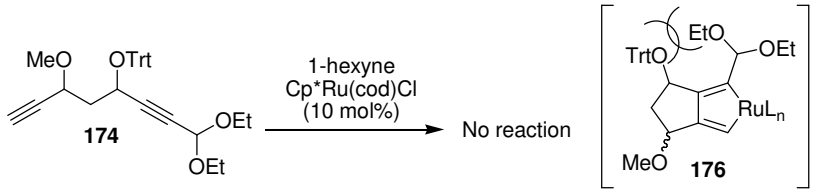
The alcohol **171** was then oxidized with Dess-Martin Periodinane (DMP)[105] in 71% yield or *via* the Swern protocol[106] (84%) to give the aldehyde **172**. On larger scale a two-step TBAF deprotection followed by a Swern oxidation of the crude material was more convenient for the preparation of the aldehyde **172** (71% over two steps). The second alkyne moiety was installed at this point by 1,2-addition of ethynyl Grignard into the aldehyde **172** providing a ~1:1 diastereomeric mixture of the alcohol **173** in 86% yield (Scheme 2.3). Subsequent methylation using standard conditions (NaH, MeI) produced methyl ether **174** in an 83% yield. Synthesis of the diyne **175** only required the removal of the triphenylmethyl ether selectively in the presence of the diethyl acetal. Using 1.5% TFA in DCM for fifteen minutes gave the diyne **175** in a moderate 62% yield with an undetermined amount of acetal hydrolysis. Gratifyingly, treatment of **174** with 1% HCl in EtOH/DCM for 100 minutes cleanly afforded the desired alcohol **175** in a 94% yield with no hydrolysis of the acetal.



Scheme 2.3. Synthesis of the 1,6-diyne **175**.

2.3 Cyclotrimerization Studies and Completion of the Synthesis

In order to determine the best conditions for the oxidation and unmasking of the aldehyde functionality, solution phase cyclotrimerization studies were undertaken. Towards this end, ether **174** was treated with 10 mol% Cp*Ru(cod)Cl and 1-hexyne at room temperature; however, no cyclotrimerization product was observed (Scheme 2.4).

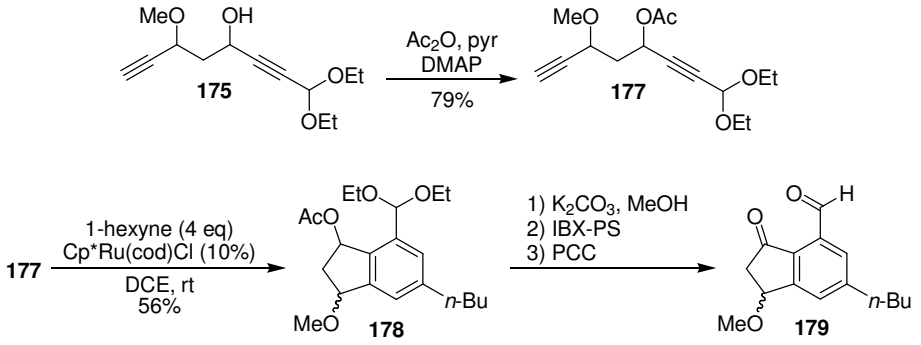


Scheme 2.4. Attempted cyclotrimerization reaction of the trityl ether **174**.

One plausible explanation for the lack of product formation is the steric demand of the triphenylmethyl ether and the diethyl acetal in **174** preventing formation of the metallacycle; if ruthenacycle **176** were to form, then the triphenylmethyl ether and diethyl acetal would undoubtedly be in close proximity and undergo undesired steric interactions.

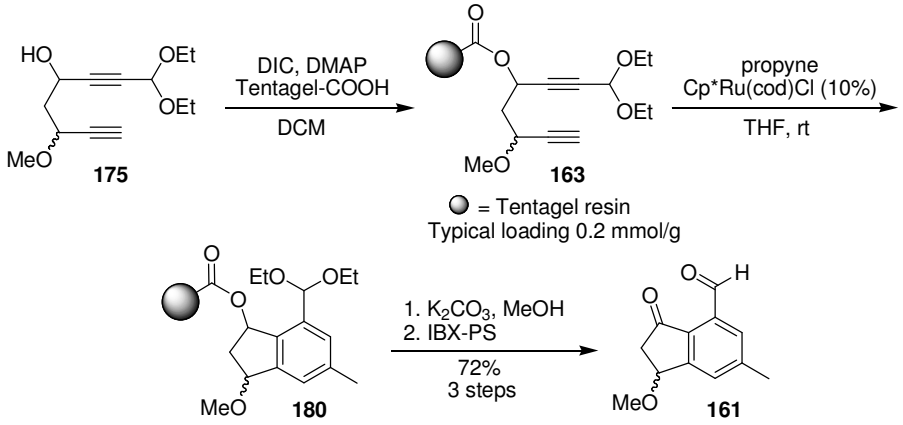
As the solid support contains an ester linker, the protecting group was changed to the acetate **177** to better approximate the steric demand in the solid-phase reaction (Scheme 2.5). Accordingly, the acetate **177** was prepared from the alcohol **175** under standard acetylation conditions and was tested with 1-hexyne in the [2+2+2] cyclotrimerization reaction. Gratifyingly, cyclotrimerization proceeded in 56% yield furnishing the benzene derivative **178** as the only regioisomer. The yield of the solution phase cyclotrimerization reaction is diminished due to unwanted dimerization of the diyne **177**. Cleavage of the ester and oxidation of the resulting alcohol with 2-iodoxybenzoic acid functionalized polystyrene (IBX-polystyrene)[107] gave a mixture of oxidized and acetal hydrolysis products. Further

oxidation with the more acidic reagent pyridinium chlorochromate (PCC) proceeded to give one homogeneous product, indanone **179**. The ^{1}H-NMR shifts are in good agreement with the corresponding protons in the natural product.



Scheme 2.5. Cyclotrimerization of the acetate **177** and conversion to the natural product analogue **179**.

With the endgame strategy established, the final steps in the synthesis of the natural product indanone were completed by Doug Young. Immobilization of the diyne **175** on a Tentagel carboxy resin under standard coupling conditions provided the immobilized diyne **163** with a typical loading of 0.2 mmol/g (Scheme 2.6).



Scheme 2.6. Completion of the synthesis of the indanone **161**.

Cyclotrimerization of the immobilized diyne **163** with propyne proceeded under ruthenium catalysis to afford the immobilized benzene product **180**. Cleavage from the resin (K_2CO_3/MeOH) followed by oxidation of the resulting indanol with IBX-polystyrene with simultaneous acetal cleavage gave the natural product as the sole regioisomer in 72% yield over the final three steps. The NMR spectra (^1H and ^{13}C) of natural and synthetic **161** are in excellent agreement (Table 2.1). With the successful synthesis of **161** accomplished, analogue development aimed at improving *in vivo* VEGF inhibition is feasible.

Table 2.1. Comparison of NMR spectra for natural and synthetic **161**.[101]

^1H NMR

Natural **161** ($CDCl_3$, 500 MHz)	Synthetic **161** ($CDCl_3$, 300 MHz)
11.01 (s, 1 H)	11.01 (s, 1 H)
7.86 (s, 1 H)	7.86 (s, 1 H)
7.74 (s, 1 H)	7.74 (s, 1 H)
5.01 (dd, *J* = 6.6 and 3.0 Hz, 1 H)	5.03-5.00 (m, 1 H)
3.52 (s, 3 H)	3.52 (s, 3 H)
3.06 (dd, *J* = 18.4 and 6.6 Hz, 1 H)	3.06 (dd, *J* = 18.6 and 6.3 Hz, 1 H)
2.73 (dd, *J* = 18.4 and 3.0 Hz, 1 H)	2.73 (dd, *J* = 18.6 and 3.0 Hz, 1 H)
2.52 (s, 3 H)	2.52 (s, 3 H)

^{13}C NMR

Natural **161** ($CDCl_3$, 500 MHz)	Synthetic **161** ($CDCl_3$, 300 MHz)
202.76	202.8
190.71	190.7
154.65	154.6
146.21	146.2
137.06	137.1
133.9	133.9
128.28	128.3
76.38	76.4
57.37	57.4
44.02	44.0
21.92	21.9

2.4 Summary

In conjunction with the solid-phase synthesis of unnatural indanone derivatives, the synthesis of the natural indanone **161** was accomplished starting from 1,3-propanediol in 11 steps and 24% overall yield from known material. Key features of the synthesis include a solid-supported [2+2+2] cyclotrimerization reaction with complete regiocontrol and traceless cleavage of the product from the solid-support.

2.5 Experimental

All reactions were performed in flame-dried glassware under a nitrogen atmosphere and stirred magnetically. Tetrahydrofuran, toluene, xylenes, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Diisopropylamine, triethylamine, DMSO, DCM, DMF, 1,2-dichloroethane, CH_3CN and pyridine were distilled from calcium hydride and stored over 4 Å molecular sieves. Other reagents and solvents obtained from commercial sources were stored under nitrogen and used directly without further purification. *n*-BuLi and MeLi were titrated against *N*-pivaloyl-*o*-toluidine.[108] Melting points were obtained from a Mel-Temp capillary melting point apparatus and are uncorrected. High resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz) or Varian Mercury 300 (300 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption (77.2) for ^{13}C NMR spectra. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer.

1-((*tert*-Butyldimethylsilyl)oxy)-6,6-diethoxy-hex-4-yn-3-ol (169). *n*-BuLi (1.6 M in hexanes, 331 μL, 0.64 mmol) was added dropwise to a solution of propargyl aldehyde diethyl acetal (88 mg, 0.69 mmol) in THF (1.5 mL) at −78 °C. After 30 min, a solution of **168** (100 mg, 0.53 mmol) in THF (1.1 mL) was added, and the reaction mixture was allowed to stir for 15 min before warming to room temperature over 30 min. Water (3 mL) and ether (3 mL) were added, and the layers were separated. The aqueous phase was extracted twice with ether (3 mL), and the combined organic phases were washed with H_2O (10 mL) and brine (10 mL),

dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (6:1), to give 125 mg (74%) of **169** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (d, *J* = 1.4 Hz, 1 H), 4.74-4.64 (m, 1 H), 4.09-3.99 (m, 1 H), 3.90-3.53 (m, 5 H), 3.43 (d, *J* = 6.0 Hz, 1 H), 2.10-1.83 (m, 2 H), 1.25 (t, *J* = 7.0 Hz, 6 H) 0.92 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.5, 86.0, 80.3, 61.8, 61.1, 61.0, 38.6, 26.1, 18.4, 15.3, −5.3, −5.3; HRMS calcd for $[M + Na]^+$ $C_{16}H_{32}O_4SiNa$ 339.1962, found 339.1970.

1-((*tert*-Butyldimethylsilyl)oxy)-6,6-diethoxy-3-(triphenylmethoxy)-hex-4-yne (170). A solution of **169** (680 mg, 2.15 mmol) in DCM (6.75 mL) was added to a solution of TrtCl (1.20 g, 4.30 mmol) and DBU (707 μL, 4.75 mmol) in DCM (3 mL) at room temperature and was allowed to stir for 2 days. H_2O (15 mL) and DCM (15 mL) were added, and the layers were separated. The aqueous layer was extracted twice with Et_2O (20 mL), and the combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1) to give 1.12 g (93%) of **170** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.48 (m, 6 H), 7.32-7.19 (m, 9 H), 4.98 (d, *J* = 1.1 Hz, 1 H), 4.21 (br t, *J* = 5.9 Hz, 1 H), 3.82-3.67 (m, 2 H), 3.61-3.37 (m, 4 H), 1.98-1.78 (m, 2 H), 1.19 (t, *J* = 7.0 Hz, 6 H), 0.83 (s, 9 H), 0.00 (s, 3 H) -0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 129.1, 127.7, 127.1, 91.4, 87.8, 85.7, 81.2, 62.0, 60.8, 60.8, 59.6, 39.8, 26.1, 18.5, 15.3, -5.1, -5.2; HRMS calcd for $[M + Na]^+$ $C_{35}H_{46}O_4SiNa$ 581.3058, found 581.3062.

6,6-Diethoxy-3-(triphenylmethoxy)hex-4-ynal (172). TBAF (1.0 M in THF, 6.04 mL, 6.03 mmol) was added over 15 min to **170** (1.12 g, 2.01 mmol) in THF (12 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature and was stirred for 2 h. H_2O (30 mL) was added, and the aqueous phase was extracted three times with Et_2O (30 mL). The combined organic extracts were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and concentrated to yield the crude alcohol. A solution of DMSO (264 µL, 3.72 mmol) in DCM (1.6 mL) was added dropwise to a solution of oxalyl chloride (179 µL, 2.09 mmol) in DCM (2.5 mL) at −78 °C, and the reaction mixture was allowed to stir at −78 °C for 1 h. A solution of the crude alcohol **171** in DCM (4.5 mL) was added dropwise, and the reaction mixture was stirred for at -78 °C for 1 h. TEA (955 µL, 6.80 mmol), was added dropwise, and the reaction mixture was allowed to stir at −78 °C for 30 min then warmed to room temperature. Water (40 mL) and DCM (40 mL) were added, and the layers were separated. The aqueous layer was extracted twice with DCM (40 mL), and the combined organic extracts were washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (6:1) to give 632 mg (71%) of **172** as a slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.4 Hz, 1 H), 7.52-7.45 (m, 6 H), 7.33-7.20 (m, 9 H), 5.04 (d, *J* = 1.2 Hz, 1 H), 4.50 (dt, *J* = 1.2, 5.4 Hz, 1 H), 3.63-3.39 (m, 4 H), 2.42 (dd, *J* = 2.4, 5.4 Hz, 2 H), 1.20 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 143.6, 128.9, 127.9, 127.4, 91.2, 88.6, 84.0, 82.7, 61.0, 60.1, 49.6, 15.3. HRMS calcd for $[M + Na]^+$ $C_{29}H_{30}O_4Na$ 465.2036, found 465.2040.

8,8-Diethoxy-5-(triphenylmethoxy)octa-1,6-diyn-3-ol (173). A solution of **172** (610 mg, 1.38 mmol) in THF (2.7 mL) was added to a solution of ethynyl Grignard (0.5 M in THF, 4.14 mL, 2.07 mmol) in THF (2.5 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature over 75 min. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with Et_2O (15 mL × 3). The combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to give 533 mg (86%, *dr* = 1:1) of **173** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.44 (m, 6 H), 7.31-7.15 (m, 9 H), 4.97 (d, *J* = 1.3 Hz, 1 H), 4.73-4.63 (m, 0.5 H), 4.58-4.48 (m, 0.5 H), 4.30 (dt, *J* = 1.3, 5.5 Hz, 0.5 H), 4.22 (dt, *J* = 1.3, 6.6 Hz, 0.5 H), 3.59-3.33 (m, 4 H), 2.83 (d, *J* = 4.7 Hz, 0.5 H), 2.31 (d, *J* = 1.9 Hz, 1 H), 2.11 (d, *J* = 6.0 Hz, 0.5 H), 2.07-1.84 (m, 2 H), 1.22-1.10 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 143.5, 129.0, 129.0, 127.9, 127.8, 127.4, 127.3, 91.3, 89.0, 88.3, 84.8, 84.3, 84.1, 84.0, 82.6, 82.4, 73.2, 73.1, 66.0, 62.6, 62.0, 61.0, 60.9, 59.9, 59.7, 44.3, 43.5, 15.5, 15.3. HRMS calcd for $[M + Na]^+$ $C_{31}H_{32}O_4Na$ 491.2193, found 491.2203.

(1,1-Diethoxy-6-methoxyocta-2,7-diyn-4-yloxy)triphenylmethane (174). NaH (60% suspension in mineral oil, 82 mg, 2.05 mmol), was added to a solution of **173** (600 mg, 1.28 mmol) in THF (7.2 mL) at 0 °C, and the reaction mixtures was allowed to warm to room temperature over 1 h. MeI (119 µL, 1.92 mmol) was added, and the resulting mixture was stirred for 24 h. H_2O (12 mL) was added, and the mixture was extracted with Et_2O (15 mL × 3). The combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried

(Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (11:1) to give 512 mg (83%, *dr* = 1:1) of **174** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.48 (m, 6 H), 7.33-7.14 (m, 9 H), 4.97 (d, *J* = 1.1 Hz, 0.5 H), 4.96 (d, *J* = 1.1 Hz, 0.5 H), 4.25 (br t, *J* = 7.0 Hz, 0.5 H), 4.21-4.14 (m, 0.5 H), 4.14-4.06 (m, 1 H), 3.61-3.34 (m, 4 H), 3.29 (s, 1.5 H) 3.21 (s, 1.5 H), 2.37 (d, *J* = 1.9 Hz, 0.5 H), 2.32 (d, *J* = 1.9 Hz, 0.5 H), 2.20-1.93 (m, 2 H), 1.24-1.13 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 144.1, 129.1, 128.0, 127.7, 127.7, 127.2, 91.3, 88.0, 87.8, 85.3, 84.7, 82.2, 82.0, 81.9, 81.8, 74.2, 68.0, 67.4, 66.0, 61.8, 60.9, 60.8, 60.8, 56.5, 56.5, 42.9, 42.3, 15.5, 15.3. HRMS calcd for $[M + Na]^+$ $C_{32}H_{34}O_4Na$ 505.2349, found 505.2357.

1,1-Diethoxy-6-methoxyocta-2,7-diyn-4-ol (175). A solution of 1% HCl (9.2 mL), prepared by adding AcCl (200 μL, 2.82 mmol) to a solution of EtOH (3 mL) in DCM (6 mL) at 0 °C and stirring for 30 min, was added to neat **174** (470 mg, 0.97 mmol) at 0 °C, and the resulting mixture was stirred for 100 min while warming to room temperature. The reaction mixture was then poured into saturated $NaHCO_3$ (15 mL) and extracted with Et_2O (15 mL × 3). The combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to give 217 mg (94%, *dr* = 1:1) of **175** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32-5.29 (m, 1 H), 4.78-4.65 (m, 1 H), 4.42-4.36 (m, 0.5 H), 4.24-4.16 (m, 0.5 H), 3.81-3.66 (m, 2 H), 3.81-3.52 (m, 2 H), 3.45 (s, 1.5 H), 3.43 (s, 1.5 H), 2.52-2.48 (m, 1 H), 2.33-2.03 (m, 2 H), 1.24 (t, *J* = 7.0 Hz, 6

H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.4, 91.3, 85.3, 85.3, 81.3, 80.7, 75.0, 74.9, 69.0, 68.8, 61.1, 61.1, 60.2, 60.0, 57.0, 56.8, 43.1, 42.3, 15.3. HRMS calcd for $[M + Na]^+$ $C_{13}H_{20}O_4Na$ 263.1254, found 263.1257.

1,1-Diethoxy-6-methoxyocta-2,7-diyn-4-yl acetate (177). Acetic anhydride (50 μL, 0.53 mmol) was added to a solution of **175** (14.8 mg, 0.062 mmol) in pyridine (100 μL) at 0 °C, and the reaction was allowed to stir for 45 min as it warmed to rt. Et_2O (1 mL) and H_2O (1 mL) were added, and the aqueous phase was extracted three times with Et_2O (2 mL). The combined organic extracts were washed with H_2O (3 mL) and brine (3 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to give 13.7 mg (79%, *dr* = 1:1) of **177** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70-5.56 (m, 1 H), 5.31-5.22 (m, 1 H), 4.20-3.98 (m, 1 H), 3.80-3.50 (m, 4 H), 3.44-3.35 (m, 3 H), 2.53-2.48 (m, 1 H), 2.20-2.03 (m, 5 H), 1.33-1.18 (m, 6 H).

6-Butyl-4-(diethoxymethyl)-2,3-dihydro-1-methoxy-1*H*-inden-3-yl acetate (178). Acetate **177** (13.7 mg, 0.049 mmol) in dry, degassed DCE (650 μL) was added to a solution of 1-hexyne (23 μL, 0.19 mmol) and Cp*Ru(cod)Cl (1.8 mg, 0.005 mmol) in dry degassed DCE (200 μL) over 20 minutes, and the reaction was allowed to stir. After consumption of starting material, the reaction was concentrated, and the residue was purified by flash chromatography, eluting with hexanes/EtOAc (6:1) to give 9.9 mg (56%, *dr* = 1:1) of **178** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1 H),

7.24 (s, 1 H), 6.50-6.20 (m, 1 H), 5.59-5.50 (m, 1 H), 5.11-4.65 (m, 1 H), 3.78-3.39 (m, 7 H), 2.65 (t, *J* = 7.6 Hz, 2 H), 2.50-2.30 (m, 2 H), 2.20-2.02 (m, 3 H), 1.67-1.54 (m, 2 H), 1.43-1.15 (m, 8 H), 0.93 (t, *J* = 7.5 Hz, 3 H).

6-Butyl-2,3-dihydro-1-methoxy-3-oxo-1*H*-indene-4-carbaldehyde (179). K_2CO_3 (5 mg, 0.04 mmol), was added to a solution of acetylated indanol **178** (6.8 mg, 0.02 mmol) in MeOH (200 μL) and the reaction was stirred at rt. When the reaction was complete, the MeOH was removed under reduced pressure, and the residue was taken up in DCM, filtered and concentrated. To the crude alcohol in DCM (1 mL) was added polystyrene-IBX (85 mg, 0.093 mmol IBX), and the reaction was shaken overnight. TLC analysis indicated incomplete conversion, and the reaction was filtered, concentrated, taken up in DCM (500 μL). PCC (12 mg, 0.06 mmol) was added, and the reaction was stirred overnight. Filtration over silica gel eluting with hexanes/EtOAc (2:1) provided 4.6 mg, (100%) of indanone **179** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.02 (s, 1 H), 7.89 (s, 1 H), 7.75 (s, 1 H), 5.10-5.02 (m, 1 H), 3.55 (s, 3 H), 3.06 (dd, *J* = 18.5, 6.3 Hz, 1 H), 2.85-2.75 (m, 3 H), 1.67-1.54 (m, 2 H), 1.44-1.26 (m, 2 H), 0.94 (t, *J* = 7.5 Hz, 3 H).

2,3-Dihydro-1-methoxy-6-methyl-3-oxo-1*H*-indene-4-carbaldehyde (161). The resin **163** (100 mg, 0.023 mmol) was suspended in THF (500 μL) and degassed with three freeze-pump-thaw cycles. A balloon of propyne was then placed on the reaction, and propyne was bubbled through the solution for approximately 10 minutes. The Cp*Ru(cod)Cl catalyst (2 mg, 0.01 mmol) was added, and the reaction was stirred under a propyne atmosphere for 24

h. The resin was then transferred to a syringe filter, washed with alternating rinses of DCM and MeOH (4 × 3mL), and subsequently dried under vacuum. The product was cleaved from the resin by the addition of 4:1 THF/MeOH (500 μL) and K_2CO_3 (20 mg, 0.14 mmol) followed by 16 h of shaking at room temperature. The reaction mixture was filtered through a silica gel plug followed by a rinse with DCM (2 mL), and subsequently concentrated. The product was then re-suspended in DCM (1 mL) and shaken with IBX resin (35 mg) for 12 h. The solution was filtered and concentrated to yield the natural product **161** (3.4 mg, 0.017 mmol, 72% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1H), 7.86 (s, 1H), 7.74 (s, 1H), 5.03-5.00 (m, 1H), 3.52 (s, 3H), 3.06 (dd, *J* = 18.6, 6.3 Hz, 1H), 2.73 (dd, *J* = 18.6, 3.0 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 190.7, 154.6, 146.2, 137.1, 133.9, 128.3, 76.4, 57.4, 44.0, 21.9. MS m/z 205.1 (M+H); HRMS calcd for $C_{12}H_{13}O_3$ [M+H] 205.0856, found 205.0851.

CHAPTER 3: DEVELOPMENT OF MICROWAVE ASSISTED [2+2+2] CYCLOTRIMERIZATION REACTIONS: TOTAL SYNTHESIS OF ILLUDININE

3.1 Microwave Assisted Organic Synthesis

Recently, the application of microwave irradiation has greatly improved the yield, lessened reaction time, and produced cleaner reaction profiles for many transition metal catalyzed reactions.[109, 110] Despite this trend, at the time this work began the microwave promoted [2+2+2] cyclotrimerization had been slow to garner attention, and investigations into these reactions seemed warranted. With the first report in 1986 by Gedye[111] and later by Giguere and Majetich,[112] microwave assisted organic chemistry (MAOS) introduced to the synthetic community a faster alternative to traditional heating approaches to several classical reactions (e.g. Diels-Alder, Claisen rearrangement, esterification, etc.). Both groups used sealed vessels in domestic microwave ovens with no temperature control, often leading to unpredictable outcomes and explosions. Solvent free systems were developed in the 1990's eliminating explosive risks but causing other technical difficulties related to non-uniform heating, mixing, and reaction temperature.[113] Currently, technology advancements have introduced microwave reactors with temperature and power controls, as well as cooling options. These technological developments have helped microwave chemistry to become a less esoteric application in synthesis labs and contributed to the more than 3,000 examples of MAOS in the literature.[114-116]

Commercially available microwave reactors emit electromagnetic radiation at 2.45 GHz corresponding to 0.0016 eV of energy. Such a low energy output is not capable of cleaving carbon-carbon single bonds (3.61 eV) or even hydrogen bonds (0.04-0.44 eV)

(Table 3.1),[117, 118] therefore, the energy absorption itself cannot cause chemical reactions to occur as it does in photochemistry.[114]

Table 3.1. Radiation energies compared to bond energies. [117, 118]

Radiation	Quantum Energy (eV)	Bond Type	Bond Energy (eV)
Gamma rays	$1.24X10^{6}$	CC single	3.61
X-rays	$1.24x10^{5}$	CC double	6.35
UV	4.1	CO single	3.74
Visible	2.5	CO double	7.71
IR	0.012	CH	4.28
Microwave	0.0016	OH	4.80
Radiowaves	$4.0X10^{-9}$	H-bond	0.04-0.44

The mechanics of heating the reaction mixture, termed microwave dielectric heating, is the cornerstone of MAOS. This heating occurs by two mechanisms: dipolar polarization and ionic conduction.[119, 120] In the dipolar polarization mechanism, molecules with dipole moments attempt to align themselves with the alternating electrical field. Heat is generated from molecular friction and dielectric loss. With ionic conduction, the ions in solution move back and forth with the electrical field colliding with other molecules or atoms. These collisions produce heat. How does microwave heating lead to enhanced rates for reactions as compared to conventional heating methods? The origin for the dramatic rate enhancements for reactions performed in microwaves is still a matter of debate. Most researchers agree that thermal effects accelerate the microwave reactions with certain specific microwave effects also noted. But, not all authors have the same opinion concerning so-called athermal or "nonthermal microwave effects".[121, 122] The majority of microwave reactions are accelerated due to thermal/kinetic effects. According to Arrhenius' Law ($k = Aexp\{-E_a/RT\}$), the higher the temperature at which a reaction is performed, the higher the rate. In the microwave under

sealed tube conditions, solvents can be heated to points far above their respective boiling points at atmospheric pressure. Methanol, for instance, can be heated to >100 °C above its boiling point.[114] These high temperatures can have a extraordinary effect on reaction rates. Through the Arrhenius equation, one can calculate the time necessary for a given reaction to proceed to a certain conversion level: if at 27 °C the reaction takes 68 days to reach 90% conversion, only 1.61 seconds is required if the reaction is performed at 227 °C.[119] However, one would expect the same rate no matter if the reaction were refluxed under microwave irradiation or by conventional methods.[121] Rate enhancements in this case are attributed partly to specific microwave effects.

Although still thermal in nature, specific microwave effects are claimed when the outcome of a reaction under microwave heating differs from the results of a reaction under conventional heating. Because the heating occurs within the solution and is not conducted through the vessel, an inverted temperature gradient arises (Figure 3.1) under microwave heating.[114] Temperature sensitive reagents, such as catalysts, will remain active for longer periods, thereby increasing conversions. Also, specific reagents can selectively absorb the microwave radiation leading to an increased temperature at the catalyst surface (heterogeneous mixture) or at microscopic hotspots (homogeneous mixture).[122] Finally, solvents, even in open-vessel situations, can be heated above their atmospheric boiling points.[123, 124] This superheating effect increases rates without the need for pressure. Controversy surrounds the last set of effects, the athermal or nonthermal microwave effects. Rate enhancements are attributed to direct coupling of the electrical component of the microwave radiation with reagents, intermediates, or catalysts.

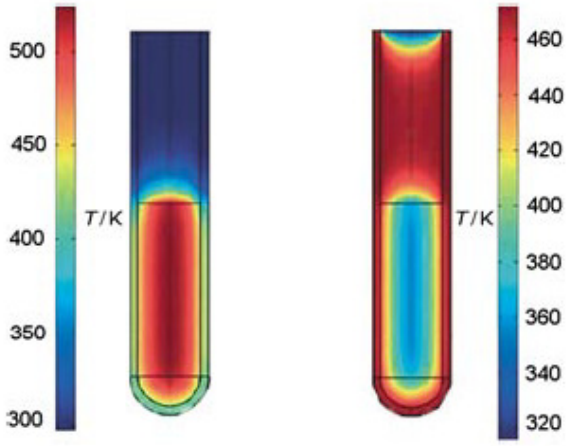


Figure 3.1. Inverted temperature gradient produced during microwave heating (left) compared to oil bath heating (right).[114]

Polar molecules can be oriented by the electrical field altering the preexponential factor A of the Arrhenius equation[125] or the activation energy.[126] Despite the uncertainty regarding the specific sources of rate enhancements observed for microwave reactions, microwave chemistry is a rapidly developing field that continues to gain popularity among chemists (for an overview of the application of microwave irradiation to [2+2+2] cyclotrimerization reactions see Chapter 1, Section 1.5).

3.2 Nickel-catalyzed [2+2+2] Cyclotrimerization Reactions

3.2.1 Nickel-catalyzed [2+2+2] Cyclotrimerization Reactions in Literature

The use of Ni complexes in [2+2+2] cyclotrimerizations can be traced to the first known transition metal catalyzed reaction performed by Reppe et al. in 1948 when he used $Ni(CO)_2(PPh_3)_2$ to cyclotrimerize acetylene to benzene.[12] During the early 1960's, Meriwether and coworkers published a series of articles describing the alkyne polymerization capabilities of this catalyst system among others.[127-130] Typically, reactions were performed

in refluxing benzene or cyclohexane for up to 24 h to give mixtures of aromatized product and linear polymers. The authors noted a general order of reactivity where acetylenic esters and ketones were more reactive than arylalkynes, and alkylalkynes were the least reactive. Disubstituted alkynes were typically inert.[1, 127] Cyclotrimerization reactions involving alkylalkynes were hindered by high levels of linear polymer formation. Moreover, the copolymerization of unconjugated diacetylenes with monoalkynes produced mixtures of linear polymers as well as fused benzenes. The ability to undergo intramolecular cyclotrimerization towards indanes was a factor of the tether length between the two alkyne moieties where indane formation was favored with 1,6-heptadiyne compared to tetralin formation with 1,7-octadiyne; 1,5-hexadiyne and 1,8-nonadiyne were least prone to forming fused benzene products.[129] This trend, the authors suggest, points to an intermediate in the reaction mechanism where both alkynes of the diyne are coordinated to the metal center consistent with the "common mechanism" that was to be elucidated in subsequent years with other metal complexes.[2, 30] Due in part to its tendency to furnish mixtures of linear and cyclic polymerization products, the $Ni(CO)_2(PPh_3)_2$ catalyst system has been limited in its synthetic applicability.[131-134]

Over the years, other nickel catalyst systems have been shown to enable cyclotrimerization reactions with alkynes. Smith and coworkers employed stoichiometric zero valent nickel in the form of $Ni(PPh_3)_4$ to cyclotrimerize diynes into tetralin derivatives in modest yield (46-78%) while Mori used catalytic (8-20%) $Ni(cod)_2$ in conjunction with chiral phosphine ligands to access enantioenriched isoindoline and tetrahydroisoquinoline derivatives.[79, 135-137] More recently, $Ni(cod)_2$ systems have been employed in the synthesis of

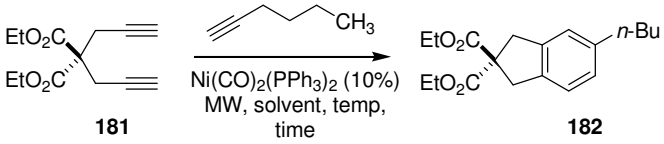
hexaborylbenzenes,[138] helicenes,[139] and perfluoroalkylarenes.[140] *In situ* formed Ni^0 catalyst systems generated through the reduction of NiX_2 (X = Cl, Br, I) with Zn,[141-143] Al,[137] Mg,[142, 144] or Na[142] have also been reported.

3.2.2 Optimization of the Microwave-mediated Nickel-catalyzed Cyclotrimerization Reaction

Being aware of the beneficial effects of microwave irradiation on Co- and Ru-catalyzed cyclotrimerization reactions,[83-87, 145] we sought to overcome the limitations of the $Ni(CO)_2(PPh_3)_2$ catalyst system and enhance its cyclotrimerization reactivity through the application of microwave irradiation, thereby enabling its use in total synthesis. In order to find optimal reaction conditions, we conducted model [2+2+2] cyclotrimerization reactions of diethyl dipropargyl malonate[146] (**181**), with 1-hexyne leading to the benzene **182**[27] (Table 3.2). Conditions previously found to be optimal for microwave-assisted solid-supported cyclotrimerization reactions (10 mol% catalyst, $PhCH_3$, 10 min)[86, 87] served as a reference point for these investigations, and, indeed, gave the aromatic product **182** in 75% yield (Entry 1). ^1H NMR analysis of the crude reaction mixture showed substantial polymerization of the 1-hexyne. Interestingly, in case of the $Ni(CO)_2(PPh_3)_2$ catalyst, decreasing the reaction time to 5 min (data not shown) and 2 min (Entry 2) still led to complete reaction of **181** and furnished **182** in 78% yield, with a final reaction temperature of 82 ^oC. By only irradiating for 2 minutes, polymerization of the 1-hexyne was greatly diminished. Conducting the identical reaction without microwave irradiation (82 ^oC final reaction temperature, 92^oC oil bath temperature, 2 min; Entry 3) did not yield any cyclotrimerization product **182**, thus

demonstrating the enhancing effects[121, 147] of microwave irradiation on the Ni-catalyzed reaction.

Table 3.2. Optimization of microwave-mediated [2+2+2] cyclotrimerization reaction under $Ni(CO)_2(PPh_3)_2$ catalysis.



181 **182**

Entry	MW / W	Solvent	Time / min	Temp / °C	Yield / %
1	300	toluene	10	117	75
2	300	toluene	2	82	78
3	---[a]	toluene	2	82	---
4	300	THF	2	105	70
5	300	1,2-dichloroethane	2	133	63
6	300	acetonitrile	2	117	47

[a] The temperature profile inside the reaction vessel was identical to the microwave reaction with a final temperature of 82°C. The oil bath temperature was 92°C.

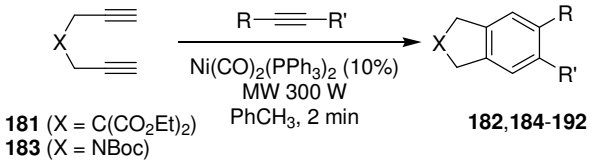
While Meriwether reported benzene, methanol, acetonitrile, and cyclohexane as optimal solvents for the catalyst under traditional heating,[130] the wide range in microwave absorptivity of theses solvents necessitated an investigation into potential solvent effects on the microwave-mediated cyclotrimerization reaction. Therefore, in addition to toluene, the cyclotrimerization was carried out in THF, 1,2-dichloroethane, and acetonitrile (Entries 4-6). In these cases the reaction temperatures raised above the 82 °C observed in the case of toluene, and generally lower yields (47-70%) were observed. Notably, no pyridine product was observed in the case of acetonitrile.

Thus, all subsequent [2+2+2] cyclotrimerization reactions were performed by microwave irradiation (300 W) of a solution of the diyne, monoyne (10 eq.), and $Ni(CO)_2(PPh_3)_2$ (10 mol%; lower catalyst loadings led to greatly diminished yields) in toluene for 2-5 min.

3.2.3 Scope of the Microwave-mediated Nickel-catalyzed Cyclotrimerization Reaction

We subsequently investigated the functional group compatibility of this reaction with several different alkynes (Table 3.3), including 1-hexyne, phenylacetylene, benzylated propargylalcohol,[148] Boc-protected propargyl amine,[149] and an internal alkyne, 3-hexyne. The reaction of the diyne **181** proceeded smoothly, delivering the indanes **184**-**187**[150] in 50-82% yield (Entries 1-5). Unfortunately, isolation of the benzylated propargyl alcohol cycloadduct **185** was hampered by polymer formation. The much less reactive internal 3-hexyne delivered **187** in 63%, which is remarkable, since internal alkynes are completely unreactive under thermal conditions.[127]

Table 3.3. Microwave-mediated $Ni(CO)_2(PPh_3)_2$ catalyzed cyclotrimerization reactions towards indanes and isoindolines.



181 (X = $C(CO_2Et)_2$)
183 (X = NBoc)

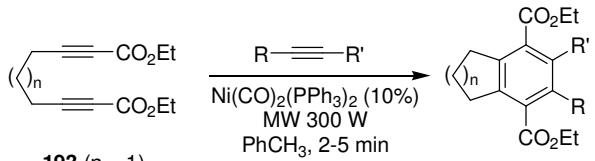
182,**184**-**192**

Entry	Cmpd.	X	R	R'	Yield	Entry	Cmpd.	X	R	R'	Yield
1	**182**	$C(CO_2Et)_2$	Bu	H	78%	6	**188**	NBoc	Bu	H	80%
2	**184**	$C(CO_2Et)_2$	Ph	H	50%	7	**189**	NBoc	Ph	H	75%
3	**185**	$C(CO_2Et)_2$	CH_2OBn	H	-	8	**190**	NBoc	CH_2OBn	H	76%
4	**186**	$C(CO_2Et)_2$	CH_2NHBoc	H	82%	9	**191**	NBoc	CH_2NHBoc	H	80%
5	**187**	$C(CO_2Et)_2$	Et	Et	63%	10	**192**	NBoc	Et	Et	55%

In order to investigate the Ni-catalyzed synthesis of isoindolines and the effect of a ring nitrogen-center on the cyclotrimerization reaction, we synthesized the Boc-protected dipropargylamine[151] **183** and subjected it to the same [2+2+2] cyclotrimerization conditions (Table 3.3, Entries 6-10). The isoindolines **188**-**192** were obtained in good yields (55-80%). Here, all terminal alkynes display comparable levels of reactivity with the internal 3-hexyne providing **192** in diminished yield.

Since Meriwether reported high reactivity of the $Ni(CO)_2(PPh_3)_2$ catalyst in the case of electron-poor triple-bonds,[127] we examined the use of an electron-deficient diyne cyclotrimerization precursor bearing carboxylates on both triple bonds. To this end, substrate **193**[152] was prepared and subjected to the microwave-mediated Ni-catalyzed cyclotrimerization reactions with the same alkynes as before, delivering up to hexa-substituted benzenes **195**-**199** in good to excellent yields (61-98%, Table 3.4, Entries 1-5). As before, the lowest yield was observed when the less reactive internal alkyne, 3-hexyne, was employed as the monoyne. However, the yields were generally higher compared to the electron-neutral diynes **181** and **183**. Moreover, we were able to construct tetralines **200**-**204** using the homologous precursor **194**.[152] The tetralin [2+2+2] cyclotrimerization yields (58-70%) where slightly lower compared to the indane synthesis, and the reaction time needed to be extended to 5 min, due to the higher activation barrier when forming six-membered rings (Table 3.4, Entries 6-10).[153]

Table 3.4. Microwave-mediated $Ni(CO)_2(PPh_3)_2$ catalyzed cyclotrimerization reactions of electron-deficient diynes.



193 (n = 1)
194 (n = 2)

195-204

Entry	Cmpd.	n	R	R'	Yield
1	**195**	1	Bu	H	79%
2	**196**	1	Ph	H	93%
3	**197**	1	CH_2OBn	H	98%
4	**198**	1	CH_2NHBoc	H	90%
5	**199**	1	Et	Et	61%
6	**200**	2	Bu	H	70%
7	**201**	2	Ph	H	64%
8	**202**	2	CH_2OBn	H	60%
9	**203**	2	CH_2NHBoc	H	61%
10	**204**	2	Et	Et	58%

By conducting cyclotrimerization reactions using the $Ni(CO)_2(PPh_3)_2$ catalyst in conjunction with microwave irradiation we discovered efficient and rapid conditions with which to conduct these transformations. With a two minute reaction time, these examples represent the fastest cyclotrimerization reactions to date. We hypothesized that the discovered conditions are suitable for an application in total synthesis and set forth to prove this hypothesis by assembling a sesquiterpenoid alkaloid natural product using a microwave-assisted Ni-catalyzed [2+2+2] cyclotrimerization reaction as the key step (see Chapter 3.3).

3.2.4 Development of Open-Vessel Microwave-Mediated [2+2+2] Cyclotrimerization Reactions

As previously demonstrated by us, performing cyclotrimerization reactions on solid-supports provides one solution to achieve high levels of chemoselectivity and to eliminate dimer and trimer formation of the starting material diyne through the spatial separation of individual diyne molecules on the polymeric support (e.g. see the solid-supported indanone

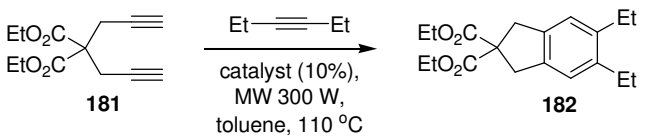
synthesis in Chapter 2.3).[154] However, using the solid-support creates new problems including the limited scale of solid-supported reactions as well as the fact that not all diynes are suitably functionalized to allow for immobilization. To circumvent these issues, we proposed performing microwave-mediated reactions under open-vessel conditions. By conducting the reactions at ambient pressure, one can slowly add reagents to the ongoing reaction. In this manner, the individual diyne molecules can be spatially separated similar to reactions conducted on the solid-support. Moreover, larger vessels (125 mL round bottom flask) can be used in the microwave reactor under open-vessel conditions compared to closed vessels (10 mL vial) allowing for larger scale reactions.

Initial experiments investigated the synthesis of fused benzenes from the reaction of the diyne **181** and the internal alkyne 3-hexyne under nickel catalysis. Being an internal alkyne, 3-hexyne has a reduced activity in cyclotrimerization reactions that leads to increased dimerization of diyne starting materials.[7, 155] This choice of monoyne will make for a more stringent test of the efficacy of the open-vessel approach towards solving polymerization of the diyne. Control experiments conducted under closed-vessel microwave conditions previously established for the microwave-mediated Ni-catalyzed cyclotrimerization reaction demonstrated the need for an alternate method giving the desired benzene product in poor yield as the number of equivalents of 3-hexyne is reduced (Entries 1-3, Table 3.5). Gratifyingly, when the diyne is slowly added to an irradiated solution of 10 equivalents of 3-hexyne and 10 mol% catalyst over 30 minutes, an 82% yield of benzene **182** was obtained (Entry 4). A decrease in equivalents of 3-hexyne to three still produced a highly efficient cyclotrimerization furnishing an 80% yield of the desired benzene (Entry 5). Using a 1:1

ratio of 3-hexyne to diyne led to a diminished 49% yield as well as unreacted starting material (Entry 6). Conducting the reaction under thermal conditions (oil bath, 110 °C) failed to produce the desired benzene product (Entry 7).

For comparison, benzene formation under Ru-catalysis was also explored. As with the Ni-catalyzed reactions closed-vessel controls gave poor yields of benzene product (Entries 8-10). As before, open-vessel conditions using 10 equivalents of 3-hexyne provided the benzene product in 81% yield (Entry 11). However, as the ratio of monoyne to diyne was decreased from 10 to 3 to 1, the yield suffered accordingly and more dramatically than under Ni-catalysis (Entries 12 and 14). Increasing the time of addition from 30 min to 90 min had no beneficial effect on reaction efficiency (Entries 13 and 15).

Table 3.5. Closed- and open-vessel [2+2+2] cyclotrimerization reactions towards benzene formation.



Entry	Catalyst	Equiv. **00**	Syringe Time/min	Yield
1[a]	$Ni(Ph_3P)_2(CO)_2$	10	-	63%
2[a]	"	3	-	33%
3[a]	"	1	-	18%
4	"	10	30	82%
5	"	3	30	80%
6	"	1	30	49%
7[b]	"	3	30	--

[a] Sealed-vessel reaction,[b] No microwave irradiation

Entry	Catalyst	Equiv. **00**	Syringe Time/min	Yield
8[a]	Cp*Ru(COD)Cl	10	-	28%
9[a]	"	3	-	10%
10[a]	"	1	-	6%
11	"	10	30	81%
12	"	3	30	68%
13	"	3	90	53%
14	"	1	30	37%
15	"	1	90	30%
16[b]	"	10	30	see text

Thus, the developed open-vessel microwave-mediated cyclotrimerization reactions have successfully addressed the chemoselectivity issue associated with cyclotrimerization

reactions. By adding the diyne slowly to the reaction mixture, high dilution conditions can be maintained while under microwave irradiation. In addition, the scale of the cyclotrimerization reactions can be increased to allow for a more expedient preparation of intermediates in synthetic schemes. This protocol should translate to other microwave-mediated transition metal catalyzed reactions that display similar chemoselectivity and scale-up issues.

3.3 Total Synthesis of Illudinine

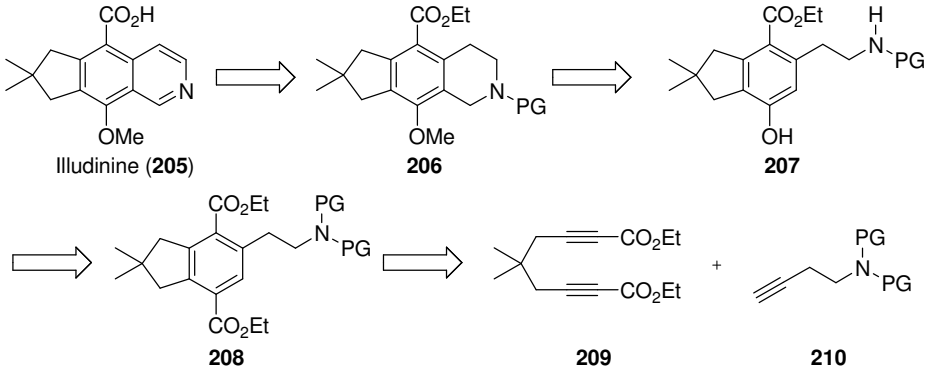
3.3.1 Background and Retrosynthetic Analysis

The sesquiterpene alkaloid illudinine (**205**) was isolated as a fungal metabolite from the basidiomycete *Clitocybe illudens* (also known as *Omphalotus olearius* or Jack-O-Lantern mushroom) and a biogenetic relationship to illudalic acid was suggested (Figure 3.2).[156] Only two total syntheses of illudinine are known. One by Woodward and Hoye,[157] requiring 15 steps from indane (including a necessary separation of regioisomers), and one by Rao and coworkers, requiring 14 steps from 6-methoxy-1,2,3,4-tetrahydronaphthalene.[158] Because of the facile cyclotrimerization reaction of the diyne **193** towards indane derivatives **195**-**199**, we hypothesized that the indane core of the sesquiterpene alkaloid illudinine (**205**) could be accessed via a [2+2+2] cyclotrimerization reaction.



Figure 3.2. *Clitocybe illudens*.
(http://en.wikipedia.org/wiki/Clitocybe_illudens)

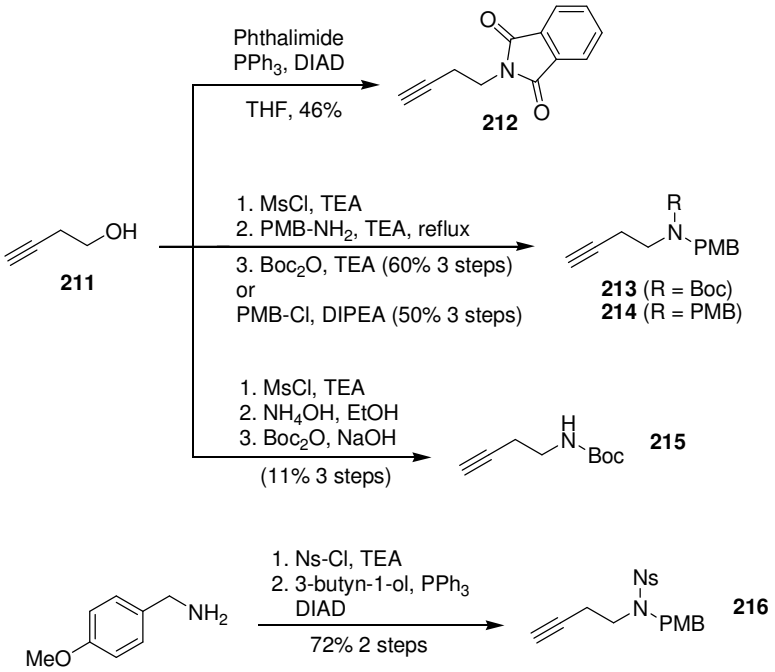
Retrosynthetically, we envisioned deriving the illudinine isoquinoline framework from the oxidation of the tetrahydroisoquinoline **206** (Scheme 3.). In turn, the tetrahydroisoquinoline **206** would be accessed from a Pictet-Spengler ring closure of the homobenzylic amine **207**. Installation of the phenol moiety in the amine **207** would necessitate differentiation of the two ester functionalities in the bicycle **208**. Inspecting the bicycle **208**, one can distinguish the imbedded indane skeleton that can be furnished by a [2+2+2] cyclotrimerization reaction between diester diyne **209** and a suitably protected homopropargyl amine **210**. Preliminary investigations would focus on delineating suitable protecting groups for homopropargyl amine **210**.



Scheme 3.1. Retrosynthetic analysis of illudinine (**205**). PG = protecting group.

3.3.2 Model Studies towards Illudinine

As with many syntheses, the careful choice of protecting groups is essential to effectively mask a functional group's reactivity while also being sufficiently labile to allow facile deprotection at the appropriate juncture of the synthesis.[159-161] Towards the synthesis of illudinine, a diprotected homopropargyl amine is required whose protecting groups must be acceptable not only in the cyclotrimerization key step, but also in subsequent steps as the architecture of illudinine is constructed. In this vein, a series of differentially protected homopropargyl amines were synthesized from 3-butyn-1-ol (**211**) in 1-3 steps in order to explore their reactivity in the cyclotrimerization step (Scheme 3.2).

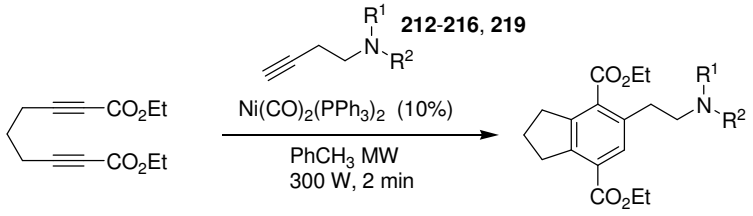


Scheme 3.2. Synthesis of the protected homopropargyl amines **212**-**216**. Ms = Mesyl, PMB = *para*-methoxybenzyl, Ns = 2-nitrobenzenesulfonamide.

Each protected amine was then subjected to cyclotrimerization reactions with the diyne **193**, a model diyne for illudinine, using the previously developed microwave-mediated nickel

catalyzed cyclotrimerization protocol (Table 3.6). The phthalimide protected homopropargyl amine **212**[162] cyclotrimerized smoothly yielding the indane **217** in 85% yield (Entry 1). Cyclotrimerization of the nosyl- and PMB-protected amine **216**, however, was problematic (Entries 2-3). Full conversion of the diyne to the product indane **218** was realized (^{1}H NMR analysis of crude mixture), but purification from the excess monoyne was not possible. Using excess diyne, though, provided indane **218** in 79% yield based on the diyne. Despite the good yield, this stoichiometry would not be feasible when a complex diyne is being used. Monoprotected amine **219**[163] had a deleterious effect on the cyclotrimerization reaction, and no reaction was observed when using six equivalents of monoyne (Entry 4). By once again using excess diyne and in this case 50 mol% catalyst loading, conversion to the indane **220** was observed in the crude mixture; however, the product was inseparable from the unreacted PMB-protected homopropargyl amine (Entry 5).

Table 3.6. Cyclotrimerization reactions of protected amines **212**-**216** and **219** with the model diyne **193**.



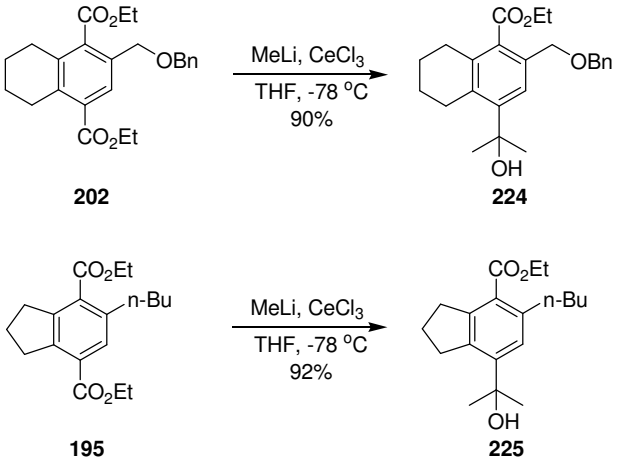
193 **217**-**218**, **220**-**223**

Entry	R^1	R^2	Eq. amine	Result	Entry	R^1	R^2	Eq. amine	Result
1	Phth	---	10	**217**, 85%	5	PMB	H	0.17	pdt inseparable
2	Ns	PMB	8	full conv.	6	Boc	PMB	6	**221**, 75%
3	Ns	PMB	0.2	**218**, 79%	7	Boc	H	6	**222**, 85%
4	PMB	H	6	no rxn.	8	PMB	PMB	6	pdt inseparable

The use of carbamates **213**[163] and **215**[164] led to efficient cyclotrimerization reactions providing indanes **221** and **222** in 75 and 85%, respectively (Entries 6-7). As before with the

mono-PMB-protected monoyne **219**, the use of bis-PMB-protected monoyne **214** gave an inseparable mixture of product **223** and monoyne (Entry 8). Based on these cyclotrimerization studies, amides cyclotrimerize readily providing indane derivatives in good yield while basic amines have a detrimental effect on the cyclotrimerization reaction. Further investigations into which protecting groups are compatible with later steps in the synthesis would still be necessary.

At this juncture of the model study, differentiation between the two ester groups was investigated. It was found that when the tetralin diester **202** was treated with excess methyllithium and $CeCl_3$, addition of the organocerium reagent would only occur at one ester group giving the tertiary alcohol **224** in 90% yield (Scheme 3.3). The same held true for indane diester **195** providing alcohol **225** in 92% yield. We speculate that this result is due to the unique steric environment of each ester, fully protecting the *ortho*-substituted ester group from nucleophilic addition due to steric hindrance.

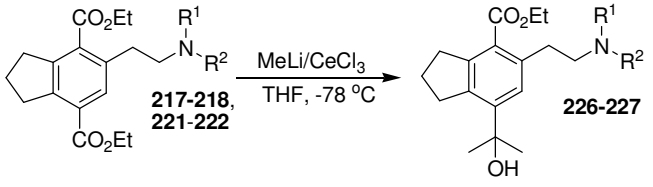


Scheme 3.3. Addition of MeLi/$CeCl_3$ into the diesters **202** and **195**.

The regioselectivity of the addition was confirmed by comparing the ^{1}H NMR spectrum of **195** and **205** where the signal of the lone aromatic proton in **225** is shifted downfield from

7.68 ppm in **195** to 7.18 ppm due to the loss of the electron withdrawing nature of the ester group in the *ortho* position.

When the model indanes were subjected to the MeLi/$CeCl_3$ conditions, the viable protecting groups became apparent. The phthalimide **217** reacted to yield a mixture of products which was not unexpected due to the instability of phthalimides towards organometallic reagents (Entry 1, Scheme 3.4).[161] Reactions with the nosyl- and PMB-protected amine **218** were equally unrewarding (Entry 2). Carbamate **222**, furnished the desired tertiary alcohol **226** in a disappointing 12% yield with 26% of unreacted starting material as well as unidentified by-products (Entry 3). On the other hand, indane **221** reacted cleanly with MeLi/$CeCl_3$ to deliver the required alcohol **227** in an excellent 92% yield (Entry 4). The use of only MeLi gave mixtures of the methyl ketone (not shown) derived from single addition of MeLi as well as the desired alcohol in 32 and 29%, respectively. From these results the PMB- and Boc-protected amine would provide the necessary protection of the amine functionality in the cyclotrimerization event as well as the compatibility with the organocerium reagent.

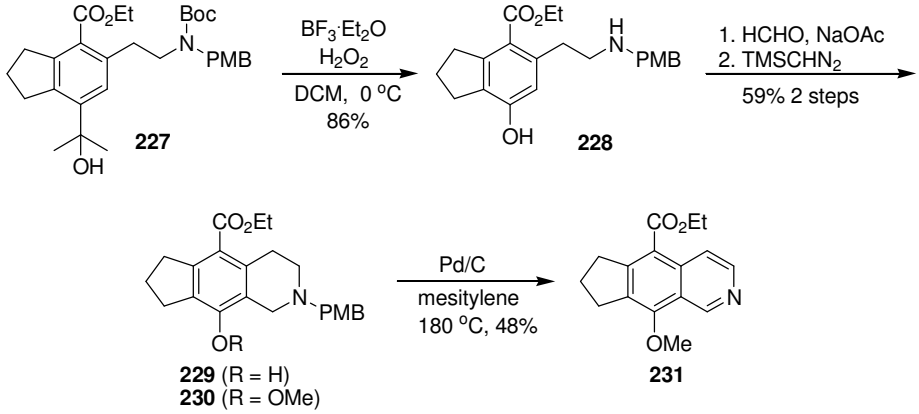


Entry	R^1/R^2	Result
1	Phth	pdt mixture
2	Ns,PMB	pdt mixture
3	Boc	12% **226**
4	Boc,PMB	92% **227**

Scheme 3.4. Addition of MeLi/$CeCl_3$ into the diester indanes **217**, **218**, **221** and **222**.

With the differentiation of the two ester groups solved, attention was turned to forming the tricyclic skeleton of illudinine. Treatment of the tertiary alcohol with boron trifluoride etherate and hydrogen peroxide promoted a facile benzylic hydroperoxide rearrangement to a

phenol with simultaneous removal of the Boc protecting group to supply aminophenol **228** in 86% yield (Scheme 3.5).[165] Initial experiments used the crude aminophenol in the Pictet-Spengler[166] cyclization to give tetrahydroisoquinoline **229** in 67% yield over two steps. It was discovered, however, that the tetrahydroisoquinoline was unstable; therefore, methylation with diazomethane would provide the methylated tetrahydroisoquinoline **230** in 31% yield over three steps. When the Pictet-Spengler and methylation reactions were carried out in series with methylation by trimethylsilyldiazomethane instead of diazomethane, the methoxy derivative **230** was obtained in 59% yield over two steps.[167]

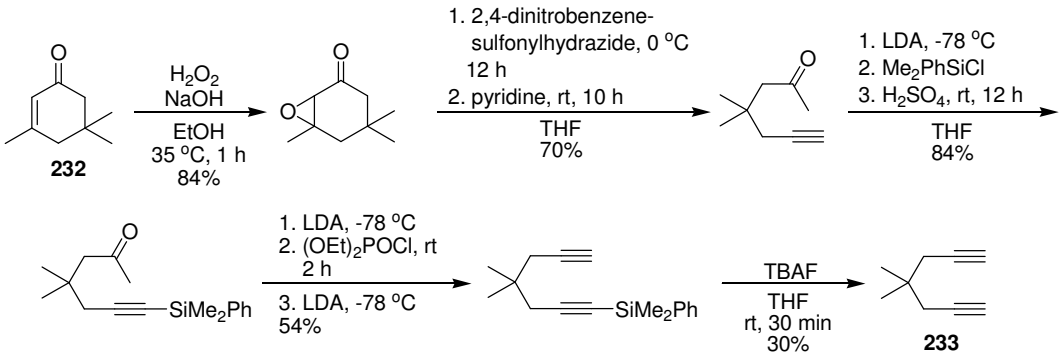


Scheme 3.5. Conversion of the tertiary alcohol **227** into the isoquinoline **231**.

Oxidation of the tetrahydroisoquinoline **230** with Pd on carbon[168] with concomitant removal of the PMB protecting group furnished ethyl-didemethyl illudinate **231** in 48% yield. The use of DDQ led to incomplete oxidation. Obtaining **231** drew a successful end to the model studies towards illudinine and provided answers to the nature of the protecting groups as well as the formation of the tricyclic core of illudinine.

3.4 Total Synthesis of Illudinine

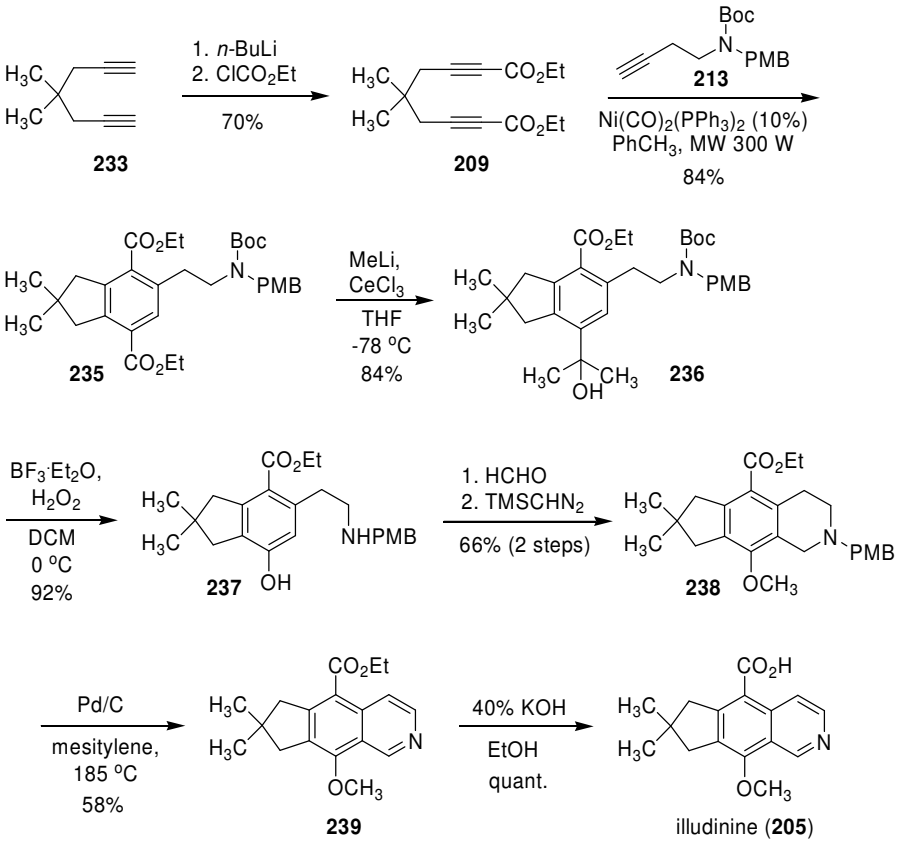
Our synthesis commences with the known diyne **233** prepared in five steps from isophorone (**232**, Scheme 3.6)[169-171] which is lithiated at both terminal triple bonds and then carboxylated to form the diester **209** in 70% yield (Scheme 3.7).



Scheme 3.6. Synthesis of the diyne **233**.

As in case of the model studies with **193**, this molecule underwent a smooth reaction with the monoyne **213** via the $Ni(CO)_2(PPh_3)_2$ catalyzed [2+2+2] cyclotrimerization reaction under microwave irradiation in toluene for 2 min at 300 W. The cyclotrimerization product **235** was isolated in 84% yield. Treatment of **235** with an excess of CH_3Li in the presence of $CeCl_3$ delivered the tertiary alcohol **236** as the only product in 84% yield. Rearrangement of **236** and removal of the Boc group provided the phenol **237** in 92% yield. Pictet-Spengler cyclization with formaldehyde in the presence of a sodium acetate buffer furnished the corresponding tetrahydroisoquinoline, which was directly converted into the methyl ether **238** through exposure to trimethylsilyldiazomethane. The oxidation and deprotection of **238** to ethyl illudinate (**239**) progressed in 58% yield. Quantitative saponification of the ester with 40% aqueous KOH in $EtOH/H_2O$ (95:5) completed the convergent and regioselective total synthesis of illudinine. The ^1H NMR spectrum of synthetic **205** shows three aromatic signals

(9.74, 9.02, and 8.53 ppm) indicative of pyridine ring protons of an isoquinoline structure as well as three singlets (3.28, 3.25, and 1.22 ppm) for two methylene units and two equivalent methyl groups suggesting a *gem*-dimethyl cyclopentane ring fused to the benzene of illudinine. The completely regioselective synthesis of **205** was completed in only eight steps from known material (13 from commercially available material) and represents the shortest synthesis of illudinine to date.[172]



Scheme 3.7. Total synthesis of illudinine (**205**).

3.5 Summary

The use of $Ni(PPh_3)_2(CO)_2$ catalysis and microwave irradiation has proven to be an effective combination for the [2+2+2] cyclotrimerization reaction. The rapid synthesis of indanes, tetralins, and isoindolines is possible, and with a two minute reaction time, these examples represent the fastest cyclotrimerization reactions to date. This new methodology was showcased in the total synthesis of a sesquiterpene alkaloid, illudinine (**205**). The synthesis comprised eight steps from known material (13 from commercially available material) in a 17% overall yield and represents the shortest synthesis of illudinine to date. Key features of the synthesis include a [2+2+2] cyclotrimerization reaction, the regioselective addition of $MeLi/CeCl_3$ into an ester and the rearrangement of a tertiary benzylic alcohol to a phenol.

3.6 Experimental

All reactions were performed in flame-dried glassware under a nitrogen atmosphere and stirred magnetically. Tetrahydrofuran, toluene, xylenes, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Diisopropylamine, triethylamine, DMSO, DCM, DMF, 1,2-dichloroethane, CH_3CN and pyridine were distilled from calcium hydride and stored over 4 Å molecular sieves. Other reagents and solvents obtained from commercial sources were stored under nitrogen and used directly without further purification. *n*-BuLi and MeLi were titrated against *N*-pivaloyl-*o*-toluidine.[108] Melting points were obtained from a Mel-Temp capillary melting point apparatus and are uncorrected. High resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz) or Varian Mercury 300 (300 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption (77.2) for ^{13}C NMR spectra. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer.

General cyclotrimerization protocol. To a flame-dried microwave vial equipped with a stir bar was added the diyne (0.085 mmol), the mono-alkyne (0.85 mmol), $Ni(CO)_2(PPh_3)_2$ (5.4 mg, 0.0085 mmol), and dry toluene (2.8 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 2-5 min in a CEM Discover microwave synthesizer at 300 W. After cooling to room temperature, the reaction mixture was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc to give the pure cyclotrimerization product.

Analytical data for compounds 186-192, 195-204.

***tert*-Butyl-(2,2-di(ethoxycarbonyl)-2,3-dihydro-1*H*-inden-6-yl)methylcarbamate (186).** Isolated in 82% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.02 (m, 3 H), 4.78 (br s, 1 H), 4.30-4.16 (m, 6 H), 3.56 (s, 4 H), 1.47 (s, 9 H), 1.26 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 156.0, 140.7, 139.3, 137.9, 126.5, 124.4, 123.5, 79.6, 61.8, 60.6, 44.7, 40.5, 40.3, 28.5, 14.1. HRMS calcd for $[M + Na]^+$ $C_{21}H_{29}NO_6Na$ 414.1887, found 414.1891.

5,6-Diethyl-indan-2,2-dicarboxylic acid diethyl ester (187). Isolated in 63% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 2 H), 4.21 (q, *J* = 7.2 Hz, 4 H), 3.56 (s, 4 H), 2.62 (q, *J* = 7.7 Hz, 4 H), 1.27 (t, *J* = 7.2 Hz, 6 H), 1.21 (t, *J* = 7.7 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 140.6, 137.7, 124.0, 61.7, 60.6, 40.4, 25.6, 15.5, 14.2. HRMS calcd for $[M + H]^+$ $C_{19}H_{27}O_4$ 319.1904, found 319.1908.

5-Butyl-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (188). Isolated in 80% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.00 (m, 3 H), 4.67 (s, 2H), 4.63 (s, 2 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 1.69-1.50 (m, 11 H), 1.46-1.30 (m, 2 H), 0.95 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 154.6, 142.3, 142.2, 137.5, 137.1, 127.7, 127.6, 122.7, 122.6, 122.5, 122.3, 79.7, 52.4, 52.3, 52.1, 52.0, 35.7, 34.1, 28.8, 22.58, 22.55, 14.2. HRMS calcd for $[M + Na]^+$ $C_{17}H_{25}NO_2Na$ 298.1778, found 298.1778.

5-Phenyl-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (189). Isolated in 75% yield as a slight yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.26 (m, 8 H), 4.81-4.66 (m, 4 H), 1.57 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 155.6, 141.0, 140.9, 138.1, 137.7, 136.5, 136.1, 128.9, 127.4, 127.2, 126.6, 126.5, 123.1, 122.9, 121.6, 121.3, 79.9, 52.5, 52.3, 52.2, 52.0, 28.8. HRMS calcd for $[M + H]^+$ $C_{19}H_{22}NO_2$ 296.1645, found 296.1653.

5-(Benzyloxymethyl)-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (190). Isolated in 76% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.18 (m, 8 H), 4.70 (s, 2 H), 4.67 (s, 2 H), 4.59 (s, 2 H), 4.57 (s, 2 H), 1.55 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 154.7, 138.3, 137.8, 137.4, 136.9, 136.6, 128.61, 128.58, 127.93, 127.85, 127.21, 127.17, 122.9, 122.6, 122.4, 122.1, 79.9, 72.5, 72.4, 72.3, 72.1, 71.8, 52.4, 52.3, 52.1, 52.0, 51.6, 51.5, 28.9, 28.5. HRMS calcd for $[M + Na]^+$ $C_{21}H_{26}NO_3Na$ 362.1727, found 362.1742.

***tert*-Butyl (2-(*tert*-butoxycarbonyl)isoindolin-6-yl)methyl carbamate (191).** Isolated in 80% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.10 (m, 3 H), 4.90 (br s, 1 H), 4.67 (s, 2 H), 4.64 (s, 2 H), 4.33 (s, 2 H), 4.31 (s, 2 H), 1.54 (s, 9 H), 1.48 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 155.6, 154.5, 138.5, 137.9, 137.5, 136.5, 136.1, 126.7, 122.9, 122.7, 121.8, 121.7, 79.8, 79.7, 52.4, 52.2, 52.1, 51.9, 44.7, 28.8, 28.6. HRMS calcd for $[M + Na]^+$ $C_{19}H_{28}N_2O_4Na$ 371.1941, found 371.1939.

5,6-Diethyl-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester (192). Isolated in 55% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1 H), 7.04 (s, 1 H), 4.66 (s, 2 H), 4.62 (s, 2 H), 2.68 (q, *J* = 7.4 Hz, 4 H), 1.54 (s, 9 H), 1.25 (t, *J* = 7.4 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 154.7, 141.13, 141.06, 135.0, 134.7, 122.5, 122.3, 79.6, 52.4, 521, 28.8, 25.7, 15.7. HRMS calcd for $[M + Na]^+$ $C_{17}H_{25}NO_2Na$ 298.1778, found 298.1778.

Diethyl-5-butyl-4,7-indanedicarboxylate (195). Isolated in 79% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1 H), 4.48-4.28 (m, 4 H), 3.25 (t, *J* = 7.4 Hz, 2 H), 2.97 (t, *J* = 7.4 Hz, 2 H), 2.72 (t, *J* = 7.7 Hz, 2 H), 2.08 (p, *J* = 7.4 Hz, 2 H), 1.58 (p, *J* = 7.7 Hz , 2 H), 1.46-1.30 (m, 8 H), 0.93 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.8, 144.6, 144.5, 139.0, 132.9, 129.7, 127.9, 61.2, 61.0, 34.2, 33.9, 33.4, 32.4, 25.1, 22.9, 14.6, 14.5, 14.2. HRMS calcd for $[M + H]^+$ $C_{19}H_{27}O_4$ 319.1909, found 319.1919.

Diethyl-5-Phenyl-4,7-indanedicarboxylate (196). Isolated in 93% yield as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.46-7.30 (m, 5 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 4.11 (q, *J* = 6.9 Hz, 2 H), 3.36 (t, *J* = 7.6 Hz, 2 H), 3.08 (t, *J* = 7.6 Hz, 2 H), 2.17 (p, *J* = 7.6 Hz, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 1.00 9t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.5, 146.4, 145.0, 140.5, 138.9, 132.5, 129.9, 128.4, 128.3, 127.9, 127.4, 61.2, 61.1, 34.0, 32.1, 25.1, 14.6, 13.9. HRMS calcd for $[M + H]^+$ $C_{21}H_{23}O_4$ 339.1596, found 339.1589.

Diethyl-5-(benzyloxymethyl)-4,7-indanedicarboxylate (197). Isolated in 98% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.41-7.26 (m, 5 H), 4.74 (s, 2 H),

4.54 (s, 2 H), 4.45-4.29 (m, 4 H), 3.30 (t, *J* = 7.6 Hz, 2 H), 3.05 (t, *J* = 7.6 Hz, 2 H), 2.12 (p, *J* = 7.6 Hz, 2 H), 1.43 (t, *J* = 7.2 Hz, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 166.5, 147.2, 145.5, 138.1, 135.2, 132.0, 128.6, 128.4, 127.9, 127.8, 127.6, 72.6, 70.3, 61.3, 61.1, 33.9, 32.4, 25.1, 14.6, 14.4. HRMS calcd for $[M + H]^+$ $C_{23}H_{27}O_5$ 383.1858, found 383.1854.

***tert*-Butyl-(4,7-di(ethoxycarbonyl)-2,3-1*H*-inden-5-yl)methylcarbamate (198).** Isolated in 90% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 5.22 (br s, 1 H), 4.51-4.32 (m, 4 H), 3.29 (t, *J* = 7.6 Hz, 2 H), 3.06 (t, *J* = 7.6 Hz, 2 H), 2.10 (p, *J* = 7.6 Hz, 2 h), 1.54-1.37 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 166.3, 155.6, 147.1, 146.1, 136.2, 131.6, 129.6, 128.7, 79.4, 61.6, 61.1, 43.3, 33.8, 33.0, 28.6, 25.1, 14.6, 14.5. HRMS calcd for $[M + H]^+$ $C_{21}H_{30}NO_6$ 392.2073, found 392.2069.

Diethyl-5,6-diethyl-4,7-indanedicarboxylate (199). Isolated in 61% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (q, *J* = 7.2 Hz, 4 H), 2.93 (t, *J* = 7.4 Hz, 4 H), 2.73 (q, *J* = 7.5 Hz, 4 H), 2.07 (p, *J* = 7.4 Hz, 2 H), 1.41 (t, *J* = 7.2 Hz, 6 H), 1.21 (t, *J* = 7.5 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 140.5, 138.0, 131.9, 61.1, 32.3, 25.0, 23.4, 16.3, 14.5. HRMS calcd for $[M + H]^+$ $C_{19}H_{27}O_4$ 319.1909, found 319.1910.

3-Butyl-5,7,6,8-tetrhydronaphthalene-1,4-dicarboxylic acid diethyl ester (200). Isolated in 70% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 4.38 (m, 4 H), 3.02 (br s, 2 H), 2.74 (br s, 2 H), 2.55 (t, *J* = 8.0 Hz, 2 H), 1.85-1.73 (m, 4 H), 1.67-1.53 (m,

2 H), 1.47-1.30 (m, 8 H), 0.94 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 168.0, 137.3, 136.0, 135.9, 134.4, 131.7, 128.3, 61.3, 61.1, 33.6, 33.2, 27.9, 27.5, 22.9, 22.8, 22.4, 14.6, 14.5, 14.1. HRMS calcd for $[M + H]^+$ $C_{20}H_{29}O_4$ 333.2066, found 333.2073.

3-Phenyl-5,7,6,8-tetrahydronaphthalene-1,4-dicarboxylic acid diethyl ester (201). Isolated in 64% yield as a slight yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1 H), 7.44-7.32 (m, 5 H), 4.36 (q, J = 7.2 Hz, 2 H), 4.08 (q, J = 7.2 Hz, 2 H), 3.12 (br s, 2 H), 2.85 (br s, 2 H), 1.92-1.77 (m, 4 H), 1.39 (t, J = 7.2 Hz, 3 H), 1.01 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 167.6, 140.0, 137.7, 136.8, 136.6, 135.2, 131.8, 128.7, 128.5, 128.3, 127.6, 61.23, 61.17, 28.1, 27.7, 22.7, 22.4, 14.6, 14.0. HRMS calcd for $[M + H]^+$ $C_{22}H_{25}O_4$ 353.1747, found 353.1753.

3-(Benzyloxymethyl)-5,7,6,8-tetrahydronaphthalene-1,4-dicarboxylic acid diethyl ester (202). Isolated in 60% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1 H), 7.41-7.28 (m, 5 H), 4.58 (s, 2 H), 4.51 (s, 2 H), 4.43-4.24 (m, 4 H), 3.08 (br s, 2 H), 2.80 (br s, 2 H), 1.89-1.75 (m, 4 H), 1.41 (t, J = 7.2 Hz, 3 H), 1.32 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 167.6, 138.5, 138.0, 136.5, 135.4, 132.2, 131.7, 128.4, 127.8, 127.7,127.6, 72.5, 70.0, 61.4, 61.1, 28.1, 27.6, 22.7, 22.3, 14.6, 14.3. HRMS calcd for $[M + Na]^+$ $C_{24}H_{28}O_5Na$ 419.1828, found 419.1836.

***tert*-Butyl-(5,8-di(ethoxycarbonyl)-1,2,3,4-tetrahydronaphthalen-7-yl)methylcarbamate (203).** Isolated in 61% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 9s, 1 H),

4.92 (s, 1 H), 4.48-4.30 (m, 4 H), 4.27 (s, 2 H), 4.25 (s, 2 H), 3.05 (br s, 2 H), 2.77 (br s, 2 H), 1.86-1.75 (m, 4 H), 1.52-1.36 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 167.5, 155.5, 138.1, 136.6, 135.4, 132.6, 132.2, 128.0, 61.7, 61.2, 42.8, 28.6, 28.0, 27.7, 22.6, 22.3, 14.54, 14.46. HRMS calcd for $[M + Na]^+$ $C_{22}H_{31}NO_6Na$ 428.2043, found 428.2051.

3,4-Diethyl-5,7,6,8-tetrahydronaphthalene-1,4-dicarboxylic acid diethyl ester (204). Isolated in 58% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (q, *J* = 7.2 Hz, 4 H), 2.74-2.53 (m, 8 H), 1.85-1.71 (m, 4 H), 1.41 (t, *J* = 7.2 Hz, 6 H), 1.20 (t, *J* = 7.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 136.1, 135.8, 131.4, 61.1, 26.9, 23.6, 22.7, 16.1, 14.5. HRMS calcd for $[M + H]^+$ $C_{20}H_{29}O_4$ 333.2066, found 333.2075.

Experimental protocols and data for compounds 214, 216-218, 221, 222, 224-228, 230, 231, 234-239, and 205

***N*,*N*-Bis(4-methoxybenzyl)but-3-yn-1-amine (214).** To a solution of *N*-(4-methoxybenzyl)but-3-yn-1-amine (**219**) (100 mg, 0.53 mmol) and DIPEA (184 µL, 1.06 mmol) in acetonitrile (900 µL) was added *p*-methoxybenzylchloride (107 µL, 0.79 mmol), and the reaction was heated to 70 °C for 5 h. After cooling, the solvent was removed *in vacuo* and the residue was taken up in H_2O (5 mL) and extracted three times with EtOAc (5 mL). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (12:1) to give 128 mg (78%) of **214** as a

colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 4 H), 6.85 (d, *J* = 8.5 Hz, 4 H), 3.81 (s, 6 H), 3.55 (s, 4 H), 2.68 (t, *J* = 7.4, 2 H), 2.35 (dt, *J* = 7.4, 2.6, 2 H), 1.95 (t, *J* = 2.5, 1 H).

***N*-(But-3-ynyl)-*N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (216).** To a solution of *N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide[173] (350 mg, 1.09 mmol), 3-butyn-1-ol (107 µL, 1.41 mmol), and PPh_3 (370 mg, 1.41 mmol) in DCM (7 mL) was added DIAD (296 µL, 1.41 mmol) dropwise and the reaction was stirred for 2 h. Additional 3-butyn-1-ol (53 µL, 0.71 mmol), PPh_3 (185 mg, 0.71 mmol), and DIAD (150 µL, 0.71 mmol) was added and the reaction was stirred for another 3 hr. After concentration, the residue was purified by silica gel chromatography, eluting with DCM/hexanes (3:1) to give 393 mg (96%) of **216** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-7.97 (m, 1 H), 7.79-7.59 (m, 3 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.53 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 7.5 Hz, 2 H), 2.28 (dt, *J* = 7.5, 2.7 Hz, 2 H), 1.89 (t, *J* = 2.7 Hz, 1 H).

Diethyl 2,3-dihydro-5-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indene-4,7-dicarboxylate (217). A solution of diyne **193** (20.3 mg, 0.86 mmol), **212** (171 mg, 0.86 mmol), and $Ni(PPh_3)_2(CO)_2$ (5.5 mg, 0.009 mmol) in $PhCH_3$ (3 mL) was irradiated in a CEM Discover microwave synthesizer for 2 min. After cooling the reaction was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1 to 2:1) to give 31.9 mg (85%) of **217** as a white solid: Mp 176-179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.64 (m, 5 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 3.94 (t, *J* = 7.7 Hz,

2 H), 3.25 (t, *J* = 7.6 Hz, 2 H), 3.10 (t, *J* = 7.7 Hz, 2 H), 2.99 (t, *J* = 7.6 Hz, 2 H), 2.08 (p, *J* = 7.7 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

(2'-(4,7-Di(ethoxycarbonyl)-2,3-dihydro-1*H*-inden-6-yl)ethyl)-4-methoxybenzyl-2-nitrobenzenesulfonamide (218). A solution of diyne **193** (95 mg, 0.40 mmol), **216** (25 mg, 0.067 mmol), and $Ni(PPh_3)_2(CO)_2$ (21.3 mg, 0.20 mmol) in $PhCH_3$ (2.5 mL) was irradiated in a CEM Discover microwave synthesizer for 2 min. After cooling the reaction was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1) to give 32.3 mg (79%) of **218** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 1 H), 7.66-7.45 (m, 4 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 4.58 (s, 2 H), 4.35 (m, 4 H), 3.80 (s, 3 H), 3.48 (t, *J* = 7.5 Hz, 2 H), 3.20 (t, *J* = 7.5 Hz, 2 H), 2.93 (t, *J* = 7.5 Hz, 2 H), 2.83 (t, *J* = 7.5 Hz, 2 H), 2.05 (p, *J* = 7.5 Hz, 2 H), 1.42 (t, *J* = 7.1 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

***tert*-Butyl 2-(4,7-di(ethoxycarbonyl)-2,3-dihydro-1*H*-inden-6-yl)ethyl4-methoxybenzyl carbamate (221).** In each of three microwave vials were added **193** (40 mg, 0.17 mmol), **213** (295 mg, 1.02 mmol), $Ni(CO)_2(PPh_3)_2$ (10.8 mg, 0.017 mmol), and $PhCH_3$ (4 mL). Each vial was irradiated for 2 min at 300 W in a CEM Discover microwave synthesizer. The reactions were combined and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1) to give 201 mg (75%) of **221** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.74-7.62 (m, 1 H), 7.23-7.10 (m, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 4.41-4.20 (m, 6 H), 3.79 (s, 3 H), 3.49-3.30 (m, 2 H), 3.25 (t, *J*

= 7.5 Hz, 2 H), 3.03-2.84 (m, 4 H), 2.07 (p, *J* = 7.5 Hz, 2 H), 1.48 (s, 9 H), 1.44-1.33 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.6, 158.9, 155.9, 155.5, 145.6, 145.0, 135.9, 133.0, 130.8, 130.5, 129.4, 128.8, 128.2, 113.9, 79.7, 61.3, 61.0, 55.4, 50.6, 49.6, 48.3, 33.7, 32.6, 28.6, 25.0, 14.4.

***tert*-Butyl 2-(4,7-di(ethoxycarbonyl)-2,3-dihydro-1*H*-inden-6-yl)ethyl carbamate (222).** A solution of diyne **193** (19.5 mg, 0.083 mmol), **215** (84 mg, 0.50 mmol), and $Ni(PPh_3)_2(CO)_2$ (5.2 mg, 0.008 mmol) in $PhCH_3$ (2.5 mL) was irradiated in a CEM Discover microwave synthesizer for 2 min. After cooling the reaction was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (5:1) to give 28.3 mg (85%) of **222** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 4.83 (bs, 1 H), 4.47-4.31 (m, 4 H), 3.48-3.33 (m, 2 H), 3.27 (t, *J* = 7.6 Hz, 2 H), 3.00 (t, *J* = 7.6 Hz, 2 H), 2.91 (t, *J* = 6.8 Hz, 2 H), 2.18-2.03 (p, *J* = 7.6Hz, 2 H), 1.52-1.33 (m, 15 H).

Ethyl 2-((benzyloxy)methyl)-5,6,7,8-tetrahydro-4-(2-hydroxypropan-2-yl)naphthalene-1-carboxylate (224). To dry $CeCl_3$ (37 mg, 0.15 mmol) at 0 °C was added THF (500 µL) and was stirred for 3 h at room temperature. The suspension was cooled to −78 °C, and MeLi (1.6 M in Et_2O, 95 µL, 0.15 mmol) was added dropwise. After stirring for 1 h at −78 °C, diester **202** (10 mg, 0.025 mmol) in THF (200 µL with 100 µL wash) was added dropwise, and the reaction was stirred for 2 h. At this point, the reaction was allowed to warm to −40 °C and was stirred an additional 2 h before being quench with NH_4Cl (sat.) (1 mL) and extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (5

mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 9.1 mg (90%) of **224** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.24 (m, 6 H), 4.55 (s, 2 H), 4.51 (s, 2 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 3.12-3.01 (m, 2 H), 2.84-2.73 (m, 2 H), 1.82-1.62 (m, 11 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

Ethyl 5-butyl-2,3-dihydro-7-(2-hydroxypropan-2-yl)-1*H*-indene-4-carboxylate (225). $CeCl_3$ (139 mg, 0.56 mmol) was dried overnight *in vacuo* at 140 °C. While the flask was hot, nitrogen was introduced, and the flask was cooled to 0 °C. THF (1.8 mL) was added at once, the ice bath removed, and the suspension was stirred vigorously for 3 h at room temperature. The flask was cooled to −78 °C, and MeLi (0.6 M in Et_2O, 942 µL, 0.56 mmol) was added dropwise. After stirring for 1 h at −78 °C, **195** (30 mg, 0.094 mmol) was added over 5 min. After 8 min the reaction was quenched at −78 °C with sat. NH_4Cl (1 mL) and allowed to warm to room temperature. EtOAc (4 mL) and water (4 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (4 mL × 2), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (7:1) to give 26.2 mg (92%) of **225** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (s, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.10 (t, *J* = 7.3 Hz, 2 H), 2.95 (t, *J* = 7.5 Hz, 2 H), 2.71 (t, *J* = 7.8 Hz, 2 H), 2.13 (m, 2 H), 1.64-1.52 (m, 8 H), 1.56-1.32 (m, 5 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

***tert*-Butyl 2-(4-(ethoxycarbonyl)-2,3-dihydro-7-(2-hydroxypropan-2-yl)-1*H*-inden-5-yl)ethylcarbamate (226).** $CeCl_3$ (81 mg, 0.33 mmol) was dried overnight *in vacuo* at 140 °C. While the flask was hot, nitrogen was introduced, and the flask was cooled to 0 °C. THF (1.1 mL) was added at once, the ice bath removed, and the suspension was stirred vigorously for 3 hrs at room temperature. The flask was cooled to −78 °C, and MeLi (1.35 M in Et_2O, 244 μL, 0.33 mmol) was added dropwise. After stirring for 1 h at −78 °C, **222** (26.7 mg, 0.066 mmol) was added over 5 min. After 7 min the reaction was quenched at −78 °C with sat. NH_4Cl (1 mL) and allowed to warm to room temperature. EtOAc (3 mL) and water (3 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 mL × 2), and the combined organic extracts were washed with H_2O (4 mL) and brine (4 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3:1 to 2:1) to give 3.2 mg (12%) of **226** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1 H), 4.90 (bs, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.37 (dt, *J* = 6.3, 12.0 Hz, 2 H), 3.11 (t, *J* = 7.4 Hz, 2 H), 2.97 (t, *J* = 7.4 Hz, 2 H), 2.89 (t, *J* = 6.3 Hz, 2 H), 2.04 (p, *J* = 7.4 Hz, 2 H), 1.76 (bs, 1 H), 1.60 (s, 6 H), 1.43-1.36 (m, 12 H).

***tert*-Butyl 2-(4-(ethoxycarbonyl)-2,3-dihydro-7-(2-hydroxypropan-2-yl)-1*H*-inden-5-yl)ethyl4-methoxybenzyl carbamate (227).** $CeCl_3$ (318 mg, 1.29 mmol) was dried overnight *in vacuo* at 140 °C. While the flask was hot, nitrogen was introduced, and the flask was cooled to 0 °C. THF (4.3 mL) was added at once, the ice bath removed, and the suspension was stirred vigorously for 3 h at room temperature. The flask was cooled to −78

°C, and MeLi (0.74 M in Et_2O, 961 µL, 1.29 mmol) was added dropwise. After stirring for 1 h at −78 °C, **221** (116 mg, 0.066 mmol) in THF (1.4 mL) was added over 10 min. After stirring 10 min the reaction was quenched at −78 °C with sat. NH_4Cl (3 mL) and allowed to warm to room temperature. EtOAc (5 mL) and water (5 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (5 mL × 2), and the combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1) to give 104 mg (92%) of **227** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.25-7.06 (m, 3 H) 6.82 (d, *J* = 8.5 Hz, 2 H), 4.40-4.20 (m, 4 H), 3.79 (s, 3 H), 3.51-3.28 (m, 2 H), 3.10 (t, *J* = 7.4 Hz, 2 H), 3.03-2.84 (m, 4 H), 2.03 (p, *J* = 7.4 Hz, 2 H), 1.79 (s, 1 H), 1.58 (s, 6 H), 1.44 (bs, 9 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

Ethyl 5-(2-(4-methoxybenzylamino)ethyl)-2,3-dihydro-7-hydroxy-1*H*-indene-4-carboxylate (228). $BF_3{\cdot}Et_2O$ (206 µL, 0.78 mmol) was added to H_2O_2 (50%, 13.3 µL, 0.2 mmol) and was stirred for 45 min at 0 °C. This solution was added to **227** (50 mg, 0.098 mmol) in dichloromethane (2.3 mL) at 0 °C. After stirring for 9 min at 0 °C, H_2O (2 mL) and EtOAc (2 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (2 mL × 2), and the combined organic extracts were washed with water (4 mL) and brine (4 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with $CHCl_3$/MeOH (10:1) to give 30.9 mg (86%) of **228** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.6 Hz, 2 H), 6.87-6.72 (m, 3

H), 4.26 (q, *J* = 7.1 Hz, 2 H), 4.01 (s, 2 H), 3.71 (s, 3 H), 3.29-3.07 (m, 4 H), 3.04 (t, *J* = 7.5 Hz, 2 H), 2.79 (t, *J* = 7.5 Hz, 2 H), 2.00 (p, *J* = 7.5 Hz, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H).

Ethyl 2-(4-methoxybenzyl)-2,3,4,6,7,8-hexahydro-9-methoxy-1*H*-cyclopenta[*g*]isoquinoline-5-carboxylate (230). Formaldehyde (37% in H_2O, 31 µL, 0.42 mmol) was added to **228** (15 mg, 0.40 mmol) in MeOH (1.5 mL), 1 N NaOAc (570 µL), and 0.1 N HOAc (570 µL), and the reaction was stirred at room temperature for 1 h. The MeOH was removed and the aqueous layer was extracted with dichloromethane (4 mL × 4). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to dryness. The crude tetrahydroisoquinoline was then taken up in CH_3CN/MeOH (9:2, 231 µL), and DIPEA (28.5 µL, 0.16 mmol) followed by trimethylsilyldiazomethane (2 M in Et_2O, 273 µL, 0.55 mmol). After 2 h, the solvent was removed under reduced pressure, and the residue was taken up in H_2O (1 mL) and EtOAc (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 mL × 2). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel chromatography, eluting with $CHCl_3$/MeOH (40:1) to give 12.8 mg (59%, 2 steps) of **230** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.64 (bs, 4 H), 3.07-2.91 (m, 6 H), 2.63 (t, *J* = 5.9 Hz, 2 H), 2.05 (p, *J* = 7.5 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H).

Ethyl 7,8-dihydro-9-methoxy-6*H*-cyclopenta[*g*]isoquinoline-5-carboxylate (231). A mixture of **230** (11.8 mg, 0.030 mmol) and Pd/C (10%, 6 mg) was heated in mesitylene (240

μL) for 45 min. The reaction was cooled, diluted with EtOAc (2 mL) and a few drops of TEA, filtered over a silica plug eluting with EtOAc then MeOH, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:1) to give 3.8 mg (48%) of **231** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (bs, 1 H), 8.55 (bs, 1 H), 8.28 (bs, 1 H), 4.49 (q, *J* = 7.1 Hz, 2 H), 4.11 (s, 3 H), 3.30 (t, *J* = 7.5 Hz, 2 H), 3.20 (t, *J* = 7.5 Hz, 2 H), 2.17 (p, *J* = 7.5 Hz, 2 H), 1.47 (t, *J* = 7.1 Hz, 3 H).

Diethyl-5,5-dimethylnona-2,7-diynedioate (209). *n*-BuLi (2.4 M in hexanes, 880 μL, 2.11 mmol) was added dropwise to a solution of **233** (110 mg, 0.92 mmol) in THF (11 mL) at −10 °C. The solution was stirred for 30 min before ethyl chloroformate (228 μL, 2.4 mmol) was added rapidly. The reaction was stirred at −10 °C for 10 min, was warmed to room temperature, and was stirred for 1 hr. The reaction was quenched with sat. NH_4Cl (2 mL) and extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (10:1) to give 167 mg (70%) of **209** as a yellow oil. IR (NaCl, thin film, neat) 2971, 2936, 2905, 2879, 2233, 1712, 1470, 1366, 1252, 1071; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (q, *J* = 7.2 Hz, 2 H), 2.38 (s, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 86.0, 75.6, 62.0, 34.6, 31.3, 26.7, 14.2. HRMS calcd for $[M + H]^+$ $C_{15}H_{21}O_4$ 265.1434, found 265.1437.

1-[*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)amino]-2-[2,2-dimethyl-4,7-di(ethoxycarbonyl)-indan-5-yl]ethane (235). In three microwave vials were added **209** (20

mg, 0.076 mmol), **213** (219 mg, 0.76 mmol), $Ni(CO)_2(PPh_3)_2$ (4.8 mg, 0.0075 mmol), and $PhCH_3$ (2.5 mL). Each vial was irradiated for 2 min at 300 W in a CEM Discover microwave synthesizer. The reactions were combined and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (7:1) to give 105 mg (84%) of **235** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.75-7.59 (m, 1 H), 7.25-7.09 (m, 2 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 4.42-4.18 (m, 6 H), 3.79 (s, 3 H), 3.48-3.28 (m, 2 H), 3.08 (s, 2 H), 3.03-2.84 (m, 2 H), 2.79 (s, 2 H), 1.48 (s, 9 H), 1.43-1.33 (m, 6 H), 1.14 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 168.4, 166.6, 158.9, 155.9, 144.9, 144.4, 136.0, 133.2, 130.8, 130.5, 129.3, 128.7, 128.5, 113.9, 79.7, 61.3, 61.0, 55.4, 50.5, 49.6, 48.4, 48.3, 47.4, 39.5, 32.5, 32.2, 29.0, 28.6, 14.4. HRMS calcd for $[M + Na]^+$ $C_{32}H_{43}NO_7Na$ 576.2932, found 576.2932.

1-[*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)amino]-2-[2,2-dimethyl-4-(ethoxylcarbonyl)-7-(2-hydroxypropan-2-yl)-indane-5-yl]ethane (236). $CeCl_3$ (69 mg, 0.28 mmol) was dried overnight *in vacuo* at 140 °C. While the flask was hot, nitrogen was introduced, and the flask was cooled to 0 °C. THF (950 μL) was added at once, the ice bath removed, and the suspension was stirred vigorously for 3 h at rt. The flask was cooled to −78 °C, and MeLi (0.9 M in Et_2O, 313 μL, 0.28 mmol) was added dropwise. After stirring for 1 h at −78 °C, **235** (26 mg, 0.047 mmol) was added over 5 min. After 9 min the reaction was quenched at −78 °C with sat. NH_4Cl (1 mL) and allowed to warm to room temperature. EtOAc (2 mL) and water (2 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 mL × 2), and the combined organic extracts were washed

with H_2O (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:7) to give 21.3 mg (84%) of **236** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.24-7.01 (m, 3 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.40-4.17 (m, 4 H), 3.78 (s, 3 H), 3.37 (br s, 2 H), 3.06-2.84 (m, 4 H), 2.78 (s, 2 H), 1.81 (s, 1 H), 1.56 (s, 6 H), 1.45 (s, 9 H), 1.35 (t, *J* = 7.2 Hz, 3 H), 1.13 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 168.9, 158.8, 156.0, 155.5, 147.2, 144.6, 139.0, 136.1, 130.75, 129.4, 128.7, 128.2, 125.5, 79.5, 73.1, 60.8, 55.3, 50.3, 49.3, 48.7, 48.4, 48.0, 47.3, 39.6, 32.7, 30.4, 28.7, 28.6, 14.4. HRMS calcd for $[M + Na]^+$ $C_{32}H_{45}NO_6Na$ 562.3139, found 562.3141.

Ethyl-5-(2-(4-methoxybenzylamino)ethyl-7-hydroxy-2,2-dimethyl-4-carboxylate (237). $BF_3{\cdot}Et_2O$ (83 μL, 0.71 mmol) was added to H_2O_2 (50%, 5.4 μL, 0.079 mmol) and was stirred for 45 min at 0 °C. This solution was added to **236** (21.3 mg, 0.039 mmol) in dichloromethane (950 μL) at 0 °C. After stirring for 9 min at 0 °C, H_2O (2 mL) and EtOAc (2 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (2 mL × 2), and the combined organic extracts were washed with water (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with $CHCl_3$/MeOH (12:1) to give 14.4 mg (92%) of **237** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br s, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 6.78 (d, *J* = 8.4 Hz, 2 H), 6.71 (s, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 3.96 (s, 2 H), 3.68 (s, 3 H), 3.14 (m, 4 H), 2.85 (s, 2 H), 2.61 (s, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.10 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 160.2, 156.3, 148.1, 138.0, 131.6, 129.6, 123.6, 119.4, 116.6, 114.4,

61.0, 55.3, 51.3, 49.8, 48.5, 43.5, 39.5, 31.5, 29.2, 14.4. HRMS calcd for $[M + H]^+$ $C_{24}H_{32}NO_4$ 398.2326, found 398.2334.

Ethyl-2-(4-methoxybenzyl)-2,3,4,6,7,8-hexahydro-9-methoxy-7,7-dimethyl-1*H*-cyclopenta[*g*]isoquinoline-5-carboxylate (238). Formaldehyde (37% in H_2O, 29 μL, 0.39 mmol) was added to **237** (14.4 mg, 0.036 mmol) in MeOH (1.2 mL), 1 N NaOAc (510 μL), and 0.1 N HOAc (510 μL), and the reaction was stirred at room temperature for 1 h. The MeOH was removed and the aqueous layer extracted with dichloromethane (2 mL × 4). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to dryness. The crude tetrahydroisoquinoline was then taken up in CH_3CN/MeOH (9:2, 160 μL), and DIPEA (18.9 μL, 0.11 mmol) followed by trimethylsilyldiazomethane (2 M in Et_2O, 181 μL, 0.36 mmol). After 4 h, 5 equivalents more trimethylsilyldiazomethane (90 μL) was added and the reaction was allowed to stir for 30 min. The solvent was then removed under reduced pressure, and the residue was taken up in H_2O (2 mL) and EtOAc (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 mL × 2). The combined organic extracts were washed with water (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel chromatography, eluting with $CHCl_3$/MeOH (45:1) to give 10.1 mg (66%, 2 steps) of **238** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 3.82 (s, 3 H), 3.76 (s, 3 H), 3.65 (s, 4 H), 3.00 (t, *J* = 5.9 Hz, 2 H), 2.82 (s, 2 H), 2.77 (s, 2 H), 2.64 (t, *J* = 5.9 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H), 1.13 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, not all quaternary carbon centers were observed) δ 166.6, 158.9, 155.3, 144.8, 134.3, 131.2,

130.4, 126.2, 123.9, 113.8, 62.0, 60.6, 59.5, 55.4, 51.9, 49.7, 48.2, 45.1, 40.1, 28.8, 28.2, 14.5. HRMS calcd for $[M + H]^+$ $C_{26}H_{34}NO_4$ 424.2482, found 424.2488.

Ethyl 7,8-dihydro-9-methoxy-7,7-dimethyl-6*H*-cyclopenta[*g*]isoquinoline-5-carboxylate (239). Pd/C (10%, 4.2 mg) was added to **238** (10.1 mg, 0.024 mmol) in mesitylene (190 μL) and the mixture was heated at 185 °C for 4 h. The reaction was cooled, diluted with EtOAc (1 mL) and a few drops of TEA, filtered over a silica plug eluting with EtOAc then MeOH, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:1) to give 4.1 mg (58%) of **239** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (br s, 1 H), 8.54 (br s, 1 H), 8.31 (d, *J* = 4.7 Hz), 4.49 (q, *J* = 7.2 Hz, 2 H), 4.09 (s, 3 H), 3.10 (s, 2 H), 3.01 (s, 2 H), 1.47 (t, *J* = 7.2 Hz, 3 H), 1.19 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, not all quaternary carbon centers were observed) δ 167.2, 155.4, 154.2, 146.9, 143.0, 135.6, 131.0, 119.1, 61.3, 61.0, 49.3, 44.9, 40.3, 28.5, 14.6. HRMS calcd for $[M + H]^+$ $C_{18}H_{22}NO_3$ 300.1594, found 300.1603.

Illudinine (205). To **239** (4.1 mg, 0.014 mmol) dissolved in 95% EtOH (400 μL) was added 40% aqueous KOH (20 drops), and the reaction was stirred for 20 h. Aqueous HCl (10%) was added to pH 3, the solution was poured into pH 7 buffer and extracted with Et_2O (4 mL × 5). The organic layer was dried (Na_2SO_4), filtered and concentrated to give 3.9 mg (100%) of pure illudinine (**205**) as a white solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ 9.74 (s, 1 H), 9.02 (d, *J* = 6.9 Hz, 1 H), 8.53 (d, *J* = 6.9 Hz, 1 H), 4.30 (s, 3 H), 3.28 (s, 2 H), 3.25 (s, 2 H), 1.22 (s, 6 H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 169.4, 164.6, 158.1, 144.2, 140.3, 134.6, 133.7,

124.8, 124.0, 121.6, 62.7, 51.7, 47.1, 42.1, 29.1. HRMS calcd for $[M + H]^+$ $C_{16}H_{18}NO_3$ 272.1281, found 272.1283.

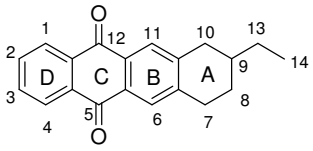
CHAPTER 4: Progress Towards the Total Synthesis of Anthraquinone Natural Products

4.1 Background

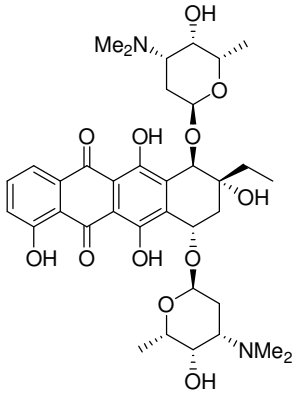
4.1.1 The Anthracycline Antibiotics

The anthracycline antibiotics are glycosidic polyketide natural products with an aglycone component consisting of a tetracyclic anthraquinone chromophore with varying degrees of oxygenation on the B and D rings and assorted substitution patterns on the A ring (Figure 4.1a and 4.1b). The first anthracycline discovered, β-rhodomycin II (**240**), was isolated by Brockman and Bauer in 1950 from the actinomycete *Streptomyces purpurascens*.[174] This anthracycline showed high antibacterial activity, but its toxicity in mice prevented further development into a clinically useful chemotherapeutic agent. During the 1960's, two key anthracyclines, daunorubicin (also termed daunomycin, **241**) and doxorubicin (also termed adriamycin, **242**), were discovered. Isolated independently by two laboratories,[175, 176] daunorubicin was shown to possess a novel sugar, daunosamine, identified as 3-amino-2,6-dideoxy-L-*lyxo*-hexose. Daunorubicin displayed potent antitumor activity especially towards leukemias but also exhibited dose-dependent cardiotoxicity limiting its application.[177] Being more potent than daunorubicin, doxorubicin created much excitement when its biological activity was disclosed, however the high risk of cardiomyopathy and irreversible heart failure limits its use.[177, 178]

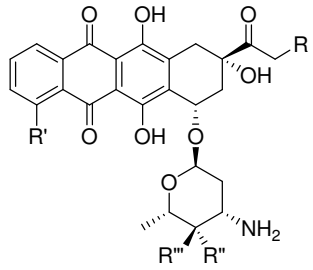
a) Numbering scheme



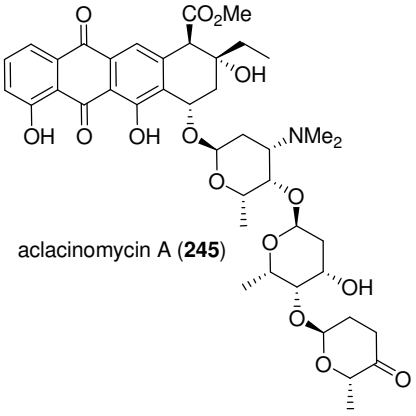
b) Representative structures



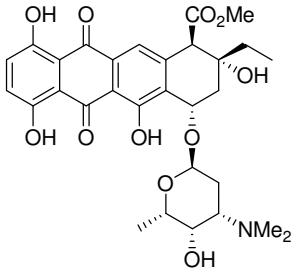
rhodomycin II (**240**)



R	R'	R"	R"'		
H	OMe	OH	H	daunomycin	(**241**)
OH	OMe	OH	H	adriamycin	(**242**)
OH	OMe	H	OH	epirubicin	(**243**)
H	H	OH	H	idarubicin	(**244**)



aclacinomycin A (**245**)



pyrromycin (**246**)

Figure 4.1. Anthracycline numbering and representative structures.

In 1984, Tewey et al. treated cells and cell free systems with adriamycin and discovered topoisomerase II as a target enzyme with the enzyme-DNA complex being stabilized after the cleavage reaction takes place thereby preventing re-ligation of the DNA.[179] Crystal structures[180-182] and models[183] of the anthracycline-DNA complex indicate that the C-9 hydroxyl is positioned outside of the double helix in the minor groove and forms

a hydrogen bond with the DNA. This interaction helps stabilize the drug-DNA-topoisomerase II complex thereby preventing normal topoisomerase II activity.[184] In addition, models of the ternary doxorubicin-DNA-Top II complex reveal key hydrogen bonds between two amino acids, serine-740 and threonine-744, with the C-12 carbonyl and the C-11 hydroxyl of doxorubicin.[183] The synthesis of a variety of anthracyclines and anthracycline analogues resulted in detailed structure-activity relationship information supporting the aforementioned key interactions. Modifications of the C-9 side chain, either elongation or substitution, had a deleterious effect on activity while C-8 and C-10 substitution had no effect as long as the conformation of the A ring was maintained.[185] Analogues that had a C-9 hydrogen in place of the hydroxyl group showed a marked reduction in activity, however, without reduction of DNA binding affinity.[186] As expected, removal of the C-11 hydroxyl group led to decreased activity.[187, 188]

Currently, duanomycin, doxorubicin, epirubicin (**243**), and idarubicin (**244**) are amongst the most effective clinical agents for cancers of many types including acute myeloid leukemia (daunorubicin); solid tumors of the breast, bile ducts, liver, esophagus, and endometrial tissue (doxorubicin); ovarian, gastric, rectal, and pancreatic cancers (epirubicin); and acute nonlymphocytic leukemia (idarubucin).[189-192] Ongoing studies consider the current understanding of the mode of action of anthracyclines as well as their mechanism for toxicity to develop higher generation analogues. Various groups have made deoxygenated[193] and fluoro-derivatives,[194] analogues with disaccharide moieties,[195] 5-imino,[196] and morpholino derivatives.[197] Different formulations have been devised to specifically target the drugs to tumors such as liposomal anthracyclines, extracellular prodrugs, and polymer bound

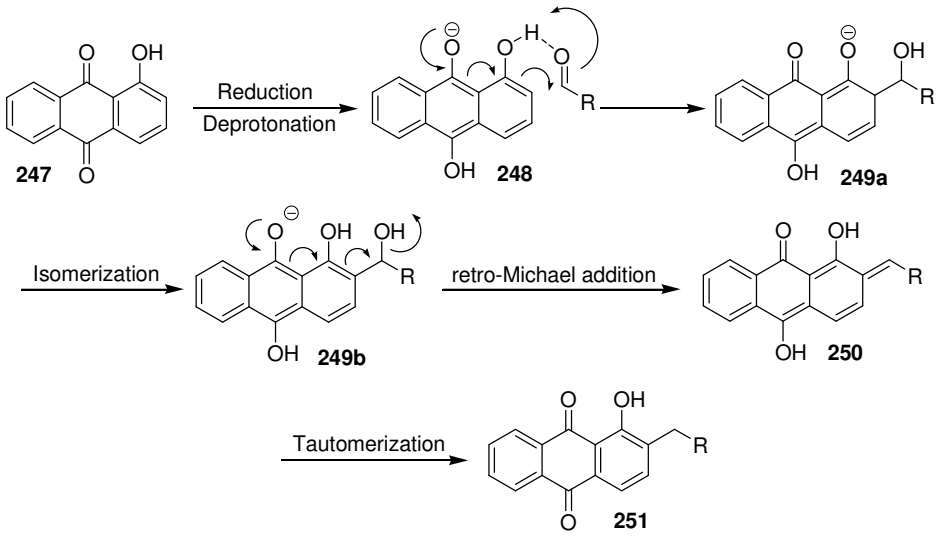
anthracyclines.[198, 199] Clearly, there have been many developments in the anthracycline field since their discovery over fifty years ago, but cardiotoxicity and questions concerning the precise mode of action sustain the still vigorous field of anthracycline research.

4.1.2 Synthetic Approaches Towards the Anthracycline Antibiotics

Owing to their importance as chemotherapeutic agents, the anthracyclines and their analogues have been popular synthetic targets by many research groups. Since the synthesis and coupling of the sugar moiety are well developed,[200, 201] the synthetic challenge resides in the efficient construction of the A-D ring system, the aglycone, with the class of molecules being termed anthracyclinones. The synthesis of the aglycone system itself poses several hurdles to the synthetic chemist. First, the A ring has two, three, or four stereocenters that must be correctly installed, with the stereochemistry of C-9 being especially important for biological activity. Also, there is a regiochemistry issue with respect to the A and D rings. Most anthracyclines have nonsymmetrically substituted D rings (e.g. aclacinomycin **245**) relative to the A ring stereocenters. Nonsymmetrical B ring anthracyclines (e.g. pyrromycin **246**) are also known. Solubility restraints and difficult separations of A/D ring regioisomers accentuate the need for a regiochemically controlled synthesis of the aglycone. With these intricacies in mind, a number of approaches towards the synthesis of anthracyclinones have been developed with three general synthetic plans utilized: anthraquinone based syntheses where anions play a key role; Diels-Alder strategies that can disconnect the A, B, and C rings in multiple ways; and cationic reactions where Friedel-Crafts chemistry takes the center

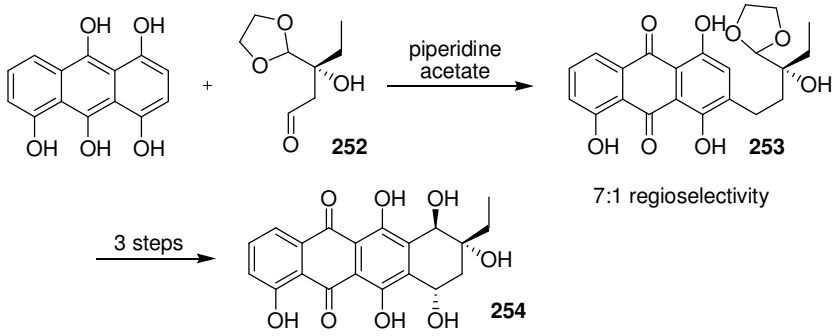
stage. These general strategies will be explored by examining several selected syntheses (for others see *Tetrahedron* **1984**, *40*, issue 22).[202, 203]

As anthraquinones are cheap, readily available compounds, and already contain three of the four rings of the aglycone, it is not surprising that many syntheses begin with various anthraquinones as starting material. There are two ways to elaborate onto the anthraquinone core structure: electrophilic or nucleophilic additions. With regards to electrophilic additions, the Marschalk reaction is perhaps the most important reaction in anthracycline syntheses beginning with anthraquinones.[202, 204] In the Marschalk reaction, as depicted in Scheme 4.1, an alkyl (or hydroxyl alkyl) group is attached to the anthraquinone core of hydroxy- or aminoanthraquinones exclusively *ortho* to the heteroatom. Marschalk noted several other features of the anthraquinone and aldehyde reaction partners that affected the reaction course:[204] reduction to the hydroquinone (if not directly employed as the starting material) is necessary and formaldehyde is the most reactive aldehyde. The course of the reaction is depicted in Scheme 4.1 where after reduction and deprotonation of the anthraquinone **247**, the hydroquinone **248** adds to the aldehyde to yield the alkoxide **249a**. This step is accelerated in less protic solvents supporting the claim that the aldehyde and phenol are aligned through a hydrogen bond.[205] Isomerization to **249b** and retro-Michael reaction to lose water yields the *ortho*-quinone methide **250**.



Scheme 4.1. Marschalk reaction mechanism.

These *ortho*-quinone methide intermediates have been isolated as intermediates in the metabolism of anthracyclines after biological reduction and elimination of the sugar.[206] Subsequent tautomerization leads to the substituted anthraquinone **251**. Since the retro-Michael reaction proceeds much slower than aldehyde addition, it is possible to reoxidize intermediates such as **249b** using hydrogen peroxide to yield the hydroxyl alkyl anthraquinones.[207, 208] This method is clearly very useful for anthracycline synthesis. In the first synthesis of (*R*)-β-rhodomycinone, two Marschalk reactions, one intermolecular and one intramolecular, are employed to install the A ring (Scheme 4.2).[209] In this example, the 1,4-dialdehyde equivalent **252** was synthesized from (*S*)-2-aminobutyric acid as a chiral building block. The shown regioisomer **253** was produced in 44% yield in a 7:1 regioisomeric ratio. Deprotection set up the second Marschalk reaction to yield the aglycone **254**.



Scheme 4.2. Krohn's synthesis of (*R*)-rhodomycinone using the chiral 1,4-dialdehyde **252**.

When only one phenol is present on the B ring, as with aklavinone (**255**) and pyrromycinone (**256**, Figure 4.2), a double Marschalk approach is not viable. In these cases, it has been advantageous to use dialkyl anthraquinones in a keto-ester cyclization event to form the A ring.

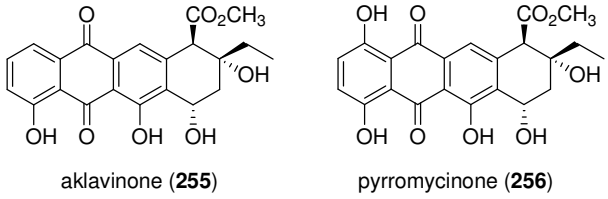
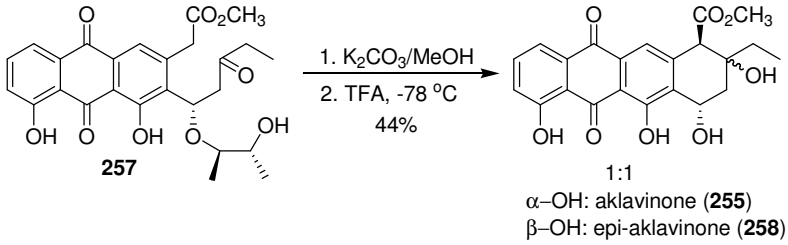


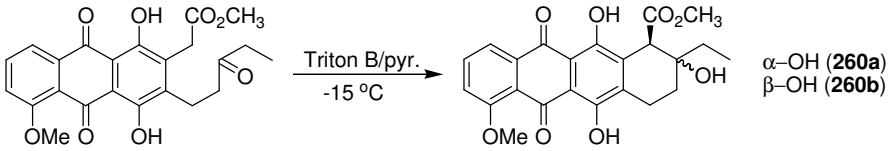
Figure 4.2. Structures of aklavinone (**255**) and pyrromycinone (2**56**).

This biogenetic approach produces the acid-labile β-hydroxy ester functionality under basic conditions.[203] In Kishi's synthesis of aklavinone (**255**), for example, the keto-ester **257** is cyclized with potassium carbonate in methanol to yield the aglycones after deprotection in 44% yield and as a 1:1 mixture of stereoisomers of **255** and **258** (Scheme 4.3).[210]



Scheme 4.3. Kishi's keto-ester cyclization towards aklavinone (**255**).

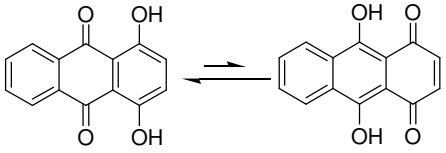
In related systems, the stereoisomeric ratio can be controlled with the proper choice of reaction conditions (Scheme 4.4); lithium amides in aprotic solvents yield the *cis*-hydroxy ester products (**260b**) exclusively while the use of Triton B and pyridine leads to a ~10:1 *trans*/*cis* ratio of **260a**/**260b** from the keto-ester **259**.[203, 211]



259

Scheme 4.4. Kinetic control of keto-ester cyclization.

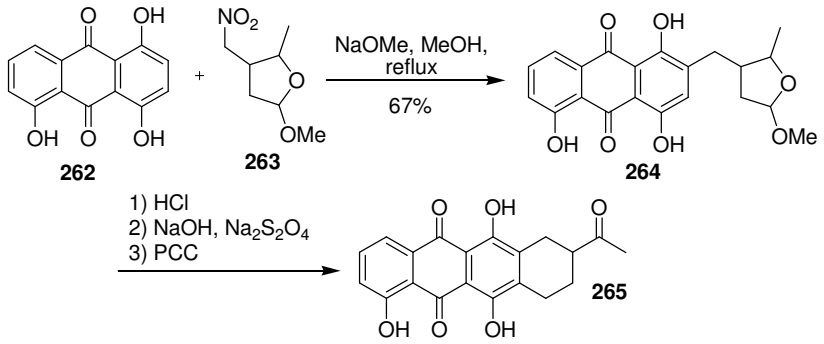
The final case where anthraquinones are used as starting materials has the quinone's role reversed: a nucleophile adds to the anthraquinone core. 1,4-Dihydroxyanthraquinone, quinizarin, has two tautomeric forms, **261a** and **261b**, with the equilibrium strongly favoring **261a**. The reaction can be viewed as a Michael addition to tautomer **261b** (Scheme 4.5). The 1,4-dihydroxy functionality allows for intermolecular additions to occur, compared to situations when only one hydroxyl group is present and only intramolecular reactions are possible.[202]



261a **261b**

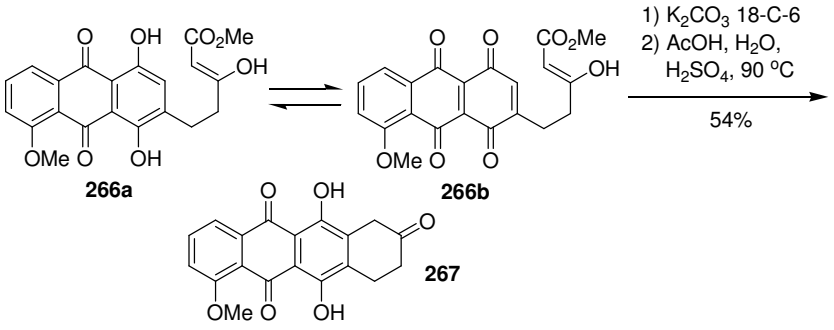
Scheme 4.5. Tautomeric forms of 1,4-dihydroxyanthraquinone.

In the case of the intermolecular nucleophilic addition, Sutherland et al. synthesized 7,9-dideoxycarminomycinone (**265**) *via* addition of the nitro-compound **263** to 1,4,5-trihydroxyanthraquinone (**262**) in sodium methoxide/methanol under reflux (Scheme 4.6).



Scheme 4.6. Intermolecular nucleophilic addition towards 7,9-bisdeoxycarminomycinone (**265**).

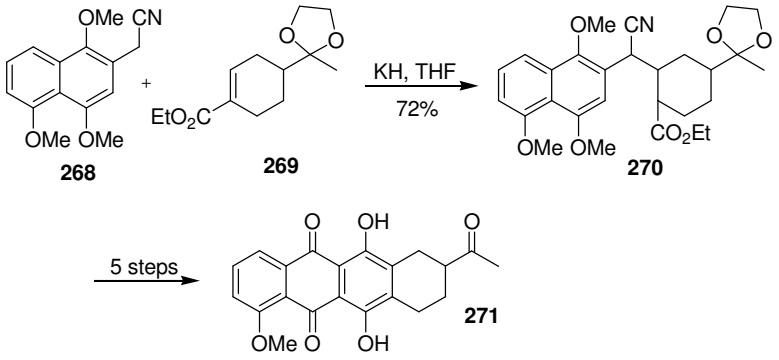
Deprotection of **264** followed by a Marschalk reaction and a PCC oxidation afforded the desired deoxygenated tetracycle **265**.[212, 213] Krohn synthesized the known daunomycinone intermediate **267** *via* an intramolecular nucleophilic addition of **266b** by treatment with potassium carbonate/18-crown-6 in THF (Scheme 4.7).[214]



Scheme 4.7. Krohn's intramolecular nucleophilic addition towards the known daunomycinone intermediate (**267**).

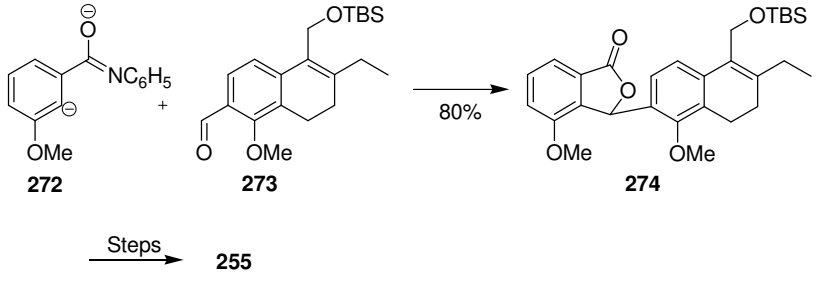
As these examples illustrate, anthraquinones are valuable starting points for anthracyclinone syntheses, however, several of the syntheses are hampered by low yields and the need to separate regio- and stereoisomers. Additional examples of Marschalk reactions, keto-ester cyclizations, and nucleophilic additions towards various natural and synthetic anthracyclines are known.[202, 203]

When anthraquinones are not used as starting materials, anions can still be utilized in the formation of the B and C rings. Parker et al. synthesized the B ring precursor of daunomycinone **270** *via* Michael addition of the benzyl cyanide **268** onto the α,β-unsaturated ester **269** (Scheme 4.8).[215] Five steps completed the synthesis of the known intermediate **271**.



Scheme 4.8. Michael addition/Friedel-Crafts approach to daunomycinone.

Likewise, the formation of the C ring can be accomplished by anionic coupling as well. Kende uses the dianion **272** and the benzaldehyde **273** as coupling partners to produce the intermediate lactone **274** (Scheme 4.9).[216] Several more steps are required to yield aklavinone (**255**). An advantage of these anionic cyclization strategies is the complete regiocontrol over the reactions. This method is very versatile as long as the appropriate, regioisomerically pure coupling partners can be synthesized.



Scheme 4.9. Anionic coupling towards aklavinone (**255**).

One of the most powerful tools in organic chemistry for the assembly of six-membered rings is the Diels-Alder reaction, and, therefore, it comes as no surprise that this reaction has been used extensively to construct rings A, B, or C through one of six possible disconnections (Figure 4.3).

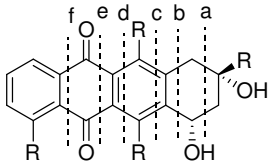
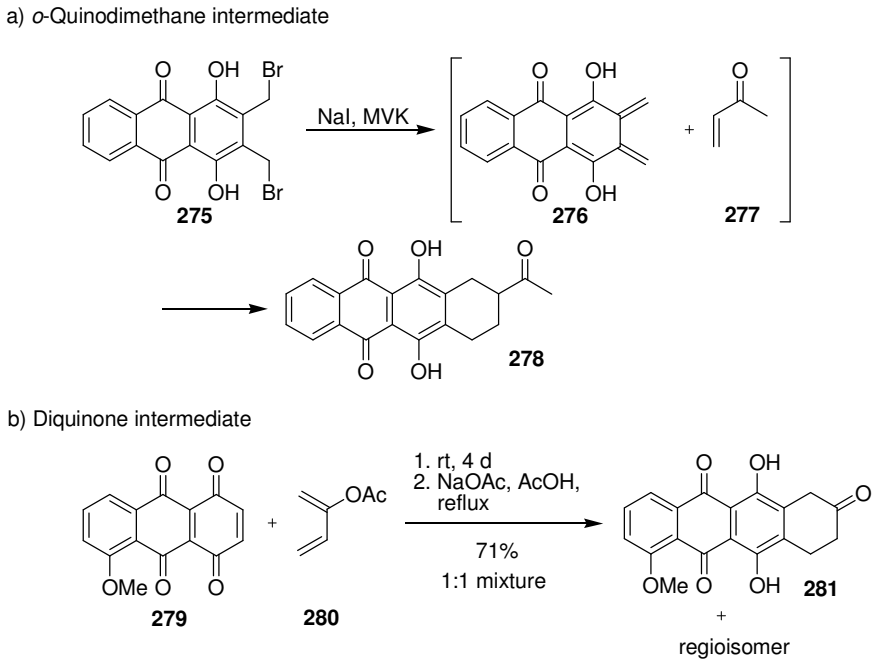


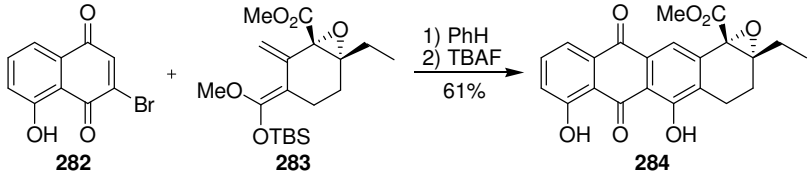
Figure 4.3. Possible Diels-Alder disconnections.

Regiocontrol varies between each individual case with the 4,6-oxygenated anthracyclinone precursors showing more regiocontrol than 4,6,11-oxygenated precursors.[203] *ortho*-Quinodimethanes provide one form of diene for the synthesis of ring A. Cava et al. reacted the *o*-quinodimethane **276** generated from the dibromide **275** with methyl vinyl ketone (**277**) to yield the 4-demethoxydaunomycinone intermediate **278** (Scheme 4.10a).[217] Alternatively, the dienophile can be present on the B ring as in Kende's synthesis of racemic daunomycinone.[218] Here, 2-acetoxybutadiene (**280**) is reacted with the diquinone **279** to give a 1:1 mixture of adducts **281** in 71% yield. Cleavage of the enol acetates gives regioisomeric ketones separable by recrystallization (Scheme 4.10b).



Scheme 4.10. Diels-Alder approaches to the A ring.

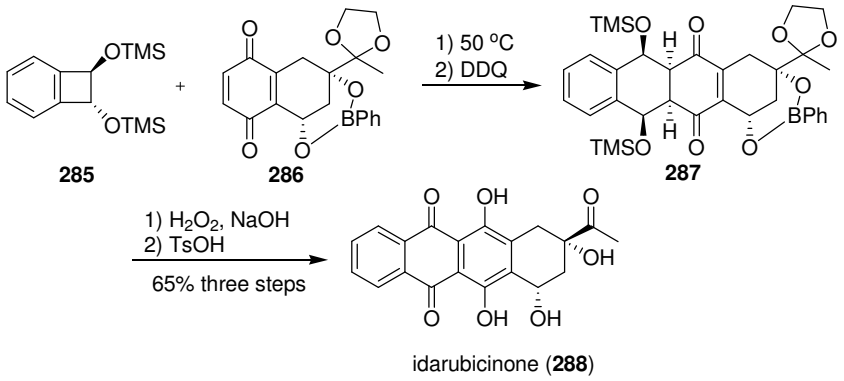
Moving down the tetracyclic framework to ring B, most disconnections come at line d (Figure 4.3). Derivatives of juglone are used extensively to produce various 4,6-oxygentated anthracyclines with excellent regiocontrol. A known aklavinone intermediate was synthesized in a highly convergent manner by Rapaport et al. by cyclizing the bromojuglone **282** with the silyl ketene acetal **283**. They obtained only the regioisomer **284** shown in 61% yield after fluoride treatment (Scheme 4.11).[219]



Scheme 4.11. Regioselective Diels-Alder approach to the B ring.

Ring C disconnections, as with ring A, typically involve *o*-quinodimethane intermediates with disconnections at line e. Only derivatives of the 6,11-dihydroxy

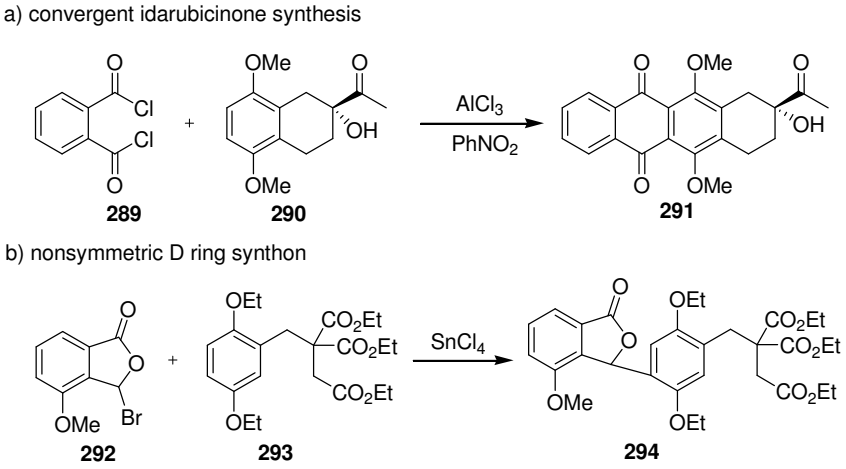
anthracyclinone derivatives are available.[203] A convenient synthesis of idarubicinone was achieved by Danishefsky et al. where the *o*-quinone dimethide precursor **285** and the tetrahydronapthoquinone **286** reacted at 50 °C to yield, after treatment with DDQ, the tetracyclic product **287** (Scheme 4.12).[220] Oxidation and deprotection gave idarubicinone (**288**) in 65% yield over three steps.



Scheme 4.12. *o*-Quinodimethide strategy in C ring synthesis towards idarubicinone (**288**).

A similar sequence with the 4-methoxy substituted **285** gave a 1:1 mixture of regioisomers one of which leads to daunomycinone. The Diels-Alder approach to the anthracyclines has provided a viable strategy to many different natural and non-natural anthracyclinones with much of the regio- and stereoselectivity questions taken into account before coupling.

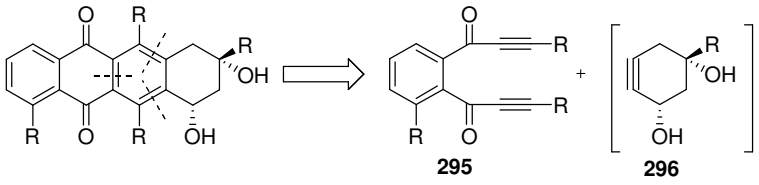
The Friedel-Crafts route to anthracyclinones only allows for one type of disconnection at line e (Figure 4.3). Certain limitations hamper the applicability of the Friedel-Crafts approach including harsh reaction conditions and regioisomer formation. The idarubicinone intermediate **291** has been prepared several times by reacting phthaloyl dichloride (**289**) with the AB ring synthon **290** (Scheme 4.13a).[221, 222]



Scheme 4.13. Friedel-Crafts approaches toward the C ring.

Non-symmetrical D ring synthons have been utilized in a racemic synthesis of daunomycinone.[2] To this end, 3-bromo-4-methoxyphthalide (**292**) and the AB ring synthon **293** react under $SnCl_4$ catalyzed conditions to give the lactone **294** which can be further elaborated to racemic daunomycinone in eleven steps (Scheme 4.13b). As can be seen from these limited examples, the Friedel-Crafts approach to anthracycline synthesis is narrow in scope, since only the disconnection 'e' in Figure 4.3 has been employed in these syntheses.

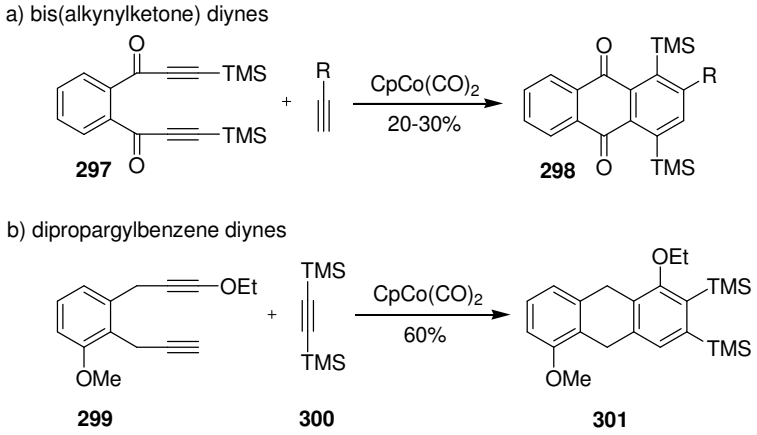
The synthesis of anthracyclines *via* the three bond disconnection in Scheme 4.14 is termed the "cobalt way" by Vollhardt.[2]



Scheme 4.14. Disconnecting via the "cobalt way" gives the diyne **295** and the monoyne **296**.

This approach assembles the B and C rings in one step from a diyne and a monoyne under transition metal catalysis by way of a [2+2+2] cyclotrimerization reaction (initially

conducted using a cobalt catalyst). D ring symmetrical diynes are clearly the most useful reaction partners for this strategy as a regioisomeric mixture will undoubtedly result if no controlling factors (e.g. electronic or steric effects) are involved. Vollhardt et. al. reported the cyclotrimerization of the bis(alkynylketone) **297** with monoynes to give the anthraquinones **298** in poor yields under cobalt catalysis (Scheme 4.15a).[78] Another approach applied the cyclotrimerization of dipropargylbenzenes such as **299** with bistrimethylsilylacetylene (BTMSA, **300**) to give the dihydroanthracene derivative **301** in moderate yield (Scheme 4.15b).[2] The low yields prevented any further exploration into elaboration towards the anthracyclinones (i.e. installation of the A ring) and requires further improvement.



Scheme 4.15. [2+2+2] cyclotrimerization reactions towards anthracyclinone core structures.

Many of the syntheses leading to the natural and non-natural anthracyclinones are limited by several factors including:

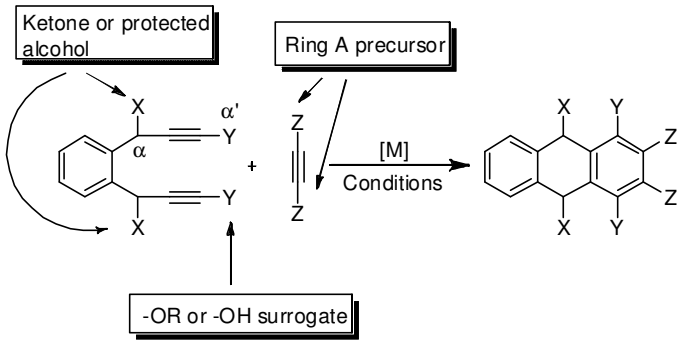
- low reaction yields,
- the formation of regio- and stereoisomer mixtures, and
- the lack of a combinatorial approach suitable for analog development.

By using the [2+2+2] cyclotrimerization reaction in conjunction with microwave irradiation, we will have the means to synthesize anthracyclinones in a rapid and highly convergent manner amenable to construction of focused compound arrays.

4.2 Synthesis of Anthraquinone Natural Products

4.2.1 Towards the Synthesis of 1,4-Dihydroxyanthraquinone Natural Products

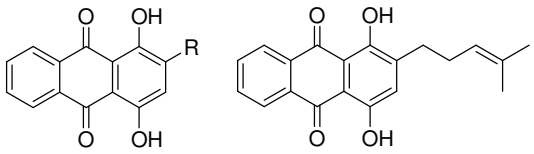
As delineated above, the anthracycline antibiotics hold a very significant role in the realm of cancer therapy. Despite numerous syntheses, many of which contain regioisomer mixtures, a combinatorial approach suited for analog development has not been realized. Towards this goal, an innovative synthetic approach towards the anthracyclines was sought with the main focus on a novel, expedient, and flexible synthesis of the tetracyclic core structure. Moreover, the synthesis will be regioselective and offers several opportunities for introducing diversity into the molecule. The envisioned key step in the assembly of the tetracyclic core is a [2+2+2] cyclotrimerization reaction. A systematic investigation of all the factors associated with the cyclotrimerization event would need to be completed including: the diyne substitution pattern at the benzylic (α) position; the nature of the α' substituent; the electronic properties of the diyne and/or monoyne; the nature of the metal catalyst; and reaction conditions such as temperature, oil bath *versus* microwave heating, and order of reagent addition (Scheme 4.16). In the case of a nonsymmetrical diyne or monoyne, the proper control of regiochemistry will be crucial.



Scheme 4.16. Variables explored in the [2+2+2] cyclotrimerization reaction towards anthraquinones.

As all of the anthracyclines possess at least one phenolic hydroxyl group on the B ring, an efficient means to install this functional group needs to be included in the synthetic planning. In order to construct the A ring, an appropriately substituted synthetic handle must be incorporated into the molecule, preferably in the monoyne to maximize convergence in the cyclotrimerization event. Taking into account all these aspects, a tandem [2+2+2] cyclotrimerization reaction / ring closing metathesis strategy was devised (described below in detail) that potentially would form three of the four rings (A, B, and C rings) in a two-step, one-pot procedure. Initial studies commenced at a much more elementary level: synthesis of 1,4-dihydroxyanthraquinone natural products as model systems for the B-C-D ring system of the anthracyclinones.

We envisioned accessing several 1,4-dihydroxyanthraquinone natural products (**302**-**306**, Figure 4.4) as a testing ground for the cyclotrimerization event and the phenol introduction portions of the anthracyclinone core structure. Both the hybridization states at the α and α' positions as well as the nature of the α' substituent were investigated under different catalyst conditions.

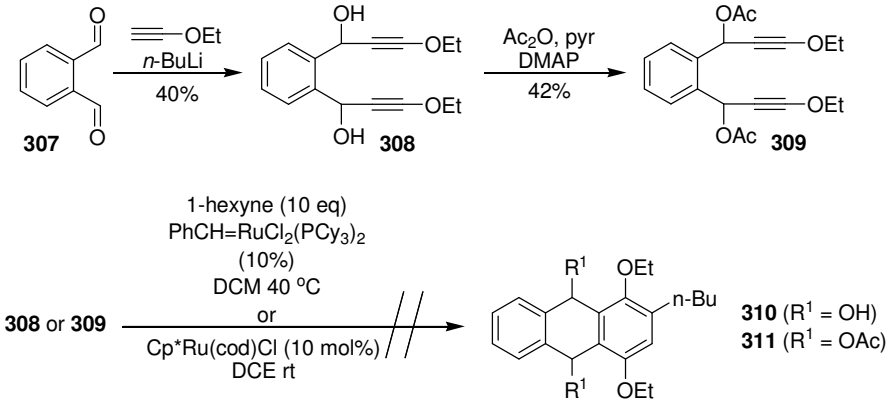


302 (R = Me)
303 (R = CH_2OH)
304 (R = CO_2Me)
305 (R = OH)

Anthrasesamone B (**306**)

Figure 4.4. Accessible 1,4-dihydroxyanthraquinone natural products.

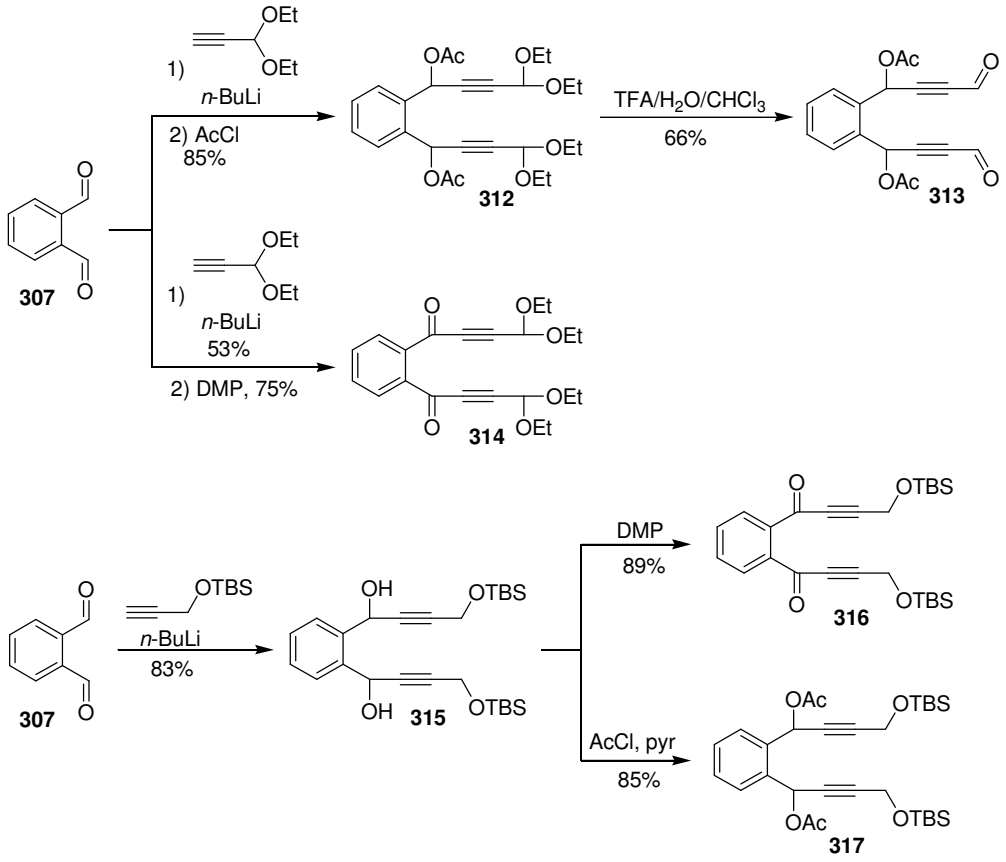
Direct installation of the oxygen (that was to become the phenol group) as the α' atom was first explored (Scheme 4.17). The diacetate **309** was prepared in a two step sequence in 17% yield from *o*-phthalaldehyde (**307**). The low overall yield is most likely the result of the instability of the ethynyl ether adjacent to the hydroxyl functionality. Attempts to oxidize the diol **308** to the diketone derivative with MnO_2 or Dess-Martin Periodinane (DMP) failed. The reaction of the diol **308** or the diacetate **309** with either Grubbs' 1st generation catalyst or Cp*Ru(cod)Cl towards **310** or **311** was equally unrewarding with both diynes decomposing rather than undergoing cyclotrimerization.



Scheme 4.17. Direct installation of an oxygen as an ether and attempted cyclotrimerization reactions.

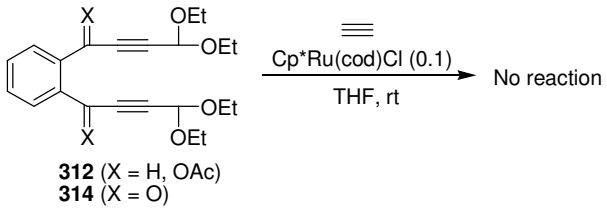
At this juncture, the approach was modified to utilize an α' substituent more amenable to the cyclotrimerization that could also be modified later into a phenol. The Baeyer-Villiger rearrangement was chosen as a means to introduce the phenol and

investigations into the cyclotrimerization reaction of a new series of diynes ensued.[223] As a prerequisite for the Baeyer-Villiger rearrangement, an aldehyde or ketone starting material is needed; for the diyne molecule, therefore, an aldehyde or a substituent that has the potential to be transformed into an aldehyde would need to be located at the α' position. Accordingly, a series of diynes, **312**-**317**, differing in substitution pattern were prepared from **307** (Scheme 4.18), and their ability to undergo a cyclotrimerization reaction was then probed.



Scheme 4.18. Preparation of diynes for the Baeyer-Villiger approach.

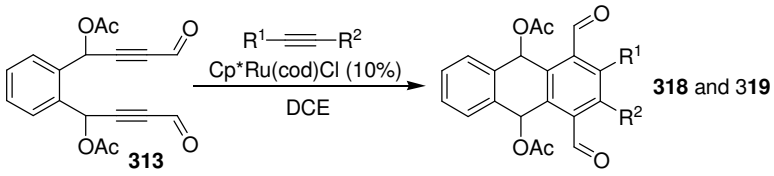
Neither acetals, **312** or **314**, underwent cyclotrimerization with acetylene under Cp*Ru(cod)Cl catalysis presumably due to the steric bulk of the tertiary α' carbon center (Scheme 4.19), and only unreacted starting material was observed.



Scheme 4.19. Attempted cyclotrimerization reactions with the acetals **312** and **314**.

Dialdehyde **313** underwent cyclotrimerization in low yield with TBS-protected propargyl alcohol or acetylene to furnish the protected 9,10-anthracenediols **318** and **319** (Table 4.1, Entries 1 and 4). The low yields were a result of the sensitive nature of the propargylaldehyde functionalities present in **313** leading to decomposition of the starting material.

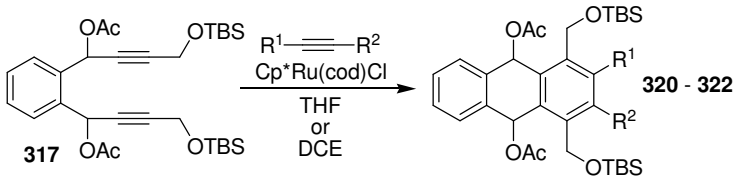
Table 4.1. Cyclotrimerization reaction results with the dialdehyde **313**. [a]300 W until temperature reached, then 5-15 W thereafter



Entry	Conditions	R^1, R^2 (eq.)	Result
1	MW[a] 110 °C 5 min	H, CH_2OTBS (6)	26%, **318**
2	rt, o/n	H, CH_2OTBS (4)	24%
3	80 °C 4 h	H, CH_2OTBS (6)	4:1 **318**/s.m.
4	rt, o/n	H, H	30-45%, **319**
5	rt, o/n	CO_2Et, CO_2Et (4)	No rxn.
6	rt, o/n	TMS, TMS (10)	No rxn.

Better cyclotrimerization results were obtained with the diacetate **317** to give the 9,10-diacetylated anthracenediols **320**-**322** (Table 4.2), but crude reaction mixtures were quite complex, hampering purification by flash-chromatography.

Table 4.2. Cyclotrimerization reaction results with the diacetate **317**. [a]300 W until temperature reached, then 5-15 W thereafter

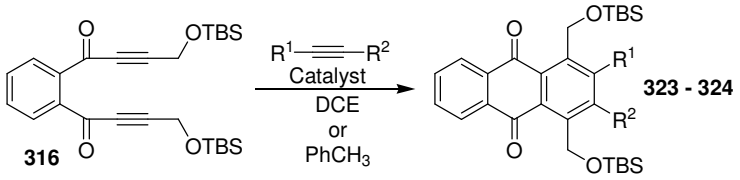


Entry	Conditions	R^1, R^2	Result
1	15% cat. rt, THF	H, H	69%, **320**
2	20% cat. rt, THF, o/n	H, *n*-Bu (6)	33%, **321**
3	20% cat. rt, THF, o/n	CH_2OMe, CH_2OMe (6)	39%, **322**
4	20% cat. MW[a] 50 °C 5 min	CH_2OMe, CH_2OMe (6)	trace **322**
5	20% cat. MW[a] 80 °C 5 min	CH_2OMe, CH_2OMe (6)	trace **322**
6	20% cat. MW[a] 140 °C 5 min	CH_2OMe, CH_2OMe (6)	trace **322**
7	15% cat. rt, DCE, o/n	CO_2Me, CO_2Me (5)	No rxn.

Interestingly, 1,4-dimethoxy-2-butyne (Entry 3) cyclotrimerized with the same efficiency as 1-hexyne (Entry 2). Microwave conditions (Entries 4-6) gave only trace product due to decomposition of the diyne starting material. Other catalyst systems based on $Mo(CO)_6$, $[Ir(cod)Cl]_2$, or $Ni(CO)_2(PPh_3)_2$, gave trace product formation at best with 1-hexyne (10 eq) under oil bath ($PhCH_3$, 80 °C, 5 h) or microwave conditions ($PhCH_3$, 5-10 min, 300 W).

By far, the most promising results were obtained with the diketone **316** after extensive optimization. Initial results were similar to other diynes (Table 4.3). Using 15 mol% of the Cp*Ru(cod)Cl catalyst only provided a 22% yield of the desired anthraquinone **323** with 1-hexyne as the monoyne, while 1,4-dimethoxy-2-butyne gave no reaction under the same conditions towards the anthraquinone **324** (Entries 1 and 2). Continuing further optimizations using 1-hexyne as a model alkyne and heating the reactions in the microwave at 100 °C for five minutes or at an oil bath temperature of 80 °C gave low conversions (1:5 product/s.m. in crude ^1H NMR spectrum) (Entries 3 and 4). The molybdenum based catalyst system, $Mo(CO)_6$ gave no reaction, only polymerization of the 1-hexyne (Entry 5).

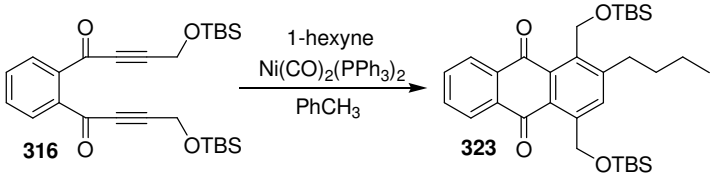
Table 4.3. Cyclotrimerization reaction results with the diketone **316**.



Entry	Conditions	R^1, R^2 (eq.)	Result
1	Cp*Ru(cod)Cl (15%) DCE, rt, o/n	H, *n*-Bu (4)	22%, **323**
2	Cp*Ru(cod)Cl (15%) DCE, rt, o/n	CH_2OMe, CH_2OMe (4)	No rxn.
3	Cp*Ru(cod)Cl (15%) MW, 100 ^oC, 5 min	H, *n*-Bu (6)	1:5 **323**/s.m.
4	Cp*Ru(cod)Cl (15%) oil bath, 80 ^oC, o/n	H, *n*-Bu (6)	1:5 **323**/s.m.
5	$Mo(CO)_6$ (30%) 4-Cl-phenol (100%) $PhCH_3$, reflux	H, *n*-Bu (10)	No rxn.
6	$[Ir(cod)Cl]_2$ (10%) DPPE (20%) MW 80 ^oC, 10 min X 2	H, *n*-Bu (5)	25%, **323**
7	$[Ir(cod)Cl]_2$ (10%) DPPE (20%) 50 ^oC, o/n	H, *n*-Bu (5)	1:4 **323**/s.m.
8	$Ni(CO)_2(PPh_3)_2$ (10%) $PhCH_3$, 80 ^oC, 2 h	H, *n*-Bu (5)	30%, **323**

Using $[Ir(cod)Cl]_2$ as the catalyst, a 25% yield was obtained after microwave irradiation at 80 °C (5-15 W after reaching 80 °C at 300 W) for two ten minute time periods with two catalyst additions (10% each), while a 1:4 product/s.m. ratio was observed under oil bath heating at 50 °C for 18 h (Entries 6 and 7). With the $Ni(CO)_2(PPh_3)_2$ catalyst, the same catalyst used by Reppe[12] for the cyclotrimerization of acetylene and by Meriwether for the cyclotrimerization of terminal electron poor alkynes,[127] the best yield was obtained (30%, 10 mol% $Ni(CO)_2(PPh_3)_2$, 5 eq 1-hexyne, 80 °C, 2 h), and these conditions were the basis of future optimization studies (Entry 8). Through modifying the catalyst loading, equivalents of monoyne, and reaction temperature under microwave irradiation (Table 4.4), the optimal conditions were found to be 20 mol% catalyst with at least fifteen equivalents of monoyne irradiated in the microwave for twenty minutes at 50 °C using a standard mode setting. Consistent 55-60% yields of **32** can be obtained (Table 4.4).

Table 4.4. Optimization of the cyclotrimerization reaction with the diketone **316** under Ni-catalysis.

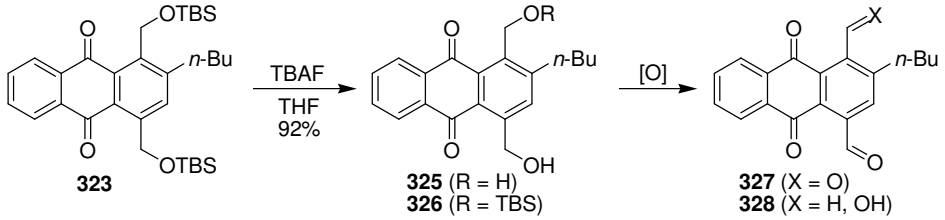


Entry	Conditions	Eq. of 1-hexyne	Result	Entry	Conditions	Eq. of 1-hexyne	Result
1	10% cat. rt, o/n	5	11%	7	30% cat., MW 50 °C, 20 min	20	65%
2	10% cat., MW 120 °C, 10 min	5	pdt. with impurity	8	10% cat., MW 40 °C, 20 min	20	63%
3	2 % cat. 80 °C, o/n	5	No rxn.	9	10% cat., MW 50 °C, 20 min	15	57%
4	10% cat., MW 85 °C, 20 min	5	38%	10	20% cat., MW 50 °C, 20 min	15	~60%
5	10% cat., MW 80 °C, 20 min	20	57%	11	100% cat., MW 120 °C, 10 min	5	no s.m. inseparable impurity
6	10% cat., MW 50 °C, 20 min	20	61%				

Higher reaction temperatures resulted in monoyne polymerization (Entries 2, 4, 5, and 11), and stoichiometric catalyst loading resulted in inseparable impurities (Entry 11). When these optimal conditions are applied to the Cp*Ru(cod)Cl catalyst system, a 71% yield was obtained, however, separation of the product **323** from an unknown by-product was tedious, requiring multiple columns for purification. The ability of the microwave irradiation to produce higher yields and greatly reduced reaction times can be attributed in part to the alternative mechanism of microwaves heating. As the power of the microwaves was, for the most part, low (often only a few watts of output once the desired temperature was reached), a major contributing factor for the higher yields could be due to the increased catalyst stability in the absence of wall effects and more efficient heating of the entire reaction mixture. Running the reaction in power mode (300 W) led to competitive polymerization of the monoyne thereby reducing the yield of **323**.

*4.2.2 Installation of Hydroxy Groups on Anthraquinone **323***

The conversion of the methylene-OTBS groups in the anthraquinone **323** to phenolic hydroxyl groups is a crucial step in the synthesis as structure-activity relationships showed the C-11 hydroxyl has a key interaction with topoisomerase-II that significantly contributes to the biological activity.[187, 188] Towards this end, removal of the two TBS groups affording the diol **325** was accomplished with six equivalents of TBAF and proceeded in an excellent 92% yield (Scheme 4.20).[224] Lower equivalents of TBAF or the use of HF/pyridine gave mixtures of the diol **325** and the alcohol **326**.

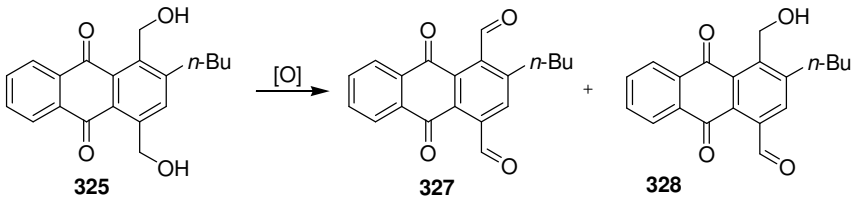


Scheme 4.20. Synthesis of the dialdehyde **327** for a Baeyer-Villiger rearrangement.

The oxidation of the diol **325** to the dialdehyde **327** proved troublesome. Oxidation with DMP (7 eq.) provided a 70% yield of the dialdehyde **327** with 18% of the monoaldehyde **328** (Table 4.5, Entry 1). Treatment of the diol **325** with a large excess of PDC (15 eq.) gave a mixture of starting material, monoaldehyde **328**, and dialdehyde **327** (Entry 2). One of the problems impeding the oxidation as well as the TBAF deprotection is the steric hindrance of the hydroxymethylene group *ortho* to the *n*-butyl group. As revealed in previous experiments towards illudinine (Chapter 3.3), this position proves difficult to modify. Also, the solubility of the diol **325** was slight at best in typical organic solvents (DCM, EtOAc, and Et_2O). Because of this fact, less common oxidation conditions were attempted (Entries 3 and 4) resulting in mixtures of starting material, **328** and **329**. At this

point, microwave irradiation was explored. Using pyridinium chlorochromate (PCC) as the oxidant, an 88% yield of the dialdehyde **327** was obtained after irradiating at 200 W for two minutes in dichloromethane (Entry 5).[225] Scaling up this reaction required an extended reaction time (3 min.) and cooling to maintain a temperature of ~50 °C and to prevent extreme temperatures (>130 °C are reached in DCM after less than 2 minutes of a 200 W irradiation of 700 μL of solvent) giving an 86% yield with an undetermined amount of the single oxidation product **328** (Entry 6). Solvents with higher boiling points such as dichloroethane gave decreased yields (30%). With the ability to scale up the sequence to the dialdehyde efficiently, studies on the Baeyer-Villiger rearrangement could commence.

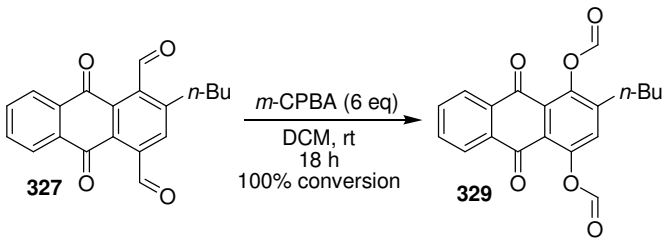
Table 4.5. Oxidation of the diol **325** to the dialdehyde **327**.



325 **327** **328**

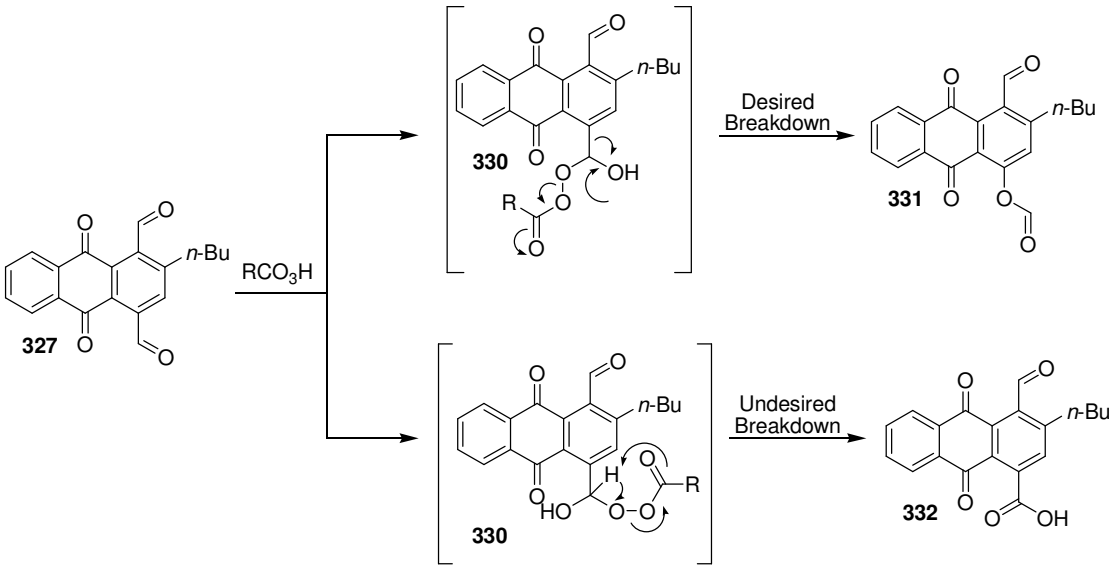
Entry	Conditions	Result
1	DMP (7 eq) CH_3CN/THF 0 °C to rt, 8 h	70%
2	PDC (15 eq) THF/DCM rt, 24 h	s.m./pdt mixture
3	NBS/pyr acetone/CCl_4 rt to 50 °C, 18 h	mixture
4	DMSO, HBr 100 °C, 24 h	mixture
5	PCC (4 eq) DCM, MW 200 W, 2 min (5 mg scale)	88%
6	PCC (4 eq) DCM, MW 200 W, 2 min (20 mg scale	45%
7	PCC (4 eq) DCM, MW 50 °C, 3 min	86%

Treatment of **327** with excess *m*-CPBA (> 4 eq.) overnight led to a product insoluble in DCM and chloroform, but soluble in methanol and presumed to be the formate ester **329** based on MS data (Scheme 4.21).



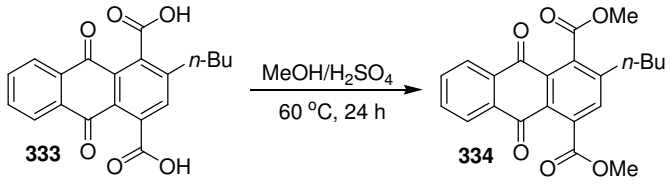
Scheme 4.21. Baeyer-Villiger rearrangement of the dialdehyde **327**.

^{1}H-NMR analysis showed no aldehyde protons, but no formyl ester protons were detected either. However, silica gel chromatography with a polar eluent system (MeOH/EtOAc) gave a solid product with an M+1 of 353 m/z corresponding to the mass of the formate ester. This information led us to reconsider the absence of the formyl proton in the NMR. When using alternative reagents for the Baeyer-Villiger reaction (TFAA/H_2O_2) that could be removed under vacuum, the same results were obtained. Careful consideration of the reaction mechanism pointed to the breakdown of the tetrahedral intermediate **330** as the step under question (Scheme 4.22). The desired decomposition of intermediate **330** provides the formate ester **331** through migration of the anthraquinone moiety of **330**. However, facile proton transfer is possible, leading to the formation of the carboxylic acid **332**. The decomposition of the tetrahedral intermediate in this fashion is most likely due to the electron-withdrawing nature of the quinone structure as well as the second aldehyde functionality increasing the acidity of the benzylic protons thereby allowing abstraction of the proton and cleavage of the oxygen-oxygen bond.



Scheme 4.22. Decomposition of the tetrahedral intermediate **330**.

This result was confirmed by treatment of the Baeyer-Villiger product **333** under Fischer esterification conditions ($MeOH/H_2SO_4$/heat) to give the methyl ester **334**, as confirmed by ^{1}H-NMR analysis (Scheme 4.23). Although disappointed by this result, alternate means to install the phenol group were then explored.

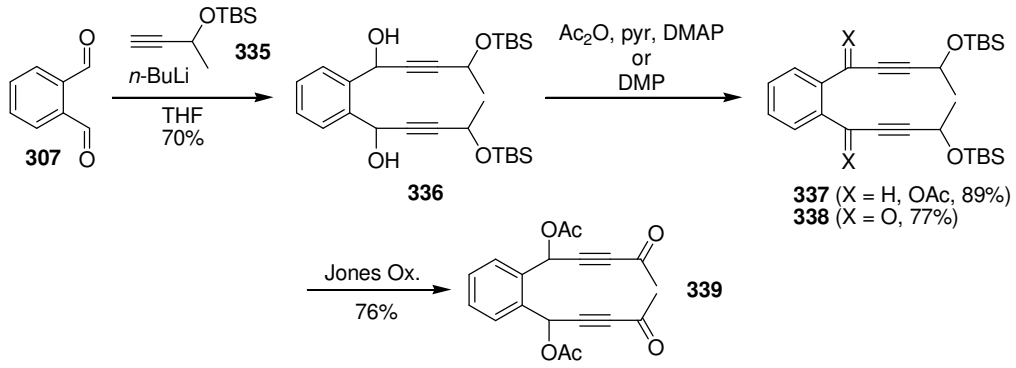


Scheme 4.23. Confirmation of the Baeyer-Villiger rearrangement product **333**.

4.2.3 Investigation of Alternative Baeyer-Villiger Substrates

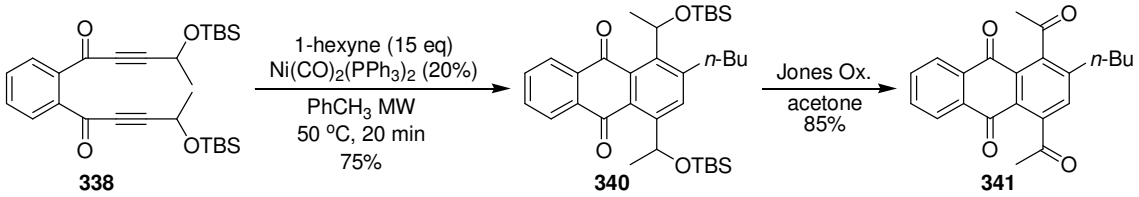
In attempts to prevent rearrangement to the benzoic acid derivative, it was postulated that a methyl ketone moiety would allow Baeyer-Villiger rearrangement to proceed. In this vein, synthesis of diynes containing a methyl ketone or equivalent were pursued. Treatment

of the dialdehyde **307** with excess lithium acetylide derived from the TBS-ether **335** gave a 70% yield of the diol **336** as a mixture of stereoisomers (Scheme 4.24). Acetylation (Ac_2O, pyr., DMAP, 0 °C, 2.5 h) or oxidation (DMP, DCM, 0 °C 70 min) of the alcohols in **336** provided either the diacetate **337** or the diketone **338** in 89 and 77% yield, respectively. Oxidation of the diacetate with Jones reagent (acetone, 0 °C, 35 min) provided the alternative diketone **339** in 76% yield. Attempted oxidation of **336** with Jones reagent failed to provide a tetraketone derivative.



Scheme 4.24. Synthesis of the methyl ketone derivatives **337**-**339**.

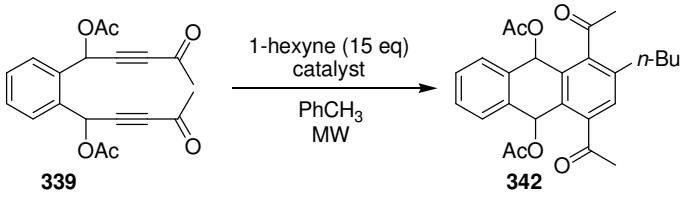
Cyclotrimerization reactions of the diynes were then investigated. Using the previously optimized conditions (15 eq 1-hexyne, 20 mol% $Ni(CO)_2(PPh_3)_2$, $PhCH_3$, MW, 50 °C, 20 min, standard mode), the diketone **338** reacted with 1-hexyne in 75% yield to give the anthraquinone **340** (Scheme 4.25). Further oxidation to the tetraketone **341** using Jones reagent proceeded in 85% yield.



Scheme 4.25. Cyclotrimerization reaction of the diketone **338**.

The cyclotrimerization of the diyne **339** proved more difficult. Microwave irradiation for 5 min only returned starting material (Entry 1, Table 4.6) while increasing the catalyst loading had no effect (Entry 2). Switching catalyst systems from $Ni(CO)_2(PPh_3)_2$ to Cp*Ru(cod)Cl provided the desired anthracenediol derivative **342** in 68% yield (20 mol% Cp*Ru(cod)Cl, 300 W, 5 min, $PhCH_3$) (Entry 3). Thermal heating also provided a similar yield of the anthracenediol product (67%, Entry 4).

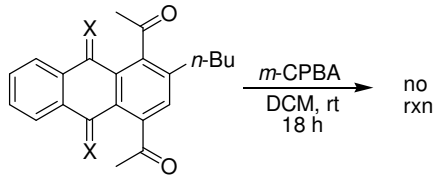
Table 4.6. Cyclotrimerization reaction of the diyne **339**.



339 **342**

Entry	Conditions	Yield (%)	Entry	Conditions	Yield (%)
1	10% $Ni(CO)_2(PPh_3)_2$ MW 300 W, 5 min	---	3	20% Cp*Ru(cod)Cl MW 300 W, 5 min	68
2	20% $Ni(CO)_2(PPh_3)_2$ MW, 80 °C, 20 min	---	4	20% Cp*Ru(cod)Cl 80 °C, o/n	67

With the Baeyer-Villiger substrates in hand, explorations into the rearrangement of **341** and **342** were conducted. Unfortunately, both the tetraketone **341** and the diacetate **342** failed to undergo any reaction when treated with *m*-CPBA (Scheme 4.26). Other Baeyer-Villiger reagents (TFAA/H_2O_2, *m*-CPBA/*p*-TsOH, NaOH/H_2O_2)[226-228] were attempted with **341**, however, each was unsuccessful at effecting the rearrangement with unreacted starting material obtained from each. The increased steric bulk of the methyl group as well as the decreased electrophilicity of the carbonyl most likely prevented 1,2-addition of the peroxide reagents.



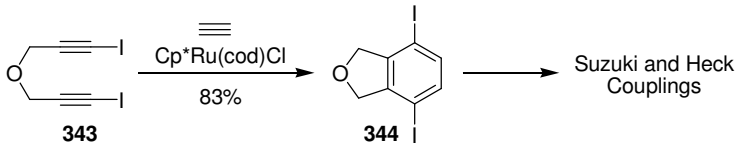
342 (X = H, OAc)
341 (X = O)

Scheme 4.26. Attempted Baeyer-Villiger rearrangement of **341** and **342**.

Due to the unsuccessful Baeyer-Villiger rearrangements towards the phenol moieties of the anthraquinone natural products other means to install the phenols were then investigated.

4.2.4 Alternative Methods for Phenol Installation

In a recent paper by Yamamoto et al., the use of alkynyl halides such as **343** in [2+2+2] cyclotrimerization reactions towards dihaloarenes **344** and subsequent coupling reactions (Suzuki and Heck) were described (Scheme 4.27).[229]

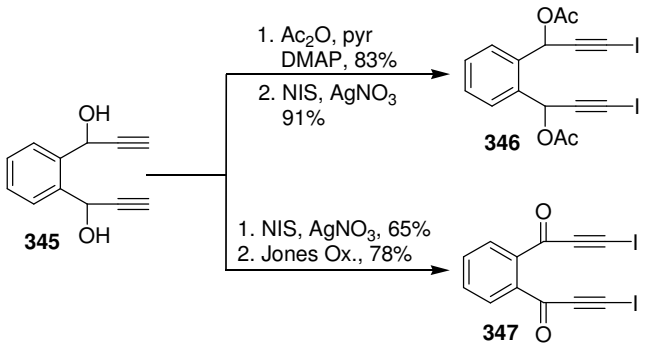


343 **344**

Scheme 4.27. Iodoalkynes in [2+2+2] cyclotrimerization reactions.[229]

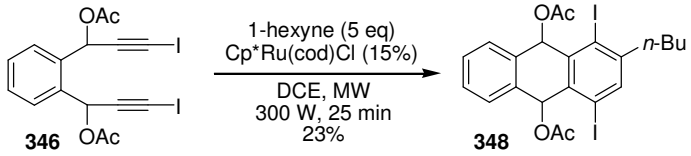
We postulated that if the cyclized anthraquinones or protected anthracenediols could be formed from alkynyl iodides, then the introduction of the phenolic hydroxyl groups could be accomplished either via lithium-halogen exchange followed by reaction with an electrophilic oxygen source or boronate,[230] by Buchwald-Hartwig chemistry,[231] or by a Suzuki coupling[232] with a diboronate. To this end, the alkynyl iodides **346** and **347** were prepared from the diol **345** (Scheme 4.28).[233] Acetylation (Ac_2O, DMAP, pyr, 0 °C, 4 h) of the diol **345** followed by iodination of the terminal triple bonds (NIS, $AgNO_3$, DMF, rt, 1.5 h)[234] provided the diiodide

346 in a 75% yield over two steps. The iodide **347** was prepared by first iodination (NIS, $AgNO_3$, DMF, rt, 1.5 h) of the terminal triple bonds then oxidation (Jones reagent, acetone, 0 °C, 30 min) of the hydroxyl groups to furnish **347** in 51% yield over two steps.



Scheme 4.28. Preparation of iodoalkynes **346** and **347**.

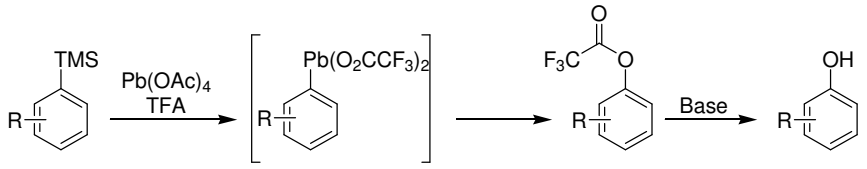
Cyclotrimerization of the diacetate **346** with 1-hexyne proceeded in only 23% yield to give the protected 9,10-dihydroxy-anthracene derivative **348** under Cp*Ru(cod)Cl catalysis and microwave irradiation (Scheme 4.29).



Scheme 4.29. Cyclotrimerization reaction of the iodoalkyne **346**.

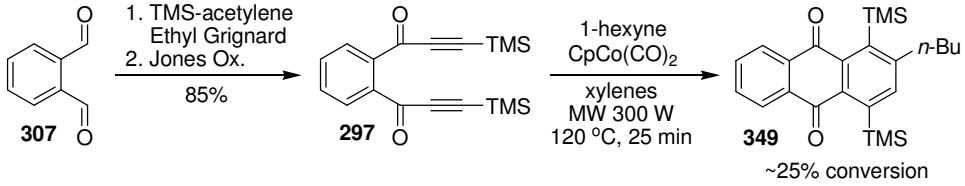
Oil bath heating (80 °C) and Ni-based catalysis resulted in no reaction. The diketone **347** did not participate in a cyclotrimerization event with 1-hexyne (5-20 eq) under Cp*Ru(cod)Cl (15 mol%, DCE, MW, 80 °C, 15 min) or $Ni(CO)_2(PPh_3)_2$ (20 mol%, $PhCH_3$, MW, 80 °C, 20 min) catalysis most likely due to its low solubility in the reaction solvents.

The next option explored hinged upon a silicon-lead transmetallation reaction of an aryl-silicon bond followed by conversion to the trifluoroacetate.[235] Subsequent hydrolysis of the trifluoroacetate would yield a phenol (Scheme 4.30).



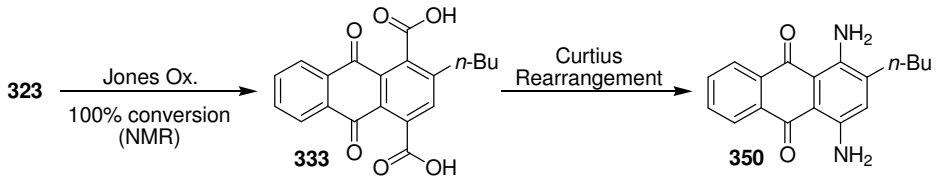
Scheme 4.30. Conversion of an aryl-silicon bond into an aryl-oxygen bond.[235]

This procedure would require cyclotrimerization products similar to those obtained by Vollhardt (Scheme 4.15); however, higher yields would be desired. The diketone **297**, prepared in 85% yield over two steps according to the procedure of Vollhardt,[78] unfortunately did not undergo cyclotrimerization with 1-hexyne (15 eq) under $Ni(CO)_2(PPh_3)_2$ or Cp*Ru(cod)Cl catalysis (20 mol%, $PhCH_3$, MW, 50 °C, 20 min) with microwave irradiation to the anthraquinone **349** (Scheme 4.31). Low conversions were observed by ^{1}H-NMR (~25%) under $CpCo(CO)_2$ catalysis with microwave irradiation (xylenes, MW 300 W, 25 min, 120 °C) most likely due to the steric bulk of the TMS groups. Therefore, a new route to the phenols was sought.



Scheme 4.31. An aryl-silicon approach to phenols.

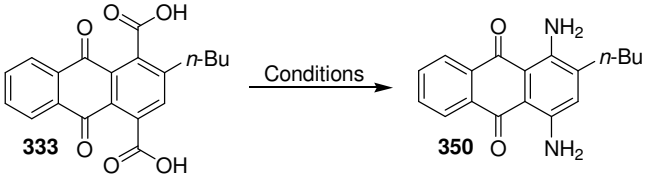
Another route attempted to the 1,4-dihydroxyanthraquinones has been met with minor success. This approach utilized the undesired Baeyer-Villiger rearrangement product **333**, more efficiently obtained by a Jones oxidation of the cyclotrimerization product **323**, as a precursor to the diamine **350** by virtue of a Curtius (or Schmidt) rearrangement (Scheme 4.32).



Scheme 4.32. A Curtius rearrangement approach to diamines.

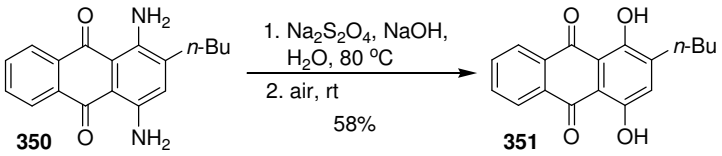
In this direction, the diacid **333** was treated with sodium azide in sulfuric acid at 80 °C to give less than 17% yield of the desired diamine **350**[236] (Table 4.7, Entry 1). Similar yields, 9-11%, were obtained using diphenylphosphoryl azide[237] as the azide source (Entries 2 and 3). Using more classical Curtius reaction conditions, the acyl azide was first generated *via* the acid chloride. Azide formation followed by heating with water led to a 19% yield of the diamine **350** (Entry 4).

Table 4.7. Curtius rearrangement of the diacid **333**.



Entry	Conditions	Result	Entry	Conditions	Result
1	NaN_3, H_2SO_4 heat	<17%	3	DPPA, TEA H_2O, heat	11%
2	1. DPPA, TEA 2. H_2O, heat	9%	4	1. $SOCl_2$, DMF 80 °C 2. NaN_3 3. H_2O, heat	19%

The diamine **350** was converted to the 1,4-dihydroxyanthraquinone derivative **351**[207] by treatment with alkaline sodium dithionite in water at 80 °C followed by air oxidation overnight in 58% yield (Scheme 4.33). Due to the low yields of diamine formation, alternative precursors for the phenols were sought.



Scheme 4.33. Conversion of the diamine **350** into the 1,4-dihydroanthraquinone **351**.

Based upon the success of the benzylic hydroperoxide rearrangement towards illudinine (Chapter 3), examination of its use towards the anthraquinones was initiated. Structurally, a benzylic hydroperoxide rearrangement substrate requires a secondary or tertiary benzylic alcohol. For the anthraquinones, this requirement would translate into a structure such as the diol **352** (Figure 4.5). Protected phenols could also be employed in the rearrangement provided that the protecting group is labile under Lewis acidic conditions (BF_3).

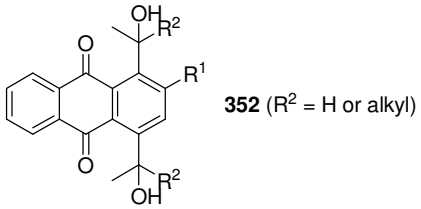
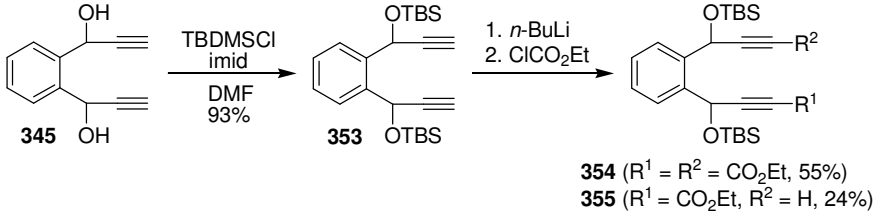


Figure 4.5. Anthraquinone structure necessary for a benzylic hydroperoxide rearrangement.

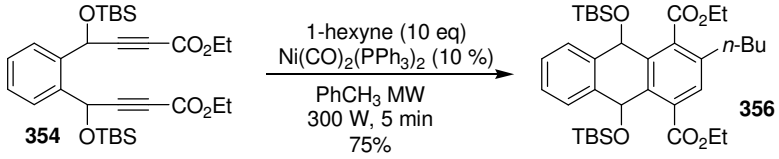
Towards this end, initial investigations relied upon ester derivatized diynes where the electron-withdrawing nature of the ester would, we hypothesized, increase the efficiency of the cyclotrimerization reaction as the benzylic ketones did in **316** towards **323**. These cyclotrimerizations, we hypothesized, would proceed similarly as in the development of the microwave-mediated nickel-catalyzed cyclotrimerizations towards tetralins.[172] Accordingly, the diol **345** was protected as the bis-TBS ether **353** in 93% yield and treated with excess *n*-BuLi (THF, − 78 °C, 1.5 h) followed by quenching with ethyl chloroformate to furnish the diester **354** in 55% yield (Scheme 4.34). Using less than a full equivalent of *n*-BuLi provided

the monoester **355** in a poor 24% yield along with a substantial amount of starting material (60%).



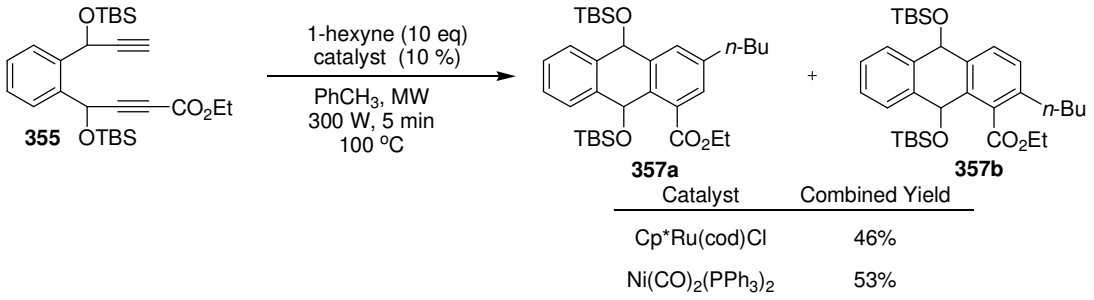
Scheme 4.34. Synthesis of the diynes **354** and **355**.

As expected, cyclotrimerization of the diester diyne **354** with 1-hexyne (10 eq) proceeded efficiently under $Ni(CO)_2(PPh_3)_2$ catalysis (10 mol%, $PhCH_3$, MW 300 W, 5 min, 100 °C) to give the anthracenediol derivative **356** in 75% yield, however, using the Cp*Ru(cod)Cl catalyst system led to product mixtures (Scheme 4.35).



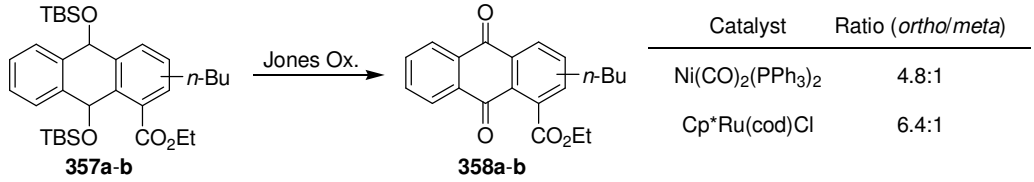
Scheme 4.35. Cyclotrimerization reaction of the diester diyne **354**.

Cyclotrimerization with the monoester diyne **355** was less efficient, though, providing the anthracenediol derivative in 46 and 53% yield under $Ni(CO)_2(PPh_3)_2$ and Cp*Ru(cod)Cl catalysis, respectively, as a mixture of the regioisomers **357a** and **357b** (Scheme 4.36). The inefficiency in the cyclotrimerization reaction of the diyne **355** can potentially be attributed to competitive dimerization of the starting material due to the presence of the terminal alkyne in the diyne; however, we do not have experimental evidence for this hypothesis.



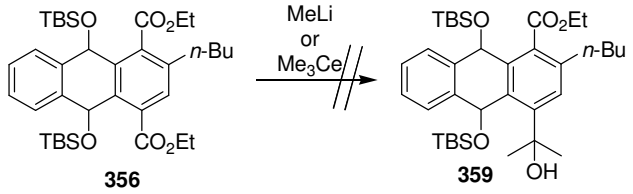
Scheme 4.36. Cyclotrimerization reaction of the monoester diyne **355**.

The regioisomer ratio was determined by first oxidizing the TBS-ethers to the anthraquinones (Jones reagent, acetone, 0 °C to rt) **358a** and **358b** and analyzing the mixture by GC/MS (Scheme 4.37). In conjunction with ^{1}H NMR analysis of the mixture, the predominant regioisomer, as expected, was the *meta*-regioisomer **358a** for both catalysts with ratios of 4.8:1 when using the Ni catalyst and 6.4:1 when using the Ru catalyst.



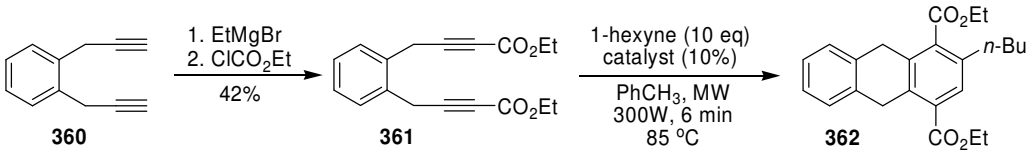
Scheme 4.37. Determination of the regioisomeric ratio of the cyclotrimerization products **357a** and **357b**.

Attempts to modify the ester groups in **356** did not yield the desired products. Treatment of **356** with excess methyllithium (THF, −78 °C to rt, 18 h) or methyllithium/$CeCl_3$ (THF, −78 °C to rt, 45 min) either produced complex product mixtures or no reaction took place (Scheme 4.38). While this result was expected for the more hindered ester group, we anticipated that the less hindered ester group would be accessible to the organometallic reagents to provide **359**.



Scheme 4.38. Attempted addition of organometallic reagents to the diester **356**.

In order to investigate whether the TBS-ether contributed to the lack of reactivity of the esters, substrates lacking this functionality were explored. By removing all functionality at the two methylene units, we hypothesized facile addition of organometallic reagents into the less hindered ester. Toward this end, dipropargyl benzene (**360**)[238] was synthesized according to known procedures and installation of the diester groups was accomplished upon treatment with excess EtMgBr (THF, rt) and ethylchloroformate to give the diester **361** in 42% yield (Scheme 4.39). An undetermined amount of the monoester **362** was also formed in this reaction. Attempts to optimize this reaction were unsuccessful with poor yields of **361** being obtained at various temperatures and with varying amounts of Grignard reagent.

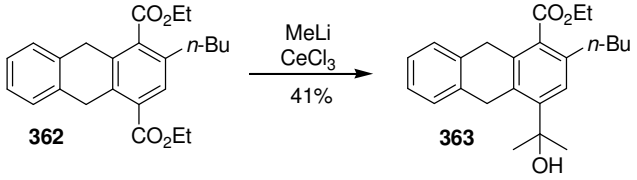


Catalyst	Yield (%)
Cp*Ru(cod)Cl	66
$Ni(CO)_2(PPh_3)_2$	71

Scheme 4.39. Synthesis and cyclotrimerization reaction of the diester **361**.

Cyclotrimerization of the diester diyne **361** proceeded under microwave irradiation with either Cp*Ru(cod)Cl or $Ni(CO)_2(PPh_3)_2$ as catalyst to furnish **362** in 66 and 71% yield, respectively. As before, the organometallic addition into the ester functionalities proved

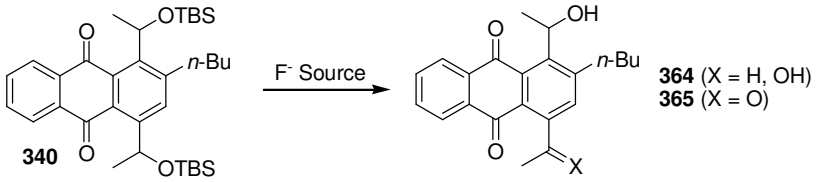
troublesome. Using the methylcerium reagent, the alcohol **363** could be obtained in 41% yield with ~30% contaminated with an unknown by-product (Scheme 4.40).



Scheme 4.40. Addition of methylcerium to the diester **362**.

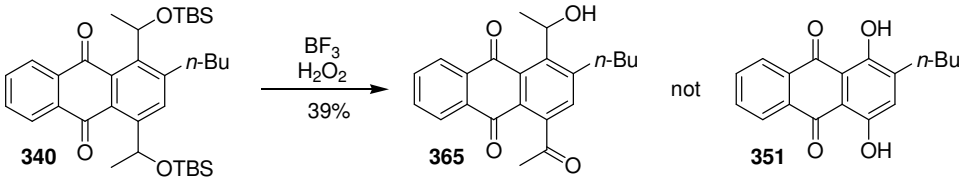
Attempts to rearrange the alcohol **363** under Lewis-acidic conditions ($BF_3{\cdot}Et_2O$, H_2O_2, DCM, 0 °C) gave impure phenol in low yields. A Baeyer-Villiger reaction for the conversion of **362** into the phenol has not been explored to date.

Recognizing the structural requirements for the rearrangement in anthraquinone **340**, investigations into its rearrangement were assessed. Initially, we wished to utilize the diol **364** in the rearrangement step; however, upon treatment of the anthraquinone **340** with TBAF (THF, 0 °C to rt, 2 h) or HF/pyridine (DCM, 0 °C, 4 h), the oxidized desilylated anthraquinone **365** (~20%) was obtained amongst other undetermined side products (Scheme 4.41).



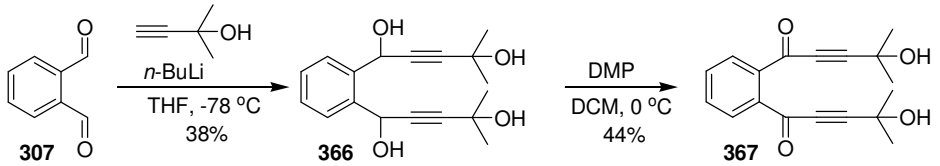
Scheme 4.41. Attempted desilylation of the anthraquinone **340**.

As TBS-ethers are labile under Lewis-acidic conditions,[161] we envisioned a one-pot desilylation/rearrangement from the anthraquinone **340** to the desired bisphenol **351**. However, the same oxidized anthraquinone **365** (39%) was obtained upon treatment with BF_3/H_2O_2 (Scheme 4.42).



Scheme 4.42. Attempted desilylation/rearrangement of the anthraquinone **340**.

In order to circumvent this oxidation side reaction, the diol **367** was synthesized via **366** with the hypothesis that, because it cannot undergo oxidation, rearrangement of its cyclotrimerization product would occur to give the desired dihydroxyanthraquinone **351** (Scheme 4.43). However, cyclotrimerization of the diyne **367** with 1-hexyne (15 eq) under $Ni(CO)_2(PPh_3)_2$ catalysis (20 mol%, $PhCH_3$, MW 50 °C, 20 min) was unsuccessful. No starting material was observed, however, ^1H NMR analysis of the crude reaction mixture provided no evidence of anthraquinone formation.



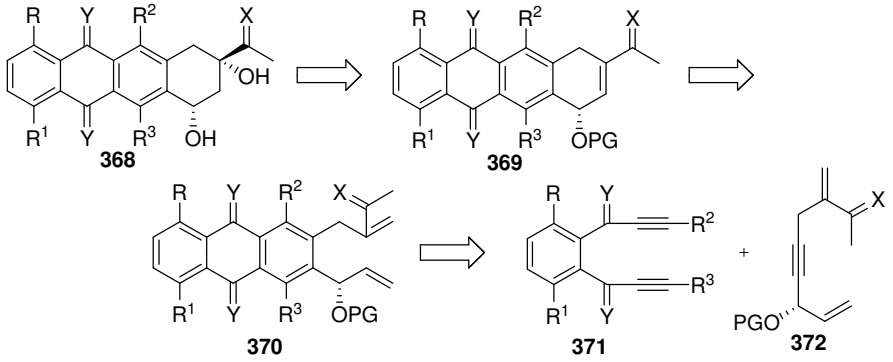
Scheme 4.43. Synthesis of the diol **367**.

Having fully explored multiple routes to install the phenol moieties with little success, further efforts in this direction were put on hold.

4.3 Towards the Synthesis of the Anthracycline Tetracyclic Core Structure

4.3.1 A [2+2+2] Cyclotrimerization/Ring Closing Metathesis Approach

As stated previously, the initial strategy towards the tetracyclic framework of the anthracyclinones featured a [2+2+2] cyclotrimerization followed by a ring closing metathesis (RCM) reaction. Considering the retrosynthetic analysis in Scheme 4.44, after removal of the tertiary hydroxyl function at C-9 of **368** to give the allylic alcohol **369**, the anthracyclinone ring A is disconnected to give the tricycle **370**. The fragments **371** and **372** would then result from a [2+2+2] cyclotrimerization disconnection.



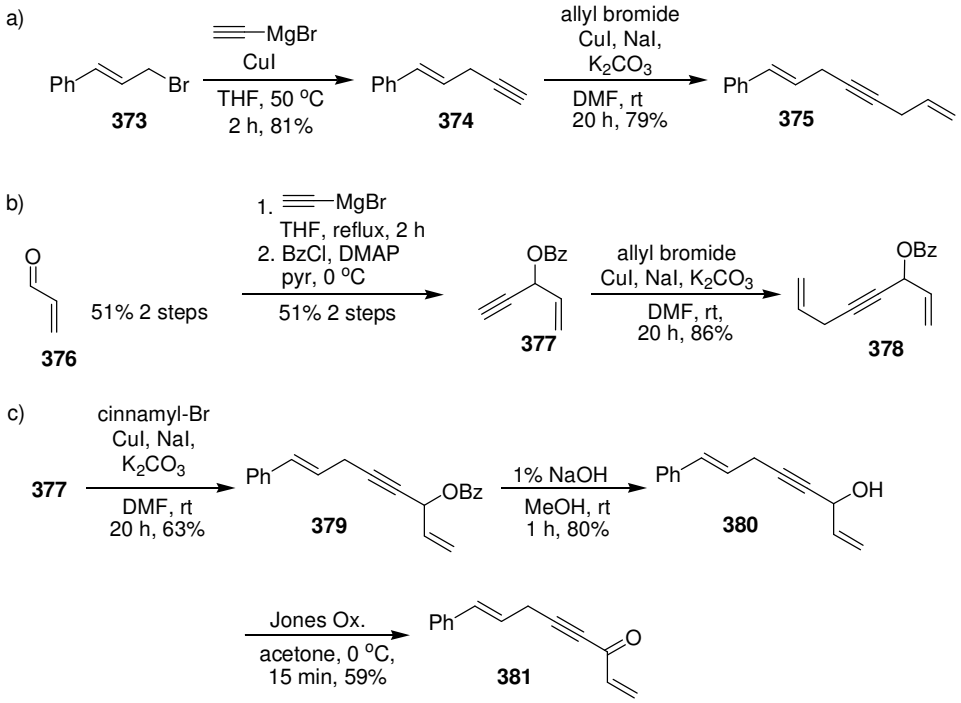
Scheme 4.44. [2+2+2] cyclotrimerization/RCM retrosynthetic analysis of the anthracyclinones. PG = protecting group.

Depending upon the anthracyclinone of interest, the monoyne would be appropriately substituted. Under ideal conditions, the cyclotrimerization catalyst would be added to promote the cyclotrimerization event, and then Grubbs' catalyst would be added to perform the ring closing metathesis. Theoretically, the two catalysts could be used at once as the ring closing event would only be possible after the [2+2+2] cyclotrimerization, or Grubbs' catalyst itself could catalyze both reactions. However, competitive cross metathesis of the monoyne would be one factor that would require attention. Going in the synthetic direction,

the allylic alcohol in **369** would be used as a synthetic handle to install the tertiary hydroxyl function at C-9 *via* a directed epoxidation and ring opening. A model study aimed at synthesizing the deoxygenated A-B-C-D ring system form was undertaken to assess the feasibility of this approach.

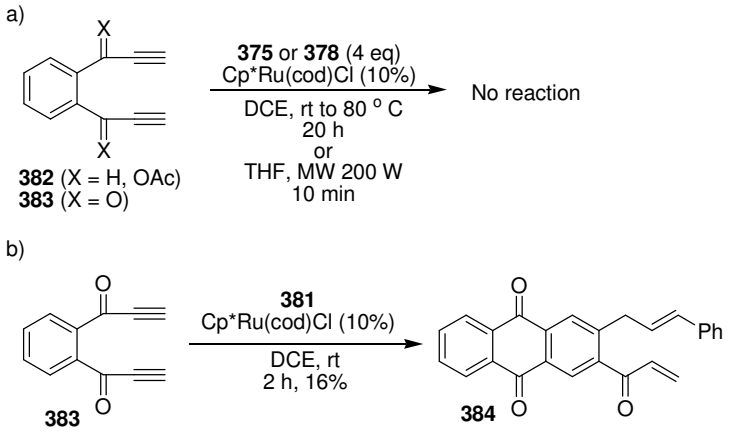
4.3.2 [2+2+2] Cyclotrimerization/RCM Model Study Towards the Anthracyclinone Core

The model study commenced with the synthesis of several monoynes **375**, **113**, and **116**, differing in substitution patterns at one of the propargylic sites (Scheme 4.45). The monoyne **375** was prepared in two steps from cinnamyl bromide (**373**) and the enyne **374**[239] via successive copper catalyzed sp-sp^3 coupling reactions and represents the simplest monoyne tested (Scheme 4.45a). The phenyl group serves a dual purpose in that it increases the molecular weight of the monoyne thereby increasing its boiling point, and it also regenerates Grubbs' catalyst during the RCM reaction. The monoyne **378**, substituted at one propargylic site with a benzoyl protected alcohol, was synthesized from acrolein (**376**) in three steps via **377** while the allyl propargyl ketone **381** was synthesized from **377** through the intermediates **379** and **380** via Jones oxidation of **380** (Scheme 4.45b and 4.45c). Other oxidation conditions (DMP, DCM, 0 °C, or PDC, DCM, rt) were slower and did not fully convert the starting material to product. The monoyne **378** would probe the steric tolerance of the cyclotrimerization event at the propargylic site. The ketone in monoyne **381** would demonstrate what effect, if any, the electronic nature of the monoyne has on the cyclotrimerization reaction.



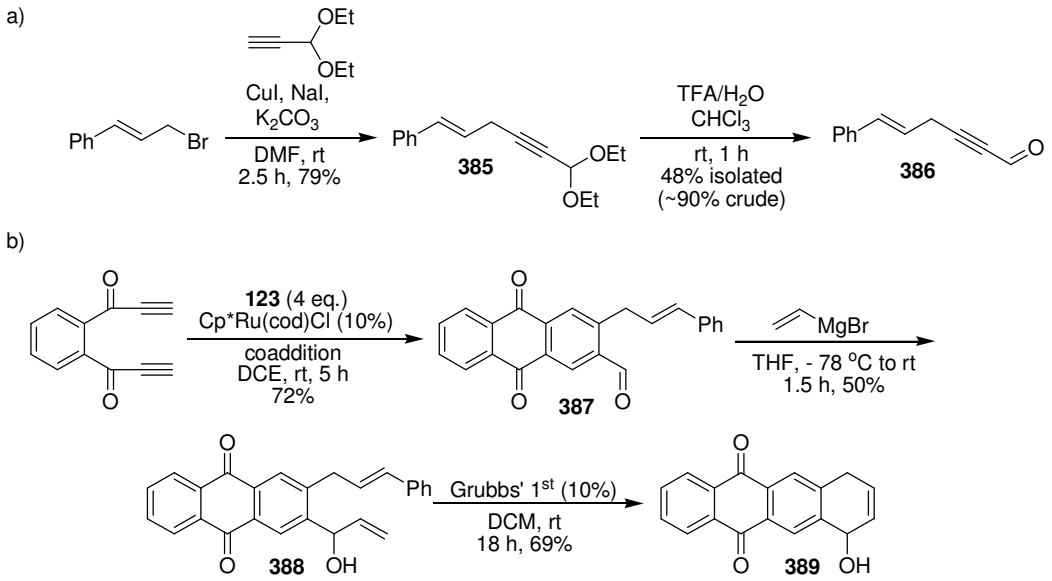
Scheme 4.45. Synthesis of monoynes for the [2+2+2] cyclotrimerization/RCM model study.

The cyclotrimerization reaction of each monoyne was tested with the diacetate **382**[233] and the diketone **383**[78] as diynes. The monoynes **375** and **378** did not undergo cyclotrimerization under Ru catalysis with oil bath heating or microwave irradiation, while the monoyne **378** cyclized in poor yield (16%) with the diketone **383** to give the anthraquinone **384** (Scheme 4.46a and 4.46b). Being internal monoynes, the reactivity is expected to be lower compared to terminal monoynes, but the fact that there was no reaction even with the monoyne **375** indicates other factors may be involved that impede the cyclotrimerization reaction. The ring closing metathesis of the anthraquinone **384** was not investigated.



Scheme 4.46. Cyclotrimerization reactions with the monoynes **375**, **378**, and **381**.

Due to the low yields in the cyclotrimerization event towards **384**, a three step procedure utilizing the aldehyde **386** was devised. The aldehyde **386** was synthesized in two steps from cinnamyl bromide by copper catalyzed sp-sp^3 coupling to give the acetal **385** followed by TFA deprotection (Scheme 4.47a). The crude aldehyde was used in the cyclotrimerization step as the yield was greatly reduced if purification by silica gel chromatography was attempted. In the cyclotrimerization event, the anthraquinone **387** was produced in up to 72% yield when the alkynes are added to the catalyst over 1.5 h. Diminished yields are obtained when the alkynes are added at a quicker rate or when the diyne is added to a mixture of the catalyst and the monoyne (Scheme 4.47b). The second olefin for the RCM reaction was installed *via* 1,2-addition of vinyl Grignard into the aldehyde **387** to give the secondary alcohol **388**. In more advanced substrates one could envision using an enantioselective Nozaki-Hiyama-Kishi[240] reaction to obtain control over the absolute stereochemistry.

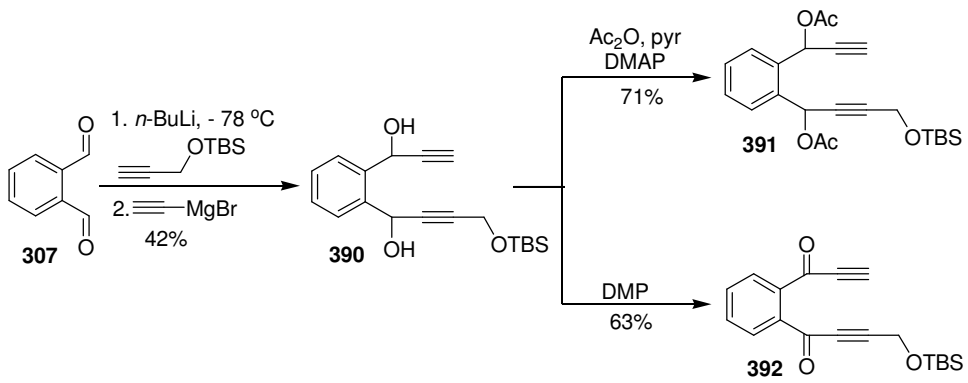


Scheme 4.47. [2+2+2] cyclotrimerization/RCM model study.

Ring closing metathesis proceeded smoothly with **388** at room temperature to give the tetracycle **389** in 69% yield. A cyclotrimerization attempt (15 mol% Cp*Ru(cod)Cl, DCE, rt, 20 h) of the monoyne **386** with the internal diyne **316** gave no reaction.

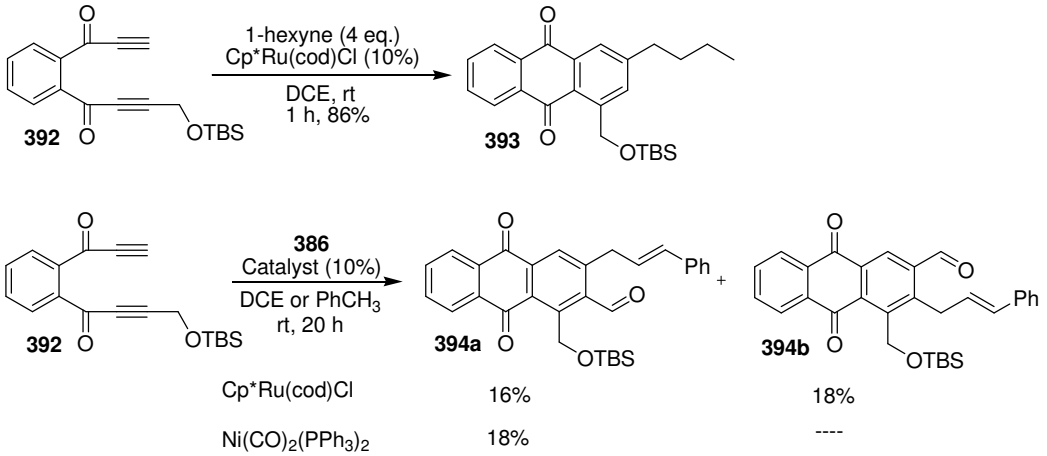
4.3.3 [2+2+2] Cyclotrimerization/RCM Model Study Towards the Pyrromycinone Core

Pyrromycinone (**256**, Figure 4.2) contains only one phenol group on the B ring, thereby potentially allowing improved results in the [2+2+2] cyclotrimerization step as only a penta-substituted benzene is being formed instead of a hexa-substituted benzene. Studies toward the core structure of pyrromycinone without the D ring phenols began with the non-symmetrical diyne **390** synthesized from *o*-phthalaldehyde via consecutive additions of the Li-acetylide of TBS-protected propargyl alcohol and ethynyl Grignard (Scheme 4.48).



Scheme 4.48. Synthesis of the diynes **391** and **392** for the pyrromycinone model study.

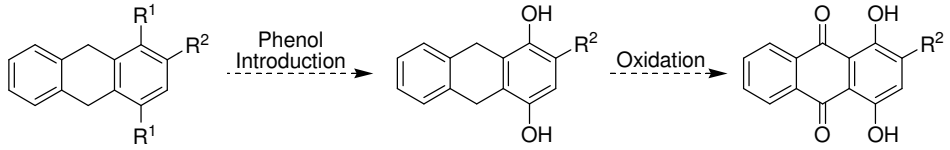
Acetylation (Ac_2O, DMAP, pyridine, 0 °C, 2 h) or oxidation (DMP, DCM, 0 °C, 1 h) gave the nonsymmetrical diacetate **391** or the diketone **392**, respectively. The reactivity of these diynes in the [2+2+2] cyclotrimerization was then investigated using 1-hexyne as the monoyne. A good yield was obtained with the diketone **392** with only one regioisomer (**393**) detected (Scheme 4.49), while no reaction was observed with the diacetate **391**. These results coincide with findings in the literature that electron-poor substrates are more reactive when using the Cp*Ru(cod)Cl catalyst. As in the model study above, the monoyne **386** was used as a reaction partner with the diketone **392** to give the anthraquinone derivatives **394a** and **394b** in 16 and 18% yield, respectively, under Ru catalysis. No starting material could be recovered. When $Ni(CO)_2(PPh_3)_2$ (10 mol%, $PhCH_3$, 80 °C, 1 h) is used as the catalyst, however, only an 18% yield of the regioisomer **394a** is obtained despite complete consumption of starting material (Scheme 4.49). Decomposition of the starting material accounted for the low yield. Further studies towards the ring closing metathesis or phenol introduction need to be performed.



Scheme 4.49. Cyclotrimerization reactions with the nonsymmetrical diyne **392**.

4.4 Summary and Future Directions

Work towards the synthesis of several 1,4-dihydroxyanthraquinone natural products as a proving ground for the cyclotrimerization approach to the anthracycline core structure has produced mixed results. The electronic and steric properties of the diyne and monoyne reaction partners have been examined in great detail in order to provide for an efficient cyclotrimerization reaction towards the anthraquinone structure, however the installation of the phenolic hydroxyl groups has impeded progress to the desired natural product structures. Potential access to the hydroxy-bearing anthraquinones may be possible utilizing 9,10-dihydroanthracene derivatives similar to **362** via a Baeyer-Villiger rearrangement or Curtius rearrangement of a suitably chosen R^1 group (Scheme 4.50). The previous Baeyer-Villiger route to the phenols was hindered by the electron deficient ring system of the anthraquinone. Alternatively, the Curtius rearrangement can be re-explored with **395** where the R^1 groups are carboxylic acids. Finally, oxidation of the 9,10-dihydroanthracene **396** to the anthraquinone **397** would provide the 1,4-dihydroxyanthraquinone natural products.

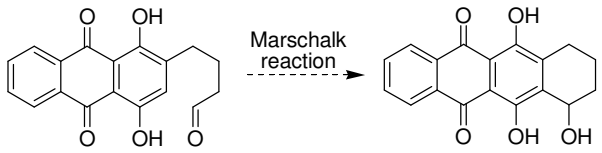


395 (R^1 = carbonyl, R^2 = alkyl) **396** **397**

Scheme 4.50. Potential future routes to the 1,4-dihydroxyanthraquinone natural products.

The [2+2+2] cyclotrimerization/RCM approach to the tetracyclic core structure of the anthracyclines has been shown to be feasible in a simple model system. However, future work towards further developing this tandem approach into a viable route to the anthracycline core structure depends on the ability to introduce the phenolic hydroxyl groups on the B ring. Once this hurdle is overcome, investigations into a suitable monoyne that will produce an efficient cyclotrimerization reaction to construct the A ring will be necessary.

Alternatively, the approach to the 1,4-dihydroxyanthraquinones can be taken a few steps further, and the A ring of the anthracyclines could be formed via a Marschalk reaction. If the R^2 group of **398** contains an aldehyde, a facile intramolecular Marschalk reaction can occur to provide the tetracyclic structure **399** (Scheme 4.51).



398 **399**

Scheme 4.51. Marschalk approach to the tetracyclic core of the anthracyclines.

4.5 Experimental

All reactions were performed in flame-dried glassware under a nitrogen atmosphere and stirred magnetically. Tetrahydrofuran, toluene, xylenes, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Diisopropylamine, triethylamine, DMSO, DCM, DMF, 1,2-dichloroethane, CH_3CN and pyridine were distilled from calcium hydride and stored over 4 Å molecular sieves. Other reagents and solvents obtained from commercial sources were stored under nitrogen and used directly without further purification. *n*-BuLi and MeLi were titrated against *N*-pivaloyl-*o*-toluidine.[108] Melting points were obtained from a Mel-Temp capillary melting point apparatus and are uncorrected. High resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz) or Varian Mercury 300 (300 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption (77.2) for ^{13}C NMR spectra. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer.

3-Ethoxy-1-[2-(3-ethoxy-1-hydroxyprop-2-ynyl)]-phenylprop-2-yn-1-ol (308). *n*-BuLi (895 μL, 1.12 mmol, 1.25 M in hexanes) was added dropwise to a solution of ethoxyacetylene (209 mg, 1.49 mmol, 50% in hexanes) in THF (400 μL) and the solution was stirred for 2 h at −78 °C. *o*-Phthalaldehyde (50 mg, 0.37 mmol) in THF (400 μL) was added and the solution stirred for 1 h. The reaction mixture was warmed to 0 °C, quenched with H_2O (4 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to

dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3:2) to give 40 mg (40%) of **308** as a mixture of diastereomers as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.60 (m, 2 H), 7.46-7.30 (m, 2 H), 6.13-5.95 (m, 2 H), 4.34-4.05 (m, 4 H), 3.28-2.88 (m, 2 H), 1.53-1.34 (m, 6 H).

3-Ethoxy-1-[2-(3-ethoxy-1-acetoxyprop-2-ynyl)]-phenylprop-2-ynyl acetate (309). To a solution of **308** (76 mg, 0.28 mmol) and DMAP (cat.) in pyridine (600 μL) was added acetic anhydride (260 μL) at 0 °C, and the solution was stirred for 2 h as it warmed to rt. The reaction was diluted with DCM (5 mL) and H_2O (5 mL), the layers were separated, and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3:1) to give 42 mg (42%) of **309** as a mixture of diastereomers as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.56 (m, 2 H), 7.43-7.31 (m, 2 H), 6.85-6.73 (m, 2 H), 4.25-4.04 (m, 4 H), 2.23-2.01 (m, 6 H), 1.48-1.30 (m, 6 H).

4,4-Diethoxy-1-[2-(4,4-diethoxy-1-acetoxybut-2-ynyl)]-phenylbut-2-ynyl acetate (312). To a solution of propargylaldehyde diethyl acetal (1.26 g, 9.8 mmol) in THF (8 mL) was added *n*-BuLi (5.6 mL, 8.9 mmol, 1.6 M in hexanes) dropwise, and the reaction was stirred at −78 °C for 1 h. *o*-Phthalaldehyde (400 mg, 3.0 mmol) was added in THF (4 mL). After 15 min, the reaction was warmed to 0 °C and was stirred for 45 min. Acetyl chloride (1.06 mL, 14.9 mmol) in THF (2 mL) was added dropwise, and the reaction was stirred for 2 h as it

warmed to rt. The reaction was quenched with H_2O (12 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3.5:1) to give 1.207 g (85%) of **312** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.59 (m, 2 H), 7.50-7.35 (m, 2 H), 6.86-6.75 (m, 2 H), 5.38-5.28 (m, 2 H), 3.85-3.49 (m, 8 H), 2.23-2.03 (m, 6 H), 138-1.15 (m, 12 H).

Phenyl-2-(4-acetoxybut-2-yn-1-al)-4-acetoxybut-2-yn-1-al (313). To a solution of **312** (73 mg, 0.15 mmol) in $CHCl_3$ (970 μL) was added H_2O (240 μL) and TFA (240 μL) and the reaction was stirred at 60 °C for 35 min. After cooling the reaction mixture to 0 °C, sat. $NaHCO_3$ (4 mL) was added and the aqueous solution was extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2.5:1) to give 33 mg (66%) of **313** as a mixture of diastereomers as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1 H), 9.24 (s, 1 H), 7.71-7.58 (m, 2 H), 7.55-7.44 (m, 2 H), 6.90 (s, 2 H), 2.19 (s, 3 H), 2.17 (s, 3 H).

4,4-Diethoxy-1-[2-(4,4-diethoxybut-2-yn-1-onyl)]-phenylbut-2-yn-one (314). To a solution of propargylaldehyde diethyl acetal (315 mg, 2.5 mmol) in THF (2 mL) was added *n*-BuLi (1.4 mL, 2.2 mmol, 1.6 M in hexanes) dropwise, and the reaction was stirred at −78 °C for 1 h. *o*-Phthalaldehyde (100 mg, 0.75 mmol) was added in THF (1 mL). After 15 min,

the reaction was warmed to 0 °C, stirred for 45 min, and quenched with H_2O (4 mL). The aqueous mixture was extracted with Et_2O (5 mL × 3), and the combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1) to give 153 mg (53%) of 4,4-diethoxy-1-[2-(4,4-diethoxy-1-hydroxybut-2-ynyl)]-phenylbut-2-yn-1-ol as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.60 (m, 2 H), 7.47-7.36 (m, 2 H), 6.13-5.94 (m, 2 H), 5.45-5.34 (m, 2 H), 3.94-3.53 (m, 8 H), 1.45-1.18 (m, 12 H). To a solution of 4,4-diethoxy-1-[2-(4,4-diethoxy-1-hydroxybut-2-ynyl)]-phenyl-but-2-yn-1-ol (89 mg, 0.23 mmol) in DCM (2 mL) at 0 °C was added DMP (230 mg, 0.55 mmol), and the reaction was stirred for 1 h at 0 °C. The reaction was quenched with sat. $NaHCO_3$ (3 mL) and was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 66 mg (75%) of **314** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.80 (m, 2 H), 7.71-7.61 (m, 2 H), 5.46 (s, 2 H), 3.89-3.59 (m, 8 H), 1.28 (t, J = 7.1 Hz, 12 H).

4-(*tert*-Butyldimethylsiloxy)-1-[2-(4-(*tert*-butyldimethylsiloxy)-1-hydroxybut-2-ynyl)]-phenylbut-2-yn-1-ol (315). To a solution of *tert*-butyldimethyl(prop-2-ynyloxy)silane[241] (733 mg, 4.3 mmol) in THF (1.2 mL) was added *n*-BuLi (2.8 mL, 3.9 mmol, 1.4 M in hexanes) dropwise, and the reaction stirred for 1.5 h at −78 °C. *o*-Phthalaldehyde (175 mg, 1.3 mmol) in THF (1.75 mL) was added, the reaction stirred for 15 min and was warmed to 0

°C. After 30 min, H_2O (6 mL) and the aqueous solution was extracted with Et_2O (8 mL × 3). The combined organic extracts were washed with H_2O (8 mL) and brine (8 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3:1) to give 513 mg (83%) of **315** as a mixture of diastereomers as a yellow oil. IR (NaCl, thin film, neat) 3357, 3071, 2952, 2931, 2895, 2859, 1930, 1634, 1464, 1364, 1256, 1131, 1085, 1002, 836, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.77 (m, 1 H), 7.71-7.61 (m, 1 H), 7.46-7.33 (m, 2 H), 6.10-5.92 (m, 2 H), 4.55-4.38 (m, 4 H), 1.05-0.88 (m, 18 H), 0.27-0.09 (m, 12 H).

4-(*tert*-Butyldimethylsiloxy)-1-[2-(4-(*tert*-butyldimethylsiloxy)-but-2-yn-1-onyl)]-phenylbut-2-yn-one (316). To a solution of **315** (831 mg, 1.8 mmol) in DCM (22 mL) at 0 °C was added DMP (1.84 g, 4.4 mmol), and the reaction was stirred for 70 min at 0 °C. The reaction was quenched with sat. $NaHCO_3$ (12 mL) and was extracted with Et_2O (15 mL × 3). The combined organic extracts were washed with H_2O (12 mL) and brine (12 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (9:1) to give 706 mg (89%) of **316** as an off white solid: Mp 62-64 °C; IR (NaCl, thin film, DCM) 2957, 2931, 2894, 2853, 2220, 1650, 1469, 1364, 1256, 1095, 836, 721; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.78 (m, 2 H), 7.68-7.58 (m, 2 H), 4.54 (s, 4 H), 0.93 (s, 18 H), 0.15 (s, 12 H).

4-(*tert*-Butyldimethylsiloxy)-1-[2-(1-acetoxy-4-(*tert*-butyldimethylsiloxy)but-2-ynyl)]-phenylbut-2-ynyl acetate (317). To a solution of **315** (30 mg, 0.063 mmol) and DMAP

(cat.) in pyridine (100 µL) was added acetic anhydride (50 µL) at 0 °C, and the solution was stirred for 2 h. The reaction was diluted with Et_2O (2 mL) and H_2O (2 mL), the layers separated, and the aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic extracts were washed with H_2O (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered and concentrated to dryness to give 30 mg (85%) of **317** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.60 (m, 2 H), 7.47-7.36 (m, 2 H), 6.82-6.72 (m, 2 H), 4.45-4.32 (m, 4 H), 2.22-2.05 (m, 6 H), 1.01-0.82 (m, 18 H), 0.20-0.02 (m, 12 H).

9,10-Diacetoxy-9,10-dihydro-1,4-diformyl-3-((*tert*-butyldimethylsilyloxy)methyl) anthracene (318). To a flame-dried microwave vial equipped with a stir bar was added **313** (15 mg, 0.046 mmol), *tert*-butyldimethyl(prop-2-ynyloxy)silane (47 mg, 0.46 mmol), Cp*Ru(cod)Cl (1.7 mg, 0.0046 mmol), and dry THF (2 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 5 min in a CEM Discover microwave synthesizer at 300 W under power mode. After cooling to room temperature, the reaction mixture was concentrated, and the residue was purified by silica gel chromatography, eluting with DCM/EtOAc (100:1) to give 6 mg (26%) of **318** as a mixture of diastereomers as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77-10.42 (m, 2 H), 8.32-8.12 (m, 1 H), 7.91-7.63 (m, 3 H), 7.53 (s, 1 H), 7.50-7.39 (m, 2 H), 5.17-4.80 (m, 2 H), 2.30-1.98 (m, 6 H), 1.13-0.88 (m, 9), 0.22-0.14 (m, 6 H).

9,10-Diacetoxy-9,10-dihydro-1,4-diformylanthracene (319). Degassed THF (6 mL) was added to **313** (21 mg, 0.64 mmol) and acetylene was bubbled into the solution for 25 min at 0 °C. Cp*Ru(cod)Cl (2.4 mg, 0.064 mmol) was added and the reaction was stirred at rt for 1.5 h. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1) to give 10 mg (44%) of **319** as a mixture of diastereomers as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.54 (s, 1 H), 10.48 (s, 1 H), 8.11 (s, 1 H), 8.01 (s, 1 H), 7.87-7.80 (m, 1 H), 7.78 (s, 1 H), 7.71 (s, 1 H), 7.64-7.57 (m, 1 H), 7.50-7.42 (m, 2 H), 2.17-2.00 (m, 6 H).

9,10-Diacetoxy-9,10-dihydro-1,4-bis((*tert*-butyldimethylsilyloxy)methyl)anthracene (320). Degassed THF (27 mL) was added to **317** (154 mg, 0.28 mmol) and acetylene was bubbled into the solution for 30 min at 0 °C. Cp*Ru(cod)Cl (15.6 mg, 0.041 mmol) was added and the reaction was stirred at rt overnight. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (12:1) to give 111 mg (69%) of **320** as a mixture of diastereomers as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.67 (m, 2 H), 7.56 (s, 2 H), 7.40-7.32 (m, 2 H), 7.22 (s, 2 H), 5.05-4.67 (m, 4 H), 2.06-1.99 (m, 6 H), 1.03-0.90 (m, 18 H), 0.23-0.06 (m, 12 H).

9,10-Diacetoxy-9,10-dihydro-1,4-bis((*tert*-butyldimethylsilyloxy)methyl)-2-butylanthracene (321). To a solution of **317** (15 mg, 0.027 mmol) and 1-hexyne (18.3 μL, 0.16 mmol) in THF (2 mL) was added Cp*Ru(cod)Cl (1 mg, 0.0025 mmol) and the reaction was stirred for 9 h. Additional 1-hexyne (18.3 μL, 0.16 mmol) and Cp*Ru(cod)Cl (1 mg,

0.0025 mmol) was added, and the reaction was stirred overnight. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1) to give 5.6 mg (33%) of **321** as a mixture of diastereomers as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.67 (m, 2 H), 7.48-7.30 (m, 4 H), 7.18 (s, 1 H), 5.03-4.68 (m, 4 H), 2.88-2.68 (m, 2 H), 2.13-1.95 (m, 6 H), 1.75-1.53 (m, 2 H), 1.52-1.36 (m, 2 H), 1.09-0.86 (m, 21 H), 0.34-0.07 (m, 12 H).

9,10-Diacetoxy-9,10-dihydro-1,4-bis((tert-butyldimethylsilyloxy)methyl)-2,3-bis(methoxymethyl)anthracene (322). To a solution of **317** (15 mg, 0.027 mmol) and 1,4-dimethoxybut-2-yne (19.5 μL, 0.16 mmol) in THF (2 mL) was added Cp*Ru(cod)Cl (1 mg, 0.0025 mmol), and the reaction was stirred for 9 h. Additional Cp*Ru(cod)Cl (1 mg, 0.0025 mmol) was added after 9 h (1 mg), and the reaction was stirred overnight. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1) to give 7.0 mg (39%) of **322** as a mixture of diastereomers as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.66 (m, 2 H), 7.43-7.30 (m, 4 H), 5.02-4.74 (m, 4 H), 4.67-4.58 (m, 4 H), 3.47 (s, 6 H), 1.99 (s, 6 H), 0.97 (s, 18 H), 0.27 (s, 6 H), 0.22 (s, 6 H).

1,4-Bis((*tert*-butyldimethylsilyloxy)methyl)-2-butylanthraquinone (323). To a solution of **316** (36 mg, 0.076 mmol) in degassed $PhCH_3$ (2.2 mL) was added 1-hexyne (132 μL, 1.15 mmol) and $Ni(PPh_3)_2(CO)_2$ (4.9 mg, 0.0076 mmol) and the reaction was irradiated in a CEM Discover microwave at 50 °C for 20 min using standard mode. The reaction was

concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 24 mg (57%) of **323** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.07 (m, 3 H), 7.80-7.66 (m, 2 H), 5.32 (s, 2 H), 5.27 (s, 2 H), 3.04-2.88 (m, 2 H), 1.82-1.61 (m, 2 H), 1.56-1.40 (m, 2 H), 1.14-0.87 (m, 21 H), 0.30-0.11 (m, 12 H).

1,4-Bis(hydroxymethyl)-2-butylanthraquinone (325). To a solution of **323** (134 mg, 0.24 mmol) in THF (1.5 mL) was added TBAF (1.45 mL, 1.45 mmol, 1 M in THF) at 0 °C, and the reaction was stirred for 2.5 h as it warmed to rt. The reaction was quenched with sat. NH_4Cl (5 mL) and extracted with EtOAc (7 mL × 3). The combined organic extracts were washed with H_2O (8 mL) and brine (8 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2.8:1) to give 72 mg (92%) of **325** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26-8.16 (m, 2 H), 7.85-7.76 (m, 2 H), 7.72 (s, 1 H), 4.98 (d, *J* = 7.3 Hz, 2 H), 4.82 (d, *J* = 7.9 Hz, 2 H), 4.16 (t, *J* = 7.9 Hz, 1 H), 3.79 (t, *J* = 7.3 Hz, 1 H), 3.01-2.89 (m, 2 H), 1.77-1.61 (m, 2 H), 1.56-1.41 (m, 2 H), 1.01 (t, *J* = 7.3 Hz, 3 H).

2-Butyl-1,4-diformylanthraquinone (327). A solution of **325** (5 mg, 0.015 mmol) and PCC (13 mg, 0.061 mmol) in DCM (500 μL) was irradiated in a CEM Discover microwave synthesizer (power mode) for 2 min at 200 W. The reaction was diluted with DCM (2 mL) filtered through a plug of celite on top of a plug of silica gel, concentrated to dryness and purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 4.3 mg (88%) of **327** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ **327**: 10.76 (s, 1 H), 10.56 (s, 1

H), 8.36-8.22 (m, 2 H), 7.96 (s, 1 H), 7.94-7.83 (m, 2 H), 2.90-2.74 (m, 2 H), 1.73-1.54 (m, 2 H), 1.51-1.32 (m, 2 H), 0.97 (t, *J* = 7.2 Hz, 3 H); **328**: 10.59 (s, 1 H), 8.32-8.19 (m, 2 H), 7.91-7.81 (m, 3 H), 4.91 (d, *J* = 8.0 Hz, 2 H), 4.13 (t, *J* = 8.0 Hz, 1 H), 3.04-2.91 (m, 2 H), 1.77-1.61 (m, 2 H), 1.56-1.40 (m, 2 H), 1.01 (t, *J* = 7.2 Hz, 3 H).

4-(*tert*-Butyldimethylsiloxy)-1-[2-(4-(*tert*-butyldimethylsiloxy)-1-hydroxypent-2-ynyl)]-phenylpent-2-yn-1-ol (336). To a solution of *tert*-butyl(but-3-yn-2-yloxy)dimethylsilane[242] (600 mg, 3.3 mmol) in THF (1.5 mL) was added *n*-BuLi (1.3 mL, 2.6 mmol, 2.0 M in hexanes) dropwise, and the reaction was stirred 1 h at −78 °C. *o*-Phthalaldehyde (125 mg, 0.93 mmol) in THF (1.5 mL) was added, the reaction was stirred for 15 min and was warmed to rt. After 60 min, H_2O (5 mL) was added and the aqueous solution was extracted with Et_2O (6 mL × 3). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4.5:1) to give 330 mg (70%) of **336** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.77 (m, 1.5 H), 7.70-7.59 (m, 0.5 H), 7.45-7.31 (m, 2 H), 6.07-5.89 (m, 2 H), 4.73-4.57 (m, 2 H), 1.52-1.47 (m, 6 H), 0.96-0.90 (m, 18 H), 0.18-0.12 (m, 12 H).

4-(*tert*-Butyldimethylsiloxy)-1-[2-(4-(*tert*-butyldimethylsiloxy)-1-acetoxypent-2-ynyl)]-phenylpent-2-ynyl acetate (337). To a solution of **336** (100 mg, 0.20 mmol) and DMAP (cat.) in pyridine (240 μL) was added acetic anhydride (190 μL) at 0 °C, and the solution was stirred for 2.5 h. The reaction was diluted with Et_2O (5 mL) and H_2O (5 mL), the layers

separated, and the aqueous layer extracted with Et_2O (5 mL × 2). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness to give 104 mg (89%) of **337** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.59 (m, 2 H), 7.45-7.34 (m, 2 H), 6.80-6.69 (m, 2 H), 4.65-4.50 (m, 2 H), 2.16-2.03 (m, 6 H), 1.47-1.33 (m, 6 H), 0.94-0.81 (m, 18 H), 0.14-0.01 (m, 12 H).

4-(*tert*-Butyldimethylsiloxy)-1-[2-(4-(*tert*-butyldimethylsiloxy)pent-2-yn-1-onyl)]-phenylpent-2-yn-one (338). To a solution of **336** (100 mg, 0.20 mmol) in DCM (2 mL) at 0 °C was added DMP (211 mg, 0.50 mmol), and the reaction was stirred for 70 min at 0 °C. The reaction was quenched with sat. $NaHCO_3$ (4 mL) and extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with H_2O (4 mL) and brine (4 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (11:1) to give 76 mg (77%) of **338** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.76 (m, 2 H), 7.66-7.57 (m, 2 H), 4.72 (q, J = 6.6 Hz, 2 H), 1.52 (d, J = 6.6 Hz, 6 H), 0.92 (s, 18 H), 0.14 (s, 12 H).

1-[2-(1-Acetoxypent-2-yn-4-onyl)]-phenylpent-2-yn-1-ol-4-one acetate (339). To a solution of **337** (215 mg, 0.37 mmol) in acetone (5.4 mL) was added Jones reagent (1.3 mL) at 0 °C, and the reaction was stirred for 35 min. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc (15 mL × 3). The combined organic extracts were washed with sat. $NaHCO_3$ (12 mL) H_2O (12 mL) and brine (12 mL), dried ($MgSO_4$), filtered and concentrated

to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1) to give 98 mg (76%) of **339** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.57 (m, 2 H), 7.53-7.42 (m, 2 H), 6.87 (s, 2 H), 2.44-2.36 (m, 6 H), 2.23-2.13 (m, 6 H).

1,4-Bis(1-(*tert*-butyldimethylsilyloxy)ethyl)-2-butylanthraquinone (340). To a solution of **338** (59 mg, 0.12 mmol) in degassed $PhCH_3$ (3.5 mL) was added 1-hexyne (200 µL, 1.18 mmol) and $Ni(PPh_3)_2(CO)_2$ (15.2 mg, 0.012 mmol), and the reaction was irradiated in a CEM Discover microwave at 50 °C for 20 min using standard mode. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 51 mg (75%) of **340** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.01 (m, 3 H), 7.80-7.68 (m, 2 H), 6.22-5.70 (m, 2 H), 3.47-2.86 (m, 2 H), 1.88-1.38 (m, 10 H), 1.10-0.66 (m, 21 H), 0.16-–0.32 (m, 12 H).

1,4-Bis(ethanonyl)-2-butylanthraquinone (341). To a solution of **340** (10 mg, 0.017 mmol) in acetone (500 µL) was added Jones reagent (200 µL) at 0 °C, and the reaction was stirred for 60 min. The reaction was diluted with H_2O (2 mL) and extracted with EtOAc (3 mL × 3). The combined organic extracts were washed with sat. $NaHCO_3$ (2 mL) H_2O (2 mL × 2) and brine (2 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 5.1 mg (85%) of **341** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29-8.20 (m, 2 H), 7.87-7.80 (m, 2 H), 7.42 (s, 1 H), 2.70-2.59 (m, 8 H), 1.80-1.55 (m, 2 H), 1.51-1.39 (m, 2 H), 0.97 (t, J = 7.2 Hz, 3 H).

1,4-Bis(ethanonyl)-2-butyl-9,10-dihydro-9,10-diacetoxyanthracene (342). To a solution of **339** (12 mg, 0.034 mmol) in $PhCH_3$ (1.1 mL) was added 1-hexyne (39 μL, 0.34 mmol) and Cp*Ru(cod)Cl (2.6 mg, 0.007 mmol), and the reaction was irradiated in a CEM Discover microwave at 300 W for 5 min using power mode. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1) to give 10.1 mg (68%) of **342** as a mixture of diastereomers as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.65 (m, 2 H), 7.54 (s, 1 H), 7.42-7.32 (m, 2 H), 7.24 (s, 1 H), 6.82 (s, 1 H), 2.73-2.52 (m, 8 H), 2.04 (s, 6 H), 1.71-1.55 (m, 2 H), 1.50-1.33 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H).

1-[2-(1-Acetoxy-3-iodoprop-2-ynyl)phenyl]-3-iodoprop-2-ynyl acetate (346). To a solution of **382** (50 mg, 0.18 mmol) in DMF (1.2 mL) was added NIS (97 mg, 0.43 mmol) and $AgNO_3$ (3 mg, 0.018 mmol), and the reaction was stirred for 105 min in the dark. H_2O (3 mL) was added, and the solution was extracted with EtOAc (4 mL × 3). The combined organic extracts were washed with H_2O (4 mL × 2) and brine (4 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3:1) to give 88 mg (91%) of **346** as a mixture of diastereomers as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.56 (m, 2 H), 7.49-7.38 (m, 2 H), 6.87-6.80 (m, 2 H), 2.21-2.09 (m, 6 H).

1-[2-(3-Iodoprop-2-yn- 1-onyl)phenyl]-3-iodoprop-2-yn-1-one (327). To a solution of **345** (50 mg, 0.27 mmol) in DMF (1.8 mL) was added NIS (141 mg, 0.63 mmol) and $AgNO_3$ (4.5 mg, 0.027 mmol), and the reaction was stirred for 85 min in the dark. H_2O (4 mL) was added, and the solution was extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with H_2O (5 mL × 2) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1) to give 75 mg (63%) of 1-[2-(1-hydroxy-3-iodo-prop-2-ynyl)-phenyl]-3-iodo-prop-2-yn-1-ol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.71 (m, 1 H), 7.67-7.57 (m, 1 H), 7.48-7.34 (m, 2 H), 6.17-5.95 (m, 2 H). To a solution of 1-[2-(1-hydroxy-3-iodo-prop-2-ynyl)-phenyl]-3-iodo-prop-2-yn-1-ol (16 mg, 0.037 mmol) in acetone (300 µL) was added Jones reagent (50 µL) at 0 °C, and the reaction stirred for 30 min. The reaction was diluted with sat. $NaHCO_3$ (1 mL) and extracted with EtOAc (2 mL × 3). The combined organic extracts were washed with sat. $NaHCO_3$ (2 mL) H_2O (2 mL × 2) and brine (2 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3:1) to give 12.3 mg (78%) of **327** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.79 (m, 2 H), 7.72-7.60 (m, 2 H).

2-Butyl-1,4-diiodo-9,10-dihydro-9,10-diacetoxyanthracene (348). To a solution of **346** (10 mg, 0.019 mmol) in DCE (750 µL) was added 1-hexyne (11 µL, 0.096 mmol) and Cp*Ru(cod)Cl (1 mg, 0.0029 mmol), and the reaction was irradiated in a CEM Discover microwave at 300 W for 25 min using power mode. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (9:1)

to give 2.6 mg (23%) of **348** as a mixture of diastereomers as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.82 (m, 2 H), 7.79 (s, 1 H), 7.47-7.34 (m, 2 H), 7.23-7.17 (m, 1 H), 7.07-6.99 (m, 1 H), 2.87-2.70 (m, 2 H), 2.11-2.00 (m, 6 H), 1.69-1.38 (m, 4 H), 1.05-0.94 (m, 3 H).

2-Butyl-1,4-dicarboxyanthraquinone (333). To a solution of **323** (156 mg, 0.28 mmol) in acetone (5 mL) was added Jones reagent (1.2 mL) at 0 °C, and the reaction was stirred for 1.5 h. The reaction was poured into cold H_2O (6 mL) and extracted with DCM (5 mL × 3). The combined organic extracts were concentrated to dryness to give 99 mg (100%) of **333** as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19-8.08 (m, 2 H), 7.99-7.88 (m, 2 H), 7.78 (s, 1 H), 2.80-2.64 (m, 2 H), 1.68-1.52 (m, 2 H), 1.43-1.27 (m, 2 H), 0.90 (t, J = 7.2 Hz, 3 H).

1-(*tert*-Butyldimethylsiloxy)-1-[2-(1-(*tert*-butyldimethylsiloxy)prop-2-ynyl)]-phenylprop-2-yne (353). To a solution of TBDMSCl (763 mg, 5.1 mmol) and imidazole (574 mg, 8.4 mmol) in DMF (4.5 mL) was added **345** (314 mg, 1.7 mmol) in DMF (1.4 mL), and the reaction was stirred for 2 h. H_2O (15 mL) and Et_2O (15 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (15 mL × 2), and the combined organic extracts were washed with H_2O (10 mL × 2) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (50:1) to give 649 mg (93%) of **353** as a mixture of

diastereomers as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.58 (m, 2 H), 7.39-7.30 (m, 2 H), 5.94-5.85 (m, 2 H), 2.56-2.49 (m, 2 H), 1.03-0.89 (m, 18 H), 0.25-0.11 (m, 12 H).

1-(*tert*-Butyldimethylsiloxy)-1-[2-(1-(*tert*-butyldimethylsiloxy)-3-ethoxycarbonylprop-2-ynyl)]-phenyl-3-ethoxycarbonylprop-2-yne (354). To a solution of **353** (204 mg, 0.49 mmol) in THF (6 mL) was added *n*-BuLi (470 μL, 1.1 mmol, 2.4 M in hexanes) dropwise at −78 °C, and the reaction was stirred for 1.5 h. Ethyl chloroformate (118 μL, 1.2 mmol) was added at once, and the reaction was stirred for 10 min and warmed to rt. After 30 min, sat. NH_4Cl (5 mL) was added and the aqueous solution was extracted with Et_2O (8 mL × 3). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (25:1) to give 152 mg (55%) of **354** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.65 (m, 0.5 H), 7.62-7.51 (m, 1.5 H), 7.42-7.32 (m, 2 H), 6.01-5.88 (m, 2 H), 4.20 (q, J = 7.1 Hz, 4 H), 1.28 (t, J = 7.1 Hz, 6 H), 1.01-0.89 (m, 18 H), 0.23 (s, 6 H), 0.15 (s, 6 H).

1-*tert*-Butyldimethylsiloxy-1-[2-(1-(*tert*-butyldimethylsiloxy)prop-2-ynyl)]-phenyl-3-ethoxycarbonylprop-2-yne (355). To a solution of **353** (300 mg, 0.72 mmol) in THF (8 mL) was added *n*-BuLi (270 μL, 0.65 mmol, 2.4 M in hexanes) dropwise at −78 °C, and the reaction was stirred for 1.5 h. Ethyl chloroformate (77 μL, 0.80 mmol) was added at once, and the reaction was stirred for 30 min and warmed to rt. After 90 min, sat. NH_4Cl (8 mL) is added and the aqueous solution extracted with Et_2O (12 mL × 3). The combined organic

extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (30:1) to give 86 mg (24%) of **355** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.62 (m, 1.2 H), 7.57-7.48 (m, 0.8 H), 7.41-7.29 (m, 2 H), 6.16-6.06 (m, 1 H), 5.83-5.70 (m, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 2.55 (d, *J* = 2.3 Hz, 1 H), 1.33-1.23 (m, 3 H), 1.03-0.87 (m, 18 H), 0.28-0.10 (m, 12 H).

2-Butyl-1,4-bis(ethoxycarbonyl)-9,10-dihydro-9,10-bis(*tert*-butyldimethylsilyloxy)-anthracene (356). To a solution of **354** (11 mg, 0.020 mmol) in $PhCH_3$ (650 μL) was added 1-hexyne (22 μL, 0.20 mmol) and $Ni(PPh_3)_2(CO)_2$ (1.2 mg, 0.002 mmol), and the reaction was irradiated in a CEM Discover microwave at 300 W for 5 min using power mode. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (30:1) to give 9.4 mg (75%) of **356** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.27 (m, 5 H), 6.84-6.71 (m, 1 H), 5.96 (s, 1 H), 4.66-4.21 (m, 4 H), 2.84-2.48 (m, 2 H), 1.68-1.51 (m, 2 H), 1.49-1.30 (m, 8 H), 1.00-0.68 (m, 21 H), 0.34-–0.28 (m, 12 H).

2-Butyl-4-(ethoxycarbonyl)-9,10-dihydro-9,10-bis(tert-butyldimethylsilyloxy)anthracene (357a) and **2-Butyl-1-(ethoxycarbonyl)-9,10-dihydro-9,10-bis(tert-butyldimethylsilyloxy)anthracene (357b).** To a solution of **355** (10 mg, 0.021 mmol) in $PhCH_3$ (650 μL) was added 1-hexyne (24 μL, 0.21 mmol) and Cp*Ru(cod)Cl (0.8 mg, 0.002 mmol), and the reaction was irradiated in a CEM Discover microwave at 300 W

for 5 min using power mode. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (45:1) to give 6.2 mg (53%) of **357a** and **357b** as a mixture of diastereomers.

1-[2(-3-ethoxycarbonylprop-2-ynyl)]-phenyl-3-ethoxycarbonylprop-2-yne (361). To a solution of **360** (25 mg, 0.16 mmol) in THF (3.2 mL) was added EtMgBr (208 µL, 0.65 mmol, 40% in Et_2O), at rt. After stirring 1 hr. ethylchloroformate (77 µL, 0.81 mmol) was added, and the reaction was stirred for 2 h. The reaction was quenched with sat. NH_4Cl (2 mL) and extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (4 mL) and brine (4 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (9:1) to give 20.2 mg (42%) of **361** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.37 (m, 2 H), 7.34-7.27 (m, 2 H), 4.24 (q, *J* = 7.1 Hz, 4 H), 3.77 (s, 4 H), 1.32 (t, *J* = 7.1 Hz, 6 H).

2-Butyl-1,4-bis(ethoxycarbonyl)-9,10-dihydroanthracene (362). To a solution of **361** (12.2 mg, 0.041 mmol) in $PhCH_3$ (1.4 mL) was added 1-hexyne (47 µL, 0.41 mmol) and $Ni(PPh_3)_2(CO)_2$ (2.6 mg, 0.004 mmol) and the reaction was irradiated in a CEM Discover microwave at 300 W for 6 min using power mode. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (35:1) to give 11 mg (71%) of **362** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 7.36-7.28 (m, 1 H), 7.26-7.17 (m, 3 H), 4.56-4.38 (m, 4 H), 4.33 (s, 1 H), 3.90 (s, 1 H), 2.67-2.57 (m, 2 H), 1.68-1.53 (m, 2 H), 1.51-1.31 (m, 8 H), 0.94 (t, *J* = 7.3 Hz, 3 H)); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 169.6, 167.8, 137.1, 136.3, 136.2, 135.9, 135.5, 135.1, 130.4, 129.0, 127.7, 127.3, 126.6, 126.4, 61.5, 61.3, 34.0, 33.6, 33.3, 22.8, 14.5, 14.0.

2-Butyl-1-ethoxycarbonyl-4-(hydroxy-*iso*-propyl)-9,10-dihydroanthracene (363). $CeCl_3$ (43 mg, 0.17 mmol) was dried overnight *in vacuo* at 140 °C. While the flask was hot, nitrogen was introduced, and the flask was cooled to 0 °C. THF (600 μL) was added at once, the ice bath removed, and the suspension was stirred vigorously for 3 h at rt. The flask was cooled to −78 °C, and MeLi (108 μL, 0.17 mmol, 1.6 M in Et_2O) was added dropwise. After stirring for 1 h at −78 °C, **362** (11 mg, 0.029 mmol) in THF (300 μL) was added over 5 min. After 10 min MeLi (108 μL, 0.17 mmol, 1.6 M in Et_2O) was added, and after 5 min the reaction was quenched at −78 °C with sat. NH_4Cl (2 mL) and allowed to warm to room temperature. EtOAc (3 mL) and water (2 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 mL × 2), and the combined organic extracts were washed with H_2O (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1) to give 4.3 mg (41%) of **363** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.30 (m, 1 H), 7.29-7.1 (m, 4 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 4.29 (s, 2 H), 3.84 (s, 2 H), 2.64-2.55 (m, 2 H), 1.73 (s, 6 H), 1.65-1.30 (m, 7 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

2-Butyl-1-(1-hydroxyethyl)-4-(ethanonyl)anthraquinone (365). $BF_3{\cdot}Et_2O$ (59 μL, 0.46 mmol) was added to H_2O_2 (50%, 7 μL, 0.10 mmol) and was stirred for 45 min at 0 °C. This solution was added to **340** (15 mg, 0.026 mmol) in dichloromethane (850 μL) at 0 °C. After

stirring for 10 min at 0 °C, H_2O (2 mL) and EtOAc (2 mL) were added and the layers separated. The aqueous layer was extracted with EtOAc (2 mL × 2), and the combined organic extracts were washed with water (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 3.5 mg (39%) of **365** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28-8.17 (m, 2 H), 8.02 (s, 1 H), 7.87-7.74 (m, 2 H), 5.80 (q, *J* = 6.5 Hz, 1 H), 2.71-2.56 (m, 5 H), 1.70-1.57 (m, 5 H), 1.51-1.34 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

4-Hydroxy-4-methyl-1-[2-(4-hydroxy-4-methyl-1-hydroxypent-2-ynyl)]-phenylpent-2-yn-1-ol (366). To a solution of 2-methylbut-3-yn-2-ol (188 mg, 2.2 mmol) in THF (18 mL) was added *n*-BuLi (1.9 mL, 4.6 mmol, 2.5 M in hexanes) dropwise, and the reaction was stirred for 2 h at −78 °C. *o*-Phthalaldehyde (100 mg, 0.75 mmol) in THF (2 mL) was added, the reaction was stirred for 1 h, warmed to rt, and was stirred overnight. Sat. NH_4Cl (10 mL) was added and the aqueous solution was extracted with EtOAc (15 mL × 3). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2.5:1) to give 86 mg (38%) of **366** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of stereoisomers) δ 7.77-7.70 (m, 1.2 H), 7.64-7.57 (m, 0.8 H), 7.43-7.34 (m, 2 H), 6.01 (s, 0.8 H), 5.90 (s, 1.2 H), 4.62 (br s, 0.5 H), 4.03 (br s, 1 H), 3.29 (br s, 0.5 H), 3.12 (br s, 1 H), 1.61-1.50 (m, 12 H).

4-Hydroxy-4-methyl-1-[2-(4-hydroxy-4-methylpent-2-yn-1-onyl)]-phenylpent-2-yn-1-one (367). To a solution of **366** (30 mg, 0.099 mmol) in DCM (1.1 mL) at 0 °C was added DMP (105 mg, 0.25 mmol), and the reaction was stirred for 75 min at 0 °C. The reaction was quenched with sat. $NaHCO_3$ (2 mL) and extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with H_2O (4 mL) and brine (4 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:1) to give 12.9 mg (44%) of **367** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.75 (m, 2 H), 7.64-7.58 (m, 2 H), 1.60 (s, 12 H).

1-((*E*)-Octa-1,7-dien-4-ynyl)benzene (375). Allyl bromide (530 µL, 6.2 mmol) was added to a solution of 1-((*E*)-pent-1-en-4-ynyl)benzene[239] (175 mg, 1.2 mmol), CuI (235 mg, 1.2 mmol), NaI (91 mg, 0.61 mmol), and K_2CO_3 (340 mg, 2.5 mmol) in DMF (4.9 mL), and the reaction was stirred overnight at rt. The reaction was diluted with Et_2O (40 mL), filtered over celite, washed with H_2O (15 mL × 2) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The crude mixture was submitted to the same conditions and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 176 mg (79%) of **375** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.16 (m, 5 H), 6.66 (dt, *J* = 1.7 and 15.5 Hz, 1 H), 6.20 (dt, *J* = 5.6 and 15.5 Hz, 1 H), 5.96-5.79 (m, 1 H), 5.37 (ddd, *J* = 1.7, 3.5 and 16.9 Hz, 1 H), 5.14 (ddd, *J* = 1.7, 3.4 and 9.9 Hz, 1 H), 3.25-3.14 (m, 2 H), 3.10-3.00 (m, 2 H).

Pent-4-en-1-yn-3-yl benzoate (377). Freshly distilled acrolein (500 mg, 8.9 mmol) was added to a solution of ethynyl Grignard (22.3 mL, 11.1 mmol, 0.5 M in THF), and the reaction was refluxed for 2 h. After cooling, sat. NH_4Cl (25 mL) was added and the mixture was extracted with Et_2O (25 mL × 3). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$) and filtered. The Et_2O was removed by distillation and the crude alcohol was dissolved in pyridine (8 mL). DMAP (cat.) and benzoyl chloride (5.2 mL, 44.8 mmol) were added at 0 °C, and the reaction was stirred for 1 h. H_2O (30 mL) was added and the aqueous mixture was extracted with Et_2O (30 mL × 3). The combined organic extracts were washed with sat. $NaHCO_3$ (30 mL), H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1) to give 854 mg (51%) of **377** as a colorless oil. IR (NaCl, thin film, neat) 3295, 3092, 3066, 3035, 2988, 2921, 2127, 1971, 1915, 1723, 1650, 1604, 1453, 1261, 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16-8.03 (m, 3 H), 7.64-7.54 (m, 1 H), 7.52-7.40 (m, 2 H), 6.17-6.13 (m, 1 H), 6.11-5.99 (m, 1 H), 5.69 (dt, *J* = 1.0 and 16.8 Hz, 1 H), 5.42 (dt, *J* = 1.0 and 10.0 Hz, 1 H), 2.65 (d, *J* = 2.2 Hz, 1 H).

Octa-1,7-dien-4-yn-3-yl benzoate (378). Allyl bromide (495 µL, 5.7 mmol) was added to a solution of **377** (150 mg, 0.81 mmol), CuI (150 mg, 0.81 mmol), NaI (60 mg, 0.4 mmol), and K_2CO_3 (218 mg, 1.62 mmol) in DMF (3 mL), and the reaction was stirred overnight. H_2O (20 mL) and Et_2O (20 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (20 mL × 2), and the combined organic extracts were washed with H_2O (15 mL × 2) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The

residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (16:1) to give 154 mg (86%) of **378** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18-8.02 (m, 2 H), 7.64-7.53 (m, 1 H), 7.53-7.39 (m, 2 H), 6.25-6.13 (m, 1 H), 6.13-5.98 (m, 1 H), 5.93-5.75 (m, 1 H), 5.63 (dt, *J* = 1.2 and 16.9 Hz, 1 H), 5.44-5.29 (m, 2 H), 5.15 (ddd, *J* = 1.7, 3.3 and 10.0 Hz, 1 H), 3.13-3.00 (m, 2 H).

(*E*)-8-Phenylocta-1,7-dien-4-yn-3-yl benzoate (379). Cinnamyl bromide (212 mg, 1.1 mmol) was added to a solution of **377** (400 mg, 2.2 mmol), CuI (204 mg, 1.1 mmol), NaI (81 mg, 0.55 mmol), and K_2CO_3 (372 mg, 2.7 mmol) in DMF (2.1 mL), and the reaction was stirred overnight at rt. The reaction was diluted with Et_2O (30 mL), filtered over celite, washed with H_2O (15 mL × 2) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (14:1) to give 206 mg (63%) of **379** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.07 (m, 2 H), 7.63-7.53 (m, 1 H), 7.51-7.41 (m, 2 H), 7.39-7.18 (m, 5 H), 6.65 (dt, *J* = 1.7 and 15.6 Hz, 1 H), 6.26-6.00 (m, 3 H), 5.72-5.63 (m, 1 H), 5.42-5.36 (m, 1 H), 3.24 (dt, *J* = 1.7 and 5.7 Hz, 1 H).

(*E*)-8-Phenylocta-1,7-dien-4-yn-3-ol (380). To a solution of **379** (75 mg, 0.25 mmol) in MeOH (8.3 mL) was added NaOH (59 mg, 1.5 mmol), and the reaction was stirred for 1 h. H_2O (5 mL) was added and the MeOH was removed under reduced pressure. The aqueous mixture was extracted with EtOAc (5 mL × 3), washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel

chromatography, eluting with hexanes/EtOAc (4:1) to give 39 mg (80%) of **380** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.17 (m, 5 H), 6.72-6.55 (m, 1 H), 6.28-5.91 (m, 2 H), 5.50 (dt, *J* = 1.2 and 17 Hz, 1 H), 5.24 (dt, *J* = 1.2 and 10 Hz, 1 H), 3.22 (dt, *J* = 1.9 and 5.7 Hz, 1 H), 1.92-1.79 (m, 1 H).

(*E*)-8-Phenylocta-1,7-dien-4-yn-3-one (381). To a solution of **380** (59 mg, 0.30 mmol) in acetone (3.2 mL) was added Jones reagent (200 μL) at 0 °C, and the reaction was stirred for 15 min. The reaction was diluted with sat. $NaHCO_3$ (2 mL) and extracted with EtOAc (3 mL × 3). The combined organic extracts were washed with sat. $NaHCO_3$ (2 mL) H_2O (2 mL × 2) and brine (2 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (10:1) to give 34 mg (59%) of **381** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.21 (m, 5 H), 6.75-6.10 (m, 5 H), 3.39 (dt, *J* = 1.7 and 5.8 Hz, 2 H).

2-Acryloyl-3-cinnamylanthraquinone (384). A solution of **383** (7.6 mg, 0.042 mmol) and **381** (32.8 mg, 0.17 mmol) in DCE (1.7 mL) was added to a solution of Cp*Ru(cod)Cl (1.6 mg, 0.0042 mmol) in DCE (100 μL) over 65 min and the reaction was stirred for 2 h. The reaction was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/DCM (1:2) to give 2.6 mg (16%) of **384** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40-8.28 (m, 3 H), 7.90-7.80 (m, 2 H), 7.40-7.18 (m, 5 H), 6.90-6.76 (m, 1 H), 6.53-6.12 (m, 4 H), 3.82 (d, *J* = 6.8 Hz, 2 H).

1-((*E*)-6,6-Diethoxyhex-1-en-4-ynyl)benzene (385). Cinnamyl bromide (500 mg, 2.5 mmol) was added to a solution of propargylaldehyde diethyl acetal (650 mg, 5.1 mmol), CuI (488 mg, 2.5 mmol), NaI (190 mg, 1.27 mmol), and K_2CO_3 (875 mg, 6.3 mmol) in DMF (5 mL), and the reaction was stirred for 2.5 h. The reaction was diluted with Et_2O (30 mL), filtered over celite, washed with H_2O (15 mL × 2) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (16:1) to give 492 mg (79%) of **385** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.19 (m, 5 H), 6.63 (dt, *J* = and 15.7 Hz, 1 H), 6.16 (dt, *J* = 5.7 and 15.7 Hz, 1 H), 5.34 (t, *J* = 1.6 Hz, 1 H), 3.88-3.55 (m, 4 H), 3.22 (dt, *J* = 1.6 and 5.7 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 6 H).

(*E*)-6-Phenylhex-5-en-2-ynal (386). To a solution of **385** (75 mg, 0.31 mmol) in $CHCl_3$ (1 mL) was added H_2O (250 μL) and TFA (250 μL) and the reaction was stirred for 60 min. Sat. $NaHCO_3$ (4 mL) was added, and the aqueous solution was extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (15:1) to give 25 mg (48%) of **386** as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1 H), 7.52-7.22 (m, 5 H), 6.66 (d, *J* = 15.8 Hz, 1 H), 6.15 (dt, *J* = 5.6 and 15.8 Hz, 1 H), 3.39 (d, *J* = 5.6 Hz, 2 H).

3-Cinnamyl-9,10-dihydro-9,10-dioxoanthracene-2-carbaldehyde (387). A solution of **383** (39.9 mg, 0.22 mmol) and **386** (150 mg, 0.88 mmol) in degassed DCE (8.3 mL) was added to

a solution of Cp*Ru(cod)Cl (8.3 mg, 0.022 mmol) in DCE (400 μL) over 85 min, and the reaction was stirred for 4 h. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/DCM (1:2) to give 55 mg (72%) of **387** as an off white solid: Mp 165-168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.45 (s, 1 H), 8.80 (s, 1 H), 8.42-8.27 (m, 2 H), 7.92-7.80 (m, 2 H), 7.39-7.18 (m, 5 H), 6.56-6.36 (m, 2 H), 4.17 (d, *J* = 5.5 Hz, 2 H).

2-Cinnamyl-3-(1-hydroxyallyl)anthraquinone (388). Vinyl magnesium bromide (65 μL, 0.045 mmol, 0.7 M in THF) was added to a solution of **387** (15.9 mg, 0.045 mmol) in THF (1 mL) over 20 min at −78 °C. The reaction was warmed to rt and quenched after 1.5 h with sat. NH_4Cl (2 mL). The aqueous mixture was extracted with Et_2O (3 mL × 3), washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with DCM/EtOAc (33:1) to give 8.6 mg (50%) of **388** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 8.39-8.26 (m, 2 H), 8.19 (s, 1 H), 7.88-7.76 (m, 2 H), 7.42-7.18 (m, 5 H), 6.52-6.31(m, 2 H), 6.21-6.06 (m, 1 H), 5.70-5.60 (m, 1 H), 5.47-5.31 (m, 2 H), 3.81 (d, *J* = 5.3 Hz, 2 H), 2.12 (br s, 1 H).

7-Hydroxytetracene-5,12(7*H*,10*H*)-dione (389). To a solution of **388** (16.7 mg, 0.044 mmol) in degassed DCM (4 mL) was added Grubbs' First Generation catalyst (3.5 mg, 0.0044 mmol), and the reaction was stirred at rt overnight. The reaction was concentrated and the residue was purified by silica gel chromatography, eluting with DCM/EtOAc (17:1) to give 8.4 mg (69%) of **389** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1 H),

8.40-8.27 (m, 2 H), 8.14 (s, 1 H), 7.89-7.75 (m, 2 H), 6.25-6.12 (m, 2 H), 5.37-5.26 (m, 1 H), 3.77-3.45 (m, 2 H), 2.08 (d, J = 8.8 Hz, 1 H).

1-[2-(4-(*tert*-Butyldimethylsiloxy)-1-hydroxybut-2-ynyl)]-phenylprop-2-yn-1-ol (390). To a solution of *tert*-butyldimethyl(prop-2-ynyloxy)silane (279 mg, 1.6 mmol) in THF (1 mL) was added *n*-BuLi (1.2 mL, 1.6 mmol, 1.32 M in hexanes) dropwise, and the reaction was stirred for 1 h at −78 °C. This solution was added to a solution of *o*-phthalaldehyde (200 mg, 1.5 mmol) in THF (2 mL), and the reaction was stirred for 10 min. Ethynylmagnesium bromide (3.6 mL, 1.8 mmol, 0.5 M in THF) was added, and the reaction was warmed to rt. After 60 min, NH_4Cl (10 mL) was added and the aqueous solution was extracted with Et_2O (10 mL × 3). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/Et_2O (1:1) to give 208 mg (42%) of **390** as a mixture of diastereomers as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.76 (m, 2 H), 7.49-7.35 (m, 2 H), 6.09-5.89 (m, 2 H), 4.52-4.40 (m, 2 H), 3.05 (d, J = 4.8 Hz, 1 H), 2.80 (d, J = 4.8 Hz, 1 H), 2.76-2.74 (m, 1 H), 1.03-0.86 (m, 9 H), 0.21-0.09 (m, 6 H).

1-[2-(4-(*tert*-Butyldimethylsiloxy)-1-acetoxybut-2-ynyl)]-phenylprop-2-ynyl acetate (391). To a solution of **390** (60 mg, 0.18 mmol) and DMAP (cat.) in pyridine (250 μL) was added acetic anhydride (170 μL) at 0 °C, and the solution was stirred for 2 h as it warmed to rt. The reaction was diluted with Et_2O (4 mL) and H_2O (4 mL), the layers separated, and the aqueous layer was extracted with Et_2O (4 mL × 2). The combined organic extracts were

washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1) to give 53 mg (71%) of **391** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.61 (m, 2 H), 7.48-7.37 (m, 2 H), 6.82-6.72 (m, 2 H), 4.41-4.34 (m, 2 H), 2.74-2.60 (m, 1 H), 2.20-2.08 (m, 6 H), 0.99-0.83 (m, 9 H), 0.16-0.05 (m, 6 H).

1-[2-(4-(*tert*-Butyldimethylsiloxy)-but-2-yn-onyl)]-phenylprop-2-yn-one (392). To a solution of **390** (50 mg, 0.15 mmol) in DCM (1 mL) at 0 °C was added DMP (154 g, 0.36 mmol), and the reaction was stirred for 60 min at 0 °C. The reaction was quenched with sat. $NaHCO_3$ (2 mL) and extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (4 mL) and brine (4 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1) to give 31 mg (63%) of **392** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.80 (m, 2 H), 7.71-7.61 (m, 2 H), 4.56 (s, 2 H), 3.43 (s, 1 H), 0.93 (s, 9 H), 0.16 (s, 6 H).

3-Butyl-1-((*tert*-butyldimethylsiloxy)methyl)anthraquinone (393). A solution of **392** (10 mg, 0.031 mmol) and 1-hexyne (14 mg, 0.31 mmol) in degassed DCE (1.2 mL) was added to a solution of Cp*Ru(cod)Cl (1.1 mg, 0.0031 mmol) in DCE (100 μL) over 30 min, and the reaction was stirred for 35 min. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (10:1) to give 10.8 mg (86%) of **393** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32-8.20 (m, 2 H), 8.13 (br s,

1 H), 8.11 (br s, 1 H), 7.84-7.72 (m, 2 H), 5.37 (s, 2 H), 2.84 (t, *J* = 7.2 Hz, 2 H), 1.84-1.65 (m, 2 H), 1.52-1.34 (m, 2 H), 1.20-0.91 (m, 12 H), 0.22 (s, 6 H).

3-Cinnamyl-1-((*tert*-butyldimethylsilyloxy)methyl)-9,10-dihydro-9,10-dioxoanthracene-2-carbaldehyde (394a) and **3-cinnamyl-4-((*tert*-butyldimethylsilyloxy)methyl)-9,10-dihydro-9,10-dioxoanthracene-2-carbaldehyde (394b).** A solution of **392** (10 mg, 0.031 mmol) and **386** (21 mg, 0.12 mmol) in degassed DCE (1.2 mL) was added to a solution of Cp*Ru(cod)Cl (1.1 mg, 0.0031 mmol) in DCE (100 μL) over 30 min, and the reaction was stirred overnight. The reaction was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/DCM (1:1.5) to give 2.4 mg (16%) of **394a** and 2.7 mg (18%) of **394b** as yellow oils. ^{1}H NMR (300 MHz, $CDCl_3$) δ **394a**: 10.53 (s, 1 H), 8.35-8.20 (m, 2 H), 7.88-7.75 (m, 2 H), 7.42-7.17 (m, 6 H), 6.53-6.23 (m, 2 H), 5.57 (s, 2 H), 3.80 (d, *J* = 6.6 Hz, 2 H), 0.97 (s, 9 H), 0.19 (s, 6 H); **394b**: 10.46 (s, 1 H), 8.84 (s, 1 H), 8.35-8.20 (m, 2 H), 7.89-7.75 (m, 2 H), 7.35-7.14 (m, 5 H), 6.54-6.38 (m, 1 H), 6.31-6.18 (m, 1 H), 5.40 (s, 2 H), 4.34 (dd, *J* = 1.5 and 5.7 Hz, 2 H), 0.95 (s, 9 H), 0.22 (s, 6 H).

CHAPTER 5: A Cyclotrimerization Approach to Cannabinoids

5.1 Background

5.1.1 Cannabinoids

The natural cannabinoids comprise a group of more than 60 terpenophenolic compounds present in *Cannabis*.[243, 244] Structurally, all phytocannabinoids contain a 5-alkyl (typically a five carbon-chain) resorcinol aromatic ring that is connected at the 2-position to a monoterpene motif. Biosynthetically this monoterpene unit undergoes cyclization yielding a diverse range of natural products including cannabinol (**400**), cannabinol methyl ether (**401**), cannabinodiol (**402**), Δ^9-tetrahydrocannabinol (THC, **403**), and cannabichromene (**404**) (Figure 5.1).

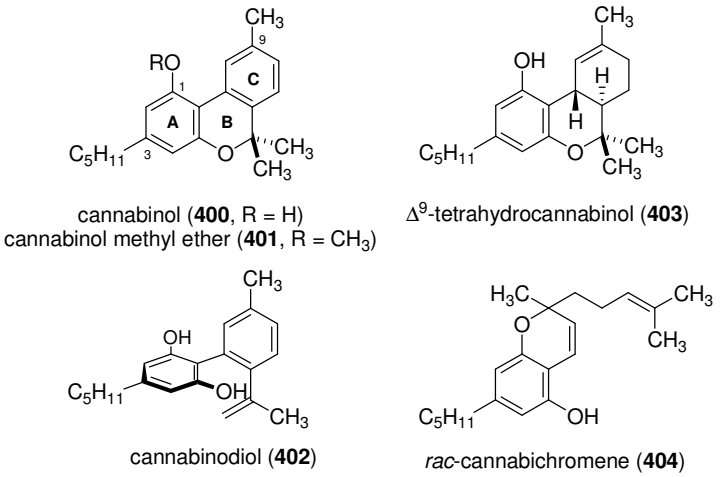
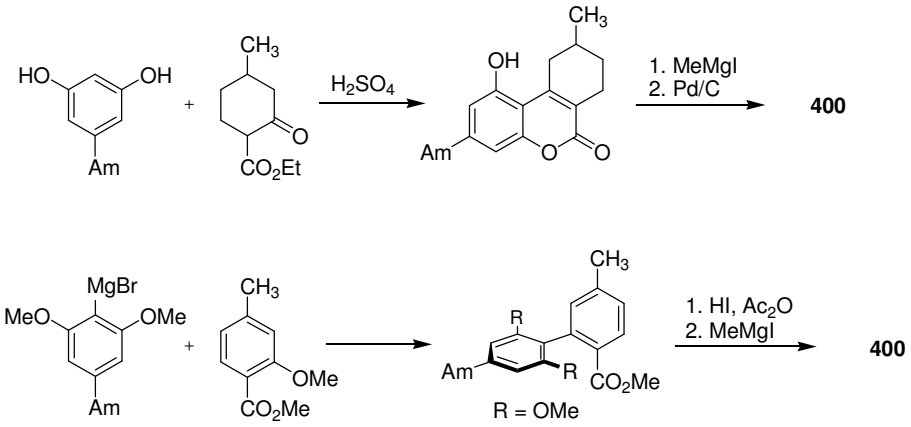


Figure 5.1. Examples of naturally occurring cannabinoids.

Besides the well known recreational use of the *Cannabis* plant for its psychotropic effects, medicinal applications have been known since the third millennium BC and include antiemetic,[245, 246] analgesic,[247, 248] antibacterial,[249] and anticonvulsant[250] properties among others.[251-253] Cannabinoids act upon two cellular receptors, the central cannabinoid receptor,

CB_1, found mainly in the brain, and the peripheral cannabinoid receptor, CB_2, found almost exclusively in the immune system.[254-256] Synthetic cannabinoids which selectively interact with only one receptor are highly desired,[257-260] especially since CB_2 selective ligands should limit the side effects associated with CB_1 receptor activation.[256, 261]

Thus far, cannabinol derivatives have primarily been modified at positions C-1, C-3, and C-9.[262, 263] Previous syntheses of cannabinol and its derivatives have relied upon two general strategies; coupling 5-alkyl resorcinols with suitably substituted arenes followed by pyran formation[264] or generating tetrahydrocannabinol derivatives first via a condensation of 5-alkyl resorcinols with appropriate cyclohexane derivatives followed by pyran formation and/or aromatization (Scheme 5.1).[262, 263, 265-267]

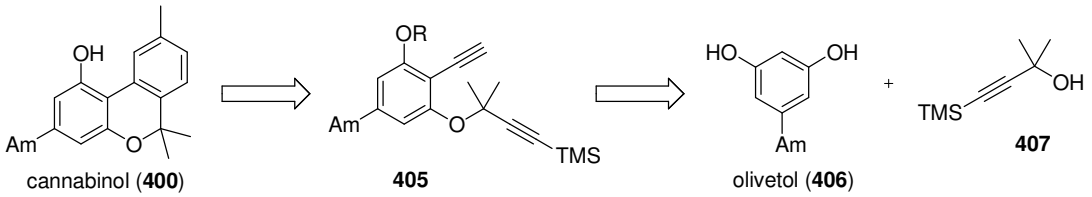


Scheme 5.1. Synthetic routes to cannabinol (**400**).

Accessing broadly substituted C ring analogs would require more elaborate arene or cyclohexene starting materials. As an alternative, we develop a flexible synthetic route to the cannabinol core structure based on a [2+2+2] cyclotrimerization reaction that is amenable to the synthesis of various C ring analogs from easily accessible alkyne precursors.

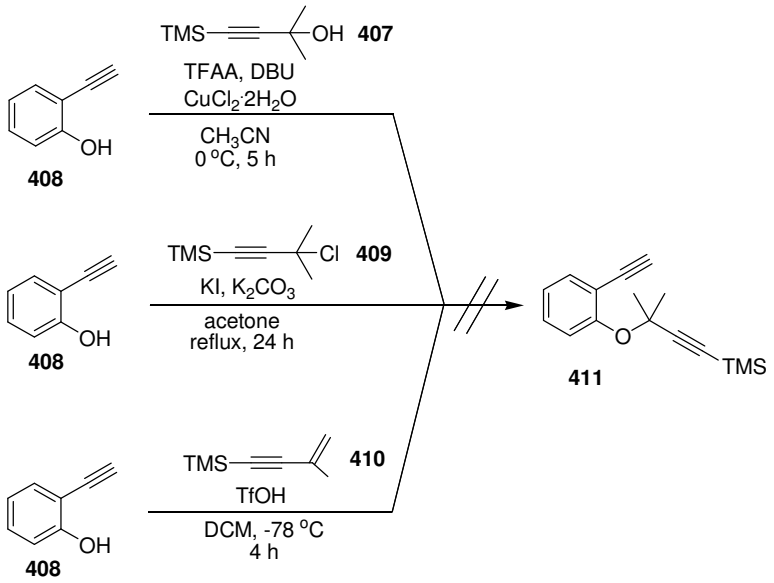
5.1.2 Retrosynthetic Analysis and Cyclotrimerization Studies

Deconstructing the C ring of the cannabinol framework using the cyclotrimerization reaction reveals the diyne structure **405** necessary for the cyclotrimerization event (Scheme 5.2). In order to achieve a highly regioselective cyclotrimerization reaction a removable regiodirecting group in the form of the sterically demanding trimethylsilyl (TMS) group will be utilized. This diyne, in turn, will be derived from commercially available olivetol (**406**) and the propargyl alcohol **407**.



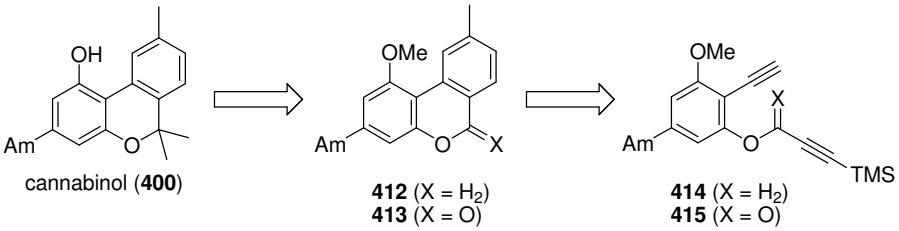
Scheme 5.2. Retrosynthetic analysis of cannabinol (**400**).

Before embarking on the synthesis of cannabinol, we first investigated the cyclotrimerization reaction of the diyne **411** with 1-hexyne. Attempts towards the synthesis of the diyne **411**, however, proved difficult (Scheme 5.3). Etherifications of *o*-ethynylphenol (**408**)[268] with the alcohol **407**,[269] the chloride **409**,[270, 271] or the alkene **410**[272] were unsuccessful in producing **411**.



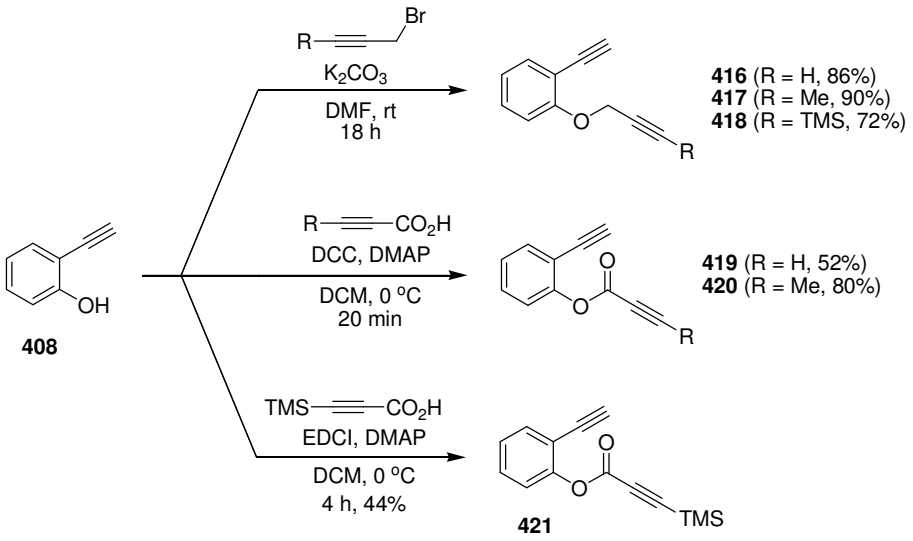
Scheme 5.3. Attempted synthesis of the diyne **411**.

Because of this stumbling block a modification in the retrosynthesis was necessary; installation of the geminal-dimethyl group will be accomplished after the cyclotrimerization event. This modification requires either a methylene or ester linkage in the tricyclic intermediate and diyne with olivetol maintaining its role as starting material (**412**-**415**, Scheme 5.4).



Scheme 5.4. Modified retrosynthetic analysis of cannabinol (**400**).

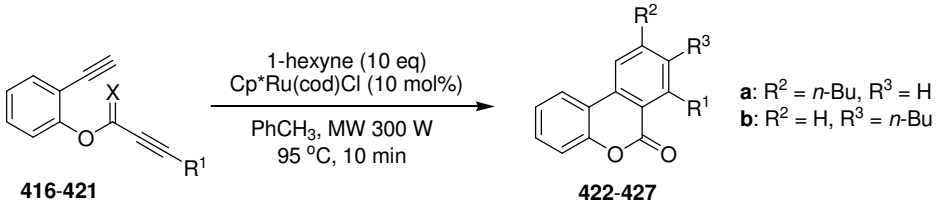
In order to determine which diyne (**414** or **415**) would produce a more efficient and selective cyclotrimerization reaction, a series of diynes were synthesized that differed in their electronic and steric properties (Scheme 5.5). All of the diynes **416**-**421**) were prepared from *o*-ethynylphenol under alkylation or coupling conditions in moderate to excellent yields.



Scheme 5.5. Synthesis of the diynes **416**-**421**.

These diynes were then subjected to Ru-catalyzed cyclotrimerization reactions with 1-hexyne under microwave irradiation (Table 5.1).

Table 5.1. Investigation of the [2+2+2] cyclotrimerization key step with the diynes **416**-**421**.



Entry	X	R^1	Yield (%), Cmpd	**a** / **b**
1	H_2	H	61, **422**	70 / 30
2	O	H	31, **423**	76 / 24
3	H_2	Me	96, **424**	95 / 5
4	O	Me	71, **425**	>95 / 5
5	H_2	TMS	97, **426**	>95 / 5
6	O	TMS	81, **427**	>95 / 5

The terminal diyne **416**[273] delivered the cyclotrimerization product **422** in a 61% yield as a 70:30 regioisomeric mixture of pyrans as determined by GC/MS and ^{1}H NMR analysis (Entry 1). The cyclotrimerization reaction of the ester analog **419**[28] led to an increased

regioselectivity in favor of the isomer **423a** over the isomer **423b** (76:24 based on ^{1}H NMR analysis) with a diminished yield of 31% (Entry 2). This result correlates well with Yamamoto's findings under non-microwave irradiation conditions (41% yield, 82:18 regioisomer ratio of **423a**:**423b**).[28] The low yields in case of **423a** and **423b** are a result of di- and trimerization of the diyne starting material, a problem commonly seen in cyclotrimerization reactions of reactive (terminal) diynes.[7, 274] The introduction of a sterically more demanding methyl group ($R^1 = CH_3$) on one of the triple bonds produced a highly efficient and regioselective cyclotrimerization reaction delivering **424a** (95:5) in 96% yield from the diyne **417** (Entry 3). The corresponding ester derivative **420** was converted into the pyrone **425a** in 71% yield with complete regioselectivity (Entry 4). These results indicate the ability to induce high levels of regioselectivity in the cyclotrimerization reaction towards the tricyclic cannabinoid core.

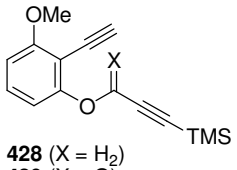
For the synthesis of the natural cannabinoids, a removable regiodirecting group was necessary. Towards this goal, the TMS-derivatized diynes **418** and **421** were investigated in the cyclotrimerization reaction. Continuing with the trend that increased steric bulk leads to a more efficient cyclotrimerization reaction, both diynes, **418** and **421**, furnished the desired products **426a** (97% yield) and **427a** (81% yield), respectively, with complete regioselectivity (Entries 5 and 6). The ability to replace the TMS group with a hydrogen has previously been shown.[53, 154] These trends underscore the necessity to balance reactivity and sterical demand in order to achieve highly efficient [2+2+2] cyclotrimerization reactions. These cyclotrimerization results also show that diynes based on both **418** and **421** are suitable cyclotrimerization precursors for the synthesis of cannabinol. Which structural motif (ester or

methylene) would be utilized in the synthesis would require additional investigations into the subsequent transformations necessary to convert the cyclotrimerization product into cannabinol.

5.2 Model Studies

5.2.1 Diyne Synthesis

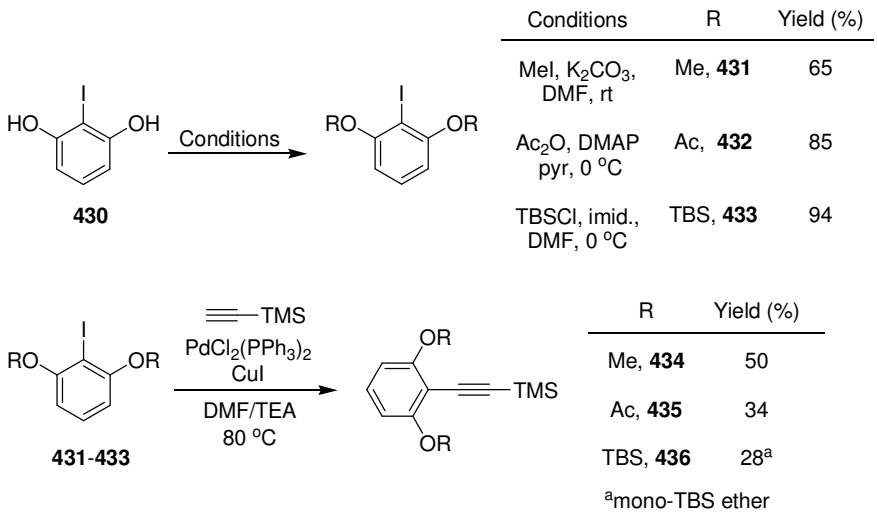
With the cyclotrimerization conditions in hand, attention was then turned to the synthesis of a model diyne, either **428** or **429**, that lacked the amyl side chain present in the cannabinoids (Figure 5.2).



428 (X = H_2)
429 (X = O)

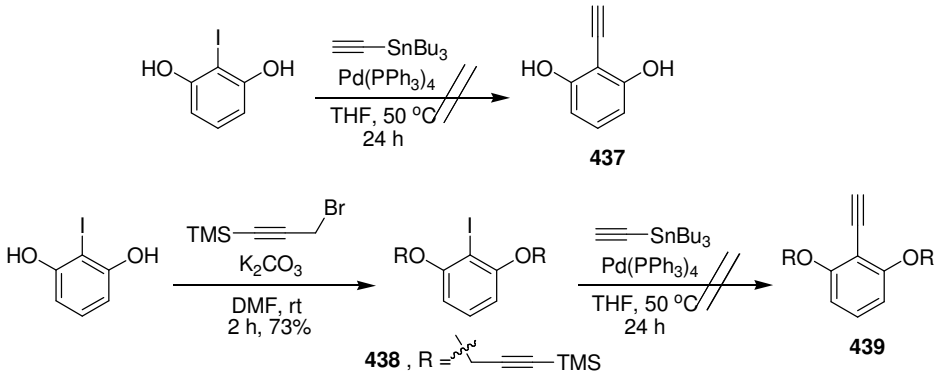
Figure 5.2. Model diynes for cannabinol synthesis.

2-Iodoresorcinol (**430**)[275] was protected as the dimethyl ether **431**,[276] diacetate **432**, and bis-TBS-ether **433** under standard conditions and subjected to Sonogashira coupling conditions with trimethylsilylacetylene (Scheme 5.6).[277] The dimethyl ether **431** furnished a 50% yield of the aryl acetylene **434**, and, as the steric bulk of the protecting group increased, the yield diminished accordingly with only a 34% yield of the aryl acetylene **435** from the diacetate **432** and a 28% yield of the mono-TBS-ether **436** from the bis-TBS-ether **433**.



Scheme 5.6. Sonogashira coupling route to the model diynes **428** and **429**.

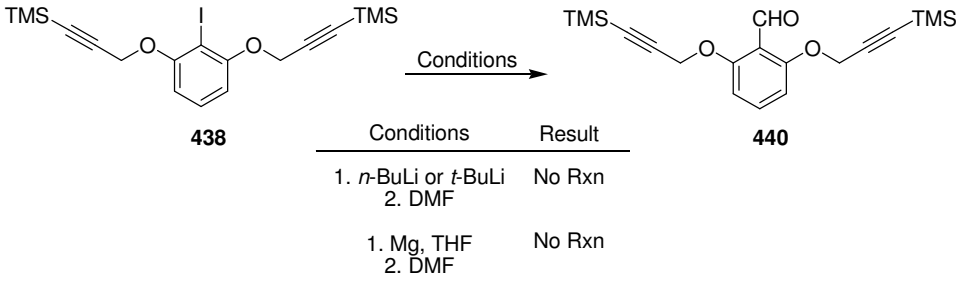
The low yields of the Sonogashira couplings prompted us to examine other palladium-catalyzed coupling reactions. However, Stille couplings towards **437** or **439** proved equally low yielding (Scheme 5.7). The coupling of the diester analogue of **438** was not investigated.



Scheme 5.7. Stille coupling route towards the diyne **439**.

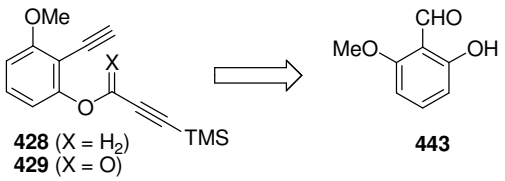
An alternative method of utilizing the iodide functionality via a metal-halogen exchange was also explored. Unfortunately, treatment of the aryl iodide **438** with *n*-butyllithium or *t*-butyllithium followed by quenching with DMF failed to produce the desired benzaldehyde **440** (Scheme 5.8). Preparation of the benzaldehyde via the Grignard reagent

was unsuccessful as well. In each case, starting material was recovered indicating the metal-halogen exchange was not occurring as expected.



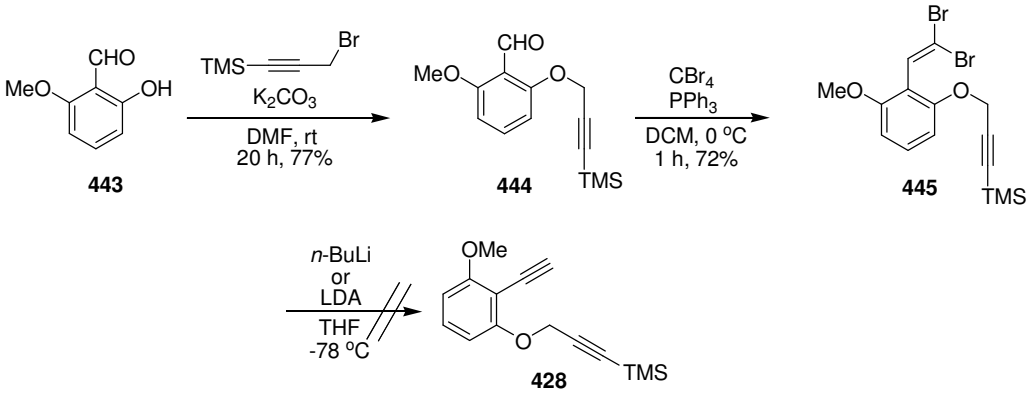
Scheme 5.8. Metal-halogen exchange route towards the benzaldehyde **440**.

The inability to take advantage of the aryl iodide functionality forced us to consider alternative means to functionalize the C-2 position of resorcinol. Thus, the known salicylaldehyde derivative **443**[278] was explored as a starting material in order to access one of the desired diynes **428** or **429** (Scheme 5.9).



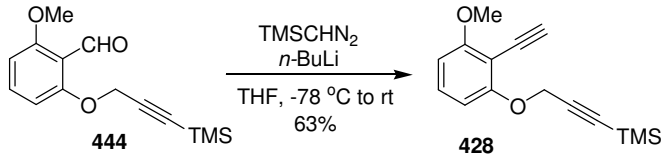
Scheme 5.9. Salicylaldehyde route to the diynes **428** and **429**.

Early attempts relied upon the Corey-Fuchs reaction[279] to convert the aldehyde **443** into the alkyne **428**. Alkylation of **443** with 3-bromo-1-trimethylsilyl-1-propyne gave the propargyl ether **444** in 77% yield (Scheme 5.10). At this point the Corey-Fuchs protocol was attempted to deliver the desired diyne **428**. Treatment of the aldehyde **444** with CBr_4 and PPh_3 provided the dibromide **445** in 72% yield. However, when the dibromide was treated with *n*-BuLi or LDA, a complex mixture of products was obtained.



Scheme 5.10. Corey-Fuchs route to the diyne **428**.

Another route to obtain aryl acetylenes from aryl aldehydes involves treating the aldehyde with Colvin's reagent,[280, 281] the lithium salt of trimethylsilyldiazomethane, and produces the desired alkyne in a single step. Gratifyingly, this reaction performed well with our system giving a 63% yield of the desired diyne **428** (Scheme 5.11).



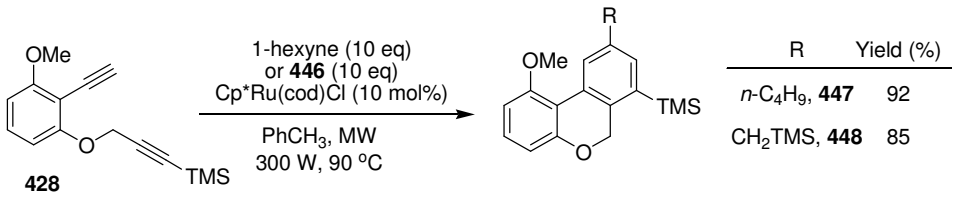
Scheme 5.11. Colvin rearrangement towards the diyne **428**.

With the successful synthesis of the diyne **428**, studies into the key cyclotrimerization event as well as the endgame strategy could commence.

5.2.2 Completion of Cannabinol Model Study

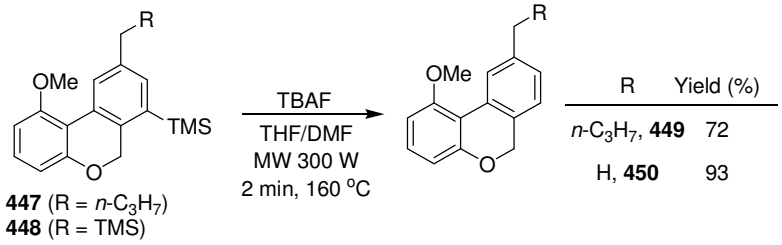
Based on the cyclotrimerization studies carried out previously, we expected the key cyclotrimerization step to proceed smoothly with the diyne **428**. Reaction of **428** with 1-hexyne or with a propyne equivalent, propargyltrimethylsilane (**446**), under ruthenium catalysis and microwave irradiation furnished the pyrans **447** and **448** in 92 and 85% yield,

respectively as the only regioisomers (Scheme 5.12). We used **446** as a reaction partner because the gaseous nature of propyne necessitated the use of a higher boiling reagent that could be converted to just a methyl group at a later stage.



Scheme 5.12. Model cyclotrimerization reactions towards the pyrans **447** and **448**.

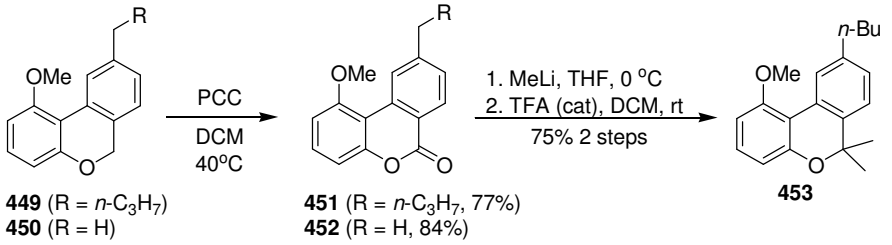
At this point, attention was turned to the removal of the aryl-TMS groups in the pyran **447**. Towards this end, **447** was treated with TBAF in THF. However, at room temperature and elevated temperatures no reaction occurred. Based on reaction conditions previously employed to desilylate aryl-TMS groups on indanone derivatives (TBAF, THF/DMF, MW 300 W, 2 min),[154] removal of the TMS group in the pyran **447** was successful in 72% yield to give **449**. These conditions translated well with the pyran **448** producing a 93% yield of the desilylated pyran **450** (Scheme 5.13).



Scheme 5.13. Desilylation of the pyrans **447** and **448**.

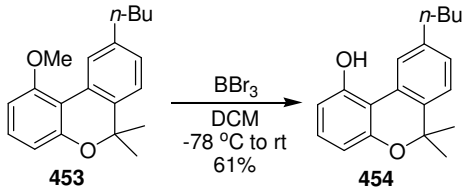
The next steps involved incorporation of the *gem*-dimethyl substituents at the 6-position of the pyran ring. First, a selective oxidation of the benzylic methylene group with PCC furnished the pyrones **451** and **452** in 77 and 84% yield, respectively (Scheme 5.14).[282]

Then, addition of methyl-lithium followed by acid catalyzed ring closure produced **453**, the desired tricyclic framework with the *gem*-dimethyl substituents in place.



Scheme 5.14. Installation of *gem*-dimethyl substituent at C-6.

Synthesis of the pyran **453** completed the model study for cannabinol methyl ether, and one more step remains in the model study towards cannabinol: deprotection of the methoxy ether. Treatment of the pyran **453** with BBr_3 effected deprotection of the phenol to provide the cannabinol analog **454** in 61% yield (Scheme 5.15).



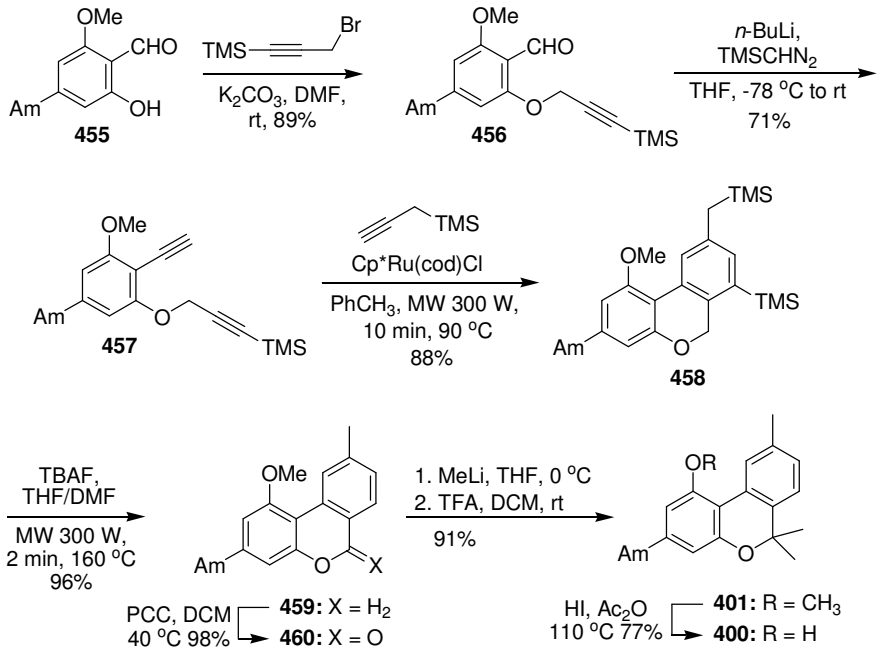
Scheme 5.15. Deprotection of the arylmethyl ether **453**.

5.3 Total Synthesis of Cannabinol, Cannabinol Methyl Ether, and Cannabinodiol

5.3.1 Cannabinol and Cannabinol Methyl Ether

Based on the previously described model studies, the syntheses of **400** and **401** commences with the known salicylaldehyde derivative **455**[283] (prepared in three steps from olivetol) which is alkylated with 3-bromo-1-trimethylsilyl-1-propyne to give the propargyl ether **456** in 89% yield (Scheme 5.16). Installation of the second triple bond was accomplished by treatment of **456** with the lithium salt of trimethylsilyldiazomethane[280, 281]

furnishing the diyne **457** in 71% yield. As in the case of the model study with the diyne **428**, the compound **457** underwent an efficient and regioselective Cp*Ru(cod)Cl-catalyzed [2+2+2] cyclotrimerization reaction with propargyltrimethylsilane under microwave irradiation to deliver the pyran **458** in 88% yield as a single regioisomer. Removal of the aryl- and alkyl-TMS groups was rapidly accomplished by exposure to TBAF under microwave irradiation for 2 min to give the desilylated pyran **459** in 96% yield. Selective oxidation of the benzylic methylene group with PCC furnished the pyrone **460** in 98% yield. Addition of CH_3Li followed by an acid-catalyzed ring closure of the crude diol provided cannabinol methyl ether (**401**), a natural product observed in plant extracts from *Cannabis sativa*,[284] in 91% yield over two steps. The structure of **401** is confirmed on the basis of the ^1H NMR spectrum where five aromatic protons are present as well as a signal for the aryl-methyl ether (3.95 ppm). Qualitatively, the spectrum of **401** resembles that of synthetic cannabinol with the addition of the methyl ether signal and loss of the signal from the phenol proton. Subsequent deprotection of the methylphenol with aqueous HI in 77% yield completed the total synthesis of cannabinol (**400**). The use of BBr_3 in the demethylation gave similar results (78% yield).



Scheme 5.16. Total synthesis of cannabinol methyl ether (**401**) and cannabinol (**400**).

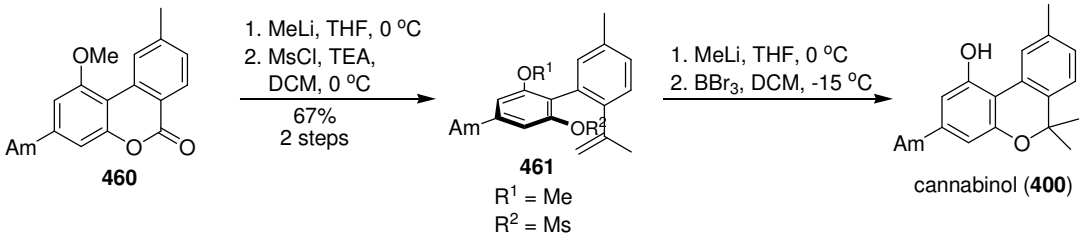
The ^{1}H NMR spectrum of **400** correlates well with the reported shifts for cannabinol (Table 5.2). [285]

Table 5.2. Comparison of the ^{1}H NMR spectrum of synthetic and natural **400**.

	^{1}H NMR
Natural **400** ($CDCl_3$, 300 MHz)	Synthetic **400** ($CDCl_3$, 300 MHz)
8.20 (s, 1 H)	8.17 (s, 1 H)
7.10 (m, 2 H)	7.19-7.03 (m, 2 H)
6.45 (d, 1 H)	6.45 (d, 1 H)
6.24 (d, 1 H)	6.30 (d, 1 H)
5.44 (s, 1 H)	5.14 (s, 1 H)
2.49 (t, 2 H)	2.49 (t, 2 H)
2.39 (s, 3 H)	2.39 (s, 3 H)
1.61 (s, 6 H)	1.68-1.58 (m, 8 H)
0.89 (t, 3 H)	0.89 (t, 3 H)

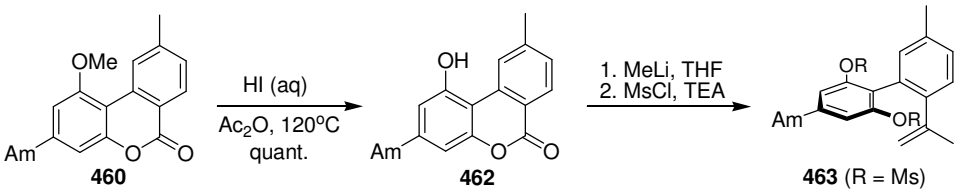
5.3.2 Cannabinodiol

We hypothesized not only that the cyclotrimerization route to cannabinol would pave the way for analogs, but also that the route would be flexible to produce the isomeric cannabinoid cannabinodiol (**402**).[286] If, instead of the acid-catalyzed cyclization to the pyran **401**, the crude diol could be dehydrated to a styrene derivative, then deprotection of the phenol would readily provide cannabinodiol. In this direction, the crude diol produced from the addition of methyl-lithium to the pyrone **460** was dehydrated via the methylsulfonate to give the mesylate **461** in 67% yield over two steps. (Scheme 5.17). Deprotection of the mesylate with methyl-lithium followed by treatment of the crude mono-phenol with BBr_3 furnished, however, cannabinol **400** instead of cannabinodiol through acid catalyzed cyclization.



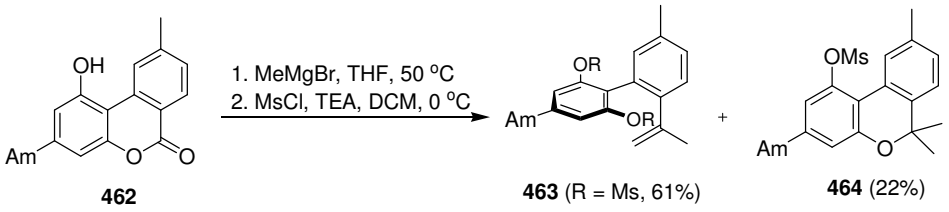
Scheme 5.17. Attempted synthesis of cannabinodiol.

Because of the high propensity for cyclization to the pyran under acid catalysis, deprotecting the phenol in the pyrone **460** was first accomplished followed by lactone opening and dehydration. Demethylation with aqueous HI in acetic anhydride smoothly provided the pyrone **462**[287] in a quantitative yield (Scheme 5.18). In this case, the lactone opening proved troublesome with methyl-lithium furnishing only a trace amount of the desired bismesylate **463**.



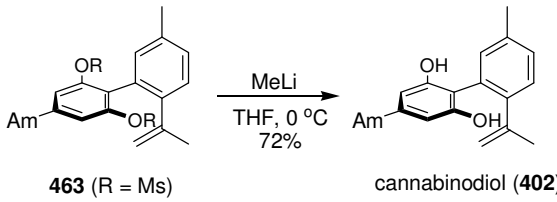
Scheme 5.18. Attempted synthesis of the bis-mesylate **463**.

By using the Grignard reagent MeMgBr in the sequence instead of methyllithium a 61% yield of the bismesylate **463** was obtained along with a 21% yield of mesylated cannabinol (**464**, Scheme 5.19).



Scheme 5.19. Synthesis of the bismesylate **463**.

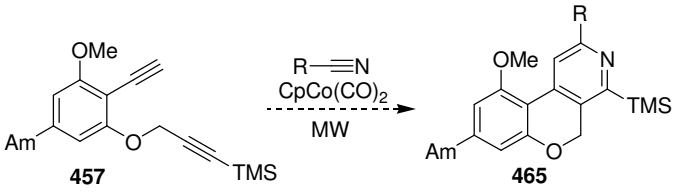
Completion of the synthesis of cannabinodiol was accomplished by deprotection of the phenols with methyl lithium[288] to provide **402** in 72% yield (Scheme 5.20). The ^{1}H NMR spectrum of synthetic **402** displays signals indicative of an α-methylstyrene derivative (4.93-4.89 and 1.80-1.78 ppm) as well as the signal for two equivalent phenol protons (4.44 ppm).



Scheme 5.20. Completion of the total synthesis of cannabinodiol (**402**).

5.4 Summary and Future Directions

A new route towards the cannabinoid framework based on the [2+2+2] cyclotrimerization reaction has been developed. Several diyne precursors for the synthesis of the tricyclic core structure were probed to investigate the steric and electronic effects on cyclotrimerization efficiency and regioselectivity. Three natural products, cannabinol (**400**), cannabinol methyl ether (**401**), and cannabinodiol (**402**), were synthesized to illustrate the flexibility of this approach to the cannabinoid architecture in high overall yields (37% for cannabinol, 48% for cannabinol methyl ether, and 23% for cannabinodiol). The developed cyclotrimerization approach enables the rapid introduction of a diverse set of substituents at the 7-, 8-, 9-, and 10-positions of the C ring through the reaction of substituted diynes with a variety of alkynes.[87] Furthermore, if nitriles are utilized instead of alkynes in the cyclotrimerization step then azacannabinoids (**465**) could be accessed (Scheme 5.21).



Scheme 5.21. Synthesis of azacannabinoids.

5.5 Experimental

All reactions were performed in flame-dried glassware under a nitrogen atmosphere and stirred magnetically. Tetrahydrofuran, toluene, xylenes, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Diisopropylamine, triethylamine, DMSO, DCM, DMF, 1,2-dichloroethane, CH_3CN and pyridine were distilled from calcium hydride and stored over 4 Å molecular sieves. Other reagents and solvents obtained from commercial sources were stored under nitrogen and used directly without further purification. *n*-BuLi and MeLi were titrated against *N*-pivaloyl-*o*-toluidine.[108] Melting points were obtained from a Mel-Temp capillary melting point apparatus and are uncorrected. High resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz) or Varian Mercury 300 (300 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption (77.2) for ^{13}C NMR spectra. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer.

General cyclotrimerization protocol for diynes

In a flame-dried microwave vial equipped with a stir bar was added diyne (0.12 mmol), 1-hexyne (1.18 mmol), Cp*Ru(cod)Cl (0.012 mmol), and dry toluene (2.8 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 10 min in a CEM Discover microwave synthesizer at 300 W. After cooling, the solution was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc to give the product.

Experimental protocols and data for compounds 417, 417, 420, and 421

2-(1-Ethynyl)phenyl 2-butynyl ether (417). To a solution of **408** (100 mg, 0.85 mmol) in DMF (1.2 mL) at rt was added K_2CO_3 (234 mg, 1.69 mmol) and 1-bromo-2-butyne (148 μL, 1.69 mmol). The mixture was stirred for 2 h and diluted with Et_2O (6 mL). The organic layer was washed with H_2O (3 × 3 mL) and brine (3 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (35:1) to give 129 mg (90%) of **417** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.5 Hz and 1.8 Hz, 1 H), 7.37-7.28 (m, 1 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 6.92 (dt, *J* = 7.5 Hz and 1.0 Hz), 4.76 (q, *J* = 2.3 Hz, 2 H), 3.31 (s, 1 H), 1.84 (t, *J* = 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 134.3, 130.1, 121.1, 112.8, 112.0, 84.3, 81.4, 80.0, 73.9, 57.2, 3.8. HRMS calcd for $[M + H]^+$ $C_{12}H_{11}O$ 171.0804, found 171.0807.

2-Ethynyl-1-(3-trimethylsilyl-2-propynyloxy) benzene (418). To a solution of **408** (107 mg, 0.91 mmol) in DMF (1.2 mL) at rt was added K_2CO_3 (250 mg, 1.81 mmol) and 1-bromo-2-butyne (384 μL, 2.72 mmol). The mixture was stirred overnight at 50 °C. After cooling, the reaction was diluted with Et_2O (5 mL) and NH_4Cl (5 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic extracts were washed with H_2O (5 mL × 2) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (60:1) to give 150 mg (72%) of **418** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.5 Hz and 1.9 Hz, 1 H), 7.37-7.28 (m, 1 H), 7.07 (dd, *J* = 8.3 Hz and 0.9 Hz, 1 H), 6.94 (dt, *J* = 7.5 Hz and 0.9 Hz, 1 H), 4.80 (s, 2 H), 3.31 (s, 1 H), 0.16 (s, 9 H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 159.0, 134.3, 130.1, 121.4, 113.4, 112.2, 99.9, 93.5, 81.5, 80.0, 57.6, -0.2. HRMS calcd for $[M + H]^+$ $C_{14}H_{17}OSi$ 229.1043, found 229.1046.

Butynoic acid 2-ethynylphenyl ester (420). To a solution of **408** (40 mg, 0.34 mmol), 2-butynoic acid (31 mg, 0.37 mmol), and DMAP (3 mg, 0.025 mmol) in DCM (700 μL) at 0 °C was added DCC (68 mg, 0.33 mmol) in DCM (200 μL with 200 μL rinse) dropwise. The reaction was stirred for 20 min before filtering, washing the solid with Et_2O, and concentrating. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (13:1) to give 49 mg (80%) of **420** as an colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.8 Hz and 1.7 Hz, 1 H), 7.37 (dt, *J* = 7.8 Hz and 1.7 Hz, 1 H), 7.22 (dt, *J* = 7.8 Hz and 1.3 Hz, 1 H), 7.13 (dd, *J* = 7.8 Hz and 1.3 Hz, 1 H), 3.31 (s, 1 H), 2.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.34, 151.31, 133.7, 130.2, 126.5, 122.3, 116.4, 88.6, 82.8, 78.2, 71.9, 4.2. HRMS calcd for $[M + H]^+$ $C_{12}H_9O_2$ 185.0597, found 185.0596.

2-Ethynylphenyl 3-(trimethylsilyl)propiolate (421). To a solution of **408** (30 mg, 0.25 mmol) and 3-(trimethylsilyl)-2-propynoic acid (72 mg, 0.51 mmol) in DCM (1.2 mL) at 0 °C was added DMAP (2 mg, 0.017 mmol) and EDCI (98 mg, 0.51 mmol), and the mixture was allowed to stir for 4 h at 0 °C. The mixture was filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 27 mg (44%) of **421** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.6 Hz and 1.6 Hz, 1 H), 7.37 (dt, *J* = 7.9 Hz and 1.6 Hz, 1 H), 7.22 (dt, *J* = 7.6 Hz and 1.1 Hz, 1 H), 7.12 (dd, *J* = 7.9 Hz and 1.1 Hz, 1 H), 3.32 (s, 1 H), 0.30 (s, 9 H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 151.3, 150.6, 133.9, 130.2, 126.6, 122.3, 116.5, 97.3, 93.8, 83.0, 78.1, -0.8. HRMS calcd for $[M + H]^+$ $C_{14}H_{15}O_2Si$ 243.0835, found 243.0835.

Analytical data for compounds 422 and 424-427

9-Butyl-6*H*-benzo[*c*]chromene (422). Isolated as a 70/30 mixture of regioisomers in 61% yield as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.80-7.67 (m, 1 H), 7.64-7.48 (m, 1 H), 7.28-7.15 (m, 2 H), 7.14-6.94 (m, 3 H), 2.75-2.59 (m, 2 H), 1.71-1.58 (m, 2 H), 1.49-1.29 (m, 2 H), 1.01-0.90 (m, 3 H). HRMS calcd for $[M - H]^+$ $C_{17}H_{17}O$ 237.1273, found 237.1279.

9-Butyl-7-methyl-6*H*-benzo[*c*]chromene (424).[i] Isolated as a 95/5 mixture of regioisomers in 96% yield as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, *J* = Hz and Hz, 1 H), 7.38 (s, 1 H), 7.26-7.18 (m, 1 H), 7.09-6.92 (m, 3 H), 2.60 (t, *J* = 7.7 Hz, 2 H), 2.28 (s, 3 H), 1.70-1.60 (m, 2 H), 1.50-1.32 (m, 2 H), 0.95 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 142.6, 133.1, 129.9, 129.8, 129.2, 127.6, 123.5, 123.4, 122.1, 120.0, 117.2, 65.7, 35.8, 33.9, 22.6, 18.5, 14.1. HRMS calcd for $[M - H]^+$ $C_{18}H_{19}O$ 251.1430, found 251.1431.

9-Butyl-7-methyl-6*H*-benzo[*c*]chromen-6-one (425). Isolated in 71% yield as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.5 Hz and 1.5 Hz, 1 H), 7.78 (s, 1 H), 7.49-7.39 (m, 1 H), 7.35-7.25 (m, 2 H), 7.20 (s, 1 H), 2.84 (s, 3 H), 2.72 (t, *J* = 7.8 Hz, 2 H), 1.80-1.62 (m, 2 H), 1.52-1.34 (m, 2 H), 0.95 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6,

[i] Only major regioisomer listed.

151.6, 149.7, 144.4, 136.2, 132.9, 130.2, 124.2, 123.1, 119.5, 118.5, 117.6, 117.4, 36.1, 33.3, 23.9, 22.6, 14.0. HRMS calcd for $[M + H]^+$ $C_{18}H_{19}O_2$ 267.1379, found 267.1382.

9-Butyl-7-(trimethylsilyl)-6*H*-benzo[*c*]chromene (426). Isolated in 97% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 1 H), 7.56 (s, 1 H), 7.32-7.20 (m, 2 H), 7.08 (t, *J* = 7.6 Hz, 1 H), 7.00 (d, *J* = 8.1 Hz, 1 H), 5.21 (s, 2 H), 2.68 (t, *J* = 7.9 Hz, 2 H), 1.74-1.56 (m, 2 H), 1.50-1.31 (m, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.38 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 142.2, 135.7, 134.4, 134.0, 129.8, 129.3, 123.7, 123.6, 122.2, 117.1, 68.7, 36.0, 34.0, 22.7, 14.1, 0.13. HRMS calcd for $[M - H]^+$ $C_{20}H_{25}OSi$ 309.1669, found 309.1667.

9-Butyl-7-(trimethylsilyl)-6*H*-benzo[*c*]chromen-6-one (427). Isolated in 81% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.0 Hz and 1.4 Hz, 1 H), 7.96 (d, *J* = 1.4 Hz, 1 H), 7.67 (d, *J* = 1.4 Hz, 1 H), 7.52-7.42 (m, 1 H), 7.39-7.28 (m, 2 H), 2.81 (t, *J* = 7.7 Hz, 2 H), 1.81-1.65 (m, 2 H), 1.54-1.37 (m, 2 H), 1.00 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 151.3, 149.0, 146.1, 137.5, 135.5, 130.2, 124.4, 123.3, 123.0, 122.2, 118.7, 117.5, 36.5, 33.5, 22.6, 14.1, 0.6. HRMS calcd for $[M + Na]^+$ $C_{20}H_{24}O_2SiNa$ 347.1437, found 347.1440.

Experimental procedures and analytical data for compounds 400-402, 428, 431-436, 438, 444, 445, 447-454, and 456-464

2-Iodo-1,3-dimethoxybenzene (431).[276] MeI (53 μL, 0.85 mmol) was added to 2-iodoresorcinol (50 mg, 0.21 mmol) and K_2CO_3 (64 mg, 0.47 mmol) in DMF (200 μL) and was stirred for 3 h. H_2O (4 mL) and Et_2O (4 mL) were added, the layers separated, and the aqueous layer was extracted with Et_2O (4 mL × 2). The combined organic extracts were washed with water (5 mL × 2) then brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (9:1) to give 37 mg (65%) of **431** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.3 Hz, 1 H), 6.51 (d, *J* = 8.3 Hz, 2 H), 3.89 (s, 6 H).

1,3-Diacetoxy-2-iodobenzene (432). To a solution of 2-iodoresorcinol (54.4 mg, 0.23 mmol) and DMAP (cat.) in pyridine (900 μL) was added Ac_2O at 0 °C and was stirred for 3 h as it warmed to rt. H_2O (3 mL) and Et_2O (3 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic extracts were washed with water (4 mL) then brine (4 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1) to give 63 mg (85%) of **432** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 2.38 (s, 6 H).

1,3-Bis(*tert*-butyldimethylsilyloxy)-2-iodobenzene (433). 2-Iodoresorcinol (50 mg, 0.21 mmol) in DMF (100 μL × 2) was added to a solution of TBDMSCl (77 mg, 0.50 mmol) and imidazole (58 mg, 0.85 mmol) in DMF (100 μL) at 0 °C and allowed to stir as it warmed to rt. After completion, H_2O (3 mL) and Et_2O (3 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic extracts were washed with water (5 mL) twice then brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to dryness to give 92 mg (94%) of **433** as a white solid: Mp 96-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (t, *J* = 8.1 Hz, 1 H), 6.45 (d, *J* = 8.1 Hz, 2 H), 1.07 (s, 18 H), 0.28 (s, 12 H).

(2-(2,6-Dimethoxyphenyl)ethynyl)trimethylsilane (434). Ethynyltrimethylsilane (21 μL, 0.15 mmol) was added to a solution of **431** (20 mg, 0.076 mmol), CuI (1.4 mg, 0.007 mmol), bis(triphenylphosphine) palladium dichloride (2.6 mg, 0.004 mmol), in DMF/TEA (1:1, 300 μL), and the reaction was heated at 80 °C overnight. After cooling, H_2O (2 mL) and Et_2O (2 mL) were added, the layers separated, and the aqueous layer was extracted with Et_2O (3 mL X 2). The combined organic extracts were washed with water (4 mL × 2) then brine (4 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (20:1) to give 9 mg (50%) of **434** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.4 Hz, 1 H), 6.51 (d, *J* = 8.4 Hz, 2 H), 3.87 (s, 6 H), 0.29 (s, 9 H).

(2-(2,6-Diacetoxyphenyl)ethynyl)trimethylsilane (435). Ethynyltrimethylsilane (44 μL, 0.31 mmol) was added to a solution of **432** (25 mg, 0.078 mmol), CuI (1.5 mg, 0.008 mmol),

bis(triphenylphosphine) palladium dichloride (2.7 mg, 0.004 mmol), in DMF/TEA (1:1, 320 μL), and the reaction was heated at 80 °C overnight. After cooling, H_2O (1 mL) and Et_2O (2 mL) were added, the layers separated, and the aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1) to give 7.7 mg (34%) of **435** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (t, *J* = 8.2 Hz, 1 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 2.33 (s, 6 H), 0.25 (s, 9 H).

(2-(2-*tert*-Butyldimethylsilyloxy-6-hydroxyphenyl)ethynyl)trimethylsilane (436). Ethynyltrimethylsilane (18 μL, 0.13 mmol) was added to a solution of **433** (30 mg, 0.065 mmol), CuI (1.2 mg, 0.006 mmol), bis(triphenylphosphine) palladium dichloride (2.3 mg, 0.003 mmol), in DMF/TEA (1:1, 260 μL), and the reaction was heated at 80 °C overnight. After cooling, H_2O (2 mL) and Et_2O (2 mL) were added, the layers separated, and the aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (60:1) to give 5.7 mg (28%) of **436** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (t, *J* = 8.2 Hz, 1 H), 6.58 (d, *J* = 8.2 Hz, 1 H), 6.37 (d, *J* = 8.2 Hz, 1 H), 5.85 (s, 1 H), 1.04 (s, 9 H), 0.27 (s, 6 H).

1,3-Bis(3-(trimethylsilyl)prop-2-ynyloxy)-2-iodobenzene (438). 3-Bromo-1-trimethylsilyl-1-propyne (360 μL, 2.5 mmol) was added to 2-iodoresorcinol (200 mg, 0.85 mmol) and K_2CO_3 (468 mg, 3.4 mmol) in DMF (1.2 mL) and was stirred for 2 h. Saturated NH_4Cl (4 mL) and Et_2O (8 mL) were added, the layers separated, and the aqueous layer was extracted with Et_2O (8 mL X 2). The combined organic extracts were washed with water (5 mL × 2) then brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (70:1 to 50:1) to give 282 mg (73%) of **438** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, *J* = 8.3 Hz, 1 H), 6.72 (d, *J* = 8.3 Hz, 2 H), 4.76 (s, 4 H), 0.17 (s, 18 H).

2-(3-(Trimethylsilyl)prop-2-ynyloxy)-6-methoxybenzaldehyde (444). 3-Bromo-1-trimethylsilyl-1-propyne (43 μL, 0.31 mmol) was added to a solution of **443** (24 mg, 0.16 mmol) and K_2CO_3 (43 mg, 0.31 mmol) in DMF (760 μL) at rt. The reaction was stirred for 14 h and quenched with NH_4Cl (1 mL). The aqueous mixture was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (3 mL × 2) then brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (5:1) to give 31.5 mg (77%) of **444** as an off-white solid: Mp 85-88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.53 (s, 1 H), 7.46 (t, *J* = 8.4 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 4.78 (s, 2 H), 3.91 (s, 3 H), 0.17 (s, 9 H).

(3-(2-(2,2-Dibromovinyl)-3-methoxyphenoxy)prop-1-ynyl)trimethylsilane (445). CBr_4 (38 mg, 0.11 mmol) was added to PPh_3 (59 mg, 0.23 mmol), in DCM (500 μL) at 0 °C, and the solution stirred for 10 min. To this solution was added **444** (15 mg, 0.06 mmol) in DCM (200 μL × 2), and the solution was stirred for 1 h at rt. The reaction mixture was concentrated to dryness and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (50:1) to give 17.3 mg (72%) of **445** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.3 Hz, 1 H), 6.69 (d, *J* = 8.3 Hz, 1 H), 6.58 (d, *J* = 8.3 Hz, 1 H), 4.70 (s, 2 H), 3.83 (s, 3 H), 0.16 (s, 9 H).

(3-(2-Ethynyl-3-methoxyphenoxy)prop-1-ynyl)trimethylsilane (428). *n*-BuLi (2.4 M in hexanes, 322 μL, 0.277 mmol) was added dropwise to a solution of trimethylsilyldiazomethane (2 M in Et_2O, 772 μL, 1.54 mmol) in THF (5 mL) at −78 °C. The solution was stirred for 30 min before **444** (135 mg, 0.51 mmol) in THF (900 μL with 300 μL wash) was added dropwise over 20 min. The reaction was stirred for 1 h, warmed to rt, and allowed to stir for 2.5 h before the reaction was quenched at 0 °C with sat. NH_4Cl (3 mL). The aqueous mixture was extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with water (3 mL), brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (12:1) to give 83 mg (63%) of **428** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.5 Hz, 1 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 6.59 (d, *J* = 8.5 Hz, 1 H), 4.79 (s, 2 H), 3.91 (s, 3 H), 3.57 (s, 1 H), 0.16 (s, 9 H).

1-Methoxy-7-(trimethylsilyl)-9-(butyl)-6*H*-benzo[*c*]chromene (447). To a flamed dried microwave vial equipped with a stir bar was added **428** (15.7 mg, 0.06 mmol), 1-hexyne (70 μL, 0.6 mmol), Cp*Ru(cod)Cl (2.3 mg, 0.006 mmol), and dry toluene (1.3 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 14 min in a CEM Discover microwave synthesizer at 300 W. After cooling, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 19.1 mg (92%) of **447** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 1.7 Hz, 1 H), 7.22 (d, *J* = 1.7 Hz, 1 H), 7.17 (t, *J* = 8.2 Hz, 1 H), 6.71-6.64 (m, 2 H), 5.07 (s, 2 H), 3.94 (s, 3 H), 2.66 (t, *J* = 7.5 Hz, 2 H), 1.72-1.58 (m, 2 H), 1.51-1.35 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H), 0.35 (s, 9 H).

1-Methoxy-7-(trimethylsilyl)-9-((trimethylsilyl)methyl)-6*H*-benzo[*c*]chromene (448). To a flamed dried microwave vial equipped with a stir bar was added **428** (15 mg, 0.058 mmol), trimethyl(2-propynyl)silane (87 μL, 0.58 mmol), Cp*Ru(cod)Cl (2.2 mg, 0.0058 mmol), and dry toluene (1.2 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 14 min in a CEM Discover microwave synthesizer at 300 W. After cooling, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 18.3 mg (85%) of **448** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.6 Hz, 1 H), 7.16 (dt, *J* = 8.2, 0.5 Hz, 1 H), 7.05 (d, *J* = 1.6 Hz, 1 H), 6.70-6.63 (m, 2 H), 5.06 (s, 2 H), 3.92 (s, 3 H), 2.11 (s, 2 H), 0.34 (s, 9 H), 0.05 (s, 9 H).

1-Methoxy-9-butyl-6*H*-benzo[*c*]chromene (449). To a flamed dried microwave vial equipped with a stir bar was added **447** (16.4 mg, 0.048 mmol), DMF (100 µL), THF (200 µL) and TBAF (1 M in THF, 250 µL, 0.25 mmol), and the mixture was irradiated for 2 min. in a CEM Discover microwave synthesizer at 300 W. After cooling, water (2 mL) and Et_2O (3 mL) were added and the aqueous phase was extracted three times. The combined organic extracts were washed with water (2 mL) twice, brine (2 mL), dried, filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 9.3 mg (72%) of **449** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.17 (t, *J* = 8.2 Hz, 1 H), 7.12-7.08 (m, 2 H), 6.74-6.64 (m, 2 H), 4.98 (s, 2 H), 3.97 (s, 3 H), 2.68 (t, *J* = 7.5 Hz, 2 H), 1.74-1.58 (m, 2 H), 1.50-1.35 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

1-Methoxy-9-methyl-6*H*-benzo[*c*]chromene (450). To a flamed dried microwave vial equipped with a stir bar was added **448** (17.4 mg, 0.047 mmol), DMF (100 µL), THF (170 µL) and TBAF (1 M in THF, 280 µL, 0.28 mmol), and the mixture was irradiated for 2 min. in a CEM Discover microwave synthesizer at 300 W. After cooling, water (2 mL) and Et_2O (2 mL) were added, and the aqueous phase was extracted three times. The combined organic extracts were washed with water (2 mL) twice, brine (2 mL), dried, filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (50:1) to give 9.9 mg (93%) of **450** as a slight yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.19 (t, *J* = 8.2 Hz, 1 H), 7.13-7.03 (m, 2 H), 6.74-6.63 (m, 2 H), 4.98 (s, 2 H), 3.97 (s, 3 H), 2.42 (s, 3 H).

1-Methoxy-9-butyl-6*H*-benzo[*c*]chromen-6-one (451). To **449** (9.3 mg, 0.035 mmol), dissolved in DCM (700 μL) was added PCC (7.5 mg, 0.035 mmol), and the mixture was heated to 40 °C. After 1 h, 7.5 mg of PCC was added, and the reaction was stirred at 40 °C. After 2 h, 15 mg of PCC was added and the reaction was stirred overnight at 40 °C. In the morning, 7.5 mg of PCC was added, and the reaction was stirred a further 2 h, after which it was diluted with Et_2O (5 mL) and filtered through a silica plug. The filtrate was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (12:1) to give 7.5 mg (77%) of **451** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1 H), 8.35 (d, *J* = 8.3 Hz, 1 H), 7.48-7.34 (m, 2 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 4.08 (s, 3 H), 2.81 (t, *J* = 7.5 Hz, 2 H), 1.72 (p, *J* = 7.5 Hz, 2 H), 1.42 (t, *J* = 7.5 Hz, 2 H), 0.98 (t, *J* = 7.5 Hz, 3 H).

1-Methoxy-9-methyl-6*H*-benzo[*c*]chromen-6-one (452). To **450** (9.9 mg, 0.044 mmol), dissolved in DCM (850 μL) was added PCC (9.4 mg, 0.044 mmol) and the mixture was heated to 40 °C. After 1 h, 9.4 mg of PCC was added, and the reaction was stirred at 40 °C. After 2 h, 18.8 mg of PCC was added and the reaction was stirred overnight at 40 °C. In the morning, 9.4 mg of PCC was added, and the reaction was stirred a further 2 h, after which it was diluted with Et_2O (5 mL) and filtered through a silica plug. The filtrate was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (12:1) to give 8.8 mg (84%) of **452** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 8.34 (d, *J* = 8.1 Hz, 1 H), 7.46-7.36 (m, 2 H), 7.04 (dd, *J* = 8.3, 1.0 Hz, 1 H), 8.89 (dd, *J* = 8.3, 1.0 Hz, 1 H), 4.08 (s, 3 H), 2.57 (s, 3 H).

9-Butyl-1-methoxy-6,6-dimethyl-6*H*-benzo[*c*]chromene (453). A solution of **451** (7.5 mg, 0.027 mmol) in THF (100 µL, 100 µL wash) was added dropwise to a solution of MeLi (1.6 M in Et_2O, 100 µL, 0.16 mmol) in THF (200 µL) at 0 °C. The reaction mixture was stirred for 45 min, warmed to rt, and was stirred for 1 h. The reaction was then cooled to 0 °C and quenched with sat. NH_4Cl (1 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (2 mL) then brine (2 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The crude diol was taken up in DCM (200 µL), treated with TFA (one drop) and allowed to stir until complete by TLC. The reaction was diluted with Et_2O (3 mL) and washed with water (2 mL) and brine (2 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (45:1) to give 5.9 mg (75%) of **453** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 1.7 Hz, 1 H), 7.2-7.06 (m, 3 H), 6.67-6.62 (m, 2 H), 3.96 (s, 3 H), 2.66 (t, *J* = 7.5 Hz, 2 H), 1.74-1.58 (m, 8 H), 1.50-1.33 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

9-Butyl-1-hydroxy-6,6-dimethyl-6*H*-benzo[*c*]chromene (454). BBr_3 (1 M in DCM, 22 µL, 0.022 mmol) was added to a solution of **453** (5.9 mg, 0.02 mmol) in DCM (200 µL), and the reaction was stirred for 35 min as it warmed to rt. The reaction was quenched with sat. NH_4Cl (1 mL) and extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (1 mL × 2) then brine (1 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (16:1) to give 5.3 mg (61%) of **455** as a white solid. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.20 (d, *J* = 1.7 Hz, 1 H), 7.22-7.00 (m, 3 H), 6.60 (dd, *J* = 8.1, 1.1 Hz, 1 H), 6.47 (dd, *J* = 8.1, 1.1 Hz, 1 H), 5.20 (s, 1 H), 2.66 (t, *J* = 7.5 Hz, 2 H), 1.71-1.60 (m, 8 H), 1.48-1.31 (m, 2 H), 0.95 (t, *J* = 7.3 Hz, 3 H).

2-(3-(Trimethylsilyl)prop-2-ynyloxy)-6-methoxy-4-pentylbenzaldehyde (456). 3-Bromo-1-trimethylsilyl-1-propyne (76 μL, 0.54 mmol) was added to a solution of **455** (60 mg, 0.27 mmol) and K_2CO_3 (75 mg, 0.54 mmol) in DMF (1.3 mL) at rt. The reaction was stirred for 14 h and quenched with NH_4Cl (2 mL). The aqueous mixture was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (3 mL × 2) then brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (5:1) to give 80 mg (89%) of **456** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (s, 1 H), 6.56 (s, 1 H), 6.43 (s, 1 H), 4.78 (s, 2 H), 3.90 (s, 3 H), 2.59 (t, *J* = 7.8 Hz, 2 H), 1.74-1.59 (m, 2 H), 1.46-1.28 (m, 4 H), 0.90 (t, *J* = 6.6 Hz, 3 H), 0.16 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.0, 162.0, 160.7, 152.3, 113.1, 106.1, 105.0, 99.6, 93.7, 57.7, 56.1, 37.3, 31.6, 30.7, 22.6, 14.1, -0.22. HRMS calcd for $[M + H]^+$ $C_{19}H_{29}O_3Si$ 333.1880, found 333.1882.

2-Ethynyl-3-methoxy-5-pentyl-(3-(trimethylsilyl)prop-2-ynyloxy)benzene (457). *n*-BuLi (2.4 M in hexanes, 120 μL, 0.29 mmol) was added dropwise to a solution of trimethylsilyldiazomethane (2 M in Et_2O, 200 μL, 0.40 mmol) in THF (1.1 mL) at −78 °C. The solution was stirred for 30 min before **456** (40.8 mg, 0.12 mmol) in THF (300 μL with 2 × 300 μL wash) was added dropwise over 20 min. The reaction was stirred for 1 h, warmed

to rt, and allowed to stir for 1.5 h before the reaction was quenched at 0 °C with NH_4Cl (2 mL). The aqueous mixture was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (3 mL), brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (45:1) to give 28.7 mg (71%) of **457** as a slight yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, *J* = 1.1 Hz, 1 H), 6.40 (d, *J* = 1.1 Hz, 1 H), 4.77 (s, 2 H), 3.89 (s, 3 H), 3.52 (s, 1 H), 2.59 (t, *J* = 7.8 Hz, 2 H), 1.72-1.55 (m, 2 H), 1.44-1.28 (m, 4 H), 0.91 (t, *J* = 6.9 Hz, 3 H), 0.16 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 160.3, 146.1, 106.2, 104.5, 100.2, 98.6, 93.3, 85.0, 76.5, 57.6, 56.2, 37.0, 31.6, 31.0, 22.6, 14.1, -0.20. HRMS calcd for $[M + H]^+$ $C_{20}H_{29}O_2Si$ 329.1931, found 329.1935.

1-Methoxy-7-(trimethylsilyl)-9-((trimethylsilyl)methyl)-3-pentyl-6*H*-benzo[*c*]chromene (458). To a flame-dried microwave vial equipped with a stir bar was added **457** (27.9 mg, 0.085 mmol), trimethyl(2-propynyl)silane (126 μL, 0.85 mmol), Cp*Ru(cod)Cl (3.1 mg, 0.0085 mmol), and dry toluene (2 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 14 min in a CEM Discover microwave synthesizer at 300 W. After cooling, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (60:1) to give 32.9 mg (88%) of **458** as a slight yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.8 Hz, 1 H), 7.02 (d, *J* = 1.8 Hz, 1 H), 6.51 (d, *J* = 1.5 Hz, 1 H), 6.74 (d, *J* = 1.5 Hz, 1 H), 5.05 (s, 2 H), 3.92 (s, 3 H), 2.57 (t, *J* = 7.7 Hz, 2 H), 2.11 (s, 2H), 1.74-1.58 (m, 2 H), 1.45-1.30 (m, 4 H), 0.90 (t, *J* = 6.7 Hz, 3 H), 0.34 (s, 9 H), 0.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 156.7, 144.4, 138.7,

134.3, 133.2, 132.6, 128.6, 127.2, 111.2, 109.8, 105.8, 69.0, 55.7, 36.3, 31.7, 30.9, 27.3, 22.7, 14.2, 0.2, -1.8. HRMS calcd for $[M + H]^+$ $C_{26}H_{41}O_2Si_2$ 441.2639, found 441.2635.

1-Methoxy-9-methyl-3-pentyl-6*H*-benzo[*c*]chromene (459). To a flame-dried microwave vial equipped with a stir bar was added **458** (34.4 mg, 0.078 mmol), DMF (100 µL), and TBAF (1 M in THF, 470 µL, 0.47 mmol) and the mixture was irradiated for 2 min in a CEM Discover microwave synthesizer at 300 W. After cooling, water (3 mL) and Et_2O (3 mL) were added, the layers were separated, and the aqueous phase was extracted with Et_2O (3 mL × 2). The combined organic extracts were washed with water (3 mL × 2), brine (3 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (60:1) to give 22.2 mg (96%) of **459** as a slight yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1 H), 7.06 (s, 2 H), 6.53 (s, 1 H), 6.49 (s, 1 H), 4.96 (s, 2 H), 3.96 (s, 3 H), 2.56 (t, *J* = 7.7 Hz, 2 H), 2.41 (s, 3 H), 1.75-1.59 (m, 2 H), 1.47-1.29 (m, 4 H), 0.90 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.8, 144.7, 137.6, 129.2, 128.9, 127.3, 126.9, 124.3,110.5, 110.1, 105.6, 69.0, 55.8, 36.3, 31.7, 30.9, 22.7, 22.0, 14.2. HRMS calcd for $[M + H]^+$ $C_{20}H_{25}O_2$ 297.1849, found 297.1848.

1-Methoxy-9-methyl-3-pentyl-6*H*-benzo[*c*]chromen-6-one (460). To **459** (19.4 mg, 0.065 mmol), dissolved in DCM (1.3 mL) was added PCC (14.2 mg, 0.065 mmol) and the mixture was heated to 40 °C. After 1 h, 14.2 mg of PCC were added and stirring was continued at 40 °C. After 2 h, 28.4 mg of PCC were added and the reaction was stirred overnight at 40 °C. In the morning, 14.2 mg of PCC were added, and the reaction was stirred a further 2 h, after

which it was diluted with Et_2O (3 mL) and filtered through a silica plug. The filtrate was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (15:1) to give 19.9 mg (98%) of **460** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1 H), 8.29 (d, *J* = 8.25 Hz, 1 H), 7.32 (d, *J* = 8.25, 1 H), 6.85 (s, 1 H), 6.68 (s, 1H), 4.06 (s, 3 H), 2.65 (t, *J* = 7.7 Hz, 2 H), 2.54 (s, 3 H), 1.77-1.61 (m, 2 H), 1.47-1.30 (m, 4 H), 0.89 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 158.3, 152.8, 145.8, 145.6, 134.9, 130.3, 128.9, 127.4, 118.4, 110.2, 107.4, 106.1, 56.0, 36.2, 31.6, 30.7, 22.8, 22.7, 14.2. HRMS calcd for $[M + H]^+$ $C_{20}H_{23}O_3$ 311.1641, found 311.1646.

Cannabinol methyl ether (401). A solution of **460** (18.5 mg, 0.060 mmol) in THF (300 µL, 2 × 200 µL wash) was added dropwise to a solution of MeLi (1.6 M in Et_2O, 373 µL, 0.60 mmol) in THF (200 µL) at 0 °C. The reaction mixture was stirred for 45 min, warmed to room temperature, and let stir for 1 h. The reaction was then cooled to 0 °C and quenched with sat. NH_4Cl (1 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The crude diol was taken up in DCM (450 µL), treated with TFA (one drop) and allowed to stir until complete by TLC. The reaction was diluted with Et_2O (3 mL) and washed with water (3 mL) and brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (60:1) to give 17.6 mg (91%) of **401** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.18-7.03 (m, 2 H), 6.49 (s, 1 H), 6.45 (s, 1 H), 3.95 (s, 3 H), 2.54 (t, *J* = 7.7 Hz, 2 H), 2.39 (s, 3 H), 1.70-1.58 (m, 8 H), 1.41-1.28 (m,

4 H), 0.88 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 154.5, 144.5, 137.0, 136.6, 127.8, 127.6, 127.2, 122.4, 111.1, 110.0, 105.2, 77.2, 55.7, 36.3, 31.7, 30.8, 27.2, 22.7, 21.7, 14.2. HRMS calcd for $[M + H]^+$ $C_{22}H_{29}O_2$ 325.2162, found 325.2161.

Cannabinol (400). To **401** (8.7 mg, 0.027 mmol) in Ac_2O (200 µL) was added 47% aqueous HI (200 µL) at rt, and the mixture was heated at 120 °C for 7 h. After cooling, water (1 mL) and Et_2O (2 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 mL × 2), and the combined organic extracts were washed with 20% Na_2SO_3 (3 mL), 1 M $NaHCO_3$ (3 mL), and water (3 mL), dried ($MgSO_4$), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (15:1) to give 6.4 mg (77%) of **400** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 7.19-7.03 (m, 2 H), 6.45 (d, J = 1.65 Hz, 1 H), 6.30 (d, J = 1.65 Hz, 1 H), 5.14 (br s, 1 H), 2.49 (t, J = 7.7 Hz, 2 H), 2.39 (s, 3 H), 1.68-1.58 (m, 8 H), 1.41-1.28 (m, 4 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$)[ii] δ 154.8, 153.1, 144.7, 137.1, 127.7, 127.6, 126.5, 122.8, 111.0, 110.0, 108.8, 77.4, 35.8, 31.6, 30.6, 27.3, 22.7, 21.7, 14.2. HRMS calcd for $[M + H]^+$ $C_{21}H_{27}O_2$ 311.2005, found 311.2005.

2-Methanesulfonyloxy-6-methoxy-2'-(prop-1-en-2-yl)-5'-methyl-4-pentyl-biphenyl (461). A solution of **460** (12.1 mg, 0.039 mmol) in THF (300 µL, 200 µL wash) was added dropwise to a solution of MeLi (1.6 M in Et_2O, 243 µL, 0.39 mmol) in THF (150 µL) at 0 °C. The reaction mixture was stirred for 45 min, warmed to room temperature, and was

[ii] Not all quaternary carbons were observed.

stirred for 1 h. The reaction was then cooled to 0 °C and quenched with sat. NH_4Cl (1 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The crude diol was taken up in DCM (400 µL) and treated with TEA (33 µL, 0.23 mmol) and MsCl (12 µL, 0.16 mmol) at 0 °C. After 1 h at 0 °C, the reaction was diluted with H_2O (1 mL) and Et_2O (2 mL), the layers separated, and extracted with Et_2O (2 mL × 2). The combined organic extracts were washed with water (2 mL) then brine (2 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (16:1) to give 10.5 mg (67%) of **461** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 1 H), 7.20-7.08 (m, 2 H), 6.85 (s, 1 H), 6.70 (s, 1 H), 4.90-4.85 (m, 1 H), 4.67-4.63 (m, 1 H), 3.76 (s, 3 H), 2.65 (t, *J* = 7.5 Hz, 2 H), 2.47 (s, 3 H), 2.36 (s, 3 H), 1.89-1.88 (m, 3 H), 1.76-1.60 (m, 2 H), 1.46-1.31 (m, 4 H), 0.93 (t, *J* = 6.7 Hz, 3 H).

1-Hydroxy-9-methyl-3-pentyl-6*H*-benzo[*c*]chromen-6-one (462).[287] To **460** (19.3 mg, 0.062 mmol) in Ac_2O (500 µL) was added 47% aqueous HI (600 µL) at rt, and the mixture was heated to 120 °C for 5 h. After cooling, water (2 mL) and Et_2O (3 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 mL × 2), and the combined organic extracts were washed with 20% Na_2SO_3 (3 mL), 1 M $NaHCO_3$ (3 mL), and water (3 mL), dried ($MgSO_4$), filtered and concentrated to give 18.5 mg (100%) of **462** as a white solid.

2,6-Bis-(methanesulfonyloxy)-2'-(prop-1-en-2-yl)-5'-methyl-4-pentyl-biphenyl (463). The lactone **462** (10.9 mg, 0.037 mmol) was dissolved in THF/Et_2O (1:2, 900 µL, 2 × 250 µL wash) and was added to a solution of MeMgBr (2.5 M in Et_2O, 370 µL, 0.919 mmol) in Et_2O (1.0 mL) at rt. The mixture was heated at 45 °C for 2 h then stirred at rt overnight. After cooling to 0 °C, the reaction was quenched with 10% NH_4Cl (1 mL), diluted with Et_2O (2 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 mL × 2), and the combined organic extracts were washed with water (2 mL) and brine (2 mL), dried (Na_2SO_4), filtered, and concentrated to give the crude triol which was used directly for the next step.

To the crude triol in DCM (500 µL) at 0 °C was added triethylamine (51 µL, 0.368 mmol) then methanesulfonyl chloride (17 µL, 0.221 mmol) dropwise. The mixture was allowed to stir for 75 min at 0 °C, was diluted with H_2O (1 mL) and Et_2O (2 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 mL × 2), and the combined organic extracts were washed with water (2 mL) and brine (2 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1 to 4:1) to give 10.4 mg (61%) of **463** as a colorless oil and 3.1 mg (22%) of **464** as a white solid. **463**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.28 (m, 1 H), 7.24-7.18 (m, 4 H), 4.97-4.92 (m, 1 H), 4.63 (s, 1 H), 2.65 (t, *J* = 8.0 Hz, 2 H), 2.60 (s, 6 H), 2.37 (s, 3 H), 2.01-1.96 (m, 3 H), 1.76-1.60 (m, 2 H), 1.47-1.30 (m, 4 H), 0.90 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 145.2, 143.3, 141.4, 136.4, 132.5, 129.6, 128.8, 128.2, 126.3, 121.8, 116.3, 38.6, 35.6, 31.5, 30.5, 23.5, 22.6, 21.0, 14.1. HRMS calcd for $[M + H]^+$ $C_{23}H_{31}O_6S_2$ 467.1556, found 467.1558. **464**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1 H),

7.21-7.10 (m, 2 H), 6.90 (d, J = 1.2 Hz, 1 H), 6.80 (d, J = 1.2 Hz, 1 H), 2.94 (s, 3 H), 2.60 (t, J = 7.3 Hz, 2 H), 2.40 (s, 3 H), 1.72-1.58 (m, 8 H), 1.41-1.29 (m, 4 H), 0.94 (t, J = 6.8 Hz, 3 H).

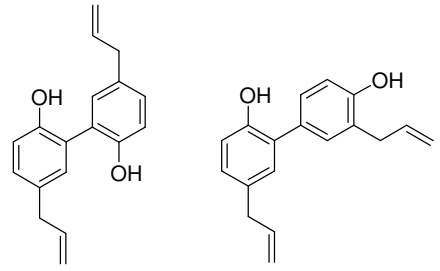
Cannabinodiol (402). To a solution of **463** (10.4 mg, 0.022 mmol) in THF (1.1 mL) was added MeLi (1.6 M in Et_2O, 170 µL, 0.267 mmol) dropwise at 0 °C. The reaction was stirred for 18 min and quenched with 10% NH_4Cl (1 mL). The aqueous layer was extracted with Et_2O (2 mL × 3). The combined organic extracts were washed with water (2 mL), then brine (2 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography deactivated with TEA, eluting with hexanes/Et_2O (4:1) to give 5.0 mg (72%) of **402** as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6) δ 7.15-7.10 (m, 1 H), 6.91-6.85 (m, 1 H), 6.83-6.79 (m, 1 H), 6.52 (s, 2 H), 4.93-4.89 (m, 2 H), 4.44 (br s, 2 H), 2.40 (t, J = 7.7 Hz, 2 H), 1.97 (s, 3 H), 1.80-1.78 (m, 3 H), 1.61-1.46 (m, 2 H), 1.28-1.12 (m, 4 H), 0.81 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D6) δ 154.1, 145.4, 145.2, 143.3, 138.4, 133.2, 130.2, 129.9, 128.9, 115.9, 113.6, 108.0, 36.2, 31.8, 31.2, 23.2, 22.9, 20.8, 14.3. HRMS calcd for $[M + H]^+$ $C_{21}H_{27}O_2$ 311.2005, found 311.2006.

CHAPTER 6: Progress Towards the Total Synthesis of Neolignan Natural Products

6.1 Background and Retrosynthetic Analysis

6.1.1 Neolignan Natural Products

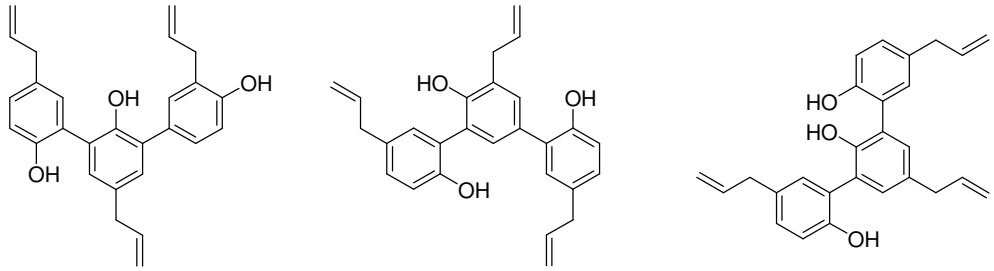
The use of botanicals for medicinal purposes dates back thousands of years and continues today.[289-291] While one does not need to know the active component(s) of the plant to benefit from its effects, scientists continually seek better therapies for numerous ailments, and active ingredients in herbal extracts have been profitable starting points. Within Chinese and Japanese folk medicine, the extract of the bark of *Magnolia officinalis* has been used for the treatment of bronchitis and emphysema.[292]



magnolol (**465**) honokiol (**466**)

Figure 6.1. Structures of magnolol (**465**) and honokiol (**466**).

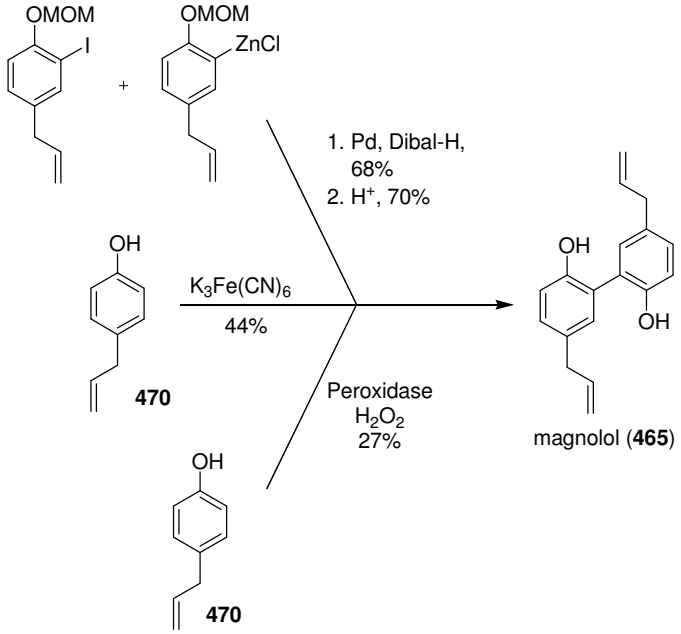
Studies on the extracts revealed two compounds, magnolol (**465**) and honokiol (**466**) (Figure 6.1), were able to inhibit Epstein-Barr virus early antigen activation.[293] These isomeric biphenyl-neolignan natural products have also shown anti-oxidant,[294-296] anti-anxiety,[297] anti-depressant,[298] anti-inflammatory,[299] anti-cancer,[300] and anti-bacterial properties.[301] The related triphenyl-neolignans simonsinol (**467**),[302] macranthol (**468**),[303] and dunnianol (**469**)[304] have been isolated from various *Illicium* species (Figure 6.2). Among these, macranthol has shown neuroprotective activity.[305]



simonsinol (**467**) macranthol (**468**) dunnianol (**469**)

Figure 6.2. Structures of simonsinol (**467**), macranthol (**468**), and dunnianol (**469**).

Previous syntheses of magnolol have relied on couplings of the monomeric allyl-phenol (**470**) or derivatives thereof (Scheme 6.1).[306, 307] Also, the use of the enzyme peroxidase provided magnolol and dunnianol, albeit in low yields.[308]

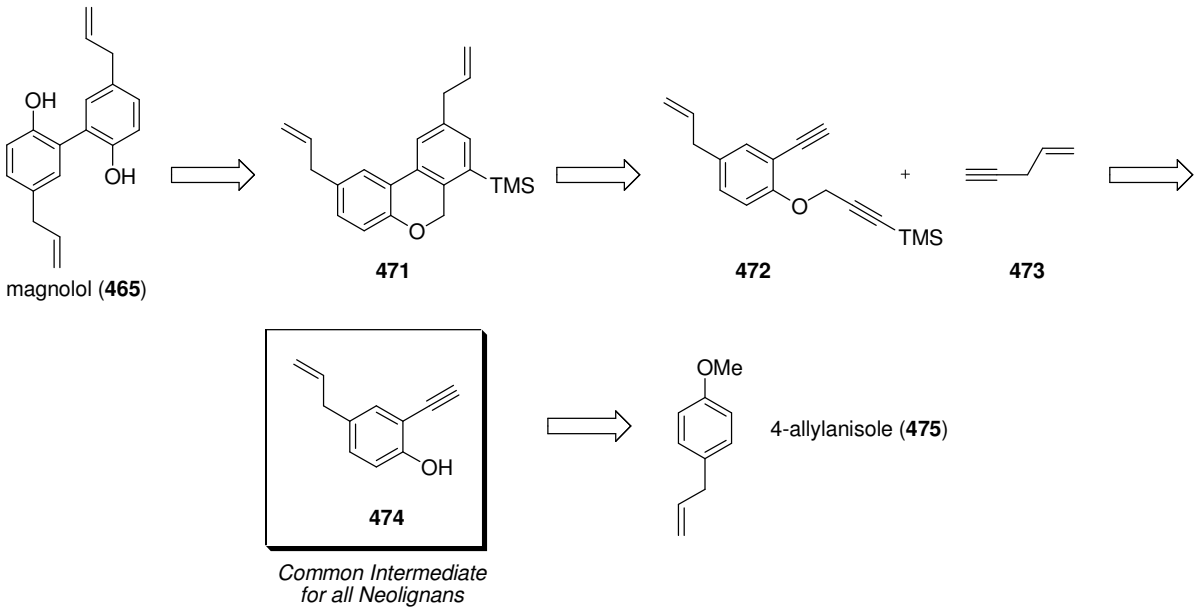


Scheme 6.1. Previous syntheses of magnolol (**465**).

6.1.2 Retrosynthetic Analysis

While these syntheses are succinct, we sought to synthesize the four neolignans **465** and **467**-**469** via one unified approach relying upon the [2+2+2] cyclotrimerization reaction.

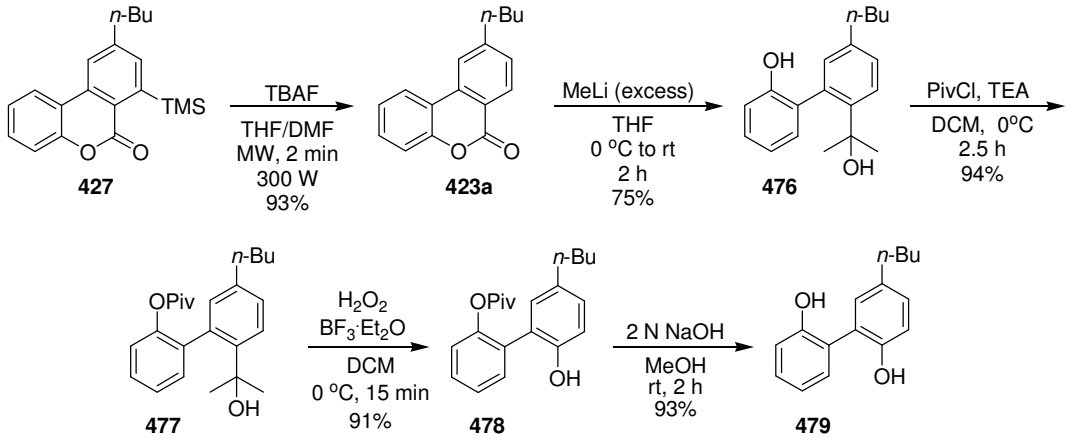
Using strategies from both the synthesis of illudinine and the cannabinoids,[172, 309] we envisioned deriving magnolol through the opening of the dibenzopyran intermediate **471** followed by oxidative rearrangement via a Baeyer-Villiger reaction or benzylic hydroperoxide rearrangement (Scheme 6.2). The dibenzopyran intermediate **471** would be derived from a [2+2+2] cyclotrimerization reaction between a suitably substituted diyne **472** and allylacetylene (**473**). As with the cannabinoids, a trimethylsilyl- group will be used to induce regiocontrol in the cyclotrimerization event. The diyne **472** would be prepared from the common intermediate **474** which in turn would be derived from commercially available 4-allylanisole (**475**). Other diynes and monoynes would be necessary for the other three neolignans, however, we foresaw the use of the common intermediate **474** in each of the syntheses.



Scheme 6.2. Retrosynthetic analysis of magnolol (**465**).

6.2 Early Model Studies Toward Phenol Introduction

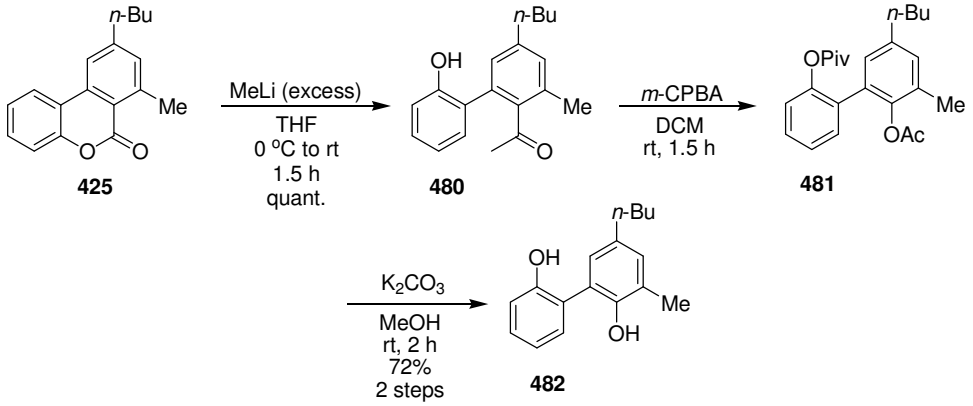
Before embarking on the syntheses of the neolignans, we first explored the installation of the second phenol from dibenzopyran intermediates. Compounds **427** and **425** were available from the cannabinoid model study and would provide simplified systems to determine whether introduction of a second phenol would be practical. Towards this end, desilylation of **427** with TBAF under microwave irradiation provided the pyrone **423a** in 93% yield, and opening of the lactone ring with excess MeLi furnished the diol **476** in 75% yield. Being aware of the sensitivity of the diol towards acid catalyzed ring closure, the phenol was first selectively protected as the pivaloate ester to provide the monoalcohol **477** in 94% yield. Subsequent treatment of **477** with BF_3/H_2O_2 in DCM effected the benzylic hydroperoxide rearrangement[165] to produce the phenol **478** in 91% yield. Hydrolysis of the pivaloate ester with 2 N NaOH afforded the bisphenol **479** (Scheme 6.3). These results indicated that formation of the bisphenolic core of magnolol was indeed feasible.



Scheme 6.3. Model study towards magnolol core structure.

The triphenyl-neolignans, on the other hand, contain substitutions *ortho* to the phenol in the central ring. This substitution will affect the MeLi addition, and, therefore, it was

necessary to investigate a route to the substituted bisphenol core. Compound **425**, where a methyl group is present, served as the model system in this situation. Treatment of **425** with excess MeLi gave a quantitative yield of the methyl-ketone **480**. This single addition of MeLi into the lactone was expected based on the results from the total synthesis of illudinine.[172] As no cyclization with the phenol could occur, direct oxidation of the methyl-ketone **480** was accomplished with *m*-CPBA (*meta*-chloroperbenzoic acid) to provide the crude acetate **481**.[223] Methanolysis of the ester provided the bisphenol **482** in 72% yield over two steps (Scheme 6.4).



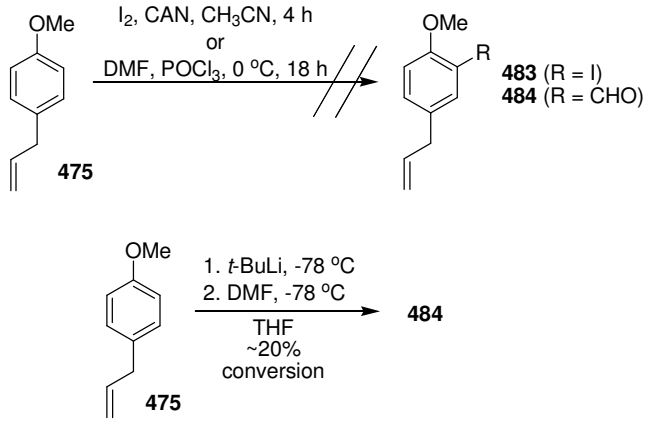
Scheme 6.4. Model study towards the bisphenol moiety of the triphenyl-neolignans.

With the success of the model studies, the synthesis of the common intermediate **474** could commence.

6.3 Synthesis of the Common Intermediate **474**

*6.3.1 Early Synthetic Attempts Towards **474***

By having one allyl group already installed in the starting material, additional steps for its introduction can be avoided. Fortuitously, 4-allylanisole (**475**) is commercially available and, as only the ethynyl group needs to be installed, could hypothetically provide an entry into the common intermediate **474** in short order. Towards this end, functionalization of the 2-position of 4-allylanisole that would provide a handle to introduce the alkyne moiety was investigated. Iodination[310] of **475** towards the iodide **483** and formylation under Vilsmeier-Haack[311, 312] conditions towards the benzaldehyde **484** were unsuccessful, and directed-*ortho*-metalation[313] utilizing *t*-BuLi as base only gave ~20% conversion to **484** (Scheme 6.5).

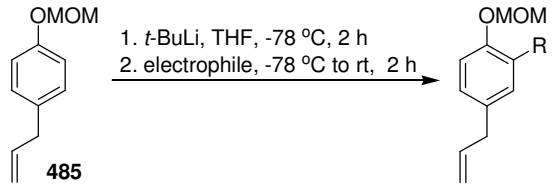


Scheme 6.5. Attempts to substitute 4-allylanisole (**475**).

4-Allylphenol (**470**)[307] was equally unreactive under various Vilsmeier-Haack conditions[311, 312] and gave a mixture of mono- and di-iodinated products when treated with I_2/$NaHCO_3$.[314]

Being aware of the ability of MOM-ethers to direct lithiation,[315] we prepared the known MOM-ether **485** and explored iodination and formylation conditions. According to

literature precedent,[307] treatment of **485** with *t*-BuLi followed by I_2 provided the desired aryliodide **486** in 90% yield (Scheme 6.6). However, in our hands, only an approx. 40% conversion was obtained. The issue was further complicated by the fact that the product and starting material could not be separated by flash-chromatography.



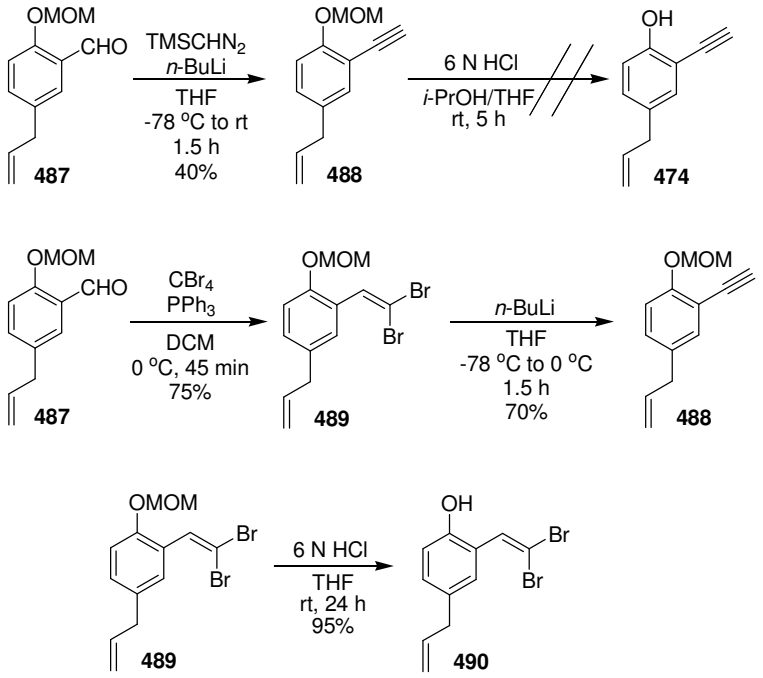
Electrophile	R	Yield (%)
I_2	I, **486**	40[a]
DMF	CHO, **487**	38
MFA[b]	CHO	36

Scheme 6.6. Directed-ortho-metalation reactions with **485**.
[a]Conversion by NMR. [b]Et_2O instead of THF.

Attempts to formylate **485** were similarly inefficient. The benzaldehyde **487** could be obtained in ~40% yield using either DMF or *N*-methylformanilide (MFA) as the electrophile (Scheme 6.6). Deuteration studies showed complete incorporation of deuterium when the MOM-ether **485** was deprotonated with *t*-BuLi and the subsequent anion was quenched with deuterated methanol. This result pointed to the formylation event as the problem with impure reagents most likely to blame. However, neither the use of freshly distilled DMF or MFA dried over sieves improved the yield of **487**.

Despite the low yields, efforts to elaborate the benzaldehyde **487** to the common intermediate were continued. Treatment of **487** with the lithium salt of trimethylsilyldiazomethane effected a Colvin rearrangement to provide the acetylene derivative **488** in a poor 40% yield. [280, 281] Only deprotection of the MOM-ether remained to complete the synthesis of the common intermediate, however, the acidic cleavage conditions[316] led to competitive decomposition of the product phenol **474** (Scheme 6.7). Using the Corey-Fuchs reaction provided **488** in a slightly better yield from the benzaldehyde

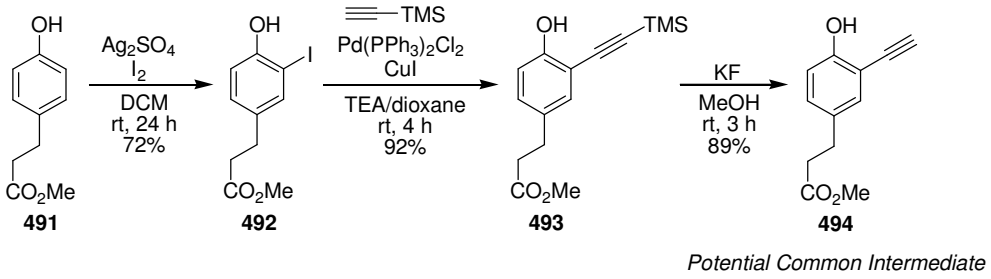
487 via the dibromide **489**,[279] but further inquests utilizing this route were suspended as the deprotection of **488** failed to cleanly provide the phenol **474** (Scheme 6.7). To circumvent the decomposition of the common intermediate under acidic conditions, we explored the use of the vinyldibromide as a masked acetylene, and, thereby, a surrogate to the original common intermediate **474**. In this direction, the MOM-ether **489** was deprotected with 6 N HCl to furnish the phenol **490** in 95% yield (Scheme 6.7). Further details into the use of **490** in the synthesis of the neolignans will be detailed below.



Scheme 6.7. Attempted synthesis of the phenol **474** and deprotection of the MOM-ether **489**.

6.3.2 Approach to a Common Intermediate Utilizing an Allyl-Group Surrogate

Due to the unforeseen problems associated with employing allylacetylene in the cyclotrimerization step (see Scheme 6.11 below), another strategy towards a common intermediate relied upon using a surrogate for the allyl group which could then be installed either before or after the cyclotrimerization event. The commercially available methyl 3-(4-hydroxyphenyl)propanoate (**491**) served as the starting point. Iodination of **491** using Ag_2SO_4[317] as the catalyst smoothly provided the iodide **492** in 72% yield. Installation of the first alkyne via Sonogashira coupling with TMS-acetylene gave the arylacetylene **493** in 92% yield. The alkyne was then deprotected with KF to provide the *o*-ethynylphenol derivative **494** in 89% yield (Scheme 6.8).



Scheme 6.8. Synthesis of the allyl-group surrogate **494**.

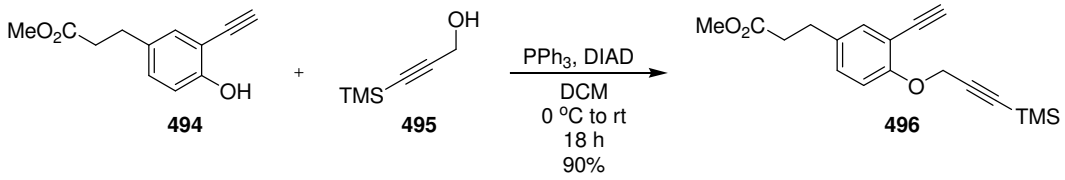
6.4 Progress Towards the Neolignan Natural Products

Because the order and conditions for several steps in the synthesis of the neolignans were in question, the simplest neolignan, magnolol (**465**), would be used as a model for the other neolignans. Each neolignan synthesis, though, contained its own unique challenges that would need to be addressed in due course. The magnolol synthesis would provide answers to

the cyclotrimerization event as well as the installation of the phenol functionalities. It was hoped that these conditions would be applicable to all the neolignans.

6.4.1 Progress Towards the Synthesis of Magnolol

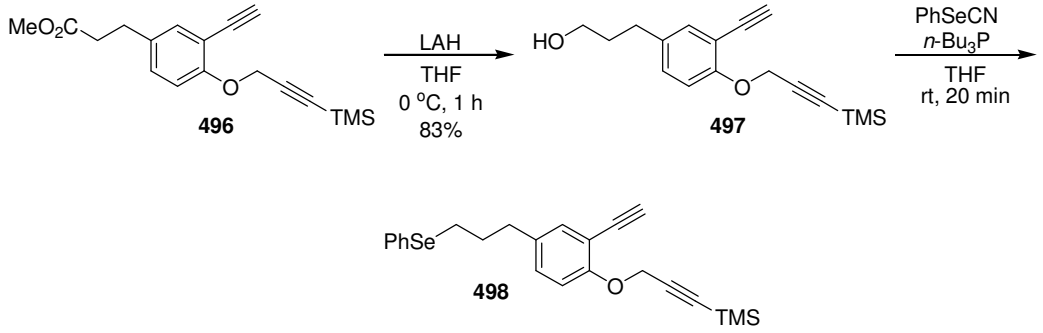
Preparation of a diyne to be used in the synthesis of magnolol began with intermediate **494**. Several factors needed to be considered to properly choose the structure of the diyne. First, we required a removable regiodirecting group during the cyclotrimerization reaction, and this functionality would need to be present in the diyne. The use of a TMS-group as a removable regiodirecting is well known in the literature and would satisfy this requirement.[53, 154, 309] Also, the linkage (either ether or ester) that connects the second alkyne to the phenol must be compatible with installation of the allyl group. If an ester linkage were used, reactions that manipulate the ester in the side chain would undoubtedly alter a lactone structure; therefore, the less reactive ether linkage would be more advantageous. With these requirements in mind, the diyne **496** was synthesized in one step and 90% yield from **494** via the Mitsunobu reaction with 3-(trimethylsilyl)prop-2-yn-1-ol (**495**) (Scheme 6.9).



Scheme 6.9. Synthesis of the diyne **496**.

At this juncture, installation of the allyl functionality was explored. We envisioned forming the double bond via elimination of an alcohol. Towards this end, reduction of the ester group in **496** with lithium aluminum hydride (LAH) gave the alcohol **497** in 83% yield.

Conversion to the phenylselenide **498** proceeded well, however, purification from the selenocyanate reagent proved difficult (Scheme 6.10).

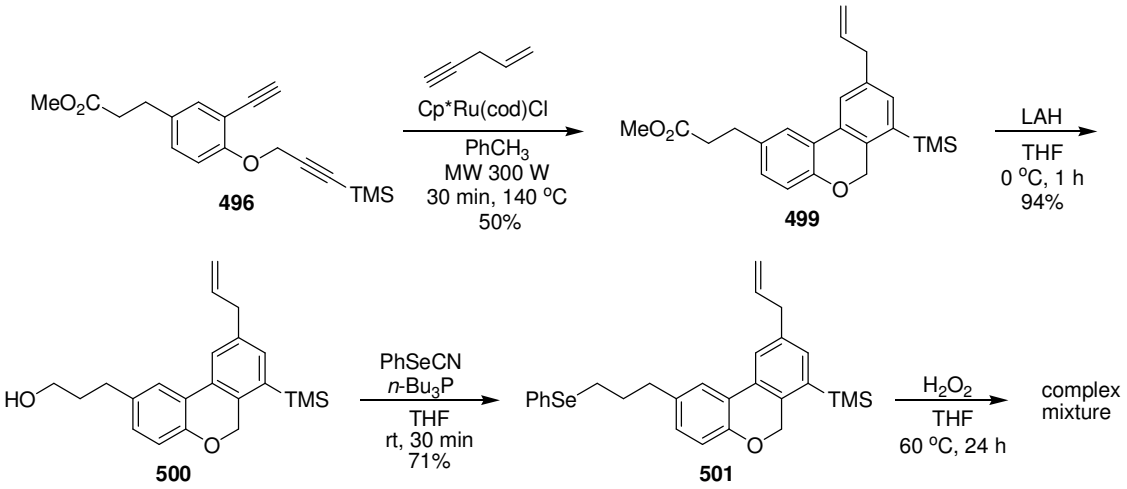


Scheme 6.10. Attempted synthesis of the selenide **498**.

Other means to eliminate an alcohol (e.g. xanthate pyrolysis or halide elimination) were not investigated with this substrate. Studies concurrent with these investigations focused on the cyclotrimerization reaction of the diyne **496**; the formation of the allyl group would then occur at a later point in the synthesis.

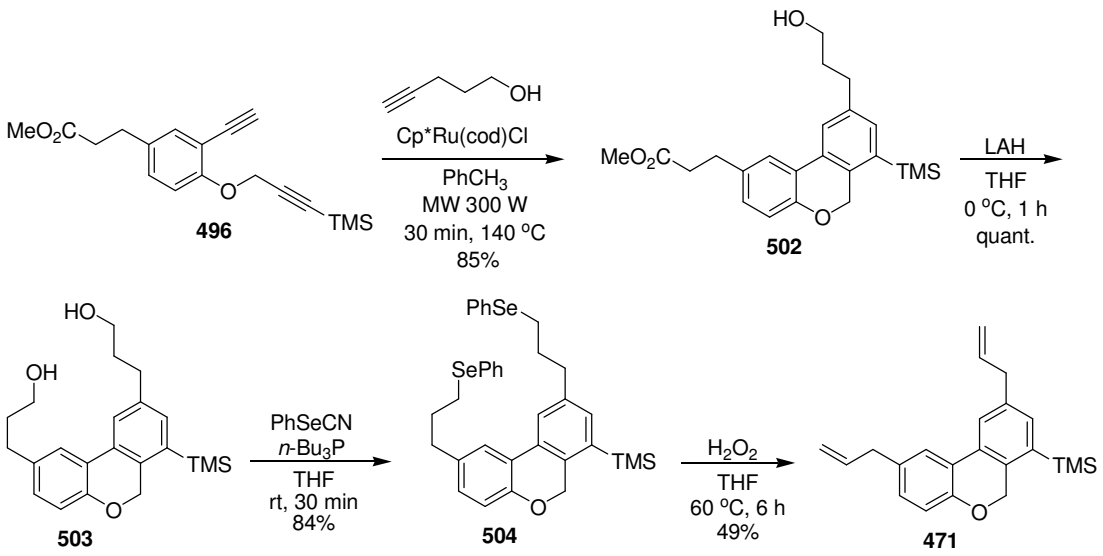
Disconnecting intermediate **471** from the retrosynthesis using the [2+2+2] cyclotrimerization transform gives allylacetylene as the monoyne reaction partner in the cyclotrimerization reaction. The diyne **496** was reacted with excess allylacetylene under Cp*Ru(cod)Cl catalysis and microwave irradiation for 15 minutes to furnish the dibenzopyran **499** in 28% yield along with unreacted starting material. Increasing the reaction time to 30 minutes led to complete consumption of starting material, but only a 50% yield of **499** (Scheme 6.11). Because of the low yield, we speculated that the double bond in the monoyne decreases the efficiency of the cyclotrimerization reaction. Nevertheless, progress towards magnolol was continued. Reduction of the ester with LAH provided the alcohol **500** in 94% yield which was converted to the phenylselenide **501** in 71% yield. The

oxidation of the selenide and elimination to the double bond, however, gave a complex mixture.



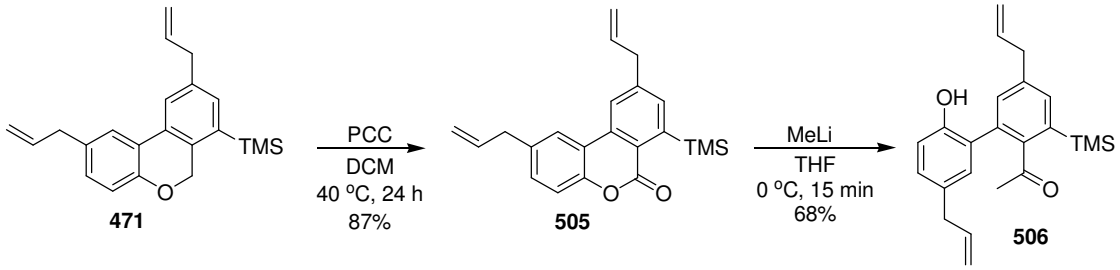
Scheme 6.11. Cyclotrimerization reaction using allylacetylene.

To overcome the low yield in the cyclotrimerization event, a different monoyne was used that contained a functional group amenable to double bond installation at a later stage. Pent-4-yn-1-ol would provide the necessary elements for a high yielding cyclotrimerization reaction and could participate in the same reactions as the other alcohol towards double bond formation. The diyne cyclotrimerized with pent-4-yn-1-ol (10 eq) under Cp*Ru(cod)Cl catalysis (10 mol%) and microwave irradiation (300 W, 30 min, 140 °C) to provide the desired dibenzopyran **502** in 85% yield as one regioisomer. Continuing as previously, reduction with LAH to give the diol **503** proceeded in quantitative yield, and conversion to the bisphenylselenide **504** was accomplished in 84% yield. Oxidation and elimination of both phenylselenides gave the tricyclic diallyl derivative **471** in 49% yield (Scheme 6.12). The next steps in the synthesis of magnolol would only require opening the pyran moiety in order to install the second phenol.



Scheme 6.12. Utilizing pent-4-yn-1-ol in the cyclotrimerization event.

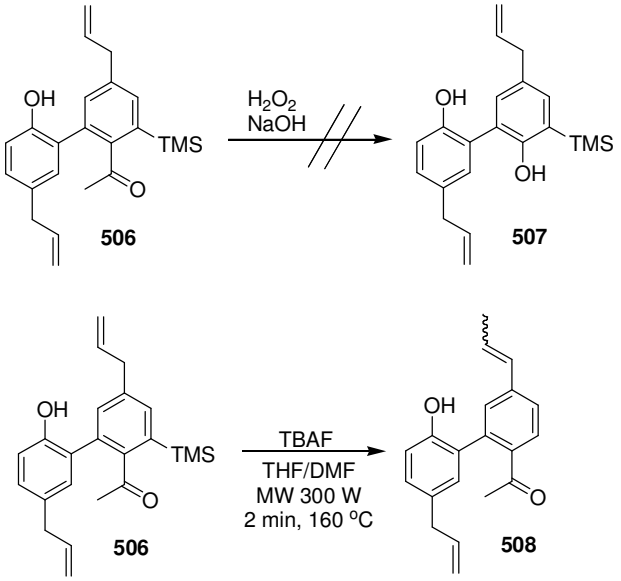
As stated previously, we hypothesized opening the pyran as achieved in the cannabinoid syntheses via a lactone intermediate. In this direction, the pyran **471** was oxidized with PCC to furnish the pyrone **505** in 87% yield. Opening of the lactone ring with methyllithium provided the methyl-ketone **506** in 68% yield. A second addition of the methyllithium reagent was thwarted by the congested steric environment created by the TMS-group and phenyl ring in the *ortho* positions (Scheme 6.13).



Scheme 6.13. Conversion of the pyran **471** to the methyl-ketone **506**.

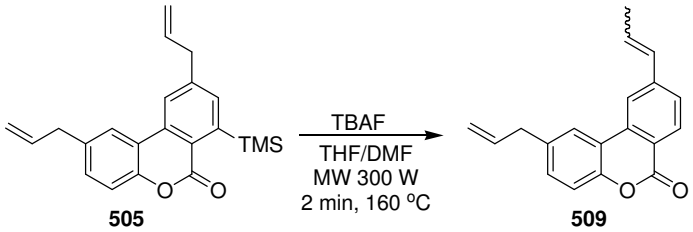
The methyl-ketone **506** was then treated with basic hydrogen peroxide in the hopes of providing the bisphenol **507**, however, no reaction occurred. Steric hindrance of the methylketone most likely prevented formation of the tetrahedral intermediate (Scheme 6.14).

Attempts were then made to desilylate **506** in order to allow for a more facile rearrangement. Treatment of **506** with TBAF under microwave irradiation led to complete desilylation, however analysis of the crude ^{1}H NMR spectrum revealed isomerization of one of the double bonds to give **508**. The allyl group *para* to the ketone is more prone to isomerization due to the increased acidity of the methylene proton.



Scheme 6.14. Attempts to manipulate the methyl-ketone **506**.

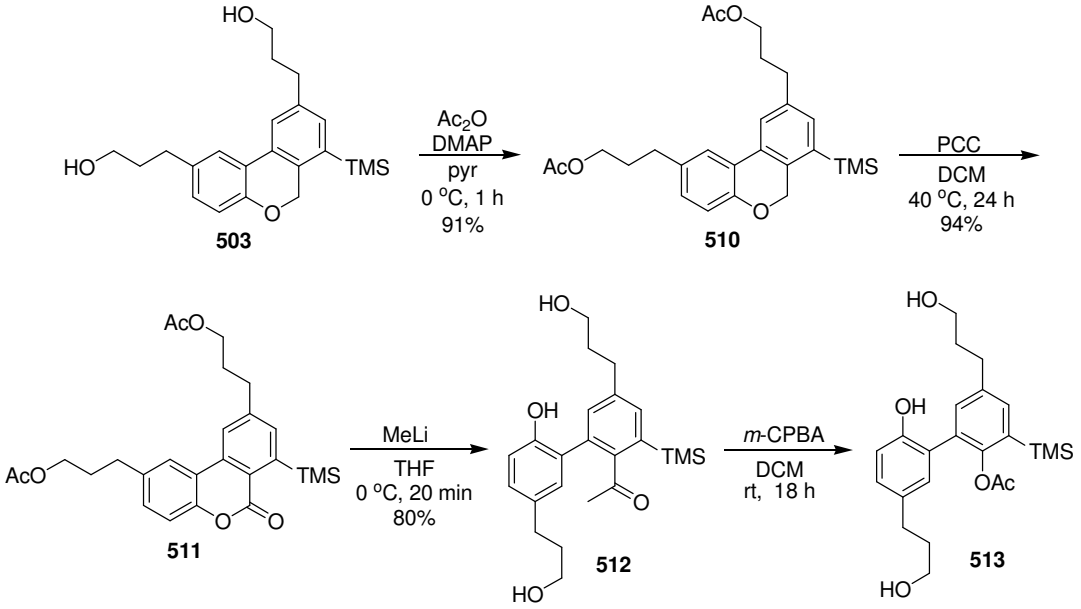
Isomerization of the double bond also occurred when the pyrone **505** was treated under the same conditions giving **509** (Scheme 6.15).



Scheme 6.15. Isomerization of the pyrone **509**.

Other means to remove the silyl group were not investigated as attempts to remove an aryl-TMS from indanone derivatives were only successful under the microwave

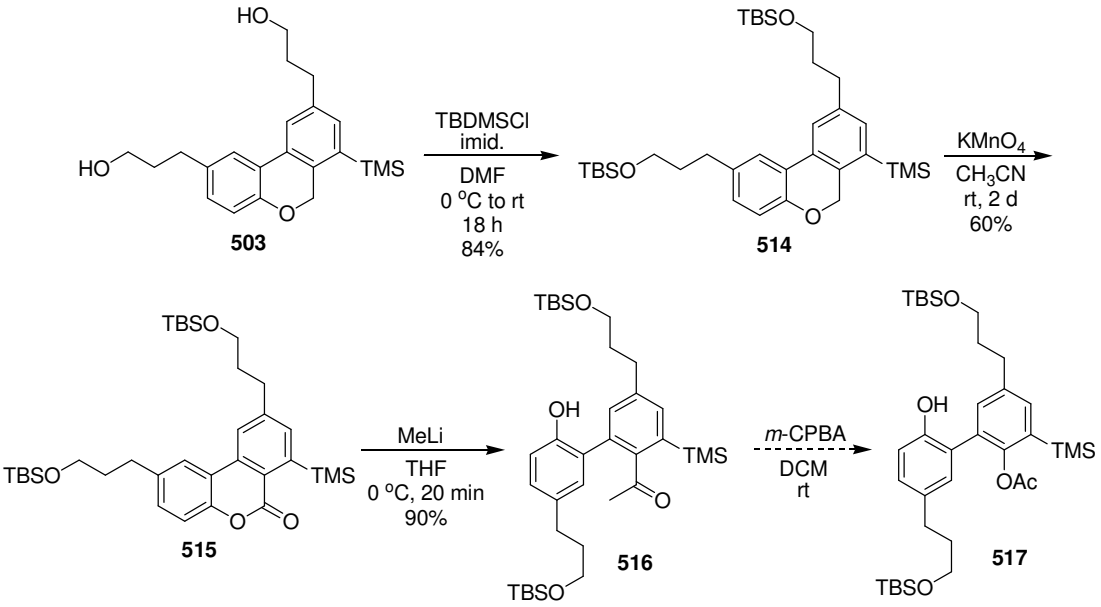
conditions,[154] therefore the route was modified to postpone double bond formation until after desilylation. The alcohols in **503** were protected as acetates in 91% yield, and oxidation of the resulting pyran **510** with PCC gave the pyrone **511** in 94% yield. Addition of excess methyllithium provided the triol **512** in 80% yield. Treatment of this triol with *m*-CPBA did lead to rearrangement with full conversion of the starting material on the basis of ^{1}H NMR analysis; however, isolation of the product **513** proved problematic due to its similar polarity as compared to the reactants and/or reaction by-products (Scheme 6.16). Alternative ways to purify **513** were not attempted.



Scheme 6.16. Synthesis and Baeyer-Villiger rearrangement of the triol **512**.

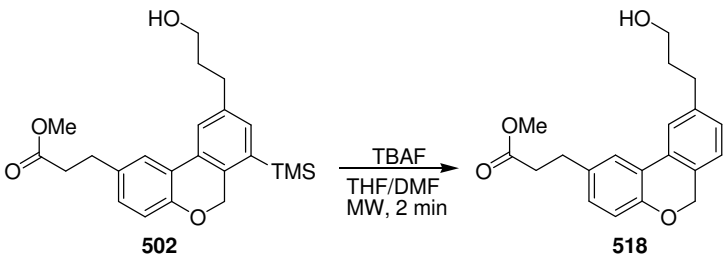
In order to make the compounds less polar, a different protecting group was sought that would allow for separation of the rearranged product from the other reagents. The *tert*-butyldimethylsilyl protecting group was chosen as it could be removed in the same step as the TMS group, thereby maintaining an efficient route. The bis-TBS-ether **514** was prepared in 84% yield from **503** under standard conditions. Oxidation of this material was plagued by

side reactions, and only a 60% yield of the pyrone **515** could be obtained when using $KMnO_4$ as the oxidant.[318] The use of PCC led to TBS removal, and **515** could only be isolated in 21% yield; using PCC/pyridine led to an increased yield of 42%. Addition of MeLi into the lactone provided the methyl ketone **516** in 90% yield (Scheme 6.17). Rearrangement of **517** with *m*-CPBA was attempted, but only led to decomposition. Attempts to deprotect the alcohols and remove the TMS group with TBAF under microwave irradiation also led to decomposition.



Scheme 6.17. Use of the bis-TBS-ether **514** towards magnolol.

One again, moving the desilylation step to earlier in the synthesis was explored. When the alcohol **502** was treated with TBAF under microwave irradiation, complete desilylation to **518** occurred as evidenced by the loss of the TMS signal in the crude ^1H NMR, however impurities from the TBAF reagent prevented isolation (Scheme 6.18).



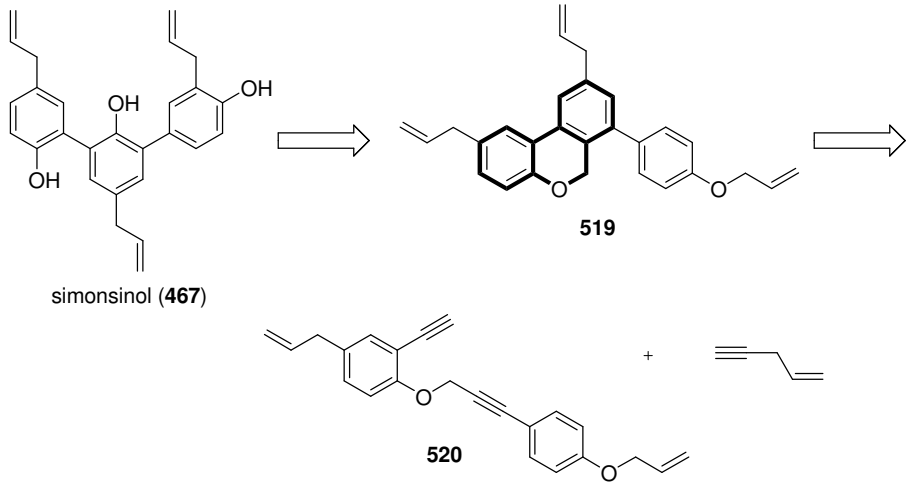
502 **518**

Scheme 6.18. Attempted desilylation of **502**.

Investigations into the desilylation at other points in the synthesis along with other desilylating reagents are currently underway.

6.4.2 Progress Towards the Synthesis of Simonsinol

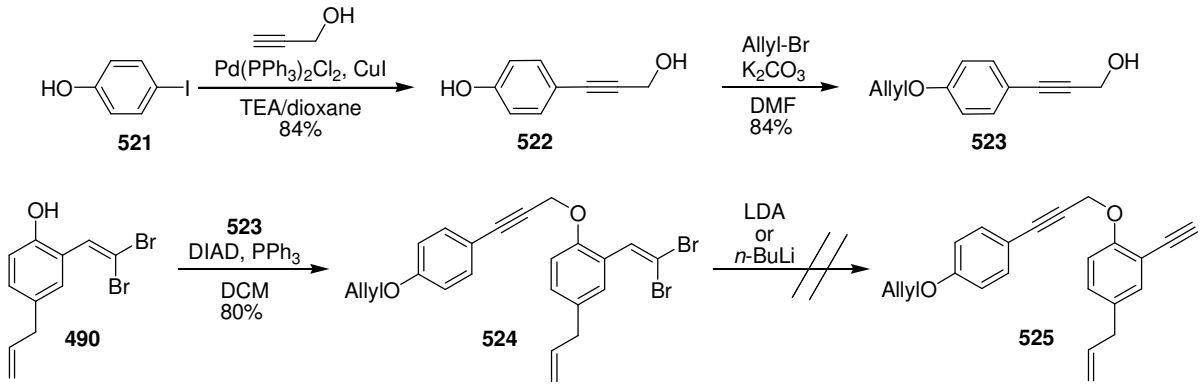
In addition to the steps required for the synthesis of magnolol, the synthesis of the neolignan simonsinol (**467**) must incorporate a third phenolic ring that contains an allyl group *ortho* to the phenol. The proper placement of this allyl group, we hypothesized, would be accomplished via a Claisen rearrangement of the allylphenol **519** (Scheme 6.19). Within this tetracyclic intermediate can be found the core structure from the magnolol synthesis (bold) with the TMS replaced by the *p*-*O*-allyl-phenyl moiety.



Scheme 6.19. Retrosynthetic analysis of simonsinol (**467**).

This phenyl ring should provide enough steric bulk to control regioselectivity in the [2+2+2] cyclotrimerization reaction. The diyne **520** would be required for the cyclotrimerization event, and explorations into its synthesis were the first step towards simonsinol.

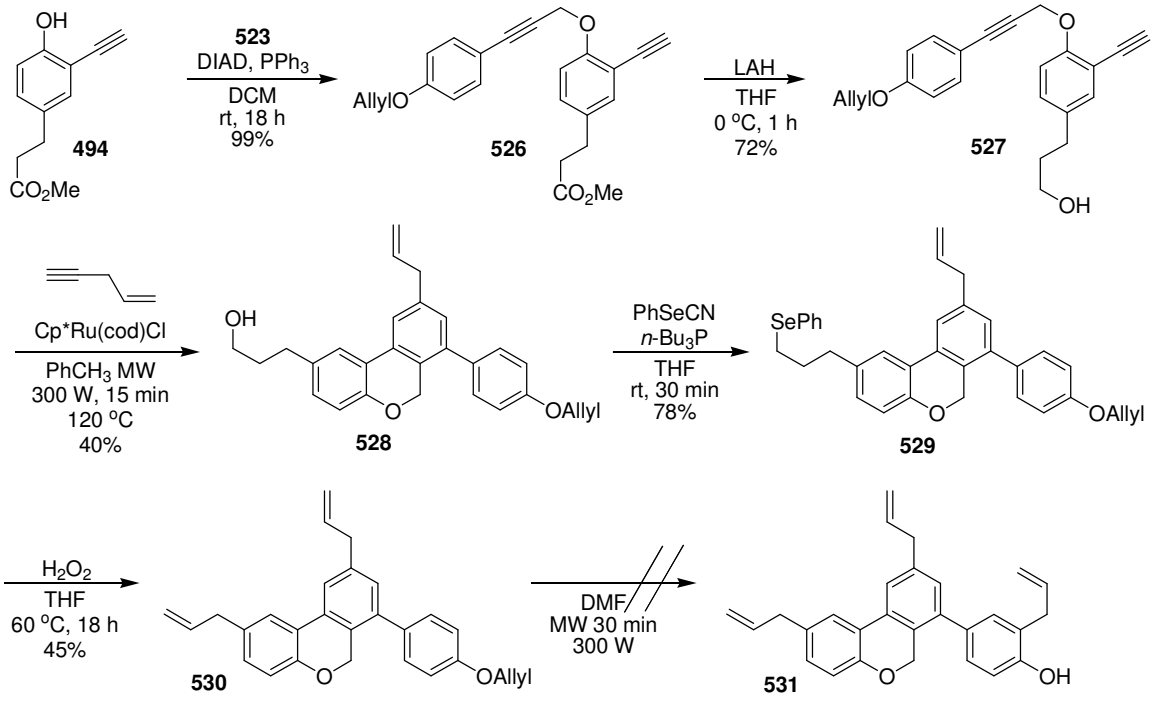
Beginning with the dibromide **490**, a Mitsunobu reaction with the propargylic alcohol **523** (prepared from 4-iodophenol (**521**) via **522**) provided the propargylic ether **524** in 80% yield.[319] In attempts toward the diyne **525**, treatment of **524** with LDA led to no reaction while treatment with *n*-BuLi gave a complex mixture with multiple spots by TLC analysis (Scheme 6.20).



Scheme 6.20. Attempted synthesis of the diyne **525**.

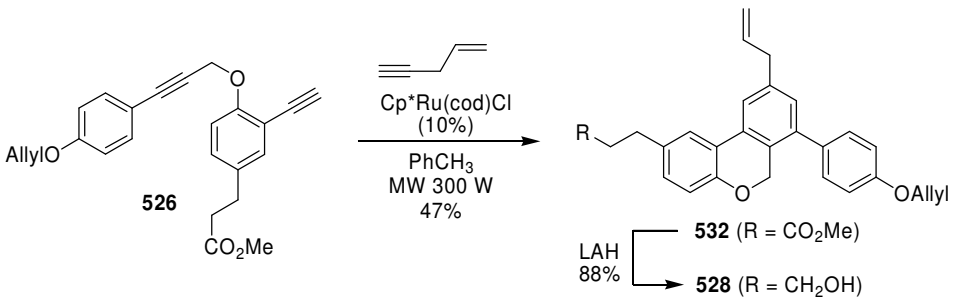
At this time, the use of the common intermediate **494** was explored. Mitsunobu reaction with **494** gave the diyne **526** in 99% yield (Scheme 6.21). Reduction of the ester group with LAH furnished the alcohol **527** in 74% yield. The cyclotrimerization reaction with this alcohol, however, was inefficient. Only a 40% yield of **528** as a single regioisomer could be obtained with allylacetylene as the monoyne under microwave irradiation and Cp*Ru(cod)Cl catalysis. Preparation of the alcohol for elimination was accomplished by converting it to the phenylselenide **529** in 78% yield. Oxidation and elimination proceeded in a 45% yield to give the tetracyclic intermediate **530**. Claisen rearrangement was necessary at

this point as any attempt to oxidize the benzylic ether could potentially oxidize the allylic ether as well. In this direction, the allyl ether **530** was heated under microwave irradiation in DMF for 30 minutes. Unfortunately, the rearranged product **531** was not obtained. Crude ^{1}H NMR analysis showed a shift in the allyl signals, but GC/MS analysis showed several peaks, none of which corresponded to the product.



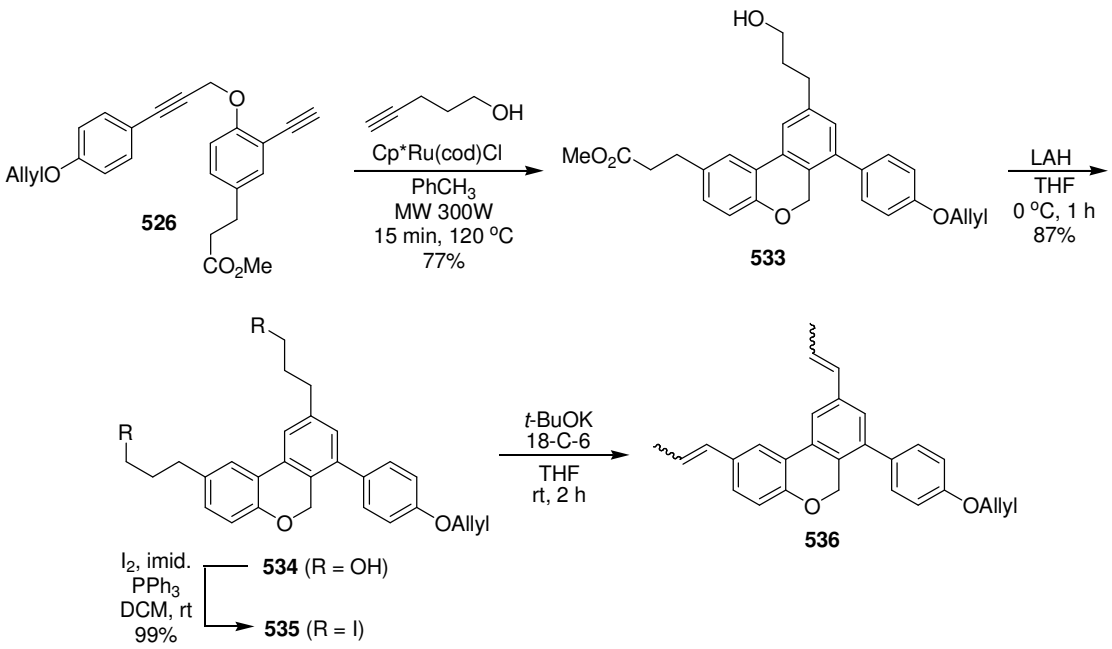
Scheme 6.21. Progress towards simonsinol (**467**).

Alternatively, a cyclotrimerization reaction of the ester derivative **526** with allylacetylene provided **532** in 47% yield. Reduction of **532** then gave the alcohol **528** in 88% yield (Scheme 6.22).



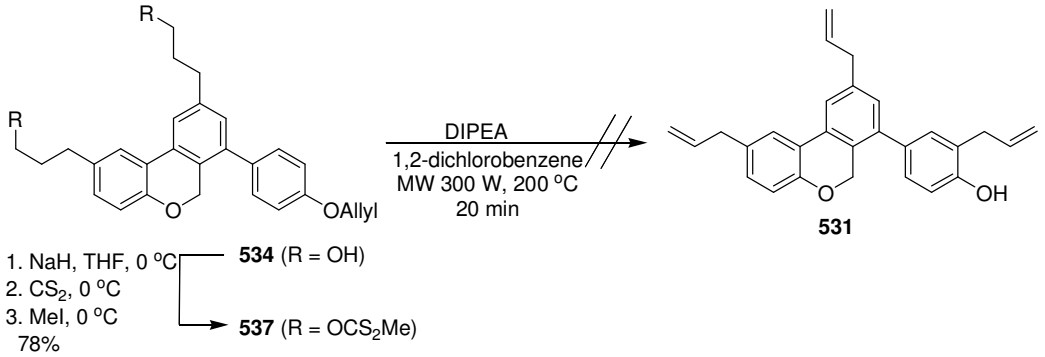
Scheme 6.22. Alternative synthesis of **528**.

In order to produce sufficient material to more fully investigate the Claisen rearrangement, a more efficient cyclotrimerization reaction was investigated. As with magnolol, pent-4-yn-1-ol was chosen. It underwent a smooth cyclotrimerization reaction with **526** giving the tetracycle **533** in 77% yield as a single regioisomer. LAH reduction then provided the diol **534** that needed to be eliminated to the double bond (Scheme 6.23). Because of the low yields obtained with the selenide elimination in other substrates (see Schemes 6.12 and 6.21), other methods of elimination were investigated. Treatment of the diol with iodine, imidazole, and triphenylphosphine furnished the diiodide **535** in 99% yield. Elimination with *t*-BuOK, while successful, led to isomerization of the double bonds furnishing **536**. Other bases such as TEA or Hunig's base were not investigated in the elimination step and may lead to the desired elimination without isomerization.



Scheme 6.23. Attempted iodide elimination towards simonsinol.

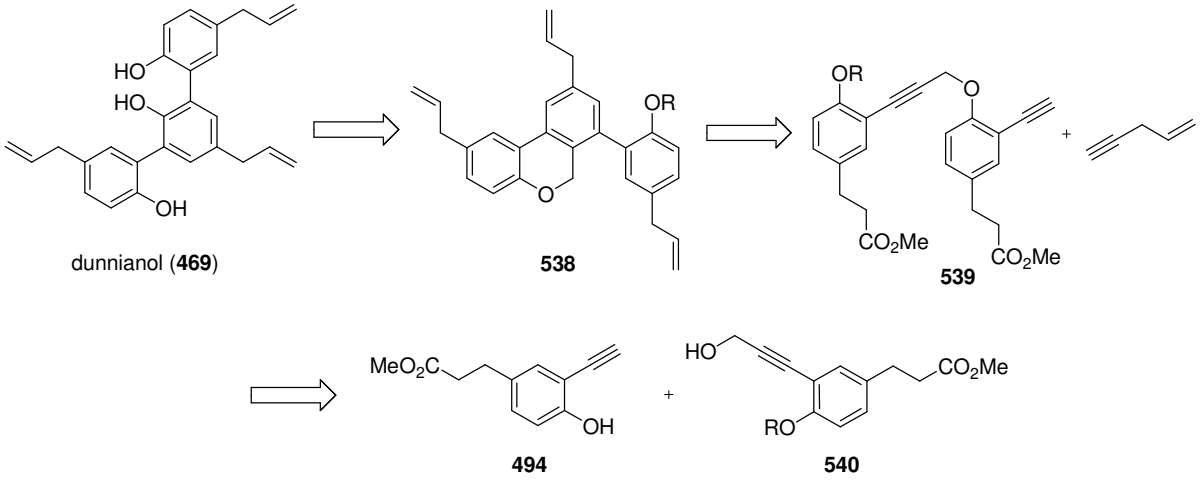
Alternatively, a Chugaev elimination[320] sequence would also produce the allyl group, and, it was hypothesized, also allow for a Claisen rearrangement of the allyl ether under the same conditions. In this direction, the bisxanthate **537** was prepared under standard conditions in 78% yield, and conditions for the tandem elimination/Claisen rearrangement were investigated (Scheme 6.24). Prolonged heating of **537** under microwave irradiation in 1,2-dichlorobenzene with Hunig's base led to decomposition of the starting material. Conventional heating at 200 °C did not fully eliminate the xanthate groups, and several products were produced. No clean product could be isolated. Work towards simonsinol was suspended at this point due to the numerous setbacks faced throughout the various routes.



Scheme 6.24. Attempted Chugaev elimination/Claisen rearrangement.

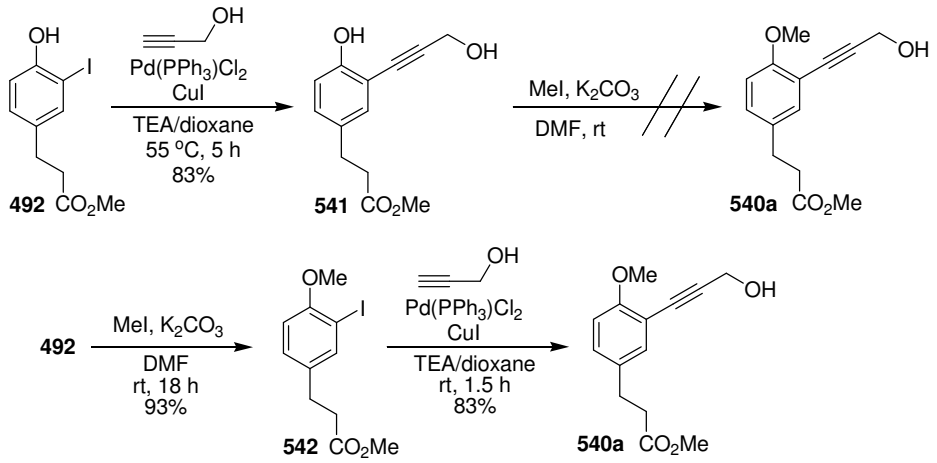
6.4.3 Progress Towards the Synthesis of Dunnianol

Towards the synthesis of dunnianol, a different propargyl alcohol was required to make the diyne **539** that would be used in the cyclotrimerization towards **538**. We envisioned synthesizing the alcohol **540** from the same starting material as the common intermediate **494** by using a different alkyne in the Sonogashira coupling and protecting the phenol (Scheme 6.25).



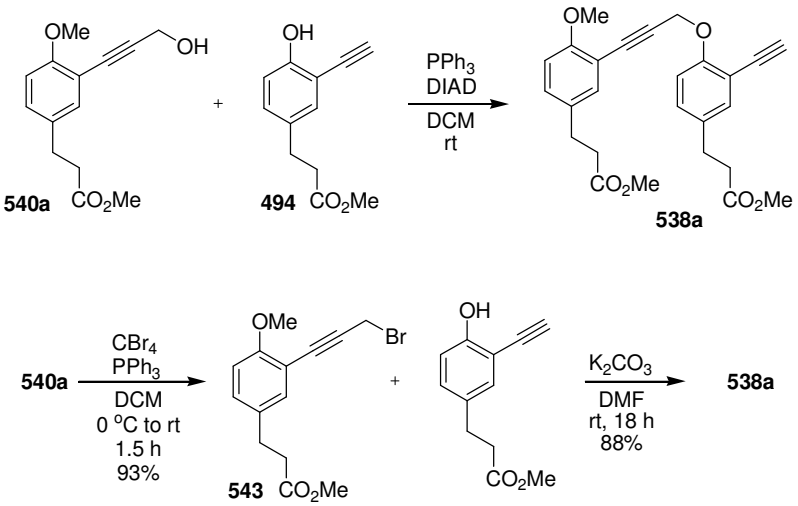
Scheme 6.25. Retrosynthetic analysis of dunnianol (**469**).

Synthesis of **540** began with a Sonogashira coupling of the iodide **492** and propargyl alcohol to provide the propargyl alcohol **541** in 83% yield. Protection of the phenol as the methyl ether **540a** (R = Me) was unsuccessful under standard conditions as well as less conventional methods such as trimethylsilyldiazomethane. Therefore, the order of the reactions was switched. Methylation of the phenol proceeded in 93% yield to furnish the methyl ether **542**, and Sonogashira coupling with propargyl alcohol gave the desired alcohol **540a** in 83% yield (Scheme 6.26).



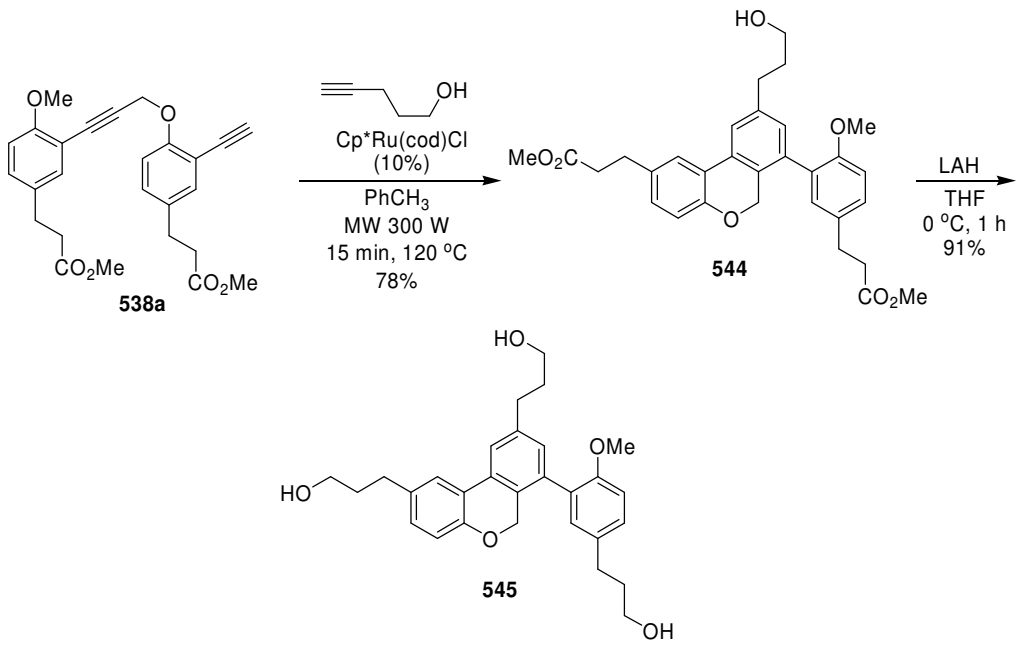
Scheme 6.26. Synthesis of the propargyl alcohol **540a**.

Incorporation of **540** into the diyne via Mitsunobu reaction with **494** went to completion, however the desired product **538a** (R = Me) was inseparable from the hydrazine by-product (Scheme 6.27). Because of this problem, the alcohol in **540a** was converted to the bromide with CBr_4/PPh_3 to provide **543** in 93% yield. Alkylation of the phenol **494** then proceeded smoothly with **543** to furnish the desired diyne **538a** in 88% yield (Scheme 6.27).



Scheme 6.27. Synthesis of the diyne **538a**.

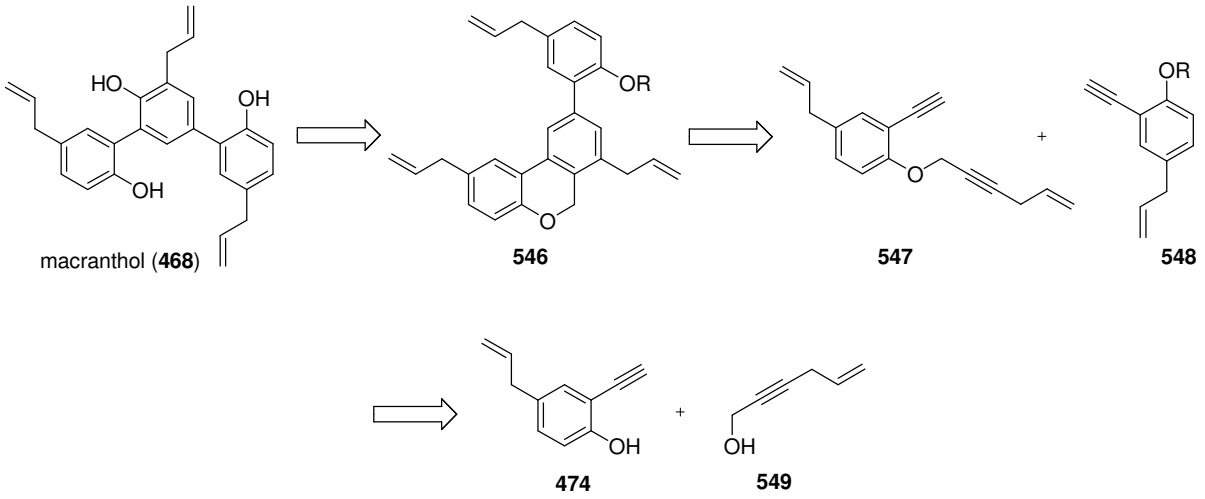
Based on the results from the cyclotrimerization reactions towards magnolol and simonsinol, allylacetylene was not utilized as the monoyne. Cyclotrimerization reaction with pent-4-yn-1-ol successfully constructed the tricycle **544** in 78% yield. Reduction of the two ester groups with LAH provided the triol **545** in 91% yield (Scheme 6.28). Further investigations into the conversion of **545** into dunnianol were not conducted as issues described above would need to be addressed.



Scheme 6.28. Cyclotrimerization reaction of the diyne **538a**.

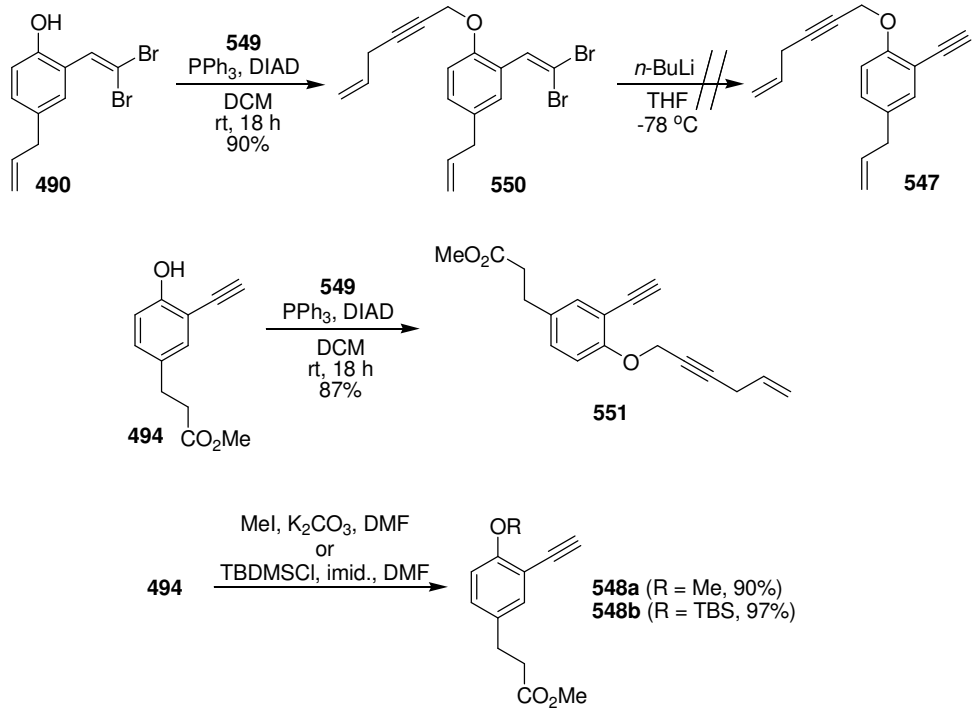
6.4.4 Progress Towards the Synthesis of Macranthol

Investigating the tetracyclic intermediate **546** necessary for the synthesis of macranthol (**468**) reveals that the monoyne required for the cyclotrimerization step would need to be an arylacetylene derivative (Scheme 6.29). Conveniently, we envisioned both the diyne **547** and the monoyne **548** being derived from the common intermediate **474**. Simple protection of the phenol on the common intermediate would provide the monoyne **548**, while alkylation of the phenol with the known propargyl alcohol **549**[321] would provide the diyne **547**. The preparation of these two fragments would initiate the studies toward the synthesis of macranthol.



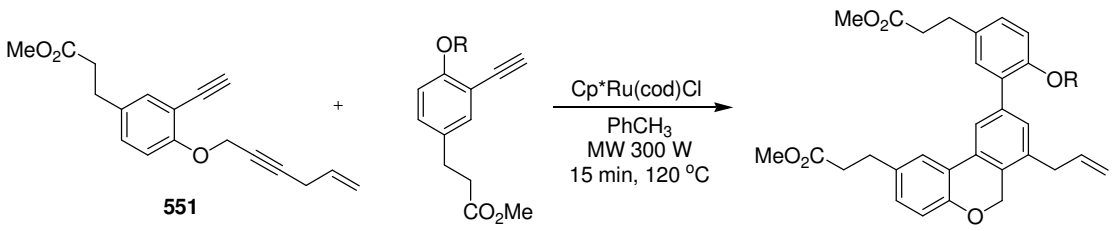
Scheme 6.29. Retrosynthetic analysis of macranthol (**468**).

Initial investigations into the synthesis of **547** began with the dibromide **490**. Mitsunobu coupling with **549** furnished the ether **550** in 90% yield. Attempted rearrangement of the vinyldibromide to the alkyne using *n*-BuLi as the base gave a low yield (<50%) of the desired alkyne **547** accompanied by an inseparable by-product. Switching to the ester **494** as the starting material, the diyne **551** was constructed via Mitsunobu reaction with the alcohol **549** in 87% yield (Scheme 6.30). Protection of the phenol as either the methyl ether or the *tert*-butyldimethylsilyl ether gave **548a** or **548b** in 90 or 97% yield, respectively.



Scheme 6.30. Synthesis of the diyne **551** and the monoynes **548a** and **548b** towards the synthesis of macranthol.

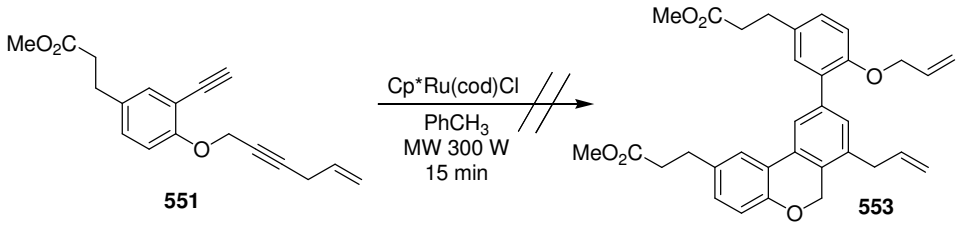
The cyclotrimerization reaction of the diyne **551** and the monoyne **548a** was then explored. Because the monoyne had to be synthesized, less than the usual ten equivalents were utilized in the cyclotrimerization reaction. In the event, **551** was reacted in the presence of five equivalents of **548a** under Cp*Ru(cod)Cl catalysis and microwave irradiation (Scheme 6.31). While all of the starting material diyne was consumed, the isolation of the tetracyclic product **552a** was difficult as the dimer of **551** could not be separated by flash chromatography. The pyran product could be obtained with a small amount of dimer impurity in roughly 67% yield. Increasing the number of equivalents of **548a** led to less dimerization, however the product was still contaminated with dimer. Fortunately, unreacted monoyne could be recovered.



Scheme 6.31. Cyclotrimerization reaction of the diyne **551**.

The use of the TBS-ether **548b** in the cyclotrimerization reaction should produce a dramatically less polar dimer, and would, therefore, simplify purification. The cyclotrimerization reaction of **551** in the presence of five equivalents of **548b** provided **552b** in 58% yield with no dimer contamination.

Recognizing the diyne as an alternatively protected monoyne, we attempted to take advantage of the dimerization of the diyne to construct the tetracyclic intermediate **553**. However, attempted dimerization of **551** via a cyclotrimerization reaction led to a mixture of several products (Scheme 6.32).



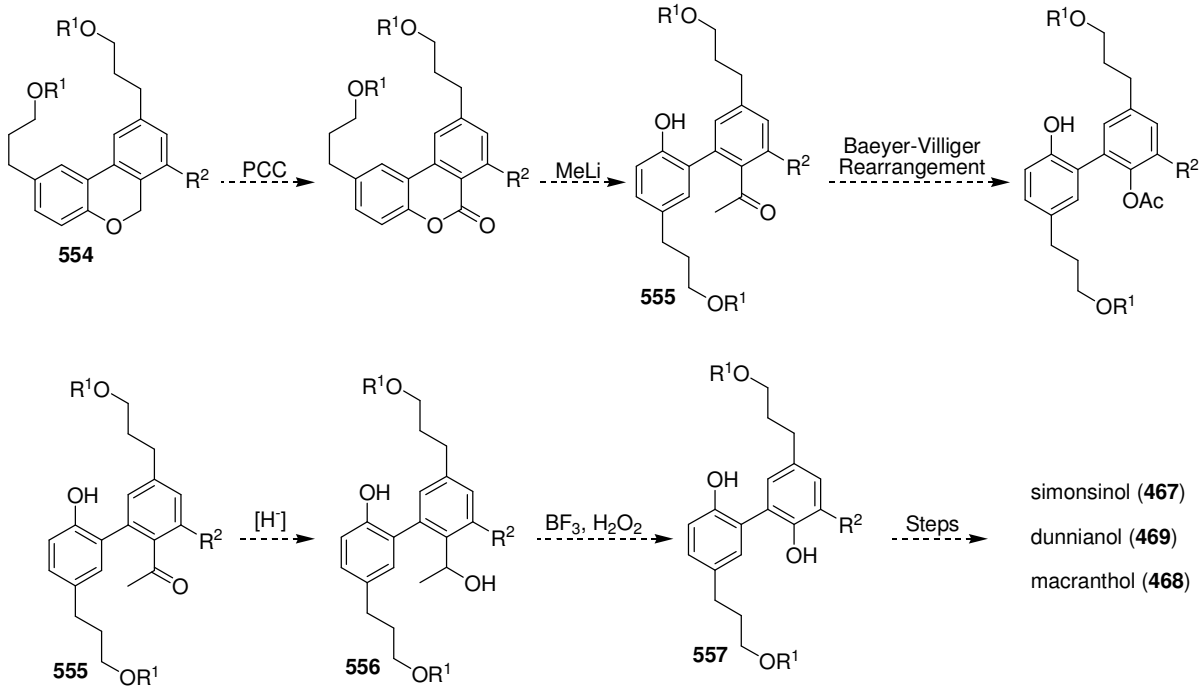
Scheme 6.32. Dimerization of the diyne **551**.

At this point, further investigations into the synthesis of macranthol were suspended.

6.5 Summary and Future Directions

While the [2+2+2] cyclotrimerization reaction towards the synthesis of the neolignan natural products was successful at constructing the desired core structures, the installation of the second phenol group and the double bonds have caused much difficulty. Modified routes to the neolignans must address these issues for any hopes of success. In the case of magnolol, removing the aryl-TMS group in **503** will allow for a benzylic hydroperoxide rearrangement to the bis-phenol after oxidation and addition of methyllithium (see Scheme 6.12).

The other neolignans each have differences that will need to be addressed individually. Due to the presence of either aryl or alkyl groups *ortho* to the lactone carbonyl (R^2 in **554**), treatment with methyllithium will furnish a ketone (**555**). If Baeyer-Villiger rearrangement fails due to the steric environment, reduction of the ketone to the secondary alcohol **556** will provide a substrate for the benzylic hydroperoxide rearrangement to **557** (Scheme 6.33). Subsequent modifications to the R^2 group (i.e. Claisen rearrangement) and installation of the double bonds will provide simonsinol, dunnianol, and macranthol. To this end, Claisen rearrangements under Lewis acid catalysis can be explored. Elimination reactions towards the double bonds may be successful with a base other than potassium *tert*-butoxide as in Scheme 6.23.



Scheme 6.33. Proposed routes to simonsinol, dunnianol, and macranthol.

6.6 Experimental

All reactions were performed in flame-dried glassware under a nitrogen atmosphere and stirred magnetically. Tetrahydrofuran, toluene, xylenes, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Diisopropylamine, triethylamine, DMSO, DCM, DMF, 1,2-dichloroethane, CH_3CN and pyridine were distilled from calcium hydride and stored over 4 Å molecular sieves. Other reagents and solvents obtained from commercial sources were stored under nitrogen and used directly without further purification. *n*-BuLi and MeLi were titrated against *N*-pivaloyl-*o*-toluidine.[108] Melting points were obtained from a Mel-Temp capillary melting point apparatus and are uncorrected. High resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz) or Varian Mercury 300 (300 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption (77.2) for ^{13}C NMR spectra. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer.

9-Butyl-6*H*-benzo[*c*]chromen-6-one (423a). To a flame-dried microwave vial equipped with a stir bar was added **427** (18.3 mg, 0.056 mmol), DMF (100 μL), THF (200 μL) and TBAF (1 M in THF, 340 μL, 0.234 mmol), and the mixture was irradiated for 2 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction vessel to rt, water (2 mL) and Et_2O (3 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic extracts were washed with water (2 mL × 2), brine (3 mL), dried ($MgSO_4$) filtered, and concentrated to dryness. The residue was

purified by silica gel chromatography, eluting with hexanes/EtOAc (25:1) to give 14.2 mg (93%) of **423a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.1 Hz, 1 H), 8.08 (dd, *J* = 8.1 and 1.4 Hz, 1 H), 7.92 (d, *J* = 1.4 Hz, 1 H), 7.57-7.29 (m, 4 H), 2.88-2.77 (m, 2 H), 1.80-1.64 (m, 2 H), 1.52-1.34 (m, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H).

2-Hydroxy-5'-butyl-2'-(1-methyl-1-hydroxyethyl)-1,1'-biphenyl (476). A solution of **423a** (13.2 mg, 0.052 mmol) in THF (900 µL) was added dropwise to a solution of MeLi (1.6 M in Et_2O, 392 µL, 0.63 mmol) in THF (200 µL) at 0 °C. The reaction mixture was stirred for 45 min, warmed to room temperature, and stirring was continued for 1 h. The reaction was then cooled to 0 °C and quenched with 10% NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (2 mL) then brine (2 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 11.2 mg (75%) of **476** as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6) δ 7.47 (d, *J* = 8.1 Hz, 1 H), 7.12-7.00 (m, 4 H), 6.91-6.89 (m, 1 H), 6.85-6.78 (m, 1 H), 2.42-2.33 (m, 2 H), 1.49-1.33 (m, 5 H), 1.28-1.12 (m, 5 H), 0.81 (t, *J* = 7.3 Hz, 3 H).

5'-Butyl-2'-(1-methyl-1-hydroxyethyl)-2-pivaloyloxy-1,1'-biphenyl (477). To a solution of **476** (11.2 mg, 0.039 mmol) and TEA (10.9 µL, 0.079 mmol) in DCM (200 µL) at 0 °C was added pivaloyl chloride (5.3 µL, 0.043 mmol) dropwise. The reaction was allowed to stir for 2.5 h as it warmed to rt, and was quenched with H_2O (1 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (2

mL) then brine (2 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (9:1) to give 13.7 mg (94%) of **477** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 4 H), 7.12 (dd, *J* = 8.0 and 1.8 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.82 (d, *J* = 1.8 Hz, 1 H), 2.66 (s, 1 H), 2.61-2.49 (m, 2 H), 1.70-1.45 (m, 8 H), 1.44-1.29 (m, 2 H), 1.08-0.87 (m, 12 H).

5'-Butyl-2'-hydroxy-2-pivaloyloxy-1,1'-biphenyl (478). $BF_3{\cdot}Et_2O$ (38 μL, 0.30 mmol) was added to H_2O_2 (50%, 5.1 μL, 0.074 mmol) and was stirred for 45 min at 0 °C. This solution was added to **477** (13.7 mg, 0.037 mmol) in dichloromethane (950 μL) at 0 °C. After stirring vigorously for 15 min at 0 °C, H_2O (2 mL) and EtOAc (4 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4 mL × 2), and the combined organic extracts were washed with water (4 mL) and brine (4 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (10:1) to give 11.0 mg (91%) of **478** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.21 (m, 2 H), 7.17 (d, *J* = 2.1 Hz, 1 H), 7.10 (dd, *J* = 7.5 and 1.7 Hz, 1 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 6.97 (dd, *J* = 8.2 and 1.1 Hz, 1 H), 6.92 (dd, *J* = 7.5 and 1.1 Hz, 1 H), 5.03 (s, 1 H), 2.74-2.59 (m, 2 H), 1.72-1.55 (m, 2 H), 1.47-1.29 (m, 2 H), 1.05 (s, 9 H), 0.94 (t, *J* = 7.3 Hz, 3 H).

5'-Butyl-2,2'-dihydroxy-1,1'-biphenyl (479). To a solution of **478** (7.6 mg, 0.023 mmol) in MeOH (200 μL) was added 2 N NaOH (100 μL), and the reaction was stirred for 2 h. 10% HCl was added to acidify the reaction mixture, and the solution was extracted with EtOAc (2

mL × 3). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4.5:1) to give 5.2 mg (93%) of **479** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.12 (m, 2 H), 7.08-6.89 (m, 4 H), 6.82 (dd, *J* = 8.1 Hz, 1 H), 5.26 (br s, 2 H), 2.61-2.39 (m, 2 H), 1.63-1.38 (m, 2 H), 0.81 (t, *J* = 7.2 Hz, 3 H).

2'-Acetyl-5'-butyl-2-hydroxy-3'-methyl-1,1'-biphenyl (480). A solution of **425** (17.1 mg, 0.064 mmol) in THF (400 µL, 300 µL wash × 2) was added dropwise to a solution of MeLi (1.6 M in Et_2O, 482 µL, 0.77 mmol) in THF (300 µL) at 0 °C. The reaction mixture was stirred for 45 min, warmed to room temperature, and stirring was continued for 1 h. The reaction was then cooled to 0 °C and quenched with 10% NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (2 mL) then brine (2 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (7:1) to give 18.1 mg (100%) of **480** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 1 H), 7.43 (s, 1 H), 7.28-7.19 (m, 1 H), 7.09-6.96 (m, 3 H), 3.22 (s, 1 H), 2.66-2.61 (m, 2 H), 2.56 (s, 3 H), 1.73 (s, 3 H), 1.72-1.57 (m, 2 H), 1.48-1.32 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

5'-Butyl-2,2'-dihydroxy-3'-methyl-1,1'-biphenyl (482). *m*-CPBA (70%, 16 mg, 0.064 mmol) was added to a solution of **480** (9 mg, 0.032 mmol) in DCM (250 µL), and the reaction was stirred for 75 min. The reaction was concentrated and taken up in MeOH (300 µL). K_2CO_3 (32 mg, 0.23 mmol) was added, and the mixture was stirred for 2 h. HCl (10%)

was added until the solution was acidic, and the mixture was extracted with EtOAc (2 mL × 3). The combined organic extracts were washed with water (2 mL) then brine (2 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1) to give 5.9 mg (72%) of **482** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.23 (m, 2 H), 7.10-7.00 (m, 3 H), 6.90 (s, 1 H), 5.21 (br s, 2 H), 2.62-2.49 (m, 2 H), 2.31 (s, 3 H), 1.67-1.51 (m, 2 H), 1.46-1.29 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

5-Allyl-2-(methoxymethoxy)benzaldehyde (487). To a solution of **485** (82 mg, 0.46 mmol) in Et_2O (820 µL) at −78 °C was added *t*-BuLi (1.6 M in pentane, 411 µL, 0.69 mmol) dropwise, and the reaction was stirred for 3 h. *N*-methylformanilide (170 µL, 1.38 mmol) was added, and the mixture was stirred for 1.5 h before warming it to rt. After 12 h, the reaction was quenched with sat. NH_4Cl (5 mL) and extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with cold 1 M HCl (3 mL × 3), water (2 mL) then brine (2 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (20:1) to give 34.1 mg (38%) of **487** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (s, 1 H), 7.67 (d, *J* = 2.3 Hz, 1 H), 7.35 (dd, *J* = 8.6 and 2.3 Hz, 1 H),7.15 (d, *J* = 8.5 Hz, 1 H), 6.03-5.83 (m, 1 H), 5.28 (s, 2 H), 5.12-5.09 (m, 1 H), 5.07-5.03 (m, 1 H), 3.52 (s, 3 H), 3.39-3.33 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 158.3, 136.9, 136.2, 133.8, 128.1, 125.4, 116.4, 115.4, 94.8, 56.5, 39.2.

4-Allyl-2-ethynyl-1-(methoxymethoxy)benzene (488). *n*-BuLi (2.3 M in hexanes, 130 µL, 0.30 mmol) was added to a solution of $TMSCHN_2$ (2 M in Et_2O, 225 µL, 0.45 mmol) in THF (1.3 mL) at −78 °C dropwise, and the solution was stirred for 30 min. Then, **487** (31 mg, 0.15 mmol) in THF (600 µL) was added dropwise, and stirring was continued for 1 h at −78 °C before warming the reaction mixture to rt. After 1.5 h at rt, the reaction was cooled to 0 °C and quenched with sat. NH_4Cl (3 mL), followed by extraction with Et_2O (3 mL × 3). The combined organic extracts were washed with water (2 mL) then brine (2 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (22:1) to give 12.1 mg (40%) of **488** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 1.9 Hz, 1 H), 7.12 (dd, *J* = 8.3 and 1.9 Hz, 1 H), 7.07 (d, *J* = 8.3 Hz, 1 H), 6.02-5.85 (m, 1 H), 5.26 (s, 2 H), 5.13-5.03 (m, 2 H), 3.53 (s, 3 H), 3.34-3.29 (m, 2 H), 3.27 (s, 1 H).

4-Allyl-2-(2,2-dibromovinyl)-1-(methoxymethoxy)benzene (489). To a solution of CBr_4 (305 mg, 0.92 mmol) in DCM (900 µL) at 0 °C was added PPh_3 (483 mg, 1.84 mmol) in two portions. After 10 min, **487** (95 mg, 0.46 mmol) in DCM (500 µL) was added dropwise, and the reaction was stirred for 30 min. H_2O (3 mL) was added, and the aqueous layer was extracted with DCM (4 mL × 3). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried (Na_2SO_4), filtered through a silica plug (eluting with DCM), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (45:1) to give 125 mg (75%) of **489** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1 H), 7.51 (d, *J* = 1.9 Hz, 1 H), 7.10 (dd, *J* = 8.4 and 1.9 Hz, 1 H),

7.04 (d, J = 8.4 Hz, 2 H), 6.05-5.86 (m, 1 H), 5.17 (s, 2 H), 5.12-5.03 (m, 2 H), 3.48 (s, 3 H), 3.39-3.32 (m, 2 H).

4-Allyl-2-ethynyl-1-(methoxymethoxy)benzene (488). Alternative synthesis from **489**: *n*-BuLi (2.3 M in hexanes, 92 µL, 0.21 mmol) was added dropwise to a solution of **489** (25.5 mg, 0.070 mmol) in THF (300 µL) at −78 °C. After 1 h, the solution was warmed to 0 °C, stirred for 15 min, and quenched with sat. NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (30:1) to give 10 mg (70%) of **488**.

4-Allyl-2-(2,2-dibromovinyl)phenol (490). 6 N HCl (277 µL) was added to a solution of **489** (25.2 mg, 0.070 mmol) in THF (330 µL), and the reaction was stirred overnight. H_2O (3 mL) and Et_2O (3 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1) to give 21 mg (95%) of **490** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1 H), 7.35 (d, J = 2.0 Hz, 1 H), 7.05 (dd, J = 8.2 and 2.0 Hz, 1 H), 6.76 (d, J = 8.2 Hz, 1 H), 6.06-5.86 (m, 1 H), 5.15-5.02 (m, 2 H), 4.89 (br s, 1 H), 3.39-3.30 (m, 2 H).

Methyl 3-(4-hydroxy-3-iodophenyl)propanoate (492). To a solution of I_2 (78 mg, 0.31 mmol) and Ag_2SO_4 (62 mg, 0.31 mmol) in DCM (5 mL) was added **491** (50 mg, 0.28 mmol) in DCM (2 mL), and the reaction was stirred for 24 h, filtered, washed with 10% $Na_2S_2O_3$ (15 mL), H_2O (10 mL), brine (10 mL), dried ($MgSO_4$), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (5:1) to give 352 mg (61%) of **492** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.0 Hz, 1 H), 7.07 (dd, *J* = 8.3 and 2.0 Hz, 1 H), 6.90 (d, *J* = 8.3 Hz, 1 H), 5.18 (s, 1 H), 3.66 (s, 3 H), 2.85 (t, *J* = 7.6 Hz, 2 H), 2.57 (t, *J* = 7.6 Hz, 2 H).

Methyl 3-(4-hydroxy-3-(2-(trimethylsilyl)ethynyl)phenyl)propanoate (493). To a solution of **492** (191 mg, 0.62 mmol) in TEA/dioxane (1:1, 1.5 mL) was added $Pd(PPh_3)_2Cl_2$ (8.4 mg, 0.012 mmol), CuI (4.6 mg, 0.025 mmol) and ethynyltrimethylsilane (176 μL, 1.25 mmol). After 4 h, the reaction was concentrated, taken up in H_2O (10 mL) and Et_2O (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic extracts were washed with water (10 mL) then brine (10 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/Et_2O (4:1) to give 159 mg (92%) of **493** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 2.2 Hz, 1 H), 7.07 (dd, *J* = 8.4 and 2.2 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 5.72 (s, 1 H), 3.66 (s, 3 H), 2.84 (t, *J* = 7.7 Hz, 2 H), 2.57 (t, *J* = 7.7 Hz, 2 H), 0.27 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 155.8, 132.4, 131.3, 130.9, 114.8, 109.6, 102.4, 99.1, 51.7, 35.9, 30.0, 0.1.

Methyl 3-(3-ethynyl-4-hydroxyphenyl)propanoate (494). KF (170 mg, 2.93 mmol) was added to a solution of **493** (232 mg, 0.836 mmol) in MeOH (3.9 mL), and the reaction was stirred for 3 h. DCM (15 mL) and H_2O (10 mL) were added and the layers separated. The aqueous layer was extracted with DCM (10 mL × 2). The combined organic extracts were washed with water (10 mL) then brine (10 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 153 mg (89%) of **494** as a reddish solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 2.1 Hz, 1 H), 7.10 (dd, *J* = 8.4 and 2.1 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 5.67 (s, 1 H), 3.67 (s, 3 H), 3.45 (s, 1 H), 2.86 (t, *J* = 7.7 Hz, 2 H), 2.58 (t, *J* = 7.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 156.1, 132.5, 131.7, 131.1, 115.1, 108.4, 84.2, 78.5, 51.8, 35.8, 29.9.

Methyl 3-(4-(3-(trimethylsilyl)prop-2-ynyloxy)-3-ethynylphenyl)propanoate (496). To a solution of **494** (100 mg, 0.49 mmol), PPh_3 (169 mg, 0.64 mmol), and 3-(trimethylsilyl)prop-2-yn-1-ol (109 μL, 0.73 mmol) in DCM (2.4 mL) was added DIAD (126 μL, 0.73 mmol) at 0 °C, and the reaction was stirred overnight. The reaction was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (12:1) to give 139 mg (90%) of **496** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.3 Hz, 1 H), 7.10 (dd, *J* = 8.5 and 2.3 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 1 H), 4.75 (s, 2 H), 3.67 (s, 3 H), 3.28 (s, 1 H), 2.87 (t, *J* = 7.7 Hz, 2 H), 2.60 (t, *J* = 7.7 Hz, 2 H), 0.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 157.5, 133.9, 133.5, 130.0, 113.5, 112.1, 100.0, 93.4, 81.4, 79.9, 57.7, 51.7, 35.7, 29.9, –0.2.

3-(4-(3-(Trimethylsilyl)prop-2-ynyloxy)-3-ethynylphenyl)propan-1-ol (497). LAH (10.6 mg, 0.28 mmol) was added to a solution of **496** (58.6 mg, 0.19 mmol) in THF (900 μL) at 0 °C, and the reaction was stirred for 1 h. Et_2O (2 mL), H_2O (17 μL), 15% NaOH (17 μL), and H_2O (34 μL), were added successively, and the mixture was stirred for 30 min. The mixture was filtered over celite, dried (Na_2SO_4), filtered, and concentrated to dryness to give 44.4 mg (83%) of **497** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.3 Hz, 1 H), 7.14 (dd, *J* = 8.5 and 2.3 Hz, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H), 4.76 (s, 2 H), 3.64 (t, *J* = 6.3 Hz, 2 H), 3.28 (s, 1 H), 2.63 (t, *J* = 7.4 Hz, 2 H), 1.92-1.78 (m, 2 H), 0.14 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 134.9, 134.0, 130.1, 113.6, 112.0, 100.1, 93.3, 81.3, 80.1, 62.1, 57.8, 34.2, 31.0, –0.2.

Methyl 3-(9-allyl-7-(trimethylsilyl)-6*H*-benzo[*c*]chromen-2-yl)propanoate (499). To a flame-dried microwave vial equipped with a stir bar was added **496** (16.1 mg, 0.051 mmol), allylacetylene (46 μL, 0.51 mmol), Cp*Ru(cod)Cl (1.9 mg, 0.0051 mmol), and dry toluene (1.6 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 30 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction vessel to room temperature, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (16:1) to give 10 mg (50%) of **499** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.1 Hz, 1 H), 7.52 (d, *J* = 1.5 Hz, 1 H), 7.26-7.24 (m, 1 H), 7.06 (dd, *J* = 8.2 and 2.1 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.10-5.92 (m, 1 H), 5.23-5.07 (m, 4 H), 3.68 (s, 3 H), 3.49-3.41 (m, 2 H), 2.96 (t, *J* = 7.8 Hz, 2 H), 2.66 (t, *J* = 7.8 Hz, 2 H), 0.35 (s, 9 H).

3-(9-Allyl-7-(trimethylsilyl)-6*H*-benzo[*c*]chromen-2-yl)propan-1-ol (500). LAH (1 mg, 0.026 mmol) was added to a solution of **499** (5.2 mg, 0.014 mmol) in THF (200 µL) at 0 °C, and the reaction was stirred for 1 h. Et_2O (0.4 mL), H_2O (3 µL), 15% NaOH (3 µL), and H_2O (6 µL), were added successively, and the mixture was stirred for 30 min The mixture was filtered over celite, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:1.5) to give 4.5 mg (94%) of **500** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.50 (m, 2 H), 7.27-7.23 (m, 1 H), 7.06 (dd, *J* = 8.2 and 2.0 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.11-5.93 (m, 1 H), 5.23-5.07 (m, 4 H), 3.72 (dt, *J* = 11.3 and 5.6 Hz, 2 H), 3.48-3.41 (m, 2 H), 2.78-2.68 (m, 2 H), 2.00-1.87 (m, 2 H), 1.29 (t, *J* = 5.6 Hz, 1 H), 0.35 (s, 9 H).

(9-Allyl-2-(3-(phenylselanyl)propyl)-6*H*-benzo[*c*]chromen-7-yl)trimethylsilane (501). Tri-*n*-butylphosphine (6.3 µL, 0.026 mmol) was added to a solution of **500** (4.5 mg, 0.013 mmol) and phenylselenocyanate (3.1 µL, 0.026 mmol) in THF (200 µL) at rt, and the reaction was stirred for 30 min. After concentration, the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:0 to 80:1) to give 4.5 mg (71%) of **501** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.57 (m, 1 H), 7.55-7.43 (m, 3 H), 7.31-7.19 (m, 5 H), 7.01 (dd, *J* = 8.2 and 2.0 Hz, 1 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 6.11-5.92 (m, 1 H), 5.23-5.07 (m, 4 H), 3.49-3.41 (m, 2 H), 2.94 (t, *J* = 7.3 Hz, 2 H), 2.81-2.70 (m, 2 H), 2.14-1.97 (m, 2 H), 0.35 (s, 9 H).

Methyl 3-(9-(3-hydroxypropyl)-7-(trimethylsilyl)-6*H*-benzo[*c*]chromen-2-yl)propanoate (502). To two flame-dried microwave vials equipped with a stir bar was added **496** (40.2 mg, 0.128 mmol), pent-4-yn-1-ol (120 µL, 1.28 mmol), Cp*Ru(cod)Cl (4.5 mg, 0.013 mmol), and dry toluene (3.2 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 30 min in a Discover microwave synthesizer at 300 W. After cooling the reaction vessel to room temperature, the solutions were combined, concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/Et_2O (2:1) to give 86.6 mg (85%) of **502** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.51 (m, 2 H), 7.26 (s, 1 H), 7.06 (dd, *J* = 8.2 and 2.0 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 5.16 (s, 2 H), 3.75-3.66 (m, 5 H), 2.97 (t, *J* = 7.7 Hz, 2 H), 2.79-2.72 (m, 2 H), 2.66 (d, *J* = 7.7 Hz, 2 H), 2.04-1.87 (m, 2 H), 1.49 (br s, 1 H), 0.35 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 153.2, 141.1, 135.9, 134.7, 134.2, 133.9, 129.8, 129.2, 123.4, 123.2, 117.1, 68.5, 62.3, 51.7, 36.1, 34.5, 32.3, 30.6, 0.0.

2,9-Di(3-hydroxypropyl)-7-(trimethylsilyl)-6*H*-benzo[*c*]chromene (503). LAH (26.5 mg, 0.70 mmol) was added to a solution of **502** (139.3 mg, 0.35 mmol) in THF (2 mL) at 0 °C, and the reaction was stirred for 1 h. Et_2O (10 mL), H_2O (33 µL), 15% NaOH (33 µL), and H_2O (66 µL), were added successively, and the mixture was stirred for 30 min The mixture was filtered over celite, dried (Na_2SO_4), filtered, and concentrated to dryness to give 129 mg (100%) of **503** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.52 (m, 2 H), 7.26 (s, 1 H),), 7.06 (dd, *J* = 8.2 and 2.0 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 5.16 (s, 2 H), 3.81-3.66 (m, 4 H), 2.84-2.67 (m, 4 H), 2.04-1.88 (m, 4 H), 1.38-1.27 (m, 2 H), 0.35 (s, 9 H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 152.9, 141.0, 135.9, 135.5, 134.7, 133.9, 129.9, 129.4, 123.3, 116.9, 68.6, 62.2, 62.1, 34.53, 34.47, 32.3, 31.7, 0.0.

(2,9-Bis(3-(phenylselanyl)propyl)-6*H*-benzo[*c*]chromen-7-yl)trimethylsilane (504). Tri-*n*-butylphosphine (200 μL, 0.80 mmol) was added to a solution of **503** (74.6 mg, 0.20 mmol) and phenylselenocyanate (99 μL, 0.80 mmol) in THF (2.3 mL) at 0 °C, and the reaction was stirred for 30 min at rt. After concentration, the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:0 to 50:1) to give 110.1 mg (84%) of **504** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.48 (m, 5 H), 7.32-7.22 (m, 8 H), 7.06 (dd, *J* = 8.2 and 2.0 Hz, 1 H), 6.94 (d, *J* = 8.2 Hz, 1 H), 5.21 (s, 2 H), 3.02-2.93 (m, 4 H), 2.90-2.74 (m, 4 H), 2.20-2.03 (m, 4 H), 0.39 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 140.5, 135.9, 134.94, 134.86, 133.9, 132.7, 132.6, 130.4, 130.3, 129.9, 129.5, 129.1, 126.9, 126.8, 123.4, 123.3, 117.0, 68.6, 35.9, 35.3, 31.9, 31.8, 27.3, 27.2, 0.1.

(2,9-Diallyl-6*H*-benzo[*c*]chromen-7-yl)trimethylsilane (471). To a solution of **504** (20 mg, 0.031 mmol) in THF (600 μL) was added H_2O_2 (62 μL, 0.68 mmol) at 0 °C. The reaction was warmed to rt and after 1 h was heated at 60 °C for 45 min. After cooling to reaction vessel to room temperature, H_2O (2 mL) and Et_2O (3 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic extracts were washed with sat. $NaHCO_3$ (2 mL), water (3 mL) and brine (3 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:0 to 60:1) to give 5 mg (49%) of **471** as a

yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2 H), 7.26-7.24 (m, 1 H),), 7.05 (dd, *J* = 8.2 and 2.0 Hz, 1 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.11-5.93 (m, 2 H), 5.23-5.04 (m, 6 H), 3.50-3.37 (m, 4 H), 0.35 (s, 9 H).

2,9-Diallyl-7-(trimethylsilyl)-6*H*-benzo[*c*]chromen-6-one (505). To **471** (5 mg, 0.015 mmol), dissolved in DCM (300 μL) was added PCC (3.2 mg, 0.015 mmol) and the mixture was heated at 40 °C. After 2 h, 7.5 mg of PCC was added, and the reaction was stirred at 40 °C. After 4 h more, 15 mg of PCC was added and the reaction stirred overnight at 40 °C. The reaction was diluted with Et_2O (7 mL) and filtered through a silica plug. The filtrate was concentrated to dryness to give 4.5 mg (87%) of **505** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1 H), 7.86 (s, 1 H), 7.67 (s, 1 H), 7.28-7.27 (m, 2 H), 6.14-5.94 (m, 2 H), 5.27-5.07 (m, 4 H), 3.65-3.47 (m, 4 H), 0.40 (s, 9 H).

2'-Acetyl-5,5'-diallyl-2-hydroxy-3'-(trimethylsilyl)-1,1'-biphenyl (506). A solution of **505** (4.5 mg, 0.013 mmol) in THF (300 μL, 300 μL wash) was added dropwise to a solution of MeLi (1.3 M in Et_2O, 120 μL, 0.16 mmol) in THF (100 μL) at 0 °C. The reaction mixture was stirred for 15 min and quenched with 10% NH_4Cl (1 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (2 mL) then brine (2 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (20:1) to give 3.2 mg (68%) of **506** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.43 (m, 3 H), 7.06 (d, *J*

= 8.1 Hz, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 6.20-5.84 (m, 2 H), 5.28-5.02 (m, 4 H), 3.58-3.35 (m, 4 H), 3.18 (s, 1 H), 1.58 (s, 3 H), 0.38 (s, 9 H).

2,9-Di(3-acetoxypropyl)-7-(trimethylsilyl)-6*H*-benzo[*c*]chromene (510). To a solution of **503** (48.6 mg, 0.13 mmol) and a catalytic amount of DMAP in pyridine (500 μL) was added Ac_2O (500 μL) at 0 °C. After 1 h, the reaction was diluted with H_2O (4 mL) and extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 54.5 mg (91%) of **510** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.50 (m, 2 H), 7.23 (d, *J* = 1.8 Hz, 1 H), 7.05 (dd, *J* = 8.2 and 1.8 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 5.15 (s, 2 H), 4.20-4.08 (m, 4 H), 2.81-2.63 (m, 4 H), 2.15-1.91 (m, 10 H), 0.35 (s, 9 H).

2,9-Di(3-acetoxypropyl)-7-(trimethylsilyl)-6*H*-benzo[*c*]chromen-6-one (511). To **510** (20.4 mg, 0.045 mmol), dissolved in DCM (900 μL) was added PCC (9.5 mg, 0.045 mmol), and the mixture was heated at 40 °C. After 2 h, 9.5 mg of PCC was added, and the reaction was stirred at 40 °C. After 4 h more, 19 mg of PCC was added and the reaction was stirred overnight at 40 °C. In the morning, 9.5 mg of PCC was added, and the reaction was stirred for an additional 2 h. It was diluted with Et_2O (7 mL) and filtered through a silica plug. The filtrate was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 19.7 mg (94%) of **511** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1 H), 7.86 (br s, 1 H), 7.64 (br s, 1 H),

7.31-7.21 (m, 2 H), 4.22-4.07 (m, 4 H), 2.98-2.71 (m, 4 H), 2.20-1.93 (m, 10 H), 0.38 (s, 9 H).

2'-Acetyl-5,5'-di(3-hydroxypropyl)-2-hydroxy-3'-(trimethylsilyl)-1,1'-biphenyl (512). A solution of **511** (19.7 mg, 0.042 mmol) in THF (400 µL, 400 µL wash) was added dropwise to a solution of MeLi (1.3 M in Et_2O, 390 µL, 0.50 mmol) in THF (400 µL) at 0 °C. The reaction mixture was stirred 15 min, warmed to rt for 1 h, and quenched with sat. NH_4Cl (2 mL). The aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with water (3 mL) then brine (3 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (10:1) to give 13.4 mg (80%) of **512** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.51 (m, 2 H), 7.48 (d, *J* = 1.8 Hz, 1 H), 7.05 (dd, *J* = 8.2 and 1.8 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 3.81-3.64 (m, 4 H), 3.56 (br s, 1 H), 2.84-2.66 (m, 4 H), 2.04-1.85 (m, 5 H), 0.38 (s, 9 H).

2,9-Di-(3-(*tert*-butyldimethylsilyloxy)propyl)-7-(trimethylsilyl)-6*H*-benzo[*c*]chromene (514). To a solution of **503** (44.2 mg, 0.12 mmol) in DMF (150 µL) was added imidazole (50 mg, 0.72 mmol) and TBDMSCl (52 mg, 0.24 mmol), and the reaction was stirred overnight. H_2O (3 mL) and Et_2O (4 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (4 mL × 2), and the combined organic extracts were washed with water (3 mL × 2) then brine (3 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 60.1 mg

(84%) of **514** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 2 H), 7.28-7.25 (m, 1 H), 7.03 (dd, *J* = 8.2 and 1.8 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 5.16 (s, 2 H), 3.68-3.59 (m, 4 H), 2.73-2.60 (m, 4 H), 1.91-1.79 (m, 4 H), 0.91 (s, 18 H), 0.32 (s, 9 H), 0.04 (s, 12 H).

2,9-Di(3-(tert-butyldimethylsilyloxy)propyl)-7-(trimethylsilyl)-6*H*-benzo[*c*]chromen-6-one (515). To a solution of **514** (26.6 mg, 0.044 mmol) in CH_3CN (1.1 mL) was added $KMnO_4$ (28 mg, 0.18 mmol), and the reaction was stirred for 24 h at rt. More $KMnO_4$ (28 mg, 0.18 mmol) was added, and the reaction was stirred for another 24 h. After removing the CH_3CN under reduced pressure, the residue was taken up in H_2O (4 mL) and extracted with EtOAc (4 mL × 3). The combined organic extracts were washed with water (3 mL × 2) then brine (3 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (40:1) to give 16.1 mg (60%) of **515** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (br s, 1 H), 7.80 (br s, 1 H), 7.59 (br s, 1 H), 7.23-7.17 (m, 2 H), 3.70-3.53 (m, 4 H), 2.88-2.66 (m, 4 H), 1.97-1.74 (m, 4 H), 0.90-0.82 (m, 18 H), 0.33 (s, 9 H), 0.05-–0.05 (m, 12 H).

2'-Acetyl-5,5'-di(3-(tert-butyldimethylsilyloxy)propyl)-2-hydroxy-3'-(trimethylsilyl)-1,1'-biphenyl (516). A solution of **515** (12.2 mg, 0.020 mmol) in THF (400 µL, 400 µL wash) was added dropwise to a solution of MeLi (1.3 M in Et_2O, 100 µL, 0.13 mmol) in THF (100 µL) at 0 °C. The reaction mixture was stirred for 30 min and quenched with 10% NH_4Cl (1 mL). The aqueous layer was extracted with Et_2O (3 mL × 3). The combined organic extracts were washed with water (2 mL) then brine (2 mL), dried (Na_2SO_4), filtered, and

concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (10:1) to give 11.3 mg (90%) of **516** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.5 Hz, 1 H), 7.52 (d, *J* = 2.0 Hz, 1 H), 7.45 (d, *J* = 1.5 Hz, 1 H), 7.05 (dd, *J* = 8.2 and 2.0 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 3.72-3.58 (m, 4 H), 3.18 (s, 1 H), 2.80-2.60 (m, 4 H), 1.95-1.77 (m, 4 H), 0.90 (s, 18 H), 0.36 (s, 9 H), 0.08-0.01 (m, 12 H).

4-(3-Hydroxyprop-1-ynyl)phenol (522). To a solution of 4-iodophenol (100 mg, 0.45 mmol) in TEA/dioxane (1:1, 720 μL) was added $Pd(PPh_3)_2Cl_2$ (3.2 mg, 0.0045 mmol), CuI (1.7 mg, 0.0091 mmol), and propargyl alcohol (32 μL, 0.55 mmol), and the reaction stirred at rt overnight. The reaction was concentrated and taken up in H_2O (7 mL) and Et_2O (7 mL). 1 N HCl (500 μL) was added and the layers separated. The aqueous layer was extracted with Et_2O (7 mL × 2). The combined organic extracts were washed with water (5 mL) then brine (5 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1.5:1) to give 56.1 mg (84%) of **522** as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 7.27 (d, *J* = 8.7 Hz, 2 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 4.35 (s, 2 H); ^{13}C NMR (75 MHz, CD_3CN) δ 158.3, 134.1, 118.4, 116.5, 115.0, 87.4, 85.2, 51.2.

3-(4-(Allyloxy)phenyl)prop-2-yn-1-ol (523). Allyl bromide (79 μL, 0.91 mmol) was added to a solution of **522** (54 mg, 0.36 mmol) in DMF (800 μL), and the reaction was stirred overnight. H_2O (5 mL) was added, and the aqueous layer extracted with Et_2O (6 mL × 3). The combined organic extracts were washed with water (3 mL × 2) then brine (3 mL), dried

($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3.5:1) to give 57.6 mg (84%) of **523** as a white solid: Mp 67-70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.9 Hz, 2 H), 6.85 (d, *J* = 8.9 Hz, 2 H), 6.13-5.96 (m, 1 H), 5.41 (ddt, *J* = 17.5, 2.4, and 1.5 Hz, 1 H), 5.30 (ddt, *J* = 10.3, 2.4, and 1.4 Hz, 1 H), 4.54 (ddd, *J* = 5.3, 1.5, and 1.4 Hz, 2 H), 4.48 (d, *J* = 6.1 Hz, 2 H), 1.61 (t, *J* = 6.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 133.3, 133.0, 118.0, 114.9, 114.8, 86.0, 85.7, 68.9, 51.8.

1-(3-(4-(Allyloxy)phenyl)prop-2-ynyloxy)-4-allyl-2-(2,2-dibromovinyl)benzene (524). To a solution of **490** (20.2 mg, 0.064 mmol), PPh_3 (25 mg, 0.095 mmol), and **523** (14.6 mg, 0.078 mmol) in DCM (310 µL) was added DIAD (19.9 µL, 0.095 mmol) at 0 °C, and the reaction was stirred overnight at rt. The reaction was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (50:1) to give 24.9 mg (80%) of **524** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (br s, 1 H), 7.55 (br s, 1 H), 7.36 (d, *J* = 8.9 Hz, 2 H), 7.14 (dd, *J* = 8.4 and 2.1 Hz, 1 H), 7.02 (d, *J* = 8.4 Hz, 1 H), 6.83 (d, *J* = 8.9 Hz, 2 H), 6.12-5.84 (m, 2 H), 5.40 (ddt, *J* = 17.3, 2.9, and 1.6 Hz, 1 H), 5.29 (ddt, *J* = 10.5, 2.9, and 1.3 Hz, 1 H), 5.12-5.03 (m, 2 H), 4.90 (s, 2 H), 4.53 (ddd, *J* = 5.3, 1.6, 1.3 Hz, 2 H), 3.41-3.31 (m, 2 H).

Methyl 3-(4-(3-(4-(allyloxy)phenyl)prop-2-ynyloxy)-3-ethynylphenyl)propanoate (526). To a solution of **494** (50 mg, 0.24 mmol), PPh_3 (83 mg, 0.32 mmol), and **523** (65 mg, 0.34 mmol) in DCM (1.2 mL) was added DIAD (63 µL, 0.32 mmol) at 0 °C, and the reaction was

stirred overnight at rt. The reaction was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6.5:1) to give 90.5 mg (99%) of **526** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 3 H), 7.16 (dd, *J* = 8.5 and 2.3 Hz, 1 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 8.83 (d, *J* = 8.9 Hz, 2 H), 6.12-5.94 (m, 1 H), 5.39 (ddt, *J* = 17.3, 2.3, 1.5 Hz, 1 H), 5.29 (ddt, *J* = 10.4, 2.3, and 1.4 Hz, 1 H), 4.98 (s, 2 H), 4.52 (ddd, *J* = 5.3, 1.5, 1.5 and 1.4 Hz, 2 H), 3.66 (s, 3 H), 3.30 (s, 1 H), 2.88 (t, *J* = 7.8 Hz, 2 H), 2.60 (t, *J* = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.0, 157.6, 134.0, 133.4, 133.3, 132.9, 130.0, 117.9, 114.8, 114.6, 113.3, 112.1, 87.6, 82.5, 81.4, 80.0, 68.8, 57.6, 51.6, 35.6, 29.9.

3-(4-(3-(4-(Allyloxy)phenyl)prop-2-ynyloxy)-3-ethynylphenyl)propan-1-ol (527). LAH (13.1 mg, 0.34 mmol) was added to a solution of **526** (85.8 mg, 0.23 mmol) in THF (1.1 mL) at 0 °C, and the reaction was stirred for 1 h. Et_2O (6 mL), H_2O (21 μL), 15% NaOH (21 μL), and H_2O (42 μL), were added successively, and the mixture was stirred for 30 min. The mixture was filtered over celite, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/Et_2O (1:1.5) to give 56.9 mg (72%) of **527** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.29 (m, 3 H), 7.14 (dd, *J* = 8.5 and 2.3, 1 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 8.9 Hz, 2 H), 6.12-5.93 (m, 1 H), 5.38 (ddt, *J* = 17.3, 2.3, 1.6 Hz, 1 H), 5.28 (ddt, *J* = 10.5, 2.3, 1.4 Hz, 1 H), 4.97 (s, 2 H), 4.51 (ddd, *J* = 5.3, 1.6, and 1.4 Hz, 2 H), 3.64 (t, *J* = 6.4 Hz, 2 H), 3.30 (s, 1 H), 2.65-2.60 (m, 2 H), 1.91-1.76 (m, 2 H), 1.62)br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9,

157.2, 134.7, 134.0, 133.4, 132.9, 130.2, 118.0, 114.7, 114.5, 113.2, 111.9, 87.5, 82.5, 81.3, 80.2, 68.8, 62.0, 57.6, 34.1, 30.9.

3-(9-Allyl-7-(4-(allyloxy)phenyl)-6*H*-benzo[*c*]chromen-2-yl)propan-1-ol (528). To a flame-dried microwave vial equipped with a stir bar was added **527** (12.5 mg, 0.036 mmol), allylacetylene (32 μL, 0.36 mmol), Cp*Ru(cod)Cl (1.4 mg, 0.0036 mmol), and dry toluene (1.2 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 15 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction vessel to room temperature, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/Et_2O (1:2) to give 6 mg (40%) of **528** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (br s, 1 H), 7.51 (br s, 1 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.13-7.04 (m, 2 H), 6.97 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.20-5.93 (m, 2 H), 5.51-5.40 (m, 1 H), 5.37-5.29 (m, 1 H), 5.21-5.08 (m, 2 H), 5.04 (s, 2 H), 4.65-4.56 (m, 2 H), 3.73 (br s, 2 H), 3.53-3.44 (m, 2 H), 2.80-2.69 (m, 2 H), 2.03-1.88 (m, 2 H), 1.33 (br s, 1 H).

9-Allyl-7-(4-(allyloxy)phenyl)-2-(3-(phenylselanyl)propyl)-6*H*-benzo[*c*]chromene (529). Tri-*n*-butylphosphine (6.3 μL, 0.026 mmol) was added to a solution of **528** (7.5 mg, 0.018 mmol) and phenylselenocyanate (4.4 μL, 0.036 mmol) in THF (250 μL) at rt, and the reaction was stirred for 30 min. After concentration, the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:0 to 70:1) to give 7.8 mg (78%) of **529** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.44 (m, 4 H), 7.29-7.16 (m, 4 H), 7.09 (d, *J*

= 1.5 Hz, 1 H), 7.05-6.95 (m, 4 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 6.24-5.92 (m, 2 H), 5.45 (ddd, *J* = 17.3 2.9, and 1.5 Hz, 1 H), 5.32 (ddd, *J* = 10.5, 2.9, and 1.4 Hz, 1 H), 5.21-5.08 (m, 2 H), 5.04 (s, 2 H), 4.60 (ddd, *J* = 5.3, 1.5, and 1.4 Hz, 2 H), 3.55-3.43 (m, 2 H), 2.96 (t, *J* = 7.3Hz, 2 H), 2.77 (t, *J* = 7.4 Hz, 2 H), 2.14-2.00 (m, 2 H).

2,9-Diallyl-7-(4-(allyloxy)phenyl)-6*H*-benzo[*c*]chromene (530). To a solution of **529** (7.8 mg, 0.014 mmol) in THF (300 µL) was added H_2O_2 (23 µL, 0.21 mmol). The reaction was heated at 60 °C overnight. After cooling the reaction vessel to room temperature, H_2O (2 mL) and Et_2O (3 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic extracts were washed with sat. $NaHCO_3$ (2 mL), water (3 mL) and brine (3 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (50:1) to give 2.5 mg (45%) of **530** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1 H), 7.50 (s, 1 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.13-7.03 (m, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.20-5.93 (m, 2 H), 5.53-5.39 (m, 1 H), 5.38-5.27 (m, 1 H), 5.23-5.08 (m, 2 H), 5.04 (s, 2 H), 4.66-4.56 (m, 2 H), 3.53-3.37 (m, 4 H).

Methyl 3-(9-allyl-7-(4-(allyloxy)phenyl)-6*H*-benzo[*c*]chromen-2-yl)propanoate (532). To a flame-dried microwave vial equipped with a stir bar was added **526** (16.6 mg, 0.044 mmol), allylacetylene (40 µL, 0.44 mmol), Cp*Ru(cod)Cl (1.6 mg, 0.0044 mmol), and dry toluene (1.4 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 15 min in a CEM Discover microwave synthesizer at 300 W. After cooling the

reaction vessel to room temperature, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1:12) to give 9.1 mg (47%) of **532** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1 H), 7.49 (s, 1 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 7.09-7.03 (m, 2 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.22-5.93 (m, 2 H), 5.45 (ddd, *J* = 17.3, 2.9, and 1.6 Hz, 1 H), 5.32 (ddd, *J* = 10.5, 2.9, and 1.4 Hz, 1 H), 5.22-5.07 (m, 2 H), 5.03 (s, 2 H), 4.59 (ddd, *J* = 5.3, 1.6, and 1.4 Hz, 2 H), 3.69 (s, 3 H), 3.49-3.45 (m, 2 H), 2.98 (t, *J* = 7.8 Hz, 2 H), 2.67 (t, *J* = 7.8 Hz, 2 H).

3-(9-Allyl-7-(4-(allyloxy)phenyl)-6*H*-benzo[*c*]chromen-2-yl)propan-1-ol (528). LAH (1.2 mg, 0.032 mmol) was added to a solution of **532** (9.1 mg, 0.021 mmol) in THF (200 µL) at 0 °C, and the reaction was stirred for 1 h. Et_2O (600 µL), H_2O (3 µL), 15% NaOH (3 µL), and H_2O (6 µL), were added successively, and the mixture was stirred for 30 min. The mixture was filtered over celite, dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/Et_2O (1:1.5) to give 7.5 mg (88%) of **528** as a colorless oil.

Methyl 3-(7-(4-(allyloxy)phenyl)-9-(3-hydroxypropyl)-6*H*-benzo[*c*]chromen-2-yl)propanoate (533). To two flame-dried microwave vials equipped with a stir bar was added **526** (45 mg, 0.12 mmol), pent-4-yn-1-ol (113 µL, 1.20 mmol), Cp*Ru(cod)Cl (4.5 mg, 0.013 mmol), and dry toluene (3 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 15 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction vessel to room temperature, the solutions were

combined, concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/Et_2O (1:3) to give 84.7 mg (77%) of **533** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.0 Hz, 1 H), 7.51 (br s, 1 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 7.13-7.03 (m, 2 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.20-6.00 (m, 1 H), 5.45 (ddd, *J* = 17.2, 2.9, and 1.5 Hz, 1 H), 5.32 (ddd, *J* = 10.5, 2.9, and 1.4 Hz, 1 H), 5.03 (s, 2 H), 4.59 (ddd, *J* = 5.2, 1.5, and 1.4 Hz, 2 H), 3.79-3.67 (m, 5 H), 2.98 (t, *J* = 7.7 Hz, 2 H), 2.83-2.76 (m, 2 H), 2.68 (t, *J* = 7.8 Hz, 2 H), 2.04-1.90 (m, 2 H), 1.33 (t, *J* = 5.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 158.1, 153.4, 141.6, 139.0, 134.2, 133.3, 133.2, 132.2, 130.6, 130.1, 129.4, 129.2, 127.1, 123.5, 123.4, 121.3, 117.9, 114.6, 68.9, 66.4, 62.1, 51.7, 36.1, 34.3, 32.1, 30.6.

7-(4-(Allyloxy)phenyl)-2,9-di(3-hydroxypropyl)-6*H*-benzo[*c*]chromene (534). LAH (17 mg, 0.45 mmol) was added to a solution of **533** (82.1 mg, 0.18 mmol) in THF (1.5 mL) at 0 °C, and the reaction was stirred for 1 h. Et_2O (5 mL), H_2O (15 μL), 15% NaOH (15 μL), and H_2O (30 μL), were added successively, and the mixture was stirred for 30 min. The mixture was filtered over celite, dried (Na_2SO_4), filtered, and concentrated to dryness to give 66.9 mg (87%) of **534** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (br s, 1 H), 7.52 (br s, 1 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.14-7.04 (m, 2 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.19-6.00 (m, 1 H), 5.45 (ddd, *J* = 17.3, 2.9, and 1.4 Hz, 1 H), 5.32 (ddd, *J* = 10.5, 2.9, and 1.4 Hz, 1 H), 5.04 (s, 2 H), 4.59 (ddd, *J* = 5.3, 1.4, and 1.4 Hz, 2 H), 3.81-3.66 (m, 4 H), 2.90-2.66 (m, 4 H), 2.06-1.86 (m, 2 H), 1.48 (br s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

158.1, 153.1, 141.6, 139.1, 135.5, 133.3, 132.3, 130.8, 130.2, 129.4, 127.1, 123.44, 123.42, 121.3, 117.9, 117.1, 114.7, 69.0, 66.4, 62.14, 62.10, 34.5, 34.3, 32.1, 31.7.

7-(4-(Allyloxy)phenyl)-2,9-di(3-iodopropyl)-6*H*-benzo[*c*]chromene (535). To a solution of **534** (13.1 mg, 0.030 mmol) in THF (200 µL) at 0 °C was added PPh_3 (24 mg, 0.091 mmol), imidazole (6.7 mg, 0.097 mmol) and I_2 (23 mg, 0.091 mmol), and the reaction was stirred for 45 min as it warmed to rt. Brine (2 mL) was added, and the aqueous layer was extracted with EtOAc (3 mL × 3). The combined organic extracts were washed with water (3 mL) and brine (3 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (14:1) to give 18.4 mg (99%) of **535** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.9 Hz, 1 H), 7.52 (s, 1 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 7.10-7.03 (m, 2 H), 6.99 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.18-6.01 (m, 1 H), 5.45 (ddd, *J* = 17.3, 2.9, and 1. Hz, 1 H), 5.32 (ddd, *J* = 10.5, 2.9, and 1.4 Hz, 1 H), 5.04 (s, 2 H), 4.60 (ddd, *J* = 5.3, 1.5, and 1.4 Hz, 2 H), 3.31-3.18 (m, 4 H), 2.90-2.71 (m, 4 H), 2.33-2.10 (m, 4 H).

7-(4-(Allyloxy)phenyl)-2,9-di((3-*S*-methylcarbonodithioatyl)-propyl)-6*H*-benzo[*c*]chromene (537). NaH (60%, 10 mg, 0.25 mmol) was added to a solution of **534** (20 mg, 0.046 mmol) in THF (1 mL) at 0 °C. After 1 h, CS_2 (28 µL, 0.46 mmol) was added, and the reaction was stirred at rt for 1.5 h. After cooling to 0 °C, MeI (14.5 µL, 0.23 mmol) was added, and the reaction was stirred for 1.5 h as it warmed to rt. The reaction was quenched with sat. NH_4Cl (2 mL) and extracted with Et_2O (3 mL × 3). The combined organic extracts

were washed with water (3 mL) and brine (3 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (12:1) to give 22.2 mg (78%) of **534** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.8 Hz, 1 H), 7.52 (s, 1 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 7.13-7.00 (m, 2 H), 6.99 (d, *J* = 8.7 Hz, 2 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.21-6.02 (m, 1 H), 5.53-5.41 (m, 1 H), 5.38-5.28 (m, 1 H), 5.04 (s, 2 H), 4.74-4.65 (m, 4 H), 4.62-4.59 (m, 2 H), 2.92-2.75 (m, 4 H), 2.59 (s, 3 H), 2.57 (s, 3 H), 2.30-2.12 (m, 4 H).

Methyl 3-(4-hydroxy-3-(3-hydroxyprop-1-ynyl)phenyl)propanoate (541). To a solution of **492** (100 mg, 0.33 mmol) in TEA/dioxane (1:1, 500 μL) was added $Pd(PPh_3)_2Cl_2$ (11.4 mg, 0.016 mmol), CuI (6.2 mg, 0.033 mmol) and propargyl alcohol (29 μL, 0.98 mmol), and the reaction was heated at 55 °C. After 5 h, the reaction was concentrated, taken up in H_2O (7 mL) and Et_2O (7 mL), and the layers separated. The aqueous layer was extracted with Et_2O (7 mL × 2). The combined organic extracts were washed with water (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1) to give 63.4 mg (83%) of **541** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.35 (m, 2 H), 7.11 (dd, *J* = 8.5 and 1.7 Hz, 1 H), 6.61 (s, 1 H), 4.76 (d, *J* = 6.3 Hz, 2 H), 3.67 (s, 3 H), 3.04 (t, *J* = 7.7 Hz, 2 H), 2.66 (t, *J* = 7.7 Hz, 2 H), 1.86 (t, *J* = 6.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 157.0, 154.1, 135.3, 128.5, 125.0, 120.6, 111.2, 104.1, 58.3, 51.7, 36.5, 31.0.

Methyl 3-(3-iodo-4-methoxyphenyl)propanoate (542). To a solution of **492** (100 mg, 0.33 mmol) in DMF (550 μL) was added K_2CO_3 (90 mg, 0.66 mmol) and MeI (51 μL, 0.82 mmol). When complete, the reaction was diluted with H_2O (5 mL) and extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with water (3 mL × 2) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (10:1) to give 97.8 mg (93%) of **542** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.1 Hz, 1 H), 7.14 (dd, *J* = 8.4 and 2.1 Hz, 1 H), 6.74 (d, *J* = 8.4 Hz, 1 H), 3.86 (s, 3 H), 3.67 (s, 3 H), 2.85 (t, *J* = 7.7 Hz, 2 H), 2.59 85 (t, *J* = 7.7 Hz, 2 H).

Methyl 3-(3-(3-hydroxyprop-1-ynyl)-4-methoxyphenyl)propanoate (540a). To a solution of **542** (100 mg, 0.31 mmol) in TEA/dioxane (1:1, 590 μL) was added $Pd(PPh_3)_2Cl_2$ (4.3 mg, 0.006 mmol), CuI (2.3 mg, 0.012 mmol) and propargyl alcohol (37 μL, 0.62 mmol), and the reaction was stirred at rt. After 1.5 h, the reaction was concentrated, taken up in H_2O (5 mL) and Et_2O (5 mL), and the layers separated. The aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic extracts were washed with water (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (1.5:1) to give 65 mg (84%) of **540a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.24 (m, 1 H), 7.13 (dd, *J* = 8.5 and 2.3 Hz, 1 H), 6.79 (d, *J* = 8.5 Hz, 1 H), 4.53 (d, *J* = 6.3 Hz, 2 H), 3.86 (s, 3 H), 3.66 (s, 3 H), 2.86 (t, *J* = 7.7 Hz, 2 H), 2.59 85 (t, *J* = 7.7 Hz, 2 H), 1.71 (t, *J* = 6.3 Hz, 1 H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 173.3, 158.5, 133.4, 132.5, 129.8, 111.7, 110.7, 91.6, 81.7, 55.8, 51.7, 51.6, 35.7, 29.7.

Methyl 3-(3-(3-bromoprop-1-ynyl)-4-methoxyphenyl)propanoate (543). To a solution of **540a** (63.8 mg, 0.26 mmol) in DCM (1.3 mL) was added PPh_3 (101 mg, 0.39 mmol) and CBr_4 (128 mg, 0.39 mmol) at 0 °C. The reaction was stirred for 1.5 h as it warmed to rt and was concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (7:1 to 5:1) to give 74.3 mg (93%) of **543** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 2.3 Hz, 1 H), 7.14 (dd, *J* = 8.5 and 2.3 Hz, 1 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.30 (s, 1 H), 2.86 (t, *J* = 7.7 Hz, 2 H), 2.58 (t, *J* = 7.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 158.9, 133.7, 132.6, 130.4, 111.2, 110.9, 88.1, 83.3, 55.9, 51.7, 35.7, 29.8, 15.8.

Methyl 3-(4-(3-(2-methoxy-5-(2-(methoxycarbonyl)-ethyl)-phenyl)prop-2-ynyloxy)-3-ethynylphenyl)propanoate (538a). To a solution of **494** (42 mg, 0.21 mmol) and **543** (74.3 mg, 0.24 mmol) in DMF (700 μL) was added K_2CO_3 (55 mg, 0.40 mmol), and the reaction was stirred overnight. The reaction was diluted with H_2O (4 mL) and extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with water (3 mL × 2) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (10:1) to give 76.3 mg (88%) of **538a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 1.7 Hz, 1 H), 7.23-7.07 (m, 4 H), 6.77 (d, *J* = 8.5 Hz, 1 H), 5.03 (s, 2 H), 3.83 (s, 3 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 3.29 (s, 1

H), 2.95-2.78 (m, 4 H), 2.66-2.50 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 158.9, 157.6, 133.9, 133.5, 133.3, 132.5, 130.1, 130.0, 113.4, 112.0, 111.4, 110.9, 87.7, 84.1, 81.3, 80.0, 57.7, 55.9, 51.6, 35.7, 35.6, 29.82, 29.77.

Methyl 3-(7-(5-(2-(methoxycarbonyl)ethyl)-2-methoxyphenyl)-9-(3-hydroxypropyl)-6*H*-benzo[*c*]chromen-2-yl)propanoate (544). To a flame-dried microwave vial equipped with a stir bar was added **538a** (29.6 mg, 0.068 mmol), pent-4-yn-1-ol (63 μL, 0.68 mmol), Cp*Ru(cod)Cl (2.6 mg, 0.0068 mmol), and dry toluene (1.7 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 15 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction vessel to room temperature, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/Et_2O (1:5) to give 27.6 mg (78%) of **544** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1 H), 7.53 (s, 1 H), 7.19 (dd, *J* = 8.4 and 2.2 Hz, 1 H), 7.06-7.02 (m, 3 H), 6.89-6.83 (m, 2 H), 4.98-4.66 (m, 2 H), 3.83-3.64 (m, 11 H), 3.06-2.89 (m, 4 H), 2.83-2.75 (m, 2 H), 2.71-2.59 (m, 4 H), 2.06-1.92 (m, 2 H), 1.73 (br s, 1 H).

2,9-Di(3-hydroxypropyl)-7-(5-(2-(methoxycarbonyl)ethyl)-2-methoxyphenyl)-6*H*-benzo[*c*]chromene (545). LAH (5.5 mg, 0.14 mmol) was added to a solution of **544** (25 mg, 0.048 mmol) in THF (500 μL) at 0 °C, and the reaction was stirred for 1 h. Et_2O (1.3 mL), H_2O (5 μL), 15% NaOH (5 μL), and H_2O (10 μL), were added successively, and the mixture was stirred for 30 min. The mixture was filtered over celite, dried (Na_2SO_4), filtered, and concentrated to dryness to give 20.4 mg (91%) of **545** as a colorless oil. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.60 (d, *J* = 1.8 Hz, 1 H), 7.53 (s, 1 H), 7.18 (dd, *J* = 8.3 and 2.1 Hz, 1 H), 7.10-7.01 (m, 3 H), 6.91-6.82 (m, 2 H), 4.99-4.68 (m, 2 H), 3.90-3.60 (m, 9 H), 2.92-2.60 (m, 6 H), 2.11-1.81 (m, 6 H), 1.78-1.53 (m, 3 H).

Methyl 3-(3-(2,2-dibromovinyl)-4-(hex-5-en-2-ynyloxy)phenyl)propanoate (550). To a solution of **490** (21 mg, 0.066 mmol), PPh_3 (22.5 mg, 0.086 mmol), and **549** (7.8 mg, 0.081 mmol) in DCM (310 μL) was added DIAD (16.9 μL, 0.086 mmol) at 0 °C, and the reaction was stirred for 2 h. More PPh_3 (3.5 mg, 0.017 mmol), DIAD (2.6 μL, 0.017 mmol) and **549** (2.5 mg, 0.026 mmol) were added, and the reaction was stirred overnight. The reaction was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (80:1) to give 23.5 mg (90%) of **550** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1 H), 7.54 (d, *J* = 2.1 Hz, 1 H), 7.13 (dd, *J* = 8.4 and 2.1 Hz, 1 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 6.05-5.70 (m, 2 H), 5.28 (ddd, *J* = 17.0, 3.4, and 1.8 Hz, 1 H), 5.16-5.01 (m, 3 H), 4.72 (t, *J* = 2.1 Hz, 2 H), 3.42-3.30 (m, 2 H), 3.03-2.97 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 137.6, 133.0, 132.6, 132.0, 129.8, 129.5, 125.1, 116.6, 116.0, 112.7, 90.0, 85.0, 57.1, 39.4, 23.2.

Methyl 3-(3-ethynyl-4-(hex-5-en-2-ynyloxy)phenyl)propanoate (551). To a solution of **494** (67.3 mg, 0.33 mmol), PPh_3 (129.6 mg, 0.49 mmol), and **549** (47.5 mg, 0.49 mmol) in DCM (1.7 mL) was added DIAD (93.2 μL, 0.49 mmol) at 0 °C, and the reaction was stirred overnight at rt. The reaction was concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1) to give 86.8 mg (87%) of **551**

as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.3 Hz, 1 H), 7.14 (dd, *J* = 8.5 and 2.3 Hz, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H), 5.87-5.68 (m, 1 H), 5.26 (ddd, *J* = 17.0, 2.5, and 1.8 Hz, 1 H), 5.09 (ddd, *J* = 10.0, 2.5, and 1.7 Hz, 1 H), 4.79 (t, *J* = 2.1 Hz, 2 H), 3.67 (s, 3 H), 3.28 (s, 1 H), 3.03-2.94 (m, 2 H), 2.87 (t, *J* = 7.7 Hz, 2 H), 2.59 (t, *J* = 7.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 157.5, 134.0, 133.3, 131.9, 130.0, 116.5, 113.1, 112.0, 85.1, 81.3, 80.0, 57.2, 51.7, 35.7, 29.9, 23.2.

Methyl 3-(3-ethynyl-4-methoxyphenyl)propanoate (548a). To a solution of **494** (181 mg, 0.89 mmol) in DMF (1.5 mL) at rt was added K_2CO_3 (245 mg, 1.77 mmol) and MeI (138 μL, 2.22 mmol), and the reaction was stirred for 20 h. H_2O (6 mL) and Et_2O (6 mL) were added, and the layers separated. The aqueous layer was extracted with Et_2O (6 mL × 2). The combined organic extracts were washed with water (5 mL × 2) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1) to give 174.7 mg (90%) of **548a** as a reddish solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 2.3 Hz, 1 H), 7.14 (dd, *J* = 8.5 and 2.3 Hz, 1 H), 6.80 (d, *J* = 8.5 Hz, 1 H), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.30 (s, 1 H), 2.86 (t, *J* = 7.7 Hz, 2 H), 2.58 (t, *J* = 7.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 159.2, 133.9, 132.5, 130.2, 111.1, 110.8, 81.1, 80.1, 55.9, 51.6, 35.7, 29.8.

Methyl 3-(3-ethynyl-4-(*tert*-butyldimethylsilyloxy)phenyl)propanoate (548b). 494 (50 mg, 0.24 mmol) in DMF (200 μL) was added to a solution of TBDMSCl (55.3 mg, 0.37 mmol) and imidazole (50 mg, 0.73 mmol) in DMF (150 μL) at 0 °C, and the reaction was

stirred overnight. H_2O (3 mL) and Et_2O (5 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (5 mL × 2), and the combined organic extracts were washed with water (3 mL × 2) then brine (3 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1) to give 74.2 mg (96%) of **548b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.3 Hz, 1 H), 7.03 (dd, *J* = 8.3 and 2.3 Hz, 1 H), 6.73 (d, *J* = 8.3 Hz, 1 H), 3.66 (s, 3 H), 3.16 (s, 1 H), 2.85 (t, *J* = 7.8 Hz, 2 H), 2.58 (t, *J* = 7.8 Hz, 2 H), 1.02 (s, 9 H), 0.21 (s, 6 H).

Methyl 3-(9-(5-(2-(methoxycarbonyl)ethyl)-2-methoxyphenyl)-7-allyl-6*H*-benzo[*c*]chromen-2-yl)propanoate (552a). To a flame-dried microwave vial equipped with a stir bar was added **551** (15.8 mg, 0.056 mmol), **548a** (122 mg, 0.56 mmol), Cp*Ru(cod)Cl (2.1 mg, 0.0056 mmol), and dry toluene (1.4 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 15 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction vessel to room temperature, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (5:1) to give 18.8 mg (67%) of **552a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (br s, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 7.27 (br s, 1 H), 7.21-7.14 (m, 2 H), 7.06 (dd, *J* = 8.2 and 2.0 Hz, 1 H), 6.97-6.88(m, 2 H), 6.07-5.88 (m, 1 H), 5.18-4.99 (m, 4 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 3.48-3.40 (m, 2 H), 3.02-2.89 (m, 4 H), 2.71-2.60 (m, 4 H).

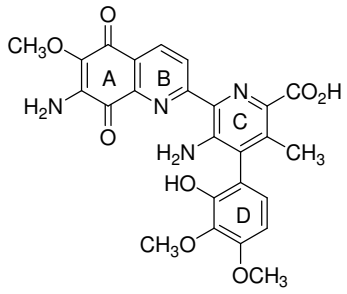
Methyl 3-(9-(5-(2-(methoxycarbonyl)ethyl)-2-(*tert*-butyldimethylsilyloxy)phenyl)-7-allyl-6*H*-benzo[*c*]chromen-2-yl)propanoate (552b). To a flame-dried microwave vial equipped with a stir bar was added **551** (12 mg, 0.043 mmol), **548b** (56 mg, 0.18 mmol), Cp*Ru(cod)Cl (1.7 mg, 0.0045 mmol), and dry toluene (1.1 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 15 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction vessel to room temperature, the solution was concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1) to give 15.1 mg (58%) of **552b** as a colorless oil. ^{1}H NMR (300 MHz, CDCl3) δ 7.70 (br s, 1 H), 7.57 (d, *J* = 2.2 Hz, 1 H), 7.29-7.24 (m, 1 H), 7.17 (d, *J* = 2.2 Hz, 1 H), 7.10-7.01 (m, 2 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.03-5.84 (m, 1 H), 5.19-4.92 (m, 4 H), 3.71-3.61 (m, 6 H), 3.46-3.36 (m, 2 H), 3.01-2.86 (m, 4 H), 2.70-2.57 (m, 4 H), 0.79 (s, 9 H), –0.05 (s, 6 H).

CHAPTER 7: Progress Towards the Total Synthesis of Streptomyces Anticancer Natural Products

7.1 Streptomyces Antitumor Natural Products

7.1.1 Streptonigrin

Streptomyces species produce a wide variety of biologically active natural products including polyketides, peptides, and polysaccharides. In 1960, Rao and Cullen isolated a novel metabolite, streptonigrin (**558**), from *Streptomyces flocculus*.[322] Streptonigrin showed broad-spectrum antibiotic activity against gram-positive and gram-negative bacteria as well as antitumor activity (Figure 7.1). The same compound was isolated in France as rufochromomycin from *S. rufochromogenes* and *S. echinatus* and in the Soviet Union as bruneomycin from *Actinomyces albus var. bruneomycini*.[323-325] In 1963, Rao, Biemann, and Woodward unveiled the structure of streptonigrin.[326] The phenylpyridylquinolinequinone core structure was unique for secondary metabolites from *Streptomyces*, and subsequent studies showed a novel biochemical pathway was responsible for the production of streptonigrin.[327-330]

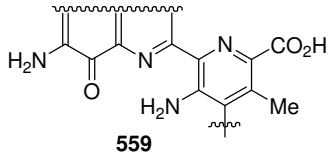


streptonigrin (**558**)

Figure 7.1. Streptonigrin (**558**).

The promise of its anticancer activity was short lived as clinical trials showed it to be highly toxic.[327, 330] In efforts to produce less toxic analogues, structure-activity studies were

conducted by various groups to determine the key components for biological activity.[331-335] Rao compiled the various studies and determined the partial structure **559** as the minimum structure required for activity (Figure 7.2).[336] Interestingly, this partial structure contains possible metal binding groups. In fact, a redox active metal such as Fe or Cu is necessary for full anticancer activity.[337-340]



559

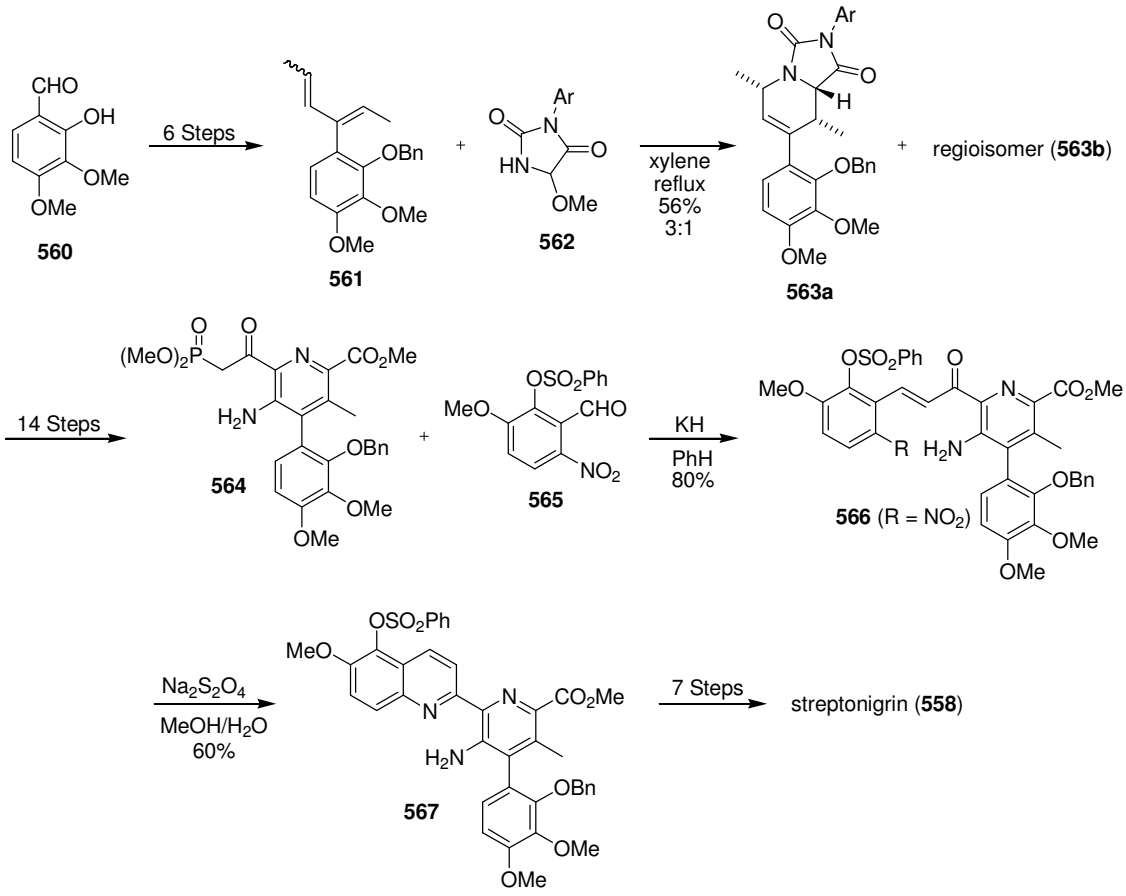
Figure 7.2. Minimal structural requirements for biological activity.

The intriguing structure and promising biological activity of streptonigrin made its synthesis quite desirable from both the chemical and biological perspectives. Accordingly, many approaches to the core structure have been developed including models of the C-, AB-, CD-, ABC-, and ABCD-ring systems (see G. Bringmann et al. *Tetrahedron* **2004**, *60*, 3539–3574 for details).[341] To date, there have been two total syntheses of streptonigrin. The first, by Weinreb, took 20 years and more than 30 steps to complete in 1980 and was followed by Kende's total synthesis in 1981.[342, 343] The Boger group completed a formal synthesis of streptonigrin in 1985.[344]

7.1.2 Previous Syntheses of Streptonigrin

As mentioned above, there have been two total syntheses of streptonigrin as well as one formal synthesis. Weinreb's synthesis of streptonigrin was accomplished in 30 steps and in 0.013% overall yield. A key transformation involved the imino Diels-Alder cycloaddition of the diene **561** (prepared in 6 steps from **560**) and the hydantoin **562** towards the C-D ring

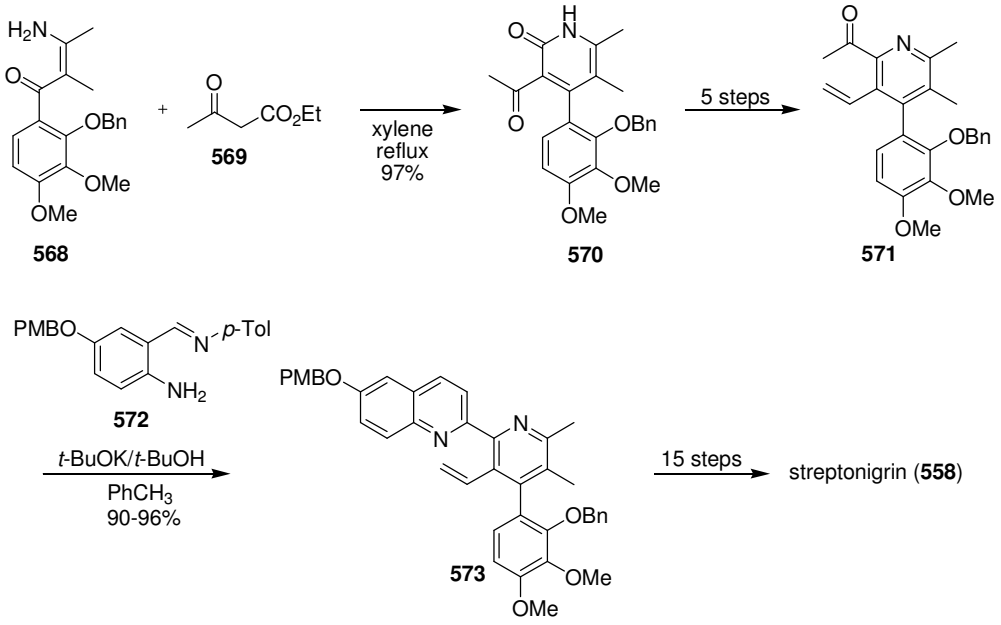
precursor **563a**. A fourteen step sequence then supplied phosphonate **564** which underwent a Horner-Wadsworth-Emmons reaction with the aldehyde **565** to provide the enone **566**. This enone then underwent a modified Friedlander reaction to **567** to construct the A-B ring system (Scheme 7.1). A further seven steps was required to furnish synthetic streptonigrin.[342]



Scheme 7.1. Weinreb's total synthesis of streptonigrin.

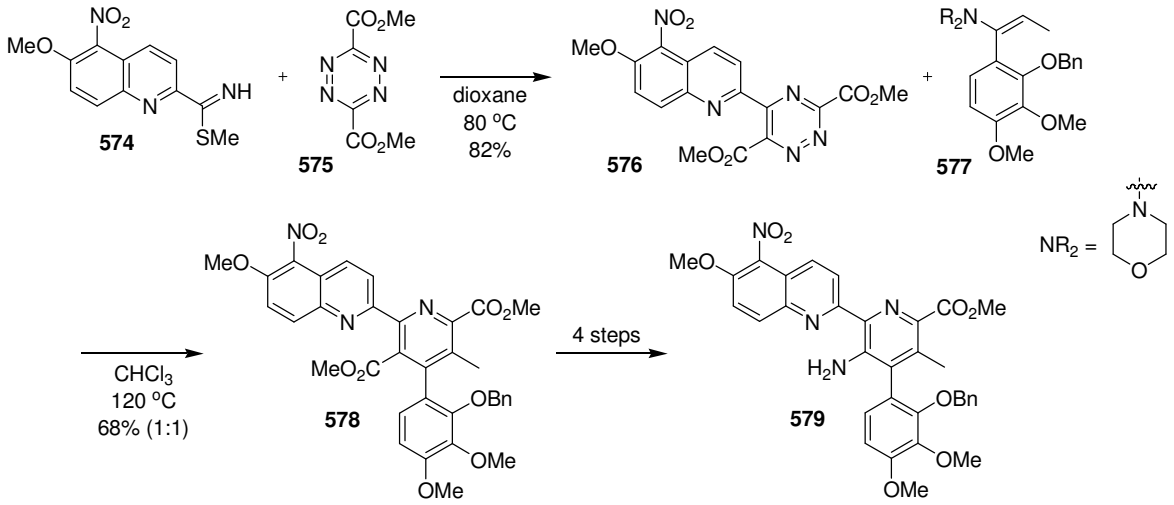
Shortly after Weinreb's report, Kende disclosed his group's approach to streptonigrin. Condensation of the known ketoenamine **568** with methylacetoacetate (**569**) to **570** provided access to the C and D rings. Further elaboration to **571** in five steps set the stage for the introduction of the A and B rings via reaction with **572** to give the complete core structure of streptonigrin **573**. Another 15 steps is required to obtain synthetic streptonigrin (Scheme

7.2).[343] Despite the length, a total yield of 0.13%, an order of magnitude better than Weinreb's synthesis, was obtained.



Scheme 7.2. Kende's approach to streptonigrin.

Boger's formal synthesis of streptonigrin relies upon two sequential inverse demand Diels-Alder reactions. The first, between **574** and **575**, provides the tricycle **576** in 82% yield and constructs the A and B rings of streptonigrin. The second Diels-Alder reaction forms the C ring by bringing together the A and B rings in **576** with the D ring in **577** to give the tetracycle **578** and its regioisomer in a 1:1 ratio. Four additional steps provide entry into an intermediate previous prepared by Kende (**579**, Scheme 7.3).[344]



Scheme 7.3. Boger's formal synthesis of streptonigrin.

7.1.3 Lavendamycin

In 1982, Doyle reported the isolation of lavendamycin (**580**) from *Streptomyces lavendulae* and established its structure as a tricyclic β-carboline subunit attached to a 7-aminoquinolinequinone (Figure 7.3).[345, 346] The structural similarity with streptonigrin is clearly distinguished and lavendamycin's role in the biosynthetic pathway of streptonigrin as an intermediate or a shunt metabolite is a possibility.[341] As streptonigrin, lavendamycin displayed antibiotic activity as well as antitumor activity[332, 345] and has attracted much synthetic interest. Several formal syntheses[347-352] and three total syntheses of lavendamycin methyl ester have been reported.[353-356]

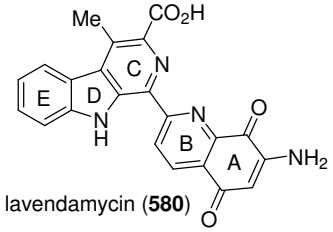
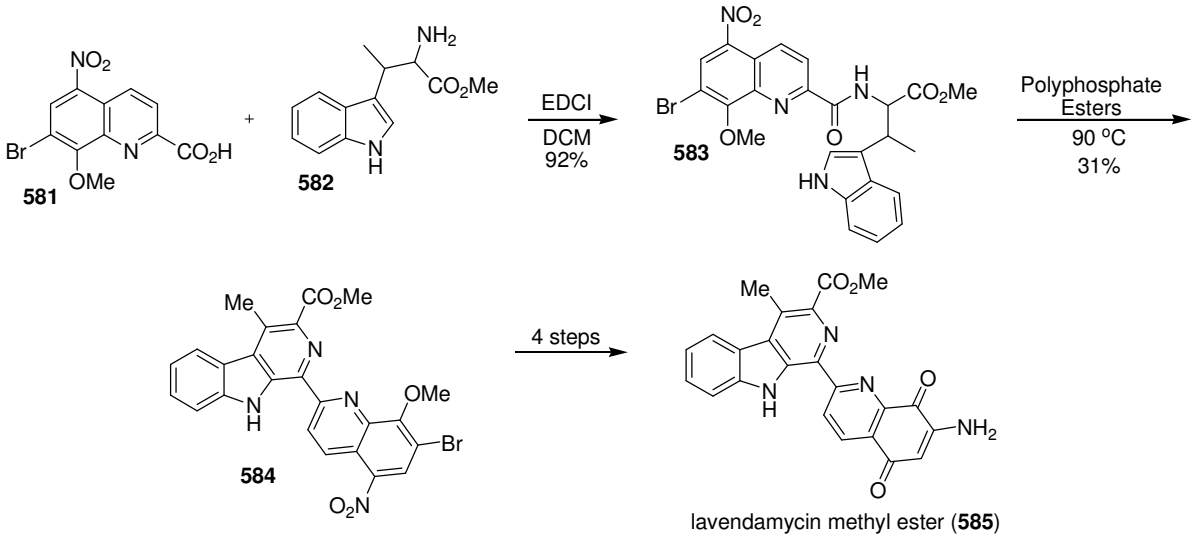


Figure 7.3. Lavendamycin (**580**).

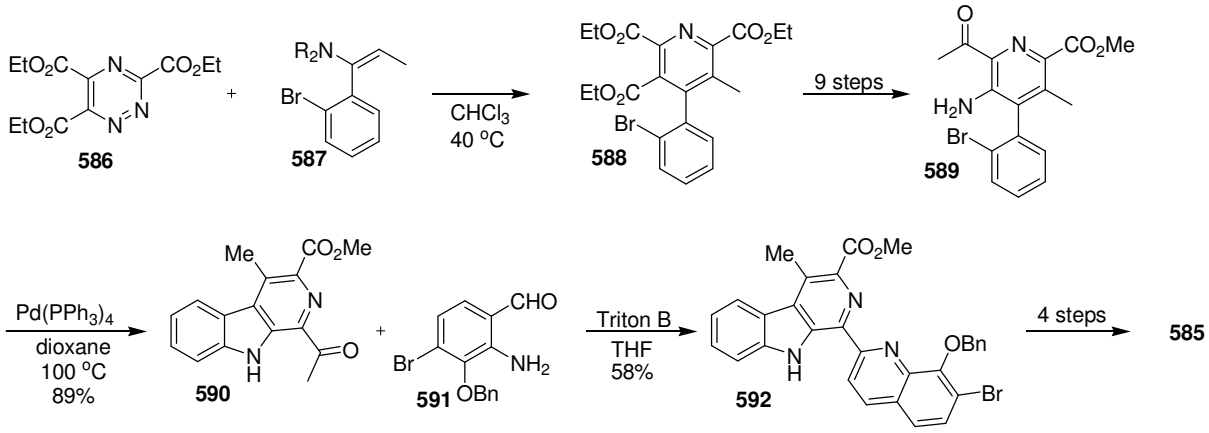
7.1.4 Previous Syntheses of Lavendamycin

The first total synthesis of lavendamycin methyl ester (**585**) was accomplished by Kende's group in 1984. Their strategy involved coupling of the acid **581** with β-methyltryptophan (**582**) to provide the amide **583** in 92% yield. Formation of the β-carboline structure was achieved via a Bischler-Napieralski condensation to **584**. Four more steps provided the methyl ester (Scheme 7.4).[353]



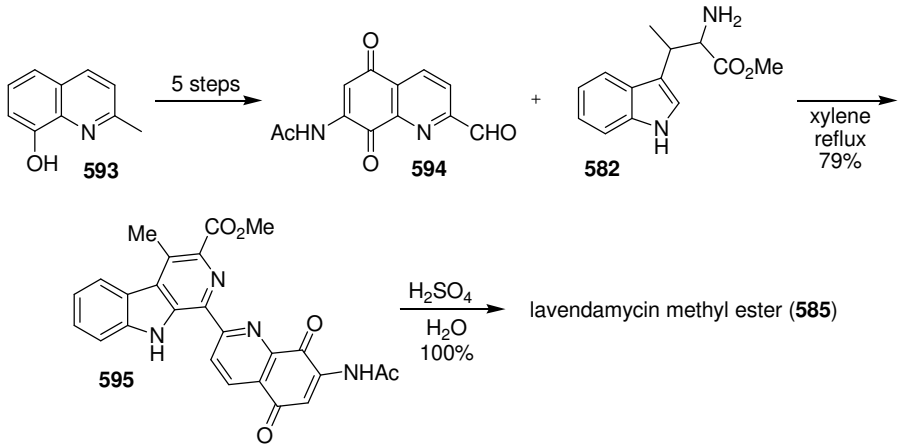
Scheme 7.4. Kende's synthesis of lavendamycin methyl ester.

Similar to his synthesis of streptonigrin, Boger takes advantage of an inverse demand Diels-Alder reaction to form the C ring of lavendamycin. In the event, the triazine **586** and the enamine **587** cyclize with loss of nitrogen to give **588**. After nine steps, the D ring is formed via Pd-catalyzed arylamine formation from the bromide **589** giving **590** in 89% yield. Friedlander condensation with the aldehyde **591** provides the pentacyclic structure **592** that is taken on to lavendamycin methyl ester in four subsequent steps (Scheme 7.5).[354]



Scheme 7.5. Boger's synthesis of lavendamycin methyl ester.

Recently, Behforouz reported an efficient synthesis of lavendamycin methyl ester in only 8 steps and >30% overall yield. Key to the synthesis is the rapid synthesis of the A and B ring precursor **594** from **593** in only six steps. Condensation of **593** with β-methyltryptophan effectively constructs the C ring furnishing **595** in 79% yield. Treatment with acid provides **585** quantitatively (Scheme 7.6).[355, 356]

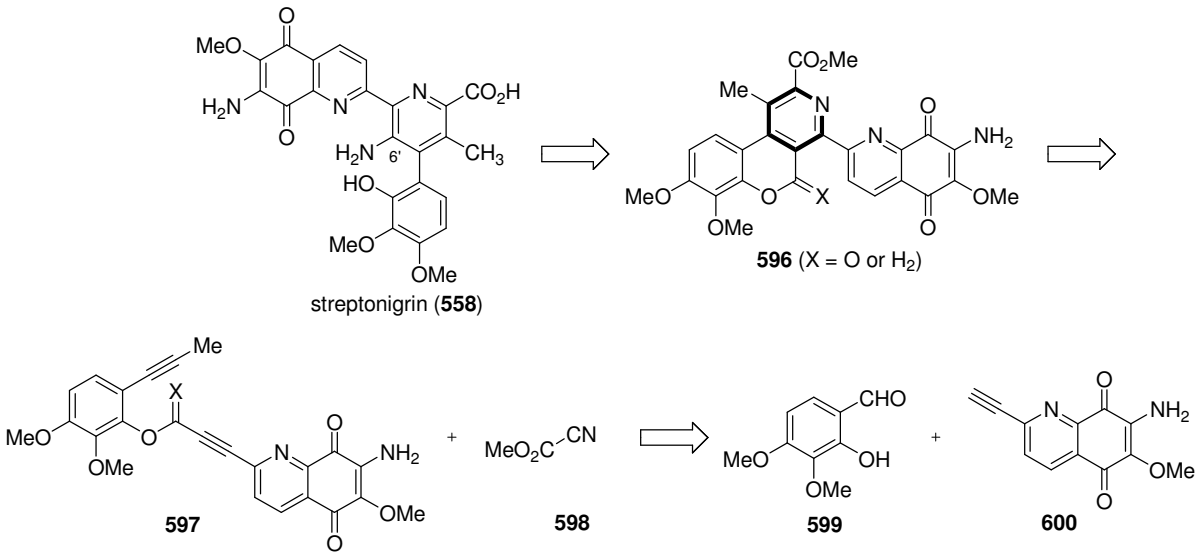


Scheme 7.6. Behforouz's synthesis of lavendamycin methyl ester.

7.2 Progress Towards the Total Synthesis of Streptonigrin

7.2.1 Retrosynthetic Analysis

At first glance, a route towards streptonigrin utilizing a [2+2+2] cyclotrimerization strategy does not seem feasible given the lack of a fused ring system. However, drawing on experience from the synthesis of illudinine and the cannabinoids, we envisioned generating streptonigrin from the opening of the tricyclic lactone **596** followed by a Curtius or a Hofmann rearrangement to the amine (Scheme 7.7). This tricyclic lactone **596** contains the familiar diarylpyran (or pyrone) structure seen previously in the cannabinoid syntheses (see Scheme 5.16). We hypothesized that the pyridine ring (shown in bold) could be formed from a regioselective [2+2+2] cyclotrimerization between the diyne **597** and the nitrile **598**. This diyne would be prepared from the commercially available salicylaldehyde derivative **599** and the suitably substituted quinolinequinone **600**. Initial investigations would focus on the [2+2+2] cyclotrimerization event towards tricyclic lactones similar to **596** and their subsequent transformations to install the amino functionality on C-6'.



Scheme 7.7. Retrosynthetic analysis of streptonigrin (**558**).

7.2.2 Early Model Studies Towards Streptonigrin

The first part of the model studies towards streptonigrin focused on the cyclotrimerization reaction of the diyne **601** or **602**, where the pyridine ring replaces the quinolinequinone portion of streptonigrin and where the methyl group from the C ring is absent (Figure 7.4). The ester diyne **602** would allow for a more streamlined synthesis, and, therefore, its synthesis was explored first.

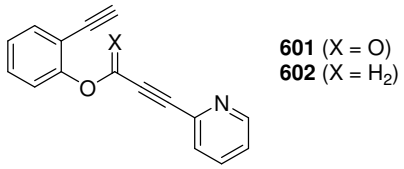
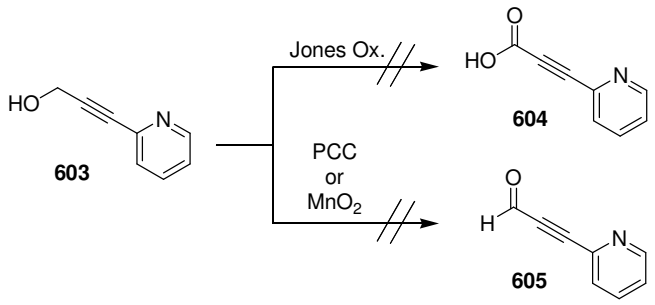


Figure 7.4. Model diynes towards streptonigrin.

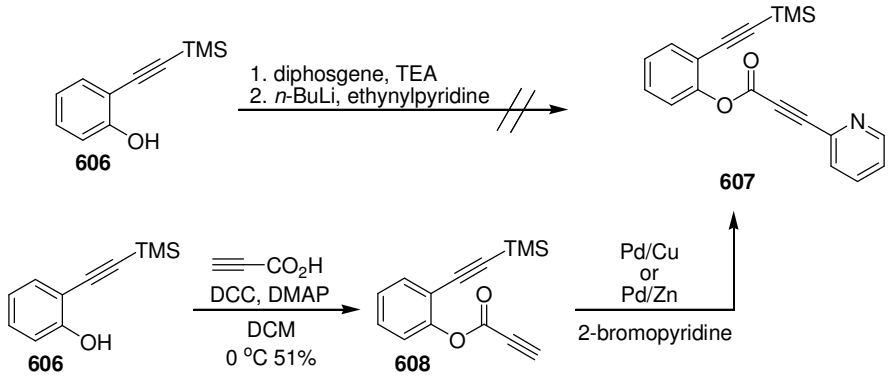
In hopes of coupling a carboxylic acid and a phenol to form **601**, attempts to oxidize the known propargyl alcohol **603**[357] to the acid **604** were investigated. Unfortunately, Jones oxidation (Jones reagent, acetone, 0 °C) of **603** failed to give any isolable product. Two step

procedures where PCC (DCM, rt) or MnO_2 (DCM, rt) were used to first oxidize the alcohol to the aldehyde **605** were equally unsuccessful resulting in decomposition of the starting material (Scheme 7.8). Disconnection in this fashion was abandoned, and other means to make the ester were then explored.



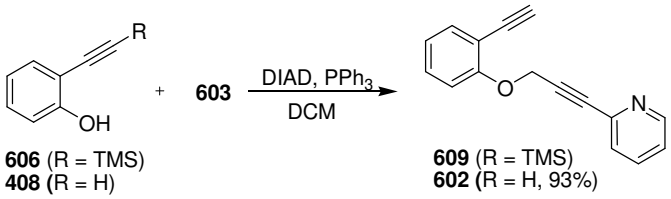
Scheme 7.8. Attempted oxidations of **603**.

Alkylation of the lithium acetylide of ethynylpyridine with the chloroformate formed from the known phenol **606**[358] was unsuccessful towards **607**. A two-step approach was then attempted. Coupling of the phenol **606** with propiolic acid provided the ester **608** in 51% yield. However, Sonogashira (2-bromopyridine, K_2CO_3, CuI, $Pd(PPh_3)_2Cl_2$, THF, 60 °C) or Negishi (2-bromopyridine, $ZnBr_2$, TEA, $Pd(PPh_3)_2Cl_2$, THF, 60 °C) coupling with 2-bromopyridine failed to yield the desired ester **607** (Scheme 7.9).



Scheme 7.9. Attempted synthesis of the ester **607**.

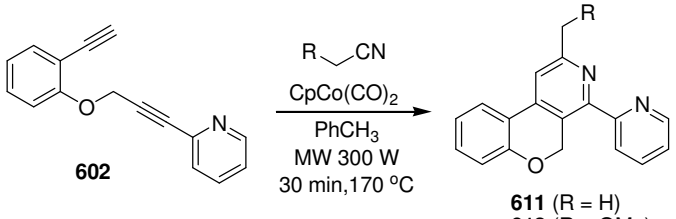
Turning our attention to the synthesis of the ether **602**, the alcohol **603** was coupled with either **606** or **408** under Mitsunobu reaction conditions. Both of the phenols were fully converted to the product ethers, **609** or **602**, respectively, however isolation of the ether **609** from the hydrazine by-product proved difficult. On the other hand, the desilylated ether **602** could be readily isolated in 93% yield (Scheme 7.10). With **602** in hand, an examination of the [2+2+2] cyclotrimerization reaction was conducted.



Scheme 7.10. Synthesis of the diyne **602**.

Initial cyclotrimerization studies employed acetonitrile as the nitrile component. Under closed vessel microwave conditions, a 42% yield of the desired tetracycle **611** as one regioisomer was obtained using the $CpCo(CO)_2$ catalyst (Entry 1, Table 7.1). This regioisomer is expected on the basis mechanism of the cyclotrimerization reaction giving pyridines and was confirmed by the ^1H NMR chemical shift of the lone proton on the newly formed pyridine ring. Increasing the equivalents of acetonitrile and the catalyst loading each led to an increase in yield of **611** (Entries 2 and 3). Performing the reaction under open vessel microwave conditions led to a diminished yield (Entry 4), while performing the reaction with acetonitrile as the solvent afforded a similar result (Entry 5). Methoxyacetonitrile cyclotrimerized in a similar fashion, providing a 51% yield of the tetracycle **612** (Entry 6).

Table 7.1. Cyclotrimerization reaction of the diyne **602**. [a] open vessel



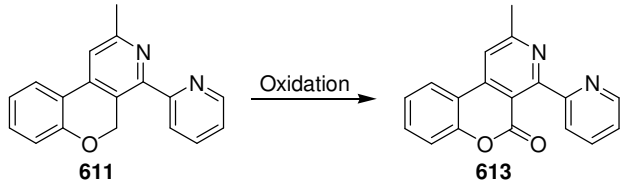
602

611 (R = H)
612 (R = OMe)

Entry	R, eq	Co mol%	Solvent	Yield (%)
1	H, 10	10	Xylenes	42
2	H, 20	10	Toluene	54
3	H, 20	20	Toluene	57
4	H, 20	20	Xylenes	43[a]
5	H, 20	20	CH_3CN	46
6	OMe, 20	20	Toluene	51

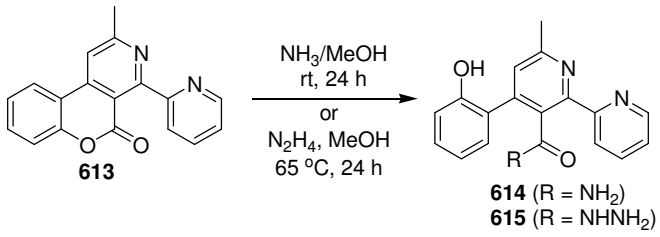
On the basis of the oxidation of **459** to **460** for the synthesis of cannabinol (see Scheme 5.16), PCC was selected as the first reagent to affect the oxidation of the benzylic ether **611**. Unfortunately, no reaction occurred, and other means to oxidize the methylene unit were surveyed (Entry 1, Table 7.2). Ruthenium catalyzed oxidation[359] was more successful; however, starting material remained (Entry 2). Other chromium based oxidants[360] fully converted the starting material, but isolation of the desired product was low (Entry 3). Oxidation with excess $KMnO_4$ proved to be the most reliable method,[318] providing the lactone **613** in a modest 49% yield (Entry 4). Attempts to oxidize **612** with $KMnO_4$ were unsuccessful.

Table 7.2. Oxidation of the benzylic ether **611**.



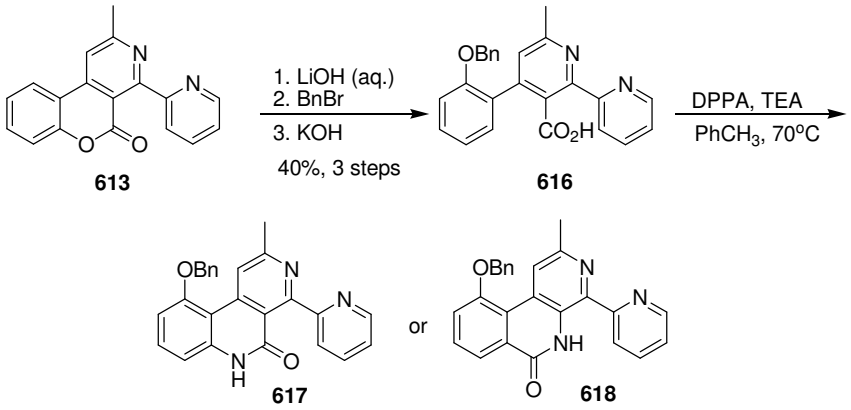
Entry	Conditions	Result
1	PCC, 40 °C DCM, 24 h	no rxn
2	$RuO_2/NaIO_4$ CCl_4, H_2O, CH_3CN 24 h	3:2 pdt/s.m.
3	CrO_3 AcOH/H_2O 65 °C, 16 h	low recovery
4	$KMnO_4$, CH_3CN rt, 2 d	49%

At this point, conditions to open the lactone ring and to form the amine functionality were needed. We hypothesized that access to the amine function would be possible through a Hofmann[361] or Curtius rearrangement.[362] For the Hofmann rearrangement, an amide is required while for the Curtius rearrangement an acyl azide intermediate is necessary. Converting the lactone **613** into an amide for the Hofmann rearrangement was first explored. Treatment of **613** with NH_3 in MeOH gave a mixture of starting material and the desired amide **614** (Scheme 7.11). Despite exposing the mixture to further NH_3/MeOH, full conversion was never realized. Furthermore, the amide underwent facile ring closure back to **613** under acidic conditions. Even when using the more nucleophilic hydrazine, full conversion to the hydrazide **615** was not accomplished. Because of these issues, efforts toward implementing a Curtius rearrangement were then attempted.



Scheme 7.11. Attempted synthesis of the amide **614** and the hydrazide **615**.

Due to the facile ring closure back to the lactone, protection of the phenol after opening the lactone ring was deemed necessary prior to Curtius rearrangement. Basic hydrolysis of the lactone followed by quenching of the resultant phenoxide and carboxylate anions with benzyl bromide provide a bis-benzylated product that was saponified with KOH/EtOH to give the acid **616** in 40% yield over three steps (Scheme 7.12). Treatment of **616** with DPPA (diphenylphosphoryl azide) and TEA in toluene at 90 °C furnished a new compound whose ^{1}H NMR spectrum did not provide conclusive evidence for the desired amine.[237] Mass analysis, however, provided the necessary information to discern the outcome of the reaction. The new compound gave the *m/z* of $[M + H]^+$ as 394, 26 units higher than the expected product. This mass difference indicated an additional carbonyl group with the loss of two hydrogen atoms. On the basis of this result and the literature precedence for alternative Schmidt rearrangement products,[363] the new compound was determined to be either **617** or **618**. This result was surprising as these reaction conditions were successfully employed in previous syntheses of streptonigrin.[342-344] Even if the rearrangement were successful on our model system, the low yields of the preceding steps were cause enough for concern, and attention was turned to alternative cyclotrimerization strategies to synthesize the core of streptonigrin.

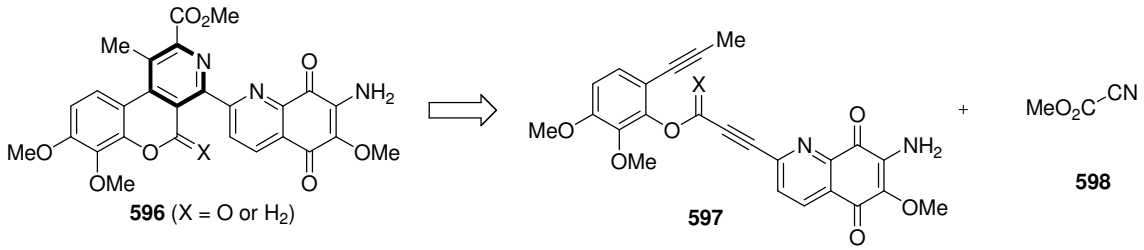


Scheme 7.12. Attempted rearrangement of the acid **616**.

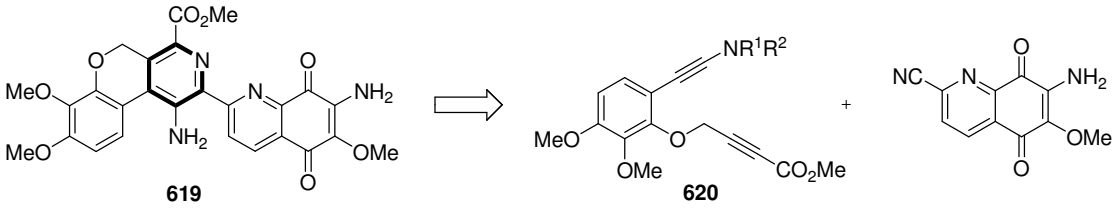
7.2.3 An Ynamide Approach to Streptonigrin

A re-examination of our desired [2+2+2] cyclotrimerization reaction towards the core of streptonigrin and the subsequent manipulations needed to install the amine functionality led to an alternative approach to linking the phenyl-pyridyl ring structure that is to be formed in the cyclotrimerization event other than with a precursor to an amine (as in the original retrosynthetic analysis Scheme 7.7). This new linker would contain the functionality to be converted into streptonigrin's C ring methyl group from **619**. This strategy would require a nitrogen-alkyne bond in the diyne **620** and would preclude the need to install the amine functionality at a later point, as it would already be present (Scheme 7.13). Encouraged by the work of Witulski[54] and others[364] in the area of ynamide cyclotrimerizations toward benzenes, we set out to extend this methodology to the formation of pyridines. Further support for the potential success of this approach came with the recently published reports of the cyclotrimerization of ynamides with alkynes and nitriles.[365]

Original Cyclotrimerization Strategy:

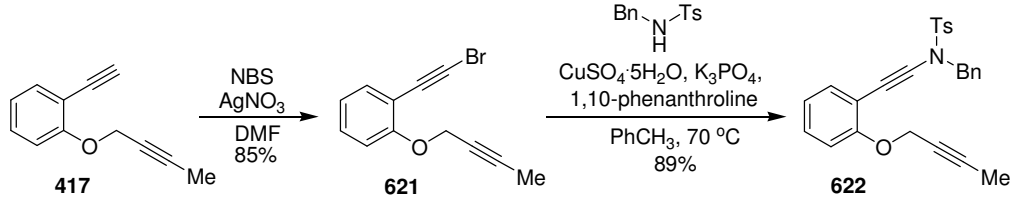


Revised Cyclotrimerization Strategy:



Scheme 7.13. Comparison of cyclotrimerization strategies.

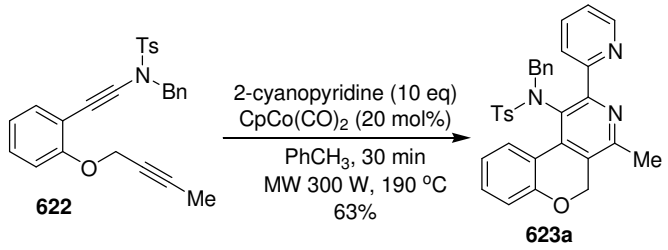
The most expedient route to an ynamide diyne utilized the diyne **417** as starting material as it had previously been prepared for the cannabinoid methodology. Bromination of the alkyne with NBS/$AgNO_3$[234] provided the alkynyl bromide **621** in 85% yield and set up the formation of the sp-C–N bond via Cu catalysis.[366] Reaction of **621** with *N*-benzyl-*p*-toluenesulfonamide[367] using $CuSO_4 \cdot 5\ H_2O$ as the catalyst smoothly furnished the ynamide **622** in 89% yield (Scheme 7.14).



Scheme 7.14. Synthesis of the ynamide **622**.

The cyclotrimerization of **622** with 2-cyanopyridine acting as the model nitrile for the quinolinequinone portion of streptonigrin could now be attempted. In this direction, **622** and

2-cyanopyridine were microwave irradiated in the presence of $CpCo(CO)_2$ to provide a single cyclotrimerization product (**623a**) in 63% yield (Scheme 7.15).



Scheme 7.15. Cyclotrimerization reaction of the diyne **622**.

Assignment as this regioisomer instead of the regioisomer **623b** was based upon the electronics of the diyne and nitrile systems[51] where the nitrile nitrogen forms a bond with the least electron rich alkyne carbon. In this instance, the nitrogen of the ynamide increases the electron density about the adjacent carbon center more than the methyl substituent. This fact is visualized in the ^{13}C NMR spectrum of **622** where the peak for the carbon adjacent to the ynamide is shifted upfield. Attempts were made to confirm the regioisomer assignment by detecting the through space coupling of the pyridine protons with either the benzyl methylene or the methyl group via 1D-NOESY experiments, but neither interaction was observed (Figure 7.5).

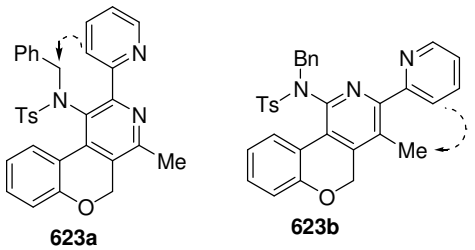
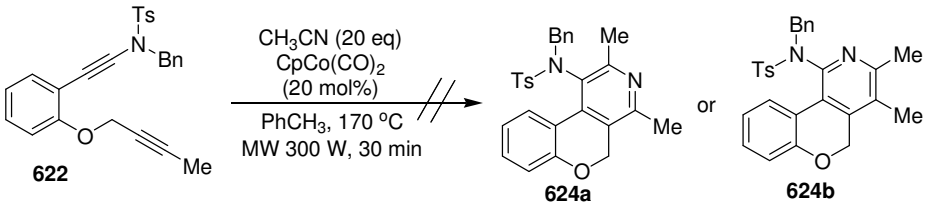


Figure 7.5. Desired NOE signals for regioisomer determination.

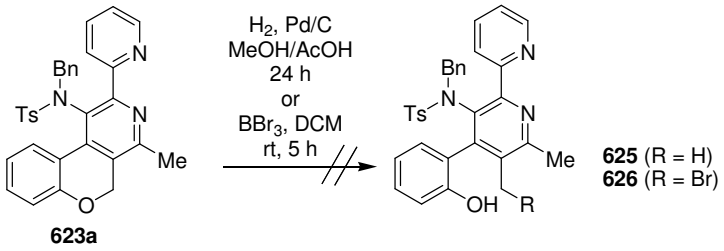
To lend credence to the regioisomer assignment, attempts to cyclotrimerize the diyne **622** with acetonitrile towards **624a** or **624b** were conducted (Scheme 7.16). We hypothesized that

the interaction between the protons of the two methyl groups in **624b** would be more easily observed in the NOESY experiment leading to a more definitive assignment of the regiochemical outcome of the cyclotrimerization reaction. Unfortunately, the cyclotrimerization with acetonitrile was unsuccessful with a large proportion of starting material remaining after irradiation. Thus, the regioselectivity of the cyclotrimerization reaction of **622** to **623** remains uncertain, however, a single regioisomer was obtained.



Scheme 7.16. Attempted cyclotrimerization reaction of **622** with acetonitrile.

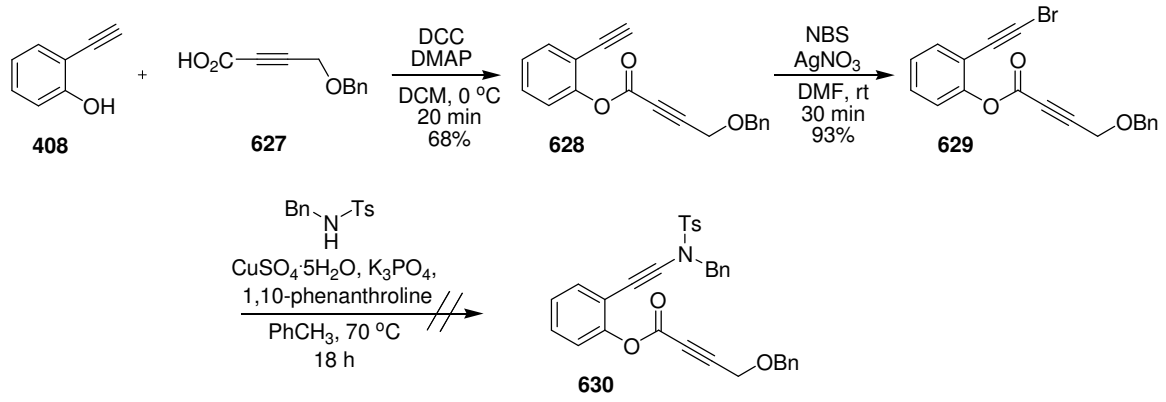
Attempts to cleave the ether linkage between the aryl rings were then explored. Hydrogenation of **623a** in MeOH/AcOH failed to open the pyran ring to **625**, but debenzylation of the amide did occur based on the mass of the crude product (Scheme 7.17). Cleavage of the ether with BBr_3 towards **626** was also unsuccessful leading to decomposition of the starting material. Other substrates more amenable to ring-opening were then pursued.



Scheme 7.17. Attempts to open the pyran ring of **623a**.

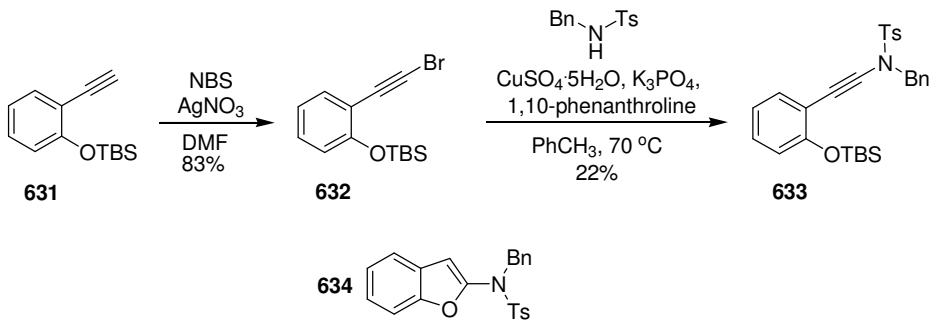
Because opening of the lactone in **613** was successful, the synthesis of the analogous compound for the 'ynamide strategy' was undertaken (Scheme 7.18). Towards this end, the phenol **408**[268] was coupled with the carboxylic acid **627** to provide a 68% yield of the ester

628. Bromination of the terminal alkyne in **628** furnished **629** in 93% yield.[234] Attempts to form the desired ynamide diyne **630** from **629** were unsuccessful with decomposition of the starting material occurring instead. The instability of the starting material most likely arises from the alkynoate structure, and a new route towards **630** was necessary. The bromide **629** failed to undergo cyclotrimerization with 2-cyanopyridine ($CpCo(CO)_2$, $PhCH_3$, MW 300 W, 30 min), however, the starting material **629** was recovered.



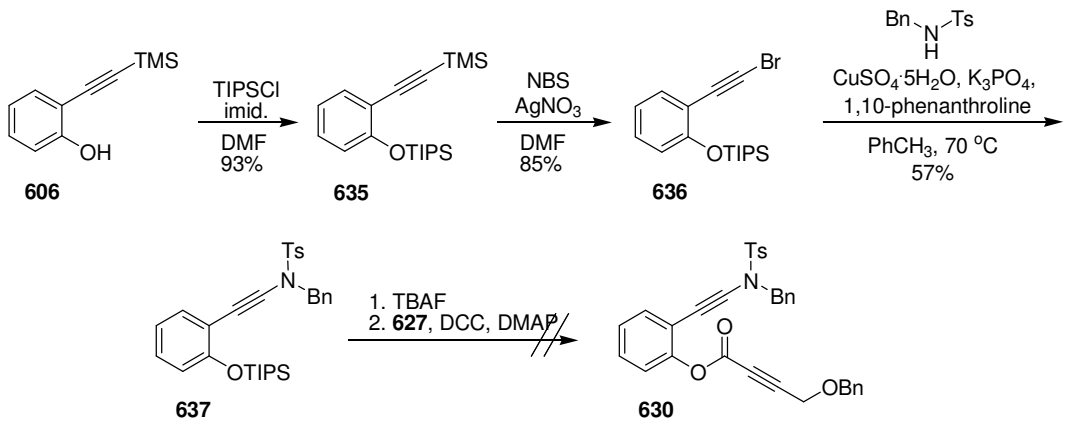
Scheme 7.18. Attempted synthesis of the diyne **630**.

A modified route to **630** would form the ynamide functionality first and then form the ester linkage to install the second alkyne. Bromination of the TBS-protected phenol **631**[368] gave the alkynylbromide **632** in 83% yield (Scheme 7.19). At this point, formation of the C–N bond was tried as before, however only a 22% yield of the desired ynamide **633** was obtained. The benzofuran side product **634** (<40%) was also present in the reaction mixture, however, purification proved difficult due to its co-elution with another side product.



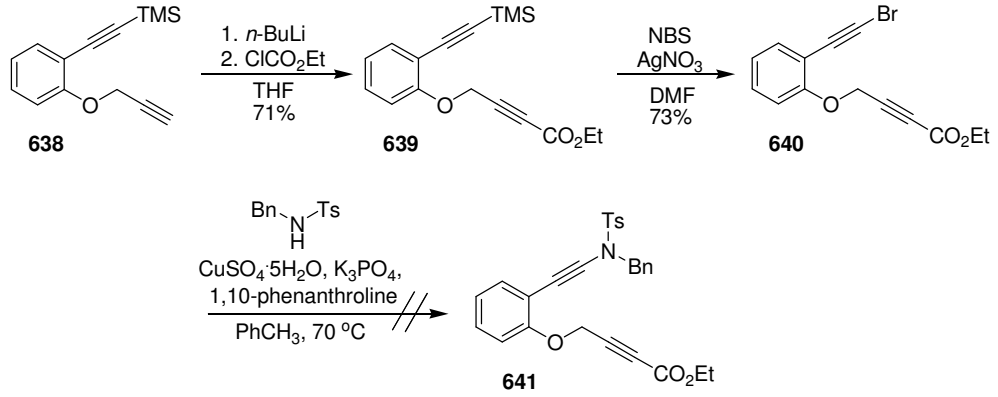
Scheme 7.19. Synthesis of the ynamide **633**.

Speculating that a more stable protecting group would provide a higher yield in the ynamide coupling step, the tri-*iso*-propylsilyl protected material was synthesized from **606** (Scheme 7.20). In this case, removal of the alkynyl-TMS group in **635** was accomplished in the same step as the bromination to provide **636** in 85% yield.[369] Just as expected, ynamide formation towards **637** proceeded in a more efficient 57% yield although the reaction progressed at a slower rate. The benzofuran by-product **634** was detected as well. Fluoride-mediated deprotection gave a crude phenol that was used in the coupling step without purification. Under these esterification conditions, however, only the benzofuran by-product **634** could be detected. Similar cyclizations to benzofurans promoted by base,[370] transition metal catalysts (e.g. Pd,[371] Cu,[372] and Pt[373]), and TBAF[374] are known. In fact, benzofuran formation from TBS-protected substrates similar to **633** is known.[375]



Scheme 7.20. Modified route to the ynamide **630**.

Attempts to synthesize the ynamide diyne **641** with the ester and ether positions switched from **638** through **639** and **640** were unsuccessful (Scheme 7.21). Once again the sensitive nature of the alkynoate led to decomposition.



Scheme 7.21. Attempted synthesis of the ynamide diyne **641**.

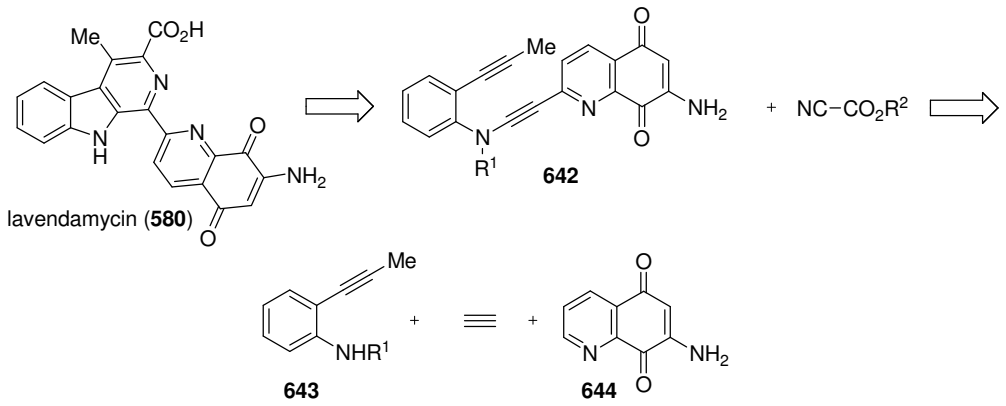
Current model studies towards streptonigrin are focusing on the ester **630** and derivatives.

7.3 Progress Towards the Total Synthesis of Lavendamycin

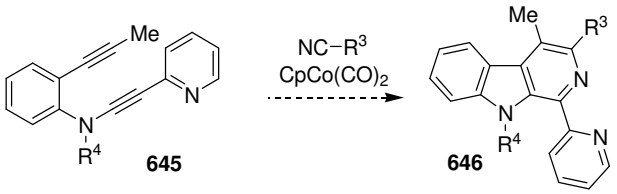
7.3.1 Retrosynthetic Analysis

Inspired by Witulski's synthesis of carbozoles,[54] we envisioned deriving lavendamycin (**280**) from a [2+2+2] cyclotrimerization reaction of the diyne **642** and a cyanoformate (Scheme 7.22). This diyne would be obtained by linking **643** and **644** via an equivalent of acetylene. In order to determine the most efficient means to synthesize the diyne, model studies were undertaken. These model studies would not only determine the best conditions for the diyne synthesis, but would also provide crucial information on the cyclotrimerization event towards β-carbolines **646**, including the regioselectivity and efficiency with different nitriles. For this model study, the diyne **645** (R^4 = Ts) was chosen as a model substrate where the pyridine ring replaces the quinolinequinone structure present in lavendamycin.

Retrosynthetic Analysis:



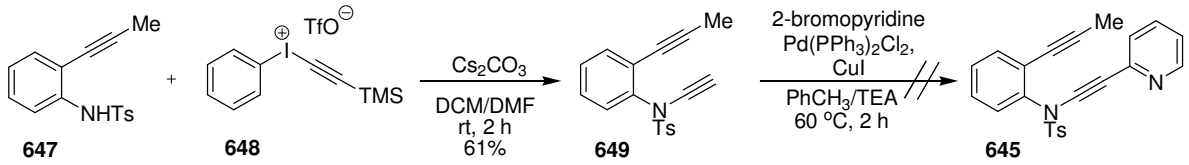
Model Study:



Scheme 7.22. Retrosynthesis of lavendamycin (**580**) and model study towards β-carbolines **646**.

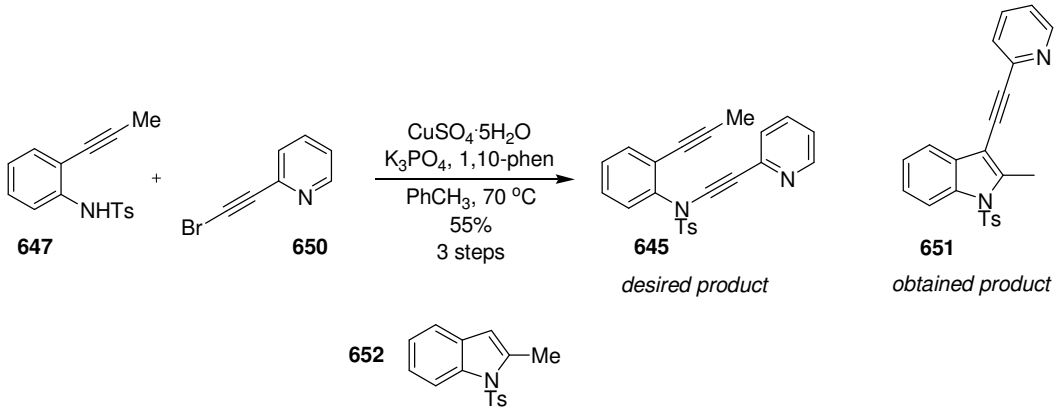
7.3.2 Current Progress Towards Lavendamycin

Beginning with the known tosylamide **647**,[54] an expedient means to install the alkynylpyridine structure of the diyne **645** was investigated. Reaction of **647** with the known iodonium salt **648**[364] effectively incorporated the second alkyne to provide **649**[54] in 61% yield (Scheme 7.23). Attempts to append the pyridine portion of the diyne via Sonogashira reaction with 2-bromopyridine, however, were unsuccessful due to decomposition of the ynamide **649**, and an alternative approach to the diyne **645** was sought.



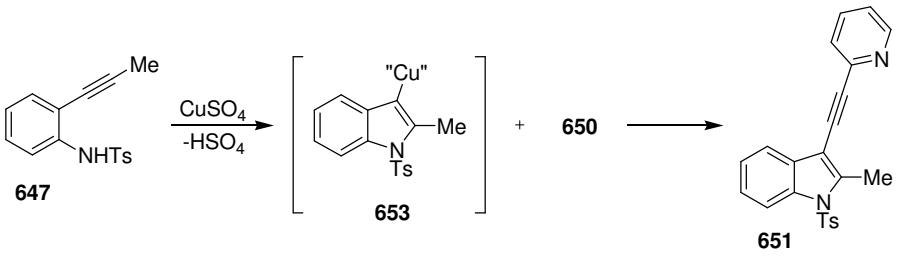
Scheme 7.23. Attempted synthesis of the diyne **645**.

By disconnecting the *N*-alkynyl bond in the diyne **645**, the previously used Cu-mediated coupling could potentially provide access to the desired diyne structure. In this direction, **647** and freshly prepared known alkynylbromide **650**[376] were heated in the presence of $CuSO_4 \cdot 5H_2O/K_3PO_4$/1,10-phenanthroline to presumably give the diyne **645** in a modest 55% yield (over 3 steps from 2-(2-(trimethylsilyl)ethynyl)pyridine[377] (Scheme 7.24). However, the spectral data for the isolated product matched the structure of **651** instead.



Scheme 7.24. Alternative attempted synthesis of the diyne **645**.

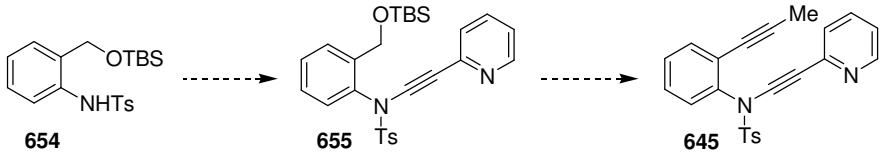
Not surprisingly, the indole **652**, formed via Cu-catalysis, was also detected in the reaction mixture.[378] We postulated that Cu-catalyzed indole formation led first to the intermediate **653** (Scheme 7.25). This intermediate then underwent coupling with the alkynylbromide **650** to provide the 3-alkynylindole **651**.



Scheme 7.25. Proposed mechanism for the formation of the indole **651**.

While the related one-pot transformations between *o*-alkynyl amides and vinyl triflates or aryl halides under palladium catalysis are known,[379, 380] this copper catalyzed variation was unprecedented. Other metals such as Zn[381] and Au[382] have been shown to effect indole formation and subsequent coupling to electrophiles. Further investigations into this novel strategy towards 2,3-substituted indoles are underway. Extension of this methodology to the formation of 2,3-substituted benzofurans and indenes is also being explored.

Despite the new-found methodology, the route for the synthesis of the diyne towards lavendamycin needed to be revised. Current explorations towards the diyne focus on installing the ethynylpyridine portion of the diyne to give **655** followed by formation of the second alkyne from the known amide **654**[383] (Scheme 7.26). Alternatively, a formamide derivative could be transformed into the ynamide via the Corey-Fuchs protocol and the pyridine unit added via Sonogashira reaction.

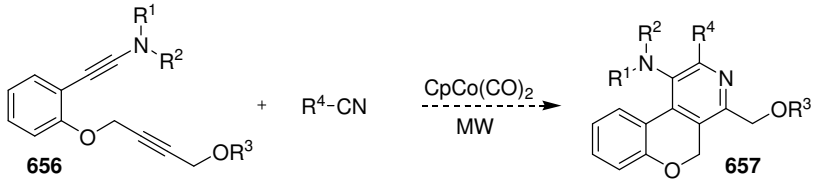


Scheme 7.26. Current route towards the diyne **645**.

7.4 Summary and Future Directions

7.4.1 Streptonigrin

Two approaches towards the synthesis of streptonigrin via a [2+2+2] cyclotrimerization reaction have been devised and investigated through model studies. The first model study relies on the cyclotrimerization reaction between the pyridyl-substituted diyne **610** and a nitrile; however, subsequent transformations towards appropriately substituting the C ring were troublesome (See Scheme 7.11 and 7.12). The second model study utilized diynes containing an ynamide (**622**) representing the amino functionality on the C ring. Initial results were promising, but the synthesis of more elaborate diynes has been problematic (See Scheme 7.18 and 7.21). Future studies will focus on the ynamide **656** whose cyclotrimerization reaction with an appropriate nitrile will provide the fully substituted C ring as in **657** with synthetic handles to install the correct functionality (Scheme 7.27)

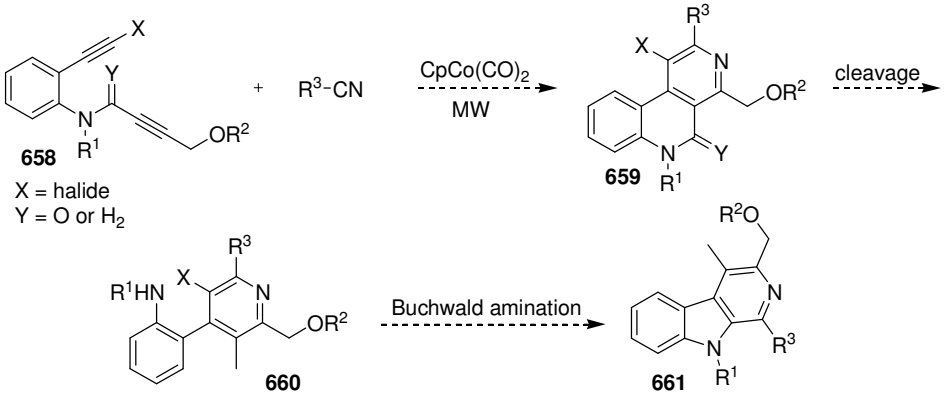


Scheme 7.27. Future model study towards the synthesis of streptonigrin.

7.4.2 Lavendamycin

Several routes to synthesize the model diyne **645** for the lavendamycin model studies have unsuccessfully attempted to furnish the desired ynamide structure. Future model studies will take an alternative approach to lavendamycin and mirror the first approach investigated

for streptonigrin (see Scheme 7.7). Instead of an ether linkage as in **597**, an amine or amide linker will be taken advantage of to provide the model diyne **658** (Scheme 7.28). After cyclotrimerization reaction with a nitrile, cleavage of the benzylamine linker of the 5,6-dihydro-benzo[*c*][*2,7*]naphthyridine **659** to **660** will set the stage for an intramolecular Buchwald-Hartwig amination reaction[384, 385] to form the tricyclic β-carboline core of lavendamycin (**661**, Scheme 7.28). The use of alkynylhalides in cyclotrimerization reactions towards pyridine derivatives is unknown; however, their use in cyclotrimerization reactions towards halogenated benzenes has been reported.[229]



Scheme 7.28. Future model study towards lavendamycin.

7.5 Experimental

All reactions were performed in flame-dried glassware under a nitrogen atmosphere and stirred magnetically. Tetrahydrofuran, toluene, xylenes, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Diisopropylamine, triethylamine, DMSO, DCM, DMF, 1,2-dichloroethane, CH_3CN and pyridine were distilled from calcium hydride and stored over 4 Å molecular sieves. Other reagents and solvents obtained from commercial sources were stored under nitrogen and used directly without further purification. *n*-BuLi and MeLi were titrated against *N*-pivaloyl-*o*-toluidine.[108] Melting points were obtained from a Mel-Temp capillary melting point apparatus and are uncorrected. High resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz) or Varian Mercury 300 (300 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption (77.2) for ^{13}C NMR spectra. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer.

2-(2-(Trimethylsilyl)ethynyl)phenyl propiolate (608). To a solution of **606** (20 mg, 0.11 mmol) and DMAP (1 mg, 0.007 mmol) in DCM (210 μL) was added DCC (24 mg, 0.12 mmol) in DCM (200 μL × 2), and the reaction was stirred for 20 min. Et_2O (2 mL) was added, and the solution was filtered over celite and concentrated. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (20:1), to give 12.9 mg (51%) of **608** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.6 and 1.5 Hz, 1 H), 7.37 (dt, J =

7.6 and 1.5 Hz, 1 H), 7.23 (dt, *J* = 7.6 and 1.5 Hz, 1 H), 7.13 (dd, *J* = 7.6 and 1.5 Hz, 1 H), 3.07 (s, 1 H), 0.27 (s, 9 H).

2-(3-(2-Ethynylphenoxy)prop-1-ynyl)pyridine (602). To a solution of **408** (19.5 mg, 0.17 mmol), **603** (20 mg, 0.15 mmol) and PPh_3 (51 mg, 0.20 mmol) in DCM (750 μL) was added DIAD (38 μL, 0.20 mmol) dropwise at rt. The reaction was stirred for 25 min and concentrated. The residue was purified by flash chromatography on SiO_2, eluting with hexanes/EtOAc (3:1 to 1:1), to give 32.7 mg (93%) of **602** as a slight yellow solid. IR (NaCl, thin film, DCM) 1563, 1487, 1464, 1448, 1429, 1372, 1291, 1265, 1225, 1165, 1110, 1048, 1023, 778, 754, 616; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64-8.54 (m, 1 H), 7.64 (ddd, *J* = 7.6, 7.6, and 1.8 Hz, 1 H), 7.49 (dd, *J* = 7.6 and 1.7 Hz, 1 H), 7.41 (ddd, *J* = 7.6, 1.1, and 1.1 Hz, 1 H), 7.35 (ddd, *J* = 8.4, 7.6, and 1.7 Hz, 1 H), 7.27-7.21 (m, 1 H), 7.15 (dd, *J* = 8.4 and 0.9 Hz, 1 H), 6.97 (ddd, *J* = 7.6, 7.6, and 1.1 Hz, 1 H), 5.06 (s, 2 H), 3.33 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 150.0, 142.4, 136.2, 134.3, 130.2, 127.4, 123.3, 121.4, 112.8, 112.0, 86.7, 83.5, 81.6, 79.8, 57.0.

2-Methyl-4-(pyridin-2-yl)-5*H*-chromeno[3,4-*c*]pyridine (611). To a flame-dried microwave vial equipped with a stir bar was added **602** (22 mg,0.094 mmol), CH_3CN (98 μL, 1.89 mmol), $CpCo(CO)_2$ (2.2 μL, 0.019 mmol), and dry toluene (2.3 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 30 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction to rt, the solution was concentrated, and the residue was purified by silica gel chromatography, eluting with

DCM/EtOAc (4:1 to 3:1), to give 14.7 mg (57%) of **611** as an off white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74-8.60 (m, 1 H), 8.13 (d, *J* = 8.1 Hz 1 H), 7.85 (dt, *J* = 7.7 and 1.8 Hz, 1 H), 7.77 (dd, *J* = 7.7 and 1.5 Hz, 1 H), 7.47 (s, 1 H), 7.40-7.27 (m, 2 H), 7.09 (dt, *J* = 7.5 and 1.1 Hz, 1 H), 7.01 (dd, *J* = 8.1 and 1.1 Hz, 1 H), 5.49 (s, 2 H), 2.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 157.2, 156.1, 152.8, 148.3, 139.3, 136.8, 131.4, 124.14, 124.09, 123.3, 123.1, 122.2, 121.3, 117.6, 115.7, 66.1, 24.8.

2-(Methoxymethyl)-4-(pyridin-2-yl)-5*H*-chromeno[3,4-*c*]pyridine (612). To a flame-dried microwave vial equipped with a stir bar was added **602** (30 mg, 0.13 mmol), methoxyacetonitrile (191 μL, 2.57 mmol), $CpCo(CO)_2$ (3.0 μL, 0.026 mmol), and dry toluene (3.1 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 30 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction to rt, the solution was concentrated, and the residue was purified by silica gel chromatography, eluting with DCM/EtOAc (3:1 to 1:1), to give 20 mg (51%) of **612** as an off white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73-8.62 (m, 1 H), 8.14 (dt, *J* = 8.0 and 0.9 Hz, 1 H), 7.91-7.80 (m, 2 H), 7.76 (s, 1 H), 7.40-7.27 (m, 2 H), 7.10 (dt, *J* = 7.6 and 1.2 Hz, 1 H), 7.02 (dd, *J* = 8.0 and 0.9 Hz, 1 H), 5.54 (s, 2 H), 4.70 (s, 2 H), 3.54 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 156.1, 152.8, 148.4, 139.9, 136.9, 131.6, 124.9, 124.4, 124.2, 123.2, 122.3, 121.4, 117.6, 113.7, 75.7, 66.1, 59.0.

2-Methyl-4-(pyridin-2-yl)-5*H*-chromeno[3,4-*c*]pyridin-5-one (613). To a solution of **611** (8.0 mg, 0.029 mmol) in CH_3CN (740 μL) was added $KMnO_4$ (27 mg, 0.17 mmol), and the

reaction was stirred for 36 h. More $KMnO_4$ (9 mg, 0.058 mmol) was added and stirring was continued for 24 h. At this point, the reaction mixture was concentrated, H_2O (3 mL) was added and extracted with EtOAc (6 mL × 3). The combined organic extracts were washed with H_2O (5 mL × 2) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness to give 4.1 mg (49%) of **613** as a white solid. ^{1}H NMR (300 MHz, CD_3CN) δ 8.68-8.55 (m, 1 H), 8.28 (d, *J* = 7.9 Hz, 1 H), 8.10 (s, 1 H), 7.88 (t, *J* = 7.7 Hz, 1 H), 7.65 (t, *J* = 7.7 Hz, 1 H), 7.56-7.30 (m, 4 H), 2.71 (s, 3 H).

4-(2-(Benzyloxy)phenyl)-6-methyl-2-(pyridin-2-yl)pyridine-3-carboxylic acid (616). To a solution of **613** (8.0 mg, 0.028 mmol) in DMSO (240 µL) was added 4 N LiOH (78 µL) and the reaction was heated to 60 °C for 7 h. Benzyl bromide (20 µL, 0.17 mmol) was added and heating was continued overnight. The reaction was cooled to rt, and sat. NH_4Cl (2 mL) was added. The aqueous layer was extracted with EtOAc (4 mL × 3). The combined organic extracts were washed with H_2O (2 mL) and brine (2 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The crude ester was taken up in EtOH (170 µL), treated with saturated aqueous KOH (170 µL), and heated at 80 °C overnight. After cooling the reaction to rt, the pH was adjusted to 7.4 using HCl (1 M) and NaOH (1 M). The aqueous layer was extracted with EtOAc (4 mL × 3), and the combined organic layers were concentrated to dryness to give 4.2 mg (40%, 3 steps) of **616** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57-8.47 (m, 1 H), 8.26 (d, *J* = 8.1 Hz, 1 H), 7.96 (t, *J* = 7.9 Hz, 1 H), 7.50-7.17 (m, 9 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 6.96 (d, *J* = 8.1 Hz, 1 H), 5.10 (s, 2 H), 4.71 (s, 1 H), 2.66 (s, 3 H).

1-(2-Bromoethynyl)-2-(but-2-ynyloxy)benzene (621). To a solution of **417** (50.0 mg, 0.29 mmol) and NBS (63 mg, 0.35 mmol) in DMF (1.2 mL) was added $AgNO_3$ (5.0 mg, 0.029 mmol). The reaction was stirred for 2 h and diluted with H_2O (4 mL). The aqueous layer was extracted with Et_2O (6 mL × 3). The combined organic extracts were washed with H_2O (5 mL × 2) and brine (5 mL), and the aqueous layer was extracted with Et_2O (5 mL). The combined organic extracts were dried (Na_2SO_4), filter and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (35:1), to give 62.1 mg (85%) of **621** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.6 and 1.7 Hz, 1 H), 7.34-7.26 (m, 1 H), 7.03 (d, *J* = 8.1 Hz, 1 H), 6.92 (dt, *J* = 7.6 and 1.0 Hz, 1 H), 4.74 (q, *J* = 2.3 Hz, 2 H), 1.85 (t, *J* = 2.3 Hz, 3 H).

***N*-Benzyl-2-(2-(but-2-ynyloxy)phenyl)-*N*-tosylethynamine (622).** A mixture of **621** (24.7 mg, 0.01 mmol), *N*-benzyl-*p*-toluenesulfonamide (26 mg, 0.099 mmol), $CuSO_4 \cdot 5H_2O$ (2.5 mg, 0.001 mmol), powdered K_3PO_4 (43 mg, 0.20 mmol), and 1,10-phenanthroline (3.6 mg, 0.020 mmol) in $PhCH_3$ (200 μL) was heated to 75 °C for 18 h. After cooling the reaction to rt, the mixture was diluted with EtOAc (3 mL) and filtered through a plug of celite on top of a plug of silica gel eluting with EtOAc. The filtrate was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (5:1), to give 37.8 mg (89%) of **622** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2 H), 7.45-7.35 (m, 2 H), 7.34-7.26 (m, 5 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.95 (d, *J* = 7.9 Hz, 1 H), 6.87 (dt, *J* = 7.7 and 1.1 Hz, 1 H), 4.64 (q, *J* = 2.3 Hz, 2 H), 4.60 (s, 2 H), 2.43 (s, 3 H), 1.84 (t, *J* = 2.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 144.5, 134.9, 134.7, 132.7, 129.7,

129.2, 128.7, 128.6, 128.3, 128.0, 121.1, 113.1, 113.0, 86.8, 84.0, 74.2, 67.8, 57.2, 56.0, 21.8, 3.9.

***N*-Benzyl-4-methyl-2-(pyridin-2-yl)-*N*-tosyl-5*H*-chromeno[3,4-*c*]pyridin-1-amine (623a).** To a flame-dried microwave vial equipped with a stir bar was added **622** (15 mg, 0.035 mmol), 2-cyanopyridine (36.4 mg, 0.35 mmol), $CpCo(CO)_2$ (0.82 μL, 0.0070 mmol), and dry toluene (900 μL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 30 min in a CEM Discover microwave synthesizer at 300 W. After cooling the reaction to rt, the solution was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3:1 to 2:1), to give 11.7 mg (63%) of **623a** as an off white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69-8.64 (m, 1 H), 8.52 (dd, *J* = 8.0 and 1.5 Hz, 1 H), 7.76-7.62 (m, 3 H), 7.36-7.16 (m, 5 H), 7.13-6.85 (m, 7 H), 5.06 (d, *J* = 14.2 Hz, 1 H), 4.95 (d, *J* = 14.2 Hz, 1 H), 4.87 (d, *J* = 12.9 Hz, 1 H), 4.55 (d, *J* = 12.9 Hz, 1 H), 2.47 (s, 3 H), 2.43 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 155.5, 153.1, 148.1, 145.2, 145.1, 143.3, 136.3, 136.1, 134.3, 130.3, 129.8, 129.1, 128.4, 128.1, 127.8, 127.4, 125.4, 124.8, 122.9, 122.4, 120.1, 116.9, 65.3, 54.8, 21.7, 15.0.

4-(Benzyloxy)but-2-ynoic acid (627). To a solution of benzylpropargyl alcohol (200 mg, 1.4 mmol) in THF (700 μL) at −78 °C was added *n*-BuLi (2.47 M in hexanes, 554 μL, 1.4 mmol) dropwise. After 1 h a stream of dry CO_2 (generated from dry ice and passed through a drying tube containing drierite) was bubbled into the solution for 10 min. After warming to rt, the reaction was quenched with H_2O (4 mL) and extracted with EtOAc (3 mL × 2) to remove

starting material. The aqueous layer was acidified with aq. HCl (1 M) and extracted with EtOAc (5 mL × 3). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness to give 239 mg (92%) of **627** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5 H), 4.63 (s, 2 H), 4.32 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 136.5, 128.7, 128.4, 86.1, 77.8, 72.3, 56.7.

2-Ethynylphenyl 4-(benzyloxy)but-2-ynoate (628). To a solution of **408** (52 mg, 0.44 mmol), **627** (94 mg, 0.49 mmol) and DMAP (spatula tip) in DCM (1 mL) was added DCC (112 mg, 0.54 mmol) in DCM (500 μL, 300 μL wash) dropwise at 0 °C. The reaction was warmed to rt and after 30 min was diluted with Et_2O (4 mL). The solution was filtered over celite, concentrated to dryness, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (9:1), to give 86 mg (68%) of **628** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.6 and 1.6 Hz, 1 H), 7.47-7.30 (m, 6 H), 7.25 (dt, *J* = 7.6 and 1.1 Hz, 1 H), 7.16 (dd, *J* = 8.1 and 1.1 Hz, 1 H), 4.65 (s, 2 H), 4.37 (s, 2 H), 3.31 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 150.7, 136.7, 133.9, 130.3, 128.7, 128.3, 126.7, 122.2, 116.4, 86.3, 83.1, 78.1, 72.3, 56.9.

2-(2-Bromoethynyl)phenyl 4-(benzyloxy)but-2-ynoate (629). To a solution of **628** (20.5 mg, 0.071 mmol) and NBS (16 mg, 0.085 mmol) in DMF (350 μL) was added $AgNO_3$ (1.3 mg, 0.007 mmol). The reaction was stirred for 25 min in the dark, followed by addition of H_2O (2 mL). The aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (3 mL × 2) and brine (2 mL), and the aqueous layer was

extracted with Et_2O (3 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1), to give 24.5 mg (93%) of **629** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.7 and 1.7 Hz, 1 H), 7.43-7.31 (m, 6 H), 7.26-7.20 (m, 1 H), 7.16 (d, *J* = 8.1 Hz, 1 H), 4.67 (s, 2 H), 4.38 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 150.8, 136.7, 133.8, 130.1, 128.7, 128.4, 128.4, 126.7, 122.3, 116.9, 86.4, 77.6, 74.8, 72.3, 56.9, 55.8.

(2-(2-Bromoethynyl)phenoxy)(*tert*-butyl)dimethylsilane (632). To a solution of **631** (83.0 mg, 0.36 mmol) and NBS (76 mg, 0.43 mmol) in DMF (1.4 mL) was added $AgNO_3$ (6.1 mg, 0.036 mmol). The reaction was stirred in the dark for 25 min and diluted with H_2O (6 mL). The aqueous layer was extracted with Et_2O (6 mL × 3). The combined organic extracts were washed with H_2O (5 mL × 2) and brine (5 mL), and the aqueous layer was extracted with Et_2O (6 mL). The combined organic extracts were dried (Na_2SO_4), filter and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (100:1), to give 92.2 mg (83%) of **632** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.6 and 1.7 Hz, 1 H), 7.21 (ddd, *J* = 8.1, 7.5, and 1.8 Hz, 1 H), 6.89 (ddd. *J* = 7.6, 7.6, and 1.0, 1 H), 6.81 (dd, *J* = 8.1 and 1.0 Hz, 1 H), 1.04 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 133.7, 130.0, 121.3, 120.0, 115.4, 77.6, 52.8, 25.8, 18.4, –4.2.

***N*-Benzyl-2-(2-(*tert*-butyldimethylsilyloxy)phenyl)-*N*-tosylethynamine (633).** A mixture of **632** (40 mg, 0.13 mmol), *N*-benzyl-*p*-toluenesulfonamide (33.5 mg, 0.13 mmol),

$CuSO_4 \cdot 5H_2O$ (3.2 mg, 0.013 mmol), powdered K_3PO_4 (55 mg, 0.26 mmol), and 1,10-phenanthroline (4.6 mg, 0.026 mmol) in $PhCH_3$ (350 μL) was heated at 75 °C for 18 h. After cooling the reaction to rt, the mixture was diluted with EtOAc (3 mL), and filtered through a plug of celite on top of a plug of silica gel eluting with EtOAc. The filtrate was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (25:1), to give 13.9 mg (22%) of **633** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2 H), 7.40-7.20 (m, 8 H), 7.14 (ddd, *J* = 8.1, 7.5, and 1.8 Hz, 1 H), 6.85 (dt, *J* = 7.5 and 1.0 Hz, 1 H), 6.77 (dd, *J* = 8.1 and 1.0 Hz, 1 H), 4.60 (s, 2 H), 2.44 (s, 3 H), 0.91 (s, 9 H), 0.12 (s, 6 H).

2-(2-(Tri-*iso*-propylsilyloxy)phenyl)-ethynyltrimethylsilane (635). To a solution of **606** (51 mg, 0.27 mmol) and imidazole (55 mg, 0.80 mmol) in DMF (300 μL) at 0 °C was added TIPSCl (86 μL, 0.40 mmol). After 1 h, the reaction was diluted with H_2O (4 mL) and extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (5 mL × 2) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (100:1), to give 86.6 mg (93%) of **635** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6 and 1.8 Hz, 1 H), 7.20-7.11 (m, 1 H), 6.91-6.79 (m, 2 H), 1.40-1.20 (m, 3 H), 1.20-1.06 (m, 18 H), 0.22 (s, 9 H).

(2-(2-Bromoethynyl)phenoxy)tri-*iso*-propylsilane (636). To a solution of **635** (84.7 mg, 0.24 mmol) and NBS (54 mg, 0.31 mmol) in DMF (1.2 mL) was added $AgNO_3$ (4.1 mg,

0.024 mmol). The reaction was stirred in the dark for 7 h and diluted with H_2O (6 mL). The aqueous layer was extracted with Et_2O (6 mL × 3). The combined organic extracts were washed with H_2O (5 mL × 2) and brine (5 mL), and the aqueous layer was extracted with Et_2O (6 mL). The combined organic extracts were dried (Na_2SO_4), filter and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (175:1), to give 73.6 mg (85%) of **636** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.6 and 1.8 Hz, 1 H), 7.22-7.13 (m, 1 H), 6.93-6.76 (m, 2 H), 1.42-1.21 (m, 3 H), 1.20-1.06 (m, 18 H).

***N*-Benzyl-2-(2-(tri-*iso*-propylsilyloxy)phenyl)-*N*-tosylethynamine (637).** A mixture of **636** (70.7 mg, 0.20 mmol), *N*-benzyl-*p*-toluenesulfonamide (52.2 mg, 0.20 mmol), $CuSO_4 \cdot 5H_2O$ (5.0 mg, 0.020 mmol), powdered K_3PO_4 (85 mg, 0.40 mmol), and 1,10-phenanthroline (7.2 mg, 0.040 mmol) in $PhCH_3$ (400 µL) was heated to 75 °C for 18 h. After cooling the reaction to rt, the mixture was diluted with EtOAc (3 mL) and filtered through a plug of celite on top of a plug of silica gel eluting with EtOAc. The filtrate was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (30:1), to give 61 mg (57%) of **637** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2 H), 7.40-7.20 (m, 8 H), 712 (ddd, *J* = 8.2, 7.5, and 1.9 Hz, 1 H), 6.89-6.73 (m, 2 H), 4.59 (s, 2 H), 2.43 (s, 3 H), 1.32-1.10 (m, 3 H), 1.09-0.95 (m, 18 H).

Trimethyl(2-(2-(prop-2-ynyloxy)phenyl)ethynyl)silane (638). To a solution of **606** (100 mg, 0.53 mmol) and K_2CO_3 (145 mg, 1.05 mmol) in DMF (600 µL) was added propargyl

bromide (80% in $PhCH_3$, 117 μL, 1.05 mmol), and the reaction was heated to 50 °C for 4 h. After cooling the reaction mixture, sat. NH_4Cl (3 mL) was added, and the mixture was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (4 mL × 2) and brine (4 mL), dried (Na_2SO_4), filter and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (50:1), to give 97 mg (81%) of **638** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5 Hz, 1 H), 7.29 (m, 1 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 6.95 (t, *J* =7.5 Hz, 1 H), 4.79 (d, *J* = 1.8 Hz, 2 H), 2.53 (br s, 1 H), 0.27 (s, 9 H).

Ethyl 4-(2-(2-(trimethylsilyl)ethynyl)phenoxy)but-2-ynoate (639). To a solution of **638** (63 mg, 0.28 mmol) in THF (1.5 mL) at −78 °C was added *n*-BuLi (2.47 M in hexanes, 123 μL, 0.30 mmol) dropwise. After 30 min, ethylchloroformate (32 μL, 0.33 mmol) was added, the reaction was stirred for 1 h and warmed to rt. Sat. NH_4Cl (4 mL) was added, and the aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (4 mL) and brine (4 mL), dried (Na_2SO_4), filter and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (20:1), to give 58.8 mg (71%) of **639** as a colorless oil. IR (NaCl, thin film, neat) 3071, 2962, 2900, 2247, 2159, 1717, 1593, 1573, 1484, 1448, 1370, 1251, 1199, 1116, 1017, 867, 841, 753; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.8 and 1.8 Hz, 1 H), 7.33-7.25 (m, 1 H), 7.01-6.93 (m, 2 H), 4.90 (s, 2 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 0.27 (s, 9 H).

Ethyl 4-(2-(2-bromoethynyl)phenoxy)but-2-ynoate (640). To a solution of **639** (21 mg, 0.070 mmol) and NBS (16 mg, 0.087 mmol) in DMF (350 μL) was added $AgNO_3$ (1.2 mg, 0.0070 mmol). The reaction was stirred in the dark for 3 h and diluted with H_2O (3 mL). The aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with H_2O (3 mL × 2) and brine (3 mL), and the aqueous layer was extracted with Et_2O (4 mL). The combined organic extracts were dried (Na_2SO_4), filter and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (7:1), to give 15.7 mg (73%) of **640** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.8 and 1.6 Hz, 1 H), 7.37-7.26 (m, 1 H), 7.00-6.92 (m, 2 H), 4.90 (s, 2 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 153.0, 134.4, 130.1, 122.1, 113.0, 81.4, 79.2, 76.0, 62.4, 56.3, 54.0, 14.1.

***N*-Ethynyl-2-(prop-1-ynyl)-*N*-tosylbenzenamine (649).** To a solution of **647** (30.5 mg, 0.11 mmol) in DMF (2.1 mL) was added Cs_2CO_3 (46 mg, 0.14 mmol), and the mixture was stirred for 30 min. To this solution was added **648** (62 mg, 0.14 mmol) in DCM (900 μL) and the reaction was stirred for 2 h. Et_2O (5 mL) and H_2O (4 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (5 mL × 2), and the combined organic extracts were washed with H_2O (3 mL × 2) and brine (3 mL), dried (Na_2SO_4), filter and concentrated. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (8:1), to give 20.2 mg (61%) of **649** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2 H), 7.45-7.24 (m, 6 H), 2.84 (s, 1 H), 2.46 (s, 3 H), 1.81 (s, 3 H).

2-Methyl-3-(2-(pyridin-2-yl)ethynyl)-1-tosyl-1*H*-indole (651). A mixture of **647** (228 mg, 0.80 mmol), 2-bromoethynylpyridine (prepared in 2 steps from 2-trimethylsilylpyridine, 112 mg, 0.61 mmol), $CuSO_4 \cdot 5H_2O$ (20.0 mg, 0.080 mmol), powdered K_3PO_4 (340 mg, 1.60 mmol), and 1,10-phenanthroline (29 mg, 0.16 mmol) in $PhCH_3$ (1.3 mL) was heated at 75 °C for 18 h. After cooling the reaction to rt, the mixture was diluted with EtOAc (5 mL) and filtered through a plug of celite on top of a plug of silica gel eluting with EtOAc. The filtrate was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1), to give 181 mg (55%) of **651** as an off white solid over 3 steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67-8.58 (m, 1 H), 8.24-8.14 (m, 1 H), 7.76 (m, 4 H), 7.55-7.51 (m, 1 H), 7.38-7.17 (m, 5 H), 2.81 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 145.4, 143.6, 142.1, 136.3, 135.9, 130.2, 129.5, 127.2, 126.6, 125.1, 124.1, 122.8, 119.8, 114.6, 104.4, 95.1, 81.3, 21.7, 14.9.

CHAPTER 8: Progress Towards the Total Synthesis of Lycopodium Alkaloids

8.1 The Lycopodium Alkaloids

8.1.1 Background

The lycopodium alkaloids comprise a group of more than 250 quinolizine or pyridine and α-pyridone type alkaloids isolated from club mosses of the genus *Lycopodium*.[386, 387] The structural framework usually consists of 16 carbon atoms, but some members contain fewer carbons, while dimers containing 32 carbon atoms are known as well.[386] The first Lycopodium alkaloid, lycopodine (**662**), was identified in 1881 by Bodeker from *Lycopodium complanatum*.[388] During the late 1980's, it was found that several lycopodium alkaloids, especially huperzine A,[389, 390] were inhibitors of acetylcholinesterase activity[391, 392] prompting a renewed interest in this family of alkaloids.[386] Unfortunately, club mosses are not abundant plants and grow slowly in only specific habitats thereby limiting their availability. Furthermore, cultivation of these plants has not been realized. With only 53 of the 500 species of club moss having been studied, the diversity of the lycopodium alkaloids is likely yet to be fully uncovered.[386]

According to Ayer, the lycopodium alkaloids are divided into four structural classes: the lycopodine class, the lycodine class, the fawcettimine class, and the miscellaneous class (Figure 8.1).[393] Each class has its own representative compound, lycopodine (**662**), lycodine (**663**), fawcettimine (**664**), and phlegmarine (**665**), respectively, with carbon numbering based upon Conroy's biogenetic hypothesis.[394] These structural classes have provided the inspiration for many total syntheses as well as the development of novel synthetic methods.[395-398]

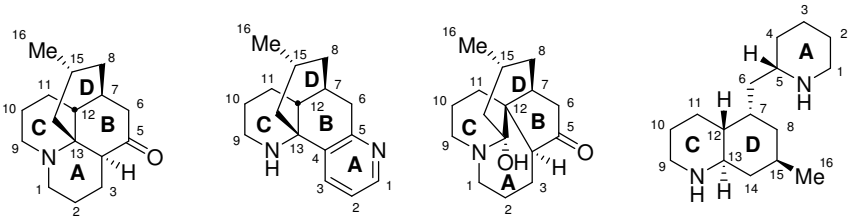
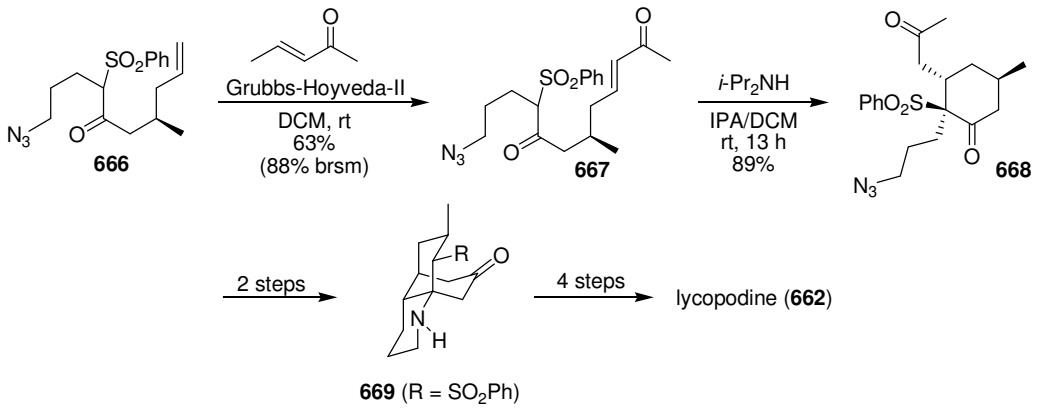


Figure 8.1. Representative lycopodium alkaloid structures for the four classes.

8.1.2 Selected Syntheses of Lycopodium Alkaloids

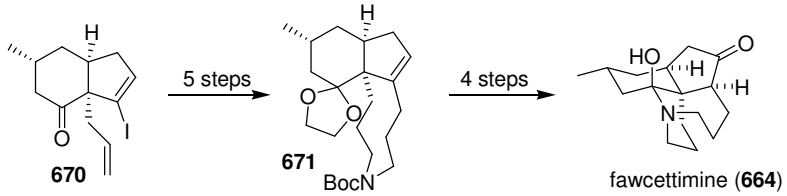
The original member of the lycopodium alkaloids, lycopodine (**662**) has been synthesized seven times in racemic fashion. Recently, Yang et al. reported the first enantioselective synthesis of **662** (Scheme 8.1). Cross metathesis of **666** (prepared in three steps) with 3-penten-2-one provided **667** that smoothly underwent an intramolecular Michael reaction when treated with base to provide the cyclohexanone **668** as the only product. A subsequent intramolecular Mannich reaction provided the tricyclic compound **669** that was taken on to lycopodine in four more steps.[398]



Scheme 8.1. First enantioselective synthesis of lycopodine.

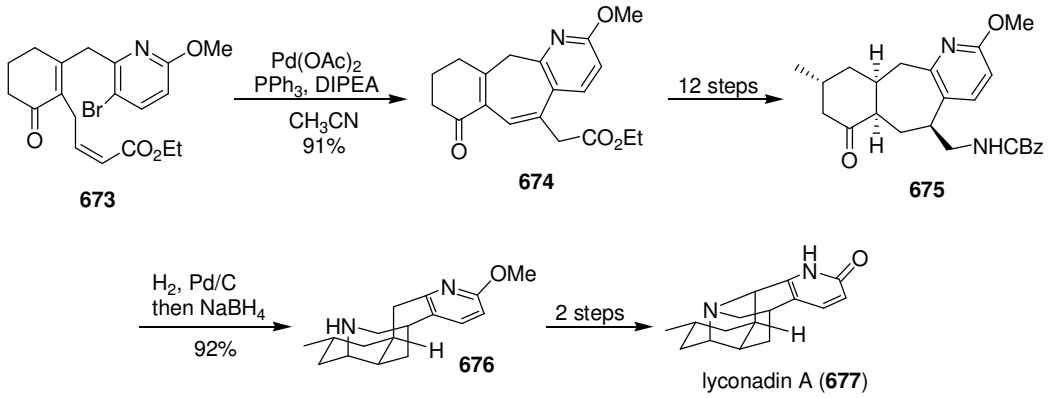
Toste recently reported the first asymmetric synthesis of fawcettimine (Scheme 8.2). His group's route utilized the vinyl iodide **670** (prepared in five steps) as a precursor to the

nine-membered ring intermediate **671**. A further five steps then provided fawcettimine (**664**).[396]



Scheme 8.2. Toste's synthesis of fawcettimine.

A member of the miscellaneous class of lycopodium alkaloids, lyconadin A (**677**) was synthesized by Sarpong in 2008 in the hopes to provide a single strategy for this class of alkaloids. Intramolecular Heck coupling of **673** (prepared in two steps from 2-methoxy-5-bromopyridine) provided the key intermediate **674** in 91% yield (Scheme 8.3). Twelve steps then provided the intermediate **675** that upon reduction formed the tetracyclic structure **676**. Two subsequent steps furnished racemic lyconadin A.[395]

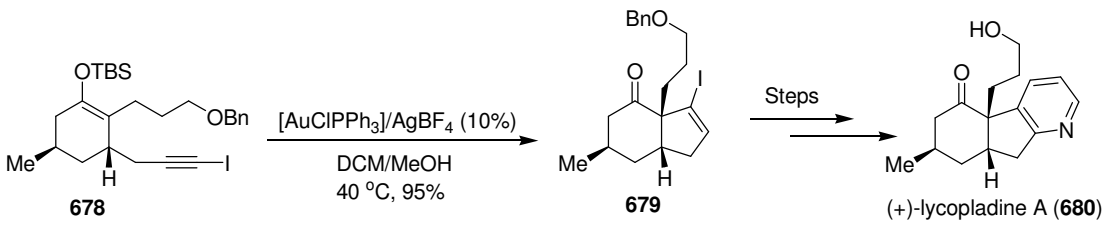


Scheme 8.3. Sarpong's synthesis of lyconadin A.

8.2 Progress Towards the Total Synthesis of Lycopladine A

8.2.1 Background and Retrosynthetic Analysis

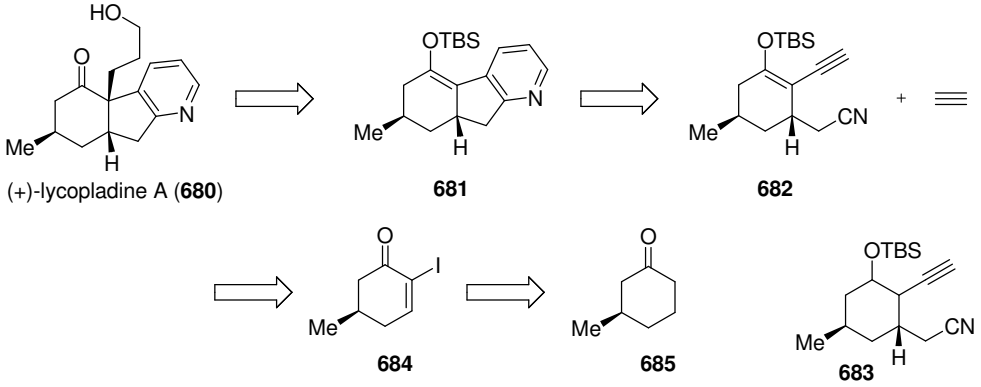
A recent addition to the growing number of Lycopodium alkaloids, (+)-lycopladine A (**680**), was isolated in 2006 from *Lycopodium complantum*.[399] Grouped with the fawcettimine alkaloids, lycopladine A showed modest cytotoxicity against murine lymphoma L1210 cells but not against human epidermoid carcinoma KB cells.[399] The unique skeleton of lycopladine A is unlike any other $C_{16}N$-type alkaloids. One total synthesis of (+)-lycopladine A was reported in 2006 utilizing a gold-catalyzed cyclization of the silylenol ether **678** towards **679** (Scheme 8.4).[400] The starting material **678** was assembled in 5 steps from (*R*)-(+)-5-methyl-2-cyclohexen-1-one, and the synthesis of **680** was completed in 3 steps from the intermediate **679**.



Scheme 8.4. First synthesis of (+)-lycopladine A.

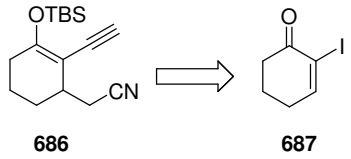
Retrosynthetically, we envisioned synthesizing lycopladine A from the silylenol ether **681** via selective alkylation to install the three carbon side chain (Scheme 8.5). This silylenol ether would in turn be derived from a transition metal mediated [2+2+2] cyclotrimerization reaction between the alkyne-nitrile **682** and acetylene. We hypothesize that the cyclotrimerization reaction of **682** will be more efficient than the corresponding cyclohexane derivative **683** due to the constraint in the system as imposed by the double bond of the silylenol ether and would provide a means to install the side chain.

The synthesis of the key alkyne-nitrile **682** would start with the known iodoenone **684**[401] available in four steps[402] from commercially available (*R*)-(+)-3-methylcyclohexanone (**685**).



Scheme 8.5. Retrosynthetic analysis of (+)-lycopladine A.

In order to investigate the key cyclotrimerization step towards the core structure **681**, we initiated a model study that lacked the stereogenic center in **681**, e.g. the alkyne-nitrile intermediate **686** which will be assembled from **687**[403] (Scheme 8.6).

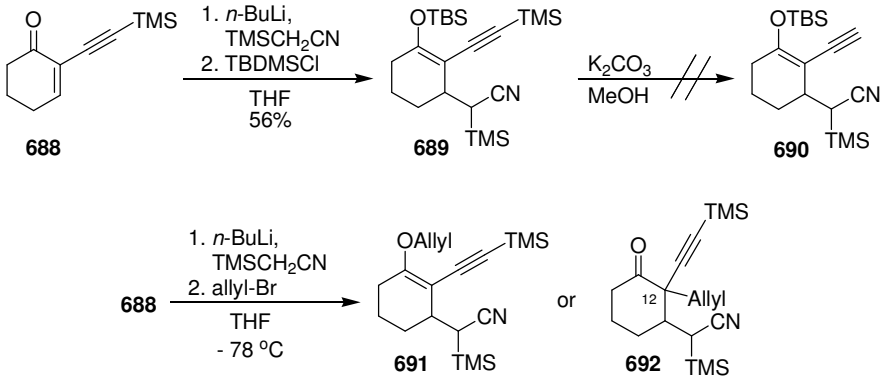


Scheme 8.6. Synthesis of the model alkyne-nitrile **686**.

8.2.2 Synthesis of Model Alkyne-Nitriles Towards Lycopladine A

Steps towards the synthesis of **686** began with the known enone **688**,[404] synthesized in two steps from 2-cyclohexen-1-one via **687**. Installation of the nitrile group was accomplished by the 1,4-addition[405] of lithiated (trimethylsilyl)acetonitrile followed by trapping of the resulting enolate as the silylenol ether furnishing **689** in 56% yield as a mixture of diastereomers (Scheme 8.7). As the steric bulk of the TMS-group may prevent the

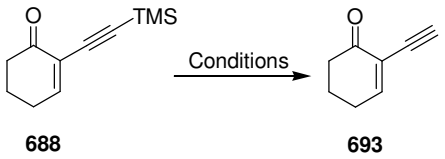
cyclotrimerization reaction (see Scheme 8.11 below), attempts to selectively deprotect the alkyne towards **690** were explored. However, the use of K_2CO_3 in methanol led to decomposition. Quenching the 1,4-addition reaction with allyl bromide to provide a more stable enol ether was unsuccessful since no enolether **691** or ketone **692** could be isolated. Successful C- or O-alkylation towards the allyl derivatives **691** or **692** would provide a handle that could potentially be converted into the carbon chain at C-12. More reactive electrophiles, e.g. methyl iodide, were not investigated due to a potential C-alkylation.



Scheme 8.7. Attempted enol ether formations from **688**.

To circumvent the decomposition of **689**, we investigated the removal of the alkynyl-TMS group prior to the 1,4-addition. More traditional[161] approaches to effect the removal of TMS-groups from alkynes were first examined, but only led to decomposition of the starting material (Entries 1-4, Table 8.1). As each of these reactions was carried out under basic conditions, we reasoned acidic conditions may favor product formation. The use of HF/pyridine resulted in a slow reaction towards the desired alkyne **693** without decomposition. Furthermore, it was found that the use of a mixture of TBAF and aqueous HF lead to efficient desilylation providing **693** in 76% yield.

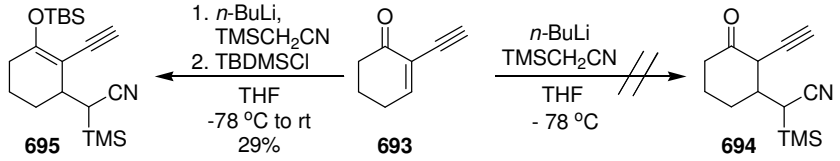
Table 8.1. Desilylation of **688**.



688 **693**

Entry	Conditions	Result
1	K_2CO_3, MeOH Et_2O, rt, 1 h	decomp
2	KF, MeOH rt, 30 min	decomp
3	$AgNO_3$, lutidine THF/Et_2O/H_2O 5 min	decomp
4	TBAF, -40 °C THF, 1 h	decomp
5	HF/pyr, THF 0 °C, 24 h	sluggish rxn
6	TBAF/HF THF, 0 °C to rt 3 h	76%

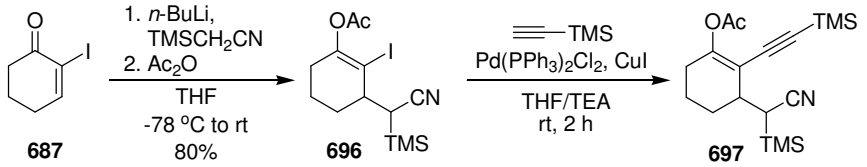
Attempts to isolate the ketone **694** from a 1,4-addition into the α,β-unsaturated system of **693** were unsuccessful, and by-products consistent with allene formation were detected. Additionally, trapping of the enolate as before with TBDMSCl furnished **695** in only 29% yield as a mixture of diastereomers (Scheme 8.8).



695 **693** **694**

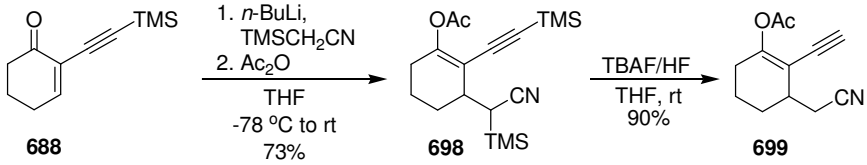
Scheme 8.8. Use of **693** in the 1,4-addition of (trimethylsilyl)acetonitrile.

In attempts to overcome the difficulties with the 1,4-addition, attention was turned to the iodide **687** in the hope that installation of the nitrile moiety followed by the introduction of the alkyne would be more advantageous. Treatment of **687** with lithiated (trimethylsilyl)acetonitrile[405] followed by trapping of the enolate with acetic anhydride furnished the vinyl acetate **696** in 80% yield as a mixture of diastereomers (Scheme 8.9). Sonogashira coupling to install the alkyne,[277] however, proved problematic, as the starting material and the product **697** could not be separated by flash chromatography.



Scheme 8.9. Attempted synthesis of **697**.

Since trapping the enolate as the acetate was more efficient than trapping as the silylether, attention was once more turned to **688** with the expectation that removing the alkynyl-TMS group under the previously determined desilylation conditions toward **693** would be possible. Thus, the vinyl acetate **698** was isolated in 73% yield from **688** as a mixture of diastereomers (Scheme 8.10). Removal of the alkynyl-TMS group was realized with the aforementioned TBAF/HF mixture to give the alkyne-nitrile **699** in 90% yield. Interestingly, this reaction required warming to room temperature to effect desilylation of the alkyne-TMS group while the alkyl-TMS group was removed at 0 °C. With a suitable alkyne-nitrile in hand, investigations into the key [2+2+2] cyclotrimerization step could commence.

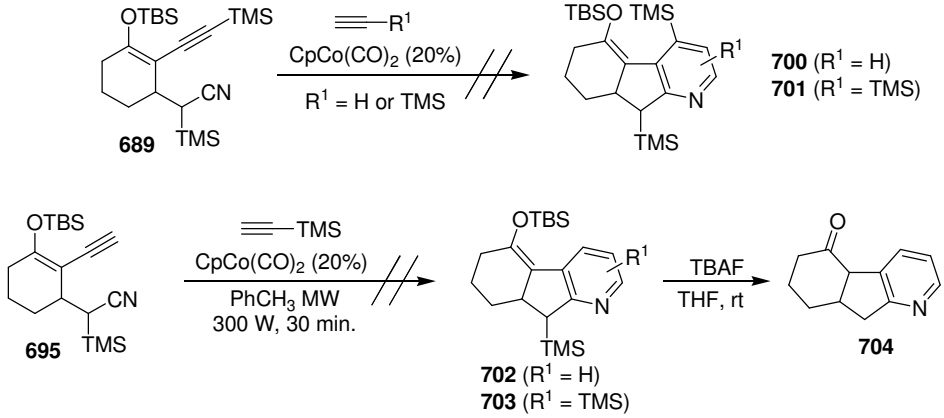


Scheme 8.10. Synthesis of the alkyne-nitrile **699**.

8.2.3 Cyclotrimerization Studies Towards Lycopladine A

With several alkyne-nitriles already accessed, attempts to form the tricyclic core of lycopladine A were explored. The TMS-protected compound **689** did not undergo cyclotrimerization with ethynyltrimethylsilane (TMSA) or acetylene towards the tricyclic

pyridines **700** or **701**, however, the starting material **689** was recovered (Scheme 8.11). This result is not surprising due to the steric bulk of the TMS-group.

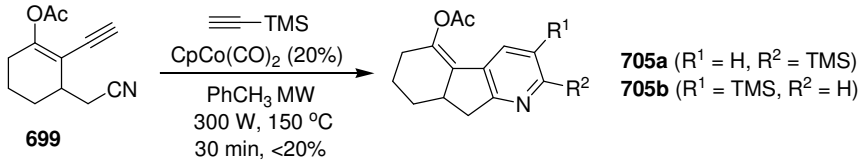


Scheme 8.11. Attempted cyclotrimerization reactions of **689** and **695**.

Similar cyclotrimerizations with the alkyne-nitrile **695** towards **702** or **703** were equally unfruitful (Scheme 8.11). Despite complete consumption of starting material, complex reaction mixtures were obtained. Results from LC/MS analysis of the reaction mixture indicated the presence of **702**, however it could not be isolated in quantities sufficient for NMR analysis. Attempts to globally desilylate the crude material towards **704** (TBAF, THF, rt) did not yield a product of the correct mass by LC/MS analysis.

The cyclotrimerization of the alkyne-nitrile **699** with TMSA, however, did yield cyclotrimerization products **705a** and **705b** (Scheme 8.12). The favored regioisomer **705a** with the TMS-group in the α-position to the pyridine nitrogen center was isolated, but could not be fully purified by silica gel chromatography. ^{1}H NMR analysis showed two doublets in the aromatic region consistent with the product, but impurities in the aliphatic region were present. Even with the impurities the yield was less than 20% of **705a**. Likewise, the other regioisomer **705b** could also be detected by ^{1}H NMR spectroscopy as evidenced by two

aromatic singlets with one shifted downfield due to its α–position to the pyridine nitrogen, but impurities were present.



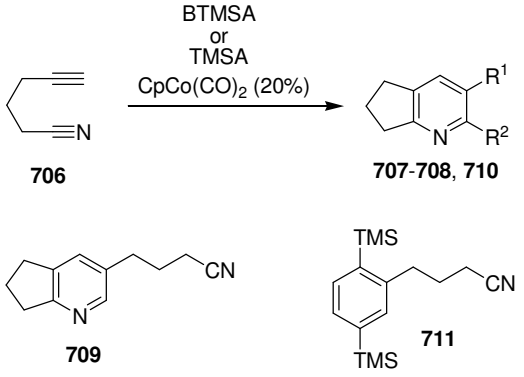
Scheme 8.12. Cyclotrimerization reaction of the alkyne-nitrile **699**.

Due to the inefficient cyclotrimerization reactions of **689**, **695**, and **699** towards the tricyclic core of lycopladine A, a simplified model for only the cyclotrimerization reaction was sought to be used in the opitimization of the cyclotrimerization reaction. Here, the cyclotrimerization reaction of 5-hexynenitrile (**706**) was chosen as a model system because the 1,4-relationship of the alkyne and nitrile is maintained. While the cyclotrimerization reaction with bis-trimethylsilylacetylene (BTMSA) is known under light irradiation to give **707** in 77% yield,[50] we intended to use microwave irradiation and wished to modify the known procedure accordingly. Despite the good yield of **707** under light irradiation, the synthesis of fused pyridines via tethered alkyne-nitriles is generally a difficult and low yielding transformation, as the initial metallacyle formation requires the coordination of two untethered alkynes.[50, 406]

Initial experiments involved microwave irradiation of **706** with ten equivalents of BTMSA under closed vessel conditions and $CpCo(CO)_2$ catalysis and gave the fused pyridine **707**[50] in 23% yield (Entry 1, Table 8.2). Open vessel microwave conditions where the 5-hexynenitrile and Co-catalyst were added to an irradiated solution of BTMSA in xylenes over 30 min furnished a 27% yield of the fused pyridine **708** with loss of the TMS

group alpha to the nitrogen (Entry 2). Using thermal heating and tetramethylammonium oxide (TMAO) as a catalyst activator[407] led to only a 7% yield of **708** with 29% of the dimer **709**[408] (Entry 3). Employing the less sterically encumbered TMS-acetylene gave slightly better results furnishing a 40% yield of **710** under closed vessel microwave conditions (Entry 4). Open vessel conditions produced only a 12% yield of **710** with the benzene side product **711** also forming in 12% yield (Entry 5). The results of these model cyclotrimerization reactions mirror those of the more complex alkyne-nitrile cyclotrimerization reactions shown in Scheme 8.12 (see above), and further investigations towards a more efficient cyclotrimerization of alkyne-nitriles is needed before more progress towards lycopladine A can be made.

Table 8.2. Cyclotrimerization studies of 5-hexynenitrile (**706**). [a]Slow addition of **706** and Co to BTMSA; [b]oil-bath heating.

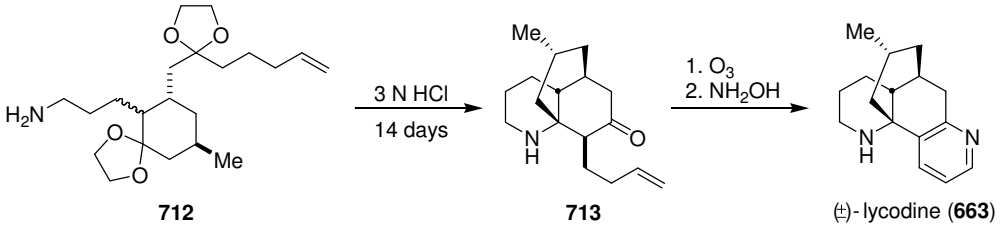


Entry	Conditions	Result
1	BTMSA (10) $PhCH_3$, MW 300 W, 30 min	**707**, $R^1 = R^2$ = TMS, 23%
2	BTMSA (5) MW, o.v., 140 °C xylenes[a]	**708**, R^1 = TMS, R^2 = H, 27% **709**, 29%
3	BTMSA (1.2) TMAO (0.2) xylenes, 140 °C[b]	**708**, 7% **710**, R^1 = H, R^2 = TMS, 40%
4	TMSA (10) $PhCH_3$, MW 300 W, 30 min	**710**, 12%
5	TMSA (5) MW, o.v., 140 °C xylenes[a]	**711**, 12%

8.3 Progress Towards the Total Synthesis of Lycodine

8.3.1 Background and Retrosynthetic Analysis

First isolated in 1958 by Anet and Eves, lycodine (**663**) is the simplest member of the dinitrogen lycopodium alkaloids.[409, 410] No biological activity of lycodine has been reported to date, however, all the lycopodium alkaloids that possess acteylcholinesterase inhibitory activity are members of this class.[386] To date, only one total synthesis of (±)-lycodine has been reported.[411, 412] Heathcock's synthesis relies on an intramolecular Mannich reaction of the amine **712** to provide the BCD-ring structure (Scheme 8.13). Conversion of the homoallyl side chain in **713** to the pyridine ring furnishes (±)-lycodine in 13% yield and only eight steps.

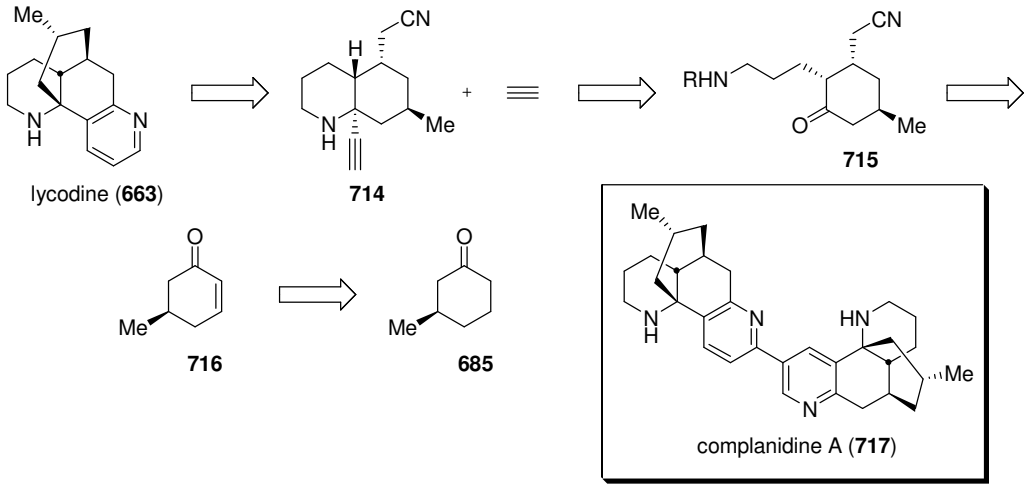


712 **713** (±)-lycodine (**663**)

Scheme 8.13. Heathcock's synthesis of (±)-lycodine (**663**).

Deconstructing the pyridine ring of lycodine reveals the alkyne-nitrile **714** as a potential precursor for a [2+2+2] cyclotrimerization reaction with acetylene (Scheme 8.14). We envisioned deriving **714** from the trisubstituted cyclohexanone **715** via ring formation and installation of the alkyne moiety. This cyclohexanone should be accessible via the same starting material as for lycopladine A (**685**) via introduction of the amine side chain and conjugate addition of acetonitrile to the enone **716**. The methyl substituent whose orientation will be set in the starting material will be used to control the stereochemistry of the other two substituents on the cyclohexanone ring via stereoelectronic effects.[413] Model studies towards

the synthesis of the essential alkynylnitrile intermediate focused on introduction of the nitrile and amine side chains without stereocontrol from cyclohexenone. In addition to lycodine, we sought to synthesize the dimeric Lycopodium alkaloid complanidine A (**717**)[414] via a second [2+2+2] cyclotrimerization reaction.

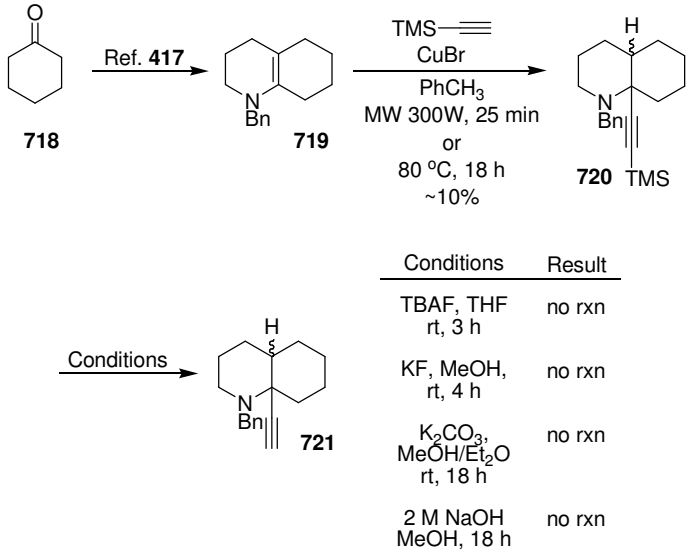


Scheme 8.14. Retrosynthetic analysis of lycodine (**663**) and structure of complanidine A (**717**).

8.3.2 Current Progress Towards Lycodine

Before embarking on the total synthesis of lycodine, we sought an expedient route to the desired alkyne-nitrile cyclotrimerization precursor **714**. Model studies aimed at synthesizing **714** were initiated and focused on two aspects of **714**: introduction of the ethynyl group and installation of the cyano and amino side chains of **715**. We envisioned forming the necessary propargylamine via a Cu-catalyzed alkynylation of an enamine based on methodology developed by Knochel (Scheme 8.15).[415, 416] In this direction, the bicyclic enamine **719**[417] was prepared via known procedures from cyclohexanone (**718**) to be used as a model system for the alkyne introduction (Scheme 8.15). Treatment of **719** with catalytic

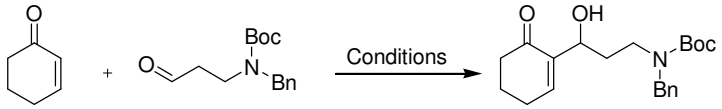
CuBr and excess TMSA under thermal or microwave heating conditions gave low yields (~10%) of the desired propargylamine **720**. Purification of the product was difficult due to the presence of a reaction byproduct presumably the TMSA dimer as only a singlet was present in the ^{1}H NMR spectrum. Attempts to remove the alkynyl-TMS groups from **720** to give **721** before purification through the use of fluoride agents (TBAF or KF) or under basic conditions (K_2CO_3 or NaOH) were unsuccessful with unreacted starting material recovered. On the basis of these results, a stepwise approach to the introduction of the alkyne may be necessary.



Scheme 8.15. Attempted Cu-catalyzed addition of TMSA into the enamine **719**.

Turning to the installation of the amino and cyano side chains, we directed our efforts first towards the amine side chain via a Baylis-Hillman reaction. Treatment of 2-cyclohexen-1-one (**722**) and the known aldehyde **723**[418] with various nitrogen bases led to low conversion of the desired alcohol **724** (Table 8.3).[419-422] Due to the low yields others means to install the side chain were explored.

Table 8.3. Baylis-Hillman approach towards **724**.

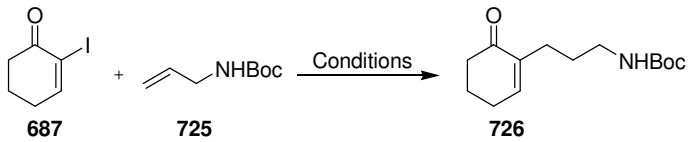


722 **723** **724**

Entry	Conditions	Result
1	DBU (1 eq) rt, 18 h	17%
2	DMAP (0.2 eq) THF/H_2O rt, 4 d	11%
3	DABCO (0.01 eq) dioxane, 0 °C	no rxn
4	DABCO (1 eq) dioxane/H_2O rt	no rxn

We hypothesized that the Suzuki-Miyaura reaction[423] would provide an efficient means to introduce the amine side chain starting with the previously utilized iodoenone **687** and Boc-protected allylamine (**725**). In this reaction, the B-alkyl species is generated *in situ* via hydroboration, followed by coupling with a vinyl iodide under Pd-catalysis. Hydroboration at room temperature, in this case, was slow and no reaction was seen under a variety of conditions (Entries 1-4, Table 8.4).[400, 423, 424] Allowing the hydroboration to proceed at 60 °C before addition of the iodide, did furnish the desired enone product **726** in a low 25% yield (Entry 5). Modifying the Pd source, solvent, and ligands was ineffective (Entries 6-7). Troubleshooting the reaction pointed to the hydroboration step as the source of the low yields, however even using excess hydroboration reagent was unrewarding possibly due to decomposition or dilution of the borane reagent. Use of the 9-BBN dimer may improve the hydroboration step.

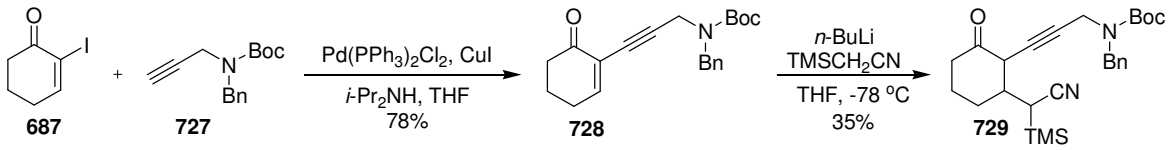
Table 8.4. Suzuki-Miyaura reaction of the iodoenone **687**.



687 **725** **726**

Entry	Conditions	Result
1	9-BBN, $Pd(PPh_3)_4$, NaOH, THF/H_2O rt to 60 °C	no rxn
2	9-BBN, $Pd(dppf)Cl_2$, Cs_2CO_3, $AsPh_3$ THF/DMF rt to 60 °C	no rxn
3	9-BBN, $Pd(PPh_3)_4$, NaOH, dioxane rt	no rxn
4	BH_3·THF, $Pd(dppf)Cl_2$, Cs_2CO_3, $AsPh_3$ DMF/H_2O rt to 60 °C	no rxn
5	9-BBN, $Pd(dppf)Cl_2$, Cs_2CO_3, $AsPh_3$, THF/DMF, 60 °C	25%
6	9-BBN, $Pd(PPh_3)_4$, NaOH, THF/H_2O, 60 °C	no rxn
7	9-BBN, $Pd(dppf)Cl_2$, Cs_2CO_3, $AsPh_3$, DMF, 60 °C	no rxn

Looking towards other Pd-catalyzed reactions to append the side chain, we chose the Sonogashira reaction.[277] Coupling of **687** with the protected propargyl amine **727**[425] furnished **728** in a 78% yield thereby successfully introducing the amine side chain (Scheme 8.16). The next step would involve 1,4-addition of (trimethylsilyl)acetonitrile. In this direction, the enone **728** was treated with the lithium salt of (trimethylsilyl)acetonitrile to give a 35% yield of the cyclohexanone derivative **729** as a mixture of stereoisomers. Analysis of the ^1H NMR spectrum was complicated by the three stereocenters present in **729**, but LC/MS analysis of the purified material confirmed the desired product. Efforts towards a model system for lycodine are ongoing.



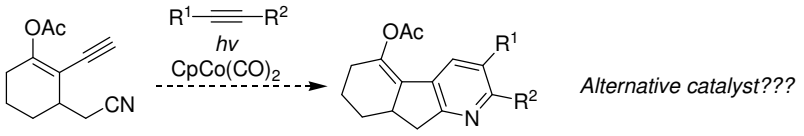
687 727 728 729

Scheme 8.16. Introduction of the amine side chain via Sonogashira coupling.

8.4 Summary and Future Directions

8.4.1 Lycopladine A

Initial model studies towards the synthesis of lycopladine A produced several tethered alkyne-nitriles that were tested for cyclotrimerization efficiency. However, the model substrates either underwent cyclotrimerization with low yield or completely failed to react. Future studies focusing on the cyclotrimerization of the alkyne-nitrile **699** are warranted as only a few reaction conditions were investigated. The use of light[50] instead of microwave irradiation may be necessary to promote the cyclotrimerization reaction, and alternative catalyst systems (e.g. $Ni(cod)_2$/NHC, CpCo(cod))[39, 42] can be explored to optimize the yield of the fused pyridine (Scheme 8.17).

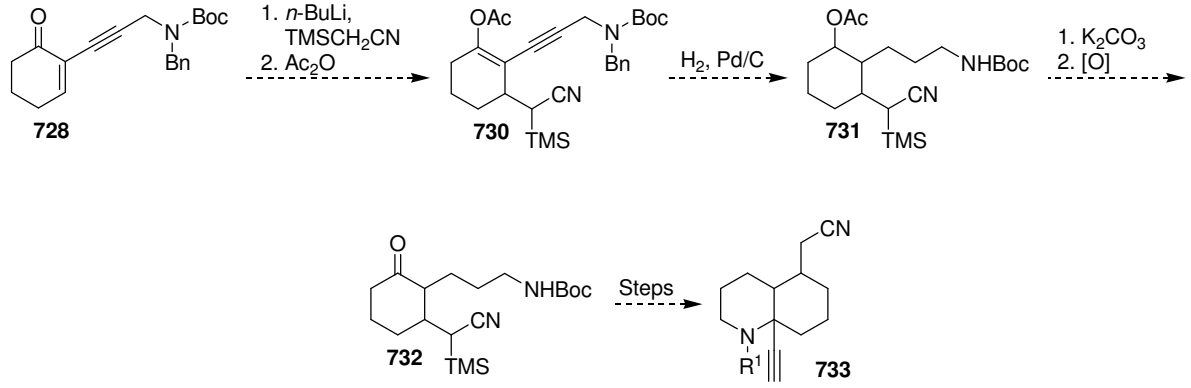


699 705

Scheme 8.17. Future work towards lycopladine A.

8.4.2 Lycodine

Progress towards lycodine has been hampered by the synthesis of a model alkyne-nitrile suitable for cyclotrimerization studies. Several approaches have been explored to install the nitrile moiety as well as the amine side chain. Continuing with the enone **728**, quenching of the intermediate enolate to give the acetate **730** may increase the efficiency of the 1,4-addition as seen in the model studies towards lycopladine A (Scheme 8.18). Global reduction[426] would then provide the protected cyclohexanol derivative **731** that could be further elaborated towards lycodine. The stereochemistry of the cyanomethyl substituent in the actual system will be determined by the methyl group at C-15, while the stereochemistry of the amine chain will be determined in the reduction barring any epimerization. Installation of the alkyne functionality and ring formation from **732** would then provide the model alkyne-nitrile **733** ready for cyclotrimerization reactions.



Scheme 8.18. Future work towards the model alkyne-nitrile **733**.

8.5 Experimental

All reactions were performed in flame-dried glassware under a nitrogen atmosphere and stirred magnetically. Tetrahydrofuran, toluene, xylenes, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Diisopropylamine, triethylamine, DMSO, DCM, DMF, 1,2-dichloroethane, CH_3CN and pyridine were distilled from calcium hydride and stored over 4 Å molecular sieves. Other reagents and solvents obtained from commercial sources were stored under nitrogen and used directly without further purification. *n*-BuLi and MeLi were titrated against *N*-pivaloyl-*o*-toluidine.[108] Melting points were obtained from a Mel-Temp capillary melting point apparatus and are uncorrected. High resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz) or Varian Mercury 300 (300 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as the internal standard for ^{1}H NMR spectra and the $CDCl_3$ absorption (77.2) for ^{13}C NMR spectra. IR spectra were recorded on a JASCO FT/IR 4100 spectrometer.

1-(*tert*-Butyldimethylsilyloxy)-3-((1-cyano-1-trimethylsilyl)methyl)-2-(2-trimethylsilylethynyl)-cyclohex-1-ene (689). To a solution of (trimethylsilyl)acetonitrile (29 μL, 0.22 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (1.13 M in hexanes, 190 μL, 0.22 mmol) dropwise. After 45 min, a solution of **688** (34.5 mg, 0.18 mmol) in THF (300 μL with 300 μL wash) was added, and the reaction was stirred for 1 h. At this point TBDMSCl (41 mg, 0.27 mmol) in THF (500 μL) was added, and the reaction was allowed to stir as it warmed to rt overnight. In the morning the reaction was cooled to 0 °C and quenched with

sat. NH_4Cl (3 mL). The aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (30:1), to give 42.2 mg (56%) of **689** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93-2.79 (bm, 1 H), 2.75-2.64 (m, 1 H), 2.26-1.83 (m, 4 H), 1.39-1.14 (m, 2 H), 0.96 (s, 9 H), 0.29-0.14 (m, 24 H).

2-Ethynylcyclohex-2-enone (693). To a solution of **688** (92 mg, 0.48 mmol) in THF (6.7 mL) in a polyethylene vial was added a mixture of TBAF (1 M in THF, 540 μL, 0.54 mmol) and aq. HF (47%, 45 μL) at rt. After 2 h, sat. $NaHCO_3$ (6 mL) was added, and the aqueous layer extracted with EtOAc (6 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (6:1), to give 43.5 mg (76%) of **693** as an off white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (t, J = 4.4 Hz, 1 H), 3.07 (s, 1 H), 2.58-2.40 (m, 4 H), 2.12-1.98 (m, 2 H).

1-(*tert*-Butyldimethylsilyloxy)-3-((1-cyano-1-trimethylsilyl)methyl)-2-ethynyl-cyclohex-1-ene (695). To a solution of (trimethylsilyl)acetonitrile (27 μL, 0.20 mmol) in THF (1.9 mL) at −78 °C was added *n*-BuLi (1.1 M in hexanes, 180 μL, 0.20 mmol) dropwise. After 45 min, a solution of **693** (20.0 mg, 0.17 mmol) in THF (300 μL with 150 μL wash) was added, and the reaction was stirred for 1 h. At this point, TBDMSCl (38 mg, 0.25 mmol) in THF (500 μL) was added, and the reaction was allowed to stir as it warmed to rt overnight. In the

morning the reaction was cooled to 0 °C and quenched with sat. NH_4Cl (3 mL). The aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (30:1), to give 16.8 mg (29%) of **695** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21-3.07 (m, 1 H), 2.94-2.81 (bm, 1 H), 2.71-2.60 (m, 1 H), 2.24-1.83 (m, 5 H), 1.43-1.22 (m, 1 H), 0.98-0.94 (m, 9 H), 0.32-0.17 (m, 15 H).

3-(Cyano(trimethylsilyl)methyl)-2-iodocyclohex-1-enyl acetate (696). To a solution of (trimethylsilyl)acetonitrile (74 μL, 0.54 mmol) in THF (1.1 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 216 μL, 0.54 mmol) dropwise. After 45 min, a solution of **687** (100.0 mg, 0.45 mmol) in THF (900 μL with 400 μL wash) was added, and the reaction was stirred for 1 h. At this point Ac_2O (64 μL, 0.68 mmol) was added, and the reaction was allowed to stir as it warmed to rt over 3 h. The reaction was cooled to 0 °C and quenched with sat. NH_4Cl (3 mL). The aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (7.5:1), to give 137 mg (80%) of **696** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17-3.02 (bm, 0.5 H), 2.81-2.65 (m, 1.5 H), 2.52-2.15 (m, 6 H), 2.02-1.59 (m, 3 H), 0.39-0.20 (m, 9 H).

3-(Cyano(trimethylsilyl)methyl)-2-(2-(trimethylsilyl)ethynyl)cyclohex-1-enyl acetate (698). To a solution of (trimethylsilyl)acetonitrile (37.4 μL, 0.27 mmol) in THF (550 μL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 110 μL, 0.27 mmol) dropwise. After 45 min, a solution of **688** (43.8 mg, 0.23 mmol) in THF (400 μL with 300 μL wash) was added, and the reaction was stirred for 1 h. At this point Ac_2O (33 μL, 0.34 mmol) was added, and the reaction was allowed to stir as it warmed to rt over 3 h. The reaction was cooled to 0 °C and quenched with sat. NH_4Cl (3 mL). The aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (9:1), to give 58 mg (73%) of **698** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99-2.50 (m, 2 H), 2.46-1.77 (m, 10 H), 1.75-1.31 (m, 2 H), 0.39-0.12 (m, 18 H).

3-(Cyanomethyl)-2-ethynylcyclohex-1-enyl acetate (699). To a solution of **698** (32.6 mg, 0.094 mmol) in THF (1.3 mL) in a polyethylene vial a 0 °C was added a mixture of TBAF (1 M in THF, 212 μL, 0.21 mmol) and aq. HF (47%, 18 μL), and the reaction was stirred for 20 min before warming to rt. After 20 min, H_2O (3 mL) was added, and the aqueous layer was extracted with EtOAc (4 mL × 3). The combined organic extracts were washed with water (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (4:1), to give 17.1 mg (90%) of **699** as a slight yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 1 H), 2.84 (dd, *J* =

16.6 and 3.6 Hz, 1 H), 2.76-2.62 (bm, 1 H), 2.46 (dd, *J* = 16.6 and 9.6 Hz, 1 H), 2.32-2.22 (m, 2 H), 2.18 (s, 3 H), 2.10-1.52 (m, 6 H).

7,8,8a,9-tetrahydro-2-(trimethylsilyl)-6*H*-indeno[2,1-*b*]pyridin-5-yl acetate (705a) and **7,8,8a,9-tetrahydro-3-(trimethylsilyl)-6*H*-indeno[2,1-*b*]pyridin-5-yl acetate (705b).** A solution of **699** (8.2 mg, 0.040 mmol), TMSA (57 μL, 0.40 mmol), and $CpCo(CO)_2$ (0.9 μL, 0.008 mmol) in xylenes (1.0 mL) was irradiated in a CEM Discover microwave synthesizer for 30 min. After cooling, the reaction mixture was filtered over a silica plug, concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (7:1 to 5:1), to give 2.5 mg (20%) of **705a** and 2 mg (16%) of **705b**. Key ^{1}H NMR shifts (300 MHz, $CDCl_3$) δ **705a**: 7.48 (d, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 3.36-3.16 (m, 1 H), 3.01 (br s, 1 H), 2.86-2.70 (m, 1 H), 2.46-2.34 (m, 2 H), 2.42 (s, 3 H), 0.30 (s, 9 H); **705b**: 8.40 (s, 1 H), 7.70 (s, 1 H), 2.25 (s, 3 H), 0.28 (s, 9 H).

6,7-Dihydro-3-(trimethylsilyl)-5*H*-cyclopenta[*b*]pyridine (708). A solution of 5-hexynenitrile (15 mg, 0.16 mmol) and $CpCo(CO)_2$ (3.8 μL, 0.032 mmol) in xylenes (1.1 mL) was added over 35 min to a solution of BTMSA (182 μL, 0.81 mmol) in xylenes (1 mL) irradiated in a CEM Discover microwave synthesizer. After 15 min of heating, the reaction was cooled, concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (50:1 to 15:1), to give 8.2 mg (27%) of **708** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.60 (s, 1 H), 3.00 (t, *J* = 7.7 Hz, 2 H), 2.93 (t, *J* = 7.4 Hz, 2 H), 2.14-2.04 (m, 2 H), 0.28 (s, 9 H).

6,7-Dihydro-2-(trimethylsilyl)-5*H*-cyclopenta[*b*]pyridine (710). A solution of 5-hexynenitrile (13.5 mg, 0.14 mmol), TMSA (202 μL, 1.4 mmol), and $CpCo(CO)_2$ (3.4 μL, 0.029 mmol) in $PhCH_3$ (2.6 mL) was irradiated in a CEM Discover microwave synthesizer at 300 W for 30 min. The reaction was cooled, concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (5:1 to 1:1), to give 11.5 mg (40%) of **710** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 1 H), 7.25 (d, *J* = 7.4 Hz, 1 H), 3.07 (t, *J* = 7.6 Hz, 2 H), 2.92 (t, *J* = 7.4 Hz, 2 H), 2.18-2.05 (m, 2 H), 0.32 (s, 9 H).

4-(2,5-Bis(trimethylsilyl)phenyl)butanenitrile (711). A solution of 5-hexynenitrile (13.9 mg, 0.15 mmol) and $CpCo(CO)_2$ (3.5 μL, 0.030 mmol) and TMSA (105 μL, 0.75 mmol) in xylenes (1.6 mL) was added over 30 min to xylenes (1 mL) irradiated in a CEM Discover microwave synthesizer. After 15 min of heating, the reaction was cooled, concentrated and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (7:1), to give 5.3 mg (12%) of **711** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.3 Hz, 1 H), 7.38 (dd, *J* = 7.3 and 1.1 Hz, 1 H), 7.31 (d, *J* = 1.1 Hz, 1 H), 2.94-2.84 (m, 2 H), 2.45 (t, *J* = 7.1 Hz, 2 H), 2.07-1.91 (m, 2 H), 0.34 (s, 9 H), 0.27 (s, 9 H).

Benzyl *tert*-butyl 3-(6-oxocyclohex-1-enyl)-3-hydroxypropylcarbamate (724). To a mixture of **722** (30 mg, 0.31 mmol) and **723** (82 mg, 0.31 mmol) was added DBU (47 μL, 0.31 mmol), and the reaction was stirred for 24 h. Et_2O (5 mL) was added, and the organic layer was washed with H_2O (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered and

concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (2:1), to give 18.8 mg (17%) of **724** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5 H), 7.13-7.02 (bm, 1 H), 4.83-4.09 (m, 4 H), 3.89-3.63 (bm, 1 H), 3.15-2.90 (bm, 1 H), 2.51-2.33 (m, 4 H), 2.12-1.90 (m, 3 H), 1.46 (bs, 9 H).

***tert*-Butyl 3-(6-oxocyclohex-1-enyl)propylcarbamate (726).** To **725** (31.8 mg, 0.20 mmol) was added 9-BBN (0.5 M in THF, 270 μL, 0.14 mmol), and the solution was heated at 60 °C for 4 h. The reaction was cooled, and **687** (15 mg, 0.068 mmol), $Pd(dppf)Cl_2$ (2.8 mg, 0.003 mmol), $AsPh_3$ (1 mg, 0.003 mmol), Cs_2CO_3 (44 mg, 0.14 mmol), and DMF (800 μL) were added. The reaction was heated at 60 °C for a further 2 h and diluted with H_2O (2 mL). The aqueous layer was extracted with Et_2O (3 mL × 3), and the combined organic extracts were washed with H_2O (2 mL × 2) and brine (2 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3:1), to give 4.3 mg (25%) of **726** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (t, *J* = 4.1 Hz, 1 H), 4.77-4.29 (m, 1 H), 3.15-3.01 (m, 2 H), 2.48-2.30 (m, 4 H), 2.25-2.16 (m, 2 H), 2.06-1.90 (m, 2 H), 1.72-1.54 (m, 2 H), 1.44 (s, 9 H).

***tert*-Butyl benzyl 3-(6-oxocyclohex-1-enyl)prop-2-ynylcarbamate (728).** To a solution of **687** (27 mg, 0.12 mmol), **727** (60 mg, 0.24 mmol), $Pd(PPh_3)_4Cl_2$ (4.2 mg, 0.006 mmol), and CuI (2.3 mg, 0.012 mmol) in THF (300 μL) was added *i*-Pr_2NH (51 μL, 0.36 mmol) slowly. After 45 min, Et_2O (5 mL) was added, and the organic layer was washed with H_2O (2 mL) and brine (2 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was

purified by silica gel chromatography, eluting with hexanes/EtOAc (5:1 to 4:1), to give 32.2 mg (78%) of **728** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.04 (m, 6 H), 4.59 (s, 2 H), 4.51-3.93 (m, 2 H), 2.56-2.38 (m, 4 H), 2.12-1.96 (m, 2 H), 1.48 (bs, 9 H).

***tert*-Butyl benzyl 3-(2-((1-cyano-1-trimethylsilyl)methyl)-6-oxocyclohexyl)prop-2-ynylcarbamate (729).** To a solution of (trimethylsilyl)acetonitrile (13.9 μL, 0.10 mmol) in THF (1 mL) at −78 °C was added *n*-BuLi (1.1 M in hexanes, 92 μL, 0.10 mmol) dropwise. After 45 min, a solution of **728** (28.7 mg, 0.085 mmol) in THF (200 μL with 200 μL wash) was added, and the reaction was stirred for 1 h. At this point, sat. NH_4Cl (2 mL) was added, and the aqueous layer was extracted with Et_2O (4 mL × 3). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/EtOAc (3.5:1), to give 13.3 mg (35%) of **729** as a mixture of diastereomers as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.12 (m, 5 H), 5.89-5.55 (m, 1 H), 4.78-4.21 (m, 3 H), 3.98-3.60 (m, 2 H), 3.15-1.68 (m, 7 H), 1.47 (bs, 9 H), 0.40-0.07 (m, 9 H).

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