CHAPTER I: ASYMMETRIC TOTAL SYNTHESES OF (+)-19-DEOXYICETEXONE, (–)-ICETEXONE, AND (+)-5-*EPI*-ICETEXONE

CHAPTER II: A PRACTICAL SYNTHESIS OF FUNCTIONALIZED 6- AND 8-HYDROXYISOCHROMENES AND ISOCOUMARINS AND A NOVEL ROUTE TO 8-HYDROXYISOCOUMARINS

by

JEREMY LEE GROVE

(Under the Direction of George Majetich)

ABSTRACT

Chapter I: The first asymmetric total syntheses of (+)-19-deoxyicetexone, (–)-icetexone, and (+)-5-*epi*-icetexone was achieved. This study featured: (1) an enzymatic resolution strategy to construct an asymmetric A-ring; (2) an efficient six step synthesis of the C-ring; (3) the development of a novel Friedel–Crafts cyclialkylation reaction to forge a 6-7-6 cycloheptatriene nucleus. Additionally, our efforts have resulted in a reassignment of the physical data of two epimeric icetexones.

Chapter II: A short synthetic route for the preparation of functionalized 8- and 6-hydroxyisochromenes has been developed. Both strategies feature novel intramolecular hydroalkoxylations of conjugated alkynes. Additionally, a novel one-pot oxidation-cyclization-aromatization of a cyclohexadienone-alcohol has resulted in a new method for preparation of functionalized 8-hydroxyisocoumarins.

INDEX WORDS: icetexane, icetexone, deoxyicetexone, 5-*epi*-icetexone, triterpene, total synthesis, Friedel–Crafts, isochromene, isocoumarin, heterocycle

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The University of Georgia
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TABLE OF CONTENTS

Page

LIST OF ABBREVIATIONS

Abbreviation	**Full name**
ACN	acetonitrile
AcOH	acetic acid
AIBN	azo-*bis*-isobutyronitrile
BPO	benzoyl peroxide
brsm	based on recovered starting material
CAN	ceric ammonium nitrate
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfate

DMSO	DMSO
EtOAc	ethyl acetate
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorus triamide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperoxybenzoic
MOM	methoxymethyl
MsOH	methanesulfonic acid
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
n-BuLi	*n*-butyllithium
n-Bu_3SnH	*tris*-(*n*-butyl)-tinhydride
PhH	benzene
PhMe	toluene
PPA	polyphosphoric acid
p-TsOH	*para*-toluenesulfonic acid

PCC	pyridium chlorochrmate
PMB	*para*-methoxybenzyl
TBAF	*tetra*-(*n*-butyl)-ammonium fluoride
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl

CHAPTER I

ASYMMETRIC TOTAL SYNTHESES OF (+)-19-DEOXYICETEXONE, (–)-ICETEXONE, AND (+)-5-*EPI*-ICETEXONE

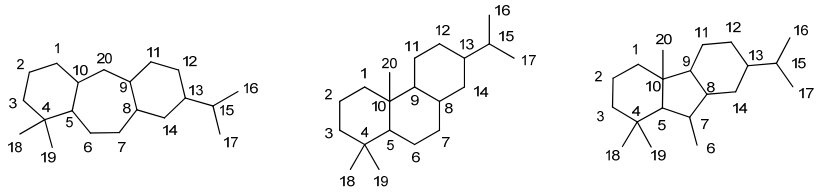
1.1 Introduction

The emphasis of this chapter is on the isolation and biosynthetic relationships between abietane and rearranged abietane frameworks, namely icetexane-related natural products. Some general synthetic approaches toward the icetexanes will be presented. En route to the icetexones and related natural products, focus will be placed on the development of a new method for the construction of their tricyclic nucleus. Strategies for the efficient preparation of an arene precursor and introduction of the key C4 stereocenter will then be presented. Next, our strategy for the installation of the C5 stereocenter will be discussed. Protecting group strategies employed during our studies will also be summarized. The first asymmetric total syntheses of (+)-19-deoxyicetexone, (–)-icetexone and (+)-5-*epi*-icetexone will be presented, as well as the contribution of the results therein to the completion of the total synthesis of several related natural products.[1]

1.2 Biosynthetic Relationships

An increasingly large number and variety of structurally novel and biologically active abietane and abietane-related diterpenoids have been isolated from the extracts of shrubs and plants from the *Salvia* genus. Species of *salvia* are found throughout the world and are comprised

of 700 to 1,000 species.[2] Many of the natural products isolated from these sources are diterpenoids and contain the abietane skeleton, which is typified by a 6-6-6 tricyclic carboskeleton (Figure 1.2.1). This general framework has been biosynthetically linked to the 6-7-6 skeleton of the icetexanes (**1.2.1**) and other types of abietanes (**1.2.2**), such as the taiwaniquinoids (**1.2.3**). While the main focus of this chapter is on our synthetic efforts toward the icetexanes, some of the biosynthetic relationships between these and other classes of diterpenoids are also introduced.



1.2.1
icetexanes
9(10→20)-abeo-abietane

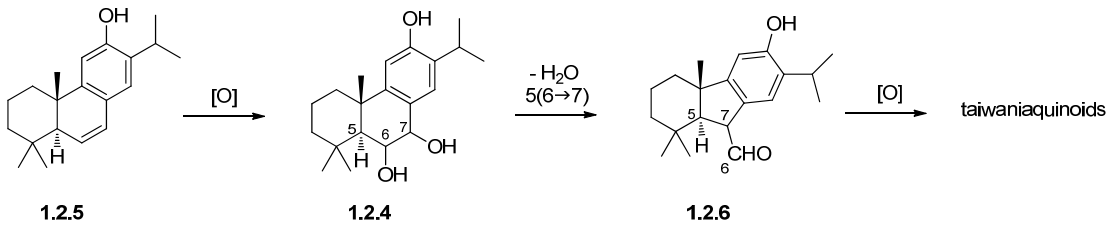
1.2.2
abietanes

1.2.3
taiwainiquinoids
5(6→7)-abeo-abietane

Figure 1.2.1

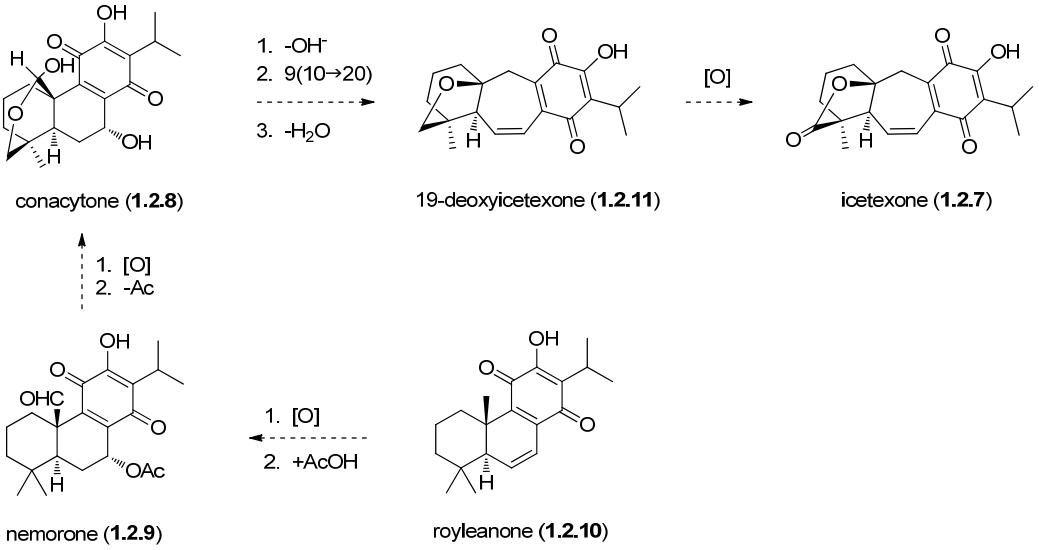
The abietane skeleton is the common name assigned to the class of diterpenoid natural products containing the 6-6-6 tricyclic carbocyle nucleus shown in Figure 1.2.1. The numbering system shown has been assigned to this skeletal arrangement and rearranged, or *abeo*, abietanes use a similar numbering.

There are several others classes of diterpenoid natural products having biosynthetic relationships to the abietanes. For example, the taiwaniquinoids have been posited to result from pinacol-type rearrangement of **1.2.4**, as it is related to 6,7-dehydroferruginol (**1.2.5**).[3] Contraction of the central ring from an 5-6 ring fusion to a 5-7 junction lends the nomenclature 5(6→7)*abeo*-abietane and gives the 6-5-6 carbocycle taiwaniquinoid skeleton (**1.2.6**).



Scheme 1.2.1

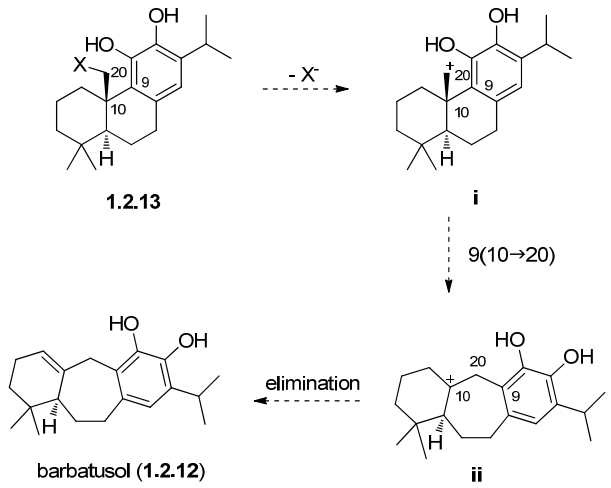
In 1976, icetexone (**1.2.7**) was extracted from the aerial parts of *salvia ballotaflorae* Benth (Labiatae), along with conacytone (**1.2.8**), which had been isolated previously.[4] In their analysis of the structural features of **1.2.7**, Taira, Watson, and Dominguez drew comparisons to several abietane natural products, namely conacytone (**1.2.8**), nemorone (**1.2.9**), and royleanone (**1.2.10**) (Scheme 1.2.2). While they did not propose a biosynthetic pathway, they suggested that icetexone can be derived from **1.2.8** via a loss of hydroxide, which could permit the necessary ring expansion and dehydration to give intermediate compound **1.2.11**, 19-deoxyicetexone.[5] Oxidation of the bridging tetrahydrofuran motif of **1.2.11** generates **1.2.7**, icetexone. The authors also suggested that an oxidative pathway could relate conacytone (**1.2.8**) to nemorone (**1.2.9**). Even further removed, royleanone (**1.2.10**) is related to **1.2.7** in its *p*- hydroxyquinone motif, and



Scheme 1.2.2

could lead to **1.2.9** via a similar oxidative dehydration pathway.

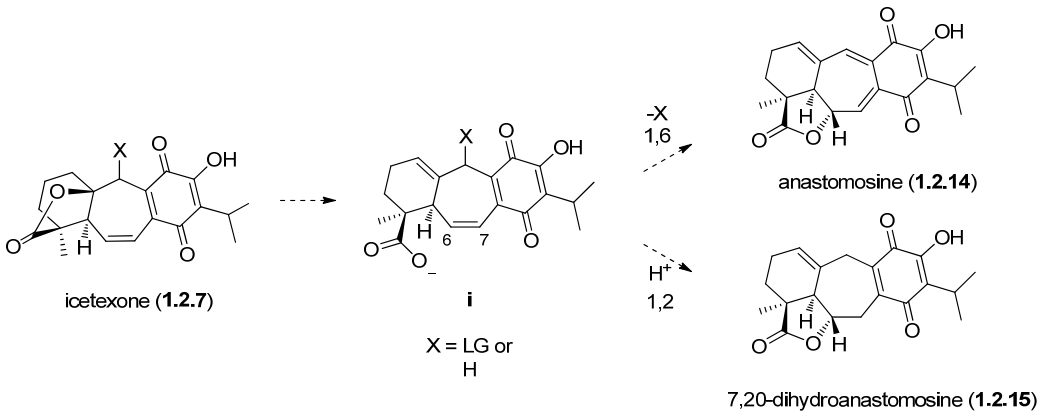
Since icetexanes are classified as 9(10→20)*abeo*-abietanes, they can result from the contraction of the abietane skeleton.[6] Scheme 1.2.3 illustrates a proposed pathway for the biosynthesis of barbatusol (**1.2.12**) in which abietane derivative **1.2.13** undergoes ionization to generate intermediate species **i**.[7] Migration of the C9-C10 sigma bond to form the C9-C20 bond yields **ii**, which, after elimination, gives barbatusol (hence, the name 9(10→20)*abeo*-abietane).



Scheme 1.2.3

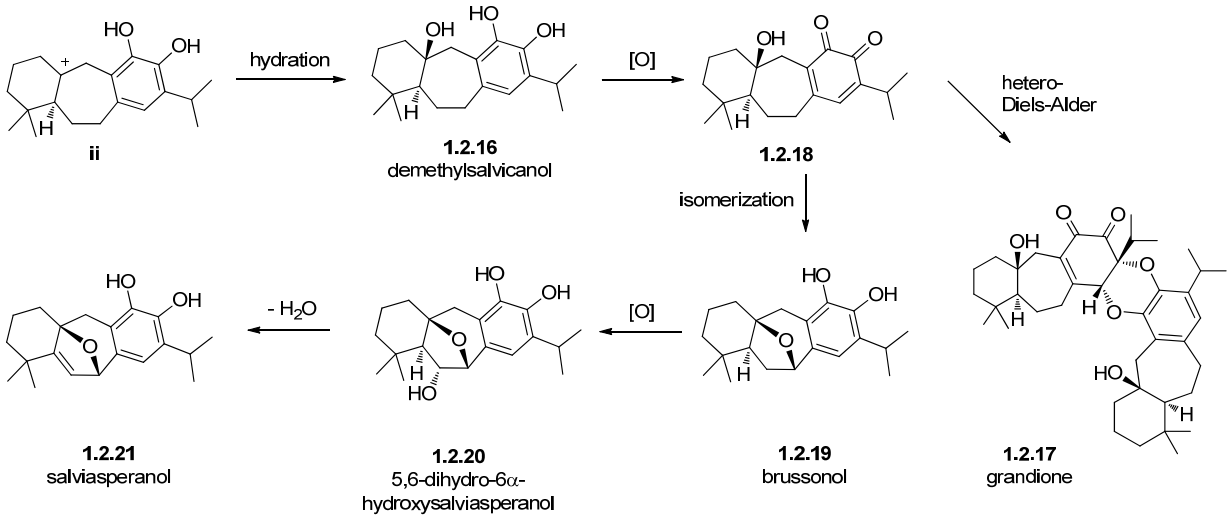
The anastomosines (**1.2.14** and **1.2.15**) have also been linked to icetexone (**1.2.7**) by the mechanism shown in Scheme 1.2.4.[8] Lactone opening generates intermediate species **i** which yields anastomosine (**1.2.14**) upon a 1,6-addition (S_N2'') at C6 with concomitant loss of X. Alternatively, lactonization onto the C6-C7 olefin generates 7,20-dihydroanastomosine (**1.2.15**) directly. It is important to note that **1.2.14** and **1.2.15** have been isolated from the same sample of *Salvia ballotaeflora*.[8a]

Other icetexane natural products have been linked biosynthetically to one another. While barbatusol is likely to result from elimination of carbocation **ii** (Scheme 1.2.5), demethylsalvicanol (**1.2.16**) is produced upon **ii** being trapped. Oxidation to *o*-quinone **1.2.18**,



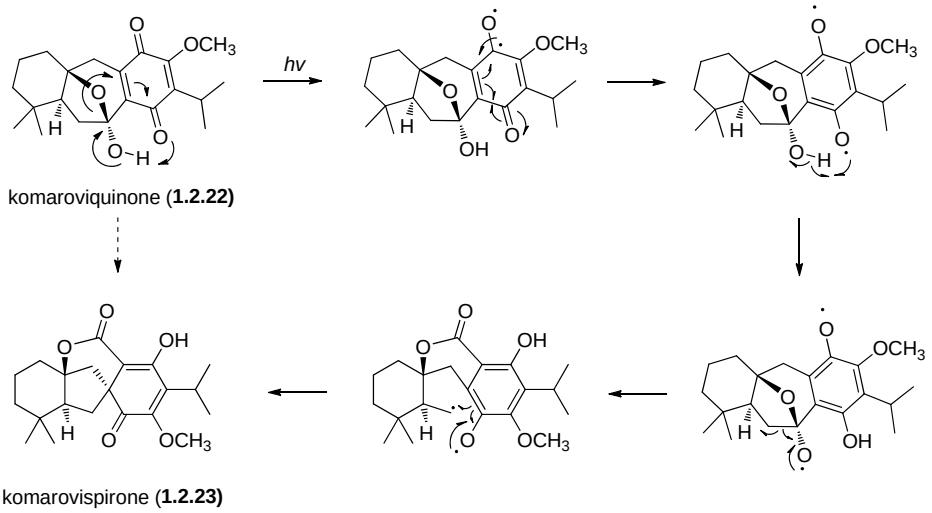
Scheme 1.2.4

followed by a hetero-Diels-Alder reaction yields grandione (**1.2.17**).[7a, 9] Alternatively, brussonol (**1.2.19**), formed by tautomerization and isomerization of **1.2.18**, yields 5,6-dihydro-6α-hydroxysalviasperanol (**1.2.20**) upon further oxidation, which can dehydrate to generate salviasperanol (**1.2.21**).



Scheme 1.2.5

Komaroviquinone (**1.2.22**) was isolated in 2003 and komarovispirone (**1.2.23**) in 2004.[10] In their isolation of **1.2.23**, the authors suggested that its biosynthesis could proceed via isomerization of **1.2.22** to **1.2.23**, according to Scheme 1.2.6. However, Majetich and Yu found that **1.2.23** is generated via a photoisomerization reaction via the radical pathway below. They



Scheme 1.2.6

also posited that, as a result of their findings in the laboratory, komarovispirone is likely an artifact from the isolation of komaroviquinone.[11]

1.3 Isolation

Since the initial discovery of the icetexanes and related natural products, a number of novel 6-7-6 carbocyclic diterpenoids have been isolated. In a comprehensive review on the icetexanes, Simmons and Sarpong noted that, while they have not been given any formal classifications, they can be logically divided into subclasses based on their oxidation states around the carbocyclic 6-7-6 tricyclic core.[12] As such, the major classes are as follows: the pisiferins, barbatusols, coulterones, taxamarins, icetexones and anastomosines, and Diels–Alder adducts of embedded icetexanes. This section will present those classes in a similar manner.

The pisiferins are characterized by a phenol in the C12 position and predominantly have modifications at the A-B ring fusion (Figure 1.3.1). Isolated from the leaves of *Chamaecyparis pisifera* in 1980, pisiferin (**1.3.1**) was the first icetexane of this type, though its structure was originally designated as an 8-6-6 abeo-abietane after **1.3.1** was isolated along with isopisiferin

(**1.3.2**).[13,14] Isolated from the seeds of *C. pisifera* in 1985 were 12-deoxypisiferanol (**1.3.4**), 1β-hydroxypisiferin (**1.3.5**), and pisiferanol (**1.3.3**), which was isolated a decade later from the roots of *Salvia lanigera*.[15] Compound **1.3.6** was isolated by different groups and was given the name pisiferdiol and pisiferadiol, with the absolute configuration determined by X-ray analysis[15-16] In 1999, the leaves of *Chamaecyparis formosensis* yielded O-methylpisiferanol (**1.3.7**) and 1β-hydroxypisiferanol (**1.3.8**). Sawaradienone (**1.3.9**), isolated from the leaves of *C. pisifera* in 2001, is the only member of this class to have an additional site of oxidation at the B-C junction.[17]

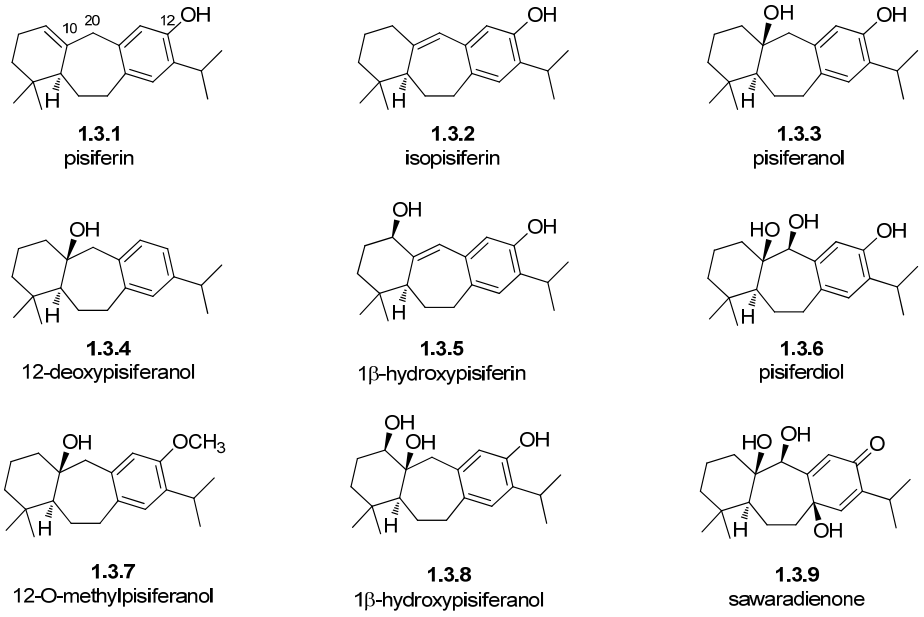


Figure 1.3.1

A second class can be defined by the presence of a catechol-like C-ring, which was first identified in 1983 when barbatusol (**1.2.12**) was isolated from the bark and heartwood of *Coleus barbatus* (Figure 1.3.2).[18] The absolute configuration of **1.2.12** was determined by comparison with carnosol, an abietane with a known configuration. Salvicanol (**1.3.10**) was isolated from both *Salvia canariensis* and *Salvia mellifera* and its structure was established by X-ray crystallography.[19] Related diterpenoids demethylsalvicanol (**1.2.16**) and isosalvicanol (**1.3.11**)

were extracted from *C. barbatus* and *Lepechinia meyeni*, respectively.[20] Grandione (**1.2.17**), a novel icetexane dimer, was isolated from the wood of *Torreya grandis* Fort and synthesized from natural **1.2.16**.[9a] In 1995, salviasperanol (**1.2.20**) and 5,6-dihydro-6α-hydroxysalviasperanol (**1.2.21**) were isolated from *Salvia aspera.*[21] Brussonol (**1.2.19**) was named as such after its isolation from Salvia broussonetii in 2005.[22] In 2005, the Chinese plant *Salvia przewalskii* Maxim yielded przewalskins C (**1.3.12**) and D (**1.3.13**), while **1.3.14** was isolated from *Salvia przewalskii* in 2009.[23]

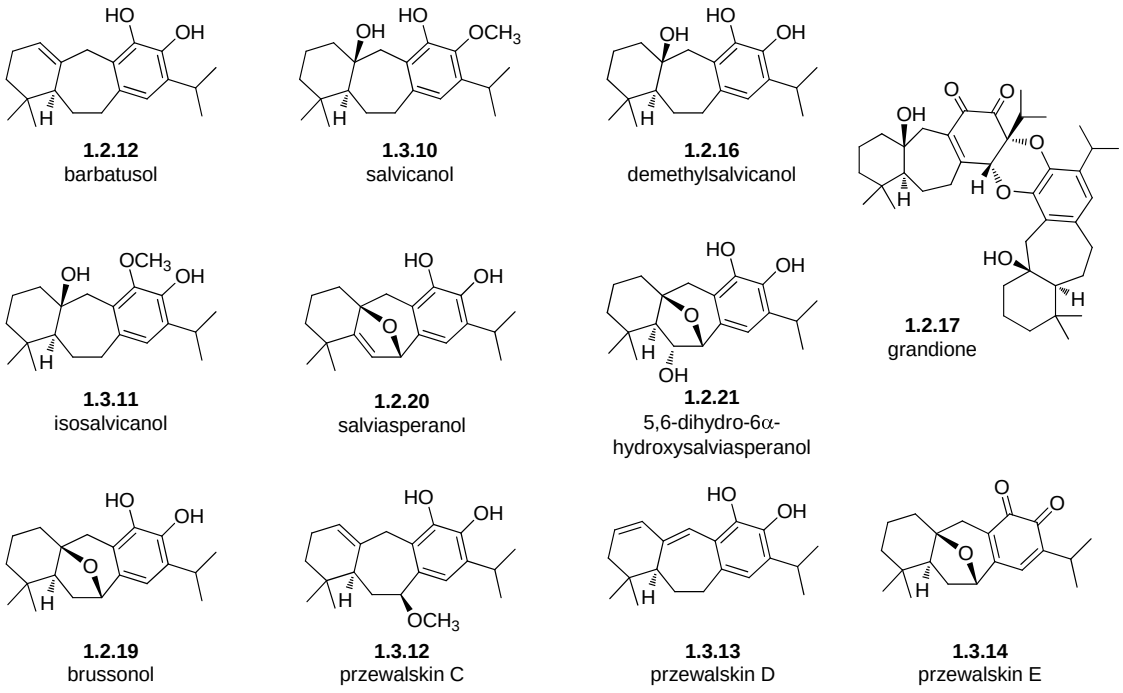


Figure 1.3.2

Coulterone (**1.3.15**), first isolated in 1994 from *Salvia coulteri*, was one of the first compounds isolated that contained an icetexane framework with a fully-oxidized C-ring (Figure 1.3.3).[24] Cyclocoulterone (**1.3.16**) and komaroviquinone (**1.2.22**), an oxidize hemiacetal of coulterone (**1.3.15**), were isolated from *Dracocephalum komarovi* in 2003.[10a] As mentioned above, isomeric komarovispirone has also been isolated from the same plant source.[10b] Both **1.2.22** and **1.2.23** were found to exhibit significant activity against *T. cruzi,* the causitive agent of

Chagas' disease.[10b, 25] Abrotanone (**1.3.17**) was originally misidentified upon its isolated from Perovskia abrotanoides in 2007, but reassigned through synthesis by Simmons, Yen, and Sarpong.[26]

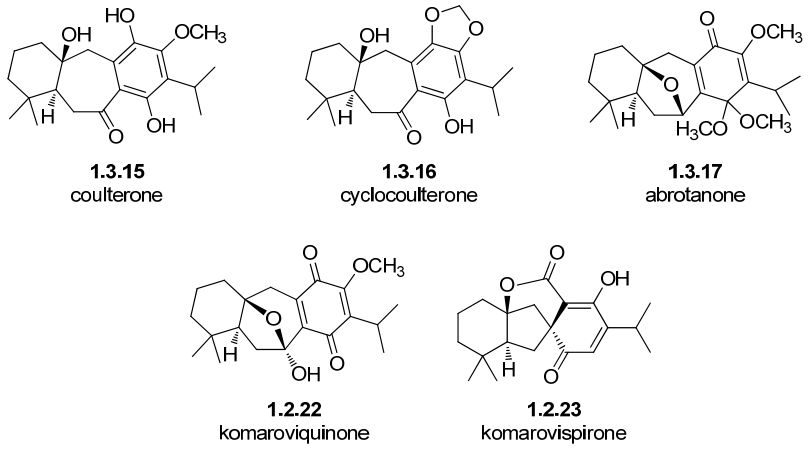


Figure 1.3.3

In 1976, icetexone (**1.2.7**) was the first 9(10→20)*abeo*-abietane to be isolated and members of this class are characterized by either an ether or lactone linkage resulting from an additional oxygenation of the C19 position (Figure 1.3.4).[4a] Extracted from the aerial parts of *Salvia ballotaeflora* Benth, **1.2.7** was found with romulogarzone (**1.3.18**), its *o*-quinone tautomer. The structure of icetexone was elucidated by X-ray analysis and its IR spectrum,

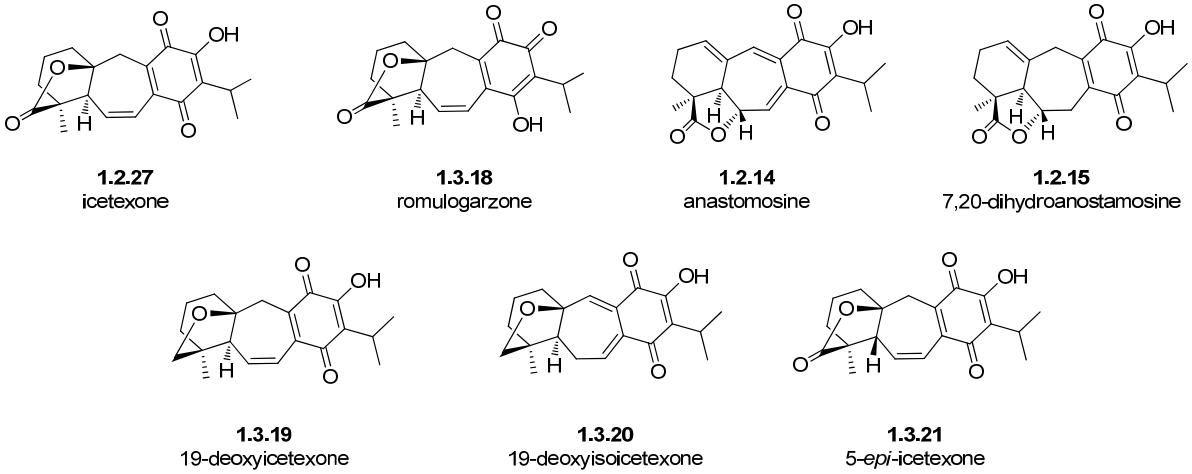


Figure 1.3.4

melting points analysis, and optical rotation data were reported. However, as mentioned in Section 1.14, these data have been reassigned for **1.2.27**, as well as for 5-*epi*-icetexone (**1.3.21**). Mentioned above, anasomosines **1.2.14** and **1.2.15** were isolated from *Salvia anastomosans* and *Salvia ballotaeflora,* respectively.[8] Also isolated from *S. ballotaeflora* were 19-deoxyicetexone (**1.3.19**) and 19-deoxyisoicetexone (**1.3.20**), which contains an ether linkage from C19 to C10.[8a] 5-*epi*-Icetexone (**1.3.21**) was found in the aerial parts of *Salvia gilliessi* Benth and its absolute stereochemistry was assigned based on comparison of both spectral data and optical rotation data as compared with icetexone (**1.2.27**).[27] Sections 1.13 and 1.14 will outline our efforts toward the synthesis of **1.2.27**, **1.3.19**, and **1.3.21**, as well as the reassignment of the physical data associated with icetexone and 5-*epi*-cetexone.

The taxamairins contain the same catechol-like substitution in the C-ring as barbatusol, while they differ greatly in their oxidation patterns and degrees of unsaturation (Figure 1.3.5). The first of this group that were isolated were taxamairins A (**1.3.22**) and B (**1.3.23**), from *Taxus*

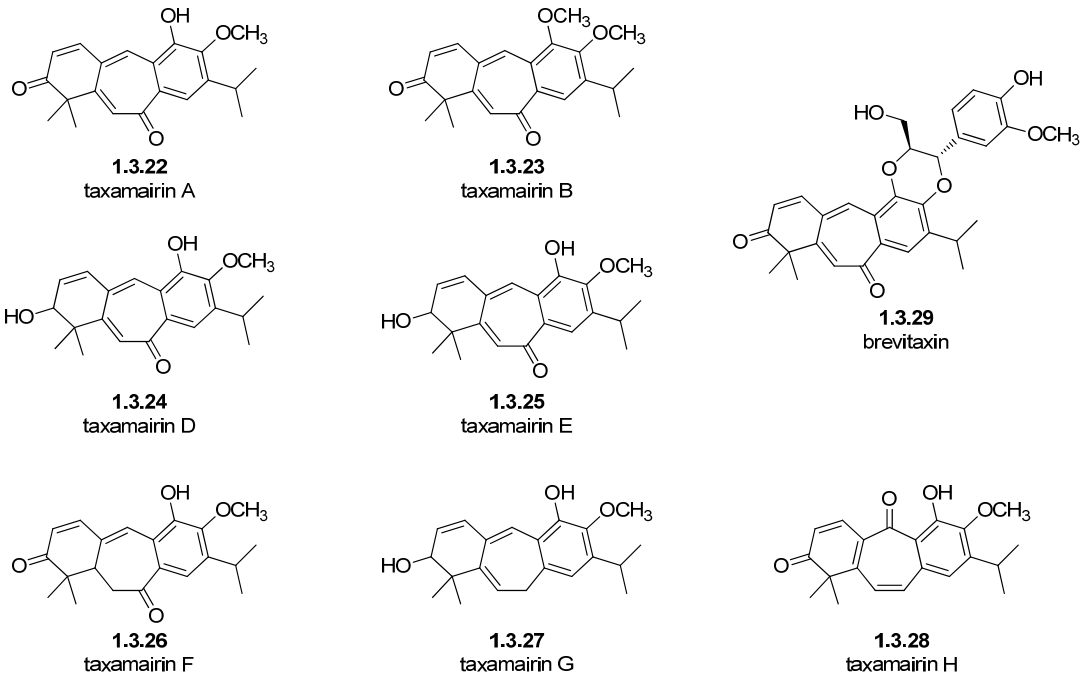


Figure 1.3.5

mairei, which also produces Taxol.[28] Taxamairins D-H (**1.3.24**-**1.3.28**) were isolated from the same source and brevitaxin (**1.3.29**), a derivative of **1.3.22**, has been extracted from *Taxus brevifolia*.[29]

Additionally, several structurally-complex natural products have been isolated that contain salient features of the icetexane skeleton (Figure **1.3.6**). Perovskone (**1.3.29**) was isolated from the whole plant of *Perovskia abrotanoides* in 1992 and X-ray chrystallography determined its absolute structure.[30] This was the first natural product of this type and Ahmad et al. posited that perovskone formed by the addition of geranylphosphate to *p*-quinone **1.3.30**. Peradione (**1.3.31**), having a similar framework, was isolated from the same source in 1993 and its structure was determined via extensive spectroscopic studies.[31] A biosynthesis was also proposed for peradione, again originating from the addition of **1.3.32** to **1.3.30**. In 1999, Ahmad and co-workers also isolated salvadiol (**1.3.33**) from *Salvia bucharica* and its structure was elucidated by means of X-ray diffraction.[32] The authors posited that icetexane **1.3.30** could undergo a Diels–Alder-type addition with **1.3.34**, derived from myrcene, which could produce salvadiol. That same year, Ahmad also reported the isolation of salvadiones A (**1.3.35**) and B (**1.3.36**) from

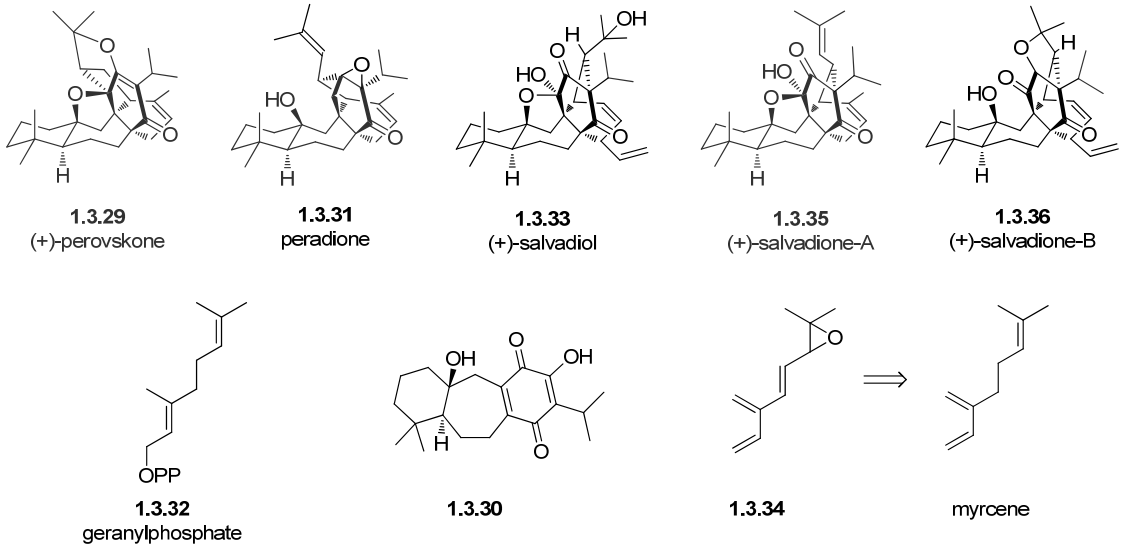


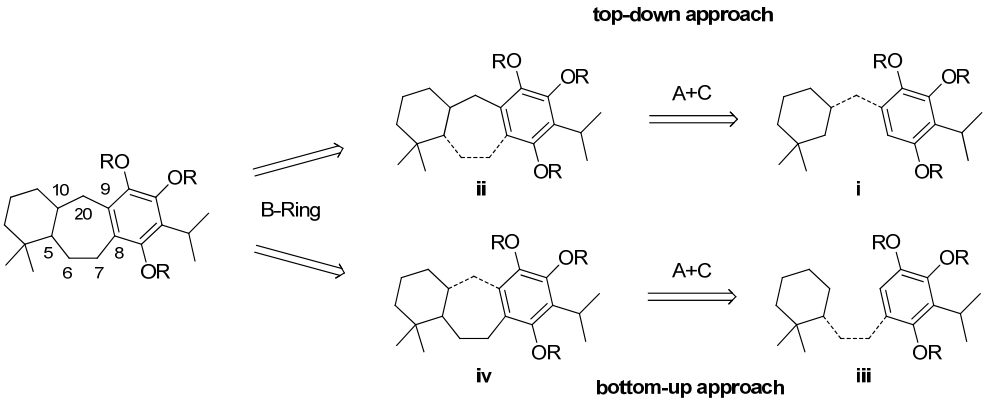
Figure 1.3.6

S. bucharia.[33] Majetich and co-workers have developed a research program directed toward the total synthesis of these and related icetexane-based natural products, which has resulted in the synthesis of **1.3.29**, **1.3.35**, and **1.3.36**.[34,35] In 2006, Maeir achieved a formal synthesis of **1.3.29** by way of an alternate route to key a benzoquinone in the Majetich approach.[34c]

1.4 General Synthetic Approaches to the Icetexanes

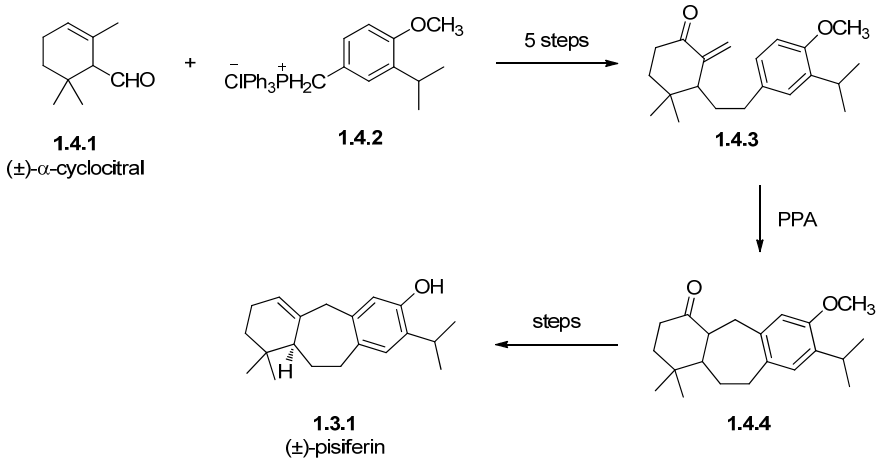
Due to their unique benzannulated cycloheptatriene and cycloheptadiene cores and their widely-varied stereochemical and functional group features, the icetexanes and related systems have been the focus of many research programs over the last few decades.[12] As shown in the preceding section, the oxidation states around the icetexane skeleton and unique heterocyclic linkages make these compounds challenging synthetic targets. This section will give a brief overview of the two key synthetic strategies common to most syntheses of these compounds. Namely, construction of their tricyclic core frequently involves coupling the A- and C-ring fragments, followed by another C–C bond forming reaction to forge the central ring. This section summarizes the efficiency of the various strategies employed for the synthesis of icetexanes and is not intended to be a comprehensive list of the syntheses of icetexane natural products.

A logical strategy for the construction of the icetexane framework would result from an A + C → ABC strategy (Scheme 1.4.1). There are several reasons for this practical approach: (1) a scarcity of methods for efficiently forming seven-membered carbocyles, especially benzannulated cases; (2) the high reactivity of the oxygenated arene subunit toward nucleophilic attack and their synthesis with pre-functionalization and protection; and (3) the rational use of either a cyclohexanone or cyclohexenone ring as a versatile A-ring analogue. These factors have influenced numerous synthetic approaches, most of which have employed either a top-down



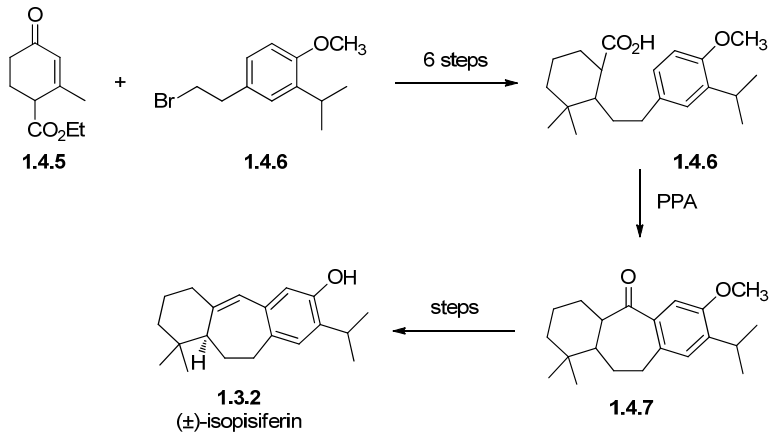
Scheme 1.4.1

approach, in which the C10-C20-C9 (**i**) bonds are formed with the appropriate functionality to allow the "bottom" C5-to-C8 (**ii**) bonds to be formed. Conversely, a bottom-up approach can be use which first forges the bottom portion of the central ring, which is allows for the subsequent ring closure via the "up" approach (**iii** to **iv**). These two approaches will be discussed both chronologically and with respect to individual research groups' approaches. It must be noted that a number of elegant approaches have been reported for the rapid construction of the icetexane nucleus that do not rely on either a top-down or a bottom-up approach. Since more of the synthetic approaches to the icetexanes and related natural products employ a bottom-up approach, these precedents will be discussed first.



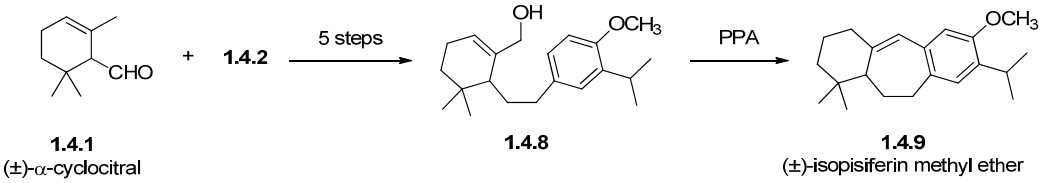
Scheme 1.4.2

In 1986, Matusmoto employed the versatile synthon (±)-α-cyclocitral (**1.4.1**) which, when coupled with aryl phosphonium **1.4.2**, forges the C6-C7 bond (Scheme 1.4,2.[36] Next, conversion to cyclization precursor **1.4.3** and treatment with PPA affords tricycle **1.4.4** upon Michael addition of the electron rich arene. This strategy yields racemic pisiferin in a few steps.



Scheme 1.4.3

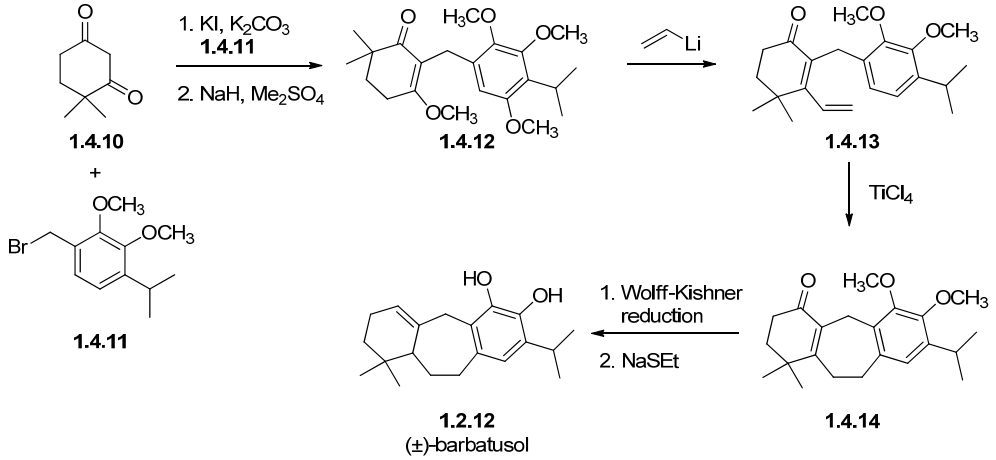
Ghatak employed another synthetically-useful starting material, Hagemann's ester (**1.4.5**), which undergoes regioselective alkylation with **1.4.6** and affords adduct **1.4.7** after additional manipulations (Scheme 1.4.3).[37] Carboxylic acid **1.4.8** undergoes an intramolecular Friedel-Crafts acylation to yield **1.4.7**, an intermediate in their synthesis of (±)-isopisiferin.



Scheme 1.4.4

Pan used an approach similar to Masumoto, starting with **1.4.1** and **1.4.2** to generate allylic alcohol **1.4.8** and form the southern part of the forthcoming tricycle (Scheme 1.4.4).[38] Friedel–Crafts alkylation delivers racemic isopisiferin methyl ether (**1.4.9**), again relying on the

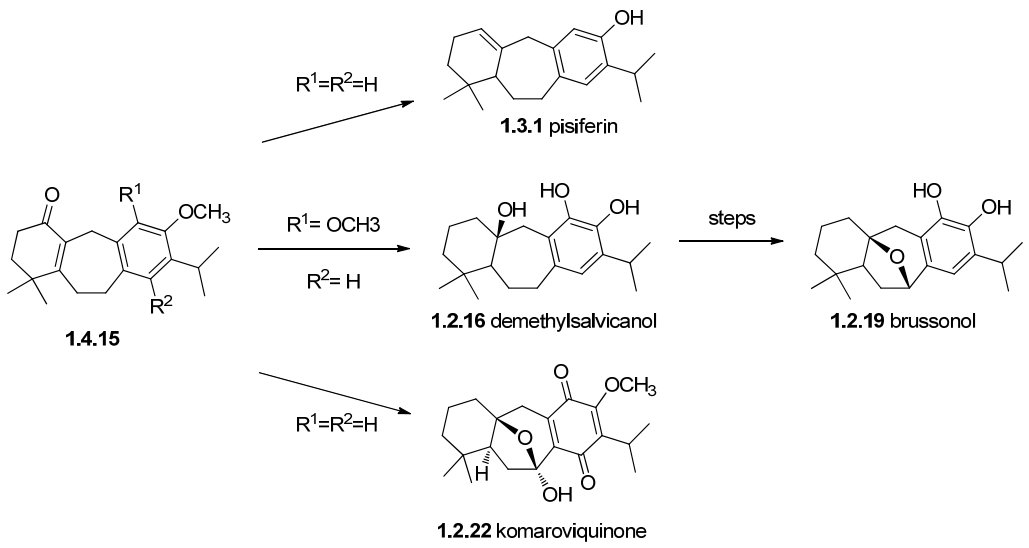
inherent nucleophilicity of the methoxyarene. This approach was also utilized in Pan's 1996 synthesis of (±)-barbatusol methyl ether.[39]



Scheme 1.4.5

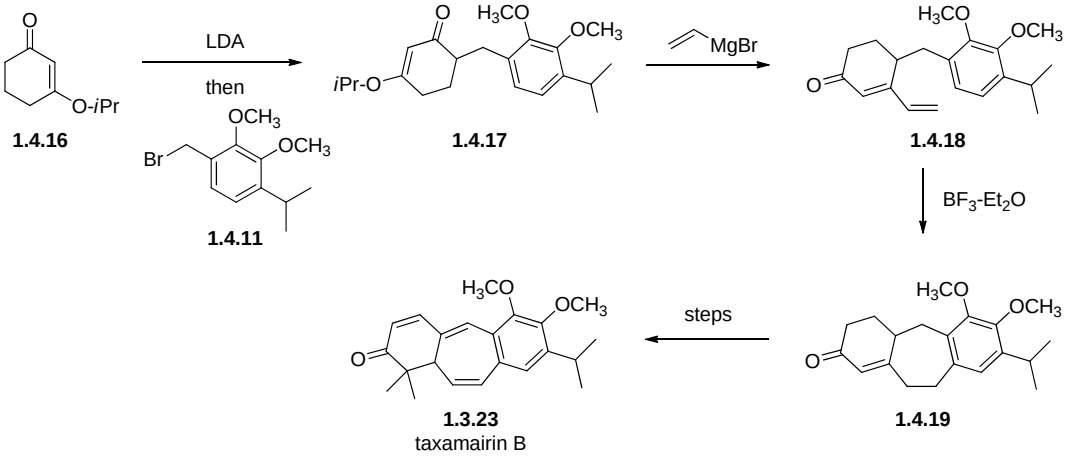
Majetich's 1993 synthesis of (±)-barbatusol, an anti-hypertensive, was the first example of the synthesis of an icetexane skeleton using a top-down approach (Scheme 1.4.5).[40] Alkylation of 6,6-dimethyl-1,3-cyclohexadione (**1.4.10**) with bromide **1.4.11** gave the monoalkylated dione, which was trapped as methyl enol ether **1.4.12**. Subsequent 1,2-addition of vinyllithium gave dienone **1.4.13**, which underwent the expected cyclialkylation, due to activation of the conjugated dienone motif and the presence of an electron rich aromatic ring. Deprotection of the aryl methyl ethers produced barbatusol (**1.2.12**).

A top-down approach has been used by Majetich and co-workers in the total syntheses of numerous interesting natural products, four of which are shown in Figure 1.4.6. Enone **1.4.15** has the key framework and is constructed by the same top-down approach with slight variations on the substitution pattern on the aromatic ring. For example, **1.3.1** was prepared in four steps from enone **1.4.15** where R^1=R^2=H.[41] The asymmetric syntheses of demethylsalvicanol (**1.2.16**) and brussonol (**1.2.19**) were achieved using a veratrole-derived C-ring.[42] This approach permitted a racemic synthesis of komaroviquinone (**1.2.22**).[43]



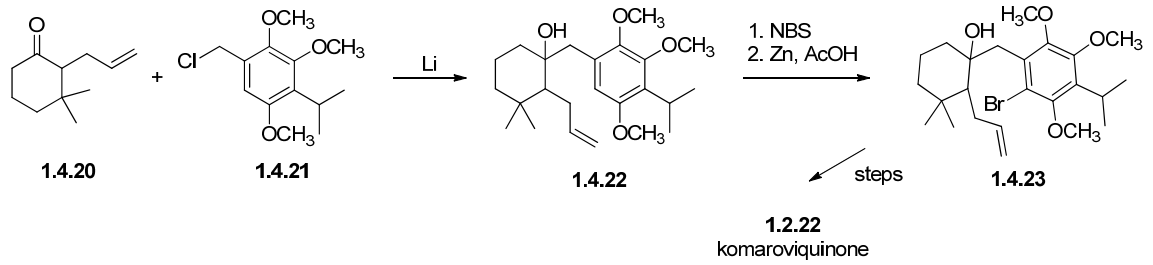
Scheme 1.4.6

In 1995, Pan took a different approach from his synthesis of isopisiferin methyl ether, completing the only synthesis of a taxamairin to date (Scheme 1.4.7).[44] Using a top-down approach, alkylation of 1,3-cyclohexadione derivative **1.4.16** with benzyl bromide **1.4.11** assembled the C10-C20 bond in **1.4.17**. Similar to Majetich's approach, construction of cyclialkylation precursor **1.4.18** and cyclization gives **1.4.19** and further oxidation of the A- and C-rings gives taxamairin B (**1.3.23**).



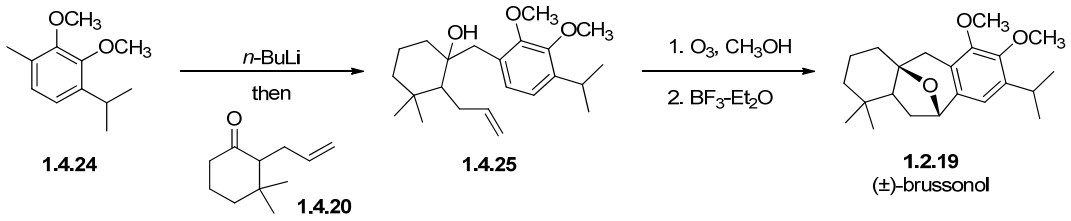
Scheme 1.4.7

Banerjee's racemic synthesis of komaroviquinone (**1.2.22**) used cyclohexanone **1.4.20**, derived from Hagemann's ester (Scheme 1.4.8).[45] Benzyl chloride **1.4.21** undergoes metal-halogen exchange to add in 1,2 fashion to **1.4.20** to give **1.4.22**. Aromatic bromination with NBS is facile due to the electron donating nature of the trimethoxy-substituted C-ring, giving **1.4.23** in two-steps. An intramolecular Heck reaction and oxidation gives (±)-komaroviquinone (**1.2.22**).



Scheme 1.4.8

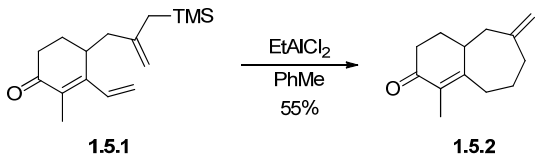
In their synthesis of (±)-brussonol, Martinez-Solorio and Jennings used arene **1.4.24** and **1.4.20** to construct a cyclization precursor, tertiary alcohol **1.4.25** (Scheme 1.4.9).[46] Ozonolysis yields an intermediate ketal and Lewis-acid activation readily forms (±)-brussonol (**1.2.19**). This approach features a versatile cyclic A-ring and an electron-rich C-ring to form the key bonds in the construction of this icetexane natural product.



Scheme 1.4.9

1.5 Majetich Group Synthetic Approach

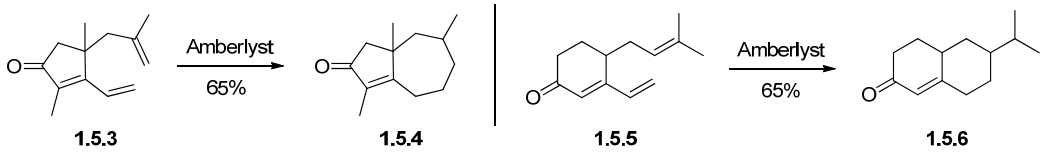
In 1985, Majetich and co-workers reported a novel annulation strategy that provided access to fused cycloheptane rings via a intramolecular 1,6-addition of an allylsilane to a conjugated dienone catalyzed by Lewis acid (Scheme 1.5.1).[47]



1.5.1 **1.5.2**

Scheme 1.5.1

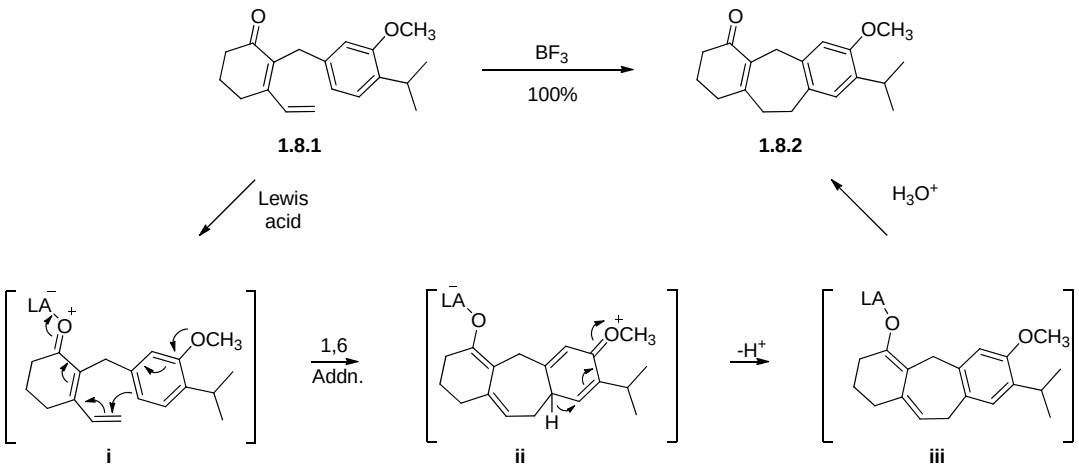
In 1990, Majetich and Khetani extended this strategy to the intramolecular 1,6-addition of unactivated alkenes to conjugated dienones under Lewis-acid activation (Scheme 1.5.1).[48]



1.5.3 **1.5.4** **1.5.5** **1.5.6**

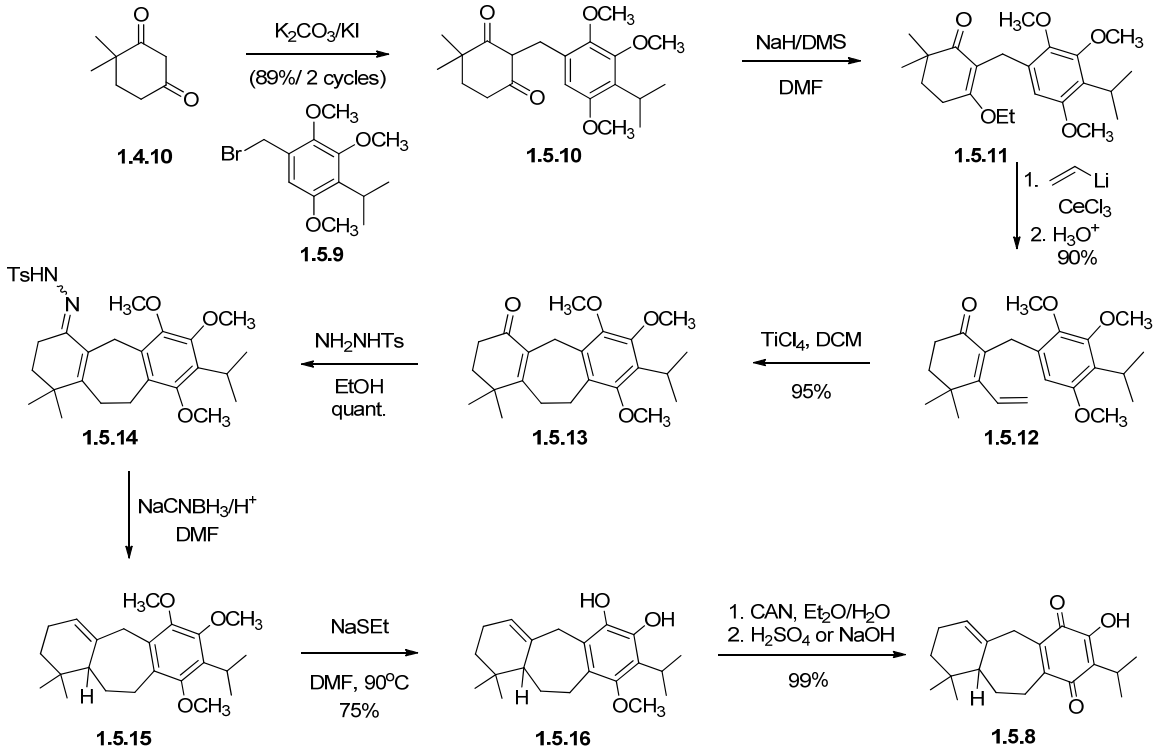
Scheme 1.5.2

A logical extension of this observed reactivity was realized in 1993 when the Majetich group investigated the intramolecular Friedel–Crafts alkylation, or cyclialkylation, reaction (Figure 1.5.3).[49] It was found that arenes tethered to 3-vinyl cyclohexenones (**1.5.7**) underwent smooth cyclialkylation to afford a central cyclohepatane ring (**1.5.8**). Additionally, the electronic properties and directing effects dictate the reaction pathway. Mechanistic studies demonstrated that Lewis-acid activation of the dienone motif of **i** permits the electrophilic addition of the arene moiety *para* to the methoxy group, which stabilizes the intermediate species **ii**. Aromaticity is then re-established (**iii**) through deprotonation and acidic workup yields the more stable tricyclic enone **1.5.7**.



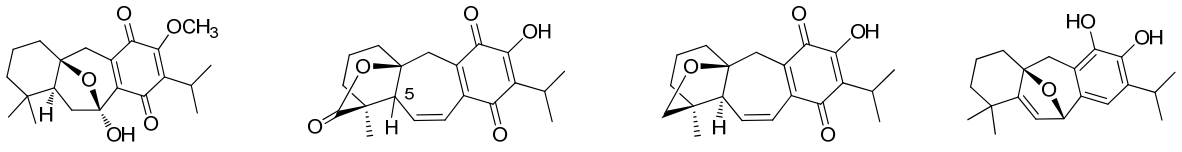
Scheme 1.5.3

Majetich and co-workers have applied this novel annulations method for the synthesis of several complex natural products containing a 6-7-6 tricyclic nucleus, including the hydroxy-*p*-benzoquinone nucleus of (±)-perovskone (**1.5.8**, Figure 1.5.4).[34a] Alkylation of 6,6-dimethyl-1,3-cyclohexanedione (**1.4.10**) with C-ring precursor, benzyl bromide **1.5.9**, yielded coupled dione **1.5.10** in excellent yield after two submissions. Regioselective enol ether formation with dimethylsulfate in the presence of K_2CO_3 afforded **1.5.11**, which is treated with a vinyl anion equivalent to give cyclialkylation precursor **1.5.12**. Cyclization with $TiCl_4$ at low temperature gave key enone **1.5.13** in excellent yield. Next, a modified Wolff–Kishner reaction, which yields a rearranged alkene in the case of α,β-unsaturated ketones, was employed (see Section 1.12). Formation and reduction of tosylhydrazone **1.5.14** with sodium cyanoborohydride in an acidic medium yielded rearranged C1-C10 olefin **1.5.15**. Next, removal of the two most accessible aryl methyl ether groups under standard conditions yields catechol **1.5.16**, which is oxidized to the corresponding *o*-quinone and isomerized to *p*-quinone **1.5.8** in good overall yield.



Scheme 1.5.4

More recently, we have become increasingly interested in members of the icetexane family having greater functional group complexity (Figure 1.5.1), such as komarovoquinone (**1.2.22**), 5-*epi*-icetexone (**1.3.21**), icetexone (**1.2.27**), 19-deoxyicetexone (**1.3.19**), and salviasperanol (**1.2.21**). When we began, no synthetic efforts had been reported toward the total synthesis of any of these interesting natural products. Thus, we were eager to explore a modified Friedel–Crafts approach for the top-down assembly of the carbocyclic framework of these natural products.



1.2.22
komaroviquinone

1.2.27 icetexone, 5β
1.3.21 5-*epi*-icetexone, 5α

1.3.19
19-deoxyicetexone

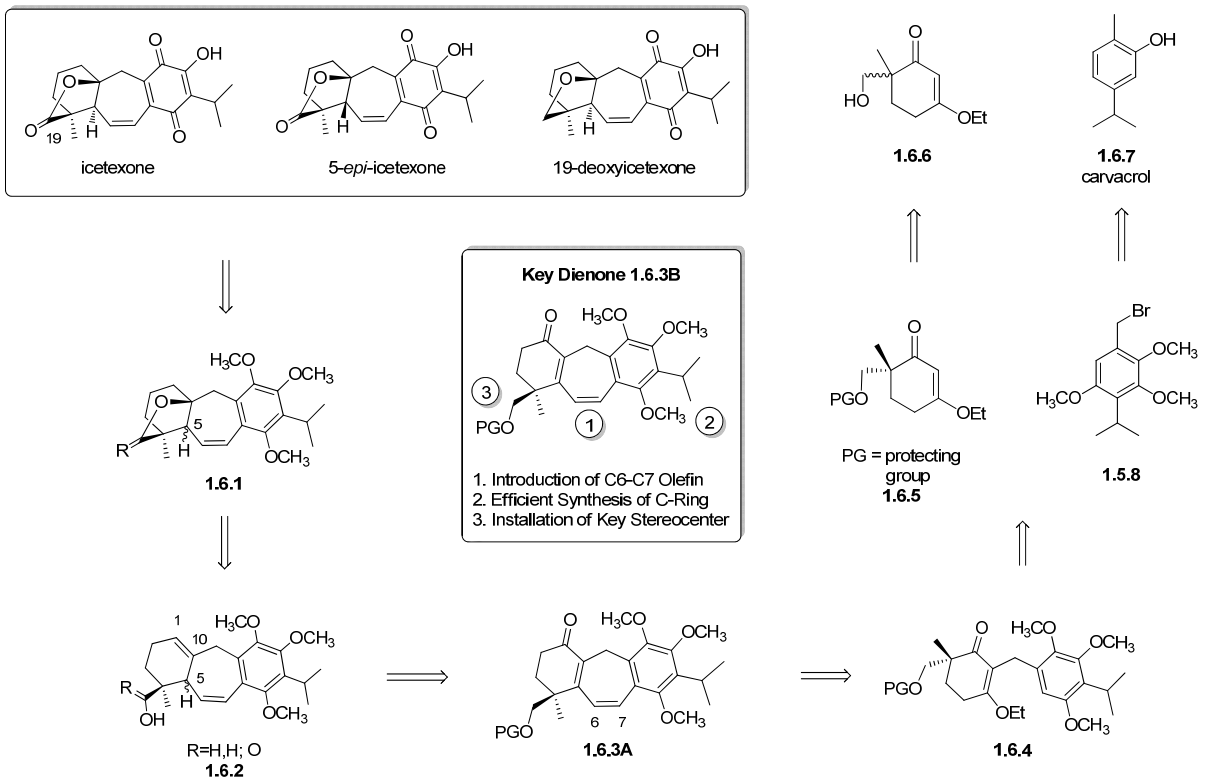
1.2.21
salviasperanol

Figure 1.5.1

1.6 Synthetic Strategy for the Icetexones

At the beginning of our studies toward **1.2.27**, **1.3.21**, and **1.3.19**, several obstacles were identified, as outlined in Scheme 1.6.1. Our retrosynthetic plan features an A + C → ABC coupling strategy and possible methods for installation of the C5-stereocenter, though a number of additional new structural features were encountered.

First, since the hydroxy-*p*-benzoquinone motif can be derived from the corresponding methoxy-protected arene (see Scheme 1.5.4), we envisioned accessing the target natural products via the appropriate C5 epimer of tris-ether **1.6.1**. The lactone and furan groups of **1.6.1** would be installed via cyclization of the acid or alcohol precursor (**1.6.2**) onto the more reactive C1-C10 olefin. Asymmetric introduction of the C5 stereocenter would be possible for the two epimeric centers via a Wolff–Kishner-like reduction of **1.6.2** under either chelation-controlled or Felkin–



Scheme 1.6.1

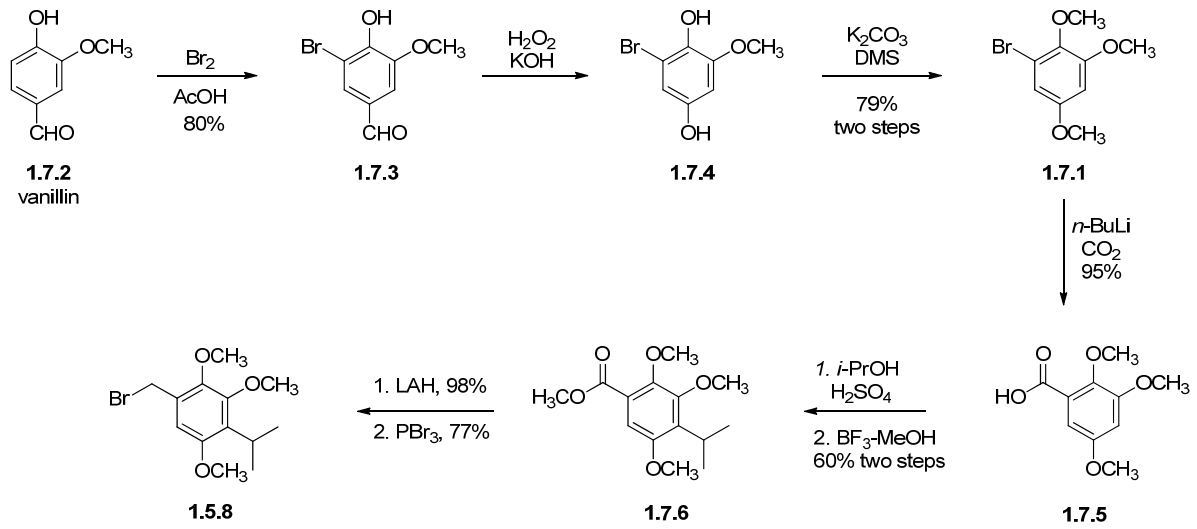
Ahn conditions. Key dienone **1.6.3A** would be accessed via a modified Friedel–Crafts cyclialkylation strategy from coupled **1.6.4**. Compound **1.6.4** would result from coupling a protected optically-active A-ring (**1.6.5**), available via a known enzymatic resolution protocol from **1.6.6**, and our C-ring benzyl bromide 1.5.8, which we envisioned could be prepared via a more efficient route from carvacrol (**1.6.7**).

There are three major synthetic challenges that must be addressed, represented by key dienone **1.6.3B** (Scheme 1.6.1). First, since our cyclialkylation route only permitted access to a saturated C6-C7 central ring (1), either a modification to the enone scaffold to an olefin or modified cyclialkylation strategy had to be realized (*cf.* Scheme 1.5.4). Secondly, a shorter and more economical route to C-ring benzyl bromide (2) was essential to the success of a total synthesis of the icetexones. Thirdly, and most importantly for an asymmetric approach, the requisite stereochemistry at the C4 position of the A-ring (3) needed to be installed with complete stereocontrol, as it both provides access to the optically pure natural products and controls the C5 stereochemistry. We realized that these challenges would be central to the completion of these and related syntheses.

1.7 Previous Methods and New Method for Preparation of C-Ring Precursor

As mentioned in Section 1.4, the construction of the icetexane skeleton typically involves an A + C → ABC strategy. Benzyl bromide **1.5.8** was the ideal C-ring for all of the target molecules involved in this study.[11, 34a, b] This section will outline the previous methods employed for the preparation of **1.5.8**.

In their 1994 synthesis of (±)-perovskone, Majetich and Zhang viewed 1-bromo-2,3,5-trimethoxybenzene (**1.7.1**) as an appropriate precursor to **1.5.8**, as it was readily available from

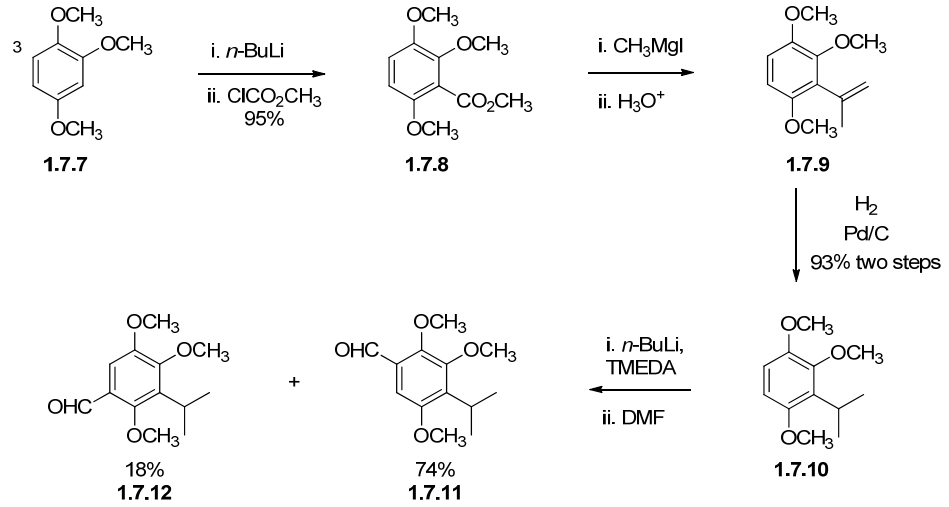


Scheme 1.7.1

vanillin (**1.7.2**) in three steps.[34a] In particular, bromination of vanillin using molecular bromine gave **1.7.3**. Dorn, Warren, and Bullock showed that vanillin underwent smooth Baeyer–Villiger oxidation to give an expected phenol, an approach that was applied to **1.7.3** to give *bis*-phenol **1.7.4**.[50] *Tris*-ether **1.7.1** was formed upon treating **1.7.4** with dimethylsulfate in the presence of K_2CO_3. Transmetallation of **1.7.1** followed by a CO_2 quench produced benzoic acid **1.7.5**. Introduction of the isopropyl moiety was achieved via an acid-catalyzed Friedel–Crafts alkylation to give **1.7.6** after esterification and methylation of a phenolic group, since the Friedel–Crafts reaction also liberated one of the aryl methyl ethers. Standard LAH reduction of**1.7.6** followed by converting the resulting benzyl alcohol to its corresponding benzyl bromide **1.5.8** proceeded smoothly to provide **1.5.8** in good overall yield in eight steps from inexpensive and readily-available vanillin. While this sequence was suitable for large scale and provide sufficient amounts of **1.5.8**, we sought more concise alternative routes.

As part of his Master's degree from the University of Georgia in 2002, John Britton developed an alternative route to bromide **1.5.8** from commercially-available 1,2,4-trimethoxybenzene (**1.7.7**).[51a] Deprotonation of **1.7.7** with *n*-butyllithium occurs at the 3-position,

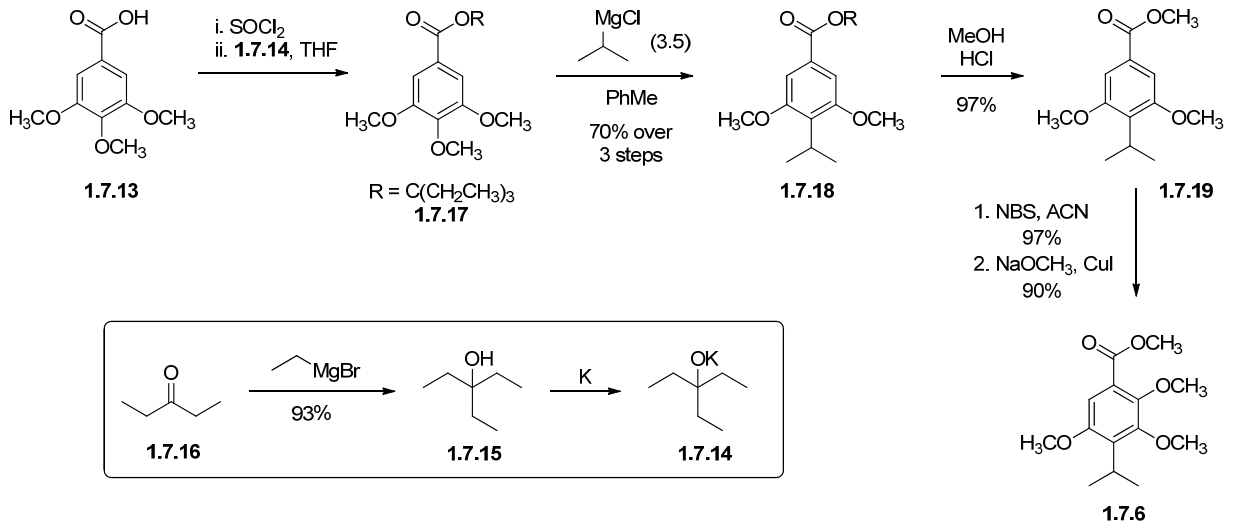
the anion of which is then trapped with methylchloroformate to give ester **1.7.8** in excellent yield.[51b] A two-step functional group interconversion of the ester to an isopropyl unit is achieved by first treating **1.7.8** with excess methylmagnesium chloride to give an alcohol, which is then dehydrated under acidic conditions. Hydrogenation effectively reduces **1.7.9** to give **1.7.10**. When **1.7.10** is treated with *n*-BuLi in the presence of TMEDA and quenched with DMF, a mixture of aldehydes **1.7.11** and **1.7.12** is generated. Though high-yielding, this step involves extensive chromatographic purification due to the low polarity of the two regioisomeric products. Standard reduction and bromination of **1.7.11** gives bromide **1.5.8** in good yield as per Scheme 1.7.1. The major drawback of this route is the extensive purification and the cost of 1,2,4-trimethoxybenzene (**1.7.7**).[52]



Scheme 1.7.2

Our group's efforts toward the synthesis of komaroviquinone (**1.2.22**) were also hampered by inadequacy in the previous routes toward bromide **1.5.8**.[43, 53] Thus, as a part of his doctoral research, Ge Zou developed a third generation route to address this issue.[54] Scheme 1.7.3 illustrated this alternative preparation for key benzyl bromide **1.5.8**. Readily-available gallic-acid derivative **1.7.13** was converted to its corresponding acid-chloride with thionyl

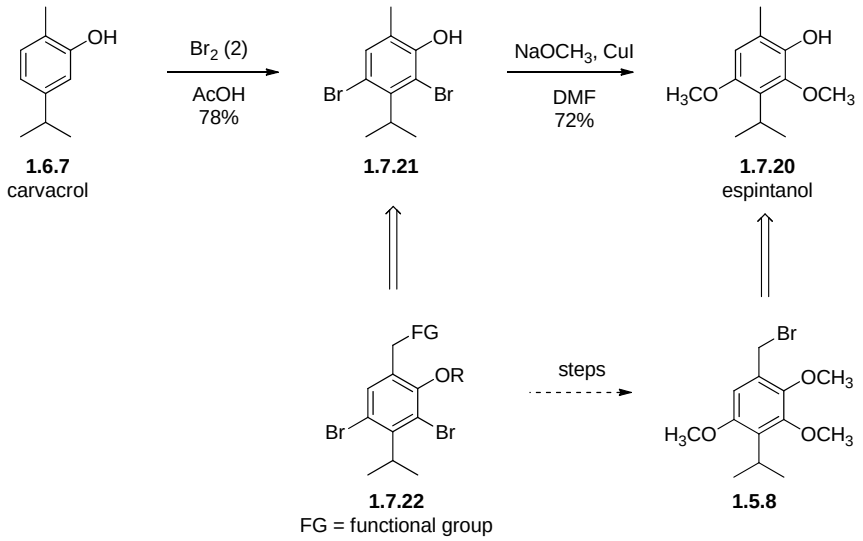
chloride, which is then treated with the potassium alkoxide of 3-ethyl-3-pentanol (**1.7.14**). Alcohol **1.7.15** can be prepared efficiently through a Grignard reaction between 3-pentanone (**1.7.16**) and ethylmagnesium bromide.[55]



Scheme 1.7.3

Preparing the subsequent bulky ester (**1.7.17**) served to hinder attack at the ester functionality in the next step. Rather than undergoing carbonyl addition at the ester, it has been shown that treating **1.7.17** with a three-fold excess of isopropylmagnesium chloride in toluene at 0 °C gave *p*-isopropyl derivative **1.7.18** in good yield as a results of nucleophilic aromatic substitution.[56] Acidic methanolysis of **1.7.18** gave methyl ester **1.7.19** and regrettably triethyl carbinol **1.7.15** could not be recovered under the liberation conditions. We next focused on a frequently-employed two-step procedure to convert an activated aromatic position to a methoxy substituent.[57] First, **1.7.19** underwent bromination with NBS, which was then subjected to a nucleophilic aromatic displacement reaction with sodium methoxide in the presence of a cuprous catalyst to yield **1.7.6**. While this seven-step procedure route had advantages over previous ones, it was hampered by overall length, sensitivity of reagents toward anhydrous conditions, and the need for chromatographic purification.

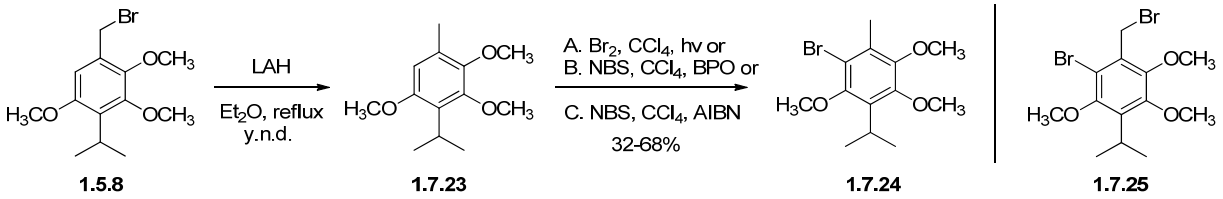
With our research into komaroviquinone, the icetexones, as well as more complex icetexane-embedded natural products (*cf.* Figure 1.3.6), a shorter and more scalable route to **1.5.8** was required. Starting from carvacrol (**1.6.7**), which already contained the isopropyl unit, a *para*-oriented benzylic carbon atom that could be appropriately functionalized, and a phenol unit that could be converted to one of the three requisite methoxy groups (Scheme 1.7.4). This route benefitted from Söderberg and Fields' synthesis of espintanol (**1.7.20**) from carvacrol, as well as access of carvacrol through acid-catalyzed isomerization of carvone by Kjonaas and Mattingly.[58] Espintanol (**1.7.20**), first isolated from the extracts of the spruce tree *Oxandra espintana* in 1991, shows in vitro leishmandicidal and trypanosomal activity, but is only obtained in small quantities from the natural source.[59] In 1996, Söderberg and Fields devised a concise synthesis of the espintanol (Scheme 1.7.4).[58a] Dibromination of carvacrol was straightforward, giving dibromide **1.7.21** in 78% yield after purification. A Cu(I)-catalyzed nucelophilic substitution onto **1.7.21** was accomplished using 11 equiv. of $NaOCH_3$ in a CH_3OH:DMF mixed solvent system at 70 °C. This gave espintanol in 72% yield in only two steps from readily-available carvacrol. Two previous routes to **1.7.20** have been reported, a nine step synthesis by Hocquemiller and co-



Scheme 1.7.4

workers with a 2% overall yield, and a seven step route resulting in an 11% overall yield.[59-60]

Scheme 1.7.4 also represents our retrosynthetic plan to prepare **1.5.8** through this inspired route. From known **1.7.20**, protection of the phenol as the aryl methyl ether, followed by benzylic bromination would afford our target in four short steps from carvacrol. Alternatively, protection of an earlier known intermediate (**1.7.21**) and functionalization of the benzylic position would generate dibromide **1.7.22**. Compound **1.7.22** could undergo the aforementioned Cu(I)-mediated nucleophilic aromatic substitution reaction to generate the desired bromide. The latter route, however, suffers from a longer reaction sequence. We were confident, though, that a similar strategy would provide us with a shorter and more efficient route to our C-ring precursor.



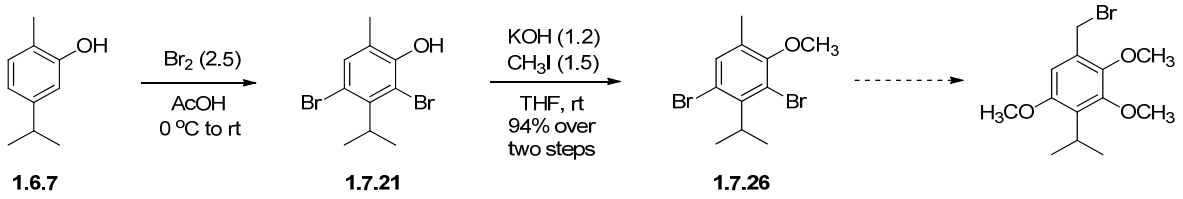
1.5.8 **1.7.23** **1.7.24** **1.7.25**

Scheme 1.7.5

Our first attempt toward this route was approached by intersecting a late-stage derivative in Söderberg and Fields' synthesis, namely **1.7.23**. Reduction of bromide **1.5.8**, which was available to us via our third-generation route with LAH in refluxing ether generates 2-isopropyl-1,3,4-trimethoxy-5-methylbenzene (**1.7.23**) as the major product.[61] We were hopeful that bromination under free-radical conditions would generate **1.5.8** directly. However, under standard condition for benzylic bromination, poor to moderate yields of aryl bromide **1.7.24** were observed. It has recently been observed, though, that modest yields of dibromide **1.7.25** can be obtained through a two-step sequence from **1.7.23**.[62] It was clear that the electronic effects resulting from the three electron donating groups in this substrate results in substitution on the

aromatic ring; thus, intersecting an earlier intermediate in the espintanol synthesis, namely dibromide **1.7.21**, would preempt this problem.

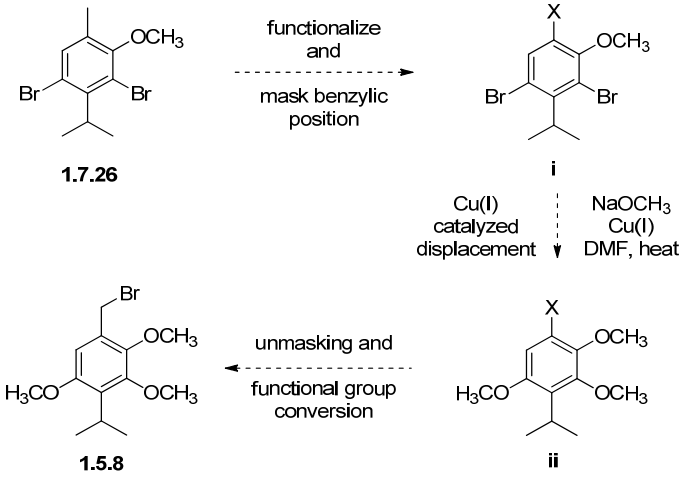
Söderberg and Fields' synthesis begins with carvacrol (**1.6.7**), a natural product that is readily available from many members of the *Origanum* species, commonly types of thyme, oregano, and marjoram, in varying amounts. Shown in Scheme 1.7.4, carvacrol can also be obtained in nearly quantitative yield by acid-catalyzed isomerization of carvone.[58b] We found that the bromination of carvacrol with molecular bromine in acetic acid and can be performed on a large scale (≤ 200g) without a noticeable loss of yield and with comparable reaction time. Extraction of the reaction mixture with petroleum ether allows for easy removal of excess acetic acid to give consistently high yields of dibromide **1.7.21**. Next, protection of the remaining phenol as the aryl methyl ether was accomplished under standard conditions, using KOH in THF with excess iodomethane at room temperature. Using potassium carbonate as the base required heating, which frequently gave significant amounts of an uncharacterized, possible polymeric, byproduct. Dibromide **1.7.26** could be obtained in 94% yield from carvacrol and purified by distillation under reduced pressure.



Scheme 1.7.6

Since *tris*-oxygenated arene **1.7.23** gave only aromatic bromination, we postulated that proceeding through dibromide **1.7.26** would represent a more promising pathway. We recognize that just as Söderberg and Fields used a Cu(I)-catalyzed double-displacement sequence with excess $NaOCH_3$ in DMF at elevated temperatures, our sequence would proceed similarly and

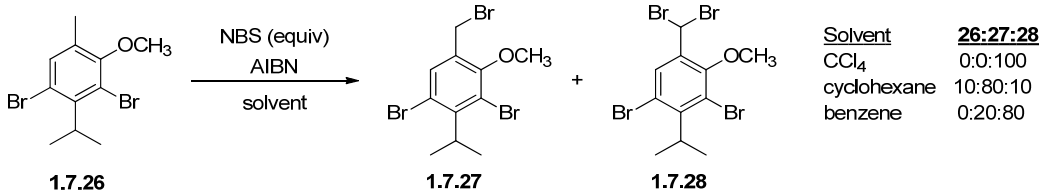
would require the appropriate functional group compatibility (Scheme 1.7.7). More specifically, benzylic oxidation of **1.7.26** to give intermediate **i** would need to be compatible with the aforementioned displacement conditions to give **ii** and permit subsequent conversion to desired bromide **1.5.8**. We realized that these criteria would be met if X corresponded to an alcohol or carbonyl-containing group.



Scheme 1.7.7

Our initial attempts at the functionalization of the methyl group of **1.7.26** to a benzylic alcohol, aldehyde, or carboxylic acid using SeO_2, $KMnO_4$, and Jones reagent resulted in recovered starting material. Since benzylic bromination had eluded us in electron-rich intermediates (Scheme 1.7.5) we decided to evaluate the same reaction conditions on an electron-poor aromatic system. Indeed, treating dibromoether **1.7.26** with a slight excess of NBS in the presence of a radical initiator (either benzoyl peroxide or AIBN) in CCl_4 resulted in only monobenzylic bromination and substitution on the aromatic ring was not observed. Temperature and the number of equivalents of NBS were the major factors affecting this selectivity, though solvent effects played the most significant role. Scheme **1.7.8** illustrates the selectivity that was observed under given conditions. Using refluxing CCl_4 as the reaction solvent resulted in greater

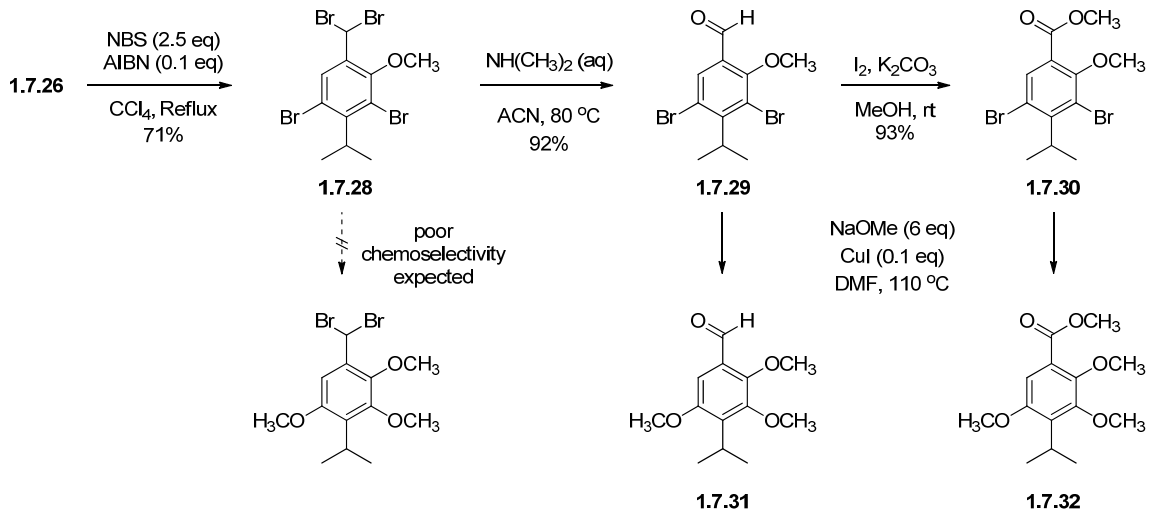
conversion to tetrabromide **1.7.28**, independent of the radical source. When 1.5 equivalents of NBS were used, an equimolar ratio of *mono*- and *bis*-bromides was produced, while 2.5 equivalents led to complete conversion to **1.7.28** in 71% yield. Changing the solvent to cyclohexane, another common solvent when benzylic bromination is desired, resulted in greater tunability. Treating **1.7.26** with 1.5 equivalent of NBS and a catalytic amount of AIBN in dry cyclohexane at 80 °C resulted in 80% conversion to **1.7.27**, with 10% of both starting material and tetrabromide **1.7.28**, as determined by ^{1}H NMR. These results were optimal for the given reaction, though significant effort was directed toward achieving complete selectivity. The yield for this reaction was not determined, since all three components were inseparable by chromatography. It must be noted that when benzene is employed as the reaction solvent with 2.5 equivalents of NBS, *bis*-bromination is the major pathway, thus providing an alternative method for the preparation of **1.7.28**.



1.7.26 **1.7.27** **1.7.28**

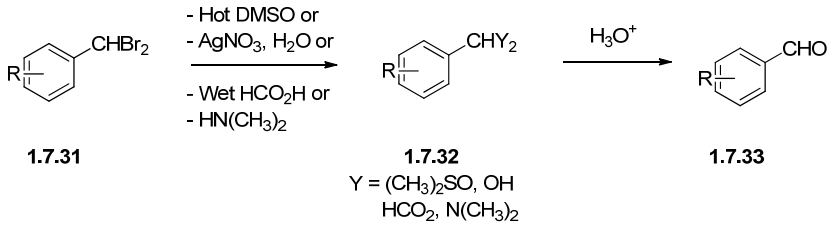
Scheme 1.7.8

Since *bis*-benzylic bromination of **1.7.26** was more straightforward and **1.7.26** and **1.7.27** were excluded from the final product, we first focused on a strategy that included this intermediate, the results of which are summarized in Scheme 1.7.9. Though not evaluated, we believed that subjecting **1.7.28** to nucleophilic aromatic substitution with Cu(I) methoxide would likely lead to undesirable results; therefore, transforming **1.7.28** to a more compatible functional group was necessary. Thus, we next focused on transforming benzal-dihalide **1.7.28** to an appropriate carbonyl-containing arene (*i.e.* **1.7.29** or **1.7.30**).



Scheme 1.7.9

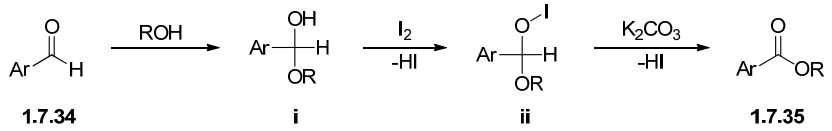
Benzyl dihalides (**1.7.31**) can be converted to benzaldehydes using hot DMSO, aqueous $AgNO_3$, or aqueous formic acid (Scheme 1.7.10).[63] All of these methods involve double-displacement of the benzylic halides to provide intermediate **1.7.32**, which acts as a masked



Scheme 1.7.10

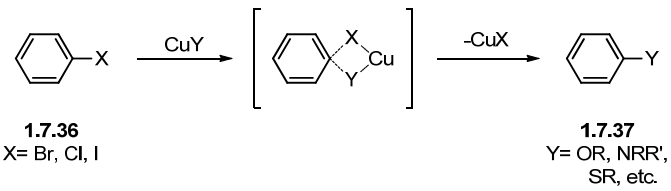
Unfortunately, heating **1.7.28** in DMSO or wet HCO_2H gave mixed results and the cost and environmental repercussions of using $AgNO_3$ dissuaded us from its use (Scheme 1.7.28). In contrast, an excellent method by Bankston was reported in which a variety of benzylic dibromides can be treated with aqueous dimethylamine in ACN:H_2O to give aldehyde **1.7.29** upon an acidic workup. We found that heating **1.7.28** in acetonitrile with excess dimethylamine afforded dibromoaldehyde **1.7.29** in 92% yield after chromatography. Due to the volatility of dimethylamine, additional portions of this reagent were often required when the reaction ceased to progress, as conversion to the *bis*-dimethylamino product could be monitored by TLC.

Although we were interested in the key step, converting the aryl dibromide portion of **1.7.28** to the corresponding dimethoxy derivative **1.7.31**, we were also interested in the reactivity of ester **1.7.30** (Scheme 1.7.9). While a slew of traditional synthetic methods are available for the one- or two-step conversion of aldehydes to esters, we were motivated by an iodine-based oxidation to give **1.7.30** directly. McDonald and co-workers demonstrated that treating aromatic or aliphatic aldehydes with NIS in the presence of an alcohol results in the formation of the corresponding alkyl ester.[64] Mori and Togo showed that I_2 in the presence of K_2CO_3 and an alcohol achieved the same transformation.[65] The mechanism for this mild reaction involves hemiacetal formation of aldehyde **1.7.34** with the alcohol to give **i**, which is oxidized to ester **1.7.35** through hypoiodite **ii** (Scheme 1.7.11). Indeed, aldehyde **1.7.29** is smoothly converted to its corresponding methyl ester in an excellent 93% yield under these conditions (Scheme **1.7.9**).



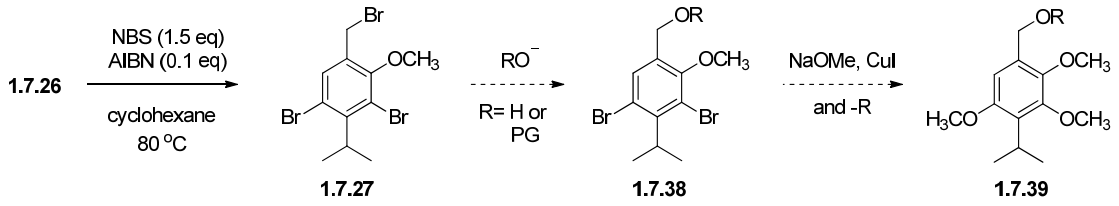
Scheme 1.7.11

With the two carbonyl-containing dibromides **1.7.29** and **1.7.30** in hand, we next turned our attention to the key aryl displacement reactions, as demonstrated in Scheme 1.7.9. Conversion of aryl bromides, chlorides, and iodides (**1.7.36**) to their corresponding aryl alkyl ethers (**1.7.37**) can be achieved using a Cu(I) catalyst in the presence of the desired sodium alkoxide (Scheme 1.7.12).[57c] This reaction has been well studied and the mechanistic considerations show that a moderately strong nucleophile is delivered through the polarization of the ArX-bond by Cu-heteroatom transition state (**i**).



Scheme 1.7.12

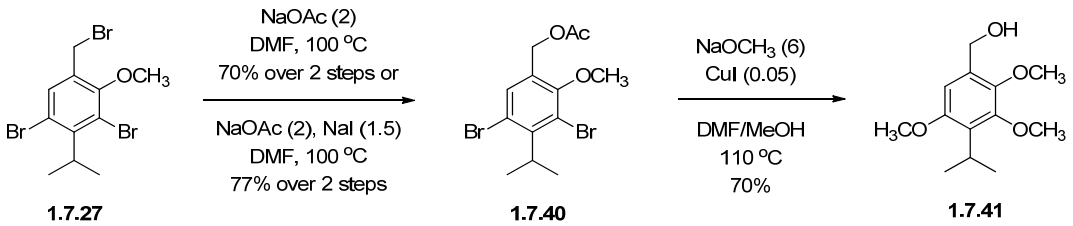
In a typical procedure, a 1.0 *M* solution of $NaOCH_3$, 3 equivalents per each aryl halide group, freshly-prepared by the addition of Na metal to methanol, was added to a room temperature DMF solution of either aldehyde **1.7.29** or methyl ester **1.7.30** in the presence of a 0.05% CuI. The resulting solution was heated to 110 °C under an inert atmosphere until TLC analysis indicated complete consumption of the starting dibromide, which typically required 12-16 hours. All attempts to optimize the reaction conditions to convert **1.7.29** to **1.7.31** or **1.7.30** to **1.7.31** were met with low yields. Since proceeding through either the aldehyde or the methyl ester required a longer reaction sequence to introduce those functional groups, a shorter reaction sequence to benzyl bromide **1.5.8** was highly desirable. We again revisited an earlier reaction to hopefully permit easier access to our target.



Scheme 1.7.13

As shown in Scheme 1.7.13, bromination of **1.7.26** with NBS in refluxing cyclohexane resulted in clean 80% conversion to tribromide **1.7.27**. While this selectivity was not optimal, we recognized that benzylic species **1.7.38** would be orthogonal in the nucleophilic aromatic substitution reaction that was central to our overall scheme (see Scheme 1.7.13). Copper-catalyzed substitution would give **1.7.39**, which gives bromide **1.5.8** using known conditions.

Attempts to access benzylic alcohol **1.7.38** directly with KOH or NaOH under a variety of conditions were unsuccessful (Scheme 1.7.14). However, displacement with sodium acetate in hot DMF gave acetate, which we viewed as a protected benzylic alcohol that would be unmasked in the copper-catalyzed substitution. This displacement step benefited from its nonreactivity toward the unsubstituted **1.7.26**, which could theoretically be recovered during purification. However, this reaction suffered from slow conversion and relatively low yield. Nonetheless, acetate was prepared in 70% overall yield from dibromide **1.7.26**. This reaction was improved to a 77% yield when a solution of sodium iodide in acetone is added to the reaction mixture before heating for 4 hours, presumably generating a more reactive benzyl iodide *in situ*.[66]



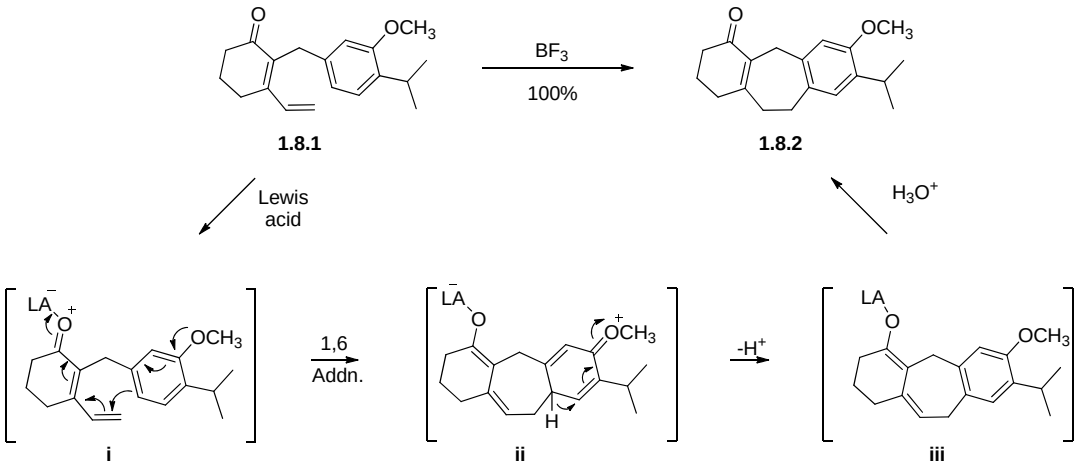
Scheme 1.7.14

Next, application of the aforementioned displacement step using 3 equivalents of $NaOCH_3$ for each aryl bromide with catalytic CuI, conversion of acetate **1.7.40** to *tris*-ether alcohol **1.7.41** was relatively straightforward. Methanolysis of the acetate group was monitored by TLC analysis and subsequent conversion affords **1.7.41** in a variable 65-70% yield. Chromatography of alcohol **1.7.41** gives material that can be converted to bromide **1.5.8** in excellent yield using PBr_3 in Et_2O at 0 °C.

In summary, we developed a six-step synthesis of our C-ring precursor starting from inexpensive carvone in which only two chromatographic separations were needed and the overall yield is 44%. This represents our best method of the different routes for the preparation of bromide **1.5.8**.

1.8 Previous Methods and Novel Method for Introducing the C6-C7 Olefin

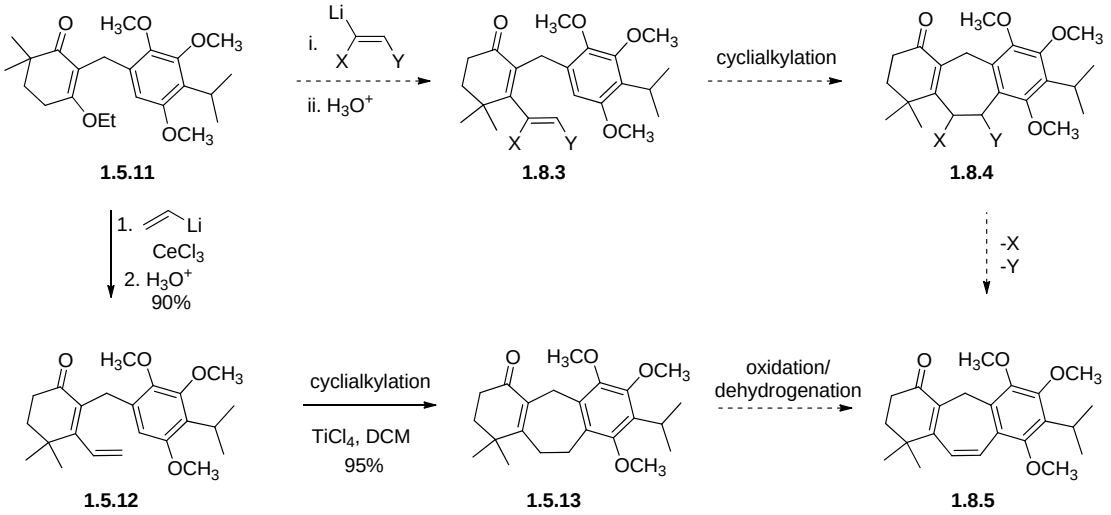
In 1993, Majetich and co-workers introduced a Friedel–Crafts cyclialkylation strategy for the construction of the 6-7-6 tricyclic icetexane nucleus, as outlined in Section 1.5.[49] When we began our synthetic efforts toward the icetexones, no work had been directed toward accessing the icetexane skeletons that contain either functionality or unsaturation at the C6-C7 positions in the central ring. Thus, accessing icetexone (**1.2.27**), 5-*epi*-icetexone (**1.3.21**), 19-deoxyicetexone (**1.3.19**) required that we somehow introduce an olefin at the C6-C7 position. This task was also required for the assembly of the core of (+)-komaroviquinone (**1.2.22**) and (–)-salviasperanol (**1.2.21**).



Scheme 1.8.1

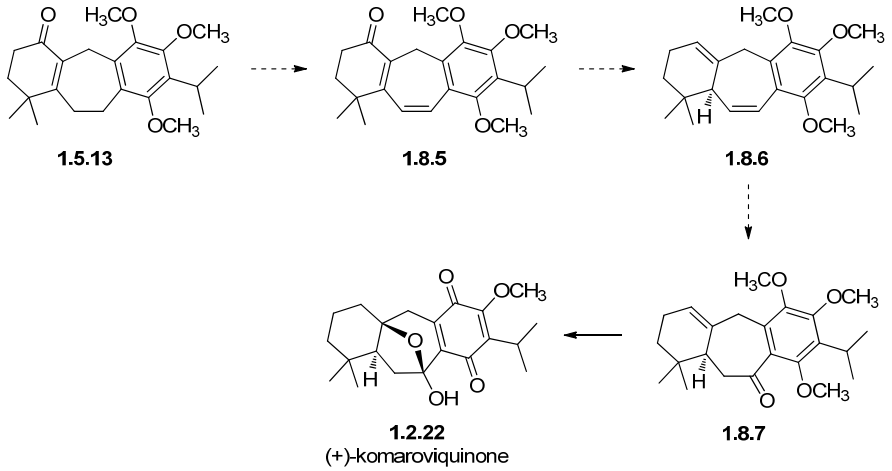
Scheme 1.8.1 illustrates the key step in the Majetich approach to the 6-7-6 tricyclic core of the icetexanes and related natural products. Once again, the electronic nature of the arene portion of dienone **1.8.1** dictates the course of the cyclization. Greater electron density at the C8 position through the presence of methoxy groups at its *ortho* and *para* positions increases the propensity of the substrate for intramolecular alkylation, or 1,6-addition. Mechanistically, Lewis acid activation of the dienone moiety (**i**) occurs with concomitant intramolecular attack of the

arene group, which leads to stabilized intermediate **ii**. Aromaticity is regained though proton transfer (**iii**), and tautomerization results in the formation of tricycle **1.8.2**.



Scheme 1.8.2

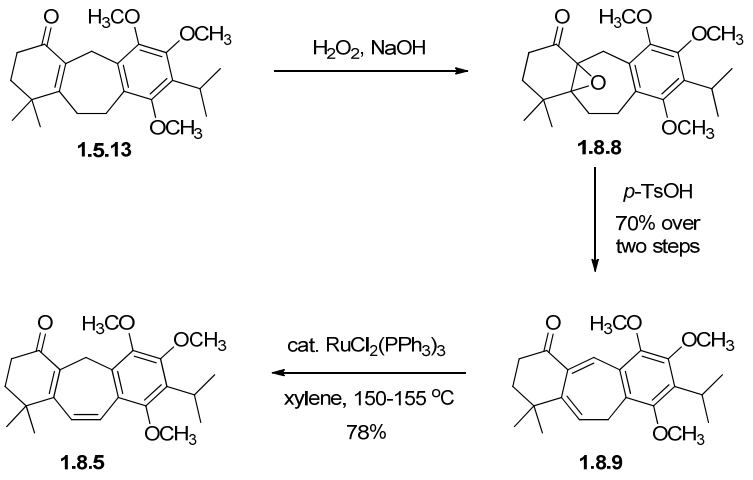
Several approaches were investigated to access the desired benzocycloheptadiene core (Scheme 1.8.2), but few were realized. Two main strategies can be envisioned: oxidation of cyclized enone **1.5.13** to give dienone **1.8.5** directly, and modification of the cyclialkylation precursor (**1.8.3**) to yield the desired dienone either directly upon ring closure or after an additional transformation. This section will summarize all of these strategies.



Scheme 1.8.3

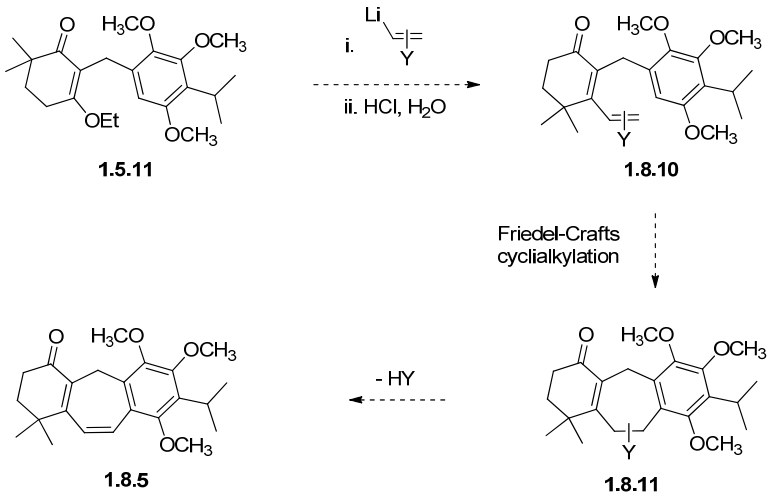
During his studies which culminated in the total synthesis of (±)-komaroviquinone (**1.2.22**), Yang Li investigated an asymmetric route to the natural product in which dienone **1.8.5** was the key intermediate and would result from oxidation of key enone **1.5.13**.[67] Compound **1.8.5** could be subjected to a known two-step procedure to give optically-active asymmetric diene **1.8.6**. Due to different electronic nature of the two olefins, diene **1.8.6** could be converted to benzylic ketone **1.8.7** using three known steps. Hydration of the C1-C10 double bond, followed by intramolecular hemiacetal formation of the C7 ketone would yield (+)-komaroviquinone. Several oxidation protocols were explored to convert **1.5.13** to **1.8.5**, such as benzylic oxidation with SeO_2 and treatment with Br_2 or NBS, followed by basic elimination. Unfortunately, these conditions resulted in either no reaction or gave undesired byproducts.

Rather than attempting to functionalize the C7 position, we explored an alternative perspective by manipulation the enone portion of **1.5.13**. Exposing **1.5.13** to 30% aqueous hydrogen peroxide in the presence of base for 72 hours resulted in clean epoxidation of the C5-C10 tetrasubstituted alkene. Epoxyketone **1.8.8** subsequently underwent a double-dehydration with *p*-TsOH acid to give diene **1.8.9**. Isomerization of diene **1.8.9** to the more stable dienone**1.8.5** was



Scheme 1.8.4

not obtained under acid or basic conditions, was cleanly produced upon exposure to Wilkinson's catalyst in refluxing xylene. While this approach was adequate for exploratory studies related to komaroviquinone, an alternative strategy was desirable, preferably one requiring fewer synthetic transformation and providing higher chemical yields.

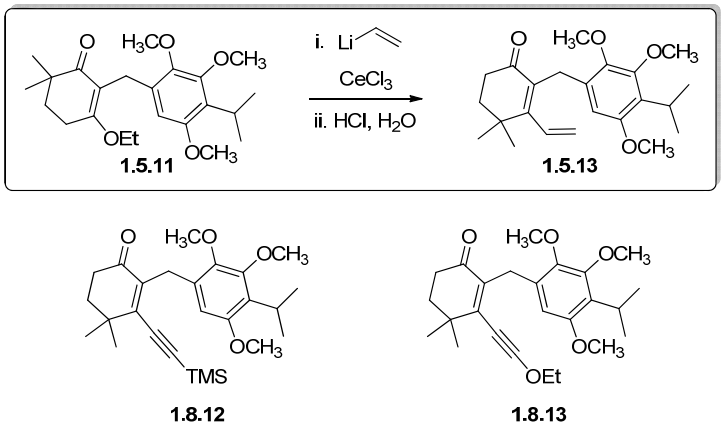


Scheme 1.8.5

The next approach that was explored was a modified Friedel–Crafts annulation strategy, as depicted in Scheme 1.8.5, in which a cyclization precursor (**1.8.10**) would be prepared with a functional group present at either the γ or δ position; ring closure under Lewis acid catalysis to give **1.8.11**, and subsequent loss of the additional functional group, would generate **1.8.5**. The work presented in Schemes 1.8.5 through 1.8.8 represent the work conducted by Yang Li.

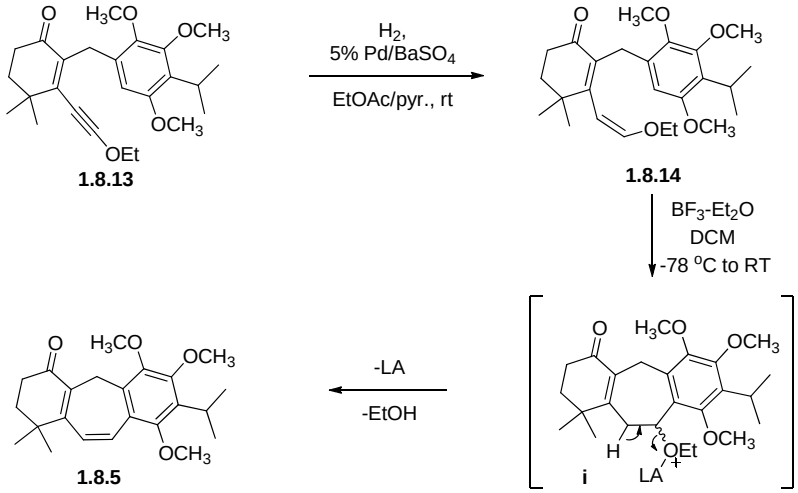
Our first attempt toward a modified cyclization, as depicted in Scheme 1.8.6, took advantage of the reactivity of vinylogous ester **1.5.11** toward 1,2-addition by strong nucleophiles. Addition of vinyllithium in the presence of cerium chloride produces dienone **1.5.13**, after an acidic workup. Cyclialkylation of **1.8.10** would produce desired 6-7-6 tricycle **1.8.11**. Lithium(trimethylsilyl)acetylide also adds to **1.5.11** to give TMS-enynone **1.8.12** in good yield;

however, no reaction was observed upon treatment with either BF_3-Et_2O or $TiCl_4$. It was clear that the bond distance between C7 and C8 was too great, thereby precluding bond formation.



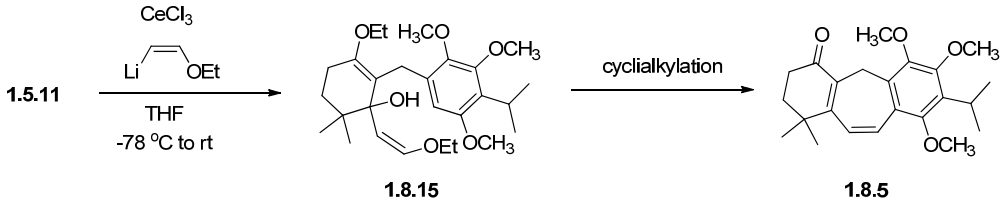
Scheme 1.8.6

Another interesting cyclization precursor was alkynyl ethyl ether **1.8.13**, prepared via the addition of lithiated ethoxyacetylene, or Aren's reagent, to **1.5.11** (Scheme 1.8.6). While **1.8.13** did not undergo cyclization under standard conditions, presumably due to the similar spacial constraints, we were excited to find that after reduction of **1.8.13** under Lindlar reduction conditions yielded ethyl vinyl ether **1.8.14**, functionalized dienone **1.8.14** cyclized with BF_3-Et_2O to give **1.8.5** in 66% yield from enynone **1.8.13**.



Scheme 1.8.7

While we were pleased to arrive at a more succinct route to dienone **1.8.5**, both the additional steps to convert enynone **1.8.13** to an appropriate cyclization precursor and the excessive cost of ethoxyacetylene, which is used in excess, prompted us to explore a more direct approach based on the previous one. Indeed, using (*Z*)-2-ethoxyvinyl-bromide, prepared using the conditions developed by Lau and Schlosser, followed by transmetallation and addition of the vinyl carbanion to **1.5.11** afforded tertiary alcohol **1.5.15**.[68] Attempted hydrolysis to form **1.8.14** gave only decomposition, though treating **1.8.15** with Lewis acid directly gave desired **1.8.5**, but only in 30-40% isolated yield. With this poor yield, the ethoxyacetylide addition-Lindar reduction-cyclialkylation sequence was adopted to access key tricyclic dienone **1.8.5**.



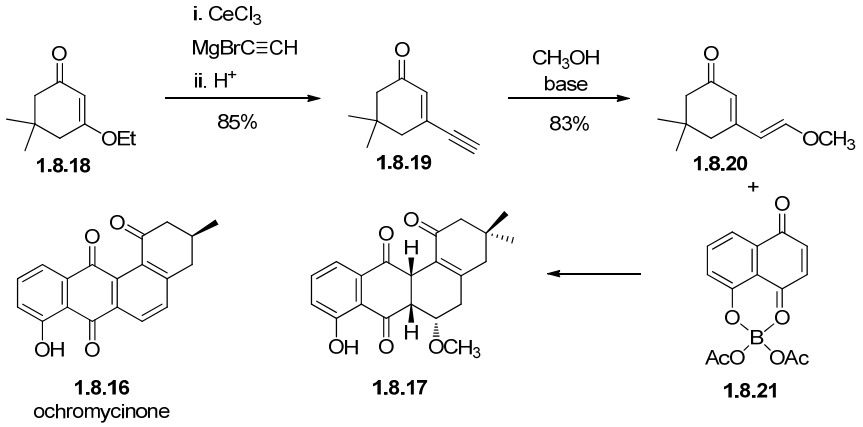
Scheme 1.8.8

The previous sections outlined the work of Yang Li to prepare key intermediates toward novel icetexane skeletons. While certain reactivities were established and conditions developed, there were several key shortcomings. The followign sections focuses on my efforts to develop a more efficient cyclialkylation strategy.

A key feature in accessing the icetexones was the installation of the C6-C7 double bond into an appropriate intermediate (Figure 1.6.1, **1.6.4** to **1.6.3A**). Before applying the aforementioned chemistry to a C19-functionalized coupled intermediate (**1.6.4**), the model system was explored using the ethoxyacetylide addition-Lindar reduction-cyclialkylation sequence described previously (see Scheme 1.8.7). A typical procedure for the 1,2-addition of a nucleophile to **1.5.11** involves using a threefold excess of the acetylide. In the case of

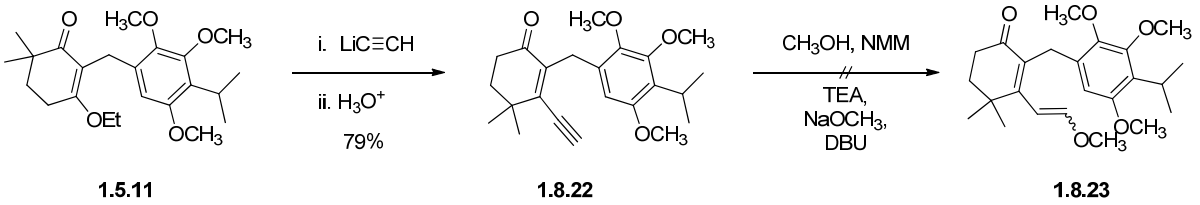
ethoxyacetylene, the relatively high cost of the reagent warranted its preparation, rather than purchasing it through a commercial source. These methods proved difficult and, at time, impractical. Due to its cost and difficulties encountered in its preparation, we instead decided to focus on accessing other intermediates in this route.

Since intermediate **1.8.14** represented a promising compound in this sequence, we explored alternative methods for introducing it that had not previously been investigated. While looking for known compounds containing a similar terminally-substituted dienone motif, we were inspired by the work of Bowie and co-workers (Scheme 1.8.9).[69] In their studies toward angucyclinones related to ochromycinone (1.8.16), Bowie's approach involved a Diels–Alder approach to construct the C-ring of a model of the natural product (**1.8.17**). To that end, a three-step sequence was employed to construct the terminally-functionalized dienone segment. Starting with ethyl enol ether **1.8.18**, from readily-available dimedone, 1,2-addition of an acetylide anion was carried out to give enynone **1.8.19**. Base-catalyzed 1,6-addition of methanol was achieved to afford **1.8.20**, which underwent Diels–Alder cycloaddition with an unsymmetrical 1,4-napthaquinone to generate the nucleus of the angucyclinones. Facile formation of **1.8.20** is a promising harbinger for *in situ* formation of the cyclization precursor.



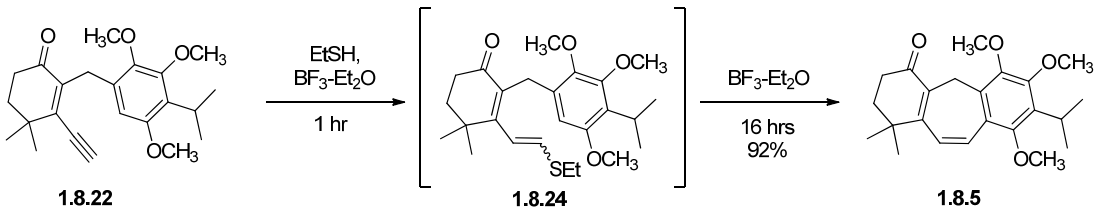
Scheme 1.8.9

Our first task toward implementing this new strategy was to prepare the necessary enynone motif, which had previous been explored (Scheme **1.8.6**). Addition of lithium acetylide to **1.5.11** gives enynone **1.8.22** in excellent yield (Scheme 1.8.10). Initial attempts toward a base-catalyzed approach for the addition of methanol were unsuccessful for the generation of **1.8.23**, with a variety of bases only resulting in recovered starting material. We decided to explore a push-pull strategy using a Lewis acid in the presence of a suitable nucleophile. Indeed, when **1.8.22** was heated in the presence of BF_3-Et_2O and methanol, **1.8.5** was generated.



Scheme 1.8.10

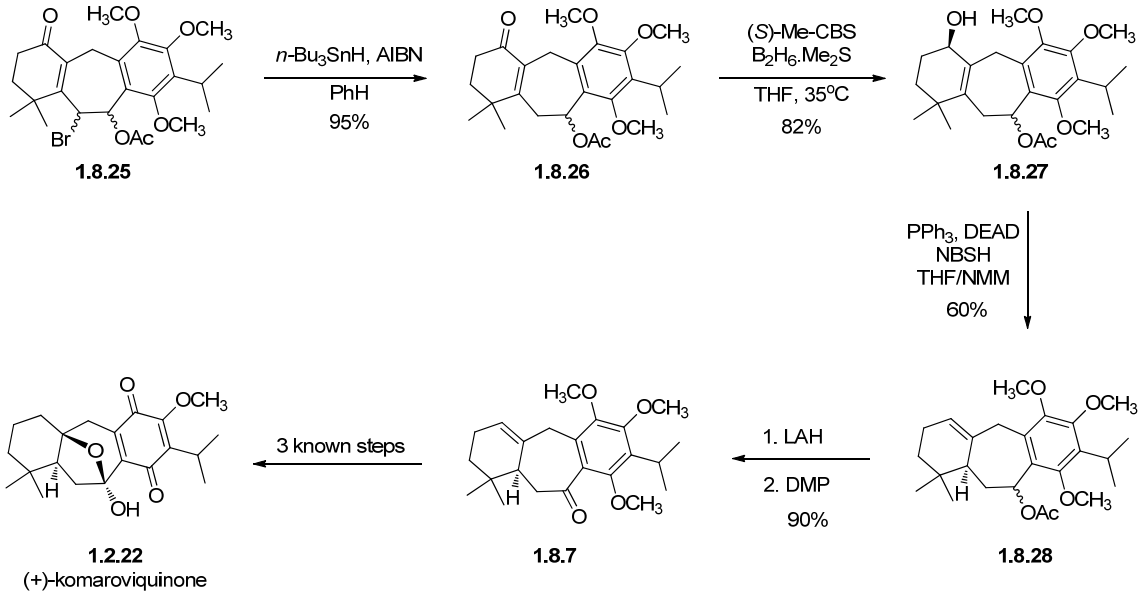
Carrying out the cyclization with EtSH, a better nucleophile than CH_3OH, afforded **1.8.5** under much milder reaction conditions, though the product was accompanied my numerous impurities. The reaction is carried out by the dropwise addition of an excess of BF_3-Et_2O to a mixture of starting enynone **1.8.22** with a slight excess of ethanethiol in DCM; TLC analysis reveals rapid conversion to vinyl sulfide **1.8.24** within an hour. Cyclialkylation and Lewis acid-catalyzed elimination of EtSH requires at least 16 hours to go to completion. We observed that the yield of **1.8.5** was greatly dependent upon concentration, as carrying out the reaction dilute in DCM resulted in less byproduct formation. Additionally, the scalability of this step was limited



Scheme 1.8.11

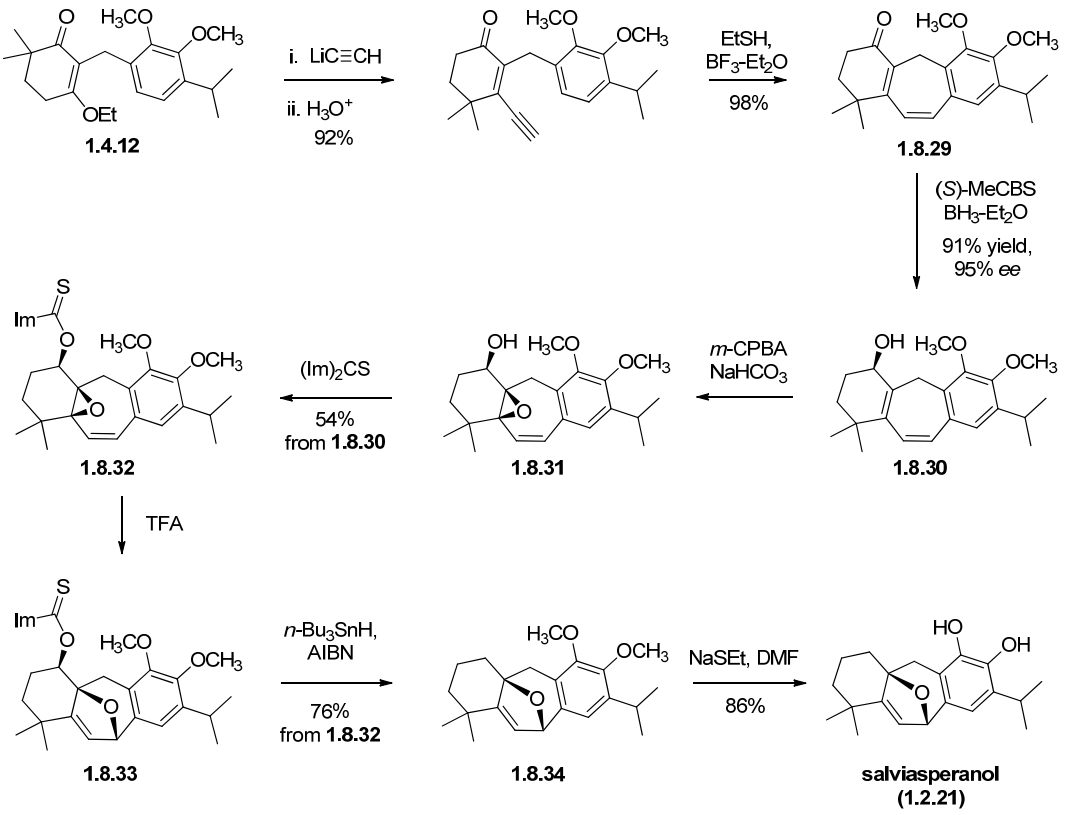
to approximately one gram of **1.8.22**, as cyclization-elimination proceeded much more slowly when a greater amount was reacted.

Shortly after this method was developed (Scheme 1.8.11), it was featured in the first asymmetric total synthesis of (+)-komaroviquinone in 2007.[53] While the ethoxyacetylene route (Scheme 1.8.7) was reported in the literature to document its discovery and applications, the practical preparation of **1.8.5** was carried out using the above chemistry. Exposing cyclized dienone **1.8.5** to NBS in the presence of acetic acid afforded bromoacetate **1.8.25**, which was debrominated under free radical-initiated conditions to give benzylic acetate **1.8.26**, introducing the C7-oxidation state present in target compound **1.2.22** (Scheme 1.8.12). A two-step method was utilized to give the necessary pre-functionalization at the C1-C10 position. First, a CBS-reduction protocol was used to reduce enone **1.8.25** to optically-active allylic alcohol **1.8.27**. This stereocenter was used to transfer chirality to the C5 methine and give **1.8.28** through chemistry developed by Myers and Zhang. Next, acetate removal with LAH, followed by oxidation with Dess–Martin periodinane, gave **1.8.7**, a known precursor to (+)-komaroviquinone.



Scheme 1.8.12

This cyclization procedure was also featured in the total synthesis of (–)-salviasperanol (**1.2.21**), reported in 2008, following the first synthesis of this natural product by Simmons and Sarpong two years prior.[70] Our cyclization approach was extended to **1.4.12**, an intermediate in the Majetich synthesis of barbatusol, to prepare the same skeleton with a C6-C7 styrenyl double bond.[71] CBS-reduction of the resulting dienone (**1.8.29**) gave enantiomerically-pure allylic alcohol **1.8.30**, which was converted to optically active epoxy-alcohol **1.8.31**. Thiocarbamate **1.8.32** was prepared to protect the sensitive alcohol functionality in the resulting isomerization of the allylic epoxide to give dihydrofuran **1.8.33**. Radical deoxygenation of **1.8.33** followed by deprotection of the aryl methyl ethers afforded (–)-salviasperanol in six steps from **1.8.29**.



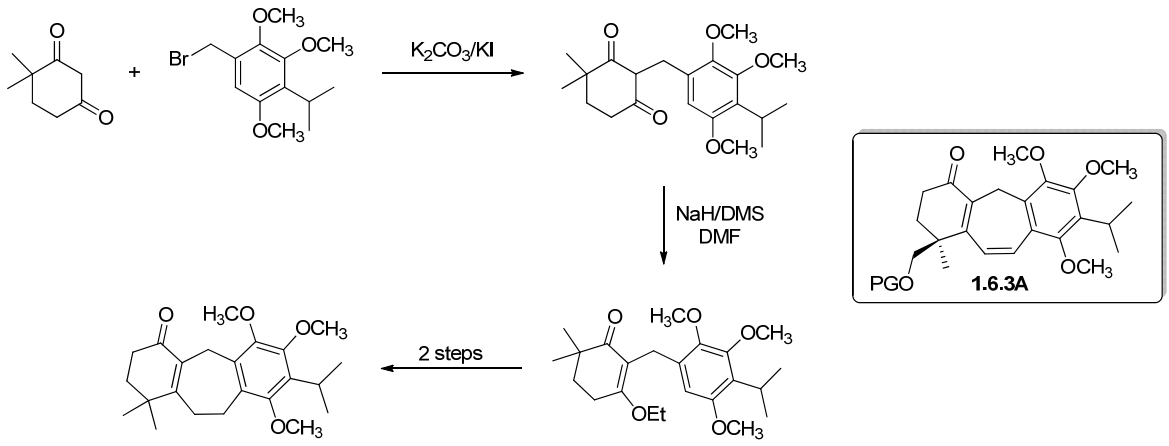
Scheme 1.8.13

In summary, a novel, chemoselective, and reproducible method for the assembly of the central benzocycloheptatriene core central to the Majetich synthesis of the icetexanes has been

developed. This protocol has been shown to provide a versatile framework for synthesis of icetexane-related natural products, as shown in the total syntheses of (+)-komaroviquinone and (–)-salviasperanol. As seen in the following Sections, this strategy has also been used for the construction of the benzocycloheptadiene core in the synthesis of icetexanes **1.2.27**, **1.3.19**, and **1.3.21**.

1.9 Asymmetric Preparation of the A-Ring

With an efficient synthesis of a C-ring precursor (**1.5.8**, Section 1.7) and a method for the introduction of the central cycloheptatriene ring using a model A-ring (Section 1.8), we next sought to introduce the appropriate stereochemistry and oxidation state into the A-ring system (Scheme 1.6.1). Additionally, modification of our previous A + C → ABC strategy needed to be investigated, since the route outlined in Scheme 1.9.1 did not permit the introduction of an asymmetric center in **1.6.3A**.



Scheme 1.9.1

Asymmetric synthesis has always been at the forefront of organic chemistry. Numerous approaches can be applied to achieve complete optical activity in a given molecule. Stereospecific transformations are among the most efficient of these, though broad applicability

can be unattainable and reagents are commonly very specialized. On the other hand, resolution strategies can be used either to separate racemic mixtures of compounds or to enrich them.

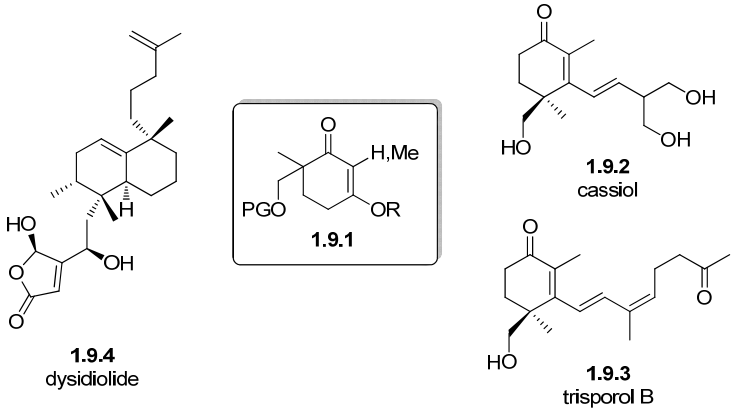
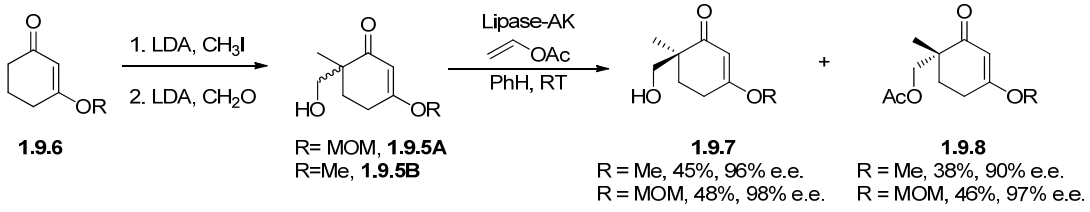


Figure 1.9.1

Toward an asymmetric approach to optically-active hydroxymethyl derivative **1.6.5** (Scheme 1.6.1), we were initially excited by a report by Yamada and co-workers where they employed an enzymatic resolution strategy to prepare optically-active 3-alkoxy-6-hydroxymethyl-6-methyl-2-cyclohexenones (Figure 1.9.1, **1.9.1**).[72] In their synthetic approach to the cyclohexenone building blocks of cassiol (**1.9.2**), and trisporol B (**1.9.3**), and the bicyclic core of dysidiolide (**1.9.4**), Yamada envisioned these natural products arising from a 3-alkoxy-2-cyclohexenone containing an α-oriented quaternary center containing a neopentyl alcohol (**1.9.1**). They found that racemic alcohol **1.9.5** could be prepared from 1,3-cyclohexadione derivative **1.9.6** in two steps (Scheme 1.9.2). Enzymes were screened for enantioselective acetylation of (±)-**1.9.5A** and (±)-**1.9.5B**, Lipase-AK giving the highest enantioselection for both substrates (R=



1.9.6

R= MOM, **1.9.5A**
R=Me, **1.9.5B**

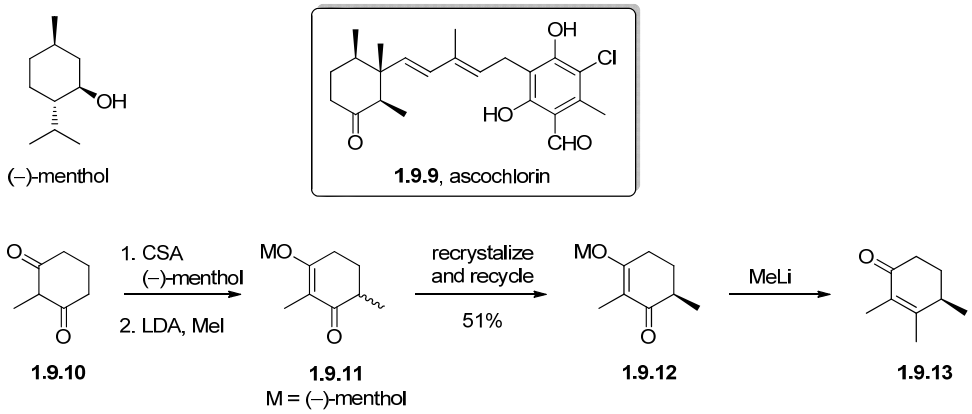
1.9.7
R = Me, 45%, 96% e.e.
R = MOM, 48%, 98% e.e.

1.9.8
R = Me, 38%, 90% e.e.
R = MOM, 46%, 97% e.e.

Scheme 1.9.2

MOM, Me). The resulting mixture of free and acetylated alcohol, *i.e.* **1.9.7** and **1.9.8**, respectively, were separated by column chromatography. Acetate **1.9.8** could then be cleaved to give the corresponding free alcohol. To assess the absolute optical activity of the enantiomers, **1.9.8** was converted to an intermediate in Suzuki's synthesis of cassiol (**1.9.2**) in a few steps.[73]

While Yamada's enzymatic resolution protocol provides access to our optically-active A-ring, we were dissuaded from this route for two reasons. First, the excessive cost of the enzyme (approximately $50 USD for 1 g from SigmaAldrich) would prohibit its use on a large-scale preparation of **1.6.5**. Additionally, since a straightforward resolution strategy will, by definition, only permit less than 50% yield in the key step, a material loss would also not be beneficial to an efficient total synthesis. Because of these two limitations, alternative strategies were explored to achieve a synthesis of optically-active alcohol **1.6.5**.



Scheme 1.9.3

In their total synthesis of (–)-ascochlorin (**1.9.9**), Dudley and Danheiser utilized a cyclobutenone-based benzannulation strategy to forge the aromatic portion of **1.9.9**, while the key distal tertiary methyl group in the cyclohexane ring was introduced in a racemic fashion and resolved using menthol as a chiral auxillary (Scheme 1.9.3).[74] Using the Stork protocol, condensation **1.9.10** with (–)-menthol and α-methylation under standard conditions led to a

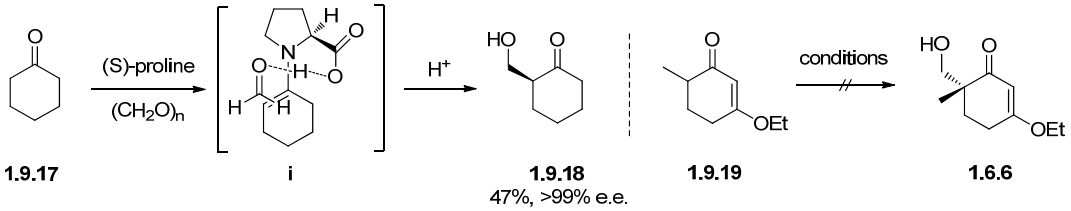
mixture of diasteromers (**1.9.11**). While this mixture was inseparable by chromatography, recrystallization with hexanes yielded optically pure **1.9.12** which was transformed to **1.9.13** in 200:1 e.r.

While this route clearly suffered from low overall yield due to a resolution step, recycling **1.9.11** by racemization was possible, though not in our system, the use of inexpensive (–)-menthol was attractive. Facile conversion of 1,3-cyclohexanedione (**1.9.14**) to its corresponding menthol enol ether was achieved under acid-catalyzed dehydration conditions to give **1.9.15** (Scheme 1.9.4). A straightforward two-step procedure, similar to Yamada's, was used to generate the quaternary center with a hydroxymethyl substituent and give **1.9.16**. Unfortunately, all attempts to exploit the physical characteristics of the diastereomeric mixture were unsuccessful; recrystallization with a variety of solvents gave no separation and the two diastereomers were inseparable by chromatography. Thus, this route was abandoned.

Scheme 1.9.4

Organocatalysis has been an increasingly attractive area of research, especially over the last decade. At the forefront of this trend has been proline, which has been shown to promote a wide range of useful synthetic transformations, such as the Mannich reaction, Michael addition, and Diels–Alder reaction, many with a high degree of stereochemical induction due to its pendant carboxylic acid moiety.[75] We were interested in using this inherent reactivity and stereochemical guidance to introduce the hydroxymethyl group to 6-methyl-3-ethoxy-2-cyclohexenone (**1.9.19**). Cordova and co-workers have shown that a number of substituted cyclohexanones, such as **1.9.17**, undergo an aldol reaction with formaldehyde in the presence of

10 mol% (*S*)-proline in DMSO, resulting from complex **i**.[76] These conditions give acceptable yields of **1.9.18** and with high stereospecificity. Subjecting **1.9.19** to these conditions, however, resulted in no conversion and complete recovery of starting vinylogous ester, likely due to the differing reactivity of ketones and esters, in the case of **1.9.17**.

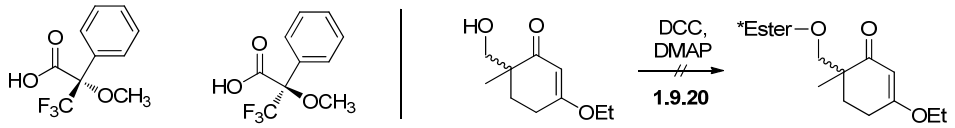


1.9.17 **i** **1.9.18** 47%, >99% e.e. **1.9.19** **1.6.6**

Scheme 1.9.5

At this time, we became aware of a supplier of Lipase-AK, the enzyme used by Yamada and co-workers, that offered the crude enzyme for roughly $1 USD for 1 g, which made the known route affordable and, in lieu of other failed attempts, our only method to access optically-active **1.6.6**.

Before preparing **1.6.6** by Yamada's enzymatic protocol, we had to explore methods for evaluating the % e.e. of the reactions. Several analytical techniques were examine and are described here. Readily accessible to our research group are cellulose-based chiral GC columns, though resolution of the enantiomers of **1.6.6** was not achieved under a variety of parameters.



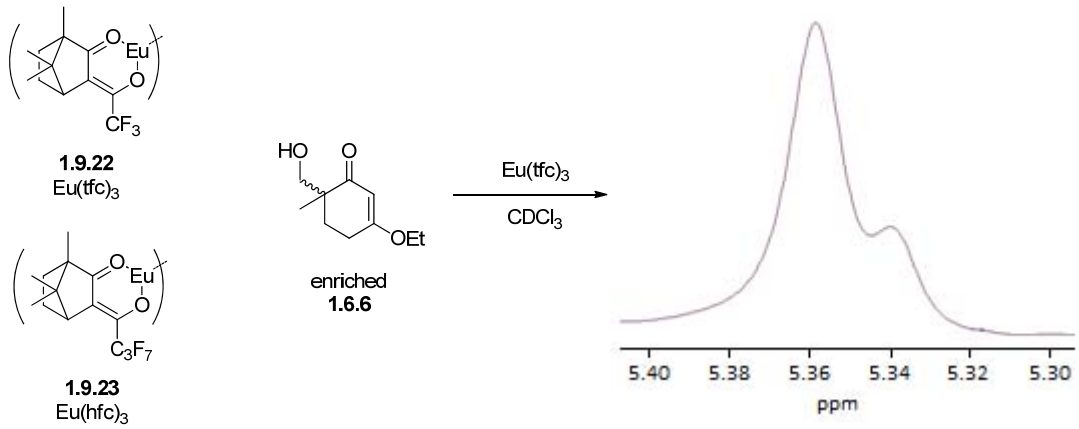
1.9.20A **1.9.20B** **1.6.6** **1.9.21**

Scheme 1.9.6

A common chemical method for the determination of enantiomeric ratio is through the preparation of Mosher's ester of the alcohol, a shown in Scheme 1.9.6.[77a] Using this method, an alcohol is reacted with Mosher's acid (**1.9.20A** or **1.9.20B**) or acid chloride, the resulting ester is

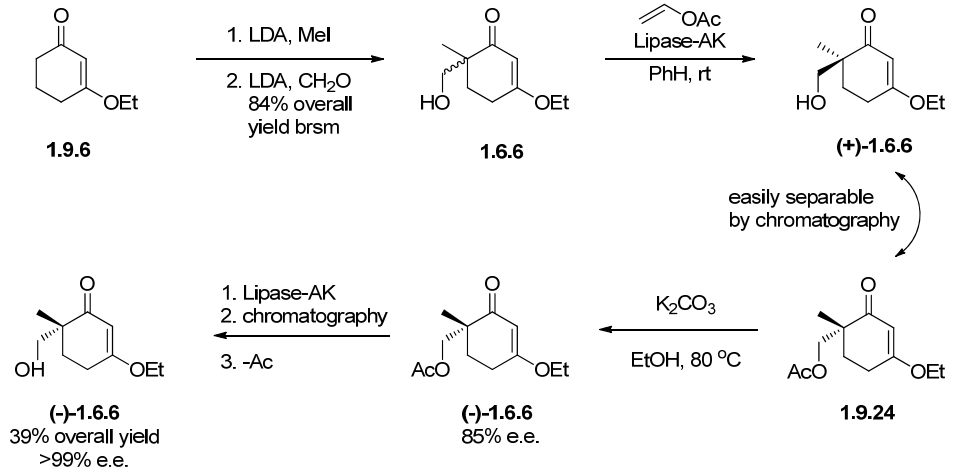
analyzed by ^{19}F NMR, and resolved ^{19}F NMR signals are compared to evaluate % e.e. The reliability of this technique is dependent upon complete conversion of both enantiomeric alcohols of **1.6.6** to the resulting Mosher's ester (**1.9.21**), since one enantiomer could have a higher affinity for the esterification reaction, resulting in a false result. Unfortunately, due to the congensted neopentyl environment, conversion of to **1.9.21** was low. Therefore, another method for % e.e. determination was needed.

Chiral shift reagents have been used to evaluate enantiomeric purity in conjunction with ^{1}H NMR analysis.[77b] While enantiomers do not differ in chemical shift in ^{1}H NMR, diastereomers can display different chemical shifts. Diastereomeric complexes, such as those signals corresponding to the vinyl protons of the diastereomers of **1.6.6** (Scheme 1.9.7). A common problem associated with chiral shift reagent is peak broadening, which results in inaccurate measurements and low resolution. This phenomenon was observed with **1.6.6**, as demonstrated in Scheme 1.9.7, where adequate resolution between the two peaks could not be obtained. Also, peak broadening resulted in low detection, which would be detrimental when high % e.e. alcohol was analyzed. Hence, another method for enantiomeric purity was evaluated.



Scheme 1.9.7

Chiral HPLC has been a powerful analytical and preparative tool in both industrial and academic settings over the past decades. The wide range and complexity of available stationary phases is due to the need for difficult separations and, as a result, many versatile columns are available for laboratory use. We were excited to find that the enantiomers of **1.6.6** were well resolved using a ChiralPak AD-H column under isocratic conditions using 9:1 hexane:isopropanol at 1.0 mL/min. with UV detection at 254 nm.[77c] Using these parameters, the minor enantiomer eluted at 3.7 minutes, while the major enantiomer eluted at 4.7 minutes.



Scheme 1.9.8

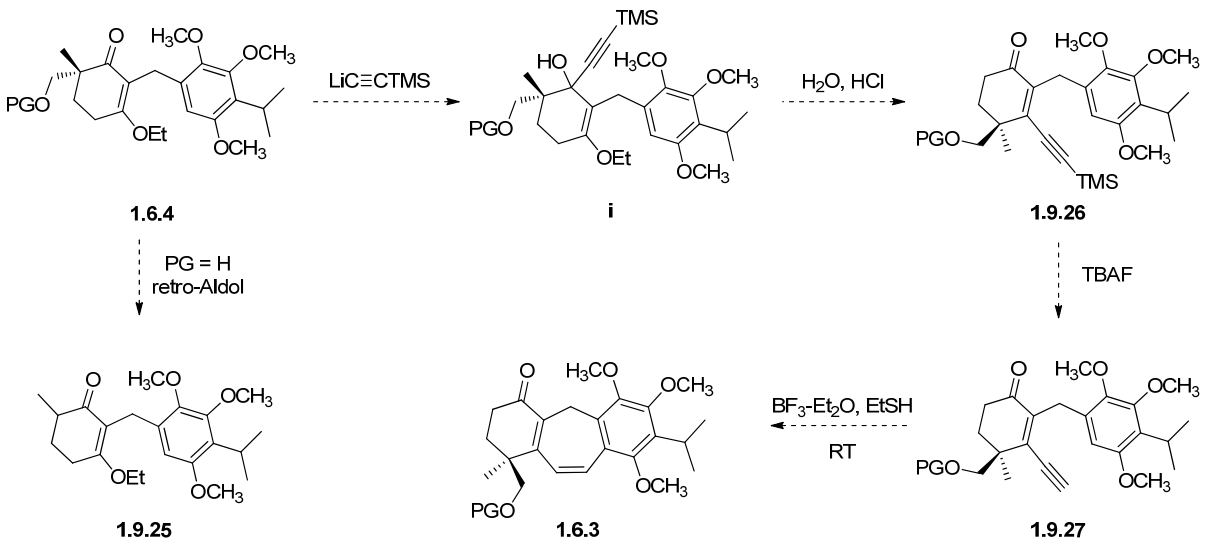
With this method established, we proceeded to prepare optically active alcohol **1.6.6** via Yamada's protocol. As presented previously, Yamada demonstrated an enzymatic resolution of (±)-3-alkoxy-6-hydroxymethyl-6-methyl-2-cyclohexenones by exposing a solution of the racemic mixture of **1.9.5** in benzene to Lipase-AK in the presence of a three-fold excess of vinyl acetate at room temperature.[72] After 24 hours, the reaction mixture is filtered, concentrated, and purified by silica gel chromatography, in which alcohol **1.9.7** and acetate **1.9.8** are easily separable. Acetate **1.9.8** is produced in 38-46% yield with 90-97% e.e. as determined through polarimetry, which is transferred after hydrolysis of the acetate group. It should be noted that the

acetate moiety of vinylogous ester **1.9.8** where R= MOM is hydrolyzed with concomitant conversion of the MOM group to a methyl group.

In our hands, when **1.6.6** was subjected to the above conditions (resolution, chromatography, and acetate removal), **(–)-1.6.6** was obtained in good yield, though only with 85% e.e. Modification of the reaction conditions did not result in greater enrichment; however, re-subjecting the enriched **(–)-1.6.6** to the same reaction conditions resulted in >99% e.e. of **(–)-1.6.6** in nearly quantitative yield. We were able to recover the Lipase AK by first filtering the reaction mixture through a short pad of Celite and rinsing the pad with ethyl acetate. The plug of crude Lipase was recovered, dried under vacuum, and stored at 0 °C, as was the original Lipase-AK; this recovered Lipase could be reused without loss of activity.

In conclusion, we have modified a known enzymatic resolution protocol for the preparation of **(–)-1.6.6** in 39% overall yield and >99% e.e from racemic **1.6.6**. This material was prepared in high optically-pure form by subjecting enriched **(–)-1.6.6**, available from one cycle of resolution, to a second sequence to gain additional % e.e. Additionally, we have shown that Lipase-AK can be recovered and re-used without noticeable loss in efficacy.

We next turned our attention to introducing an appropriate protecting group to **1.6.4** to avoid either a retro-Aldol process, which would yield **1.9.25** or other undesired reactivity resulting from the free-alcohol motif. Several constraints motivated our choice of protecting group, which are presented in Scheme 1.9.9. We have developed a synthetic sequence that would introduce the C6-C7 olefin into the central ring, which proceeds via 1,2-addition of a silylated acetylide to **1.6.4**, followed to yield **i**, and acid hydrolysis gives enynone **1.9.26**. Exposure of **1.9.26** to fluoride to remove the silyl protecting group gives enynone **1.9.27**. Cyclization with BF_3-Et_2O in the presence of EtSH would yield **1.6.3.** Thus, a successful route would necessitate a

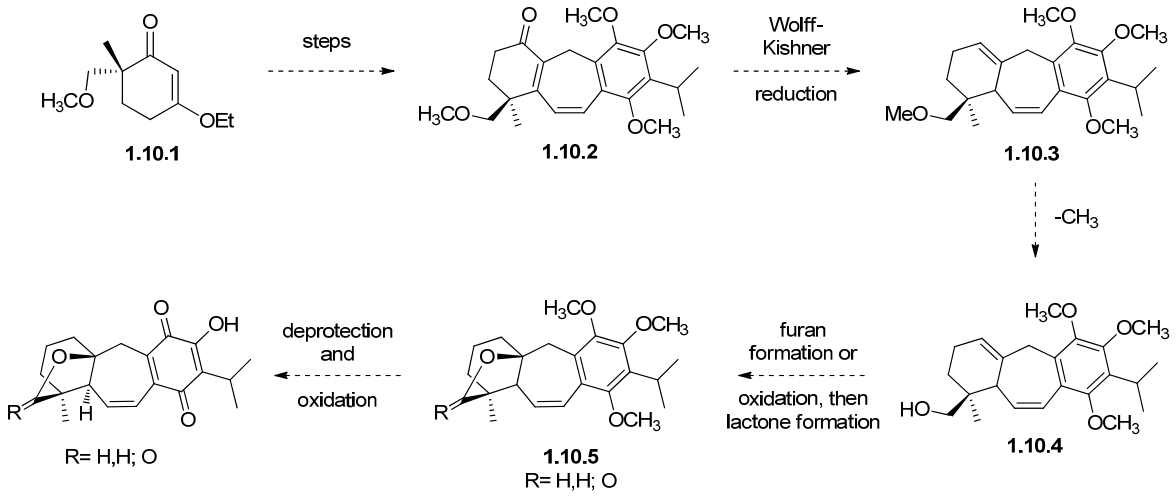


Scheme 1.9.9

protecting group stable to (1) a strong nucleophile, (2) aqueous acidic conditions, and (3) fluoride ion. Additionally, as the key cyclization required extended exposure of **1.9.27** to Lewis acid and a strongly nucleophilic thiol, a suitable masking group would be stable under those conditions. Equally important is recognition that unmasking the protected alcohol had to be done in the presence of the C6-C7 olefin and the trisubstituted C1-C10 olefin. As a result of these constraints, silicon-based protection groups, while somewhat tuneable in stability profile, were not considered. The use of acidic aqueous conditions also eliminated MOM-protection of the primary alcohol. Also, protection as an ester would not be compatible with the initial 1,2-addition reaction (**1.6.4** to **1.9.26**). The next two sections will highlight two routes that were explored, each incorporating different protection group strategies and gave interesting results.

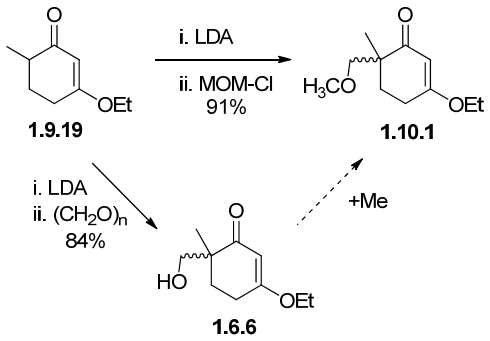
1.10 Methyl-Protected Route

Our initial choice for the protection of the optically active and functionalized A-ring was a methyl ether (Scheme 1.10.1). Methyl ether **1.10.1** could be converted to key dienone **1.10.2** and a Wolff–Kishner strategy introduced the C1-C10 olefin into **1.10.3**. Deprotection of the C19



Scheme 1.10.1

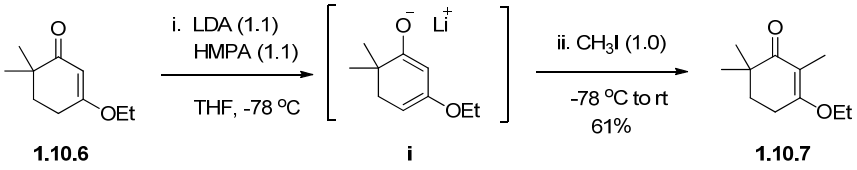
alkyl methyl ether should proceed more readily than the aryl methyl ethers, which would give diene alcohol **1.10.4**. Cyclization or either the alcohol or the corresponding carboxylic acids would give heterocycles **1.10.5** and deprotection would afford target compounds **1.2.27**, **1.3.19**,and **1.3.21**. It should be noted that elaboration of some of the key steps involved in this route will be discussed in greater detail in later sections.



Scheme 1.10.2

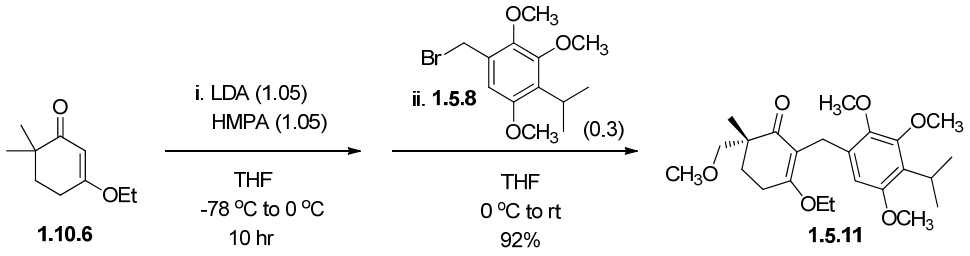
To explore this strategy, an alternative preparation of methyl-protected A-ring **1.101.1** was derived. We have already shown that the yield for the formation of racemic alcohol **1.6.6** is can be variable, due to low conversion and byproduct formation. Rather, alkylation of mono-methyl **1.9.19** with MOM-Cl under standard conditions produced **1.10.1** in excellent yield.

With **1.10.1** in hand, we next sought to introduce the appropriate benzylic functionality at the α-position. An earlier approach used a two-step procedure to achieve this goal, alkylating a 1,3-cyclohexanedione with bromide **1.5.8** (Scheme 1.5.4). Unfortunately, this approach was not applicable to our C4 unsymmetric A-ring. However, in 1981, Smith and co-workers alkylated 3-ethoxy-6,6-dimethylcyclohexen-2-en-1-one (**1.10.6**) with iodomethane at the α-position in 61% yield using LDA in the presence of HMPA, which proceeds through enolate **i** to give **1.10.7.** Their protocol represents an alternative way to couple the A- and C-fragments.[78]



Scheme 1.10.3

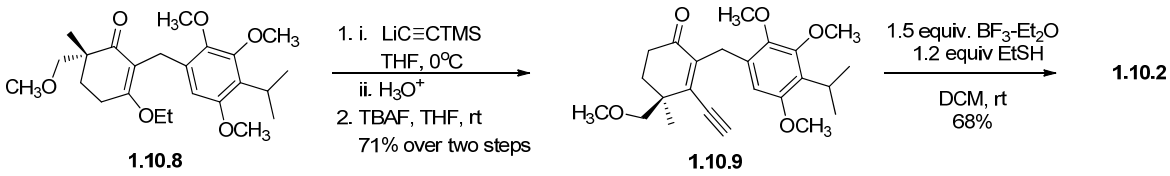
An extension of Smith's strategy was explored by John E. Britton in 2002 in his studies toward a synthesis of (+)- and (–)-perovskone.[49] It was found that optimal reaction yields were achieved when **1.10.6** was treated with LDA in the presence of HMPA and the enolate was allowed to form over ten hours. Next, a solution 0.3 equivalents of bromide **1.5.8** in THF was added to the resulting reaction mixture in one portion to give **1.5.11** in an excellent 92% yield, with excess **1.10.6** recovered by vacuum distillation.



Scheme 1.10.4

When this strategy was applied to the alkylation of methyl-protected **1.10.1** a considerable amount of *bis*-alkylated product was obtained, though not fully characterized with

regards to the regiochemistry of the *bis*-alkylation. However, this side reaction could be overcome by replacing HMPA with DMPU using of a four-fold excess of the enolate of **1.5.8** to give **1.10.8** in good yield.

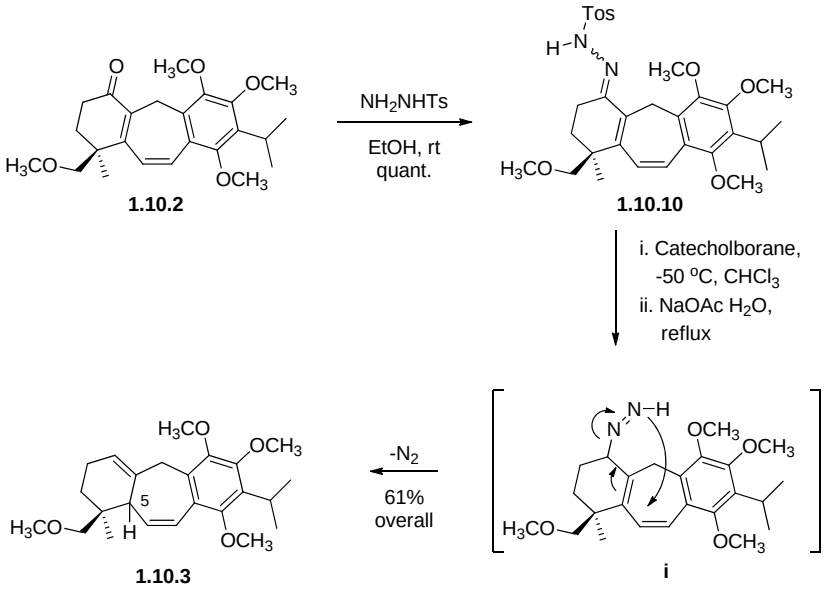


Scheme 1.10.5

With coupled **1.10.8** available in gram quantities, we next turned our attention to the key sequence to introduce the central C6-C7 olefin. We were certain that enynone **1.10.9** could be prepared without incident. We were concerned, however, that the C19 methyl-protected alcohol might be susceptible to deprotection under the cyclization conditions. Indeed, **1.10.8** underwent smooth 1,2-addition of lithium (trimethylsilyl)acetylide. The hydrolysis step must be carried out at 0 °C with ~3N HCl until the resulting aqueous layer gives a strongly acidic reading on litmus paper. If this sequence was carried out at room temperature, cleavage of the terminal silyl group was observed. The acetylene moiety was unmasked by treating crude product with excess TBAF in THF at room temperature to give enynone **1.10.9** in excellent yield from **1.10.8**. While this reaction did not exhibit an exotherm on small scale preparation (≤ 2.0 g), large scale deprotection required cooling to 0 °C. As with our model system (Scheme 1.8.11), **1.10.9** underwent clean cyclialkylation with BF_3-Et_2O in the presence of EtSH to give dienone **1.10.2** without cleavage of alkyl or the aryl methyl ethers.

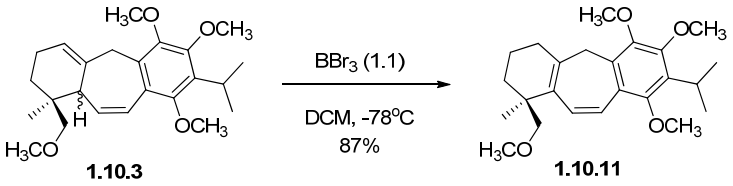
Next, reaction conditions first discovered by Wolff and Kishner in the early 20th century and modified by Huang-Minlon in 1945 and Hutchins and Kabalka in the 1970's were adopted for the transformation of **1.10.2** to **1.10.3** (see Section 1.12 for additional discussion).[84-86] In particular, dienone **1.10.2** was converted to tosylhydrazone **1.10.10** by stirring with *p*-

toluenesulfonyl hydrazide in absolute ethanol. Crude **1.10.10** was first reacted with catecholborane in chloroform at -50 °C, then with sodium acetate under refluxing conditions to give diene **1.10.3**. This two-step reduction of the tosylhydrazone group produces allylic diazene **i** *in situ*, which undergoes an intramolecular [1,5]-sigmatropic rearrangement. This rearrangement consists of hydride transfer, olefin migration, and loss of molecular nitrogen to give **1.10.3**. With the influence of an additional stereocenter in **1.10.10**, this transformation affords **1.10.3** as a 4:1 mixture of C5-epimers. Unfortunately, the resulting C5-epimeric dienes were inseparable by chromatography, necessitating their separation at a later stage.



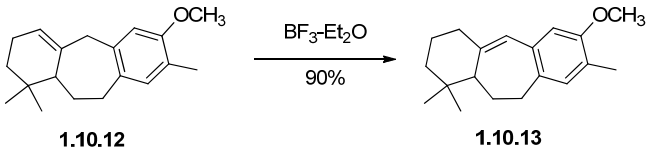
Scheme 1.10.6

While methyl is one of the most rugged protecting groups for ordinary alcohols, we were confident that the C19 alkyl methyl ether in **1.10.3** could be removed selectively in the presence of the three aryl methyl ethers. Of the conditions known for its removal (TMS-I, BBr_3, Lewis acid-thiol complexes), we first used boron tribromide, which has been reported to be effective at low temperatures and in the presence of other sensitive functionalities.[79]



Scheme 1.10.7

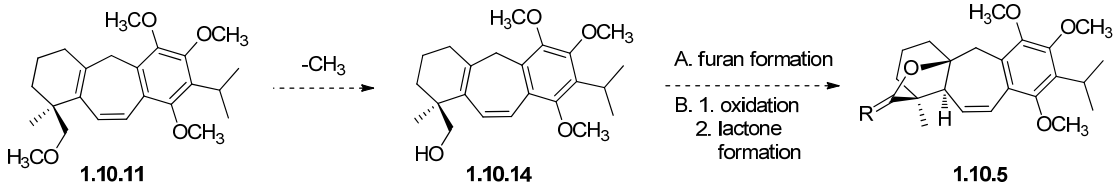
Exposing **1.10.3** to a slight excess of BBr_3 in DCM at -78 °C led to the rapid formation (< 5 min.) of a new component by TLC analysis (Scheme 1.10.7). It was found, however, that the trisubstituted C1-C10 olefin in **1.10.3** undergoes rapid Lewis acid-catalyzed isomerization to give **1.10.11**, resulting from isomerization of the more stable tetrasubstituted C1-C5 olefin conjugated to the C6-C7 double bond. In fact, deprotection of the C19 methyl ether was not observed in this reaction. Other methods to affect the deprotection were attempted, such as treatment with TMS-I, generated *in situ* by addition TMS-Cl to a suspension of **1.10.3** and NaI; however, these conditions also resulted in only olefin isomerization. This observed migration is somewhat consistent, however, with results reported by Majetich and co-workers in their total synthesis of faveline methyl ether in 1996, in which isomerization of **1.10.12** is accomplished with BF_3-Et_2O to give the more stable styrenyl olefin **1.10.13** in 90% yield.[41]



Scheme 1.10.8

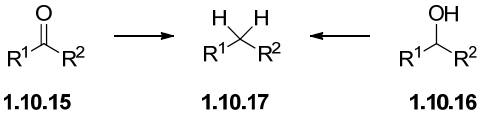
This unexpected reactivity necessitated a revision of our original synthetic strategy (*cf.* Scheme 1.10.1). Still, we expected deprotection of conjugated diene **1.10.11** could be accomplished by known procedures to give alcohol **1.10.14**. We envisioned 5-*endo*-trig cyclization of **1.10.9** could be accomplished under acidic conditions to give furan **1.10.5** with an α-oriented C5-methine, by the nature of the cyclization (Route A, Scheme 1.10.9). Additionally,

oxidation of **1.10.14** to its corresponding carboxylic acid would be amenable to the same cyclization to give lactone **1.10.5** (Route B, Scheme 1.10.9).



Scheme 1.10.9

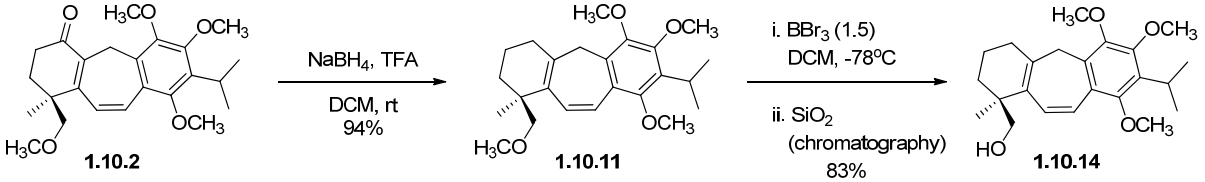
To produce **1.10.11** more directly, rather than Wolff–Kishner reduction of **1.10.2** followed by Lewis acid-catalyzed isomerization of **1.10.3**, we instead explored the direct decarbonylation of **1.10.2** (Scheme 1.10.11). The hydrogenolysis of ketones and alcohols by a mixed-hydride system has been studied since the mid-1950's. First reported by Broome and Brown in 1956 and expounded upon by Nystrom and Berger in 1958, it has been shown that aromatic ketones (**1.10.15**) and alcohols (**1.10.16**) are reduced to their corresponding alkane products (**1.10.17**) by a mixed hydride system consisting of a hydride source and a Lewis acid (Scheme 1.10.10).[80] Variations of these conditions include LAH with $AlCl_3$, BH_3 or $NaBH_4$ with BF_3-Et_2O, and $NaBH_4$ with $AlCl_3$.[81]



Scheme 1.10.10

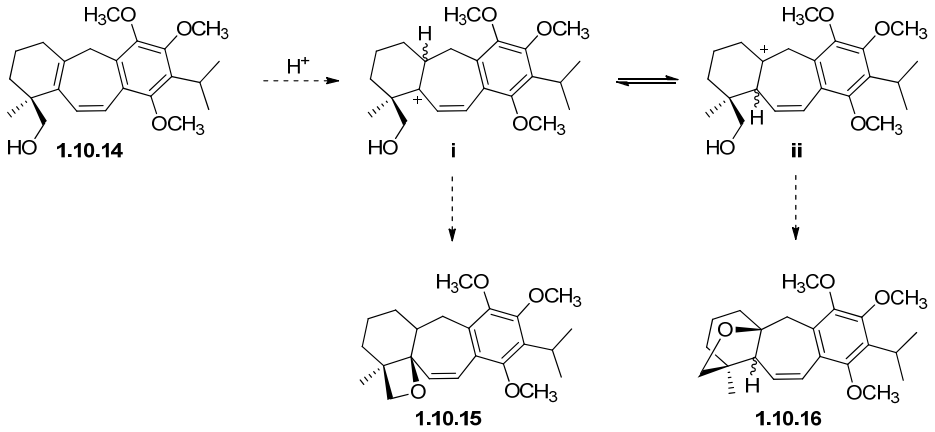
Of these variants for the hydrogenolysis of activated carbonyl groups, we found that the best results were obtained when a solution of **1.10.2** in DCM was treated with 5 equiv. of $NaBH_4$ and 3 equiv. TFA at room temperature over 7 hours, which afforded diene **1.10.11** directly in 94% yield. It should be noted that the allylic alcohol generated though reduction of **1.10.2** with

common reducing agents also underwent smooth hydrogenolysis under the same conditions to afford **1.10.11** in a good, though undetermined, yield.



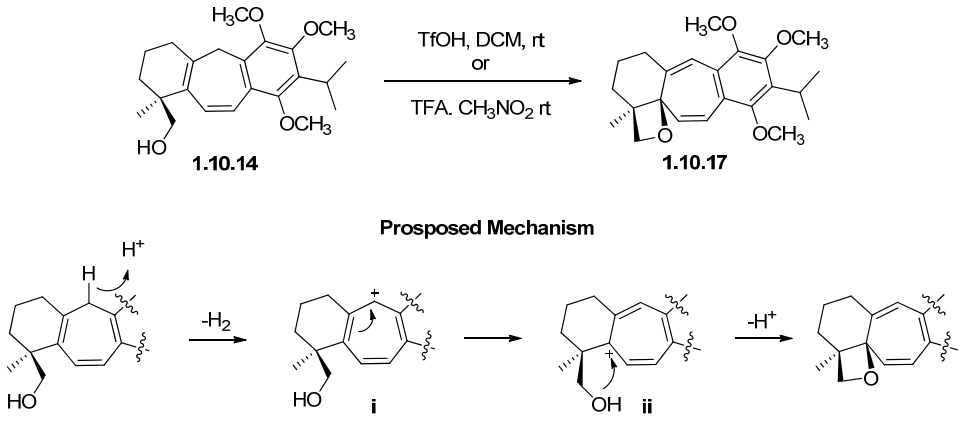
Scheme 1.10.11

Deprotection of the C19 hydroxyl group of **1.10.11** was accomplished with excess boron tribromide in DCM at -78 °C to give dienone alcohol **1.10.14** in good overall yield. It is important to note that a boron complex of **1.10.14** is initially formed, which is manifested by a more nonpolar component by TLC analysis. However, aqueous ethereal workup and silica gel chromatography results in the isolation of free alcohol **1.10.14** in excellent yield. With **1.10.14** in hand, we envisioned that furan formation to **1.10.5** would take place under acidic conditions, through protonation of the more substituted C10-C5 double bond. The carbocation resulting from protonation would generate either allylic carbocation **i** or tertiary carbocation **ii**, which would produce oxetane **1.10.15** or tetrahydrofuran **1.10.16**, respectively.



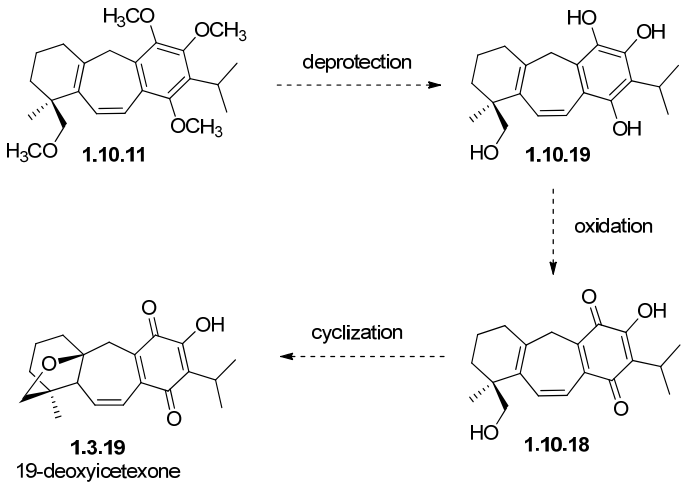
Scheme 1.10.12

Treating **1.10.14** with TfOH in DCM or TFA in CH_3NO_2 resulted in the formation of a new component. Analysis of the ^1H NMR indicated the presence of an additional vinylic methine and ^{13}C NMR confirmed this assignment, indicating formation of oxetane **1.10.17**. We rationalize that the formation of **1.10.17** results from tropylium ion formation with strong acid to



Scheme 1.10.13

generate **i**, which rearranges to the more stable *bis*-allylic carbocation **i** and intramolecular cyclization then gives **1.10.17**. This unexpected cyclization forced us to abandon this approach.

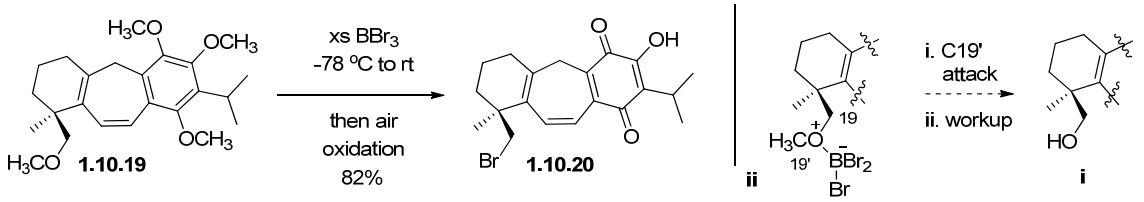


Scheme 1.10.14

At this same time, though, we were curious whether removal of the aryl methyl ether protecting groups and subsequent oxidation would give *p*-benzoquinone **1.10.18**. We envisioned

that a global deprotection of methyl ether **1.10.11** would give *tris*-phenol **1.10.19**, which could undergo oxidation, either by air or via a number of known oxidants, to afford *p*-benzoquinone **1.10.18**. We also wanted to examine the intramolecular cyclization of **1.10.18**, as in Scheme 1.10.13.

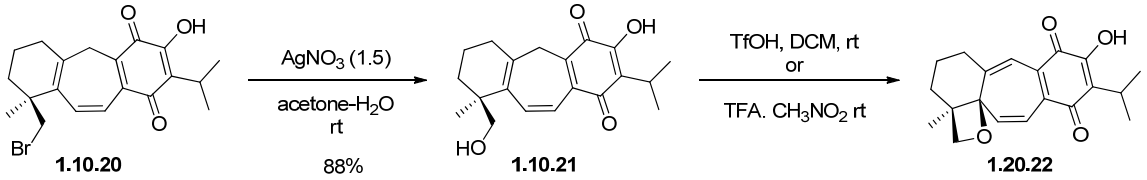
Treating **1.10.11** with boron tribromide at -78 °C and warming the reaction mixture to room temperature resulted in rapid consumption of **1.10.11** (Scheme 1.10.15). We have found that compounds with an arene portion similar to **1.10.19** demonstrated a characteristic dark stain with Hanessian stain; this was observed in the reaction of **1.10.19** with excess BBr_3. Next, when the crude product was exposed to a stream of air a new component was observed by TLC analysis that was orange on TLC; this color is indicative of *p*-benzoquinones related to **1.10.20**. Surprisingly, NMR and MS analysis indicated that **1.10.20** was the major component, resulting from complexation of BBr_3 with the alkyl methyl ether and subsequent bromide displacement at C19. Alcohol **ii** would result from a bromide attacking the C19' position of **i** (Scheme 1.10.15).



Scheme 1.10.15

Corey and co-workers used $AgNO_3$ in a THF:H_2O solvent system to convert a bromoisoleucine derivative to its corresponding primary alcohol.[82] Bromoquinone **1.10.20** was converted to alcohol **1.10.21** with $AgNO_3$ in a 4:1 acetone:H_2O solvent system to produce**1.10.21** in excellent yield (Scheme 1.10.16). Attempted acid-catalyzed tetrahydrofuran formation under conditions employed previously resulted only in oxetane formation, again likely due to tropylium ion formation (**1.10.22**). Due to these unexpected cyclization results, this protecting group

strategy was abandoned in favor of one in which the protecting group could be cleaved under more mild conditions and be compatible with the presence of the C1-C10 double bond.

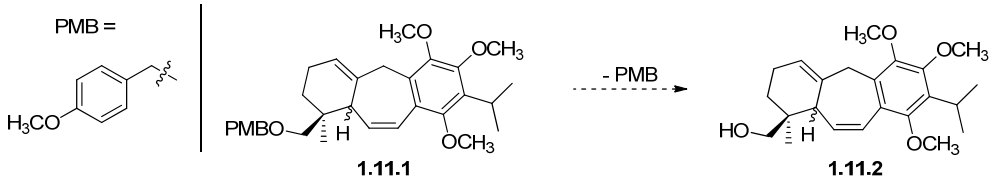


1.10.20 **1.10.21** **1.20.22**

Scheme 1.10.16

1.11 PMB-Protected Route

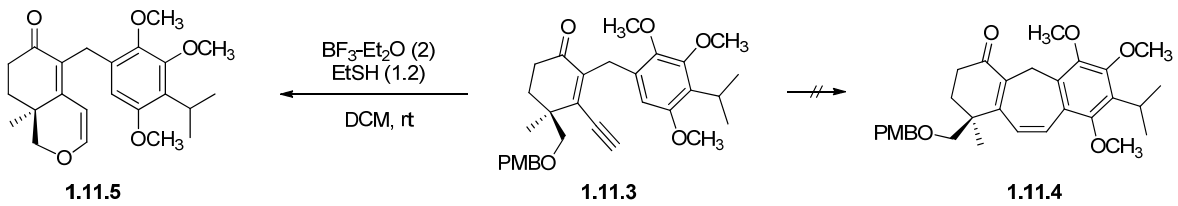
Having used a robust protecting group and struggled with its chemoselective removal, we sought a protecting group that was stable to nucleophilic attack, Brønstead and Lewis acids, and toward fluoride ion (see Scheme 1.9.9). We expected that protecting the C19 hydroxyl group as a *p*-methoxybenzyl ether would meet these criterions and permit its removal (Scheme 1.11.1).[79]



1.11.1 **1.11.2**

Scheme 1.11.1

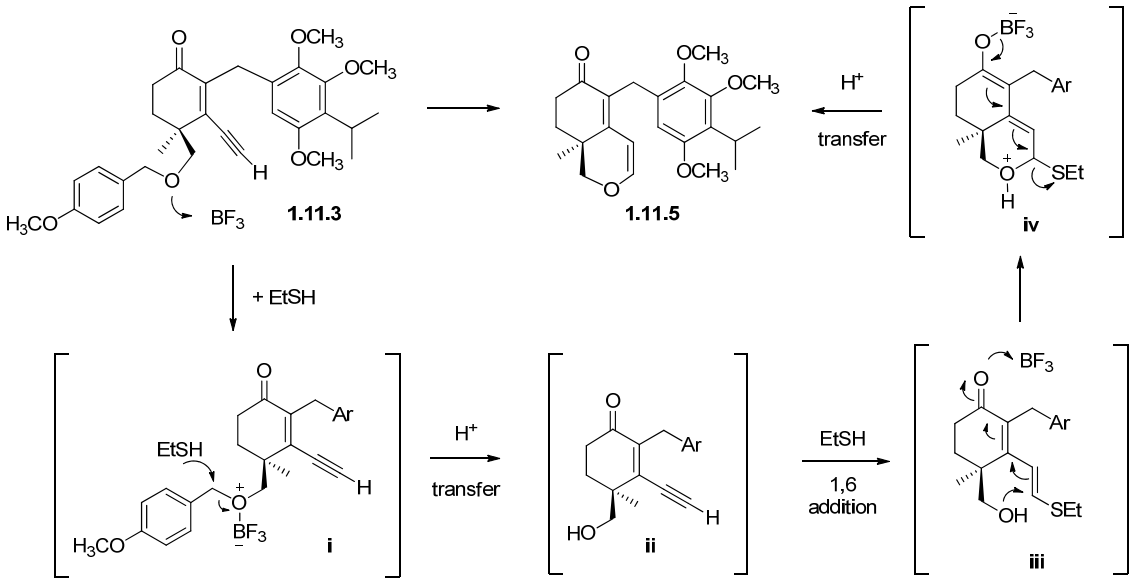
Benzyl ethers are among the most widely used protecting group.[79] They are both robust and can be removed under a variety of reductive, oxidative, acid-base, and radical conditions. While the removal of a simple benzyl ether is susceptible to undesired side reactions, due to its relative stability, aryl-substituted benzyl ethers are more easy to remove. Most notable is the *p*-methoxylbenzyl (PMB) ether, which can be easily introduced and removed under a variety of more mild and selective conditions, such as those available to the removal of benzyl ethers and, more commonly, single-electron transfer with DDQ in an aqueous medium.[79]



Scheme 1.11.2

With this protecting group in mind, we turned our attention to investigating this new strategy (Scheme 1.11.2). Protection of alcohol **1.6.6** with PMB-Cl under standard conditions resulted in the formation of a PMB-protected A-ring, which was converted to enynone **1.11.3** by conditions outlined in Schemes 1.10.4 and 1.10.5 (Scheme 1.11.2).

Cyclization of **1.11.3** to dienone **1.11.4** seemed relatively straightforward, as literature precedence did not indicate otherwise for its Lewis-acid stability.[79] However, when **1.11.3** was subjected to the usual cyclization conditions [2.0 equiv. of BF_3-Et_2O and 1.2 equiv. of ethanethiol in DCM at room temperature] the rapid consumption of **1.11.3** was observed. This reaction immediately produced a more polar component by TLC analysis, which gradually was converted to a less polar one. Analysis of the ^{1}H NMR revealed the disappearance of the PMB



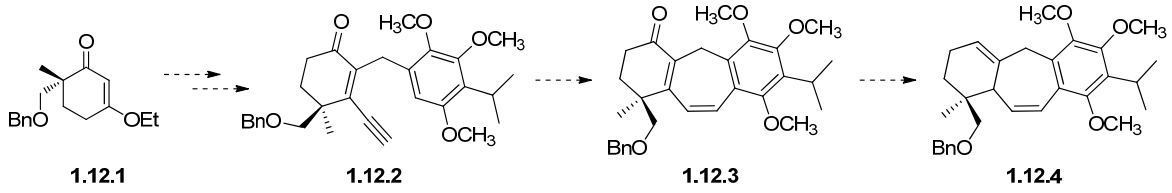
Scheme 1.11.3

functional group as well as the terminal alkyne, and exhibited a set of isolated vicinal olefinic signals. It was determined that this new component corresponded to pyran **1.11.5**. We postulated that Lewis acid activation of the benzylic oxygen gives intermediate **i** and rapid displacement at the benzylic C19' site gives rise to **ii** after proton transfer. Enynone **ii** undergoes Lewis acid-mediated 1,6-addition of EtSH to generate vinyl sulfide **iii**, which undergoes intramolecular displacement via the mechanism outlined in the conversion of **iii** to **iv** to generate dihydropyran **1.11.5**. This observation, however, did iterate the necessity to mask the C19 hydroxy group, a requirement originally imposed to eliminate retro-aldol of the free hydroxymethyl motif (see Scheme 1.9.9).

Although the formation of dihydropyran **1.11.5** compelled us to explore yet another protecting group strategy, this observation initiated a new area of research into strategies for the preparation of functionalized hydroxyisochromenes and hydroxyisocoumarins (see Chapter II).

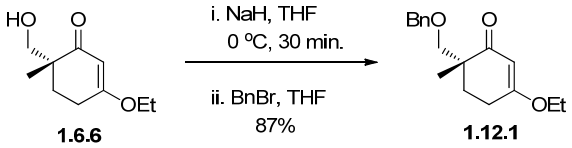
1.12 Benzyl-Protected Route

Since the two previously-explored protecting group strategies (methyl- and PMB-ethers) suffered from poor chemoselectivity, we turned our attention to the benzyl ether of alcohol **1.6.6** (**1.12.1**, Scheme 1.12.1). This strategy would permit the permanence of the protecting group to the enynone (**1.12.2**), dienone (**1.12.3**), and isolated diene (**1.12.4**) stages, at which time it could be removed by a myriad of chemoselective deprotection conditions.[79]



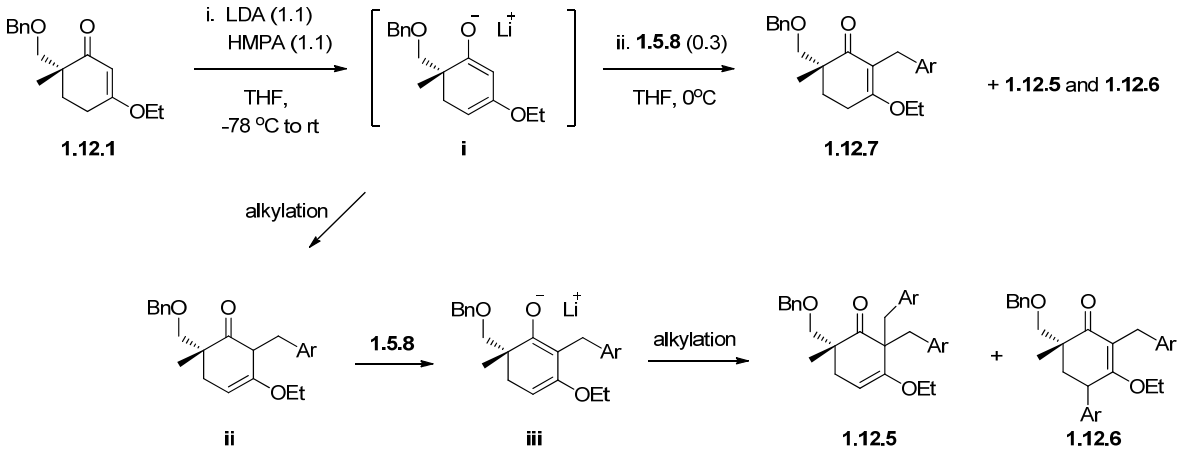
Scheme 1.12.1

The first step in investigating a route employing a benzyl-protected C19 hydroxyl group was the preparation of **1.12.1**, accomplished by treating **1.6.6** with 1.3 equiv. NaH in THF at 0 °C and benzyl bromide which gave **1.12.1** in 87% yield. This reaction required the slow, portion-wise addition of NaH to ensure acceptable yield and to avoid byproducts formation.



Scheme 1.12.2

As mentioned in Section 1.10, we adopted the alkylation strategy developed by A.B. Smith and co-workers to introduce the aryl C-ring at the α-position of **1.10.6** and **1.10.1**. Upon direct application of these conditions, which required the formation of the enolate of **1.12.1** in the presence of HMPA, significant byproduct formation was observed; these products were identified as the regioisomeric *bis*-alkylated products (Scheme **1.12.2**, **1.12.5** and **1.12.6**). This can be rationalized through intermediate **i**, which gives rise to **1.12.7** upon α-alkylation with benzyl bromide **1.5.8**. β,δ-Unsaturated **ii** isomerizes to desire enone **1.12.7** upon aqueous workup. However, if consumption of bromide **1.5.8** is not complete, deprotonation of **ii** by



Scheme 1.12.3

enolate intermediate **i** can give **iii**, which reacts with a second equivalent of **1.5.8** to give **1.12.5** upon α-alkylation and **1.12.6** upon δ-alkylation. These products were obtained in variable ratios under a variety of different conditions. We believe that the slow reactivity of **1.12.1** toward alkylation was a result of the protected α-hydroxymethyl group which, upon treatment with LDA, results in a stabilized enolate (**i**, Scheme 1.12.3). Even in the presence of HMPA, which tightly binds with lithium to increase the enolate's reactivity, the alkylation was slow, leading to the byproducts by the sequence shown in Scheme 1.12.3.

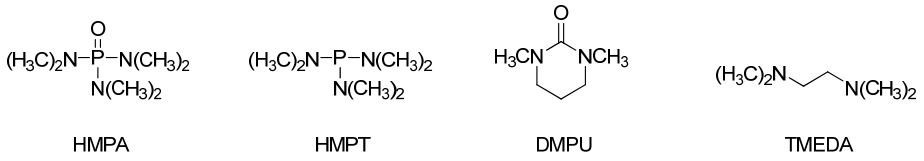
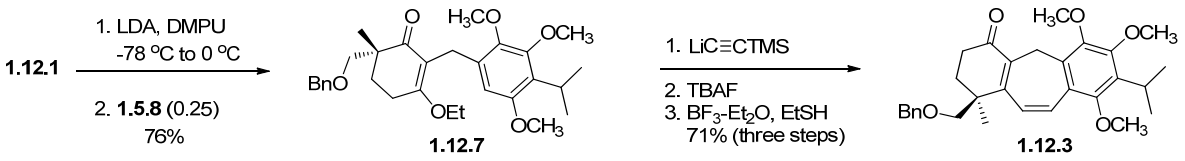


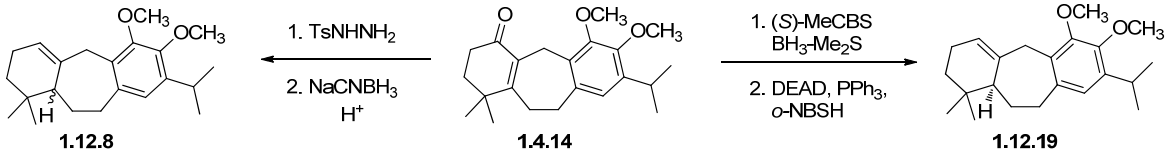
Figure 1.12.1

Through an extensive survey of reaction conditions, (temperature variations, concentration, enolization time, equivalents of reactants and reagents, etc.) enhanced reactivity was attained when DMPU was used as the additive. Other reagents that facilitate similar reactivity are shown in Figure 1.12.1. Thus, treating **1.12.1** with a slight excess of LDA in the presence of DMPU at -78 °C for 30 minutes, allowing the reaction mixture to warm to room temperature for 60 min. and adding **1.5.8** (0.25 equiv.) rapidly in THF gave **1.12.7** cleanly (Scheme 1.12.4). This resulted in both a rapid consumption of bromide **1.5.8** and minimal *bis*-substituted by-products. Excess **1.12.1** could be recovered by vacuum distillation (210 °C to 270 °C @ 3 Torr) and column chromatography afforded **1.12.7** in 76% yield.



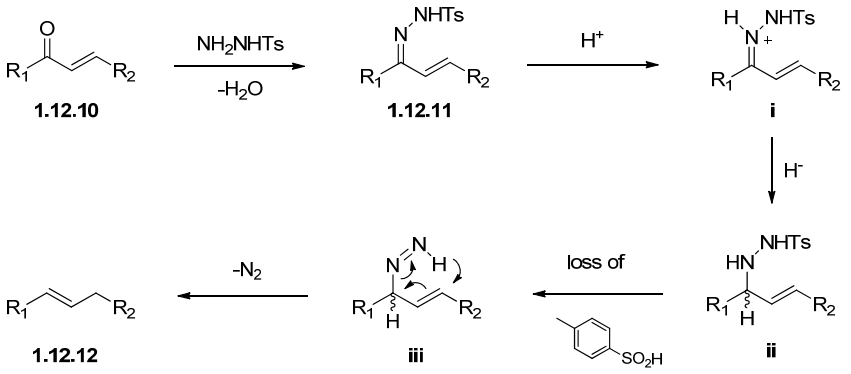
Scheme 1.12.4

Transformation of **1.12.7** to its corresponding enynone was straightforward and Friedel–Crafts cyclialkylation gave tricycle **1.12.3** in 71% yield over three steps. Deprotection of the benzyl ether group was not observed under standard cyclization condition, demonstrating the dramatic differences in reactivity of ordinary benzyl ethers and *p*-methoxybenzyl ethers (*c.f.* Scheme 1.11.2). However, benzyl ethers can be cleaved in good yields with Lewis acids in the presence of thiols.[83] Dienone **1.12.3** represents a key intermediate in our original synthetic strategy, as the key oxygenated stereocenter at the C4 position represents an important handle for controlling the stereoselective introduction of the C5 methine. In contrast to the use of a C19 methyl- or PMB-ether to protect the C19 alcohol, we expected its removal to be routine. At this point, methods for the introduction of the C5 stereocenter should be discussed.



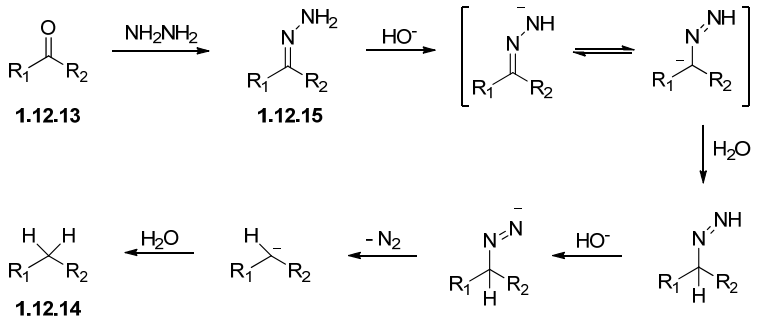
Scheme 1.12.5

One of the key stereochemical transformations in the Majetich syntheses of (±)-barbatusol and (–)-barbatusol is shown in Scheme 1.12.5.[71,42] Non-stereospecific introduction of the C5 methine was accomplished through a Wolff–Kishner-like reduction of the tosylhydrazone of **1.4.14**. The mechanism for this transformation is shown in Scheme 1.12.6. Activation of the tosylhydrazone (**1.12.11**), from enone **1.12.10** with an acid source gives **i** and hydride delivery gives intermediate **ii**, which readily undergoes elimination of *p*-toluenesulfinic acid to give the corresponding monoalkyl allylic diazene (**iii**). The intermediate diazene species undergoes an intramolecular [1,5]-sigmatropic rearrangement by transfer of hydride, double bond migration, and loss of molecular nitrogen to yield **1.12.12**



Scheme 1.12.6

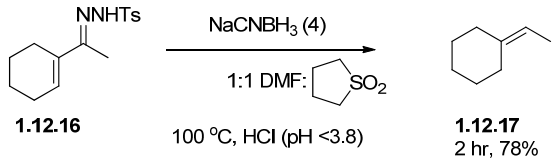
The basis for this approach was developed in the early 1970's and numerous advances have been made since. The overall transformation of **1.12.10** to **1.12.12** can be related to the Wolff–Kishner reduction (Scheme 1.12.7). In the Wolff–Kishner reduction, a ketone or an aldehyde (**1.12.13**) is reduced to a methylene (**1.12.14**) by first converting the carbonyl to a hydrazone (**1.12.15**) and then subjecting the hydrazone to basic conditions to give an alkane by the mechanism shown in Scheme.[84] Improvements that have been made to the original procedure include the Huang–Minlon modification, a one-pot procedure to carry out the same reaction.[85]



Scheme 1.12.7

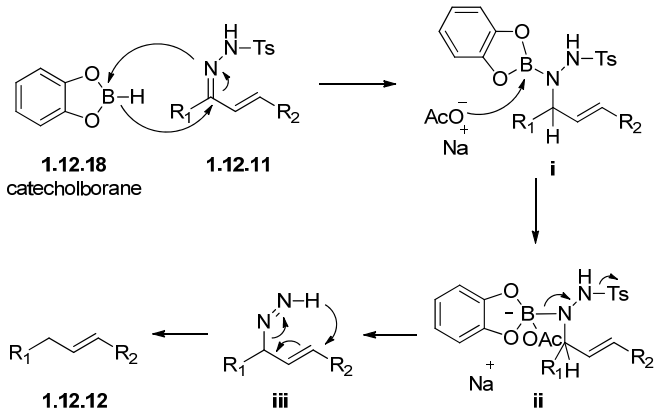
Tremendous advances were made in the mid-1970's that offered milder alternatives to the Wolff–Kishner reduction. In 1971, R.O. Hutchins found that carbonyl compounds have the same reactivity as previous methods in the presence of tosylhydrazide and sodium cyanoborohydride in an acid 1:1 DMF:sulfolane at 100 °C, as in the reduction of **1.12.16** to give **1.12.17** (Scheme

1.12.8).[86] Following these findings, Hutchins and Djerassi proposed the mechanism presented in Scheme 1.12.6.[87]



Scheme 1.12.8

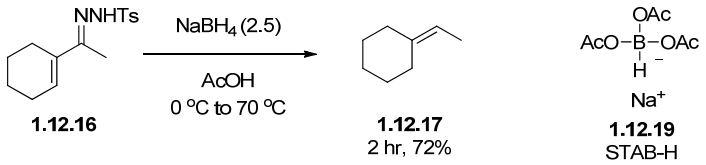
In 1976, Kabalka demonstrated that catecholborane (**1.12.18**) reduces α,β-unsaturated tosylhydrazones to give rearranged olefins via a similar overall mechanism.[88] This involves first reduction of α,β-unsaturated tosylhydrazone **1.12.11** in chloroform at -50 °C to give intermediate **i**. Upon the formation of **i**, a portion of sodium acetate trihydrate is added to the reaction mixture is allowed to warm to room temperature and then heated to reflux. This step forms **ii** and causes fragmentation of the B-N bond and elimination of the tosyl group to generate allylic diazene **iii** and then alkene **1.12.13** upon [1,5]-sigmatropic rearrangement.



Scheme 1.12.9

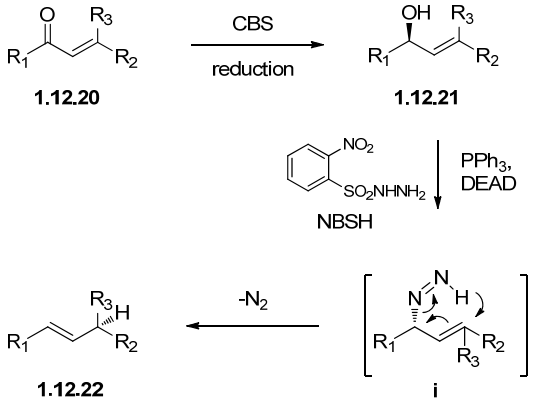
A third modification of the Wolff–Kishner reduction and Minlon modification was reported by Hutchins and Natale in 1978.[89] As an alternative to the reduction being carried out in DMF-sulfolane at 100 °C with HCl, it was found that $NaBH_4$ in acetic acid at a lower temperature is a more convenient and inexpensive way to accomplish the same transformation,

as seen in Scheme 1.12.10. By the same mechanism shown in Scheme 1.12.6, these conditions gave good yields of olefins from α,β-unsaturated tosylhydrazones. Sodium triacetoxyborohydride (**1.12.19**), commonly referred to as STAB-H, has been identified as the active reducing agent under these conditions and has been used for numerous transformations.[90]



Scheme 1.12.10

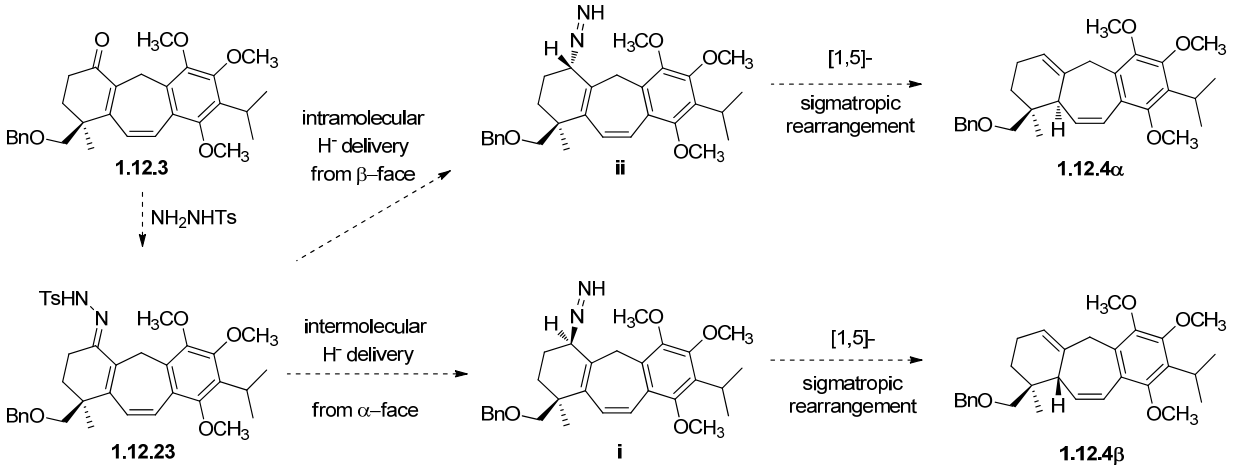
An effective method for the asymmetric introduction of the C5-stereocenter was reported in 2008 in Majetich and Zou's synthesis of (–)-barbatusol (**1.4.14** to **1.12.8**, Scheme 1.12.5).[42] Enone **1.12.20** was subjected to an asymmetric reduction using Corey's CBS-protocol to give allylic alcohol **1.12.21**. Next, a procedure developed by Myers in which a Mitsunobu-like reaction of allylic alcohol **1.12.21** was achieved using NBSH and leads to the inversion of stereochemistry.[91] Warming the reaction mixture allows for elimination of the *o*-nitrosulfinic acid and the formation of diazene **i**, which spontaneously decomposes to olefin **1.22.22**.



Scheme 1.12.11

With benzyl-protected tricycle **1.12.3** in hand, we were optimistic that the C5 methine could be installed stereospecifically. Thus a β-oriented C5 hydrogen would serve as a precursor to 5-*epi*-icetexone (**1.3.21**), icetexone (**1.2.27**) and 19-deoxyicetexone (**1.3.19**) (Scheme 1.6.1).

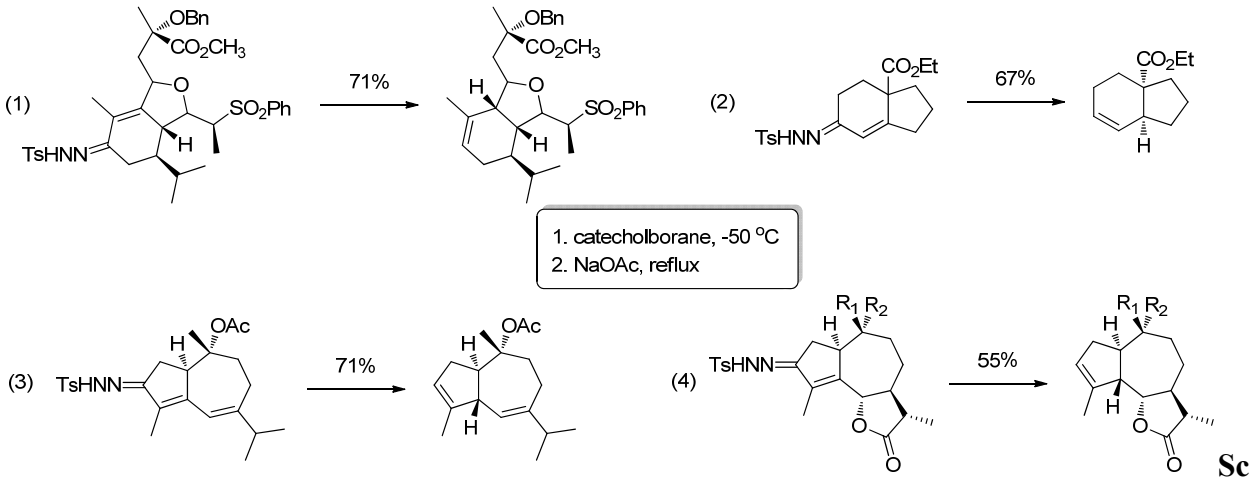
Though CBS-reduction, followed by Myers' inversion chemistry, has been shown to proceed with complete stereocontrol (Scheme 1.12.11), we were confident that a stereospecific transformation could be developed to create both α- and β-methines (Scheme 1.12.12). We envisioned that a Felkin-Ahn model for borohydride delivery to tosylhydrazone **1.12.23** would allow for reduction from the more accessible α-face and the formation of diazene **i**, which generates diene **1.12.4β**. On the other hand, intramolecular delivery of a hydride would generate the epimeric diazene intermediate (**ii**), which would undergo the requisite [1,5]-sigmatropic rearrangement to give **1.12.4α**. With these goals, we focused on the tosylhydrazone reduction strategies presented in the previous section.



Scheme 1.12.12

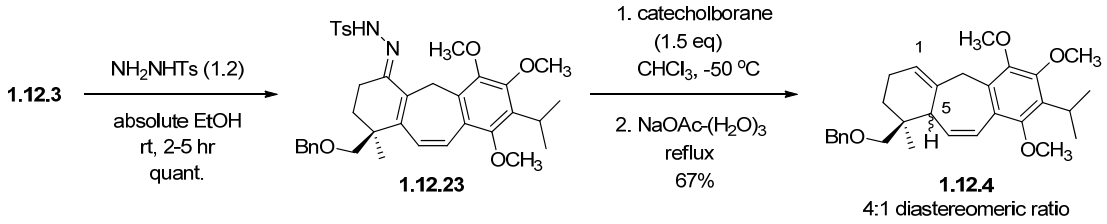
Others have showcased the preparation of allylic diazenes in their research, wherein the catecholborane-NaOAc sequence generates optically pure intermediates (Scheme 1.12.13). For example, McIntosh and co-workers' synthesized cladiell-11-ene-3,6,7-triol featuring this method (eq. 1);[92] hydrindanes and Topiramate, by Maryanoff (eq. 2);[93] Pedro and co-workers' syntheses

of (+)-alismoxide and (+)-4-*epi*-alismoxide (eq. 3);[94] as well as Greene's 1978 synthesis of (+)-pachydictyol A (eq. 4).[95] We were confident that reduction of **1.12.23** with the catecholborane-NaOAc system would permit intermolecular reduction from the more sterically-accessible α-face of tricycle **1.12.23**, which would result in formation of **i** (Scheme 1.12.12).



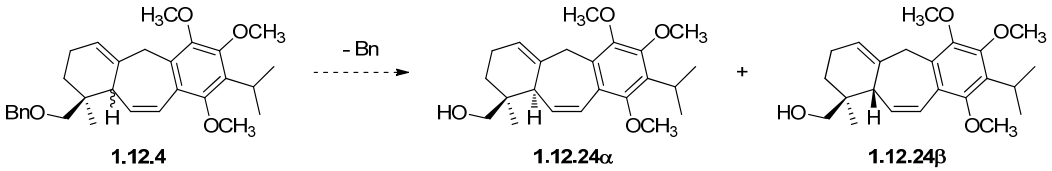
Scheme 1.12.13

Conversion of dienone **1.12.3** to tosylhydrazone **1.12.3** was, at times, a problematic reaction (Scheme 1.12.14). Some report the formation of similar species using a slight excess of tosylhydrazide in ethanol with no catalyst, while others have found that acid catalysts assist in hydrazone formation. Initial attempts involved refluxing a solution of **1.12.3** in the presence of 1.2 equivalents of tosylhydrazide, which sometimes underwent rapid formation of **1.12.23** and others resulted in recovery of starting ketone, even in the presence of catalytic acetic acid. We found that simply adding the two components together in absolute ethanol gave clean conversion to **1.12.23** in 2-5 hours reaction time. It was concluded that adventitious water resulted in hydrolysis of the tosylhydrazone. Work-up consisted of removal of the solvent under reduced pressure to afford a fluffy orange powder that was homogeneous by TLC and contained a small amount of tosylhydrazide by ^{1}H NMR; this material was used without purification.



Scheme 1.12.14

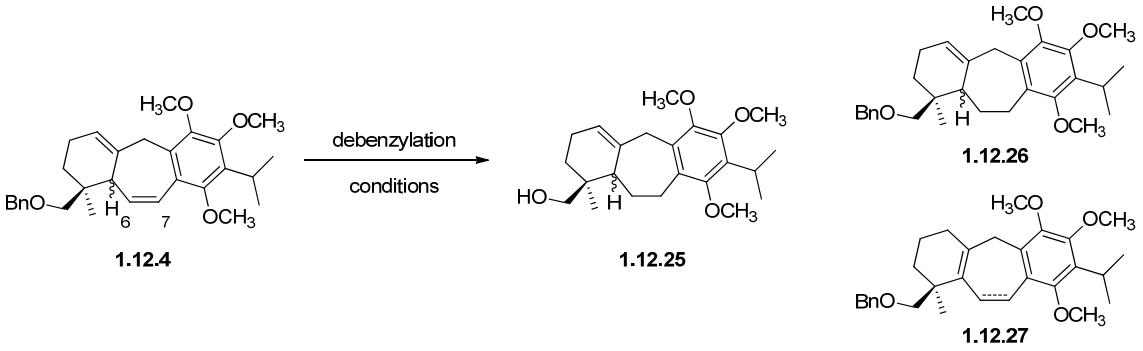
Reduction of α,β-unsaturated tosylhydrazone **1.12.23** using catecholborane:NaOAc resulted in a surprising 4:1 diastereomeric ratio in a 67% overall yield. This ratio was determined by examination of the ^{1}H NMR, in which the chemical shifts for the C1 methine of each diastereomer were resolved from one another. Many reports detailed cooling the reaction mixture after the reflux step and filtering the solution through a pad of silica; however, we found that subjecting the reaction to an ethereal workup gave the best results. Unfortunately, though, the mixture of **1.12.4** was homogeneous by TLC, indicating that the diastereomers were inseparable by column chromatography. Selective recrystallization of the two products was not attempted. Extensive 2D-NMR experiments were performed to arrive at absolute stereochemical assignments for the epimers; however, those experiments were inconclusive. Thus, we turned our attention to the next step in our synthetic sequence, removal of the benzyl ether, which would permit resolution of the epimeric alcohols of **1.12.24** (Scheme 1.12.15).



Scheme 1.12.15

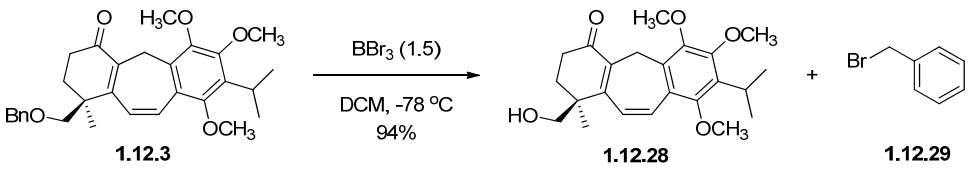
Even though diene **1.12.4** contained two double bonds, both likely sensitive to conditions used in debenzylation reactions, we were confident that chemoselective removal of the C19 benzyl ether could be accomplished using hydrogenation using catalytic Pd/C or $Pd(OH)_2$ in the

presence of H_2 or a suitable hydrogen transfer reagent, dissolving metal reduction with Li, Ca, or Na in NH_3, the use of lithium naphthalenide, DDQ, and others.[79] Unfortunately, despite an extensive survey of these and other conditions for the selective debenzylation of **1.12.4**, none were found to give acceptable selectivity to **1.12.24** (Scheme 1.12.16). Over-reduction of **1.12.4** to **1.12.25** was commonly observed, though reduction of the C6-C7 olefin with retention of the benzyl ether was also seen (**1.12.26**). Isomerization to diene **1.12.37** was also observed in cases.



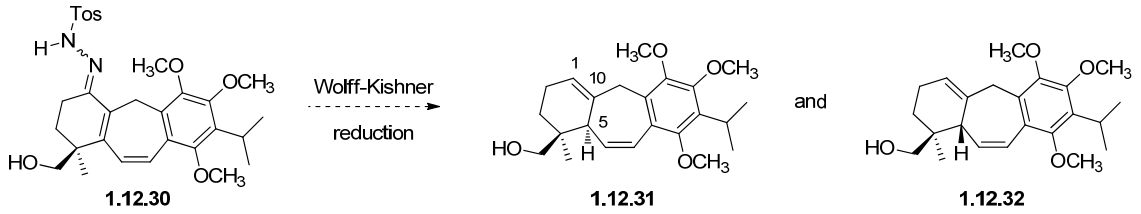
Scheme 1.12.16

With the unexpected, though not surprising, reactivity of the C6-C7 olefin toward reduction, and the tendency of the C1-C10 olefin to migrate, we were forced, yet again, to reevaluate our synthetic plan. We realized that proceeding with a benzyl-protection strategy was the most logical approach, given its reactivity profile in lieu of other protecting groups and the reactivity shown in Scheme 1.12.16. The only established intermediate that had not been deprotected was dienone **1.12.3**, though the preceding and proceeding intermediates demonstrated undesirable reactivity upon attempted deprotection. (see Schemes 1.11.2 and 1.12.16). Initial attempts at the deprotection of benzyl ether **1.12.3** with BBr_3 in DCM at -78 °C resulted in rapid consumption of the starting material, accompanied by the formation of a more polar component by TLC, identified as **1.12.28**. It is useful to note that the formation of benzyl bromide (**1.12.29**) could also be detected by TLC as a nonpolar spot that dissipates over time.



Scheme 1.12.17

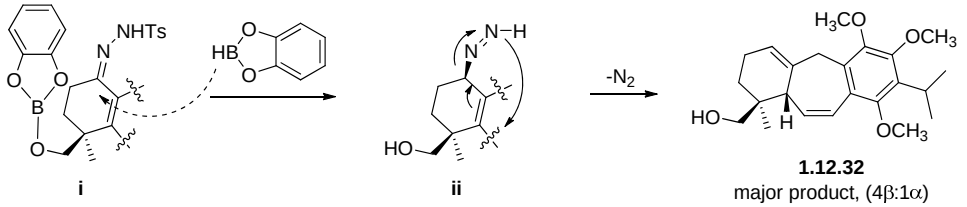
With alcohol **1.12.28** in hand, we were next focused on the stereoselective introduction of the requisite C1-C10 olefin via modified Wolff–Kishner conditions. We expected that reduction of tosylhydrazone **1.12.30** could be controlled to give reduction from the β-face to give **1.12.31** or from the α-face, which would generate **1.12.32** (Scheme 1.12.18).



Scheme 1.12.18

Kabalka's catecholborane protocol frequently results in high facial selectivities in fused α,β-unsaturated tostylhydrazones (see Scheme 1.12.13). Formation of tosylhydrazone **1.12.30** was straightforward and proceeded in near quantitative yield with a slight excess of tosylhydrazide in EtOH at room temperature. Indeed, upon exposure of a solution of **1.12.30** in $CHCl_3$ to 1.5 equivalents of catecholborane at -50 °C, then treating the resulting intermediate with NaOAc-$(H_2O)_3$ under refluxing conditions, resulted in a 1:4 mixture of diastereomeric alcohols **1.12.31** and **1.12.32** in a 70% overall yield. This ratio was determined based on integration of the C1 vinyl proton of the products in ^{1}H NMR, as the two reduction products have different and distinct chemical shifts. This ratio remained unchanged when using either more or fewer equivalents of the borane, operating at higher or lower temperatures, or when the concentration of reagents was modified.

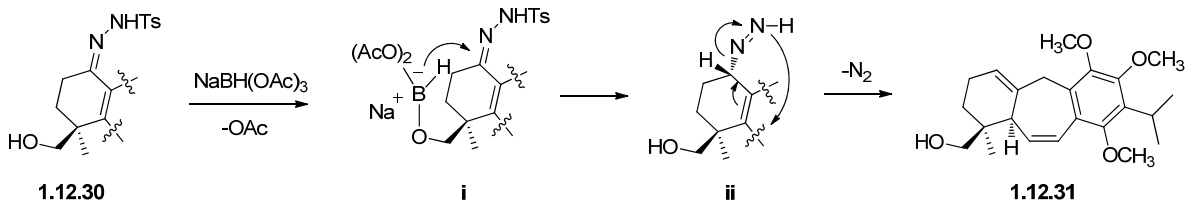
Fortunately, dienes **1.12.31** and **1.12.32** were separable by chromatography, but resolved enough to give complete separation when a careful silica gel column was performed using a gradient elution of ethyl acetate to petroleum ether. Some decomposition was observed upon prolonged exposure of **1.12.31** and **1.12.32** to silica gel, as demonstrated by the appearance of unidentified polar constituents. The epimers were also sensitive when stored as neat solids; as a result, the alcohols were purified and immediately stored in an ethereal solution at -20 °C and used within a one month-period.



Scheme 1.12.19

It was later made clear through synthetic studies that alcohol **1.12.32** was produced as the major product in the Wolff–Kishner reduction of **1.12.30** (see Section 1.13 for elucidation). We postulated that this selectivity was a result of the complexation of one molecule of catcholborane to tosylhydrazone **1.12.30**, thus rendering the β-face of intermediate **i** inaccessible; a second borane added to the less sterically hindered α-face. This reduction leads to the formation of allylic diazene **ii**, which undergoes extrusion of N_2 to give major diastereomer **1.12.32**.

We believed epimeric alcohol **1.12.31** would arise from the intramolecular delivery of an appropriate reducing agent to tosylhydrazone **1.12.30**, guided by the distal hydroxymethyl group (Scheme 1.12.20). Using conditions pioneered by Hutchins, we were confident that this reduction could be achieved with STAB-H (see Scheme 1.12.10). Tosylhydrazone **1.12.30** would react with STAB-H, displacing an acetate group to form intermediate **i**. Intramolecular reduction would generate diazene **ii**, then undergo a [1,5]-sigmatropic rearrangement to give **1.12.31**.

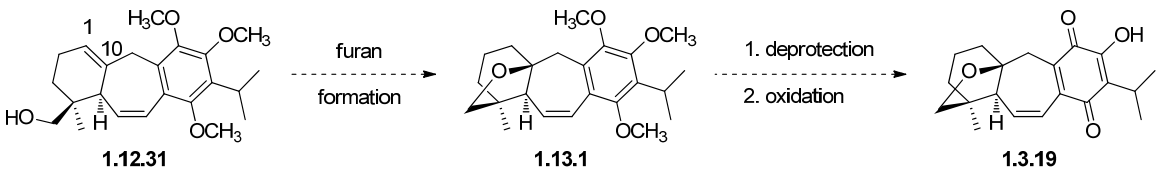


Scheme 1.12.20

We first treated **1.12.30** with Hutchins' conditions, 2.5 equivalents of $NaBH_4$ in acetic acid at room temperature. While Hutchins reported heating the reaction mixture to 70 °C for two hours, our system underwent reduction and rearrangement at room temperature in 16 hours and produced **1.12.31** and **1.12.32** in equal amounts. This ratio was unchanged when different reduction agents were used (*i.e.* $LiBH_4$, KBH_4, $NaCNBH_3$), when reaction temperature was varied, and when a co-solvent was used. A slightly cleaner reaction was observed, though, when $NaCNBH_3$ was used, generating an equimolar ratio of epimers in an 84% overall yield. We postulated that the requisite coordination to give intermediate **i** was not achieved under these reaction conditions, leading to unbiased hydride delivery to alcohol **1.12.30**.

1.13 Synthesis of 19-Deoxyicetexone

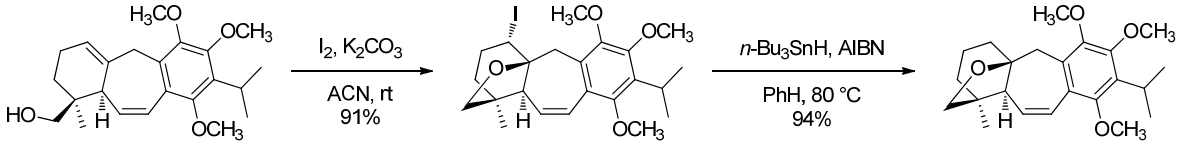
With alcohols **1.12.31** and **1.12.32** in hand from the Wolff–Kishner-like reduction of **1.12.30**, the absolute stereochemistry of the two products was yet to be determined. We envisioned that we could access 19-deoxyicetexone in just a few steps; therefore, synthesis of **1.3.19** from the appropriate epimer would establish the stereochemical assignments for **1.12.31**



Scheme 1.13.1

and **1.12.32**. Since we postulated that reduction of **1.12.30** with catecholborane should proceed from the less hindered α-face, this would generate the β-oriented C5 stereocenter preferentially (see Scheme 1.12.19). Since the major stereoisomer is the wrong one for the synthesis of 19-deoxyicetexone, we decided to carry forward with the minor diastereomer, which we initially posited as **1.12.31.**

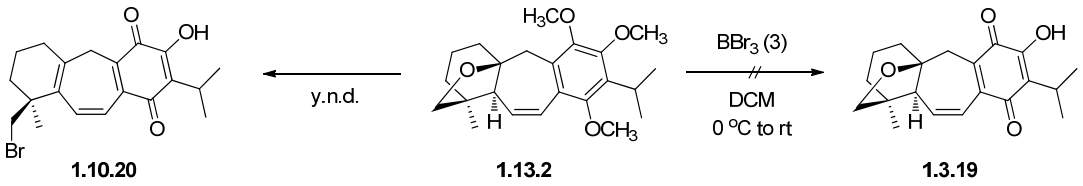
We opted for a common halofuran formation, followed by radical dehalogenation, to access **1.13.31** (Scheme 1.13.1). In our syntheses of salvadione-A and (+)-komaroviquinone, we found that the C1-C10 olefin underwent facile intramolecular bromohydrin formation with NBS. Optimal reaction conditions for furan formation were achieved when **1.12.31** was treated with I_2 in the presence of K_2CO_3 (Scheme 1.13.2). Iodofuran **1.13.2** underwent smooth free-radical induced deiodination with tri-*n*-butyltin hydride in the presence of AIBN in refluxing benzene, giving tetrahydrofuran **1.3.1** in 86% yield from **1.12.31**.



1.12.31 **1.13.2** **1.13.1**

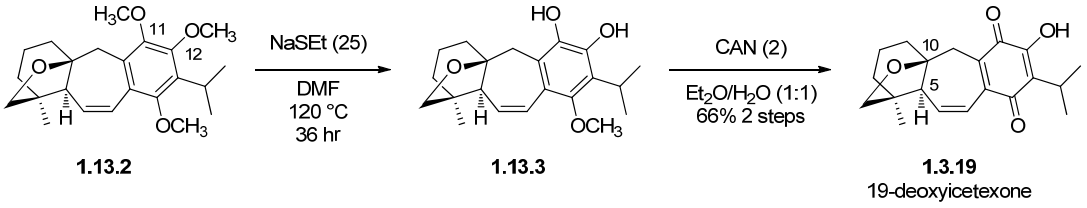
Scheme 1.13.2

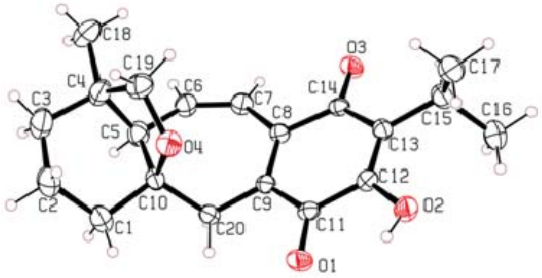
Deprotection of aryl methyl ethers to their corresponding unmasked phenols can be achieve under a variety of conditions.[79] Initially, we were curious whether BBr_3 would achieve a global deprotection of **1.13.1**, which would give **1.3.19** after oxidation (Scheme 1.13.3). However, treating **1.13.2** with 3 equivalents of BBr_3 and allowing the reaction mixture to warm to room temperature resulted in **1.10.20** after exposing the crude product to air. This product was observed previously when global deprotection of methyl-protected **1.10.19** was attempted (*cf.* Scheme 1.10.15).



Scheme 1.13.3

In our syntheses of related icetexane natural products, selective removal of aryl methylethers could be accomplished using excess sodium ethanethiolate in DMF at elevated temperatures.[96] Sodium ethanethiolate is prepared by adding NaH (60 wt% in mineral oil) to a solution of EtSH in DMF. When a solution of **1.13.2** in DMF at was exposed to 25 equivalents of sodium ethanethiolate and heated to 120 °C, TLC analysis revealed dealkylation of the C11-methoxy group within a several hours. Upon further heating, generation of catechol **1.13.3** could be observed and was the major product after 36 hours at 120 °C. The crude product was then oxidized to the natural product in 66% yield from **1.13.2** by treating **1.13.3** with CAN in a 1:1 mixture of Et_2O:H_2O. The spectral and optical rotation data for synthetic 19-deoxyicetexone matched that of the natural material isolated by Esquivel and co-workers, as compiled in Section 1.15.[8a] More importantly, single crystal X-ray diffraction analysis of **1.3.19** confirmed the





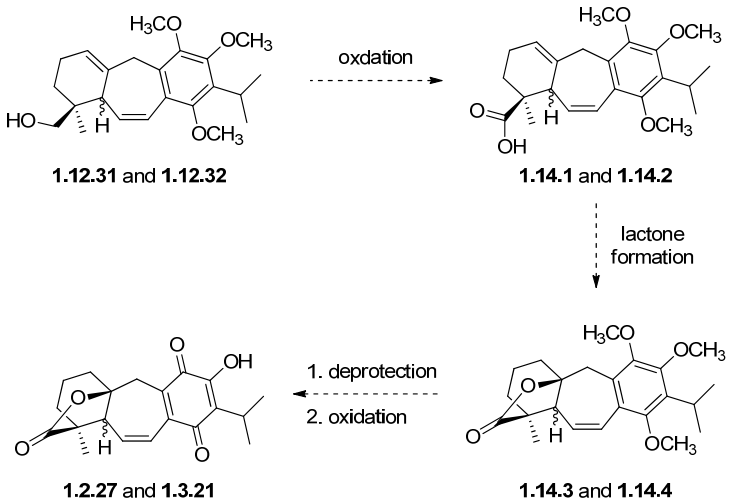
Scheme 1.13.4

relative configuration of the C5 methine in relation to the bridging C1 heterocycle. This analysis permits the stereochemical assignments of alcohols **1.12.31** and **1.12.32** (see Scheme 1.12.18). The absolute stereochemistry was extrapolated from Yamada's proof, wherein an optically-active cyclohexenone was converted to an intermediate in Suzuki's synthesis of cassiol (see Section 1.9). The optically rotation for the natural product was +75°, whereas the synthetic 19-deoxyicetexone was +95° under the same parameters.

In summary, we successfully forged the key heterocyclic ring in 19-deoxyicetexone via an iodofuran-deiodination strategy and deprotection and oxidation of the arene ring liberated the hydroxy-*p*-benzoquinone motif to give **1.3.19**. This exercise not only verified the absolute configuration of the C5-methine resulting from the alkene walk, but also reaffirmed the configuration of the C4 hydroxymethyl group.

1.14 Synthesis of Icetexone and 5-*epi*-Icetexone

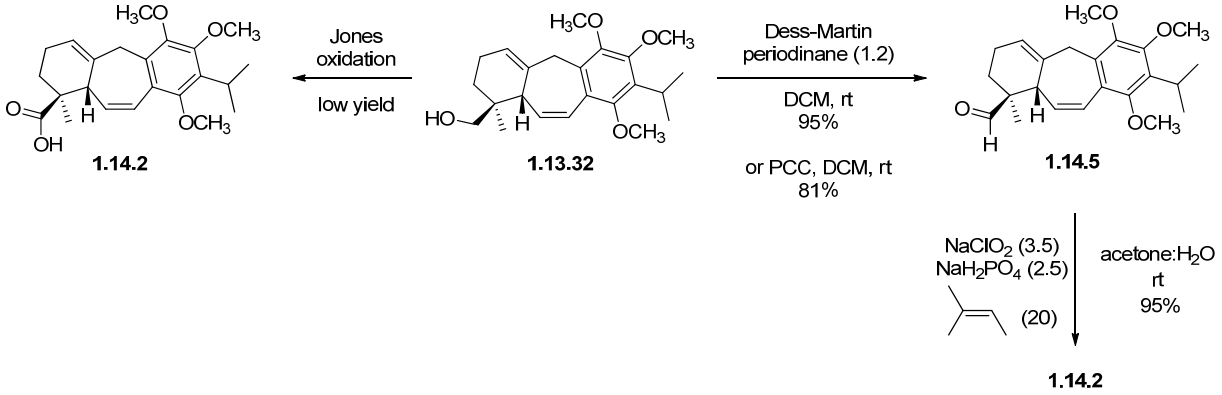
Since the absolute configuration for alcohols **1.12.31** and **1.12.32** was established by synthetic means, conversion of these intermediates to icetexone and 5-*epi*-icetexone seemed



Scheme 1.14.1

straightforward, through oxidation of the neopentyl alcohol to carboxylic acids **1.14.1** and **1.14.2** and utilizing a similar iodocyclization-deiodination strategy to access **1.14.3** and **1.14.4**. Finally, deprotection and oxidation would give the title compounds.

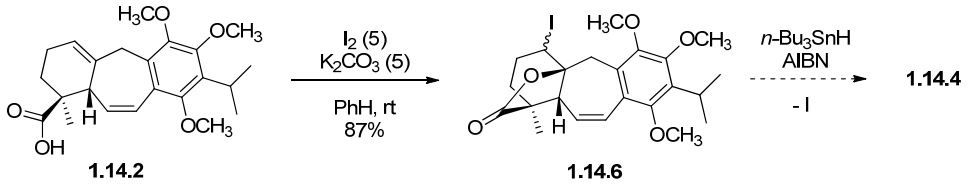
In reviewing the isolation papers for icetexone and 5-*epi*-icetexone, we found that in the 1976 isolation of **1.2.27**, ^{1}H and ^{13}C data for the natural product was absent. As a result, we decided to focus first on the synthesis of 5-*epi*-icetexone (**1.3.21**), as the isolation paper contained both ^{1}H and ^{13}C NMR data. Since the two epimers contained similar functional groups, conditions for their preparation should be similar.



Scheme 1.14.2

Oxidation of the neopentyl alcohol in **1.3.32** to the corresponding carboxylic acid was straightforward, though we initially thought that the crowded neopentyl center might be too hindered for efficient oxidation. Direct oxidation to carboxylic acid **1.14.2** with Jones reagent was unsuccessful, likely due to competing isomerization of the C1-C10 double bond. However, we were confident that a two-step oxidation sequence would deliver **1.14.2.** Indeed, oxidation with Dess–Martin periodinane gave aldehyde **1.14.5** in excellent yield, while PCC oxidation resulted in a slightly lower yield of the desired aldehyde. The Lindgren oxidation was developed in the early 1970's by Lindgren and Nilsson and is a commonly-used and mild condition for the

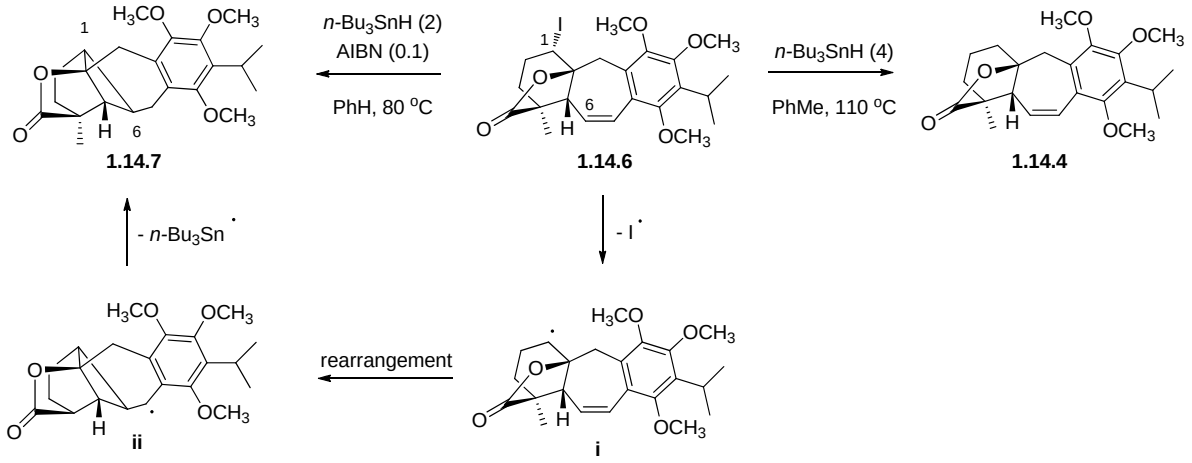
next oxidation step.[97] In this oxidation, $NaClO_2$ is the oxidant in a mixed solvent system is used, which consists of a water-miscible organic solvent and H_2O under slightly acidic conditions. More reactive hypochlorite can be scavenged with numerous compounds, including sulfamic acid, resorcinol, H_2O_2, and 2-methyl-2-butene. Oxidation of aldehyde **1.14.5** to is corresponding acid was accomplished under these conditions to give **1.14.5** in excellent yield without competing side reactions. While ACN and *t*-BuOH were efficient co-solvents under the above conditions, we found that an increased reaction rate was observed when acetone was employed.



Scheme 1.14.3

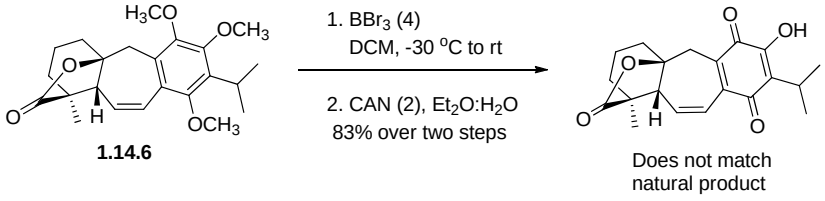
Lactonization of **1.14.2** to **1.14.4** was carried out under similar conditions employed for furan formation in the synthesis of 19-deoxyicetexone. First, iodolactonization was accomplished with 5 equivalents of both I_2 and K_2CO_3 in benzene to give **1.4.6** in good yield. Next, radical deiodination to give **1.14.4** seemed trivial, since previous results indicated that tri-*n*-butyltin hydride in the presence of catalytic amounts of AIBN gives efficient dehalogenation.

To our surprise, treating iodolactone **1.14.6** with 2 equivalents tri-*n*-butyltin hydride in refluxing benzene with catalytic AIBN resulted in the formation of a new product containing neither the C1-iodide nor the C6-C7 olefin, identified as tetracycle **1.14.7**. We postulate that this byproducts results from the initially-formed C1 radical of **i** adding intramolecularly to the C6 position to generate **ii**, which is in close proximity, instead of abstracting a hydrogen atom from the tri-*n*-butyltin hydride. The use of a large excess of tri-*n*-butyltin hydride, without AIBN, suppressed this undesired side reaction and gave lactone **1.14.4** in excellent yield.

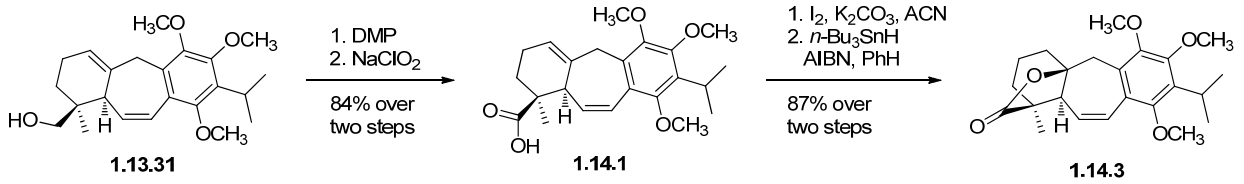


Scheme 1.14.4

We envisioned the removal of the C11 and C12 aryl methyl ethers in **1.14.6** would be achieved with BBr_3, followed by subsequent oxidation to the *p*-benzoquinone motif by CAN. Ethanethiolate in hot DMF, used in the synthesis of 19-deoxyicetexone, would be incompatible with the lactone group. When **1.14.6** was treated with 4 equivalents of BBr_3 in DCM at -30 °C and allowed to rise to room temperature over 20 minutes, removal of the C11 and C13 protecting groups was observed by TLC analysis. Subsequent oxidation of the crude product with CAN in Et_2O:H_2O gave a characteristic *p*-benzoquinone product, as evident by its orange color on silica gel. NMR analysis revealed a product with the salient features of the natural product, though direct comparison with the natural material revealed that a different product had formed. Even when the deprotection and oxidation conditions were changed, no other products were generated.

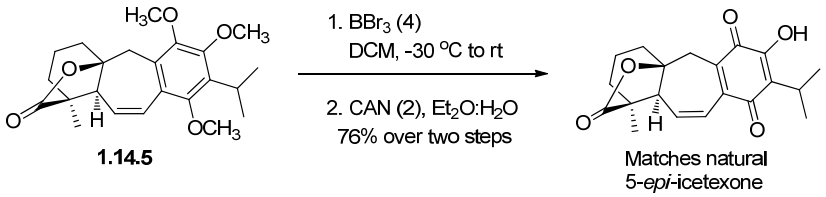


Scheme 1.14.5



Scheme 1.14.6

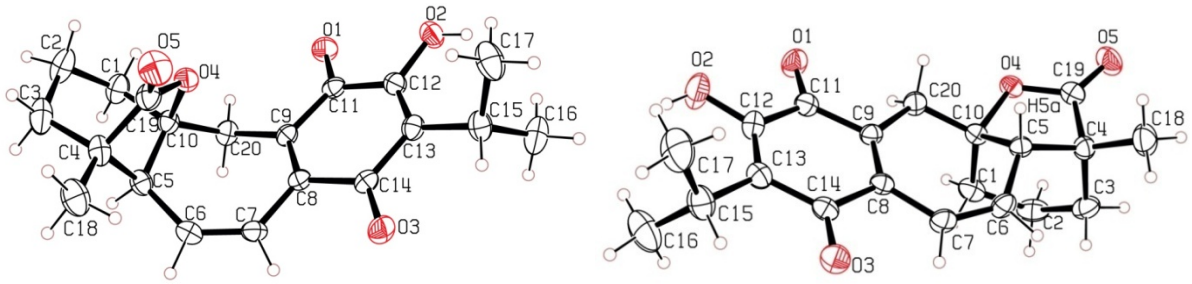
During our synthetic approaches toward 5-*epi*-icetexone, we were also carrying **1.3.21** forward to prepare its epimeric lactone natural product, icetexone (**1.2.27**). Through a similar series of transformation, lactone **1.14.3** was prepared (Scheme 1.14.6). Oxidation to acid **1.4.1** was achieved by conversion of **1.13.31** to the corresponding aldehyde (**1.14.8**) with Dess-Martin periodinane, followed by oxidation to acid **1.14.1** under Lindgren oxidation conditions. Iodolactonization was carried out in ACN, while the C5-epimer was **1.4.2** was cyclized in benzene. In this system, we found that radical-promoted deiodination could be achieved under normal conditions, with only a slight excess of *tris*-*n*-butyltin hydride in refluxing benzene, which gave lactone **1.14.3** in 87% yield over two steps.



Scheme 1.14.7

Deprotection and oxidation of the aromatic portion to the *p*-benzoquinone motif found in the natural product could be carried out using excess BBr_3, followed by CAN oxidation of the resulting catechol (Scheme 1.14.7). Since the structural elucidation for icetexone (**1.2.27**) was carried out using single-crystal X-ray diffraction and without ^1H or ^{13}C NMR analysis, spectral comparison could not be performed. We did recognize, however, that both the ^1H and ^{13}C NMR for the synthetic product matched the data for natural 5-*epi*-icetexone (**1.3.21**) and X-ray analysis

confirmed our structural assignment regarding the C5 stereochemistry for both epimers (Figure 1.14.1). The optical rotation data and melting points were the only two analyses that were obtained for the two natural products, which were also reversed for the two compounds. Thus, there was clearly an error in assigning the stereochemistry and physical data for icetexone (**1.2.27**) and 5-*epi*-icetexone (**1.3.21**).



Synthetic icetexone (**1.2.27**) Synthetic 5-*epi*-icetexone (**1.3.21**)

Figure 1.14.1

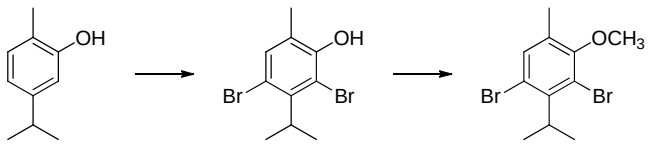
We have heretofore reassigned the ^{1}H and ^{13}C NMR, melting point, and optical rotation data for the natural product with the structure corresponding to icetexone (**1.2.27**), which had been assigned to the structure corresponding to 5-*epi*-icetexone (**1.3.21**). A comparison of this data is presented in Section 1.15. We have also assigned the correct melting point and optical rotation data for 5-*epi*-icetexone (**1.3.21**), which had been assigned to the structure corresponding to icetexone (**1.2.27**) and assigned the correct ^{1}H and ^{13}C NMR data to 5-*epi*-icetexone, which has not previously been reported. This new data is presented in Section 1.15

To conclude we have developed an efficient strategy toward the synthesis of icetexone (**1.2.27**), 5-*epi*-icetexone (**1.3.21**), and 19-deoxyicetexone (**1.3.19**). We adopted an enzymatic resolution strategy to introduce chirality into the A-ring portion and prepared the C-ring in six steps from carvacrol. We developed a novel cyclialkylation method to introduce the C6-C7 olefin into the central ring, which has been used in the total synthesis of five icetexanes.

Additionally, total synthesis has led to reassignment of the spectral and physical data for icetexone (**1.2.27**) and 5-*epi*-icetexone (**1.3.21**)

1.15 Experimental Procedures

General Procedures: All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all extractive workups consisted of the following procedure: the organic reaction solvent was removed under reduced pressure on a rotary evaporator, and the residue was taken up in diethyl ether. The combined extractive extracts were washed with water, brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 4 torr to a constant weight, afforded a crude residue which was purified by flash chromatography using silica gel 60 (230-400 mesh ASTM) and distilled reagent grade petroleum ether (pet ether), diethyl ether, and ethyl acetate. Melting points were recorded on a Laboratory Devices Mel-Temp 3.0. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVB-400 and DRX-500 MHz spectrometers with ^{13}C operating frequencies of 100 MHz and 125 MHz, respectively. Proton NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference. Carbon NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 77.23) as an internal reference. The IR spectra were obtained using an Avatar 360FT-IR and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbances are reported. High resolution MS were taken using a Waters LCT Premier.

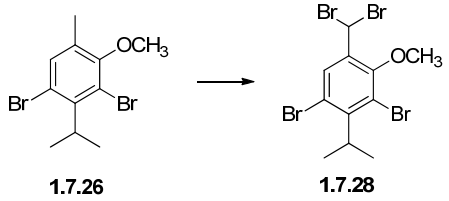


1.6.7 **1.7.21** **1.7.26**

Preparation of 1,3-dibromo-2-isopropyl-4-methoxy-5-methylbenzene (1.7.26): To a solution of carvacrol (**1.6.7**) (15.00 g, 0.10 mol) in glacial acetic acid (100 mL) at 0 °C was added bromine (11.20 mL, 0.22 mol) over a 5-min. period. The resulting mixture was warmed to rt and stirred until TLC analysis indicated the complete consumption of **1.6.7**. The reaction mixture was poured over ice and after the ice had melted, 100 mL of saturated aqueous Na_2SO_3 was added. The aqueous phase was extracted with pet ether (3 x 50 mL). The combined organic extracts were washed with water (25 mL), saturated aqueous sodium bicarbonate (2 x 25 mL), and then brine (25 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure. The crude phenol was used in the next step without further purification or characterization.

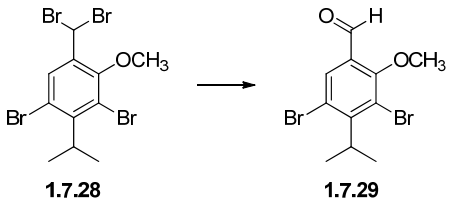
To a solution of the above phenol (~0.10 mmol) in THF (100 mL) was added finely crushed KOH (8.40 g, 0.15 mol). The solution was stirred for 10-min, and iodomethane (9.34 mL, 0.15 mol) was added drop-wise over a 15-min. period. The resulting mixture was stirred until TLC analysis indicated the complete consumption of the phenol. The solids were removed by filtration and standard extractive workup furnished **1.7.26** as a dark brown oil. Vacuum distillation (110 °C @ 7 Torr) gave 30.22 g (94% over two steps) of **1.7.26** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.7.26**) = 0.75, 10:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.36 (d, *J* = 17.6 Hz, 1H), 3.90 (dsept, *J* = 46.8, 5.6 Hz, 1H), 3.78 (s, 3H), 2.28 (s, 3H), 1.43 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 155.9, 155.0, 143.4, 136.3, 134.4, 131.7, 122.8, 120.9, 119.4, 117.1, 60.2, 60.1, 36.5, 35.8, 19.7, 16.3, 16.3; IR (film) λ_{max}

1454, 1337, 1325, 1270 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 319.9411, found *m/z* 319.9410.



1.7.26 **1.7.28**

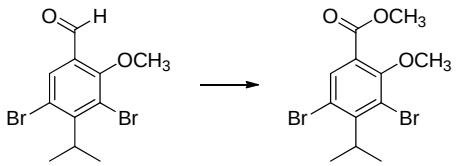
Preparation of 1,3-dibromo-5-(dibromomethyl)-2-isopropyl-4-methoxybenzene (1.7.28): To a solution of **1.7.26** (12.1 g, 37.6 mol) in freshly-distilled CCl_4 (125 mL) was added NBS (16.7 g, 094 mmol) and AIBN 623 mg, 3.8 mmol). The resulting solution was refluxed for 12h under a N_2 atmosphere with vigorous stirring. The reaction mixture was cooled to rt and filtered through filter paper. The resulting solids were rinsed with ether (3 x 50 mL). The CCl_4 and extractive washings were combined and washed with water (3 x 20 mL), brine (25 mL), and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure, gave a crude residue which was purified by silica gel chromatography (elution with pet ether/EtOAc = 10:1) to provide 12.8 g (71%) of **1.7.28** as a viscous orange oil which was homogeneous by TLC analysis [R_f (**1.7.28**) = 0.70, 10:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.03 (d, *J* = 22.1 Hz, 1H), 6.97 (s, 1H), 3.84-4.04 (m, 1H), 3.92 (s, 3H), 1.44 (d, *J* = 7.0 Hz, 6H).



1.7.28 **1.7.29**

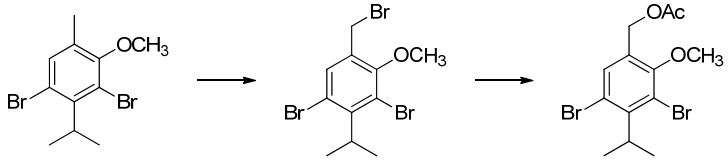
Preparation of 3,5-dibromo-4-isopropyl-2-methoxybenzaldehyde (1.7.29): To a solution of **1.7.28** (10.6 g, 22.1 mmol) in acetonitrile (50 mL) was added aqueous dimethylamine (40 wt% in H_2O, 130 mL). The resulting solution was refluxed for 4h with a high-efficiency

condenser. If TLC analysis did not indicate reaction completion, additional portions of dimethylamine were added. The reaction mixture was cooled to rt, then to 0 °C, at which time the reaction mixture was acidified by the addition of 6 *M* HCl and stirred for an additional 1h at rt. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 10:1) to provide 6.8 g (92%) of **1.7.29** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.7.29**) = 0.65, 10:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 10.2 (s, 1H), 7.99 (d, *J* = 19.8 Hz, 1H), 3.96 (s, 3H), 3.85-4.11 (m, 1H), 1.46 (s, 6H).



1.7.29 **1.7.30**

Preparation of methyl 3,5-dibromo-4-isopropyl-2-methoxybenzoate (1.7.30): To a solution of **1.7.29** (9.6 g, 28.6 mmol) in MeOH (100 mL) was added K_2CO_3 (5.9 g, 42.9 mmol) and I_2 (10.9 g, 42.9 mmol). The resulting solution was stirred at rt for 16 h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 10:1) to provide 9.7 g (93%) of **1.7.30** as a dark yellow oil which was homogeneous by TLC analysis [R_f (**1.7.30**) = 0.68, 10:1 pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.01 (d, *J* = 18.2 Hz, 1H), 3.87-4.10 (m, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 1.44 (s, 6H).

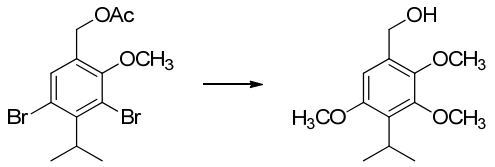


1.7.26 **1.7.27** **1.7.40**

Preparation of 3,5-dibromo-4-isopropyl-2-methoxybenzyl acetate (1.7.40): To a solution of **1.7.26** (31.80 g, 0.10 mol) in freshly-distilled cyclohexane (200 mL) was added NBS (44.20 g, 0.25 mol) and AIBN (814 mg, 5.00 mmol). The resulting solution was refluxed for 12h

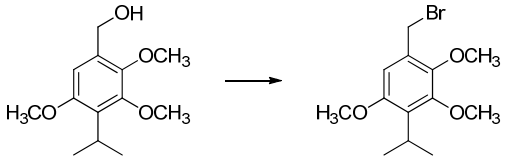
under a N_2 atmosphere with vigorous stirring. The reaction mixture was cooled to rt and filtered through filter paper. The resulting solids were rinsed with ether (3 x 50 mL). The cyclohexane and extractive washings were combined and washed with water (2 x 25 mL), brine (25 mL), and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure yielded the crude benzyl bromide as an orange oil which was used immediately in the next step without further purification or characterization.

To a solution of the above crude benzylic bromide in 300 mL DMF was added anhydrous NaOAc (16.30 g, 0.20 mol). The resulting solution was refluxed for 8h or until TLC analysis indicated the complete consumption of the bromide. The reaction mixture was cooled to rt and diluted with ether (500 mL) and water (100 mL). The organic phase was separated and was then washed with water (5 x 25 mL), brine (25 mL), and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure, gave a crude residue which was purified by silica gel chromatography (elution with pet ether/EtOAc = 6:1) to provide 26.72 g (70% over two steps) of **1.7.40** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.7.40**) = 0.36, 10:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.56 (d, *J* = 19.6 Hz, 1H), 5.12 (s, 2H), 3.93 (dsept, *J* = 43.2, 6.8 Hz, 1H), 3.85 (s, 3H), 2.13 (s, 3H), 1.43 (t, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 170.7, 155.7, 155.0, 146.3, 135.3, 133.4, 129.6, 123.0, 121.3, 119.6, 117.5, 61.6, 61.5, 61.1, 36.7, 35.9, 21.1, 19.5, 19.4; IR (film) λ_{max} 1742, 1220, 1021 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 377.9466, found 377.9450.



1.7.40 **1.7.41**

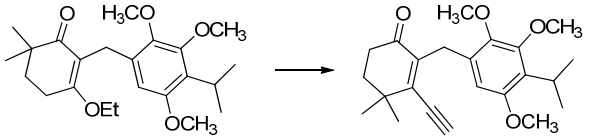
Preparation of (4-isopropyl-2,3,5-trimethoxyphenyl)methanol (1.7.41): A solution of sodium methoxide was prepared by the addition of small portions of sodium metal (4.61 g, 0.20 mol) to anhydrous methanol (75 mL). After the consumption of the sodium, a solution of **1.7.40** (12.70 g, 33.00 mmol) dissolved in anhydrous DMF (60 mL) was added, followed by the addition of CuI (635 mg, 3.30 mmol). The reaction mixture was heated at 110 °C under a N_2 atmosphere for 12h. The reaction mixture was cooled to rt and 50 mL of an aqueous 6 *M* solution of HCl was added drop-wise. Standard extractive workup, followed by silica gel chromatography (elution with DCM/MeOH = 0% to 1% MeOH in DCM), gave 5.62 g (70%) of **1.7.41** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.7.41**) = 0.48, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.60 (s, 1H), 4.67 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.50 (sept, *J* = 6.8 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 154.9, 151.8, 145.3, 131.8, 130.4, 106.6, 61.8, 61.0, 61.0, 56.0, 25.4, 21.4; IR (film) λ_{max} 3401, 2955, 2869, 2834 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$ = *m/z* 241.1362, found 241.1437.



1.7.40 **1.5.8**

Preparation of 1-(bromomethyl)-4-isopropyl-2,3,5-trimethoxybenzene (1.5.8): A solution of **1.7.41** (24.00 g, 0.10 mol) dissolved in Et_2O (250 mL) was cooled to 0 °C and PBr_3 (10.3 mL, 0.11 mol) was added drop-wise. The resulting reaction mixture was allowed to warm to rt and then stirred for 1h. The reaction mixture was cooled to 0 °C and 50 mL of brine was

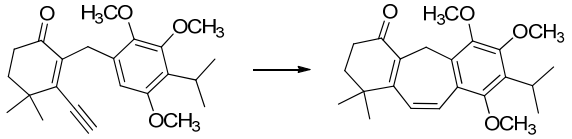
added drop-wise. The brine layer was separated and the organic phase was dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure, and silica gel chromatography (elution with pet ether/EtOAc = 10:1), gave 29.02 g (96%) of bromide **1.5.8** as a white solid which was homogeneous by TLC analysis [R_f (**1.5.8**) = 0.61, 10:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.60 (s, 1H), 4.55 (s, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.50 (sept, *J* = 7.2 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 154.8, 152.1, 145.9, 132.1, 128.8, 108.1, 77.4, 60.9, 60.9, 55.9, 29.0, 25.5, 21.3; IR (film) λ_{max} 2956, 2935, 1409, 1129 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 303.0518, found 303.0601.



1.5.11 **1.8.22**

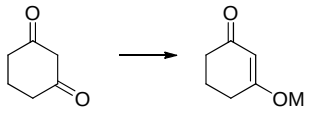
Preparation of 3-ethynyl-2-(4-isopropyl-2,3,5-trimethoxybenzyl)-4,4-dimethylcyclo-hex-2-enone (1.8.22): To a solution of acetylene (4.30 mL, 114 mmol) in THF (40 mL) at -78 °C, *n*-butyllithium (2.5 M, 41.2 mL, 104 mmol) in THF (100 mL) was added over a 15-min. period. After stirring for 30-min. at -78 °C, **1.5.11** (7.70 g, 19.7 mmol) in THF (15 mL) was added slowly. The resulting mixture was allowed to warm to rt and then stirred at rt for an additional 8h. Aqueous 1.0 *M* HCl (20.0 mL) was added dropwise at 0 °C and the resulting mixture was stirred for 30 minutes. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc, 8:1), gave 2.90 g of unreacted **1.5.11** and 4.01 g (79%, brsm) of **1.8.22** as a white solid which was homogeneous by TLC analysis [R_f (**1.8.22**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H (400 MHz) δ 6.29 (s, 1H), 3.87 (s, 3H), 3.83 (s, 2H), 3.82 (s, 3H), 3.70 (s, 1H), 3.68 (s, 3H), 3.45 (septet, *J* = 7.2 Hz, 1H), 2.51 (t, *J* = 6.8 Hz, 2H), 1.93 (t, *J* = 6.8 Hz, 2H), 1.34 (s, 6H), 1.27 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz) δ 197.3, 154.3, 151.9,

147.1, 145.5, 142.0, 130.1, 128.3, 106.5, 91.9, 80.7, 61.0, 60.5, 55.7, 36.5, 35.8, 34.7, 28.1, 27.9, 25.3, 21.6.



1.8.22 **1.8.5**

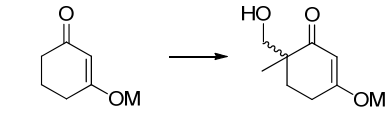
Preparation of 8-isopropyl-6,7,9-trimethoxy-1,1-dimethyl-2,3-dihydro-1H-dibenzo [a,d][7]annulen-4(5H)-one (1.8.5): To a solution of **1.8.22** (4.36 g, 11.8 mmol) and ethanethiol (97%, 0.500 mL, 6.57 mmol) in freshly distilled CH_2Cl_2 (50 mL) at 0 °C was added dropwise 5.0 mL of BF_3-Et_2O (40.0 mmol). The resulting mixture was stirred for 1h at 0 °C and 16h at rt. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc, 10:1), gave 4.01 g (92%) of **1.8.5** which was homogeneous by TLC analysis [R_f (**1.8.5**) = 0.65, 4:1, pet ether/EtOAc]: ^{1}H (400 MHz) δ 7.46 (d, *J* = 12.4 Hz, 1H), 6.75 (d, *J* = 12.4 Hz, 1H), 3.91 (s, 3H), 3.86 (d, *J* = 23.2 Hz, 1H), 3.83 (s, 3H), 3.76 (d, *J* = 23.2 Hz, 1H), 3.67 (s, 3H), 3.44 (septet, *J* = 7.2 Hz, 1H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.84 (t, *J* = 7.2 Hz, 2H), 1.33 (d, *J* = 7.2 Hz, 6H), 1.23 (bs, 6H); ^{13}C (100 MHz) 196.61, 157.32, 154.21, 151.86, 146.23, 133.90, 133.55, 132.33, 130.38, 127.66, 124.93, 62.11, 61.17, 60.47, 37.06, 34.81, 34.58, 27.69, 27.69, 25.66, 22.34, 22.06, 22.06.



1.9.14 **1.9.15**
M = (-) menthol

Preparation of 3-((2-isopropyl-5-methylcyclohexyl)oxy)cyclohex-2-enone (1.9.15): A solution of **1.9.14** (4.4 g, 39.2 mmol), (–)-menthol (5.0 g, 32.0 mmol), and *p*-toluenesulfonic acid (50 mg, 2.6 μmol) in toluene:diglyme (4:1, 50 mL) is refluxed for 30-min, at which time H_2O is removed azeotropically through the use of a Dean–Stark apparatus. After 20h, toluene and

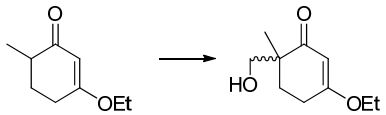
diglyme are removed via vacuum distillation. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc, 4:1), gave 6.1 g (62%) of **1.9.15** as a white solid which was homogeneous by TLC analysis [R_f (**1.9.15**) = 0.61, 4:1, pet ether/EtOAc]: ^{1}H (400 MHz) δ 5.41 (s, 1H), 4.98 (dt *J* = 4.1, 6.6 Hz, 1H), 2.37 (m, 5H), 2.12 (m, 1H), 1.98 (m, 3H), 1.71 (m, 2H), 1.43 (m, 2H), 1.02 (m, 2H), 0.91 (m. 9H), 0.74 (d, *J* = 7.0 Hz, 3H).



1.9.15
M = (-) menthol

1.9.16

Preparation of 6-(hydroxymethyl)-3-((2-isopropyl-5-methylcyclohexyl)oxy)-6-methyl cyclohex-2-enone (1.9.16): 1.9.16 was prepared using the same procedure that was used to prepare alcohol **1.6.6** (see below). **1.9.15** (3.2 g, 12.8 mmol) gave 2.1 g (56%) **1.9.16** as a white solid which was homogeneous by TLC analysis [R_f (**1.9.16**) = 0.32, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.31 (s, 1H), 3.98 (m, 1H), 3.56 (d, *J* = 6.4 Hz, 2H), 2.58 (m, 1H), 2.35 (m, 1H), 2.10 (m, 1H), 1.99 (m, 2H), 1.71 (m, 3H), 1.56 (m, 1H), 1.45 (m, 2H), 1.17 (t, *J* = 6.1 Hz, 3H), 0.93-1.11 (m, 3 H), 0.91 (t, *J* = 6.4 Hz, 6H), 0.74 (dd, *J* = 2.1, 6.9 Hz, 3H).

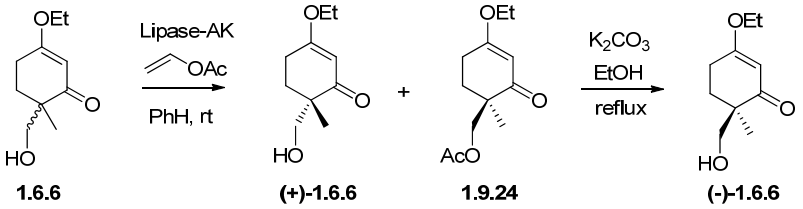


1.9.19

1.6.6

Preparation of 3-ethoxy-6-(hydroxymethyl)-6-methylcyclohex-2-enone (1.6.6): To a solution of diisopropylamine (33 mL, 0.23 mol) dissolved in 250 mL THF at -78 °C was added *n*-butyllithium (93.6 mL, 0.23 mol) over a 5-min. period. The resulting mixture was stirred at -78 °C for 30-min. A solution of 6-methyl-3-ethoxy-cyclohex-2-en-1-one (**1.9.19**, 30.00 g, 0.19 mol) dissolved in 300 mL of THF was added using a cannula to the reaction mixture over a 5-min. period and the resulting mixture was warmed to rt over a 30-min. period. Formaldehyde gas,

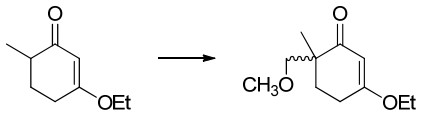
generated by heating paraformaldehyde at 135 °C, was bubbled into the reaction mixture under a constant N_2 flow until TLC analysis indicated the consumption of the starting material was complete. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/Et_2O = 1:2), gave 31.12 g (84%) of **1.6.6** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.6.6**) = 0.26, 1:2, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.25 (s, 1H), 3.89 (m, 2H), 3.54 (q, *J* = 11.2 Hz, 2H), 2.57 (m, 1H), 2.34 (m, 1H), 2.01 (m, 1H), 1.55 (m, 1H), 1.35 (t, *J* = 7.2 Hz, 6H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 205.8, 177.3, 101.6, 69.5, 64.6, 44.7, 29.9, 26.0, 19.3, 14.3; IR (film) λ_{max} 1634, 1599, 1378, 1360 cm^{-1}; HRMS (ESI) calculated for M^+: *m/z* 184.1099, found 184.1098.



Resolution of 1.6.6: (*Step A*): To a solution of **1.6.6** (20.00 g, 0.11 mol) in 200 mL benzene at rt was added vinyl acetate (20 mL, 0.22 mol), followed by 10.00 g of Amano Lipase AK. After stirring at rt for 16 h, the reaction mixture was filtered through a pad of Celite, which was washed with EtOAc (2 x 50 mL). Removal of the solvent under reduced pressure, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 12.50 g (51%) of acetate **1.9.24** as a yellow oil which was homogeneous by TLC analysis [R_f **1.9.24** = 0.55, 2:1 pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.26 (s, 1H), 4.27 (d, *J* = 7.6 Hz, 1H), 3.93 (d, *J* = 7.2 Hz, 1H), 3.87 (m, 2H), 2.48 (m, 1H), 2.38 (m, 1H), 2.05 (m, 1H), 1.98 (s, 3H), 1.69 (m, 1H), 1.32 (t, *J* = 5.6 Hz, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.8, 176.3, 171.0, 101.7, 68.5, 64.4, 43.9, 29.8, 25.9, 20.9, 19.7, 14.2; IR (film) λ_{max} 1739, 1649, 1603, 1377 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 227.1283, found 227.1277.

(*Step B*): To a solution of **1.9.24** (12.50 g, 0.056 mol) in 125 mL of ethanol at rt was added K_2CO_3 (23.10 g, 0.17 mol). The resulting reaction mixture was refluxed for 2h. After cooling to rt, the reaction mixture was filtered through a small pad of Celite. Removal of the solvent under reduced pressure, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1), gave 8.22 g (41% overall yield over two steps) of enriched alcohol **(−)-1.6.6** as a yellow oil which was homogeneous by TLC anaylsis [R_f **(−)-1.6.6** = 0.26, 1:2 pet ether/EtOAc].

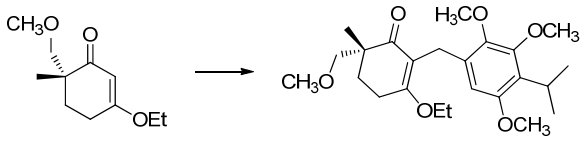
Re-submission of this 85% e.e. enriched material to steps A and B ultimately yielded 7.8 g (39% through four steps) of **(−)-1.6.6** as a yellow oil: $[\alpha]^{20.4}_{D}$ = -75° ($CHCl_3$, c 7.4); > 99% e.e. The enantiomeric excess (%e.e.) was determined using a ChiralPak AD-H column using 9:1, hexane:isopropanol operating at 1.0 mL/min. with UV detection at 254 nm. Using these parameters, the minor enantiomer **(+)-1.6.6** eluted at 3.7 minutes while the major enantiomer, **(−)-1.6.6** eluted at 4.7 minutes.



1.9.19 **1.10.1**

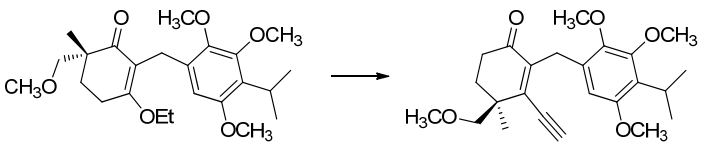
Preparation of 3-ethoxy-6-(methoxymethyl)-6-methylcyclohex-2-enone (1.10.1): To a solution of diisopropylamine (2.3 mL, 16.5 mmol) in 25 mL THF at -78 °C was added *n*-butyllithium (6.6 mL, 16.5 mmol) over a 5-min. period. The resulting mixture was stirred at -78 °C for 30 min. A solution of **1.9.19** (2.3 g, 15.1 mmol) in 15 mL of THF was added using a cannula to the reaction mixture over a 5 min. period and the resulting mixture was stirred at -78 °C for an additional 30-min. To the resulting reaction mixture was added a solution of MOM-Cl (1.4 mL, 19 mmol) in 10 mL THF and the reaction mixture was allowed to stir at -78 °C for an additional 1h. Standard extractive workup, followed by silica gel chromatography (elution with

pet ether/EtOAc = 4:1), gave 2.39 g (81%) of **1.10.1** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.10.1**) = 0.45, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.30 (s, 1H), 3.89 (q, *J* = 7.0 Hz, 2H), 3.64 (d, *J* = 8.9, 1H), 3.33 (s, 3H), 3.19 (d, *J* = 8.9, 1H), 2.44 (m, 1H), 2.20 (m, 1H), 1.72 (m, 1H), 1.376 (t, *J* = 7.0 Hz, 3H), 1.07 (s, 3H).



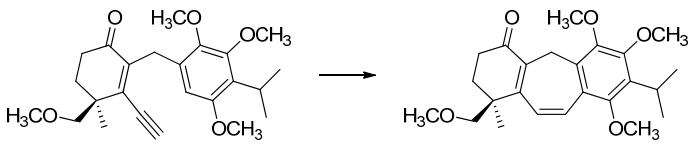
1.10.1 **1.10.8**

Preparation of (R)-3-ethoxy-2-(4-isopropyl-2,3,5-trimethoxybenzyl)-6-(methoxy methyl)-6-methylcyclohex-2-enone (1.10.8): To a solution of diisopropylamine (0.68 mL, 4.8 mmol) in 15 mL of THF at -78 °C was added *n*-butyllithium (1.8 mL, 4.6 mmol) over a 5-min. period. The resulting mixture was stirred at -78 °C for 30 min. A solution of **1.10.1** (804 mg, 4.1 mmol) and HMPA (1.1 mL, 6.3 mmol) in 5 mL of THF was added using a cannula over a 5 min. period. The resulting mixture was warmed to rt over 30-min. and was stirred at rt for 1h. The resulting mixture was cooled to 0 °C and a solution of **1.5.8** (311 mg, 1.03 mmol) in 5 mL of THF was added rapidly via a cannula and the ice bath was removed. The reaction mixture was stirred at rt until TLC analysis indicated the complete consumption of bromide **1.5.8**. Water (5 mL) and ether (15 mL) were then added and the resulting mixture was stirred for 5-min. Standard extractive workup, followed by filtration through a small pad of silica gel, furnished a dark brown oil; the excess **1.10.1** was recovered by simple vacuum distillation. The remaining pot residue was purified by silica gel chromatography (elution with pet ether/EtOAc = 2:1) and gave 950 mg (56%) of **1.10.8** as a viscous brown oil which was homogeneous by TLC analysis [R_f (**1.10.8**) = 0.47, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.21 (s, 1H), 4.05 (pentet, *J* = 6.7 Hz, 2H), 3.82 (s, 6H), 3.60-3.70 (m, 5H), 3.39-3.50 (m, 2H), 3.31 (s, 3H), 3.23 (d, *J* = 8.9 Hz, 1H), 2.67 (m, 2H), 2.24 (m, 1H), 1.82 (m, 1H), 1.15-1.32 (m, 9H), 1.10 (s, 3H).



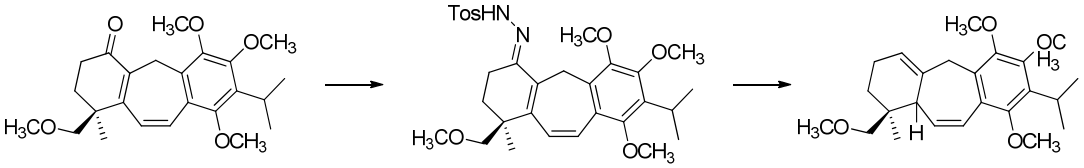
Preparation of (S)-3-ethynyl-2-(4-isopropyl-2,3,5-trimethoxybenzyl)-4-(methoxy methyl)-4-methylcyclohex-2-enone (1.10.9): To a solution of trimethylsilylacetylene (14 mL, 0.1 mol) in 100 mL of THF at -78 °C was added *n*-butyllithium (39 mL, 98 mmol) over a 5-min. period. The resulting mixture was stirred at -78 °C for 30 min, and then warmed to 0 °C over a 30-min. period. A solution of **1.10.8** (8.34 g, 20 mmol) dissolved in 60 mL of ether was then added over a 5-min. period using a cannula. The resulting reaction mixture was stirred at 0 °C for 30-min, and then stirred at rt for 90-min. The reaction mixture was then cooled to 0 °C and water (25 mL) was slowly added, followed by the addition of aqueous 6 *M* HCl (50 mL). The resulting solution was allowed to warm to rt and stir for an additional 1h. Standard extractive workup gave the crude silyl-enynone, which was used in the next step without further purification or characterization.

To a solution of crude silyl enynone dissolved in 100 mL of THF at rt was added TBAF-trihydrate (9.4 g, 30 mmol) in a single portion. The resulting solution was stirred for 5-min. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1), gave 7.9 g (71% over two steps) of enynone **1.10.9** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.10.9**) = 0.36, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.3 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.64-3.72 (m, 4H), 3.44 (m, 1H), 3.36 (s, 3H), 3.30 (d, *J* = 10.0 Hz, 1H), 2.30-2.69 (m, 3H), 1.82 (m, 1H), 1.27 (m, 9H).



1.10.9 1.10.2

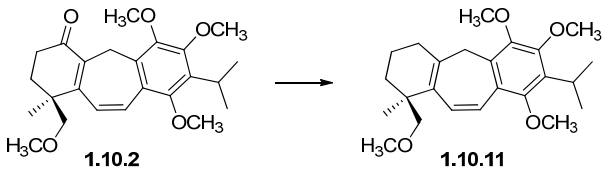
Preparation of (S)-8-isopropyl-6,7,9-trimethoxy-1-(methoxymethyl)-1-methyl-2,3-dihydro-1H-dibenzo[a,d][7]annulen-4(5H)-one (1.10.2): To a solution of enynone **1.10.9** (2.35 g, 5.9 mmol) and ethanethiol (510 mL, 7.1 mmol) in 150 mL of DCM at 0 °C was added BF_3-Et_2O (1.1 mL, 8.9 mmol) over a 2-min. period. The resulting solution was stirred at rt for 24 h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 1.60 g (68%) of dienone **1.10.2** as a dark red oil which was homogeneous by TLC analysis [R_f **(1.10.2)** = 0.32, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.46 (d, *J* = 12.2 Hz, 1H), 6.72 (d, *J* = 12.2 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.67 (s, 3H), 3.38-3.56 (m, 2H), 3.32 (s, 3H), 3.24 (d, *J* = 8.6 Hz, 1H), 2.50 (m, 2H), 2.21 (m, 1H), 1.69 (m, 1H), 1.33 (d, *J* = 7.0 Hz, 6H), 1.18 (s, 3H).



1.10.2 1.10.10 1.10.3

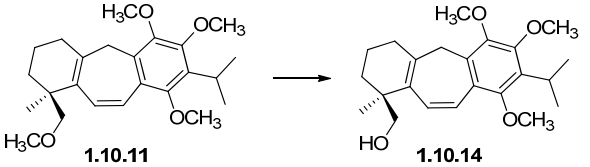
Preparation of (1S)-8-isopropyl-6,7,9-trimethoxy-1-(methoxymethyl)-1-methyl-2,3,5,11a-tetrahydro-1H-dibenzo[a,d][7]annulene (1.10.3): A solution of enone **1.10.2** (506 mg, 1.3 mmol) and *p*-toluenesulfonylhydrazide (306 mg, 1.9 mmol) dissolved in 20 mL of absolute ethanol was stirred at rt for 4h, or until TLC analysis indicated complete consumption of enone **1.10.2**. The solvent was removed under reduced pressure to afford an orange foamy solid. The crude tosylhydrazone (**1.10.10**) was used in the next step without further purification or characterization.

To a solution of the above crude tosylhydrazone dissolved in $CHCl_3$ (15 mL) at -50 °C was added catecholborane (606 mg, 5.2 mmol). The resulting solution was stirred at -50 °C for 2h. To the reaction mixture was added NaOAc-trihydrate (1.38 g, 10.4 mmol) with vigorous stirring. The reaction was warmed to rt and was then refluxed for 2h. After cooling to rt, standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 300 mg (61%) of an inseparable mixture of **1.10.3** in a 3:2 ratio which was homogeneous by TLC analysis [R_f (**1.10.3**) = 0.84, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.69 (m, 1H), 6.05 (m, 1H), 5.49 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 3.11-3.59 (m, 9H), 2.01 (m, 2H), 1.33 (m, 9H), 0.87 (m, 2H), 0.82 (s, 3H).

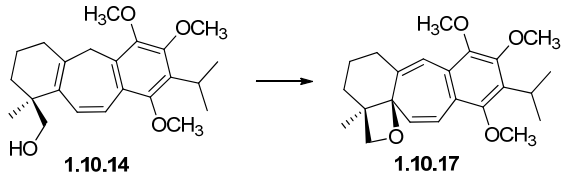


Preparation of (S)-8-isopropyl-6,7,9-trimethoxy-1-(methoxymethyl)-1-methyl-2,3,4,5-tetrahydro-1H-dibenzo[a,d][7]annulene (1.10.11): To a solution of **1.10.2** (198 mg, 0.5 mmol) in DCM (15 mL) at 0°C was added $NaBH_4$ (94 mg, 2.5 mmol) in one portion. A solution of TFA (10% v/v, 200 μL) is added in a dropwise fashion to the resulting suspension and the reaction mixture is stirred at rt for 8h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 10:1), gave 178 mg (93%) of **1.10.11** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.10.11**) = 0.78, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.10 (d, *J* = 12.0 Hz, 1H), 6.60 (d, *J* = 12.0 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.46 (septet, *J* = 7.3 Hz, 1H), 3.30 (m, 4H), 3.16 (d, *J* = 9.0 Hz, 1H), 2.98 (bs, 2H), 2.36 (m, 2H), 1.79 (m, 1H), 1.63 (m, 2H), 1.34 (d, *J* = 7.0 Hz, 7H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 152.8, 151.4, 145.7, 135.2, 133.6, 132.5,

131.8, 129.5, 127.0, 125.6, 80.3, 61.9, 61.0, 60.6, 59.5, 38.2, 33.4, 32.7, 32.2, 25.9, 24.4, 22.4, 19.3.

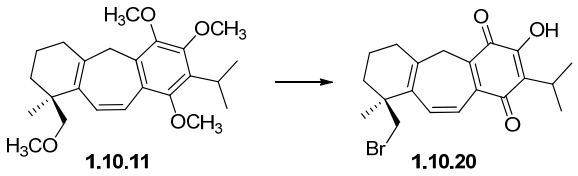


Preparation of (S)-(8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3,4,5-tetrahydro-1H-dibenzo[a,d][7]annulen-1-yl)methanol (1.10.14): To a solution of **1.10.11** (206 mg, 0.54 mmol) in freshly-distilled DCM (10 mL) at -78 °C was added BBr_3 (1.0*M*, 800 μL, 0.8 mol). The resulting solution was stirred at -78 °C for 30-min, at which time the reaction was quenched by the addition of Et_2O (10 mL) and saturated $NaHCO_3$ (2 mL). Standard extractive workup, followed by silica gel chromatography (slow elution with pet ether/EtOAc = 10:1), gave 90 mg (83%) of **1.10.14** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.10.14**) = 0.87, 10:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.11 (d, *J* = 11.7 Hz, 1H), 6.41 (d, *J* = 11.7 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 3.48 (septet, *J* = 8.5 Hz, 1H), 3.05 (m, 2H), 2.51 (m, 3H), 1.71 (m, 2H), 1.58 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 6H), 1.12 (s, 3H).

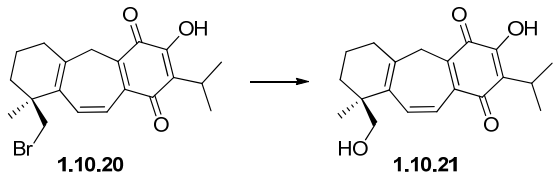


Preparation of (2aR,12aR)-9-isopropyl-7,8,10-trimethoxy-2a-methyl-2a,3,4,5-tetrahydro-2H-benzo[4',5']cyclohepta[1',2':1,6]benzo[1,2-b]oxete (1.10.17): To a solution of **1.10.14** (17 mg, 46 μmol) in CH_3NO_2 (1 mL) was added a catalytic amount of TfOH. The resulting reaction mixture was allowed to stir at rt for an additional 1h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1), gave **1.10.14** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.10.14**) = 0.21,

4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.70 (d, *J* = 12.4 Hz, 1H), 6.39 (d, *J* = 12.4 Hz, 1H), 6.05 (s, 1H), 3.97 (d, *J* = 13.1 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.70 (s, 3H), 3.45 (septet, *J* = 7.0 Hz, 1H), 2.95 (m, 2H), 2.65 (d, *J* = 13.1 Hz, 1H), 1.13-1.60 (m, 13H).

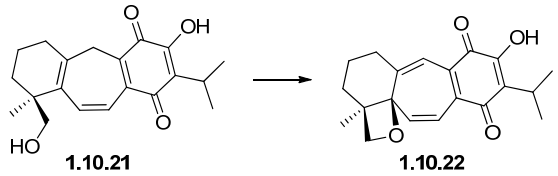


Preparation of (S)-9-(bromomethyl)-3-hydroxy-2-isopropyl-9-methyl-6,7,8,9-tetrahydro-1H-dibenzo[a,d][7]annulene-1,4(5H)-dione (1.10.20): To a solution of **1.10.11** (134 mg, 0.35 mmol) in freshly-distilled DCM (15 mL) at -78 °C was added a solution BBr_3 (1.0*M*, 1.75 mL, 1.75 mmol) diluted with 3 mL DCM. The resulting solution was allowed to warm to rt over 30-min, and stirred at rt for an additional 3h. The reaction was quenched by the addition of saturated $NaHCO_3$ (2 mL). The reaction mixture was neutralized with 1*M* HCl and standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 10.1), gave 111 mg (82%) of **1.10.20** as a red oil which was homogeneous by TLC analysis [R_f (**1.10.20**) = 0.68, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.31 (d, *J* = 12.0 Hz, 1H), 7.15 (d, *J* = 12.0 Hz, 1H), 7.13 (s, 1H), 3.47 (d, *J* = 10.2 Hz, 1H), 3.35 (d, *J* = 10.4 Hz, 1H), 3.24 (septet, *J* = 7.0 Hz, 1H), 2.38 (m, 2H), 2.00 (m, 1H), 1.60 (m, 2H), 1.19-1.31 (m, 13H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 187.1, 183.2, 151.5, 138.5, 137.1, 136.0, 135.8, 125.7, 125.0, 124.0, 44.0, 39.0, 33.8, 32.6, 30.5, 30.0, 26.3, 24.5, 20.1, 18.7.

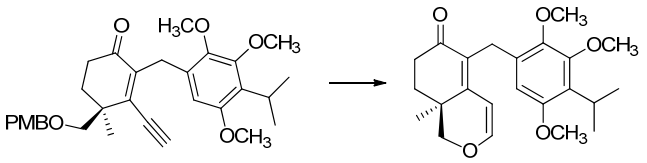


Preparation of (S)-3-hydroxy-9-(hydroxymethyl)-2-isopropyl-9-methyl-6,7,8,9-tetrahydro-1H-dibenzo[a,d][7]annulene-1,4(5H)-dione (1.10.21): To a solution of **1.10.20**

(247 mg, 0.63 mmol) in acetone:H_2O (4:1, 12 mL) was added $AgNO_3$ (216 mg, 1.3 mmol). The resulting reaction mixture was stirred at rt for 24h, as which time standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 1:), gave 183 mg (88%) of **1.10.21** as a red oil which was homogeneous by TLC analysis [R_f (**1.10.21**) = 0.23, 1:2, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.26 (m, 1H), 7.15 (s, 1H), 7.01 (d, *J* = 11.7 Hz, 1H), 2.81 (bs, 1H), 2.67 (d, *J* = 14.2 Hz, 1H), 2.45-2.62 (m, 3H), 1.77 (m, 2H), 1.25 (m, 10H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 187.2, 183.2, 151.6, 144.2, 138.2, 136.0, 133.2, 125.0, 124.1, 121.0, 70.1, 66.1, 47.0, 45.4, 36.4, 32.8, 24.4, 23.2, 20.1, 15.5.

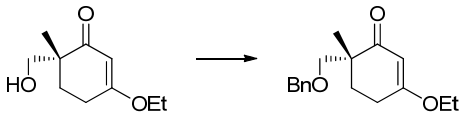


Preparation of (2aR,12aR)-8-hydroxy-9-isopropyl-2a-methyl-2a,3,4,5-tetrahydro-2H-benzo[4',5']cyclohepta[1',2':1,6]benzo[1,2-b]oxete-7,10-dione (1.10.22): To a solution of **1.10.21** (22 mg, 67 μmol) in THF (1 mL) was added a catalytic amount of PPTS. The resulting reaction mixture was heat to reflux for 24h. After cooling to rt, standard extractive workup and silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave **1.10.22** as a red oil which was homogeneous by TLC analysis [R_f (**1.10.22**) = 0.77, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.24 (s, 1H), 6.82 (m, 2H), 6.23 (s, 1H), 3.75 (d, *J* 14.4 Hz, 1H), 3.23 (septet, *J* = 4.4 Hz, 1H), 2.38 (d, *J* = 14.4 Hz, 1H), 1.39 (s, 3H), 1.13-1.30 (m, 9H).



1.11.3 1.11.5

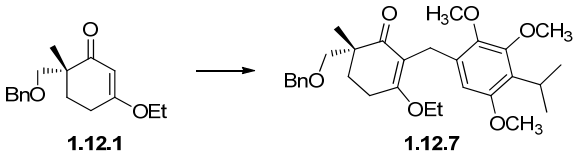
Preparation of (S)-5-(4-isopropyl-2,3,5-trimethoxybenzyl)-8a-methyl-8,8a-dihydro-1H-isochromen-6(7H)-one (1.11.5): To a solution of enynone **1.11.3** (prepared similar to **1.12.1**) (49 mg, 89 μmol) and ethanethiol (8 μL, 0.1 mmol) in 2 mL of freshly-distilled DCM at rt was added BF_3-Et_2O (17 μL, 0.14 mmol). The resulting solution was stirred at rt for 1h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), pyran **1.11.5** as a clear colorless oil which was homogeneous by TLC analysis [R_f **(1.11.5)** = 0.3, 3:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.77 (d, *J* = 5.9 Hz, 1H), 6.22 (s, 1H), 5.77 (d, *J* = 5.9 Hz, 1H), 3.95 (d, *J* = 10.8 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.67-3.77 (m, 2H), 3.66 (s, 3H), 3.59 (d, *J* = 10.8 Hz, 1H), 3.44 (septet, *J* = 7.0 Hz, 1H), 2.71 (m, 1H), 2.58 (m, 1H), 1.76 (m, 2H), 1.32 (s, 3H), 1.27 (d, *J* = 7.1 Hz, 6H).



(-)-1.6.6 1.12.1

Preparation of (R)-6-((benzyloxy)methyl)-3-ethoxy-6-methylcyclohex-2-enone (1.12.1): To a solution of **(−)-1.6.6** (8.20 g, 44.50 mmol) in 200 mL of THF at 0 °C was added NaH (1.87 g, 46.80 mmol) and the solution was stirred for 5-min. A solution of benzyl bromide (5.57 mL, 46.8 mmol) dissolved in 10 mL of THF was then added and the reaction was warmed to rt and stirred for 4h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1), gave 8.01 g (87%) of **1.12.1** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.12.1**) = 0.58, 2:1, pet ether/EtOAc]: $[\alpha]^{22.9}_D$ = -33° ($CHCl_3$, c 6.4); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.32 (m, 5H), 5.32 (s, 1H), 4.52 (q, *J* = 11.6 Hz, 2H), 3.90

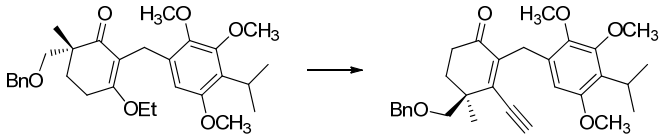
(q, *J* = 7.6 Hz, 2H), 3.72 (d, *J* = 8.8 Hz, 1H), 3.32 (d, *J* = 9.2 Hz, 1H), 2.44 (m, 2H), 2.26 (m, 1H), 1.77 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 202.4, 176.7, 138.8, 128.4, 127.6, 127.5, 102.0, 75.3, 73.5, 64.3, 45.0, 30.2, 26.2, 20.2, 14.4; IR (film) λ_{max} 1648, 1604, 1378, 1187 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 275.1647, found 275.1631.



1.12.1 **1.12.7**

Preparation of (R)-6-((benzyloxy)methyl)-3-ethoxy-2-(4-isopropyl-2,3,5-trimethoxy benzyl)-6-methylcyclohex-2-enone (1.12.7): To a solution of diisopropylamine (20.8 mL, 0.148 mol) in 110 mL of THF at -78 °C was added *n*-butyllithium (56.5 mL, 0.141 mol) over a 5-min. period. The resulting mixture was stirred at -78 °C for 30 min. A solution of **1.12.1** (37.00 g, 0.135 mol) and DMPU (16.3 mL, 0.135 mol) in 80 mL of THF was added using a cannula over a 5-min. period. The resulting mixture was warmed to rt over 30-min. and was stirred at rt for 1h. The resulting mixture was cooled to 0 °C and a solution of benzylic bromide **1.5.8** (10.22 g, 33.60 mmol) in 55 mL of THF was added rapidly via a wide-bore cannula and the ice bath was removed. The reaction mixture was stirred at rt until TLC analysis indicated the complete consumption of bromide **1.5.8**. Water (50 mL) and ether (150 mL) were then added and the resulting mixture was stirred for 5-min. Standard extractive workup, followed by filtration through a small pad of silica gel, furnished a dark brown oil; the excess **1.12.1** was recovered by simple vacuum distillation at 210-270 °C @ 3 Torr. The remaining pot residue was purified by silica gel chromatography (elution with pet ether/EtOAc = 2:1) and gave 12.74 g (76%) of **1.12.7** as a viscous brown oil which was homogeneous by TLC analysis [R_f (**1.12.7**) = 0.61, 2:1, pet ether/EtOAc]: $[\alpha]^{20.4}_{D}$ = -22° ($CHCl_3$, c 6.9); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.27 (m, 5H), 6.18

(s, 1H), 4.49 (m, 2H), 4.01 (q, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.72 (d, *J* = 8.8 Hz, 1H), 3.62 (d, *J* = 4.0 Hz, 1H), 3.55 (s, 3H), 3.42 (sept, *J* = 7.2 Hz, 1H), 3.32 (d, *J* = 8.8 Hz, 1H), 2.62 (m, 2H), 2.27 (m, 1H), 1.84 (m, 1H), 1.23 (m, 9H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.5, 171.4, 154.2, 151.4, 145.3, 138.7, 132.4, 128.3, 127.5, 127.3, 117.1, 106.6, 75.3, 73.5, 63.4, 60.9, 60.4, 55.5, 44.4, 29.7, 25.1, 22.4, 21.8, 21.5, 20.2, 15.3; IR (film) λ_{max} 1609, 1374, 1236, 1116 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 497.2903, found 497.2906.

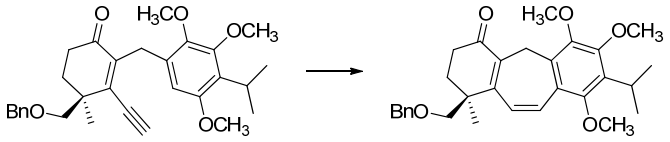


1.12.7 **1.12.2**

Preparation of (S)-4-((benzyloxy)methyl)-3-ethynyl-2-(4-isopropyl-2,3,5-trimethoxy benzyl)-4-methylcyclohex-2-enone (1.12.2): To a solution of trimethylsilylacetylene (7.30 mL, 51.5 mmol) in 100 mL of THF at -78 °C was added *n*-butyllithium (19.30 mL, 48.00 mmol) over a 2-min. period. The resulting mixture was stirred at -78 °C for 30-min, and then warmed to 0 °C over a 30-min. period. A solution of **1.12.7** (8.00 g, 16.10 mmol) dissolved in 40 mL of ether was then added using a cannula over a 5-min. period. The resulting reaction mixture was stirred at 0 °C for 30-min, and then stirred at rt for 90-min. The reaction mixture was then cooled to 0 °C and water (25 mL) was slowly added, followed by the addition of aqueous 6 *M* HCl (50 mL). After warming the resulting solution to rt, and stirring for 1h, the aqueous phase was extracted with ether (2 x 50 mL). The combined organic extracts were washed with 50 mL brine, dried over anhydrous magnesium sulfate, filtered, and then concentrated at reduced pressure. The crude silyl-enynone was used in the next step without further purification or characterization.

To a solution of crude silyl enynone dissolved in 100 mL of THF at rt was added TBAF-trihydrate (6.32 g, 24.20 mmol) in a single portion. The resulting solution was stirred for 5-min.

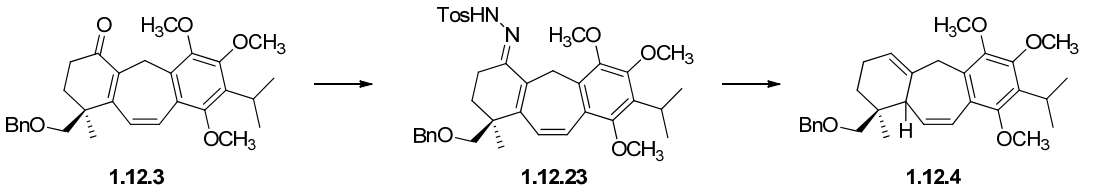
Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1), gave 6.44 g (83% over two steps) of enynone **1.12.2** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.12.2**) = 0.48, 4:1, pet ether/EtOAc]: $[\alpha]^{22.9}_{D}$ = -12° ($CHCl_3$, c 8.9); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.32 (m, 5H), 6.29 (s, 1H), 4.56 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.75 (d, *J* = 8.8 Hz, 1H), 3.63 (s, 1H), 3.57 (s, 3H), 3.44 (sept, *J* = 7.2 Hz, 1H), 3.39 (d, *J* = 8.8 Hz, 1H), 2.64-2.38 (m, 3H), 1.81 (m, 1H), 1.29 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 197.4, 154.3, 151.9, 145.4, 144.0, 143.8, 138.3, 130.0, 128.6, 128.2, 127.9, 127.8, 106.5, 91.4, 80.4, 76.8, 73.7, 61.0, 60.5, 55.6, 40.3, 34.4, 31.5, 28.3, 25.2, 22.8, 21.5, 21.5; IR (film) λ_{max} 1660, 1452, 1400, 1340 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 477.2641, found 477.2630.



1.12.2 **1.12.3**

Preparation of (S)-1-((benzyloxy)methyl)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3-dihydro-1H-dibenzo[a,d][7]annulen-4(5H)-one (1.12.3): To a solution of enynone **1.12.2** (2.00 g, 4.20 mmol) and ethanethiol (311 μL, 4.20 mmol) in 75 mL of DCM at 0 °C was added BF_3-Et_2O (0.55 mL, 4.20 mmol) over a 2-min. period. The resulting solution was stirred at rt for 36 h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 1.72 g (85%) of dienone **1.12.3** as a dark red oil which was homogeneous by TLC analysis [R_f **(1.12.3)** = 0.4, 4:1, pet ether/EtOAc]: $[\alpha]^{23}_{D}$ = -32° ($CHCl_3$, c 3.1); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.45 (d, *J* = 4.4 Hz, 1H), 7.34-7.16 (m, 5H), 6.73 (d, *J* = 5.2 Hz, 1H), 4.48 (m, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 3.60 (s, 3H), 3.55 (bs, 1H), 3.46-3.37 (m, 2H), 2.59-2.42 (m, 2H), 2.23 (m, 1H), 1.78 (m, 1H), 1.32 (dd, *J* = 7.2, 2.4 Hz, 6H), 1.21 (bs, 3H); ^{13}C

NMR (100 MHz, $CHCl_3$) δ 196.7, 154.5, 154.1, 152.0, 146.65, 138.4, 134.1, 133.7, 132.5, 132.3, 128.5, 127.8, 127.8, 127.5, 125.2, 73.6, 62.2, 61.4, 60.6, 39.6, 34.5, 32.8, 25.9, 23.4, 22.7, 22.3, 22.2; IR (film) λ_{max} 1658, 1453, 1400, 1660 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 477.2641, found 477.2636.

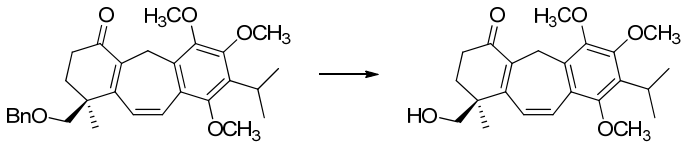


1.12.3 **1.12.23** **1.12.4**

Preparation of (1S)-1-((benzyloxy)methyl)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3,5,11a-tetrahydro-1H-dibenzo[a,d][7]annulene (1.12.4): A solution of enone **1.12.3** (301 mg, 0.65 mmol) and *p*-toluenesulfonylhydrazide (153 mg, 0.95 mmol) dissolved in 10 mL of absolute ethanol was stirred at rt for 4h, or until TLC analysis indicated complete consumption of enone **1.12.3**. The solvent was removed under reduced pressure to afford an orange foamy solid. The crude tosylhydrazone (**1.12.23**) was used in the next step without further purification or characterization.

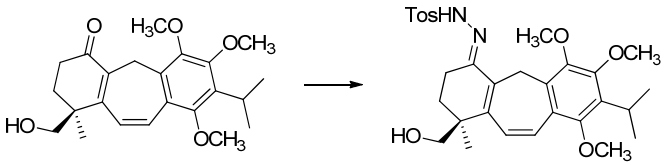
To a solution of the above crude tosylhydrazone dissolved in $CHCl_3$ (10 mL) at -50 °C was added catecholborane (303 mg, 2.7 mmol). The resulting solution was stirred at -50 °C for 2h. To the reaction mixture was added NaOAc-trihydrate (690 mg, 5.2 mmol) with vigorous stirring. The reaction was warmed to rt and was then refluxed for 2h. After cooling to rt, standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 211 mg (72%) of an inseparable mixture of **1.12.4** in a 4:1 ratio which was homogeneous by TLC analysis [R_f (**1.12.4**) = 0.71, 2:1, pet ether/EtOAc]: ^1H NMR (400 MHz, $CHCl_3$) δ 7.29 (m, 5H), 6.66 (m, 1H), 6.02 (m, 1H), 5.48 (bs, 1H), 4.52 (m, 2H), 3.89 (s, 3H)< 3.81 (s, 3H),

3.66 (s, 3H), 3.17-3.54 (m, 5H), 2.02 (m, 2H), 1.80 (m, 1H), 1.42 (m, 1H), 1.33 (m, 6H), 0.81 (s, 3H).



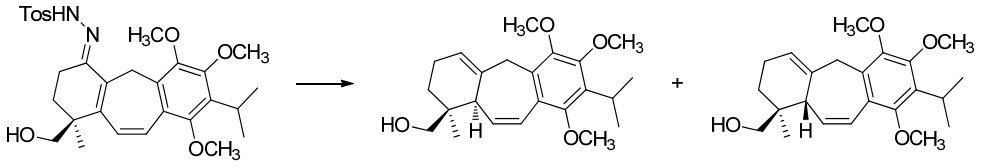
1.12.3 **1.12.28**

Preparation of (S)-1-(hydroxymethyl)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3-dihydro-1H-dibenzo[a,d][7]annulen-4(5H)-one (1.12.28): To a solution of benzyl ether **1.12.3** (3.81 g, 7.90 mmol) in 100 mL of DCM at -78 °C was added BBr_3 (1*M*, 16.00 mL, 16.00 mmol) over a 2-min. period. The resulting solution was stirred at -78 °C for 10-min. While at -78 °C, 100 mL of ether was added and the resulting solution stirred at -78 °C for 2-min. Brine (25 mL) was added and the resulting solution was vigorously stirred at rt for 15-min. The aqueous phase was extracted with ether (2 x 25 mL) and the combined organic extracts were washed with brine (25 mL), and dried over anhydrous magnesium sulfate. Filtration and concentration of the extractive phase, followed by silica gel chromatography (elution with pet ether/EtOAc, 1:1), gave 2.93 g (94%) of alcohol **1.12.28** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.12.28**) = 0.38, 1:2, pet ether/EtOAc]: $[\alpha]^{23.1}_{D}$ = -20° ($CHCl_3$, c 4.7); ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.48 (d, *J* = 12.4 Hz, 1H), 6.75 (d, *J* = 12.4 Hz, 1H), 3.90 (s, 3H), 3.81-3.75 (m, 4H), 3.65 (s, 3H), 3.53-3.38 (m, 2H), 2.53 (m, 2H), 2.21 (m, 1H), 1.73 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 6H), 1.20 (bs, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.5, 154.7, 153.6, 152.2, 146.5, 134.5, 133.7, 133.2, 132.7, 127.3, 124.9, 69.6, 62.4, 61.3, 60.6, 40.4, 34.4, 31.9, 25.9, 22.7, 22.5, 22.2, 22.2; IR (film) λ_{max} 2936, 1652, 1453, 1401 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 387.2171, found 387.2164.



1.12.28 1.12.30

Preparation of Tosylhydrazone 1.12.30: A solution of enone **1.12.28** (3.10 g, 8.00 mmol) and *p*-toluenesulfonylhydrazide (1.94 g, 10.00 mmol) dissolved in 25 mL of absolute ethanol was stirred at rt for 4 h, or until TLC analysis indicated complete consumption of enone **1.12.28**. The solvent was removed under reduced pressure to afford an orange foamy solid. The crude tosylhydrazone (**1.12.30**) was used in the next step without further purification or characterization.



1.12.30 1.12.31 1.12.32

Preparation of ((1S,11aR)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3,5,11a-tetra hydro-1H-dibenzo[a,d][7]annulen-1-yl)methanol (1.12.31) and ((1S,11aS)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3,5,11a-tetrahydro-1H-dibenzo[a,d][7]annulen-1-yl)methanol (1.12.32) using Sodium Triacetoxyborohydride (STAB-H): To a solution of **1.12.30** (~1.20 g, 2.00 mmol contaminated with 0.20 equiv.of tosylhydrazine) in 30 mL of DCM at rt was added $NaCNBH_3$ (250 mg, 4.00 mmol) over a 15-min. period. To the stirred solution was added glacial acetic acid (575 μL, 10.00 mol) drop-wise over a 1-min. period. The resulting solution was stirred at rt for 18 h and then quenched with 2 mL of saturated aqueous $NaHCO_3$. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 471 mg (40.5% yield) of alkene **1.12.31** as an off-white foam which was homogeneous by TLC analysis [R_f (**1.12.31**) = 0.53, 2:1, pet ether/EtOAc)]: $[\alpha]^{24.6}_{D}$ = -109° ($CHCl_3$, c 6.9); ^1H

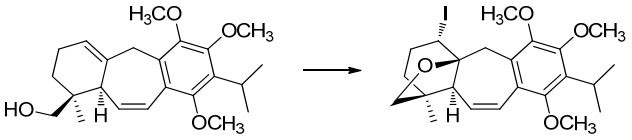
NMR (400 MHz, $CHCl_3$) δ 6.70 (dd, *J* = 12.0, 2.0 Hz, 1H), 6.08 (dd, *J* = 12.0, 5.6 Hz, 1H), 5.52 (bs, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.63 (d, *J* = 13.6, 1H), 3.51 (s, 2H), 3.43 (septet, *J* = 7.2, 1H), 3.09 (d, *J* = 13.2 Hz, 1H), 3.05 (bs, 1H), 2.04 (m, 2H) 1.74 (m, 1H), 1.40 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 6H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 152.5, 152.2, 146.4, 140.7, 132.3, 132.3, 130.7, 126.2, 124.9, 122.0, 66.1, 62.2, 60.9, 60.7, 50.9, 37.6, 33.9, 32.4, 25.8, 24.5, 22.7, 22.3, 22.3; IR (film) λ_{max} 2936, 1452, 1399, 1340 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 373.2379, found 373.2370.

Continued elution with pet ether/EtOAc (4:1) gave 417 mg (40.5% yield) of alkene **1.12.32** as an off-white foam which was homogeneous by TLC analysis [R_f (**1.12.32**) = 0.50, 2:1, pet ether/EtOAc]: $[\alpha]^{24.6}_{D}$ = 116° ($CHCl_3$, c 7.1); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.70 (dd, *J* = 2.0, 12.0 Hz, 1H), 6.03 (dd, *J* = 6.0, 12.0 Hz, 1H), 5.49 (bs, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.59 (d, *J* = 11.2 Hz, 1H), 3.42 (d, *J* = 13.6 Hz, 1H), 3.44 (m, 3H), 3.25 (d, *J* = 13.6, 1H), 3.12 (bs, 1H), 2.06 (m, 2H), 1.62 (m, 1H), 1.42 (m, 1H), 1.33 (dd, *J* = 7.2, 4.0 Hz, 6H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 152.4, 151.9, 146.7, 142.8, 132.3, 132.3, 131.0, 127.0, 125.8, 120.2, 71.4, 62.0, 61.0, 60.8, 45.3, 37.7, 34.3, 31.7, 25.8, 22.4, 22.3, 16.6; IR (film) λ_{max} 2934, 1452, 1399, 1340 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$: *m/z* 373.2379, found 373.2369.

Under these conditions the reduction products **1.12.31**: **1.12.32** were produced in a 1:1 ratio and in a combined yield of 81%.

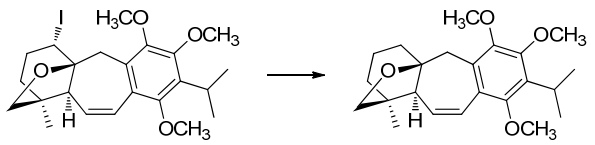
Preparation of 1.12.31 and 1.12.32 using Catecholborane: To a solution of **1.12.30** (540 mg, 0.90 mmol contaminated with 0.20 equiv. of tosylhydrazine) dissolved in $CHCl_3$ at –50 °C was added catecholborane (1*M*, 2.00 mL, 1.90 mmol). The resulting solution was stirred at –50 °C for 2 h. To the reaction mixture was added NaOAc-trihydrate (536 mg, 3.80 mmol) with

vigorous stirring. The reaction was warmed to rt and was then refluxed for 2 h. After cooling to rt, standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 87 mg of **1.12.31** and 261 mg of **1.12.32** in a 1:4 ratio and in 70% yield of the reduction products as off-white foams which were identical to that previously characterized.



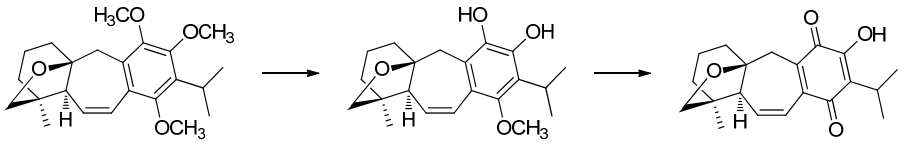
1.12.31 **1.13.2**

Preparation of (1S,4S,4aS,11aS)-4-iodo-8-isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3, 4,5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulene (1.13.2): To a suspension of **1.12.31** (123 mg, 0.33 mmol) and K_2CO_3 (228 mg, 1.65 mmol) in 8 mL of acetonitrile at rt was added iodine (419 mg, 1.65 mmol) in a single portion. The reaction mixture was stirred for 30-min. at rt. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (2 mL). Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 112 mg (91%) of iodide **1.13.2** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**1.13.2**) = 0.46, 10:1, pet ether/EtOAc]: $[\alpha]^{21.8}_{D}$ = 139° ($CHCl_3$, c 8.5); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.78 (d, *J* = 13.2 Hz, 1H), 5.90 (dd, *J* = 14.0, 5.6 Hz, 1H), 4.37 (d, 8.0 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.59 (d, *J* = 7.6 Hz, 1H), 3.39 (m, 2H), 3.17 (d, *J* = 14.4 Hz, 1H), 3.01 (d, *J* = 14.4 Hz, 1H), 2.54 (m, 1H), 1.98 (m, 2H), 1.46 (m, 1H), 1.34 (dd, *J* = 10.8, 7.2 Hz, 6H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 152.6, 152.0, 147.3, 132.3, 130.4, 128.8, 126.1, 124.4, 78.3, 62.3, 60.8, 60.6, 55.2, 45.0, 40.9, 35.3, 34.4, 33.1, 29.9, 25.9, 22.4, 22.4, 20.1; IR (film) λ_{max} 2929, 1452, 1401, 1341 cm^{-1}; HRMS (ESI) calculated for $[M+H]^+$ = *m/z* 499.1345, found 499.1357.



1.13.2 **1.13.1**

Preparation of (1S,4aS,11aS)-8-isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3,4,5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulene (1.13.1): A solution of iodide **1.13.2** (112 mg, 0.225 mmol) in anhydrous benzene (7 mL) was refluxed for 2-min, at which time tri-*n*-butyltin hydride (0.3 mL, 1.13 mol) was added drop-wise via a plastic syringe, followed immediately by AIBN (4 mg, 23 μmol). The reaction mixture was refluxed for 15-min, or until TLC analysis indicated the complete consumption of iodofuran **1.13.2**. The reaction mixture was cooled to rt, concentrated, and silica gel chromatography (elution with pet ether/EtOAc = 10:1 to 2:1), gave 79 mg (94%) of **1.13.1** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**1.31.1**) = 0.34, 10:1, pet ether/EtOAc]: $[\alpha]^{21.4}_{D}$ = -189° ($CHCl_3$, c 8.7); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.73 (dd, *J* = 11.2, 2.0 Hz, 1H), 6.17 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.86 (s, 3H), 3.82 (t, *J* = 11.2 Hz, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 3.43 (septet, *J* = 6.8 Hz, 1H), 3.09 (d, *J* = 12.0 Hz, 1H), 2.57 (d, *J* = 12.4 Hz, 1H), 2.00 (bs, 1H), 1.92-1.72 (m, 3H), 1.62 (m, 1H), 1.52 (m, 1H), 1.42 (m, 1H), 1.34 (t, *J* = 6.0 Hz, 6H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 152.0, 151.6, 147.8, 132.8, 130.8, 130.5, 127.8, 127.3, 97.4, 78.4, 61.9, 60.5, 60.4, 55.1, 43.1, 39.1, 37.0, 36.2, 25.8, 22.3, 20.2, 19.3; IR (film) λ_{max} 2935, 1453, 1339, 1120 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 372.2301, found 372.2288.



1.3.2 **1.13.3** **1.3.19**
(+)-19-deoxyicetexone

Preparation of (+)-deoxyicetexone (1.3.19): To a solution of **1.31.2** (74 mg, 0.19 mmol) in 3.00 mL DMF at 0 °C was added ethanethiol (300 μL, 3.80 mmol), followed by 120 mg of NaH (60%, 120 mg, 2.90 mol) and the cold bath was removed. The resulting solution was stirred for 30-min. at rt, then heated at 120 °C for 30 h. After cooling to rt, the reaction mixture was diluted with ether (10 mL), quenched with water (2 mL) and acidified by the drop-wise addition of aqueous 6 *M* HCl (500 μL). The organic phase was washed with water (3 x 5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting oil was passed through a small pad of silica gel to yield a red oil that was used directly in the next step.

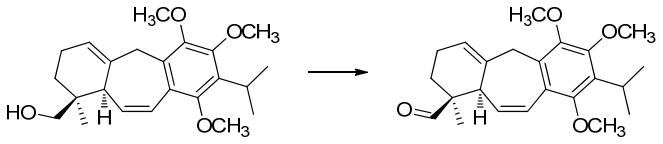
To a solution of crude catechol **1.13.3** in 8 mL of a 1:1 mixture of ether and water at rt was added ceric ammonium nitrate (331 mg, 0.60 mmol). The resulting reaction mixture was stirred for 1h, at which time the layers were separated and the aqueous phase was extracted with ether (2 x 10 mL). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification of the crude residue on silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 43 mg (66%) of 19-deoxyicetexone (**1**) as a an orange solid which was homogeneous by TLC analysis [R_f (**1.3.19**) = 0.62, 4:1, pet ether/EtOAc]: $[\alpha]^{18.9}_{D}$ = 75° ($CHCl_3$, c 0.2); MP = 206-212 °C; ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.16 (s, 1H), 6.82 (dd, *J* = 10.0, 1.2 Hz, 1H), 6.52 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.70 (d, *J* = 6.4 Hz, 1H), 3.50 (dd, *J* = 6.4, 1.2 Hz, 1H), 3.23 (sept, *J* = 5.6 Hz, 1H), 3.00 (d, *J* = 10.8 Hz, 1H), 2.60 (d, *J* = 10.8 Hz, 1H), 2.32 (d, *J* = 2.8 Hz, 1H), 1.94-1.95 (m, 6H), 1.24 (d, *J* = 5.6 Hz, 6H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 186.7, 183.5, 151.0, 142.0, 140.2, 135.8, 124.7, 124.3,

93.3, 77.9, 59.5, 44.1, 40.1, 39.4, 33.5, 24.5, 20.4, 20.3, 20.2, 20.1; IR (film) λ_{max} 2925, 1638, 1260, 1015 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 328.1675, found 328.1664.

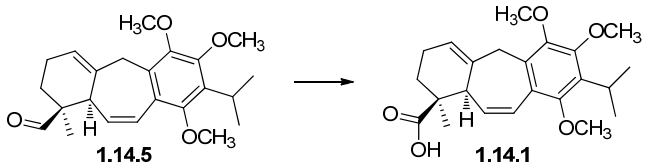
Crystal data for $C_{20}H_{24}O_4$ (**1.3.19**); MW = 328, orthorhombic, *P2(1)2(1)2(1)*, *a* = 7.7110(5) Å, *b* = 10.5025(7) Å, *c* = 20.8344(14) Å, α = 90°, β = 90°, γ = 90°, *V* = 1687.27(19) $Å^3$, Z = 4, *T* = 273(2) K, μ = 0.089 mm^{-1}, *d* = 1.293 g/cm^3, R(1) = 0.0482 for 1689 observed reflections ($I > 2\sigma(I)$). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were treated as idealized contributions.

Comparison of Spectral and Physical Data for 1.3.19

	Natural	**Synthetic**		
X-ray diff.	No	Correspond to **1.3.19**		
^{1}H NMR	Yes	Matches reported data for **1.3.19**		
^{13}C NMR	Yes	Matches reported data for **1.3.19**		
Optical Rotation	$[\alpha]_D$ = +95° ($CHCl_3$, c 0.2)	$[\alpha]^{18.9}_D$ = +75° ($CHCl_3$, c 0.2)		
MP	228-230 °C	206-212 °C		
^{1}H NMR: Natural (300 MHz)	**^{1}H NMR: Synthetic (400 MHz)**	**^{13}C NMR: Natural (75 MHz)**	**^{13}C NMR: Synthetic (100 MHz)**	**Δ ppm**
7.17 (s, 1H)	7.16 (s, 1H)	19.5	20.1	0.6
6.80 (dd, *J* = 1.8, 12.0)	6.82 (dd, *J* = 10.0, 1.2 Hz, 1H)	19.9	20.2	0.3
6.50 (dd, *J* = 4.8, 12.0)	6.52 (dd, *J* = 10.0, 4.0 Hz, 1H)	19.9	20.3	0.4
3.69 (d, *J* = 7.8, 1H)	3.70 (d, *J* = 6.4 Hz, 1H)	20.2	20.4	0.2
3.49 (dd, *J* = 1.8, 7.8, 1H)	3.50 (dd, *J* = 6.4, 1.2 Hz, 1H)	24.3	24.5	0.2
3.21 (sept, *J* = 6.9, 1H)	3.23 (sept, *J* = 5.6 Hz, 1H)	33.2	33.5	0.3
2.98 (d, *J* = 13.8, 1H)	3.00 (d, *J* = 10.8 Hz, 1H)	39.1	39.4	0.3
2.58 (d, *J* = 13.8, 1H)	2.60 (d, *J* = 10.8 Hz, 1H)	39.8	40.1	0.3
2.30 (dd, *J* = 1.8, 4.8, 1H)	2.32 (d, *J* = 2.8 Hz, 1H)	43.9	44.1	0.2
---	1.94-1.95 (m, 6H)	59.3	59.5	0.2
1.23 (d, *J* = 6.9, 3H), 1.23 (d, *J* = 6.9, 3H)	1.24 (d, *J* = 5.6 Hz, 6H)	77.6	77.9	0.3
1.03 (s, 3H)	1.05 (s, 3H)	92.9	93.3	0.4
		124.1	124.3	0.2
		124.4	124.7	0.3
		135.5	135.8	0.3
		138.6	140.2	1.6
		141.8	142.0	0.2
		150.7	151.0	0.3
		183.3	183.5	0.2
		186.5	186.7	0.2
		Average ppm difference = 0.4		

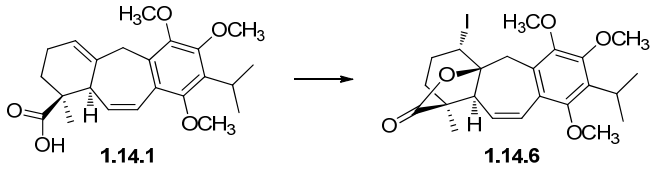


Preparation of (1S,11aR)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3,5,11a-tetra hydro-1H-dibenzo[a,d][7]annulene-1-carbaldehyde (1.14.5): To a solution of alcohol **1.12.31** (479 mg, 1.29 mmol) in 10 mL of DCM at rt was added Dess-Martin periodinane (657 mg, 1.55 mmol) in a single portion. The reaction mixture was stirred at rt until TLC analysis indicated the complete consumption of **1.12.31**. The reaction mixture was filtered through a small pad of silica gel and eluted with additional DCM (10 mL) to yield a yellow oil. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 429 mg (90%) of aldehyde **1.14.5** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.14.5**) = 0.46, 10:1, pet ether/EtOAc]: $[\alpha]^{22}_D$ = -184° ($CHCl_3$, c 4.0); ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.71 (s, 1H), 6.77 (dd, *J* = 12.0, 2.4 Hz, 1H), 6.02 (dd, *J* = 12.0 Hz, 5.6 Hz, 1H), 5.59 (d, *J* = 2.8 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 3.58 (d, *J* = 13.2 Hz, 1H), 3.43 (septet, *J* = 7.2 Hz, 1H), 3.33 (d, *J* = 13.6 Hz, 1H), 3.08 (bs, 1H), 2.07 (m, 2H), 1.90 (m, 1H), 1.61 (m, 1H), 1.33 (dd, *J* = 11.2 4.4 Hz, 6H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 206.2, 152.8, 152.3, 146.6, 140.8, 132.7, 132.0, 129.8, 127.4, 125.2, 120.4, 62.3, 61.1, 60.9, 48.8, 44.8, 34.0, 29.4, 25.9, 22.9, 22.5, 22.5, 21.2, 13.9; IR (film) λ_{max} 2933, 1721, 1452, 1399 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 370.2144, found 370.2132.



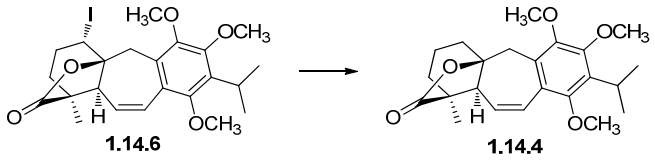
Preparation of (1S,11aR)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3,5,11a-tetrahydro-1H-dibenzo[a,d][7]annulene-1-carboxylic acid (1.14.1): To a solution of aldehyde **1.14.5** (429

mg, 1.20 mmol) and 2-methyl-2-butene (2.30 mL, 22.00 mmol) in 75 mL of acetone at rt was added 21 mL of an aqueous solution of NaH_2PO_4 (915 mg, 6.60 mmol) and $NaClO_2$ (80%, 925 mg, 10.00 mmol) in 50 mL of water. The resulting reaction mixture was stirred at rt until TLC analysis indicated the complete consumption of aldehyde **1.14.5**. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1), gave 412 mg (92%) of acid **1.14.1** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.14.1**) = 0.59, 1:2, pet ether/EtOAc]: $[\alpha]^{21.3}_D$ = -238° ($CHCl_3$, c 4.7); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.70 (dd, *J* = 11.2, 2.4 Hz, 1H), 6.16 (dd, *J* = 11.2, 4.4 Hz, 1H), 5.53 (bs, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 3.54 (d, *J* = 14.0 Hz, 1H), 3.46 (septet, *J* = 4.4 Hz, 1H), 3.25 (d, *J* = 14.4 Hz, 1H), 2.83 (bs, 1H), 1.97-2.25 (m, 3H), 1.62 (m, 1H), 1.34 (m, 9H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 182.3, 152.2, 151.9, 147.2, 144.2, 132.6, 132.3, 131.8, 126.7, 126.4, 119.1, 61.9, 61.1, 60.9, 47.6, 45.1, 34.3, 33.4, 25.8, 25.3, 23.2, 22.4; IR (film) λ_{max} 2982, 1700, 1453, 1122 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 386.2093, found 386.2079.



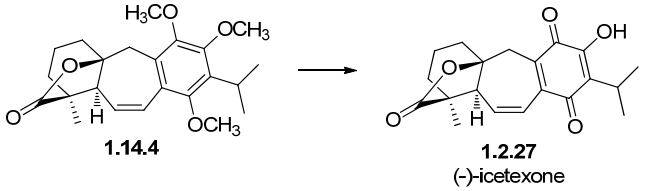
Preparation of (1S,4S,4aS,11aS)-4-iodo-8-isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3, 4,5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulen-13-one (1.14.6): To a mixture of **1.14.1** (412 mg, 1.10 mmol) and K_2CO_3 (736 mg, 5.31 mmol) in acetonitrile (15 mL) at rt was added iodine (1.35 g, 5.30 mmol) in a single portion. The reaction mixture was stirred for 10-min. at rt. The reaction was quenched by the addition of 15 mL ether, followed by 5 mL of saturated aqueous Na_2SO_3. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 486 mg (89%) of **1.14.6** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.14.6**) = 0.27, 10:1, pet ether/EtOAc]: $[\alpha]^{21.3}_D$

= 67° ($CHCl_3$, 5.9); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.81 (dd, *J* = 13.0, 3.5 Hz, 1H), 5.80 (dd, *J* = 13.0, 5.5 Hz, 1H), 4.55 (d, *J* = 5.0 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.68 (d, *J* = 5.0 Hz, 1H), 3.62 (s, 3H), 3.42 (septet, *J* = 7.0 Hz, 1H), 3.11 (d, *J* = 14.5 Hz, 1H), 2.46 (m, 1 H), 2.17 (m, 1H), 1.97 (m, 1H), 1.64 (m, 1H), 1.33 (dd, *J* = 16.5, 7.0 Hz, 6H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 179.3, 153.0, 152.6, 147.6, 133.4, 127.6, 126.9, 126.0, 123.9, 62.5, 60.7, 60.7, 54.0, 49.1, 34.6, 34.1, 32.9, 32.3, 25.9, 22.3, 22.2, 18.6; IR (film) λ_{max} 1782, 1453, 1402, 1341 cm^{-1}; HRM**S** (ESI) calculated for M^+ = *m/z* 512.1060, found 512.1059.



Preparation of (1S,4aS,11aS)-8-isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3,4,5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulen-13-one (1.14.4): A solution of iodide **1.14.6** (486 mg, 0.95 mmol) in 15 mL of anhydrous toluene was vigorously refluxed for 2-min, before tri-*n*-butyltin hydride (1.00 mL, 3.70 mmol) was added drop-wise via a plastic syringe. The reaction mixture was refluxed until TLC analysis indicated the complete consumption of iodolactone **1.14.6**. The reaction mixture was cooled to rt, concentrated, and purified by silica gel chromatography (elution with pet ether/EtOAc = 4:1) to provide 330 mg (90%) of **1.14.4** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.14.4**) = 0.20, 10:1, pet ether/EtOAc]: $[\alpha]^{20.3}_{D}$ = -247° ($CHCl_3$, c 6.5); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.78 (dd, *J* = 10.8, 2.0 Hz, 1H), 6.08 (dd, *J* = 10.8, 2.0 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 3.42 (septet, *J* = 7.2 Hz, 1H), 3.32 (d, *J* = 12.4 Hz, 1H), 2.72 (d, *J* = 10.0 Hz, 1H), 2.27 (bs, 1H), 1.96-1.36 (m, 6H), 1.33 (dd, *J* = 7.2, 4.8 Hz, 6H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 179.8, 152.2, 152.1, 148.1, 133.8, 129.5, 127.7, 127.7, 126.5, 62.0, 60.4, 60.4, 54.5, 47.0, 35.9, 34.7,

33.1, 30.5, 25.9, 22.2, 22.2, 19.6, 17.6; IR (film) λ_{max} 1773, 1453, 1340, 1120 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 386.2093, found 386.2097.



Preparation of (–)-icetexone (1.2.27): To a solution of **1.14.4** (29 mg, 0.075 mmol) in 3 mL of DCM at -30 °C was added BBr_3 (1*M*, 300 μL, 0.30 mmol). The reaction mixture was stirred at -30 °C for 30-min, then warmed to 0 °C over a 20-min. period. At this time, ether (10 mL) was added, followed by water (5 mL), and stirred at 0 °C for 5-min. Standard extractive workup yielded a black oil to which was added ether (2 mL) and water (2 mL). To the resulting solution was added ceric ammonium nitrate (123 mg, 0.225 mmol) and the resulting mixture was stirred for 2 h at rt. Standard extractive workup, followed by silica gel chromatography (elution with pet ether /EtOAc = 4:1), gave 19.5 mg (76%) of (–)-icetexone (**1.2.27**) as a orange solid which was homogeneous by TLC analysis [R_f (**1.2.27**) = 0.23, 4:1, pet ether/EtOAc]: $[\alpha]^{20}_D$ = -70° ($CHCl_3$, c 0.65); MP = 247-253 °C; ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.14 (s, 1H), 6.86 (dd, *J* = 12.0, 2.0 Hz, 1H), 6.44 (dd, *J* = 12.0, 5.0 Hz, 1H), 3.22 (septet, *J* = 5.6 Hz, 1H), 3.16 (d, *J* = 13.5 Hz, 1H), 2.80 (d, *J* = 14.0 Hz, 1H), 2.56 (dd, *J* = 4.5, 1.5 Hz, 1H), 2.04-1.56 (m, 6H), 1.27 (s, 3H), 1.24 (dd, *J* = 7.0, 4.5 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 185.8, 183.0, 179.0, 151.1, 140.7, 138.9, 133.8, 125.5, 125.3, 92.5, 57.9, 47.9, 36.1, 32.9, 29.9, 24.6, 20.1, 20.1, 19.7, 18.4; IR (film) λ_{max} 1770, 1638, 1254, 1125 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 342.1467, found 342.1458.

Crystal data for $C_{20}H_{22}O_5$ (**1.2.27**); MW = 342, orthorhombic, *P2(1)2(1)2(1)*, *a* = 7.747(3) Å, *b* = 10.338(4) Å, *c* = 20.948(9) Å, α = 90°, β = 90°, γ = 90°, *V* = 1677.8(12) $Å^3$, Z = 4, *T* =

273(2) K, μ = 0.097 mm^{-1}, *d* = 1.355 g/cm^3, R(1) = 0.0462 for 1930 observed reflections ($I > 2\sigma(I)$). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were treated as idealized contributions.

Comparison of Spectral and Physical Data for 1.2.27

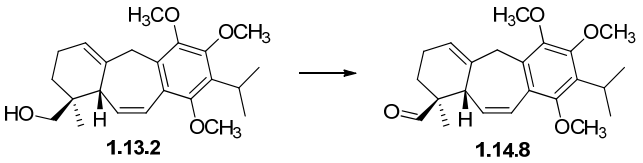
	Natural	**Synthetic**
X-ray diff.	Yes	Corresponds to **1.2.27**
^{1}H NMR	Not reported	Matches reported data for **1.3.21**
^{13}C NMR	Not reported	Matches reported data for **1.3.21**
Optical Rotation	$[\alpha]^{26}_D$ = +33.3° $CHCl_3$, c 1.0)	$[\alpha]^{20}_D$ = -70° ($CHCl_3$, c 0.65)
MP	240 °C	247-253 °C

Reassigned Spectral Data for 1.2.27

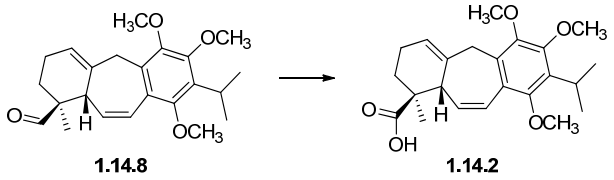
^{1}H NMR: Natural (400 MHz)*	^{1}H NMR: Synthetic (500 MHz)**	^{13}C NMR: Natural (100 MHz)*	^{13}C NMR: Synthetic (125 MHz)**	Δ ppm
7.0 (s, 1H)	7.14 (s, 1H)	16.8	18.4	1.6
6.80 (dd, *J* = 12.3, 3.8, 1H)	6.86 (dd, *J* = 12.0, 2.0 Hz, 1H)	18.2	19.7	1.5
6.40 (dd, *J* = 12.3, 4.5, 1H)	6.44 (dd, *J* = 12.0, 5.0 Hz, 1H)	18.7	20.1	1.4
3.29 (h, *J* = 6.8, 1H)	3.22 (septet, *J* = 5.6 Hz, 1H)	18.9	20.1	1.2
3.10 (d, *J* = 14.3, 1H)	3.16 (d, *J* = 13.5 Hz, 1H)	22.8	24.6	1.8
2.81 (d, *J* = 14.3, 1H)	2.80 (d, *J* = 14.0 Hz, 1H)	28.2	29.9	1.7
2.60 (dd, *J* = 4.5, 3.8, 1H)	2.56 (dd, *J* = 4.5, 1.5 Hz, 1H)	31.3	32.9	1.6
----	2.04-1.56 (m, 6H)	34.0	36.1	2.1
1.25 (s, 3H)	1.27 (s, 3H)	46.2	47.9	1.7
1.20 (d, *J* = 6.8, 1H), 1.20 (d, *J* = 6.8, 1H)	1.24 (dd, *J* = 7.0, 4.5 Hz, 6H)	55.8	57.9	2.1
		91.3	92.5	1.2
		123.6	125.3	1.7
		124.0	125.5	1.5
		132.8	133.8	1.0
		136.8	138.9	2.1
		138.0	140.7	2.7
		151.6	151.0	-0.6
		175.0	179.0	4.0
		181.5	183.0	1.5
		184.6	185.8	1.2
		Average ppm difference = 1.7		

*Spectral data originally associated with 5-*Epi*-icetexone

** Reassigned spectral data for 5-*Epi*-icetexone

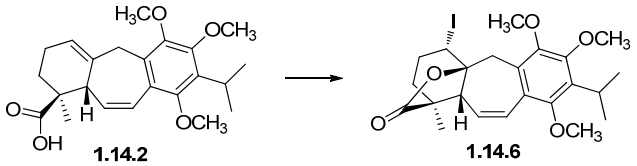


Preparation of (1S,11aS)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3,5,11a-tetrahydro-1H-dibenzo[a,d][7]annulene-1-carbaldehyde (1.14.8): To a solution of alcohol **1.13.2** (492 mg, 1.32 mmol) in 10 mL of DCM at rt was added Dess-Martin periodinane (672 mg, 1.58 mmol) in a single portion. The reaction mixture was stirred until TLC analysis indicated the complete consumption of **1.13.2**. The reaction mixture was filtered through a small pad of silica gel and further eluted with 10 mL of additional DCM. Concentration of the combined organic phase gave a yellow oil, followed by silica gel chromatography (elution with pet ether/EtOAc = 8:1), gave 465 mg (95%) of aldehyde **1.14.8** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.14.8**) = 0.49, 10:1, pet ether/EtOAc]: $[\alpha]^{24.5}_{D}$ = 121° ($CHCl_3$, c 3.5); ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.54 (s, 1H), 6.70 (dd, *J* = 11.6, 1.6 Hz, 1H), 5.71 (dd, *J* = 11.6, 4.8 Hz, 1H), 5.51 (d, *J* = 2.8 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 3.59 (d, *J* = 13.6 Hz, 1H), 3.49 (bs, 1H), 3.43 (septet, *J* = 7.2 Hz, 1H), 3.22 (d, *J* = 13.2 Hz, 1H), 2.12 (m, 2H), 1.71 (m, 1H), 1.50 (m, 1H), 1.33 (dd, *J* = 7.2, 1.6 Hz, 6H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 206.0, 152.7, 152.2, 146.5, 140.6, 132.5, 131.9, 129.7, 127.2, 125.1, 120.2, 62.2, 61.0, 60.8, 48.6, 44.6, 33.9, 29.2, 25.8, 22.3, 22.3, 21.1, 13.8; IR (film) λ_{max} 1724, 1452, 1399, 1340 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 370.2144, found 370.2128.



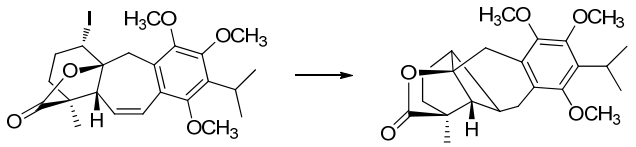
Preparation of (1S,11aS)-8-isopropyl-6,7,9-trimethoxy-1-methyl-2,3,5,11a-tetrahydro-1H-dibenzo[a,d][7]annulene-1-carboxylic acid (1.14.2): To a solution of aldehyde **1.14.8** (465

mg, 1.30 mmol) and 2-methyl-2-butene (2.50 mL, 24.00 mol) in 75 mL of acetone at rt was added 23 mL of an aqueous solution of NaH_2PO_4 (915 mg, 6.60 mmol) and $NaClO_2$ (80%, 925 mg, 10.00 mmol) in 50 mL of water. The resulting reaction mixture was stirred at rt until TLC analysis indicated the complete consumption of **1.14.8**. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1), gave 441 mg (91%) of acid **1.14.2** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**1.14.2**) = 0.51, 1:2, pet ether/EtOAc]: $[\alpha]^{21.2}_{D}$ = 107° ($CHCl_3$, c 6.6); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.72 (dd, *J* = 12.0, 2.0 Hz, 1H), 5.88 (dd, *J* = 12.0, 5.6 Hz, 1H), 5.49 (d, *J* = 2.8 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.43 (septet, *J* = 7.2 Hz, 1H), 3.16 (d, *J* = 13.2 Hz, 1H), 2.09 (m, 2H), 1.97 (m, 1H), 1.77 (m, 1H), 1.32 (t, *J* = 6.8 Hz, 6H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 184.2, 152.7, 152.1, 146.4, 140.7, 132.4, 132.0, 130.3, 126.9, 125.1, 120.0, 62.2, 61.0, 60.8, 47.5, 45.0, 33.9, 33.2, 25.8, 22.4, 22.4 21.9, 22.4, 15.7; IR (film) λ_{max} 2934, 1698, 1452, 1399 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 386.2093, found 386.2082.



Preparation of (1S,4S,4aS,11aR)-4-iodo-8-isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3, 4,5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulen-13-one (1.14.6): To a suspension of **1.14.2** (441 mg, 1.10 mmol) and K_2CO_3 (788 mg, 5.71 mmol) in benzene (15 mL) at rt was added iodine (1.45 g, 5.71 mmol) in a single portion. The reaction mixture was stirred for 10-min. at rt. The reaction was quenched by the addition of ether (15 mL) and saturated aqueous Na_2SO_3 (5 mL). Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 509 mg (87%) of **1.14.6** as a yellow oil which was homogeneous by TLC analysis [R_f **(1.14.6)** = 0.34, 10:1, pet ether/EtOAc]: $[\alpha]^{19.9}_{D}$ = 173°

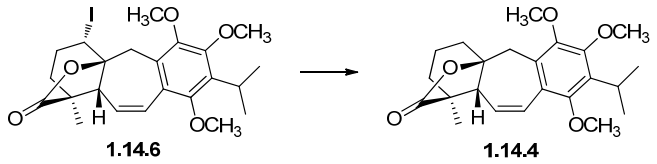
($CHCl_3$, c 5.2); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.83 (d, *J* = 10.0 Hz, 1H), 6.45 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.51 (d, *J* = 5.2 Hz, 1H), 3.91 (s, 3H), 3.86 (d, *J* = 16.8 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 3.42 (septet, *J* = 6.8 Hz, 1H), 3.24 (d, *J* = 16.4 Hz, 1H), 2.86 (d, *J* = 7.2 Hz, 1H), 2.36-2.59 (m, 2H), 2.09 (m, 1H), 1.55 (m, 1H), 1.31 (t, *J* = 6.8 Hz, 6H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 179.6, 162.7, 152.6, 148.8, 133.8, 128.7, 128.5, 127.2, 125.5, 95.8, 61.9, 61.2, 60.7, 52.6, 45.7, 33.7, 32.9, 26.6, 26.0, 25.2, 22.3, 22.1, 19.9; IR (film) λ_{max} 1786, 1452, 1340, 1118 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 512.1060, found 512.1053.



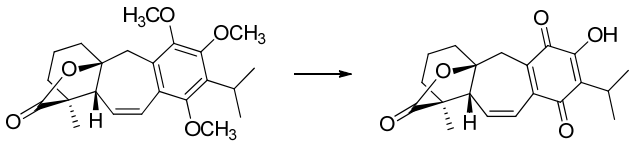
1.14.6 **1.14.7**

Preparation of (3S,12aR,13R)-9-isopropyl-8,10,11-trimethoxy-3-methyl-3,4,5,5a,6,7-hexahydro-3,6,12a-(epimethanetriyl)benzo[5,6]cyclohepta[1,2-b]oxepin-2(12H)-one (1.14.7): To a solution of **1.14.6** (41 mg, 0.08 mmol) and AIBN (catalytic) in 3 mL of anhydrous benzene was added tri-*n*-butyltin hydride (43 μL, 0.16 mmol) via a plastic syringe. The reaction mixture was refluxed until TLC analysis indicated the complete consumption of iodolactone **1.14.6**. The reaction mixture was cooled to rt, concentrated, and silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave **1.14.7** in good, though undetermined, yield as clear colorless oil which was homogeneous by TLC analysis [R_f (**1.14.7**) = 0.20, 10:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.87 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.62 (d, *J* = 18.0 Hz, 1H), 3.34–3.42 (m, 2H), 3.16 (d, *J* = 17.6 Hz, 1H), 2.97 (dd, *J* = 18.0, 2.4 Hz, 1H), 2.52 (dd, *J* = 5.2, 3.2 Hz, 1H), 2.34 (d, *J* = 5.6 Hz, 1H), 2.28 (m, 1H), 1.91–1.93 (m, 2H), 1.81–1.86 (m, 1H), 1.63–1.67 (m, 1H), 1.35(dd, *J* = 7.2, 2.4 Hz, 6H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 182.7, 152.4, 151.1, 148.5, 133.3, 126.7, 126.4, 84.6, 61.2, 60.3, 59.5, 54.6, 49.2, 41.5,

34.8, 29.4, 28.4, 27.1, 26.3, 22.5, 22.3, 22.3, 20.6; MS (ESI) calculated for M^+ = *m/z* 386, found 386.



Preparation of (1S,4aS,11aR)-8-isopropyl-6,7,9-trimethoxy-1-methyl-1,2,3,4,5,11a-hexahydro-4a,1-(epoxymethano)dibenzo[a,d][7]annulen-13-one (1.14.4): A solution of **1.14.6** (509 mg, 1.00 mmol) in 15 mL of anhydrous toluene was heated to a vigorous reflux, at which time tri-*n*-butyltin hydride (1.00 mL, 3.70 mmol) was added via a plastic syringe. The reaction mixture was refluxed until TLC analysis indicated the complete consumption of iodolactone **1.14.6**. The reaction mixture was cooled to rt, concentrated, and silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 342 mg (89%) of **1.14.4** as a yellow oil which was homogeneous by TLC analysis [R_f (**1.14.4**) = 0.22, 10:1, pet ether/EtOAc]: $[\alpha]^{21.1}_{D}$ = 95° ($CHCl_3$, c 4.7); ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.95 (dd, *J* = 12.4, 3.2 Hz, 1H), 5.66 (dd, *J* = 12.4, 3.2 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.61 (s, 3H), 3.56 (d, *J* = 16.4 Hz, 1H), 3.39 (septet, *J* = 6.8 Hz, 1H), 3.10 (d, *J* = 16.4 Hz, 1H), 2.85 (bs, 1H), 1.78 (m, 1H), 1.43–1.68 (m, 5H), 1.31 (d, *J* = 6.8 Hz, 6H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 180.2, 153.4, 153.1, 148.7, 133.7, 127.1, 126.7, 124.8, 122.3, 85.5, 62.5, 60.5, 60.1, 55.5, 47.2, 37.4, 27.5, 27.1, 26.1, 22.1, 22.1, 19.5, 19.1; IR (film) λ_{max} 1775, 1396, 1339, 1254 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 386.2093, found 386.2079.



1.14.4 **1.3.21**
(+)-5-*epi*-icetexone

Preparation of (+)-5-*epi*-icetexone (1.3.21): To a solution of **1.14.4** (56 mg, 0.145 mmol) in 3 mL of DCM at –30 °C was added drop-wise BBr_3 (1*M*, 0.58 mL, 0.58 mmol). The reaction mixture was stirred at –30 °C for 30-min, then warmed to rt over a 20-min. period. At this time, the reaction mixture was cooled to 0 °C and ether (10 mL) was added, followed by water (5 mL), and stirred at 0 °C for 5-min. Standard extractive workup yielded a black oil to which was added ether (3 mL) and water (3 mL). To the resulting solution was added ceric ammonium nitrate (238 mg, 0.435 mmol) and the resulting reaction mixture was stirred for 2 h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 4:1), gave 41 mg (83%) of (+)-5-*epi*-icetexone (**1.3.21**) as an orange solid which was homogeneous by TLC analysis [R_f (**1.3.21**) = 0.38, 4:1, pet ether/EtOAc]: $[\alpha]^{20.4}_{D}$ = 327° ($CHCl_3$, c 0.75); MP = 219-223 °C; ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.20 (s, 1H), 7.14 (dd, *J* = 10.0, 2.8 Hz, 1H), 6.18 (dd, *J* = 14.0, 2.0 Hz, 1H), 3.58 (d, *J* = 15.6 Hz, 1H), 3.24 (septet, *J* = 5.6 Hz, 1H), 2.94 (d, *J* = 15.6 Hz, 1H), 2.86 (bs, 1H), 1.51-1.71 (m, 6H), 1.27 (s, 3H), 1.25 (dd, *J* = 5.6, 0.8 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 185.8, 184.0, 179.0, 150.8, 137.8, 133.7, 133.0, 125.5, 124.1, 82.1, 54.7, 46.9, 38.8, 27.8, 27.5, 25.0, 20.1, 20.1, 19.3, 18.9; IR (film) λ_{max} 1775, 1639, 1235, 1124 cm^{-1}; HRMS (ESI) calculated for M^+ = *m/z* 342.1467, found 342.1464.

Crystal data for $C_{20}H_{22}O_5$ (**1.3.21**); MW = 342, orthorhombic, *Pca2(1)*, *a* = 12.306(4) Å, *b* = 12.827(4) Å, *c* = 10.576(3) Å, α = 90°, β = 90°, γ = 90°, *V* = 1669.5(8) Å^3, Z = 4, *T* = 273(2) K, μ = 0.097 mm^{-1}, *d* = 1.362 g/cm^3, R(1) = 0.0472 for 1628 observed reflections ($I > 2\sigma(I)$). All

non-hydrogen atoms were refined anisotropically. Hydrogen atoms were treated as idealized contributions.

Comparison of Spectral and Physical Data for **1.3.21**

	Natural	**Synthetic**
X-ray diff.	No	Corresponds to **1.3.21**
^{1}H NMR	Yes	Does not match natural **1.3.21**
^{13}C NMR	Yes	Does not match natural **1.3.21**
Optical Rotation	$[\alpha]^{25}_{D}$ = -92.8 ($CHCl_3$; c 1.04)	$[\alpha]^{20.4}_{D}$ = +327° ($CHCl_3$, c 0.75) $[\alpha]^{22.6}_{D}$ = +289° ($CHCl_3$, c 0.4) $[\alpha]^{22.4}_{D}$ = +297° ($CHCl_3$, c 0.3)
MP	259-260 °C	219-223 °C

Reassigned Spectral Data for **1.3.21***

^{1}H NMR: Synthetic (500 MHz)	^{13}C NMR: Synthetic (125 MHz)	
7.20 (s, 1H)	18.9	82.1
7.14 (dd, *J* = 10.0, 2.8 Hz, 1H)	19.3	124.1
6.18 (dd, *J* = 14.0, 2.0 Hz, 1H)	20.1	125.5
3.58 (d, *J* = 15.6 Hz, 1H)	20.1	133.0
3.24 (septet, *J* = 5.6 Hz, 1H)	25.0	133.7
2.94 (d, *J* = 15.6 Hz, 1H)	27.5	137.8
2.86 (bs, 1H)	27.8	150.8
1.51-1.71 (m, 6H)	38.8	179.0
1.27 (s, 3H)	46.9	184.0
1.25 (dd, *J* = 5.6, 0.8 Hz, 6H)	54.7	185.8

* Spectral data not available for icetexone

1.16 References and Notes

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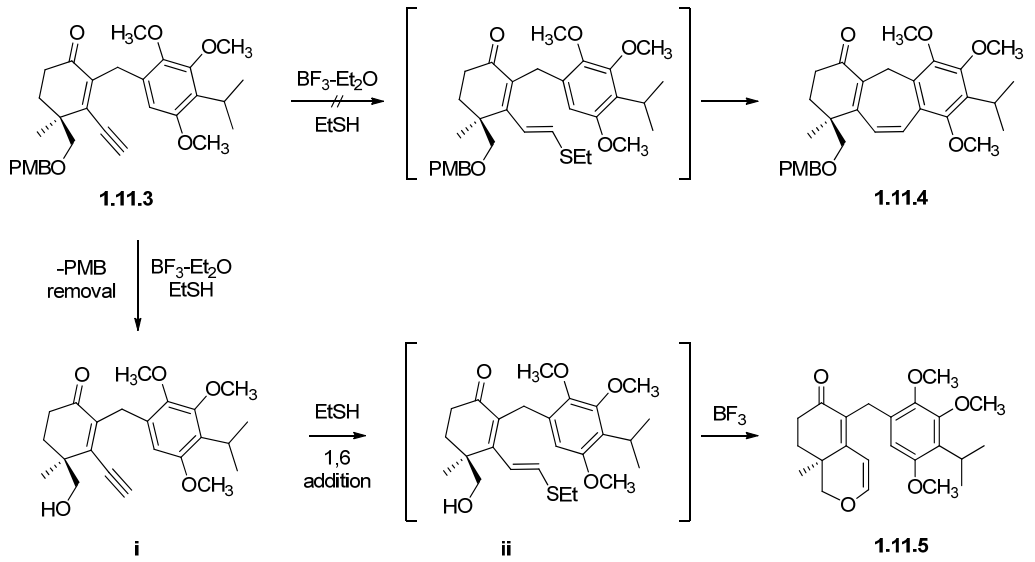
CHAPTER II

A NOVEL SYNTHESIS OF FUNCTIONALIZED 6- AND 8-HYDROXYISOCHROMENES AND ISOCOUMARINS AND A NOVEL ROUTE TO 8-HYDROXYISOCOUMARINS

2.1 Introduction and Classifications

During the total synthesis of the icetexone natural products (Chapter I), the unexpected reactivity of a synthetic intermediate yielded an interesting structural motif, resulting in an exciting new research project. While attempting to convert PMB-protected enynone **1.11.3** into tricycle **1.11.4**, **1.11.5** was produced (Scheme 2.1). We rationalized that this was formed through deprotection to give **i**, followed by Lewis acid-catalyzed 1,6-addition of EtSH to form vinyl



Scheme 2.1.1

sulfide **ii**, then intramolecular displacement of the EtS- moiety to yield dihydropyran **1.11.5** (*cf.* Section 1.11). We recognized that the rapid and efficient nature of this reaction could allow us to use it to prepare the isochromene and isocoumarin skeletons. This chapter presents a general introduction to the isochromenes and the isocoumarins as well as recent methods for their synthesis and report a practical, new approach to prepare functionalized 6- and 8-hydroxyisochromenes and isocoumarins, as well as a novel route toward 8-hydroxyisocoumarins.[1]

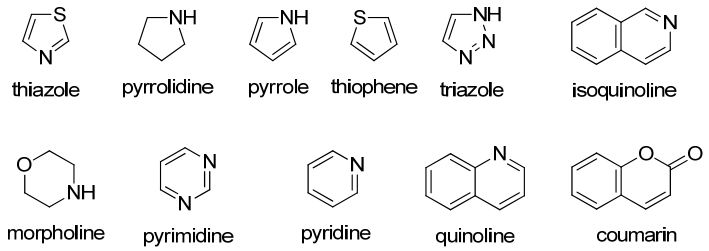


Figure 2.1.1

Heterocyclic organic compounds represent some of the most prevalent and widely studied class of organic molecules. Of the more than 20 million registered chemical compounds, about half contain a heterocyclic motif.[2] These structural features are frequently responsible for a portion of a given molecule's activity, whether it be related to its role as a pharmaceutical agent, herbicide, dye, sensitizer, corrosion inhibitor, etc. Within this vast class of compounds, nitrogen and oxygen-based heterocycles predominate, as shown in Figure 2.1.1. Not surprisingly, there is a wide array of synthetic methods for the rapid, efficient, and versatile construction of many of these frameworks. Such methods have aided in the synthesis and strategic introduction of these important chemical building blocks.

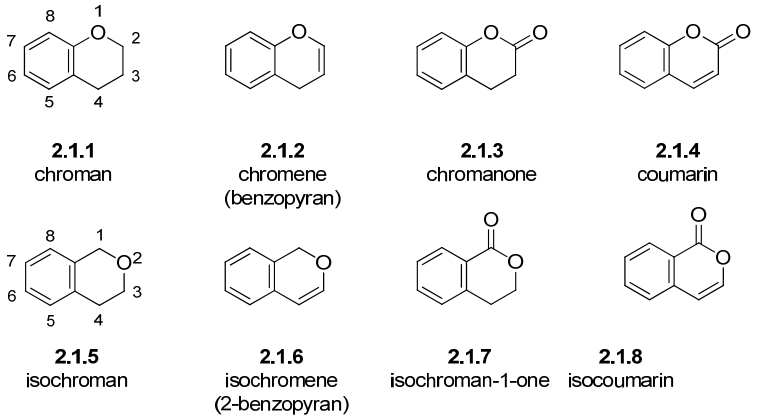


Figure 2.1.2

Isochromenes and isocoumarins, as their name suggests, are isomeric forms of two other common structural units found in nature, chromenes and coumarins, respectively, shown in Figure 2.1.2. The top row of Figure 2.1.1 represents the chroman-based skeletons, which differ in the presence or absence of a double bond in the heterocyclic ring and the presence or absence of a carbonyl group at the C2-position (**2.1.1-2.1.4**). The bottom row of Figure 2.1.2 shows the isochroman-based analogs, which differ similarly (**2.1.5-2.1.8**). Isochromenes are characterized by a benzannulated pyran ring with the oxygen linking the C1 and C3 carbons, which frequently lends to the name 2-benzopyrans. Isocoumarins, 1*H*-isochromene-1-ones, on the other hand, are C1-oxidized isochromene derivatives, and are also commonly called 2-benzopyran-1-ones.

Several excellent reviews focused on the isolation and synthetic approaches related to isocoumarins: Barry (1964)[3], Narasimhan and Mali (1983)[4], Hill (1986)[5], Napolitano (1997)[6], and Hussain (2000).[7] These resources and the primary articles cited within are an invaluable source of information related to these systems.

Surprisingly, there have been no comprehensive reviews on the isolation, activity, or synthetic importance the isochromenes, although general treatise portions of articles outlining the studies related to their isolation, preparation, and reactivity provide significant overviews on this

class. The research articles of Larock and Yamamoto and co-workers have been particularly noteworthy.

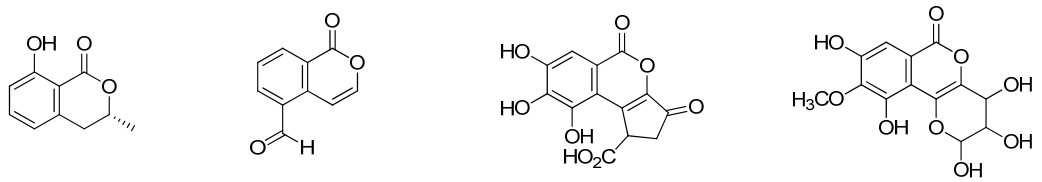
2.2 Natural and Synthetic Isocoumarins and Isochromenes and Activity

A large number of both naturally-occurring and synthetic isochromans, isocoumarins and isochromenes exhibit a wide range of pharmacological properties. This section will only focus on some of the most interesting and investigated compounds containing either an intact or modified isochromene or isocoumarin motif. Since the isochroman (**2.1.5**) and isochromanone (**2.1.7**) frameworks are also present in a number of natural products, certain compounds of interest will be discussed. This section is not intended to be a compilation of all of the biologically-active isocoumarin- and isochromene-based synthetic and natural products, but rather a primer.

A "Sci-Finder Scholar" search for the term "isochromene" resulted in 224 references, whereas more than 1500 results were found for the term "isocoumarin," which is consistent with the number of reported naturally-occurring compounds containing those structural motifs.[8] The range of occurrence and activity for the latter class is more vast and well studied; therefore, the more populated isocoumarin class will be presented first.

A wide range and number of naturally-occurring isocoumarins have been isolated from plants, molds, lichens, bacteria, and insect sources, commonly identified as secondary metabolites of those sources. They exhibit an impressive array of biological activity, including antifungal, cytotoxic, antitumor, antiallergic, antimalarial antimicrobial, anti-inflammatory, antidiabetic, phytotoxic, and immunomodulatory activities. Some synthetic isocoumarins have also attracted attention for their interesting activity.

Figure 2.2.1 presents two of the simplest isocoumarin-based natural products. Mellein (**2.2.1**), a 3,4-dihydroisocoumarin originally isolated from *Aspergillus melluss*, was isolated from several different sources of fungi and insects and has been shown to play a pheromonal role.[9] Erythrocentaurin (**2.2.2**) was isolated from the root of *Gentiana macrophylla* and interrupts the enzyme system of skin cells.[10]



2.2.1 mellein

2.2.2 erythrocentaurin

2.2.3 brevifolin carboxylic acid

2.2.4 bergenin

Figure 2.2.1

Isocoumarins which contain the gallic acid skeleton are also shown in Figure 2.1.3. Brevifolin carboxylate derivatives of **2.2.3**, isolated from the Rose plant *Geranium Bellum,* inhibited triosephosphate isomerase from *Trypsanoma cruzi* and show cytotoxic activity in the low micromolar range.[11] Bergenin (**2.2.4**) has demonstrated hepatoprotective effects in rats and has been identified as the antiarrhythimic constituent in *Fluggea virosa*.[12]

Selected isocoumarins that exhibit significant biologically activity are shown in Figure 2.3.2 and are organized by substitution pattern. Capillarin (**2.2.5**), isolated from *Chrysanthemum frutescens L., Artemisia dracunulus L.,* and *Artemisia lamprocaulos*, has been shown to possess antifungal activity, as well as act as an insect antifeedant.[13] Artemidin (**2.2.6**), also isolated from *Artemisia dracunulus L.*, and cercophorin A (**2.2.15**), from the coprophilous fungus *Cercophora areolata*, also exhibit antifungal activity.[14] Reticulol (**2.2.7**) has also shown *in vitro* cytotoxicity against a human lung tumor cell line and a mouse melanoma cell line.[15] Cytogenin (**2.2.8**), originally isolated from *Streptoverticillium eurocidicum* in 1990, has been exhaustively evaluated and is the first isocoumarin shown to have anticancer activity against experimental

tumor cells and human cancer cells.[16] Cytogenin has also been evaluated as an immunomodulator and antiarthritic agent. Thunberginol A and B (**2.2.9** and **2.2.10**), isolated from *Hydrangeae Dulcis Folium,* show potent histamine release inhibition, as well as antimicrobial and immunomodulatory activities.[17] Phyllodulcin (**2.2.11**), a hydrangenol derivative isolated from *Hydrangea opuloides* that is 1000 times sweeter than table sugar, has played a significant role in the discovery and development of novel low-calorie sweeteners.[18]

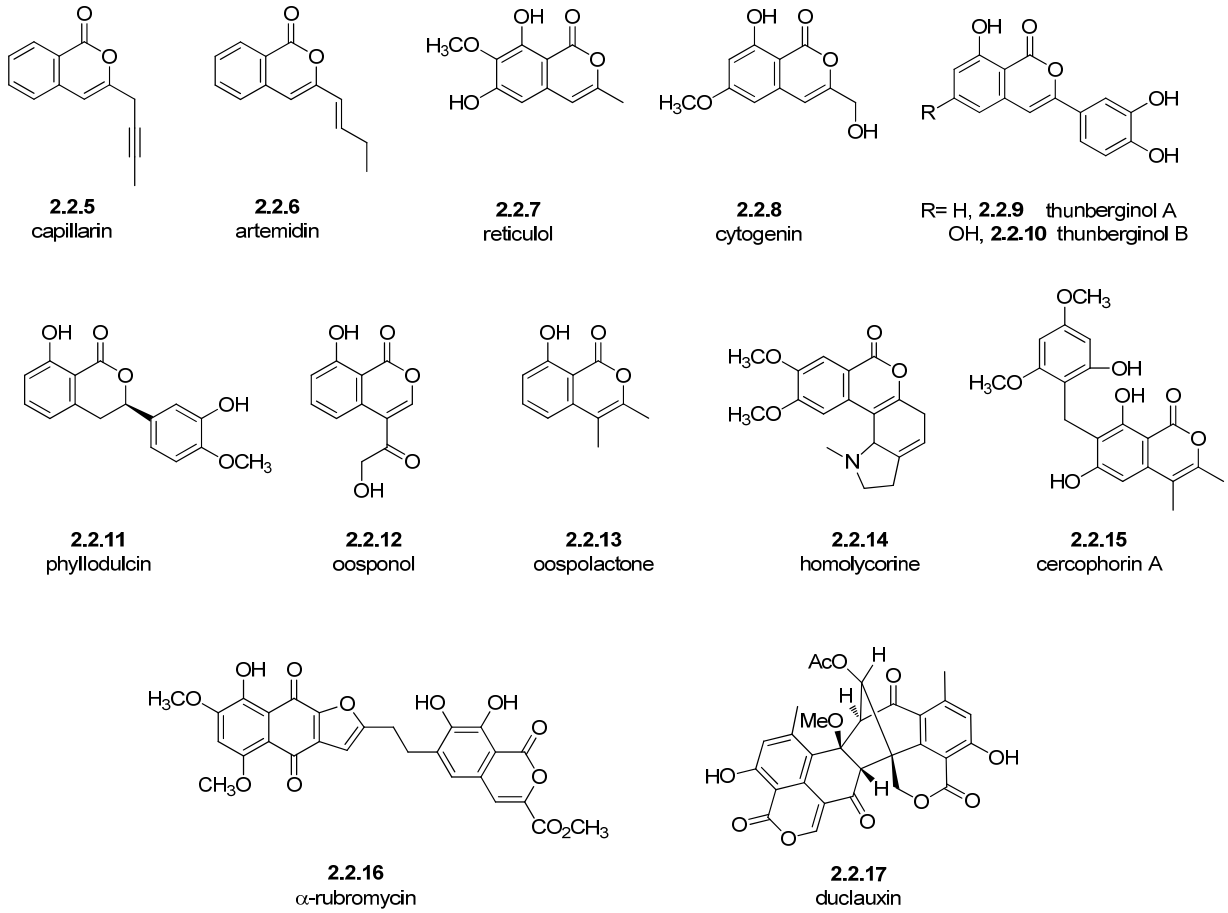
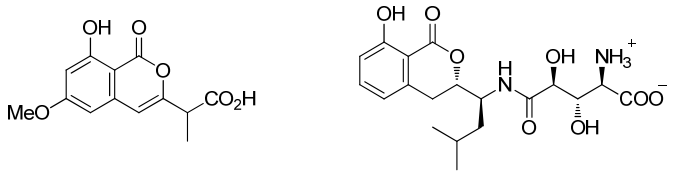


Figure 2.2.2

Oosponol (**2.2.12**) is a secondary fungal metabolite isolated from many basidiomycetes and is a prominent toxin with antibiotic activity against plants and Gram-positive bacteria.[19] Ospolactone (**2.2.13**), commonly isolated along with **2.2.12**, also exhibits antifungal activity.[20] Homolycorine (**2.2.14**) isolated from *Lycoris radicata, Narcissus poeticus, Leucojum vernum*, and *Pancratium*

maritimum, has recently been shown to have high antiretroviral activity, though accompanied by a low therapeutic index.[21] The rubromycins, such as α-rubromycin (**2.2.16**) have also been the focus of many research groups, as the structurally-related members of this family have a wide range of biological activity, including activity against human telomerase, the reverse transcriptase of HIV-1, and the moloney murine leukemia virus.[22] Duclauxin (**2.2.17**), a metabolite of *Penicillium herquei*, *P. duclauxii*, and *P. stipitatum,* consists of a heptacyclic ring system comprised of an isocoumarin subunit and a dihydroisocoumarin subunit.[23] Duclauxin has been shown to have excellent antitumor properties, demonstrated by its effectiveness against Ehrlich's ascites carcinoma cells, lymphadenoma L-5178, HeLa cells, tumor cells of the line P 388, and murine leukemia L1210 culture cells.



2.2.18
NM-3

2.2.19
AI-77-B

Figure 2.2.3

Many synthetic isocoumarins exhibit a similar range of biological activity (Figure 2.3.3). Isocoumarin NM-3 (**2.2.19**) is particularly noteworthy since it is highly effective in the treatment of solid tumors and is currently in clinical trials.[24] Additionally, there has been significant interest in the AI-77's, such as **2.2.19**, which exhibit gastroprotective properties without the common CNS effects.[25]

Several natural products have been isolated with an isochroman-based motif (Figure 2.2.4). Obionin A (**2.2.20**), isolated from cultures of the marine fungus *Leotosohaeria obiones,* contains a C3-alkyl chain and a benzanulated *o*-quinone and has demonstrated CNS activity.[26] The pentalongin-based hydroquinone diglycoside harounoside (**2.2.21**) was isolated from

Mitracarpus scaber, an annual plant used in traditional African medicine for its antifungal and antiparasitic activities.[27] Compounds **2.2.22-2.2.25** were isolated from *Penicillium expansum*, of which **2.2.22**, **2.2.23**, and **2.2.24** were active against *Lasiodiplodia theobromae*, the causative agent of stem rot in fruits.

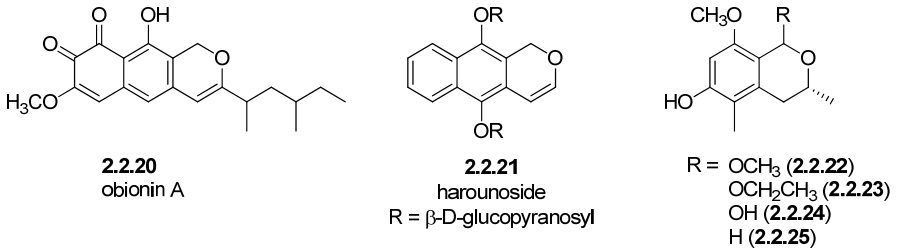


Figure 2.2.4

One of the largest and most important classes of isochroman-related natural products are the pyranonaphthoquinone antibiotics, which are typified by the structural motifs **2.2.26** and **2.2.27** (Figure 2.2.5). Many member of this family have been isolated from various strains of bacteria and fungi, the majority of which are microbial in origin.[28] Members also show activity against a variety of Gram-negative bacteria, as well as pathogenic fungi and yeasts, which makes them interesting synthetic targets. The simplest of these compounds is pentalongin (**2.2.28**).[29] Ventiloquinone L (**2.2.29**) was isolated from the root bark of the *Ventilago vitiensis* and exhibits a diverse range of topoisomerase II inhibition properties.[30] BCH-2051 (**2.2.30**) was synthesized in 1998 and demonstrated excellent activities in screens against the human ovarian cancer cell line SKOV3 and a multi-drug resistant variant (SKVLB), as well as the HT-29 colon carcinoma cell line.[31] Other members of this class are the 3,4- dihydroisochroman-based frenolycin (**2.2.31**), eleutherin (**2.2.32**), nanaomycin (**2.2.33**), and psychorubin (**2.2.34**), whereas two related isochromene-based natural products are dehydroherbarin (**2.2.35**) and anhydrofusarubin (**2.2.36**).

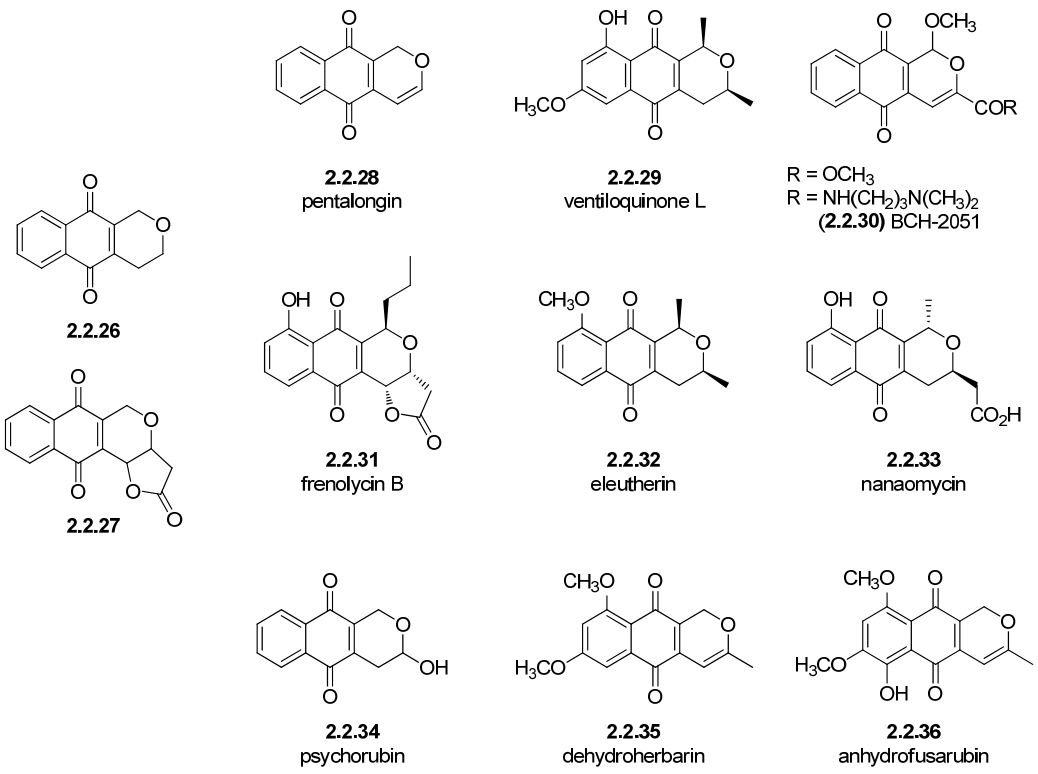


Figure 2.2.5

2.3 Synthetic Approaches to Isocoumarins

Synthetic approaches toward the isocoumarin skeleton are vast and have been widely studied by the synthetic community. The interest in isocoumarins, isocoumarins, and analogues has been of steady interest from 1961 to 2000 and has seen a steady increase in publications since the turn of the century. Several excellent literature reviews for the isolation, characterization, synthesis, and reactions of the isocoumarins have been published during the past fifty years. These include a seminal review by Barry covering the topic of isocoumarin synthesis and reactivity, as well as their natural occurrence, from 1950 to 1964.[3] In his 1986 compilation on natural isocoumarins, R. Hill presented an exhaustive list of references on isocoumarin synthesis.[5] Napolitano has also presented a more recent review, spanning chemistry from 1987 to 1997, which presented an approach toward classification of some general

approaches and strategies toward the synthesis of isocoumarins.[6] Numerous research articles have presented broad overviews of the expanding research into isocoumarin synthesis and reactivity. This section will focus on the many strategies used to access the isocoumarins, as well as some used to prepare isochromanones (**2.1.7**).

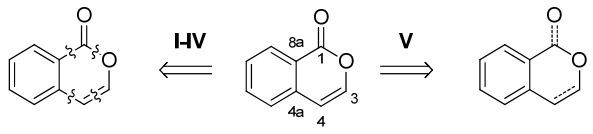
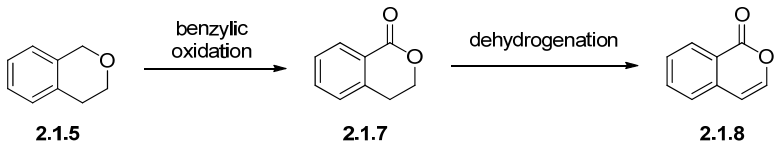


Figure 2.3.1

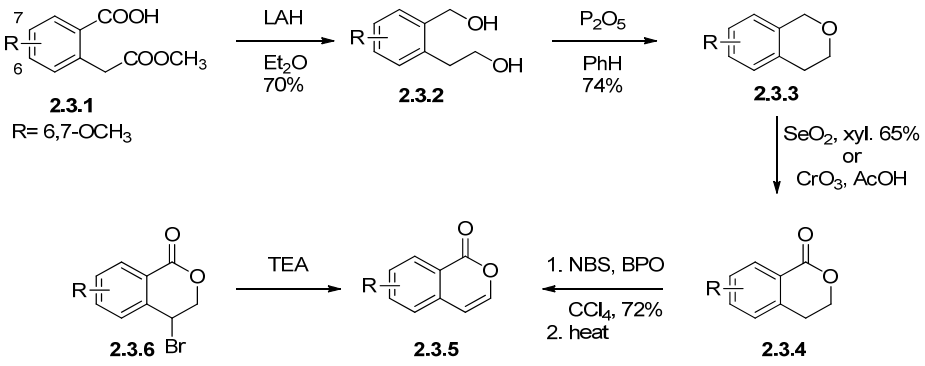
Napolitano presented five general strategies toward isocoumarins: starting from an aromatic precursor containing (I) only carbon 1, (II) carbons 3 and 4, (III) carbons 1 and 4, and (IV) carbons 1,3, and 4 (Figure 2.3.1). One can also imagine that interconversion between the isochroman, isochromanone, isochromene, and isocoumarin skeletons can be achieved (**V**). This system for reaction classification permits the generalization of the methods. However, as several areas within those classifications have expanded greatly since this review, I have chosen to highlight some of the most widely-studied traditional and modern methods.

It is apparent that the isocoumarin framework is accessible through heterocyclic precursors containing the 2-benzopyran framework (see Scheme 2.3.1). As a result, numerous methods have been developed that achieve the benzylic oxidation, whereas limited research for the conversion of an intermediate of the type **2.1.7** to **2.1.8** has been reported. Srivastava and Chaudhury reported an early and excellent summary of their efforts toward isocoumarins from isochromans, which were accessed through substituted homophthalates, represented in Scheme



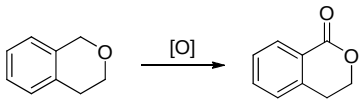
Scheme 2.3.1

2.3.2.[32] For the preparation of 6,7-dimethoxyisocoumarin (**2.3.1**) , LAH reduction of **2.3.1** gives diol **2.3.2**, which can undergo cyclodehydration with P_2O_5 to afford isochroman (**2.3.3**). Next, depending upon the arene functionality, oxidation can be carried out either under Riley oxidation conditions or by CrO_3 in wet acetic acid to give the corresponding isochromanone (**2.3.4**). Introduction of the styrenyl olefin is accomplished by radical-promoted benzylic bromination followed by thermal elimination to give isocoumarin derivative **2.3.5**. Alternatively, treating benzylic bromide **2.3.6** with TEA affords an isocoumarin. While this route represents a logical approach to synthesize isocoumarins, numerous groups have achieved more efficient routes while still having the same access to a broad range of functional groups.



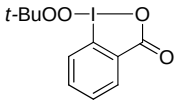
Scheme 2.3.2

Many methods have been reported for the conversion of isochroman (**2.1.5**) to their corresponding isochroman-1-one (**2.1.7**), some of which are outlined in Scheme 2.3.3. Shaabani has developed a green approach to the oxidation of activated benzylic positions, using $KMnO_4$ supported on MnO_2, both with and without solvent and under sonication (entries 1-3).[33] They demonstrated high yields, as well as the recyclability of the oxidant. Lee also demonstrated a similar heterogeneous oxidation protocol, using $KMnO_4$ on a $CuSO_4$ pentahydrate support to afford **2.1.7** in excellent yield under longer reaction times (entry 4).[34] Another approach using a metal-based oxidant was investigated by Reetz and Töllner, who found that catalytic Co(III)



2.1.5 **2.1.7**

Entry	Oxidant (co-oxidant)	Solvent	Temp.	Time	Yield
1	$KMnO_4$ on MnO_2	DCM	rt	24hr	96%
2	$KMnO_4$ on MnO_2	Neat	rt	4hr	80%
3	$KMnO_4$ on MnO_2	Neat/Sonic.	rt	30min	79%
4	$KMnO_4$ on $CuSO_4$-$(H_2O)_5$	ACN:H_2O	50 ^oC	72hr	96%
5	$Co(acac)_3$ (O_2)	EtOAc	70 ^oC	24hr	98%
6	Bi(0), picolinic acid (*t*-BuOOH)	py:AcOH	100 ^oC	72hr	91%
7	CrO_3 ($NaIO_4$)	ACN	rt	10min	99%
8	PCC	DCM	rt	24hr	80%
9	DMDO	Acetone	rt	30min	65-80%
10	$NaClO_2$:*t*-BuOOH	ACN:H_2O	50 ^oC	18hr	75%
11	**2.3.7**	DCM	rt	20hr	86%



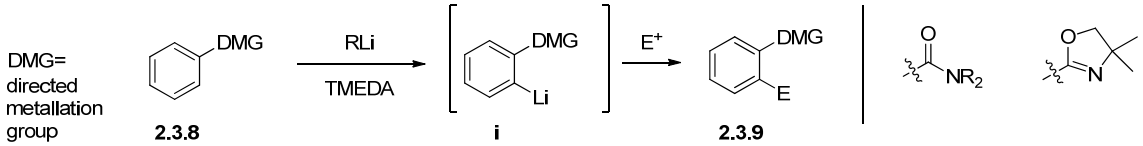
2.3.7

Scheme 2.3.3

effectively oxidized **2.1.5** under aerobic conditions (entry 5).[35] *t*-Butyl hydroperoxide in the presence of a bismuth catalyst oxidizes **2.1.5** to **2.1.7** (entry 6).[36] Oxidation with CrO_3 was also shown to be catalytic in the oxidant when $NaIO_4$ is present as a co-oxidant (entry 7).[37] PCC also gave **2.1.7** in excellent yield, as it can oxidize pyrans to pyranones under similar conditions (entry 8).[38] DMDO, another mild nonmetal-based oxidant, was shown to oxidize activated methylenes in a variable 65-80% yield in 30 min (entry 9).[39] The use of $NaClO_2$ in combination with *t*-BuOOH was also found to selectively oxidized allylic and benzylic positions and gives **2.1.7** in 75% under these benign reaction conditions (entry 10).[36b] This reaction is also effected by hypervalent (*tert*-butylperoxy)iodinane **2.3.7**, which oxidizes a variety of other heterocyclic and carbocyclic systems (entry 11).[40]

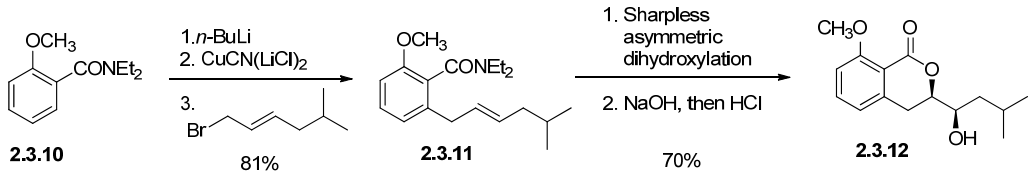
While numerous methods permit the oxidation of isochromans to isochromanones (**2.1.5** to **2.1.7**), no general one-pot methods for the dehydrogenation of isochromanones (*i.e.* **2.1.7** to **2.1.8**) are known, except for a two-step bromination-elimination sequence (Scheme 2.3.2).[32]

The directed *o*-metallation of aromatic amides, carbamates, or other directing groups allows for electrophile trapping, to permit the formation of an isocoumarin with a high degree of structural diversity (Scheme 2.3.4). An excellent review on this strategy has been compiled by Sneikus.[41]



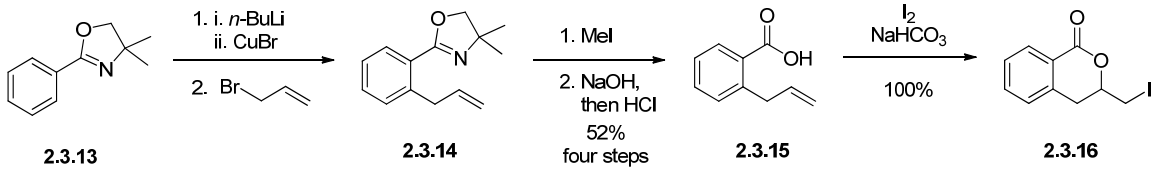
Scheme 2.3.4

Application of this strategy has been applied to the synthesis of some 3,4-dihydroisocoumarins. For example, the enantioselective synthesis of the isocoumarin portion of AI-77B (**2.2.19**) was accomplished by metallation of **2.3.10** and trapping its copper derivative with an allyl group to give **2.3.11** (Scheme 2.3.5). Sharpless asymmetric dihydroxylation and amide hydrolysis produces dihydroisocoumarin **2.3.12** directly, which can then be functionalized further to produce the isocoumarin motif in AI-77B.



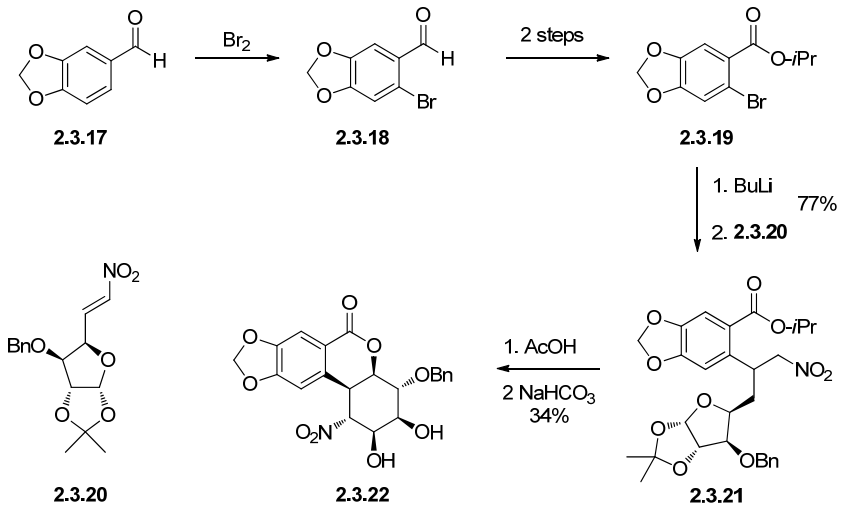
Scheme 2.3.5

This strategy can also be effected using the (4,4-dimethyl)oxazolin-2-yl group, shown in Scheme **2.3.6**. Lithiation of **2.3.13** with butyllithium is selective and allylation is accomplished by transmetallation with a Cu(I) species to give **2.3.14**. Subsequent hydrolysis and iodolactone formation gives **2.3.16**, which is amemable to additional elaboration by a host of reactions.



Scheme 2.3.6

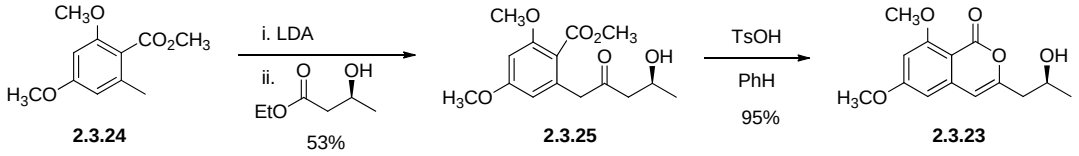
A similar *o*-functionalization method is demonstrated in Scheme **2.3.7**, in which *o*-lithiation is accomplished by metal-halogen exchange. While this approach requires an additional step (*i.e.* aryl halogenations) its distinct advantage is that is extends greater regiochemical control to the functionalization. In their synthesis of (+)-lycoricidin, Paulsen and Stubbe adopted this approach to achieve direct bromination of **2.3.17** to afford **2.3.18**, metallation, a eventually coupling of **2.3.19** to vinyl nitro **2.3.20** to give **2.3.21**, which after hydrolysis and ring closure forms the isochroman portion (**2.3.22**) of the natural product.[42]



Scheme 2.3.7

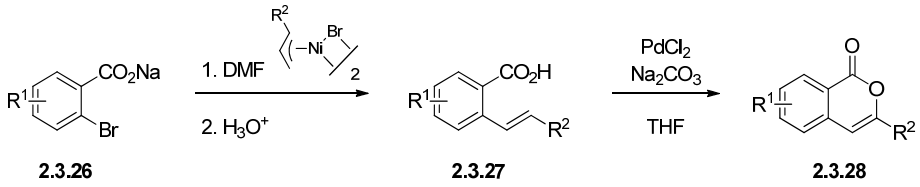
When an alkyl group is present at the *ortho* position of a suitable benzoic acid derivative, direct functionalization via lithiation is also possible (Scheme 2.3.8). For example, the synthesis of dimethylorthosporin (**2.3.23**) was achieved by treating methyl ester **2.3.24** with LDA, then

alkylation with ethyl-(*S*)-3-hydroxybutyrate to give **2.3.25**. Next, isocoumarin formation delivers the natural product.



Scheme 2.3.8

O-alkynyl benzoic acid derivatives represent an ideal template for the synthesis of isocoumarins, as activation of the triple bond can be accomplished either using a suitable electrophile, an acid catalyst, or a transition metal catalyst, which is followed by the subsequent trapping by an internal nucleophile (i.e. aldehyde, acid, or ester).

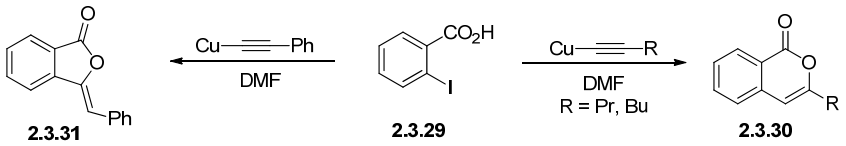


Scheme 2.3.9

Perhaps the mildest and most versatile method for the construction of isocoumarins is the transition-metal mediated cycloisomerization of alkynyl benzoic acid derivatives. The first report of using a transition metal to construct the isocoumarin skeleton was made by Hegedus and co-workers in 1977, in which the sodium salt of *o*-bromobenzoates (**2.3.26**) were treated with π-allylnickel bromide to afford allyl benzoate **2.3.27** (Scheme 2.3.9).[43] This intermediate was then reacted with $PdCl_2$ in the presence of Na_2CO_3 to yield 3-substituted isocoumarin **2.3.28** in excellent yield.

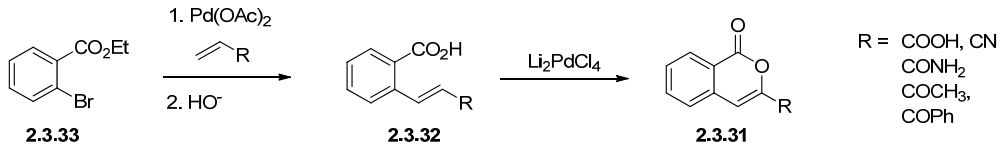
In 1980, Stevenson demonstrated that *o*-iodobenzoic acid (**2.3.29**) underwent isocoumarin formation when exposed to cuprous *n*-propylacetylide in hot DMF to give **2.3.30** (Scheme 2.3.10).[44] While the details and a mechanism for this transformation were not provided,

it represents the first and only Cu(I)-mediated isocoumarin synthesis. Additionally, the formation of **2.3.31** presents one of the major obstacles in the metal catalyzed synthesis of C3-substituted isocoumarins: the selectivity between 5-*exo*-trig and 6-*endo*-trig cyclization is highly dependent upon the C3-precursor in the alkyne.



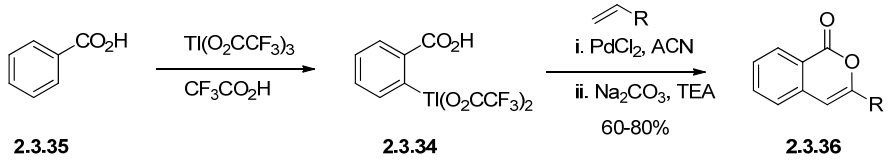
Scheme 2.3.10

Also in 1980, Izumi, Saito, and Kasahara reported a direct synthesis of isocoumarins (**2.3.31**) via the palladium-catalyzed cycloisomerization of *o*-vinylbenzoic acids **2.3.32** (Scheme 2.3.11). Their route mimicked that of Hegedus, though a Pd(II)-catalyzed cross-coupling was used to install the olefin from **2.3.33**.



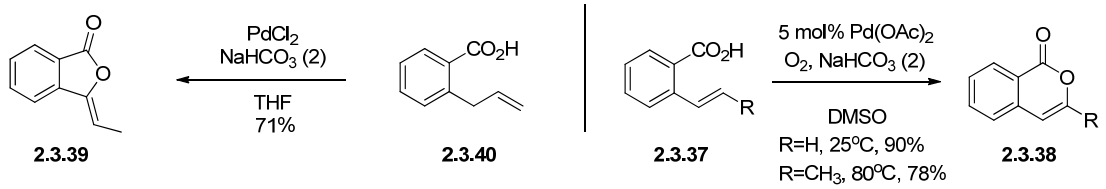
Scheme 2.3.11

In 1984, Larock reported that *o*-thallated benzoic acid derivative **2.3.34** could be obtained by treating benzoic acid (**2.3.35**) with $Tl(O_2CCF_3)_3$ (Scheme 2.5.12) Compound **2.3.34** underwent vinylation and subsequent Pd(II)-catalyzed cyclization afforded 3-substituted isocoumarin **2.3.36** directly.[45]



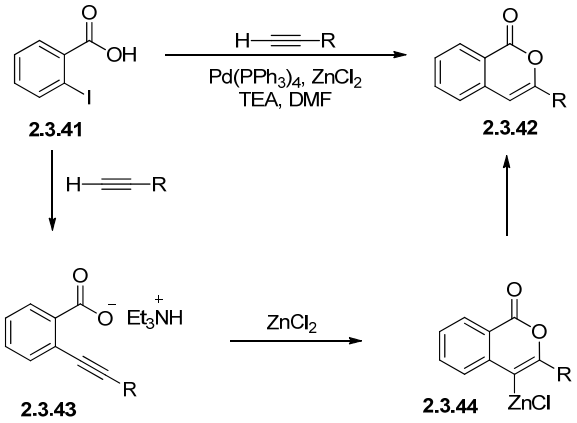
Scheme 2.3.12

Among other related cyclization reactions, Larock and co-workers presented their initial investigations into a generalized approach to isocoumarins via the Pd(II)-catalyzed cyclization of alkenoic benzoic acids (**2.3.37** to **2.3.38**, Scheme 2.3.13).[46] They applied a more selective synthesis of isocoumarin using $Pd(OAc)_2$ with O_2 as the oxidant, instead of Hegedus's $PdCl_2$, which gives mixtures of isocoumarins and phthalides (**2.3.39** to **2.3.40**).



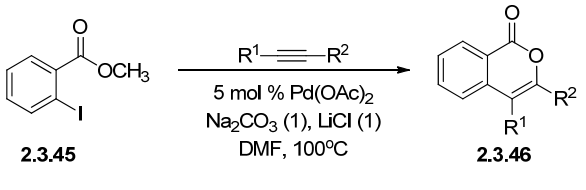
Scheme 2.3.13

In 1995, Cheng and Liao improved upon Stevenson's Cu(I)-catalyzed acetylide approach (Scheme 2.3.10) and developed a general method for isocoumarins by tandem cross-coupling and cyclization of iodobenzoic acids (**2.3.41**) and alkynes using $Pd(PPh_3)_4$, TEA, and $ZnCl_2$ in DMF.[47] This approach affords good yields of (**2.3.42**) and phthalide formation is minimal under the given conditions. In their report, the authors also present a mechanism different from that presented by Larock and others, in which a Pd(II) species generates the corresponding aryl alkyne (**2.2.43**) and cyclization is catalyzed by $ZnCl_2$ to give **2.4.44** as shown in Scheme 2.3.14.



Scheme 2.3.14

Larock made another contribution to this area by elaborating upon both Cheng and Heck's observations.[48] Using an internal alkyne and an *o*-iodo or *o*-triflate benzoic ester (**2.3.45**), Larock developed conditions for introducing C3 and C4-functionality in the isocoumarin product (**2.3.46**), employing 5 mol% $Pd(OAc)_2$, and 1 equiv. of both Na_2CO_3 and LiCl in DMF.[49] This protocol is tolerant of a wide range of sensitive and bulky functional groups and phthalates were not observed under the given conditions.



2.3.45 2.3.46

R^1	R^2	%
Ph	$C(CH_3)_2OH$	77
Et	CyOH	63
Ph	PH	74
Et	TMS	51
n-but	TBDMS	72
CH_3	TIPS	76

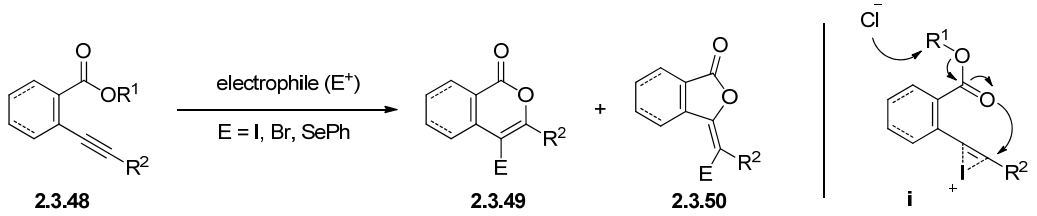
Scheme 2.3.15

Pal and co-workers offered a variation of this method whereby *o*-iodobenzoic acids could be converted into 3-substituted isocoumarins by exposure to a variety of terminal alkynes in the presence of 10% Pd/C, TEA, CuI, and PPh_3.[50] This method was amenable to a number of hydroxylated and alkyl acetylenes, yielding 40-75%, and gave 60-78% yields in the case of electron rich and electron-poor benzoic acids.

The above methods represent efficient, mild, and chemoselective options for the generation of complex isocoumarin frameworks. However, it is obvious that their drawback is the availability of the starting *o*-substituted benzoic acid derivative.

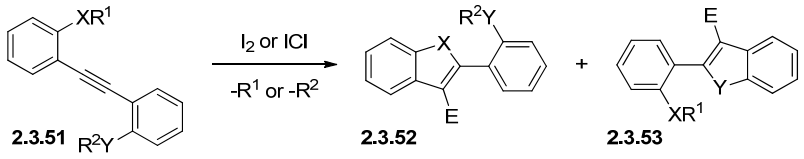
Another useful method for rapid construction of the isocoumarin core has been pioneered by the work of Larock and others. The electrophilic activation of aryl alkynes, followed by internal addition, has resulted in many general methods for the synthesis of many carbocycles and heterocycles including, but not limited to, benzofurans, furans, naphthols, indoles, quinolines, isoxazoles, chromones, bicyclic lactams, and pyrroles.[51] While the application of this

strategy to isocoumarins (*i.e.* **2.3.47** to **2.3.48**) is plagued by competing 5-*exo*-dig cyclization when R = H (**2.3.49**), some useful examples have been reported.



Scheme 2.3.16

In 2002, Larock reported the first general approach to the synthesis of α-pyrones and isocoumarins via an iodocyclization protocol, wherein the methyl ester of **2.3.48** was treated with ICl at room temperature to afford 4-iodoisocoumarin **2.3.49** in excellent yield (Scheme 2.3.16).[52,53] A variety of sources of electrophiles were examined, including ICl, I_2, *p*-$O_2NC_6H_4SCl$, PhSeCl, and HI to produce the corresponding C4-substituted isocoumarins in 90-95% yield. This reaction proceeds through intermediate **i** and affords only one regioisomer when R = aryl or alkyl, with the formation of **2.3.50** predominating when R = H.



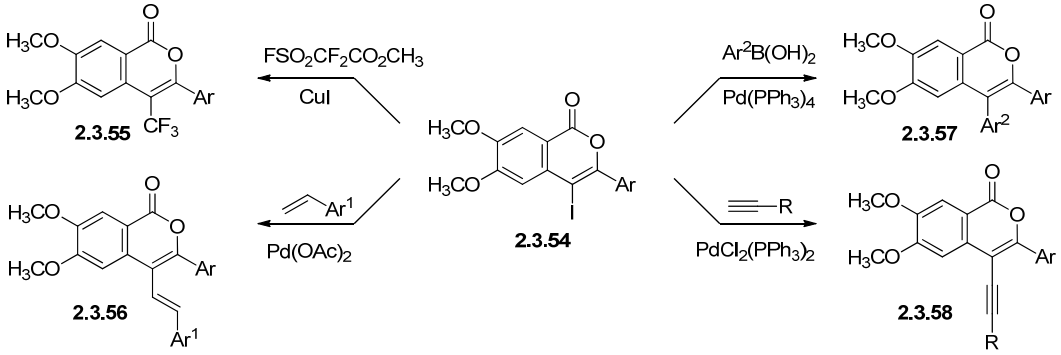
Relative reactivity of functional groups toward cyclization

$SeCH_3 > SCH_3 > CO_2CH_3 > N(CH_3)_2 > Aryl > OCH_3 > OBNCHN^tBu > OCH_3 > OAc > CONHPh > CO_2CH_3 > CHO$

Scheme 2.3.17

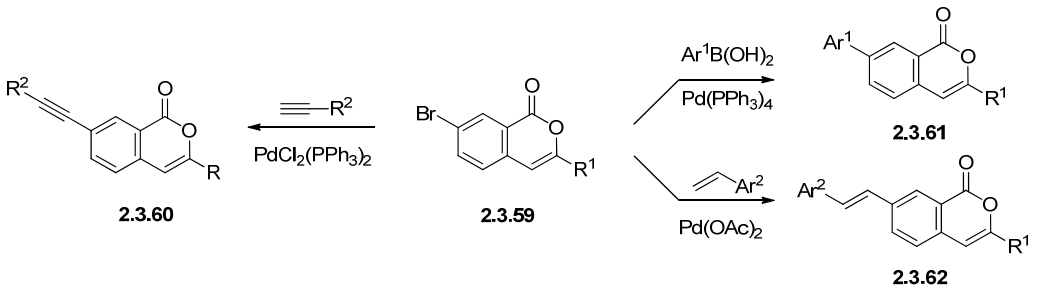
To further extend the scope of this method, Larock and co-workers evaluated the relative reactivity of various functional groups toward alkyne electrophilic cyclization using a diaryl alkyne (**2.3.51**).[51] The results are generalized in Scheme 2.3.17, where it was found that the nucleophilicity of the competing functional groups, polarizability of the triple bond, and the

stability of the intermediate cation are the driving factors for determining the relative reactivity in the formation of **2.3.52** or **2.3.53**.



Scheme 2.3.18

Perhaps the most compelling examples of Larock's protocol was presented in late 2009.[54] He addressed the fact that both natural and synthetic biologically active isocoumarins contain a broad range of functional groups by developing a combinatorial strategy to generate an extensive 167 member isocoumarin library. Through his generation of a wide range of 4-iodoisocoumarins via from the aforementioned method, a varied isocoumarin library was rapidly generated by subsequent cross-coupling reactions, such as **2.3.54** to **2.3.55**, **2.3.56**, **2.3.57**, and **2.3.58** (Scheme 2.3.18). An important feature of this study was that the library was prepared via solution phase chemistry and could be automated. Larock also prepared C7-substituted isocoumarins via 7-bromo-3-substituted isocoumarin **2.3.59** via similar Pd-catalyzed cross coupling reactions to give **2.3.60**, **2.3.61**, and **2.3.62** (Scheme 2.3.19).



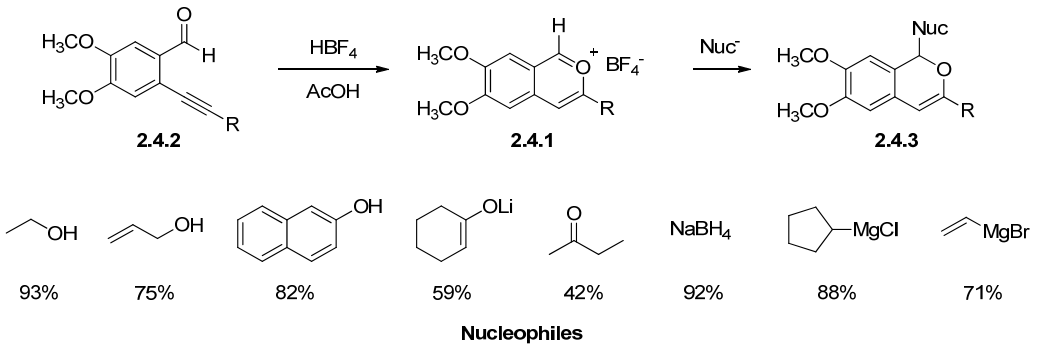
Scheme 2.3.19

2.4 Synthetic Approaches to Isochromenes

Isochromenes are characterized by a benzanulated pyran system, seen in Figure 2.1.2, and characteristics of this motif are present in several natural products (Section 2.2). A SciFinder Scholar search using the term "isochromene" lead to only 224 references containing the concept "isochromene." Upon closer investigation of those results, it can be seen that many advances toward general methods for their preparation have made over the past fifteen years. Generalizations can also be made for these methods and some coincide with those developed for the synthesis of isocoumarins (Section 2.3). First, cyclization of *o*-alkynyl benzaldehydes to form isochromenylium intermediates can be trapped with a variety of nucleophiles. Also, metal- and electrophile-induced cyclization of *o*-alkynyl alcohols assembles the isochromene skeleton.

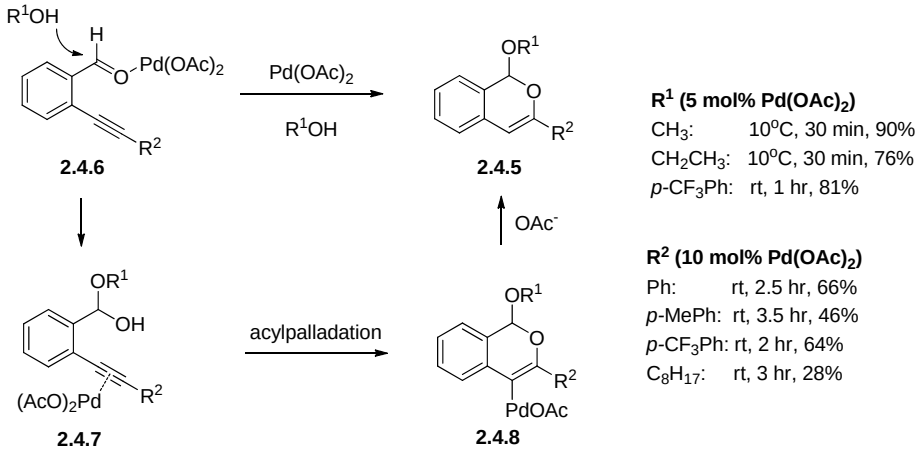
It is important, at this time to iterate what was noted by Pedrosa, Sayalero, and Vicente.[55] In their synthesis of enantiopure C1-substituted isochromenes, they noted that the isochromenes are less common natural metabolites and their synthesis has been studied less probably because they are not very stable and show a tendency towards oxidation and polymerization. Nevertheless, many approaches have been developed toward this goal.

Isochromenylium, or 2-benzopyrylium, cations are a unique class of reactive intermediates.[56] Many have utilized their unique reactivity in a number of cycloisomerization reactions of *o*-alkynylbenzaldehydes. Recently, Yao and co-workers isolated and characterized such an intermediate, moisture- and air-stable isochromenylium tetrafluoroborate **2.4.1** readily prepared from **2.4.2** through treatment with HBF_4 in AcOH.[57] This species is capable of reacting with a variety of nucleophiles to generate C1-substituted isochromenes (**2.4.3**), as demonstrated in Scheme 2.4.1. Compound related to **2.4.2** could be exposed to a variety of nucleophilic species in 5-10 minutes at room temperature in THF to give good yields of C1-substituted isochromenes.



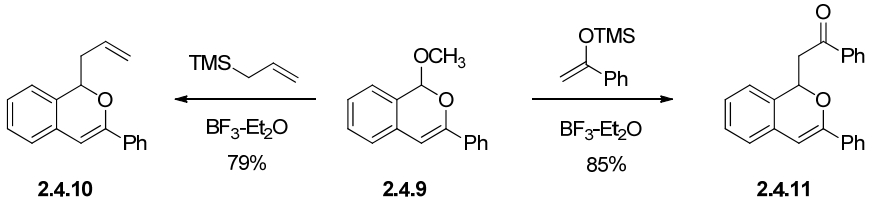
Scheme 2.4.1

Prior to Yao's work, many seminal contributions to this area were made by Yamamoto and others. In 2002, Yamamoto and co-workers found that $Pd(OAc)_2$ served a dual role in the formation of C1-substituted isochromenes (**2.4.4**) from *o*-alkynylbenzaldehydes (**2.4.5**) in the presence of an alcohol.[58] They found that the product ratio resulting from 6-*endo*-cyclization or 5-*exo*-cyclization was largely dependent upon the R^2 electronics. This reaction was also effective when other alcohols were used. More importantly, though, Yamamoto demonstrated the reactivity of 1-alkoxy-isochromenes (**2.4.9**), as allyl and acetophenone groups could be introduced via the reactions shown in Scheme 2.4.3 to give **2.4.10** and **2.4.11**, which proceeds through an isochromenylium intermediate (see Scheme 2.4.1). These additional manipulations



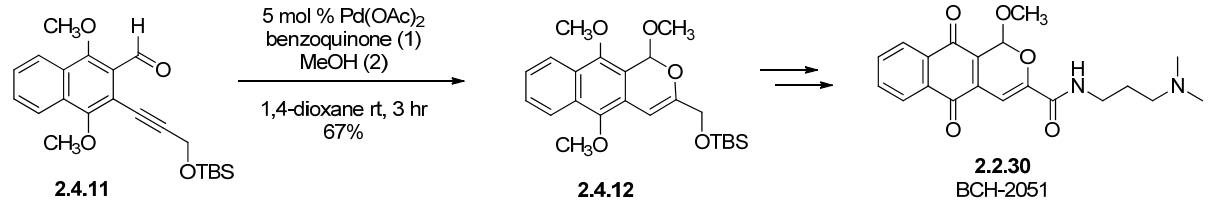
Scheme 2.4.2

were studied further in 2005 by Yamamoto and resulted in a one-pot two-component reaction system to arrive at **2.4.10** and other related frameworks.[59]



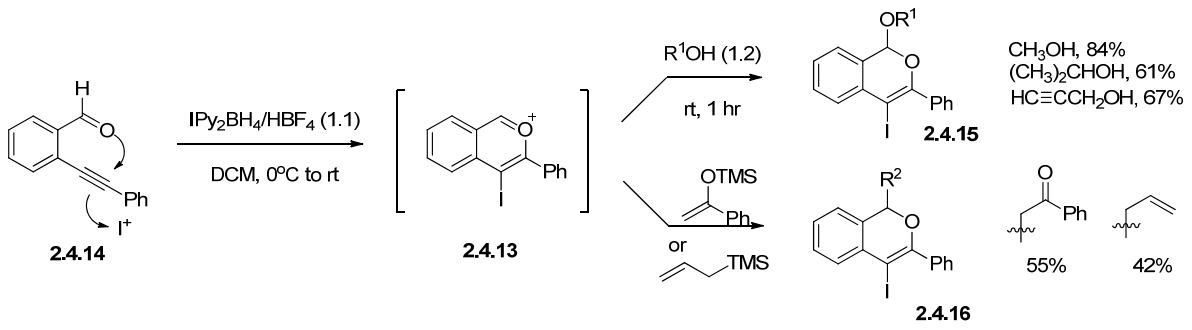
Scheme 2.4.3

Yamamoto applied this Pd(II)-catalyzed cyclization to the synthesis of BCH-2051 (**2.2.30**), a derivative of pentagolin (**2.2.30**) that exhibits antitumor properties (Scheme 2.6.4).[60] When aldehyde **2.4.12** is treated with $Pd(OAc)_2$ in the presence of CH_3OH, isochromene **2.4.13** is delivered in good yield, which is then converted into **2.2.30**.



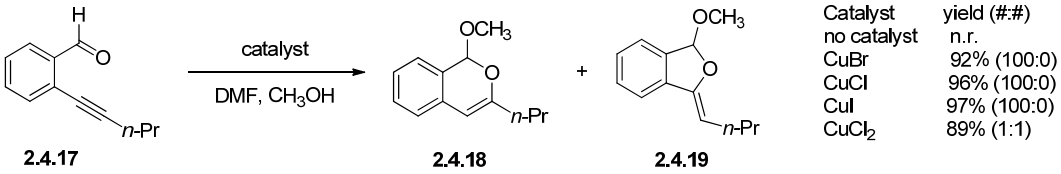
Scheme 2.4.4

Barluenga approached the isochromene skeleton via a similar strategy, though an iodocyclization approach was used to access reactive isochromenylium species **2.4.13** from **2.4.14** (Scheme 2.4.5).[61] Using *bis*-(pyridine) iodonium tetrafluoroborate (IPy_2BH_4) as an iodonium source, activation of the alkynyl moiety of **2.4.14** is followed by intramolecular trapping by the adjacent aldehyde to form **2.4.13**. Addition of an alcohol gives **2.4.15**, while, they showed that carbon-based species could be introduced easily, as demonstrated by the addition of allyl and acetophenone groups to give **2.4.16** and other frameworks.



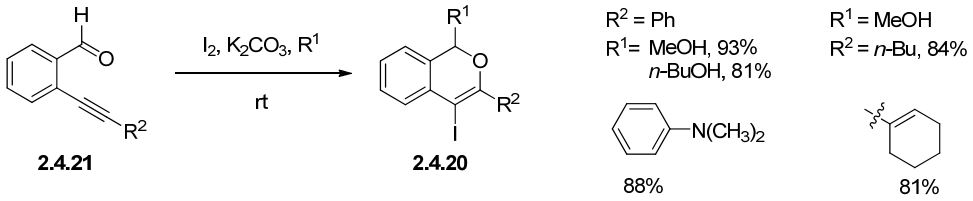
Scheme 2.4.5

Yamamoto and co-workers extended their initial findings to the Cu(I)-catalyzed cyclization of *o*-alkynylbenzaldehydes (**2.4.17**) in the presence of an alcohol to give **2.4.18** (Scheme 2.4.6).[62] They found that Cu(I) catalysis resulted in complete selectivity for the isochromene product, while Cu(II) followed a different mechanism and resulted in the formation of **2.4.18** and **2.4.19** in a 1:1 ratio.



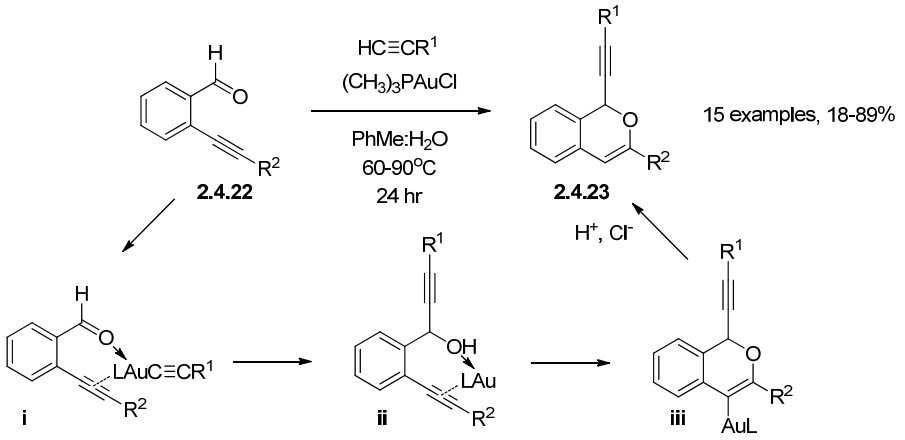
Scheme 2.4.6

Larock's approach paralleled his earlier work toward synthesizing 4-iodoisocoumarins (see Section 2.3).[63] It was noted that Barluenga's cyclization conditions were costly and difficult, while the use of I_2 in the presence of a K_2CO_3 and an alcohol gave excellent yield of **2.4.20** under the mild and facile cyclization conditions from **2.4.21** (Scheme **2.4.7**). It was shown that a variety of alcohols and other nucleophiles could be introduced at the C1-position, including *N*,*N*-dimethylamino benzene, which substitutes *para* to the amine functionality. Variation on the alkynyl side chain gives excellent yield and selectivity of isochromenes.



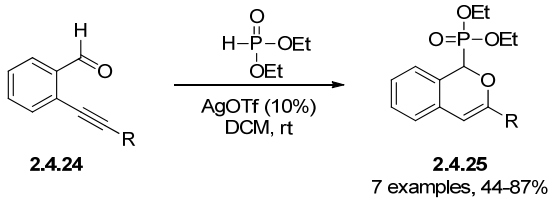
Scheme 2.4.7

Li used a Au-catalyzed approach toward a one-pot, two-step synthesis of C1-acetylenic isochromenes, shown in Scheme 2.4.8.[64] They found that the Au catalyst activates the aldehyde portion of **2.4.22** toward addition to give **i** then **ii**, at which time Au-catalyzed cycloisomerization gives intermediate **iii**, then **2.4.22** upon reductive elimination.



Scheme 2.4.8

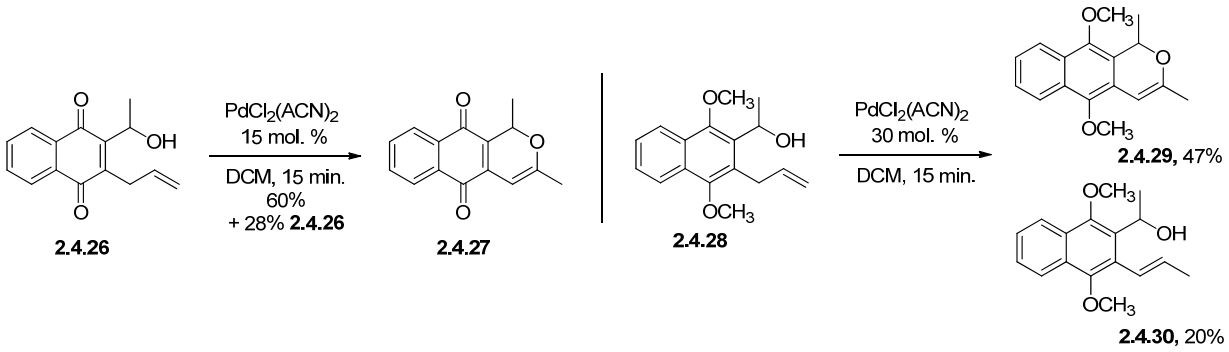
Wu and co-workers screened Lewis acids for the addition of phosphonate group to the C1-position of isochromenes and found that AfOTf sufficiently activates *o*-alkynylbenzaldehydes (**2.4.24**) toward cyclization and C1-addition to give **2.4.25** (Scheme 2.4.9).[65] The mechanism for the transformation is analogous to the above examples and similar selectivity was observed. The report is of considerable interest due to the prevalence of organophosphorus compounds in natural and pharmaceutically-important organic compounds.



Scheme 2.4.9

While the utility of *o*-alkynylbenzaldehydes in their conversion to versatile isochromenylium-based intermediates cannot be denied, the availability of the appropriate *o*-alkynylbenzaldehyde starting material remains a major drawback.

Isochromenes have also been prepared through the cycloisomerization of an *ortho*-substituted hydroxymethyl group onto an aryl alkyne. As outlined in the previous section, this type of reactivity can be affected through either a transition-metal or electrophile-activation of the alkyne (see Section 2.3).



Scheme 2.4.10

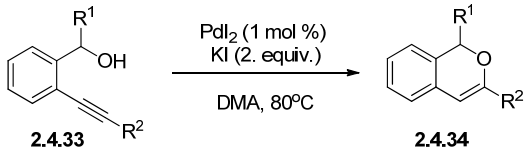
In 1999, Giles and co-workers demonstrated that 2-allyl-1,4-naphthaquinone **2.4.26** undergoes rapid cyclization to benzoisochromenequinone **2.4.27** with $PdCl_2(ACN)_2$, with 28% recovered **2.4.26**. A similar reaction of related 2-allyl-1,4-dimethoxynaphthalene **2.4.28** affords a similar cyclization product (**2.4.29**), with isomerized (*E*)-olefin **2.4.30** as the major byproduct. Also, the authors reported the cycloisomerization of benzyl alcohol **2.4.31** under the same

conditions, with isochromene **2.4.32** generated in an optimized yield of 44%, though with stoichiometric $PdCl_2(ACN)_2$ (Scheme 2.4.11).

2.4.31 **2.4.32** 44%

Scheme 2.4.11

Gabriele and co-workers also investigated the synthesis of isochromenes, but through the cycloisomerization of *o*-alkynyl benzyl alcohol (Scheme 2.4.12). They demonstrated that treating **2.4.33** with 1% PdI_2 and 2 equiv. KI in *N,N'*-dimethylacetamide at 80 °C gave good yield and selectivity of isochromenes with **2.4.34** species being the major byproduct.[66] Their exhaustive study into this selectivity provides an excellent primer for this approach to isochromenes, as catalyst, solvent, and co-oxidant types, as well as temperature variations were evaluated with respect to their impact on 6-*exo*-dig versus 5-*exo*-dig cyclization.



2.4.33 **2.4.34**

R^1= H, H; R^2= *n*-but	63%
R^1= Et, Et; R^2= *n*-but	73%
R^1= *n*-but; R^2= *n*-but	74%
R^1= H,H; R^2= Ph	40%
R^1= *n*-but; R^2= Ph	40%

Scheme 2.4.12

Crabtree has demonstrated that a variety of *o*-substituted aryl alkynes undergo *endo*-cyclization with hydroiridium catalysts (Scheme 2.4.13).[67] Benzyl alcohols (**2.4.35**), as well as phenols and amines (**2.4.36**), undergo cyclization with 3-4 mol% **2.4.37** in either DCM or $CHCl_3$ with complete selectivity for the *endo* process to give isochromenes (**2.4.38**) and benzofurans and indoles (**2.4.39**).

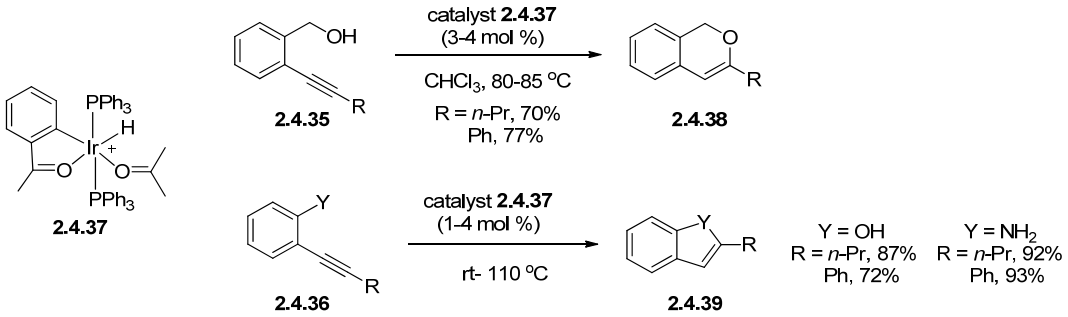
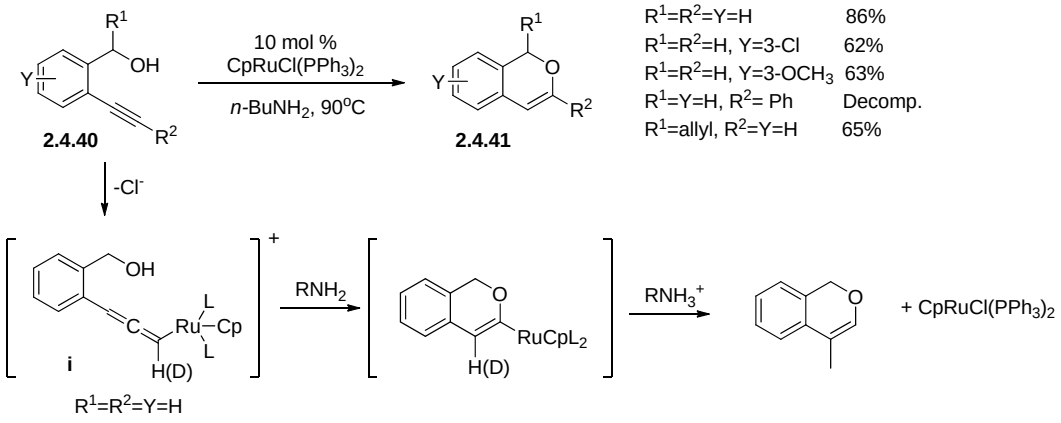


Figure 2.4.13

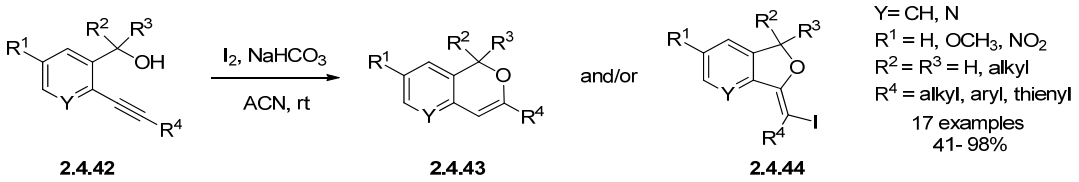
Recently, Saá and co-workers reported the used of catalytic $CpRuCl(PPh_3)_2$ in conjugation with an amine base to affect the isomerization of *o*-alkynyl benzylic alcohols (**2.4.40**) to isochromenes (**2.4.41**, Scheme 2.4.14).[68] In contrast to many previously-described methods, this approach gives poor selectivities when aryl-substituted alkynes are cyclized onto (R^2 = Ph). This reaction proceeds through a cationic metal vinylidene intermediate (**i**) as shown in Scheme 2.4.14. This catalyst system has been used in the preparation of benzofurans as well.



Scheme 2.4.14

Larock and co-workers have applied their iodocyclization strategy for the preparation of 4-iodoisochromenes (Scheme **2.4.15**), similar to their isochromenylium-based approach under similar conditions (see Scheme 1).[69] They have shown that electron-rich and electron-deficient hydroxymethyl *o*-alkynyl arenes and pyridines (**2.4.42**) undergo clean iodocylization to afford

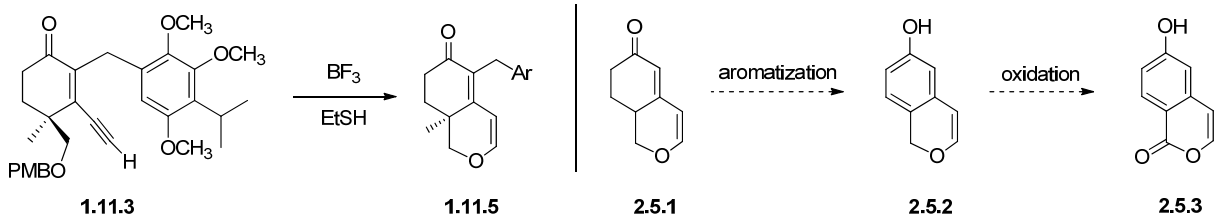
the corresponding 6-membered heterocyclic products (**2.4.43**) in most cases, with **2.4.44** as the major side-product.



Scheme 2.4.15

2.5 Impetus and Initial Investigations: 6-Hydroxyisochromenes and Isocoumarins

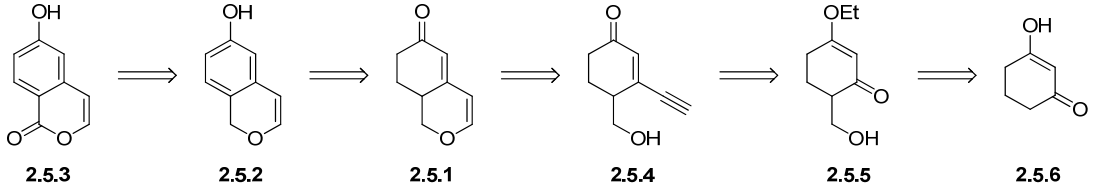
Introduced in Section 2.1, the rapid and efficient conversion of enynone **1.11.3** to pyran **1.11.5** inspired our investigations into the synthesis of isochromenes and isocoumarins (Scheme 2.1.1). We viewed this detour as an opportunity to develop a short synthetic approach toward the synthesis of these two important structural motifs. Isolation of the dihydropyran motif of **1.11.5** gives **2.5.1**, which could permit access to isochromene **2.5.2** and isocoumarin **2.5.3** (Scheme 2.5.1). Not only did we realize the novelty of synthesizing simple heterocycles, but we were also interested in expanding the scope to access highly-functionalized frameworks.



Scheme 2.5.1

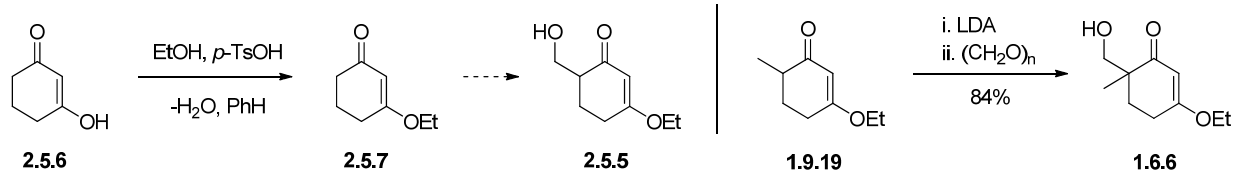
Our initial retrosynthetic analysis toward examining this method is shown in Scheme 2.5.2. First, 6-hydroxyisocoumarin **2.5.3** would result from benzylic oxidation of **2.5.2**. Isochromene **2.5.2** would result from the aromatization of pyran **2.5.1**, the product resulting from

a formal intramolecular hydroalkoxylation of enynone **2.5.4**. Enynone **2.5.4** could be generated from alcohol **2.5.5**, readily available in just two steps from 1,3-cyclohexanedione (**2.5.6**)



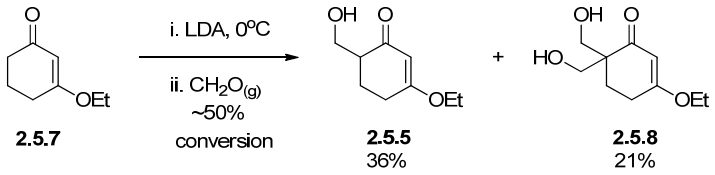
Scheme 2.7.2

The starting 3-alkoxy-cyclohex-2-en-1-one (**2.5.5**) was readily available via chemistry developed by Stork and Danheiser.[70] Acid-catalyzed enol ether formation of 1,3-cyclohexanedione (**2.5.6**) gives **2.5.7** in excellent yield (Scheme 2.5.3). Initially, the aldol reaction between **2.5.7** and formaldehyde to introduce the requisite α-hydroxymethyl group seemed trivial. In our synthesis of the A-ring motif in our icetexone synthesis (see Section 1.9), treating **1.9.19** with LDA at 0 °C followed by bubbling in a stream of gaseous formaldehyde into the reaction mixture afforded **1.6.6** in 84% yield.



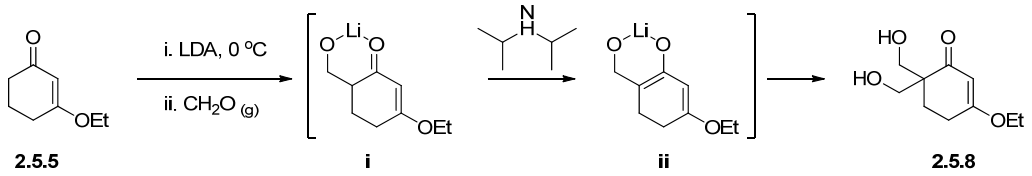
Scheme 2.5.3

We used a similar approach in our initial attempts toward the preparation of **2.5.5**. To generate monomeric formaldehyde gas, a portion of paraformaldehyde was heated to 140 °C and bubbled into a solution of the enolate of **2.5.7** at 0 °C (Scheme 2.5.4). This reaction, however, gave unexpected results, proceeding in low conversion and poor yield. Upon further analysis, desired alcohol **2.5.5** was generated in 36% yield brsm, with diol **2.5.8** produced in 21% yield.



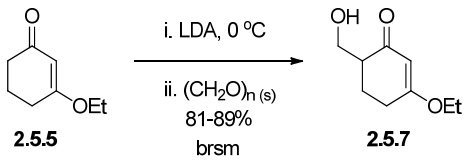
Scheme 2.5.4

The formation of this product was rather interesting, as only 1.05 equivalents of LDA were used to ensure complete enolate formation. We rationalize that formation of the initially-formed intermediate (**i**), due to the formation of 6-membered chelate **ii**, increases the acidity of **i**. This permits the enolization of **i** by diisopropylamine to give **ii**, which can react with another formaldehyde equivalent to generate diol **2.5.8**.



Scheme 2.7.5

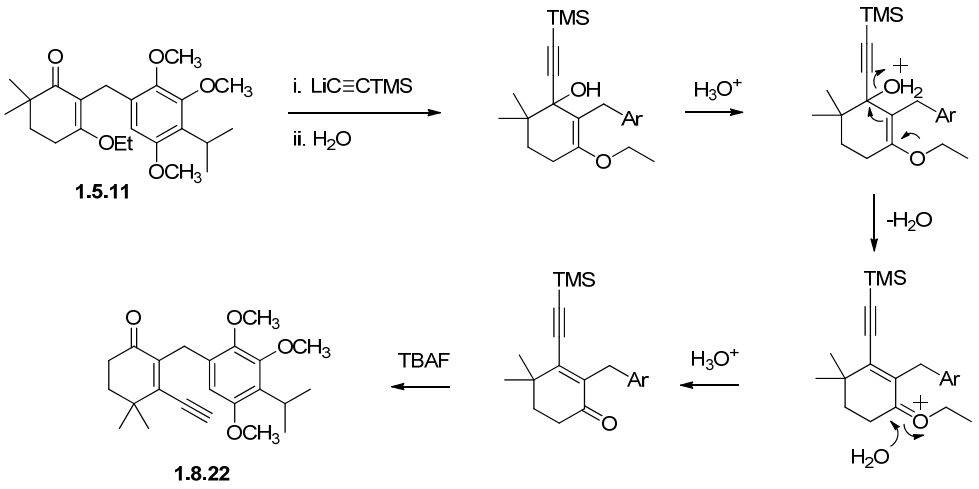
This initial obstacle was partially overcome when solid paraformaldehyde was added to the lithium enolate of **2.5.5** at 0 °C under the same conditions (Scheme 2.5.6). Interestingly, under these conditions, paraformaldehyde reacted like the monomeric form. Carefully monitoring the reaction by TLC until conversion remains constant allows for the elimination of **2.5.8** from the crude product. While this methods leads to only a 53-61% conversion, determined by ^{1}H NMR, the percent yield based on recovered starting material is high, typically 81-89% and the two components (**2.5.5** and **2.5.8**) are easily separable by silica gel chromatography.



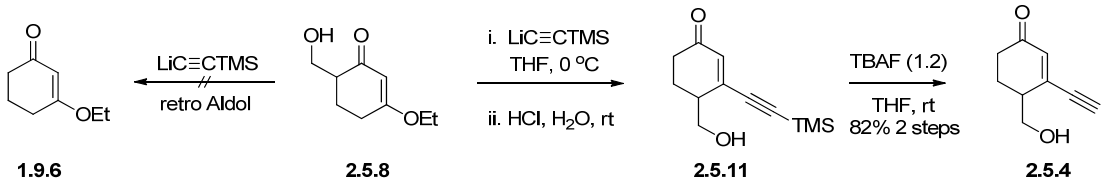
Scheme 2.5.6

The next step was the introduction of the enynone motif (see Scheme 2.5.7). This reaction is analogous to the generation of a more complex intermediate in our synthesis of the icetexones, as demonstrated in Section 1.8. First, 1,2-addition of lithium (trimethylsilyl)acetylide to **1.5.11** gives propargylic alcohol **2.5.9** upon aqueous workup. Elimination of the resulting alcohol was accomplished during workup to give intermediate **i**, which underwent dehydration to give **ii** and acetal hydrolysis and TMS removal to give **1.8.22**.

Though treating **2.5.8** with lithium acetylide would give **2.5.4** directly, the more convenient silylated analogue, lithium (trimethylsilyl)acetylide, was used as an acetylide equivalent (Scheme 2.5.8). Preparation of lithium (trimethylsilyl)acetylide was achieved by treating a THF solution containing a 3.0 equiv. TMS-acetylene at -78 °C with 2.5 equivalents of *n*-BuLi and allowing the solution to warm to 0 °C over a 30 minute period. Next, a THF solution of alcohol **2.5.8** was added dropwise via cannula and stirred at 0 °C until TLC indication reaction completion. We were surprised to find that alcohol **2.5.8** readily underwent 1,2- addition without undergoing retro aldol, which would give **1.9.6**. Using this procedure, enynone **2.5.4** could be obtained in 82% yield after **2.5.11** was deprotected with TBAF at room temperature.

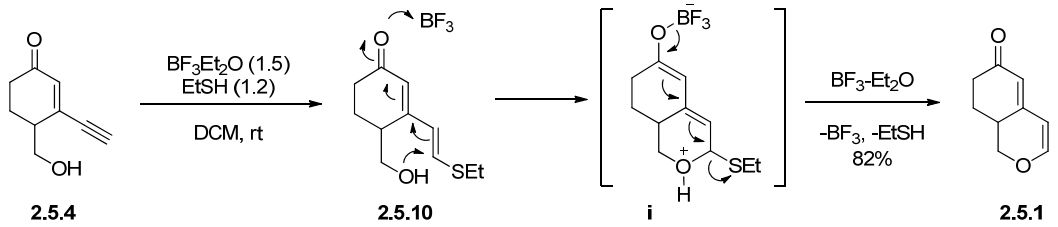


Scheme 2.5.7



Scheme 2.5.8

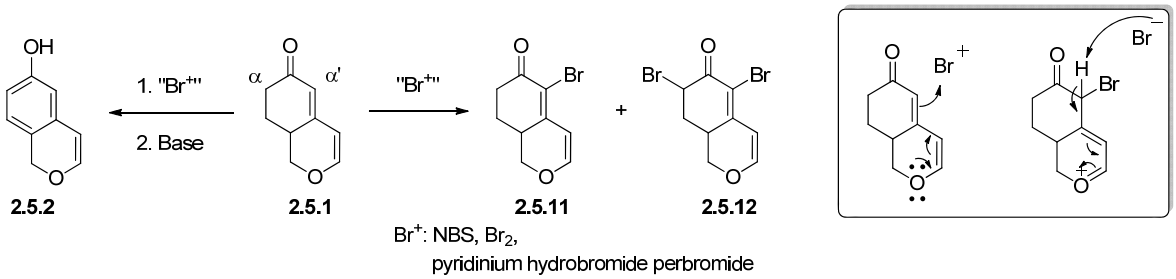
We were curious if the aforementioned cyclization conditions could be applied to the cyclization of enynone **2.5.4**. Treating **2.5.4** with 1.5 equivalent of BF_3-Et_2O in the presence of 1.2 equivalents of EtSH leads to the rapid formation of vinyl sulfide **2.5.10** by 1,6-addition the thiol, which can be observed by TLC and isolated as a dark oil (Scheme 2.5.9). Upon continued exposure of **2.5.10** to Lewis acid, though, dihydropyran **2.5.1** is produced in 82% yield. We posit that an intramolecular attack then proceeds via Lewis acid activation of the dienone motif to generate intermediate **i**, which permits the formation of the dihydropyran after loss of ethenethiol.



Scheme 2.5.9

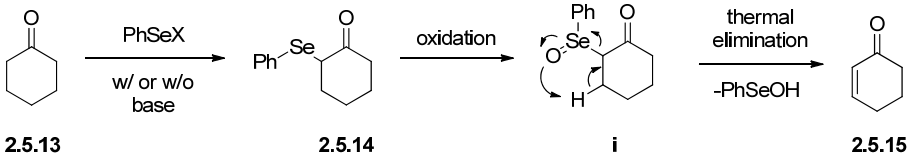
Aromatization of dihydropyran **2.5.1** would give 6-hydroxyisochromene (**2.5.2**). We were hopeful that this transformation could be achieved through a one-pot α-bromination/elimination sequence (Scheme 2.5.10). Unfortunately, treating **2.5.1** with NBS, Br_2, or pyridinium hydrobromide perbromide under a variety of different conditions led only to mixtures of vinyl bromide **2.5.11** and dibromide **2.5.12**. It was clear that vinyl bromide **2.5.11** was generated first, indicating that bromination at the α-position was only occurring after α'-substitution. This can be

rationalized through the mechanism shown, in which donation from the enol ether oxygen permits substitution at the α'-position.



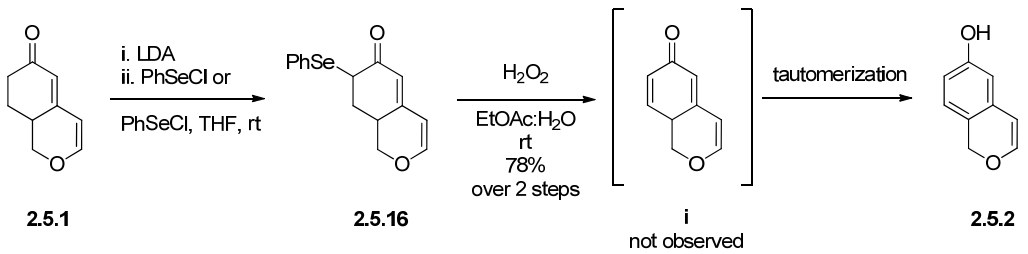
Scheme 2.5.10

Fortunately, aromatization via a two step selenylation-selenoxide elimination sequence permitted access to the isochromene framework. In his comprehensive review on the conversion of ketones to enone via selenoxide elimination, Reich compiled and reviewed many of the methods and parameters in which to achieve this transformation. [71] Shown in Scheme 2.5.11 in the case of cyclohexanone, alkylation of **2.5.13** with either PhSeCl or PhSeBr gives α-phenylselenide **2.5.14**. Oxidation of isolable **2.5.14** with H_2O_2, *m*-CPBA, $NaIO_4$, or other oxidants gives the corresponding selenoxide (**i**), which undergoes thermal syn-elimination, at or below room temperature, to give α,β-unsaturated ketone **2.5.15** and phenylselenic acid.



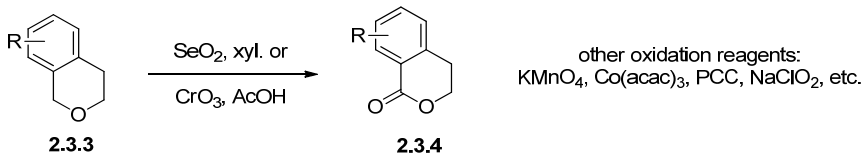
Scheme 2.5.11

Initial attempts at introduction of the α-phenylselenide group gave mixed results (Scheme 2.5.12). Though successfully demonstrated by Reich in numerous examples, simply stirring solution of **2.5.1** in EtOAc with PhSeCl resulted in decomposition. Treating **2.5.1** with LDA at -78 °C, followed by the addition of a solution of PhSeCl in THF, gave irreproducible results. Fortunately, we found that simply adding 1.5 equiv. of solid PhSeCl to a solution of **2.5.1** in THF



Scheme 2.5.12

at room temperature resulted in complete and clean conversion to the phenylselenide (**2.5.16**) within a few hours. Phenylselenide **2.5.16** was carried forward into the oxidation step, in which the crude product was dissolved in EtOAc and a threefold excess of 30% H_2O_2 in H_2O was added. Though THF is more common used as a solvent when aqueous hydrogen peroxide is employed as the oxidant, the reaction time was shortened greatly when EtOAc was used, and without a discernable decrease in yield. The reaction was stirred at room temperature until TLC indicated reaction completion, usually within 30 minutes. Reaction completion is also accompanied by a significant exotherm that can be felt from the outside of the reaction flask. Ethereal workup consisted of several washes with water and two washes with a saturated $NaHCO_3$ solution to ensure complete removal of excess oxidant and PhSeOH; if these washes are not carried out, significant decomposition is usually observed upon concentration of the crude sample. Overall, we were surprised by the selectivity and efficiency of this sequence, as the seemingly sensitive enol ether motif was not affected by the strong oxidation conditions. This sequence afforded isochromene **2.5.2** in a 78% yield without degradation of the olefin.



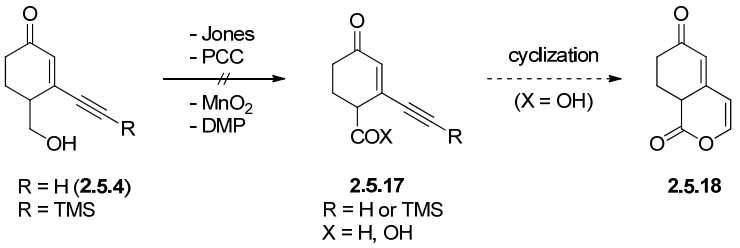
Scheme 2.5.13

Since the preparation of 6-hydroxyisochromene could be obtained via our original sequence, we next focused in the oxidation of **2.5.2** to its corresponding isocoumarin. A similar transformation was presented in Scheme 2.3.2 where Srivastava and Chaudhury presented their oxidation of isochromans **2.3.3** to their corresponding isochromanones **2.3.4** with either SeO_2 in refluxing xylene or CrO_3 in AcOH:H_2O. Additionally, numerous reports have been published reporting the same transformation, presented in Scheme 2.3.3. With this compendium of known conditions for the oxidation of isochromans, the oxidation of isochromene **2.5.2** was thought to be equally facile. Unfortunately, under the conditions described in the literature, none were optimal for the generation of **2.5.3**, though treating oxidation with 3 equiv. CrO_3 in wet acetic acid at low temperatures resulted in a 37% yield of 6-hydroxyisocoumarin. Serendipitously, as discussed in Section 2.10, we developed novel conditions for the preparation of 8-hydroxyisocoumarins in which we found that isochromenes undergo oxidation to their corresponding isocoumarins with DDQ in 1,4-dioxane at room temperature. Similarly, treating 6-hydroxyisochromene (**2.5.2**) with 2.0 equiv. DDQ in 1,4-dioxane in an open flask resulted in excellent yield of the corresponding isocoumarin (**2.5.3**). As discussed later, this transformation is assumed to proceed through an isochromenylium intermediate.

Scheme 2.5.14

We also envisioned an alternative approach to the 6-hydroxyisocoumarin skeleton, as outlined in Scheme 2.5.15. Oxidation of the hydroxymethyl group of **2.5.4** or the silylated analogue, to the corresponding carboxylic acid should give **2.5.17**, which would undergo

cyclization with BF_3-Et_2O and EtSH to give pyranone **2.5.18**. All attempts to oxidize **2.5.4** or the protected alkyne to either an aldehyde or carboxylic acid were met with difficulty, as the primary allylic alcohol was resistant to oxidation under normal conditions. While we were interested in the cyclization of other functional groups onto the alkyne motif of derivatives of **2.5.4**, attempts toward this approach were not studied further.

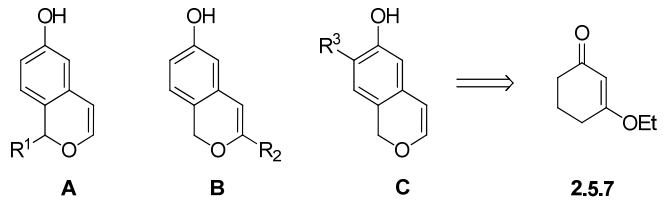


Scheme 2.5.15

To summarize, a novel method for the formation of a fused dihydropyran motif has been developed. A general strategy for the synthesis of 6-hydroxyisochromenes and 6-hydroxyisocoumarins has been realized.

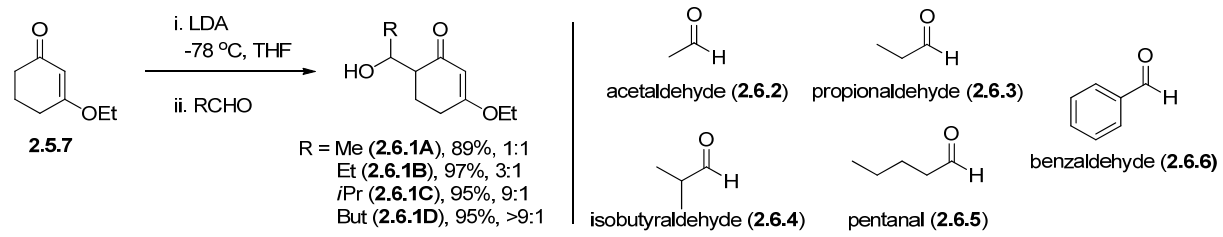
2.6 Elaboration of 6-Hydroxyisochromene and Isocoumarin Skeleton

With an initial strategy toward the 6-hydroxyisochromene and 6-hydroxyisocoumarin frameworks, we next sought to expand the scope of this methodology by modifying the general strategy. As cyclohexenones like **2.5.7** are amenable to a large number of synthetic transformations and maniupulations, we sought to investigate the synthesis of a wide range of isochromene derivatives using this methodology (Scheme 2.8.1). First, we sought to investigate the influence of carrying out the aldol reaction of **2.5.7** with more substituted aldehydes to give **A**. Secondly, we were curious to see whether or not substitution at the terminal position of the alkyne moiety would still allow cyclization to occur (*i.e.* **B**). Additionally, a late-stage alkylation would give 7-substituted isochromene **C**.



Scheme 2.6.1

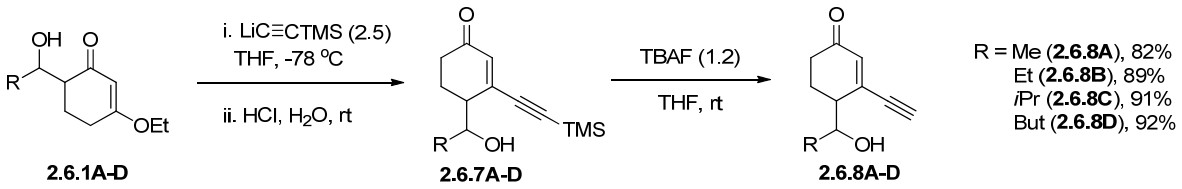
Our first attempted modification to the 6-hydroxyisochromene skeleton was to introduce additional functionality at the C1-position (**A**, Scheme 2.6.1). We knew that this would originate from conducting an aldol reaction between **2.5.7** and a substituted aldehyde. We were first interested in introducing various branched and linear alkyl chains at the C1-position; therefore, we chose acetaldehyde (**2.6.2**), propionaldehyde (**2.6.3**), isobutyraldehyde (**2.6.4**), pentanal



Scheme 2.6.2

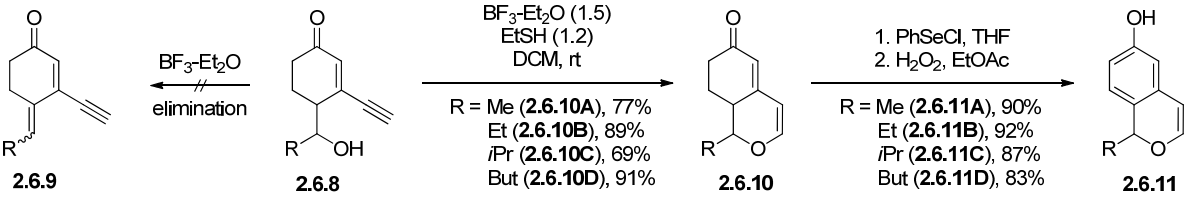
(**2.6.5**), and benzaldehyde (**2.6.6**) as the coupling partners. Initially, we attempted the aldol reaction between **2.5.7** and **2.6.2-2.6.6** using LDA at 0 °C, though no reaction was observed under those conditions. However, when enolate formation was carried at -78 °C in THF and a solution of the aldehyde in THF was added to the reaction mixture, the desired aldol adducts were formed in excellent yields and with the diastereomeric ratios shown in Scheme 2.6.2. This difference in reactivity can be rationalized by the formation of the aldol adduct, though a retro-aldol process occurred at elevated temperatures. Additionally, while all sets of diastereomers (**2.6.1A-D**) could all be separated by silica gel chromatography, they were carried forward as diastereomeric mixtures. It should be noted that when benzaldehyde was used as the aldehyde

partner in the reaction with **2.5.7**, some retro aldol was observed at -78 °C and the product could not be generated in an appreciable yield. Therefore, attempts to introduce an aromatic substituent at the C1-position of the 6-hydroxyisochromene skeleton were abandoned (**A**, Scheme 2.6.1).



Scheme 2.6.3

Conversion of α-hydroxyketones **2.6.1A-D** to their corresponding enynones could be accomplished via the same conditions developed previously (see Scheme 2.5.8). It was clear that retro aldol would be an obstacle under the strongly basic conditions. Indeed, a retro-aldol process was observed when 2.5 equivalents of lithium (trimethylsilyl)acetylide was added to the staring material at 0 °C. Fortunately, carrying out the 1,2-addition at -78 °C prevented these side reactions and cleanly gave TMS-enynones **2.6.7A-D**. Unmasking the terminal silyl group with TBAF gave enynones **2.6.8A-D** in good yields over two steps from **2.6.1A-D**. Interestingly, while the diastereomeric starting compounds were separable by chromatography, the resulting products were homogeneous by TLC.

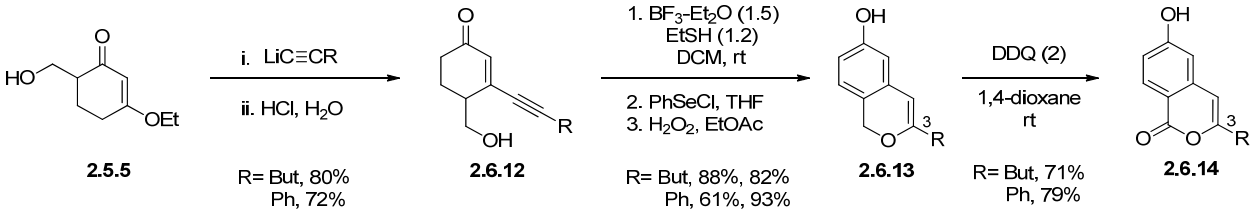


Scheme 2.6.4

Next, subjecting enynones **2.6.8A-D** to cyclization conditions was successful and afforded substituted dihydropyrans **2.6.10A-D** in good yields (Scheme 2.6.4). We were initially concerned that the secondary alcohol motif in the cyclization precursors would be prone to

elimination to give **2.6.9**, especially being adjacent to a vinylogous ketone. However, elimination was not observed under the reaction conditions: 1.5 equivalents BF_3-Et_2O and 1.2 equivalents EtSH in DCM at rt for 4-6 hours. Aromatization was achieved through a selenylation/oxidation strategy to generate C1-substituted isochromenes **2.6.11A-D** in excellent yield.

We were also interested in introducing of a substituent at the C3-position of the 6-hydroxyisochromene and isocoumarin skeletons (**B**, Scheme 2.6.1). This could be accomplished by 1,2-addition of an appropriate terminal acetylide to alcohol **2.5.5**, followed by intramolecular cyclization and aromatization (Scheme 2.6.5). We were interested in introducing alkyl and aryl substituents at these positions, as these are common motifs introduced using known methods (see

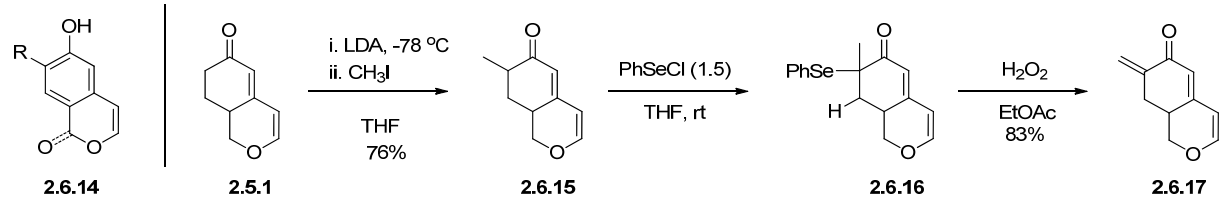


Scheme 2.6.5

Sections 2.3 and 2.4). Indeed, treating alcohol **2.5.5** with an excess of the lithium anion of 1-hexyne at 0 °C, followed by acid hydrolysis gave **2.6.12** (R = butyl) in excellent yield. Phenylacetylene, which would introduce an aromatic ring at the C3-position, proceeds similarly. Cyclization and aromatization of **2.6.12** have similar reactivity, though cyclization proceeds with lower yield than **2.5.4** and **2.6.8.** Oxidation to the C3-substituted isocoumarin is accomplished with DDQ in 1,4-dioxane at room temperature to give **2.6.14** in excellent yield. This extension of the current methodology compares well with known methods, which often employ functionalized alkynes to introduce alkyl and aryl functionality at the C3 position in both isochromenes and isocoumarins.

Our method for the preparation of pyran **2.5.1** also permits the introduction of a substituent adjacent to the ketone (Scheme 2.6.6). In theory, α-alkylation of **2.5.1** would permit

the synthesis of C7-substituted isochromenes and isocoumarins (**2.6.14**) via the selenylation-oxidation strategy demonstrated above. Indeed, α-methylation was achieved by treating **2.5.1** with LDA at -78 °C, then adding a solution of CH_3I in THF to give **2.6.15** in 76% yield. Introduction of a phenylselenide group to give **2.6.16** was straightforward and oxidation with hydrogen peroxide gave one major component by TLC. Unfortunately, this product was identified as exocyclic olefin **2.6.17**, which results from the elimination of the more accessible methyl hydrogens of **2.6.16**, rather than the one syn-oriented β-hydrogen to give isochromene**2.6.14**. It was interesting that **2.6.17** did not undergo rearrangement under workup conditions or purification, though the resulting product would be an aromatic system. Subsequent attempts to promote aromatization of **2.6.17**, such as stirring with Brønstead and Lewis acids, or treatment with $RhCl(PPh_3)_3$ (Wilkinson's catalyst) in refluxing xylene were unsuccessful. Thus, realizing the possible generality of generating an exocyclic olefin in the attempted aromatization of α-substituted pyrans such as **2.6.15**, we abandoned this extension of our current methodology.



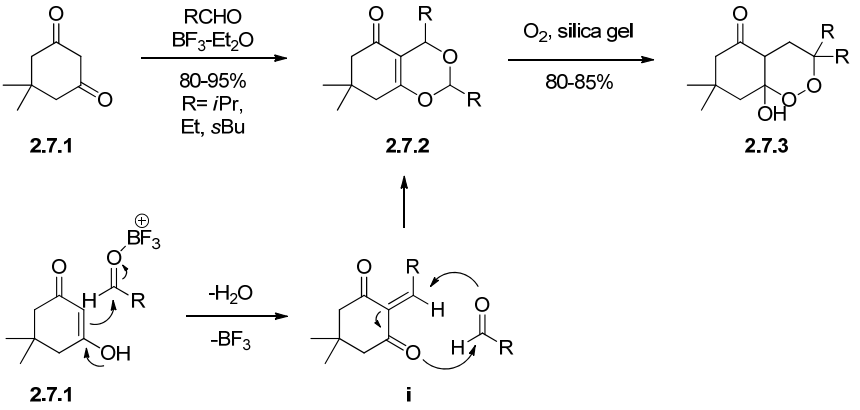
2.6.14 **2.5.1** **2.6.15** **2.6.16** **2.6.17**

Scheme 2.6.6

In conclusion, we have developed a short synthetic sequence to prepare 6-hydroxyisochromenes and 6-hydroxyisocoumarins via a novel intramolecular hydroalkoxylation reaction. Additionally, this method permits access to C1- and C3-substituted 6-hydroxyisochromenes via modifications to the synthetic route. A convenient oxidation protocol has been applied to the synthesis of 6-hydroxyisocoumarins from 6-hydroxyisochromenes.

2.7 Impetus and Initial Investigations: 8-Hydroxyisochromenes and Isocoumarins

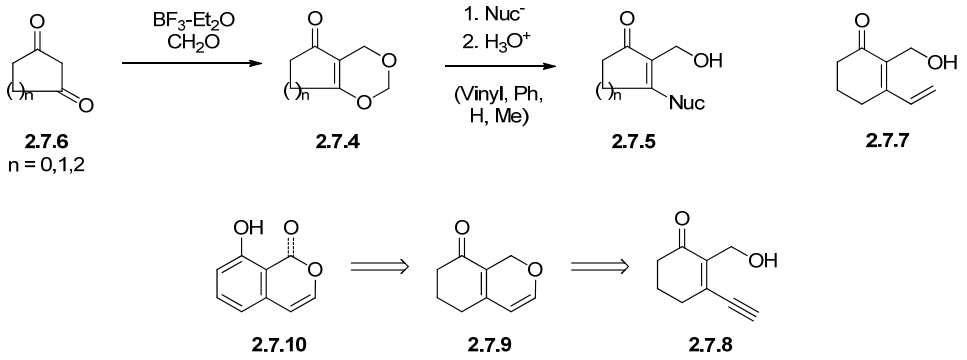
Early in our initial studies (Sections 2.5 and 2.6), we became aware of work by Crow and co-workers in 1982, and investigated more thoroughly by Smith and co-workers in 1988, which reported the synthesis and reactivity of 1,3-dioxin vinylogous ester.[72] We recognized that those studies would grant access to the 8-hydroxyisochromene and 8-hydroxyisocoumarin skeletons. In 1986, Crow and co-workers discovered that 1,3-diketone **2.7.1** undergoes a Prins reaction with aliphatic aldehydes in the presence of BF_3-Et_2O to give 1,3-dioxin vinylogous esters **2.7.2** in good yield (Scheme 2.7.1). They proposed a mechanism wherein activation of an aldehyde equivalent facilitates the initial Prins reaction with the tautomer of **2.7.1**, then dehydration gives intermediate enedione **i**. 1,3-Dioxin vinylogous ester **2.7.2** is formed when another aldehyde undergoes a second cyclization. Unfortunately, these compounds were unstable and rearranged to **2.7.3** upon exposure to air or silica gel.



Scheme 2.7.1

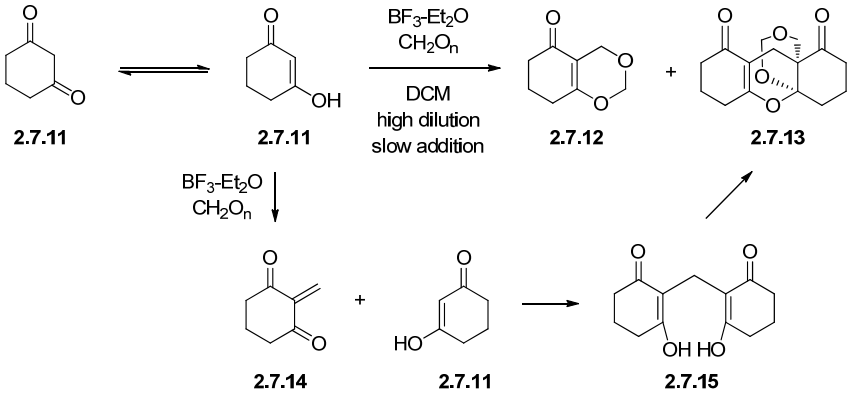
Shortly after Crow's publication, Smith and co-workers presented an efficient synthesis of related 1,3-dioxin vinylogous esters (**2.7.4**) from cyclic 1,3-diketones (**2.7.5**) and investigated the reactivity of those systems (Scheme 2.7.2). It was found that these compounds undergo smooth 1,2-addition with a variety of nucleophilic species to give α-hydroxymethyl β-substituted

cyclohexen-2-ones (**2.7.6**). We were interested in their addition of vinyllithium to **2.7.4**, which, after hydrolysis, gave dienone **2.7.7** in 76% yield. Dienone **2.7.7** contained interesting structural features, but we were interested in the analogous addition of an alkyne to **2.7.4** to generate enynone **2.7.8**, an isomer of cyclization precursor **2.5.4** (see Section 2.5). This strategy would permit access to pyran **2.7.9**, which allows the synthesis of 8-hydroxyisochromenes and 8-hydroxyisocoumarins (**2.7.10**).



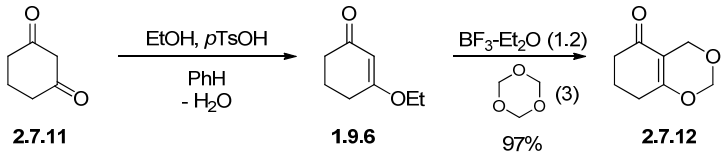
Scheme 2.7.2

Smith demonstrated that treating 1,3-cyclohexanedione (**2.7.11**) with 3 equivalents of BF_3-Et_2O and a slight excess of either paraformaldehyde or 1,3,5 trioxane leads to a 40% and 84% yield, respectively, of 1,3-dioxin vinylogous ester **2.7.12**. Propellane dimer **2.7.13** was identified as the major byproduct and was generated when insufficient quantities of an activated aldehyde equivalent is present, which leads to intermediate **2.7.14** reacting with starting **2.7.11**. Dimeric **2.7.15** is then formed, which gives rise to propellane **2.7.13** in the presence of Lewis acid and the aldehyde. To overcome this obstacle, high dilution and slow addition of the starting β-diketone were required.



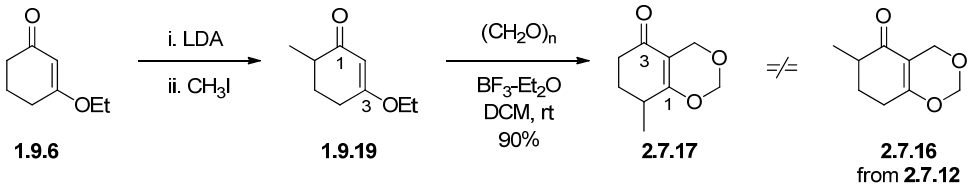
Scheme 2.7.3

In our hands, Smith's conditions did not result in reproducible reactivity and the reported conditions did not give good yields of desired **2.7.12**. We speculated that trapping the diketone as enol ether **1.9.6** might preclude byproduct formation, as shown in Scheme 2.7.4.[70] Indeed, when reacting **1.9.6** under the same conditions employed by Smith and co-workers, **2.7.12** was produced in 97% yield under standard concentrations with either trioxane or paraformaldehyde with no special method of addition.



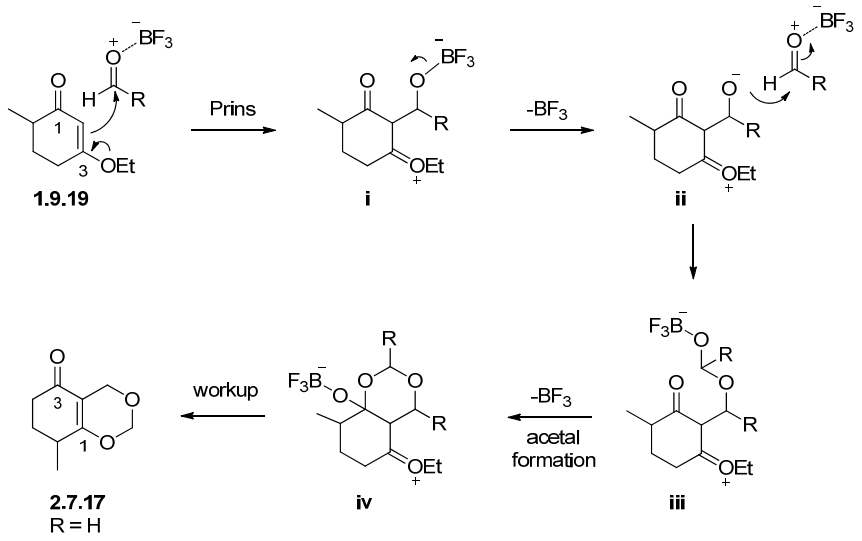
Scheme 2.7.4

A possible mechanism for this transformation was elucidated via observations made during a series of routine alkylations (Scheme 2.7.5). Since Smith reported that yields for the α-alkylation of **2.7.12** were low, we were interested in a two-step transformation of **1.9.19** to methylated dioxin **2.7.16**, which we presumed would proceed in high yield. The methylation of **1.9.6** was achieved by treating **1.9.6** with excess LDA at -78 °C and trapping the resulting enolate with CH_3I (*cf.* **1.9.19**). Next, when **1.9.19** was subjected to the above conditions for



Scheme 2.7.5

dioxin formation from, the H^1 and C^{13} spectra for the product contained all of the salient features of **2.7.16** but indicated that regioisomeric **2.7.17** had likely been generated. The only isomer that could result from the formation of 1,3-dioxin vinylogous ester **2.7.17** can be rationalized through the mechanism given in Scheme **2.7.6**. First, a Prin's reaction between **1.9.19** and the activated aldehyde yields **i**. After transfer of the Lewis acid, **ii** undergoes Lewis acid-mediated hemiacetal formation to give **iii**, which can undergo intramolecular acetal formation to give **iv**. 1,3-Dioxin vinylogous ester **2.7.17** is generated upon workup, which liberates the Lewis-acid and promotes elimination to form the central olefin and loss of the ethyl group.

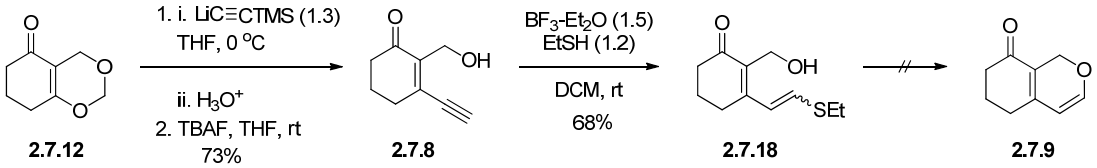


Scheme 2.7.6

This new procedure represents an improvement over Smith's protocol. While it is hampered by an additional reaction (**2.7.11** to **1.9.6**), formation of **1.9.6** is rapid and facile, and the yield for the formation of the 1,3-dioxin vinylogous ester is excellent without the need for

high dilution or a slow rate of addition. Additionally, the preparation of γ-substituted dioxin **2.7.17** represents a method for the selective introduction of functional groups at this position, possibly leading to a higher degree of complexity in a molecule.

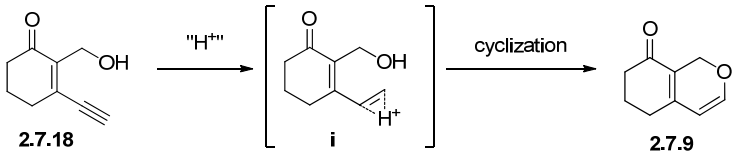
With an efficient route to **2.7.12**, we next sought to develop a route to install the pyran motif (*i.e.* **2.7.8** to **2.7.9**, Scheme 2.7.2). Similar to our route presented in Section 2.5, 1,2-addition of lithium (trimethylsilyl)acetylide to **2.7.12**, followed by acid hydrolysis and desilylation, led to the formation of enynone **2.7.8** in good overall yield.



Scheme 2.7.7

To our surprise, while **2.7.8** underwent the requisite 1,6-addition of EtSH in the presence of BF_3-Et_2O to yield intermediate **2.7.18**, further activation of the vinyl sulfide did not produce the expected pyran (**2.7.9**), even with increased reaction time, temperature, or amount of BF_3-Et_2O, all of which led to decomposition. In this reaction, vinyl sulfide **2.7.18** could be isolated in 68% yield after only 1 hour of reaction time.

Since conjugated enynone **2.7.8** did not undergo the expected cyclization above, we decided to focus on acid-catalyzed activation of the enynone motif (Scheme 2.7.8). We realized that this route would proceed through the protonation of the alkyne to give **i**, which would serve to both activate the terminal position and promote the necessary geometry for addition to occur and give **2.7.9**. Addition of common mineral acids, such as H_2SO_4 and HCl, resulted in either decomposition of the starting substrate or addition of HCl across the triple bond, though these results were not thoroughly investigated. We turned our attention to triflic acid (TfOH) and

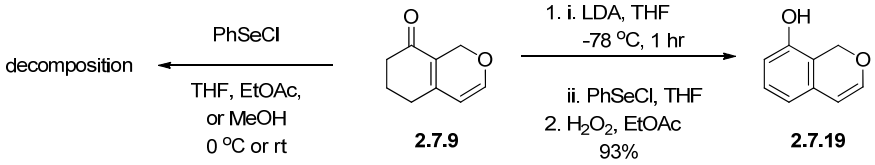


Acid (equiv.)	Solvent	Temp (°C)	Results
p-TsOH (1)	DCM	40	low conversion, low yield
BF_3 (1)	DCM	25	low conversion, low yield
TfOH (1)	DCM	25	slow, high conversion, low yield
TfOH (1)	DCM	40	high conversion, low yield
TfOH (1)	DCE	84	high conversion, low yield
TfOH (1)	DCM:ACN	25	slow, low conversion, low yield
MsOH (0.1)	DCM	40	slow, very low conversion, high yield
MsOH (1)	DCM	40	fast, high conversion, high yield
MsOH (2)	DCM	40	faster, high conversion, high yield

Scheme 2.7.8

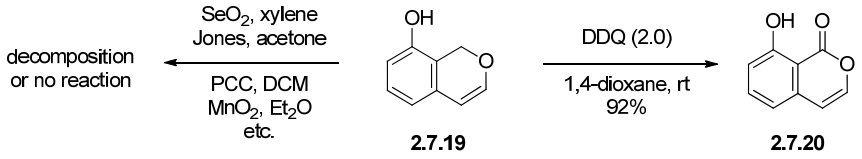
methanesulfonic acid (MsOH), which are known to promote addition of alcohols and amines across olefins. These results are briefly summarized in Scheme 2.7.8. To examine its inherent reactivity, **2.7.8** was treated with excess *p*-TsOH in DCM, though cyclization was only observed at reflux and after long reaction time, which was also observed when BF_3-Et_2O in DCM was used. It was observed that TfOH, a much stronger acid, gave seemingly excellent TLC yield of pyran **2.7.9** in DCM at room temperature in a few hours. Higher conversion in less time was accomplished by gently refluxing the reaction mixture. Unfortunately, significant deposition was observed on the inside of the reaction vessel, which accounted for a low 33% yield of pyran **2.7.9** under these conditions. Changing the solvent to 1,2-dichloroethane also did not result in an acceptable reaction profile. While published procedures do not indicate otherwise, TfOH has poor solubility in DCM and the acid remains at the bottom of the flask during the reaction and results in a black residue on the inside. The addition of a co-solvent increased the solubility of TfOH in the reaction medium and also led to a decrease in reactivity, which generated byproducts with extended reaction times.

Optimal results for conversion of **2.7.8** to **2.7.9** were obtained when MsOH was employed. While catalytic MsOH did produce the desired pyran, conversion was low, even with the addition of heat. Treating enynone **2.7.8** with 1 equivalents of MsOH in dilute DCM gave pyran **2.7.9** in 61% yield. However, when 2 equivalents of MsOH was used in refluxing DCM, pyran **2.7.9** was produced in 79% yield with no considerable decomposition. Workup consisted of cooling the reaction mixture to room temperature, diluting with Et_2O, and filtering the resulting mixture through a short pad of silica, followed by concentration and column chromatography. It should be noted, however, that compounds like **2.7.9** containing a cyclohexenone-fused pyran, were very unstable when concentrated; thus, purified compound was typically stored in the column solvent at -20 °C until further use, limited to two weeks.



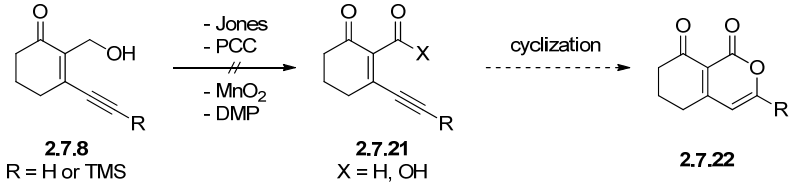
Scheme 2.7.10

As in the case of dihydropyran **2.5.1** (Section 2.5), an attempted α-bromination/ elimination sequence to achieve aromatization of **2.7.9** did not give the desired 8-hydroxyisochromene, but instead yielded a complex mixture of unidentified products. α-Selenylation, followed by oxidation, was the method employed to access model 8-hydroxyisochromene **2.7.19**. Unlike in the case of pyran **2.5.1** and its congeners, simply stirring **2.7.9** in an appropriate solvent in the presence of PhSeCl or PhSeBr did not generate the corresponding α-phenylselenide. However, by treating **2.7.9** with LDA at -78 °C for one hour and alkylating with PhSeCl, oxidation of the selenylated intermediate with H_2O_2 in EtOAc gave 8-hydroxyisochromene (**2.7.19**) in excellent yield.



Scheme 2.7.11

While some positive results were obtained upon the attempted oxidation of 6-hydroxyisochromene (**2.5.2**) to isocoumarin **2.5.3** with CrO_3 in wet AcOH, all attempts to oxidize **2.7.19** to **2.7.20** using literature procedures resulted in either decomposition or recovered starting material (Scheme 2.7.11). However, as demonstrated in Section 2.5, treating **2.7.19** with 2.0 equivalents of DDQ in dioxane at room temperature gave **2.7.20** in 92% yield. Isocoumarin **2.7.20** was also obtained in 61% yield when pyran **2.7.9** is heated in dioxane in the presence of 3 equivalents of DDQ, which is discussed in Section 2.9.



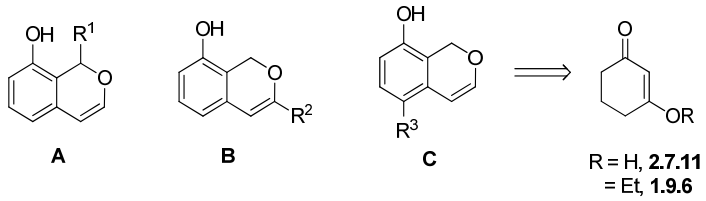
Scheme 2.7.12

Alternatively, oxidation of the primary allylic alcohol of **2.7.8** would generate a cyclization precursor (**2.7.21**) to give pyranone **2.7.22**. All attempts to achieve this oxidation, however, were unsuccessful and precluded the investigation of **2.7.21** to **2.7.22**.

2.8 Elaboration of 8-Hydroxyisochromene and Isocoumarin Skeleton

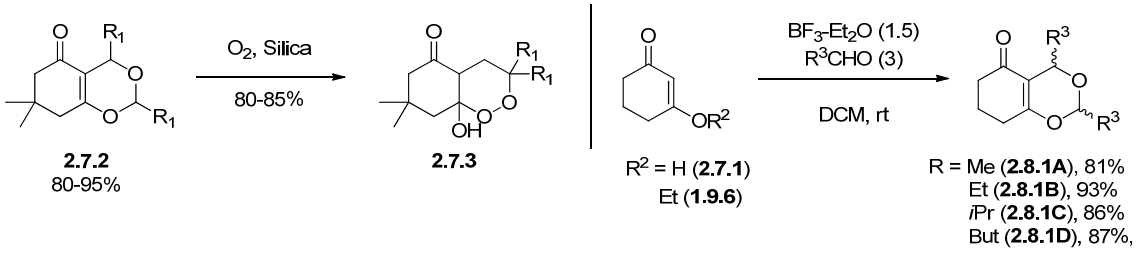
With an initial strategy toward the aforementioned skeleton, we again sought to decorate the core via changes in the synthetic sequence (Scheme 2.8.1). First, altering the aldehyde equivalent used in the formation of the 1,3-dioxin vinylogous ester would give **A**. Secondly, we were curious to see whether or not substitution at the terminal position of the alkyne moiety

would still permit cyclization to occur and give a C3-substituted isochromene (**B**). Additionally, alkylation of the core dioxin would give **C**, a C5-substituted isochromene. These could all be accessed through formation of the appropriate 1,3-dioxin vinylogous ester from either **2.7.11** or **1.9.6**.



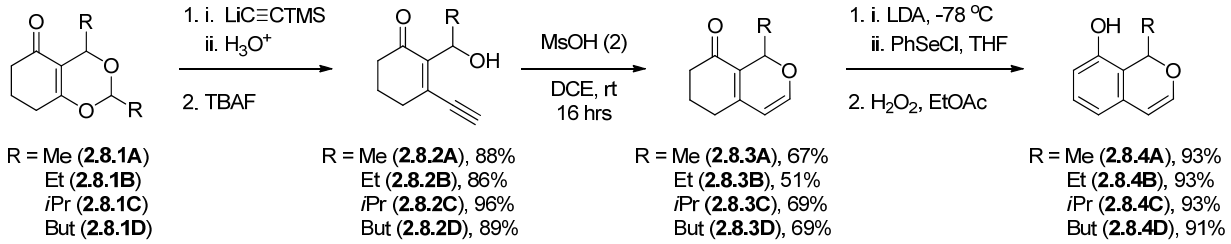
Scheme 2.8.1

Crow and co-workers found that Lewis-acid mediated condensation of dimedone (**2.7.1**) with aliphatic aldehydes gives **2.7.2**, which decomposed to **2.7.3** when exposed to air and silica gel (*cf.* Section 2.7). Given this undesirable reactivity, we were still curious whether or not simple 1,3-diketone derivative **2.8.1** could be prepared without decomposition (Scheme 2.8.2). Indeed, when **2.7.1** was treated with 3 equivalents of BF_3-Et_2O and an aliphatic aldehyde in DCM and allowed to stir for 6-10 hours, disubstituted 1,3-dioxin vinylogous esters **2.8.1A-D** were generated in excellent yield. Similar to the synthesis of C1-substituted 6-hydroxyisochromenes, we carried out the reaction of **2.7.1** with acetaldehyde, propionaldehyde, isobutyraldehyde, and pentanal. Interestingly, the reaction of 1,3-cyclohexanedione with **2.6.2-2.6.6** did not require special reaction conditions or high dilution, a sharp contrast to when



Scheme 2.8.2

formaldehyde was used (*cf.*Scheme 2.7.3). The diastereomeric mixtures of **2.8.1A-D** were purified using silica gel chromatography with no noticeable decomposition. Another contrast with the case where R^3= H, using the trapped enol ether (**1.9.6**) to achieve this variation led to decreased reactivity and pooryields of the desired 1,3-dioxin vinylogous esters was obtained. It should be noted that all attempts to generate aryl-substituted dioxins, using either the β-diketone **2.7.1** or **1.9.6** with benzaldehyde (**2.6.6**) were unsucessful.

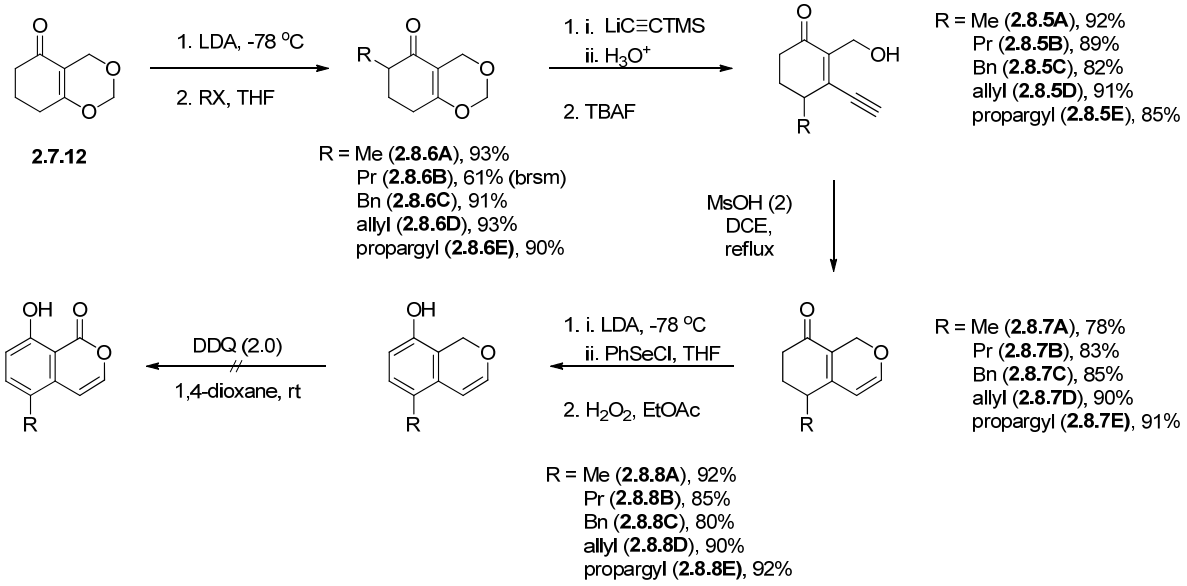


Scheme 2.8.3

Establishing the enynone motif was straightforward, as treating **2.8.1A-D** with 1.5 equivalents of lithium (trimethylsilyl)acetylide at 0 °C then hydrolysis and TBAF deprotection gave **2.8.2A-D** in excellent overall yield (Scheme 2.8.3). Cyclization to form pyrans **2.8.3A-D** was accomplished with 2 equivalents of MsOH in DCE at room temperature for 16 hours. When previously employed conditions were attempted (*i.e.* 1 equivalent MsOH in refluxing DCM), significant decomposition was observed and **2.8.3A-D** could not be generated in an appreciable yield. Aromatization was straightforward and gave C1-substituted isochromenes **2.8.4A-D** in excellent yield. This sequence is analogous to the cyclization of *o*-alkynyl aldehydes with subsequent trapping with a carbon-based nucleophile (*cf.* Section 2.4).

We also recognized that introducing an alkyl substituent at the α-position of 1,3-dioxin vinylogous ester **2.7.12** would generate **2.8.5** after acetylide addition, leading to the generation of C5-substituted isochromenes and isocoumarins (Scheme 2.8.4). In order to introduce versatile and commonly-found substituents, we decided to alkylate with methyl, *n*-propyl, benzyl, allyl,

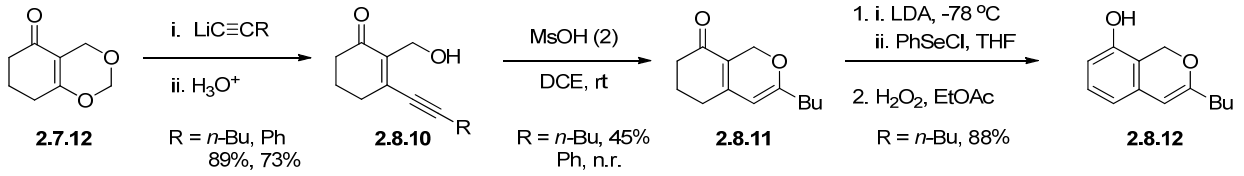
and propargyl groups at this position. Indeed, when **2.7.12** was treated with LDA at -78 °C and trapped with a variety of carbon-based electrophiles, the alkylation products were generated in good yields. Conducting these alkylations at 0 °C failed, presumably due to the instability of the newly-formed enolate. Also, introduction of a propyl group to **2.7.12** resulted in poor conversion overall and no reaction was observed at -78 °C. Fortunately, **2.8.6B** could be obtained in 61% yield after a low 73% conversion. This low conversion is likely due to the enolate acting as a base toward iodopropane, which would quench the enolate and generate propene. Next, the same



Scheme 2.8.4

three-step sequence was employed to access C5-substituted isochromenes and isocoumarins. Acetylide addition and desilylation afforded enynones **2.8.5A-E** in excellent yield. Optimal conditions for pyran formation were when a refluxing solution of **2.8.5A-E** in DCE was treated with 2 equivalents of MsOH and heated for an additional 15-min. period. Lower conversion and yield were observed when refluxing DCM was employed, while the absence of additional substitution permitted pyran formation in DCM. Again, these products were not stable upon concentration and should be purified immediately and stored at -20 °C until further use.

Aromatization was accomplished via a phenylselenylation-oxidation pathway to give C5-substituted isochromenes **2.8.6A-E** in good overall yield. Oxidation of the resulting isochromenes to their C5-isocoumarins was unsuccessful with excess DDQ in 1,4-dioxane at room temperature. The marked difference in the reactivity between these C5-substituted isochromenes and **2.7.19** is likely due to the reactivity of DDQ toward those functional groups, which will be explained further in Section 2.9.

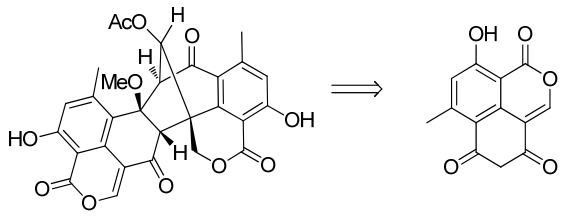


Scheme 2.8.5

The preparation of C3-substituted 8-hydroxyisochromenes required the modification of the acetylide anion used in the second key step in this sequence (*cf.* Scheme 2.8.5). To explore the introduction of both alkyl and aryl substituents at this position, 1-hexyne and phenylacetylene were each treated with *n*-BuLi at -78 °C then added to 1,3-dioxin vinylogous ester **2.7.12**. Acid hydrolysis of the 1,2-adduct afforded substituted enynone **2.8.10** in good yield. However, we found that the functionalized alkynes were not as reactive as the terminal alkyne analogue (**2.7.18**)**.** The aryl enynone of **2.8.10** was unaffected when treated with either TfOH and MsOH under a variety of reaction conditions, giving only unreacted enynone. The alkyl-substituted enynone of **2.8.10** (R= *n*-butyl) gave a 45% yield (bsrm) of desired pyran **2.8.11** after a 55% conversion. Nonetheless, **2.8.11** was converted to C3-substituted isochromene **2.8.12** under the aforementioned aromatization conditions. Isochromene **2.8.12** was unable to be oxidized to its corresponding isocoumarin with DDQ, again likely due to competing reactivity.

2.9 A Novel Preparation of 8-Hydroxyisocoumarins

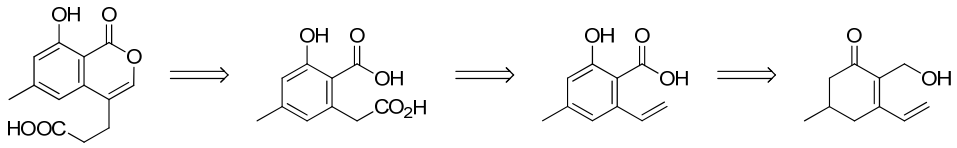
During our studies toward the total synthesis of the isocoumarin-based natural product duclauxin (**2.2.17**), we recognized that the isocoumarin-based tricycle (**2.9.1**) would be a logical



2.2.17 **2.9.1**

Scheme 2.9.1

precursor (Scheme 2.9.1). However, the synthesis of **2.9.1** proved to be rather challenging, leading to numerous routes directed toward its preparation. One such route is presented in Scheme 2.9.2, wherein the target tricycle could be accessed via the Friedel–Crafts acylation of **2.9.2**. Isocoumarin **2.9.2** would arise from condensation of an appropriate side chain with homophthalic acid **2.9.3**, generated by oxidation of **2.9.4**, an aromatic derivative of **2.9.5**.

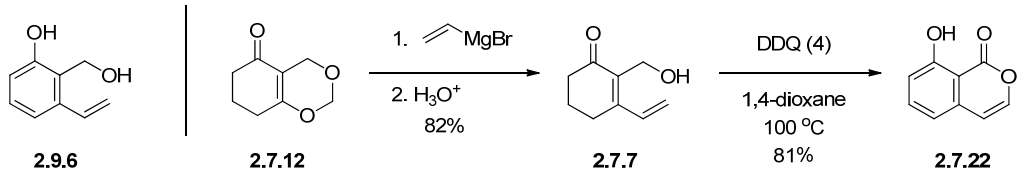


2.9.2 **2.9.3** **2.9.4** **2.9.5**

Scheme 2.9.2

As a model system toward the retrosynthesis shown in Scheme 2.9.2, dienone **2.7.7** was prepared from 1,3-dioxin vinylogous ester **2.7.12** (*cf.* Scheme 2.7.2). While many conditions have been reported for the aromatization of cyclohexenones, DDQ was an attractive oxidant, since aromatization could be performed in a single operation and in high yield. DDQ has been used in the synthesis of chromenes from chromans, quinolines from saturated precursors, aromatic compounds from substituted cyclohexa-1,4-dienes, as well as in the oxidation of benzylic positions to carbonyl groups.[73] Surprisingly, our initial attempt toward oxidation of

dienone **2.7.7** with an excess of DDQ in hot 1,4-dioxane did not generate **2.9.6**, but instead gave isocoumarin **2.7.22** in good yield. Attempts to modify these conditions by decreasing the equivalents of oxidant resulted in the formation of product, though mostly recovered starting material, demonstrating that intermediate species were being rapidly converted to 8-hydroxyisocoumarin (**2.7.22**). Additionally, no reaction was observed when the reaction was carried out at room temperature. These results prompted us to examine the mechanism of this transformation and its application to more complex systems.



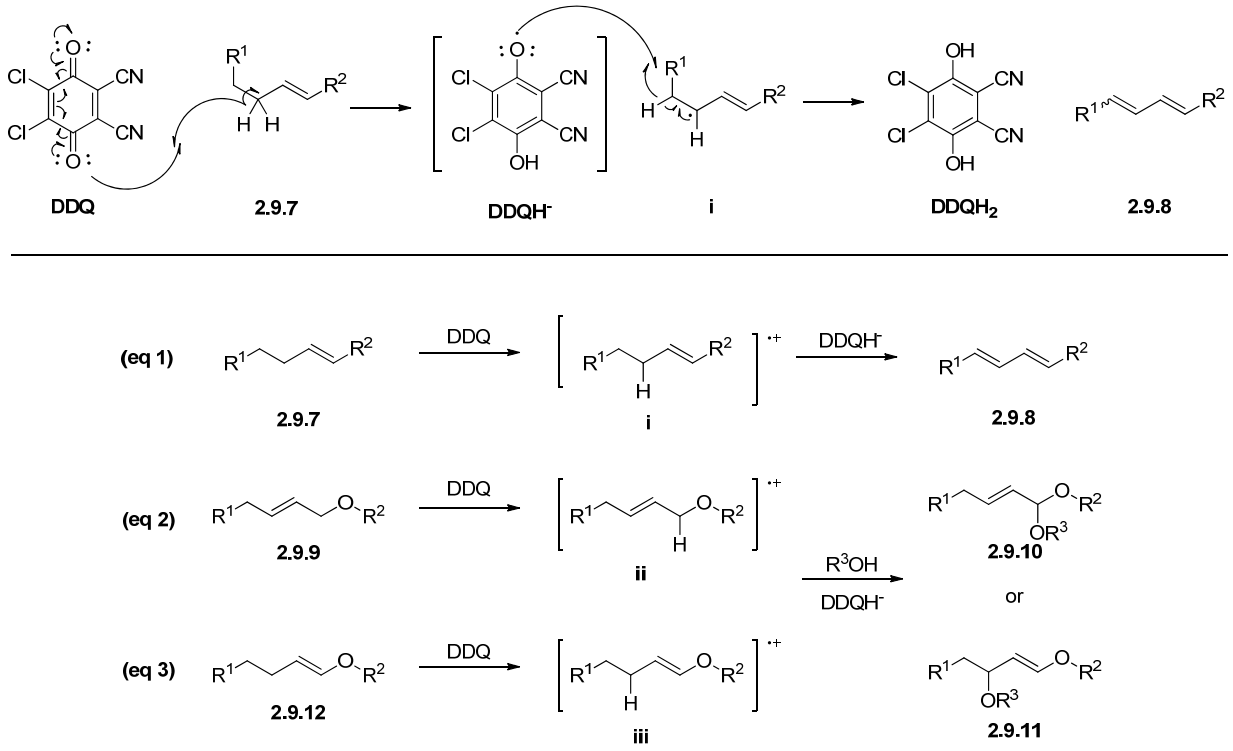
2.9.6 **2.7.12** **2.7.7** **2.7.22**

Scheme 2.9.3

We recognized that the conversion of **2.7.7** to **2.7.22** was the result of multiple oxidation/dehydrogenation steps and the introduction of an oxygen atom. Since no intermediates were observed, a possible mechanism in which these transformations occurred could not be proven. Given the known reactivity of DDQ and through synthetic studies, though, we have derived possible mechanisms for the above transformation, outlined in this section.

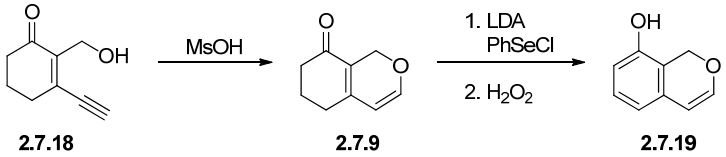
As shown in Scheme 2.9.4, DDQ has been shown to react with benzylic, allylic, and heteroatom-stabilized methylenes and methines through a radical-based mechanism.[73] For example, the allylic position of **2.9.7** undergoes a hydrogen atom transfer to give a phenoxy radical anion (**DDQH**$^-$) and radical cation **i**. Subsequent transfer of another hydrogen atom generates dehydrogenated product **2.9.8** and **DDQH**$_2$. Other systems demonstrate similar reactivity (Scheme 2.9.4). Allylic ether **2.9.9** undergoes hydrogen abstraction to give **ii**, which would generate either **2.9.10** via direct addition of either an alcohol or H_2O or **2.9.11** via olefin

migration and subsequent trapping. Enol ether **2.9.12** would also have similar reactivity, producing **2.9.10** or **2.9.11** and **$DDQH_2$**.



Scheme 2.9.4

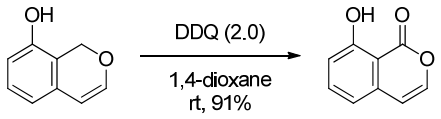
Since **2.7.19** was accessed through the multistep sequence shown in Scheme 2.9.5, we decided to examine those compounds as possible intermediates toward **2.7.22** (*cf.* Section 2.7).



Scheme 2.9.5

First, we were interested in the conversion of isochromene **2.7.19** to the corresponding isocoumarin (Scheme 2.9.6). In sharp contrast to the harsh reaction conditions required for the multistep transformation of **2.7.7** to its isocoumarin analogue, the oxidation of 8-hydroxyisochromene was carried out at room temperature in 15 minutes with 2.0 equivalents of

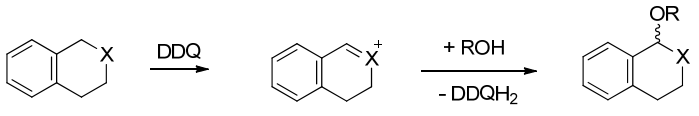
DDQ. We speculate that additional oxygen is introduced by H_2O present in the *p*-dioxane, rather than O_2 in the atmosphere. To exclude this possibility, oxidation of isochromene **2.7.19** was carried out in degassed *p*-dioxane and still gave isocoumarin **2.7.22**. Furthermore, the reaction is performed exposed to the air, which permits the introduction of moisture.



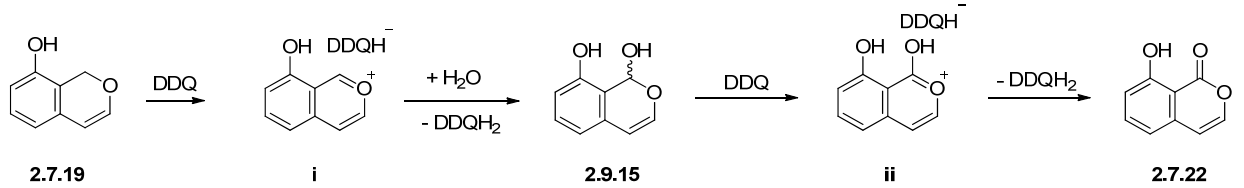
2.7.19 **2.7.22**

Scheme 2.9.6

Xu and others have reported the DDQ-induced oxidative coupling of isochromans and isothiochromans (**2.9.13**) with aliphatic alcohols and in the presence of DDQ.[74] Through a charge-transfer complex, it was demonstrated that isochromenylium-like intermediate **i** undergoes addition of an aliphatic alcohol to the C1-position to give **2.9.14** (Scheme 2.9.7). We propose that oxidation of isochromene **2.7.19** could take place through by the addition of H_2O to isochromenylium intermediate **i** to generate cyclic hemiacetal **2.9.15** (Scheme 2.9.8). With a second equivalent of DDQ, oxidation of the acetal via intermediate species **ii** gives **2.7.22**. We have also shown that this oxidation is general for the oxidation of 6-hydroxyisochromenes (*cf.* Sections 2.5 and 2.6).

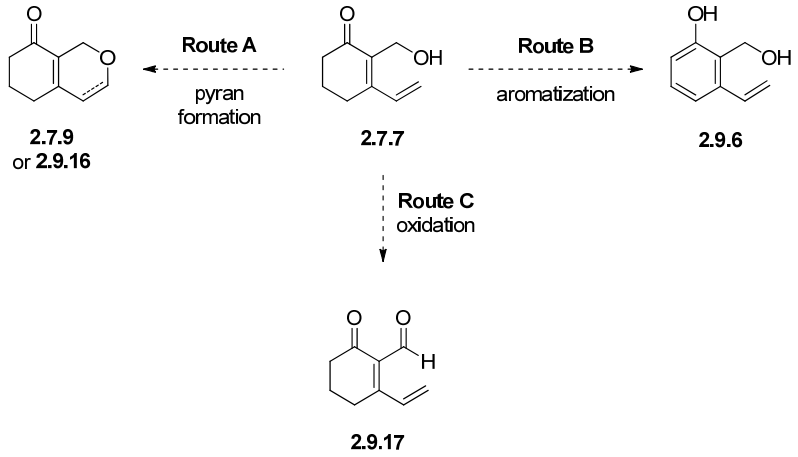


Scheme 2.9.7



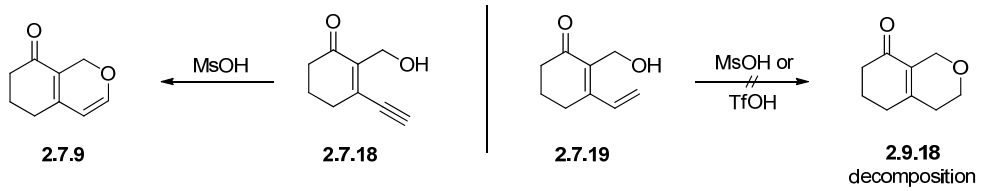
Scheme 2.9.8

Next, we were uncertain which transformation occurs first in this one-pot sequence: (1) cyclization to form the dihydropyran ring (Route A), (2) dehydrogenation and aromatization of the cyclohexenone motif (Route B), or (3) oxidation of the allylic primary alcohol to its corresponding aldehyde (Route C, Scheme 2.9.9). Our analysis of the relative bond dissociation energies for the starting material and proposed intermediates has guided the rationale behind our proposed mechanisms.[75]



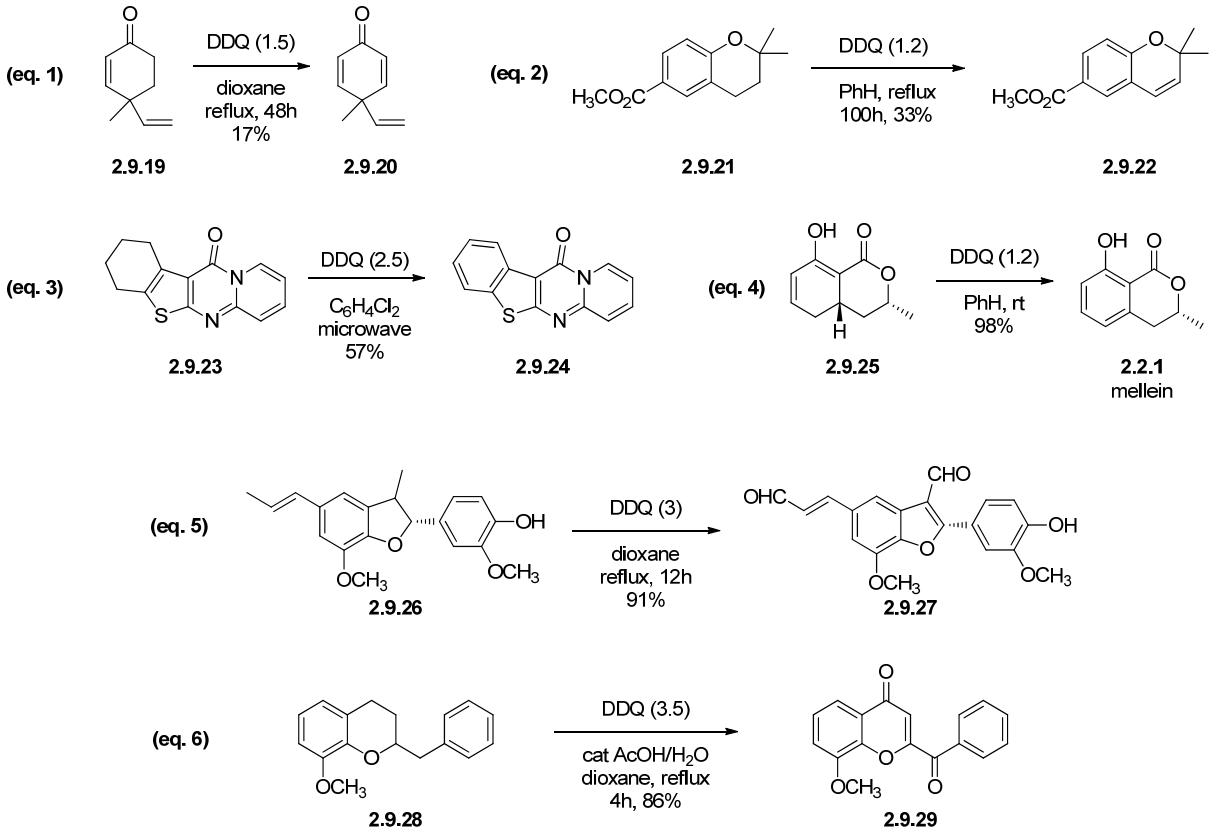
Scheme 2.9.9

First, DDQ has been shown to abstract a hydrogen from both allylic and benzylic methylenes, as well as from the *ispo* position of alcohols and ethers (Scheme 2.9.4). Since the calculated bond dissociation energy for the O–H bond of primary alcohols is approximately 110 kcal/mol, which is significantly higher than the other bond energies present in either dienone **2.7.7** or *o*-vinyl benzyl alcohol **2.9.6**, pyran formation via a radical-based hydrogen abstraction



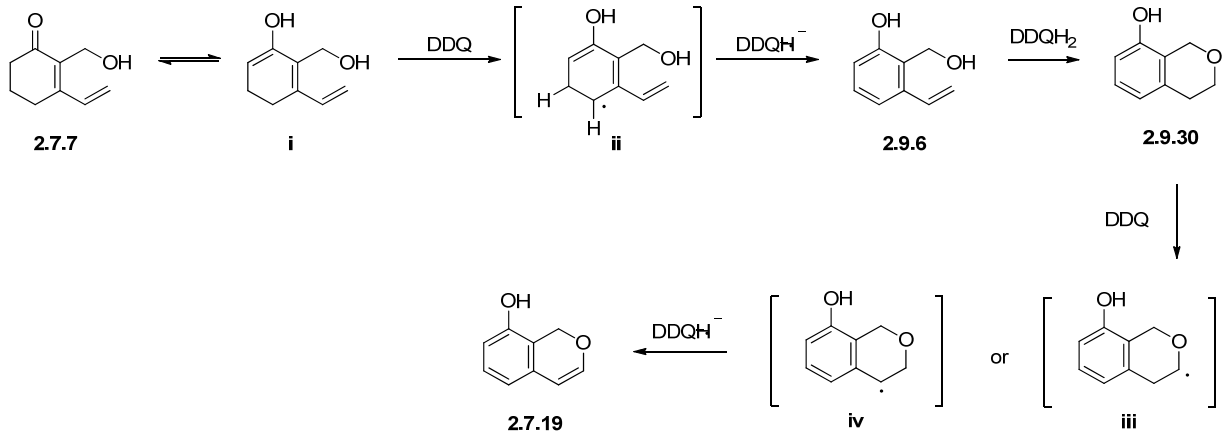
Scheme 2.9.10

mechanism does not predominate by either route A or B. However, acid-promoted cyclization of either **2.7.7** or **2.9.6** would give **2.9.10** or **2.9.11**, respectively. However, while enynone analogue **2.7.18** undergoes smooth cyclization with MsOH in refluxing DCM, acid-catalyzed cyclization of **2.7.7** under a variety of conditions resulted only in decomposition of the starting dienone (Scheme 2.9.10). Thus, we have discounted both a radical-based pathway for heterocycle formation from an alcohol substrate and an acid-catalyzed cyclization route for the conversion of **2.7.7** to **2.9.16** via route A. Alternatively, both routes B and C represent potential pathways.



Scheme 2.9.11

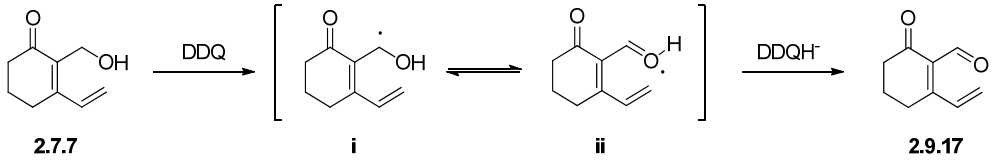
DDQ has been used for the oxidation, olefination, and aromatization of unsaturated cyclohexanes, including steroids and other complex frameworks, as demonstrated by the examples shown in Scheme 2.9.11.[76] In all of the cases shown, dehydrogenation is initiated by the abstraction of a hydrogen atom to generate a stabilized radical cation. In the case of **2.7.7**, aromatization could proceed through enol **i** which, after initial abstraction of a hydrogen atom to generate **ii**, undergoes dehydrogenation to give **2.9.6** (Scheme 2.9.12). Next, acid-catalyzed cycloisomerization of *o*-vinyl benzyl alcohol **2.9.6** can be envisioned as taking place in the presence of acidic $DDQH_2$ which, at 100 °C in 1,4-dioxane, could facilitate cycloisomerization of **2.9.6** to isochroman **2.9.30** (Scheme 2.9.10). Next, dehydrogenation to form the C3-C4 olefin is initiated by abstraction of either a heteroatom-stabilized hydrogen atom to give **iii** or a benzylic hydrogen atom to give **iv**. Since the calculated bond dissociation energy for an aliphatic alcohol is 96.1 kcal/mol and that of a benzylic hydrogen is approximately 90 kcal/mol, **2.7.19** likely results from intermediate **iv**. Next, oxidation to isocoumarin **2.7.22** is accomplished with 2 equivalent of DDQ in the presence of H_2O (Scheme 2.9.8).



Scheme 2.9.12

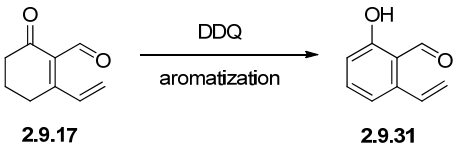
Route C in Scheme 2.9.9 presents another possible first step in the formation of 8-hydroxyisocoumarin from dienone **2.7.7**. The calculated bond dissociation energy for the

methylene protons of an allylic alcohol is approximately 80.1 kcal/mol, lower than that of the other allylic methylene (89 kcal/mol). This indicates that oxidation of the primary allylic alcohol in **2.7.7** likely occurs first, through initial hydrogen atom abstraction to give **i**, which is heteroatom-stabilized as intermediate **ii**. Aldehyde **2.9.17** is delivered through another hydrogen atom abstraction from **ii**.



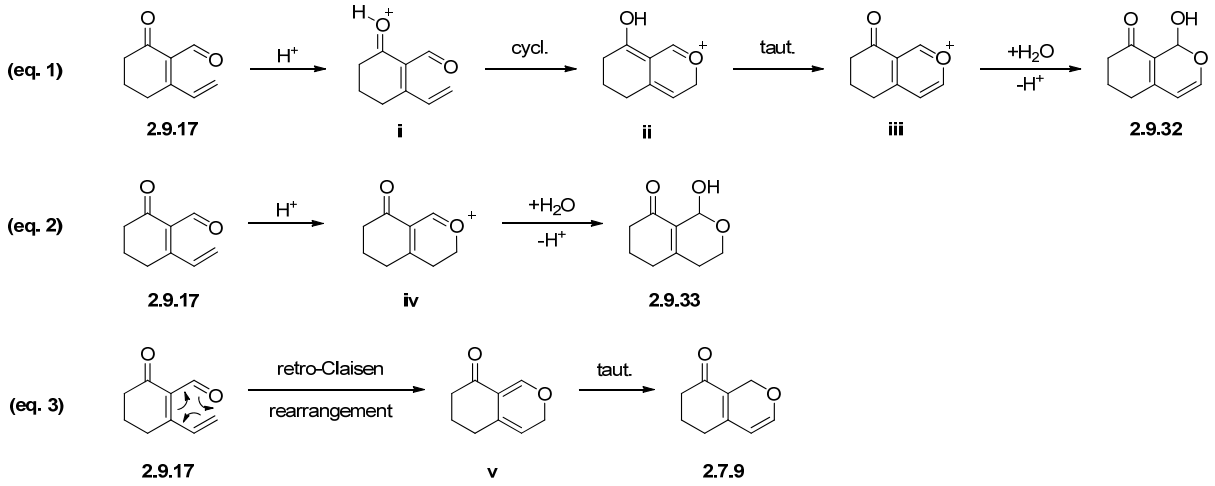
Scheme 2.9.13

One can envision two possible routes for formation of the heterocyclic ring from **2.9.17**. Aromatization of **2.9.17** gives **2.9.31** through a mechanism discussed previously (Scheme 2.9.14). Either **2.9.17** or **2.9.31** could undergo cyclization to form the heterocyclic motif by eq. 1-5 in Schemes 2.9.15 and 2.9.16. All acid-catalyzed reactions are likely to take place in the presence of $DDQH_2$, which is generated through the oxidation of **2.7.7** to aldehyde **2.9.17**.



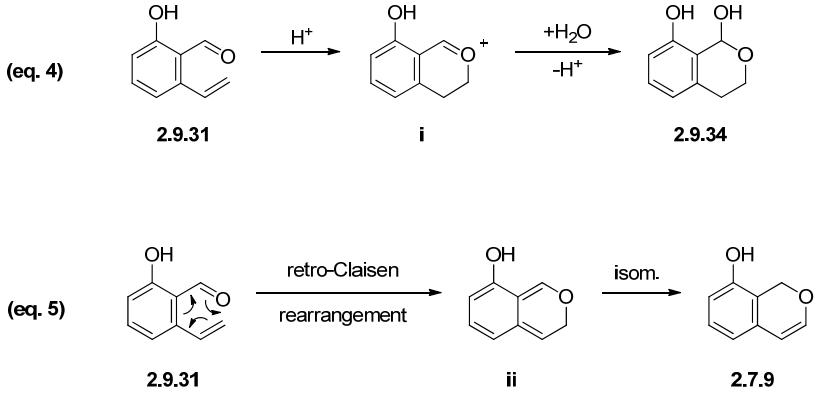
Scheme 2.9.14

Isomerization of aldehyde **2.9.17** to a heterocyclic product can be rationalized by eq. 1-3 (Scheme 2.9.15). First, an acid-mediated 1,6-addition of the aldehyde can take place through activation of the dienone to give **i** (eq. 1). Intramolecular cyclization generates an intermediate oxocarbenium ion (**ii**), which can undergo tautomerization to give **iii**. Addition of H_2O to the resulting species gives **2.9.32**, which gives 8-hydroxyisocoumarin after oxidation and aromatization. Eq. 2 represents another acid-mediated cyclization, in which activation of the



Scheme 2.9.15

olefin directly promotes the formation of **iv**, which can also undergo an addition of H_2O to give cyclic acetal **2.9.33**. We have also suggested that a retro-Claisen-like reaction of **2.9.17** would forge the heterocyclic ring structure (eq. 3). DDQ oxidation of **2.9.17** is carried out at 100 °C; therefore, under thermal conditions, rearrangement to form intermediate **v** could be envisioned. This would generate pyran **2.7.9** after tautomerization, which can undergo aromatization and oxidation to yield 8-hydroxyisocoumarin.



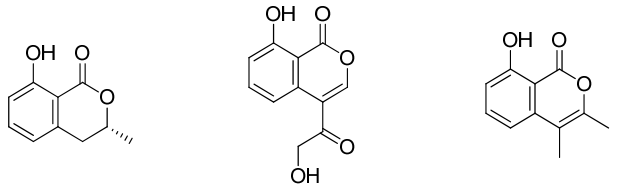
Scheme 2.9.16

A second series of mechanisms for heterocycle formation proceeds through aromatic aldehyde **2.9.31** (Scheme 2.9.16). Similar to the acid-catalyzed isomerization of **2.9.17** (eq. 1), **2.9.31** could undergo a similar isomerization to afford oxocarbenium ion **i** (eq. 4). Acetal **2.9.34**

is produced by addition of H_2O to **i**, followed by subsequent loss of a proton and oxidation takes place with 1 equivalent of DDQ. A retro-Claisen-like pathway can also be envisioned under thermal conditions, as outlined in eq. 5. Intermediate **ii** is formed upon rearrangement, which undergoes isomerization to yield 8-hydrxyisochromene (**2.7.9**). This pathway is a less likely route for heterocycle formation due to the loss of aromaticity in the transition state.

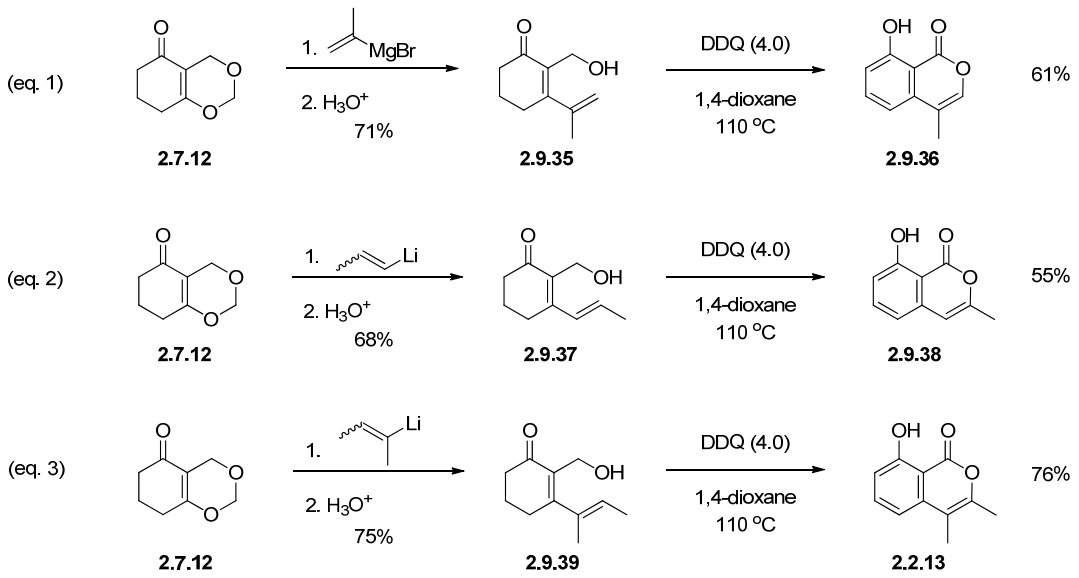
In light of the above results, several possible mechanisms for the formation of 8-hydroxyisocoumarin (**2.7.22**) from dienone **2.7.7** have been presented based on relative bond dissociation energies and possible reaction pathways. Further synthetic studies are required to evaluate these reaction pathways.

With a general procedure for the one-pot oxidation-cyclization-dehydrogenation of dienone **2.7.7** to 8-hydroxyisocoumarin (**2.7.22**), we wanted to functionalize the 8-hydroxyisocoumarin skeleton. Many isocoumarin-based natural products contain functional groups at the C3 and C4 positions, a few of which are depicted in Figure 2.9.1 (*cf.* Section 2.2). These groups could be introduced by introduction of a substituted vinyl group to the dienone precursor, as illustrated in Scheme 2.9.16. We have only chosen to introduce methyl groups at these positions; additional studies are required to explore the reactivity of these allylic methyl groups and other functional groups during isocoumarin formation. First, 1,2-addition of a 2-propenyl Grignard reagent to 1,3-dioxin vinylogous ester **2.7.12** gave dienone **2.9.35**, which



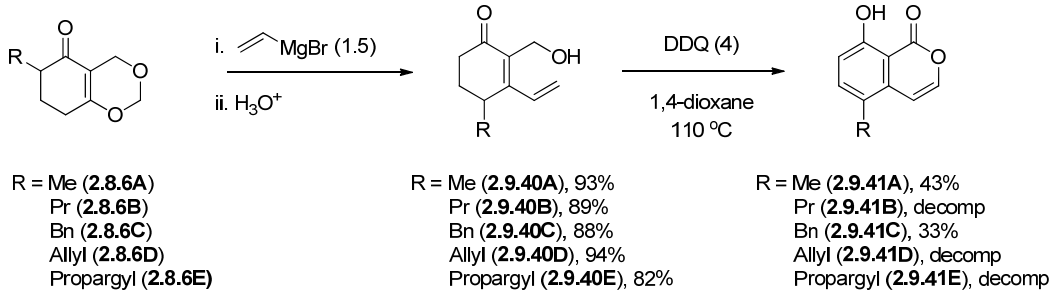
2.2.1 mellein　　**2.2.12** oosponol　　**2.2.13** oospolactone

Figure 2.9.1



Scheme 2.9.16

gives isocoumarin **2.9.36** after treatment with DDQ. Oosponol (**2.2.12**) could be accessed via this isocoumarin through the functionalization of the C4 methyl group. A C3 methyl group was introduced when **2.7.12** was treated with 1-propen-1yllithium and the product (**2.9.37**) was oxidized with DDQ to produce **2.9.38** in 55% yield. This skeleton is a possible precursor to mellein (**2.2.1**), which should be accessible by catalytic dehydrogenation of **2.9.38**. It is important to note that 1-propen-1yllithium was prepared from a 1:1 mixture of *E:Z* 1-bromo-1-propene, giving **2.9.37** as a 1:1 mixture of *E:Z* dienones; yet, both geometric isomers gave isocoumarin **2.9.38.** Oospolactone (**2.2.13**) was accessed when **2.7.12** was treated with 2-buten-2-yllithium, obtained from a 3:1 mixture of *E:Z* 2-bromo-2-butene, and the product (**2.9.39**) treated with DDQ. These results offer rapid access to C3- and C4-substituted 8-hydroxyisocoumarins and changing the vinyl equivalent and further functionalization of the products could offer a powerful method for the preparation of isocoumarins.



Scheme 2.9.17

1,3-Dioxin vinylogous ester **2.7.12** has been alkylated at the α-position with a variety of electrophiles to give **2.8.6A-E**, outlined in Section 2.8. 1,2-Addition of a vinyl Grignard to **2.8.6A-E** generated dienones **2.9.40A-E** in excellent yield (Scheme 2.9.17). However, treating **2.9.40A-E** with 4.0 equivalents of DDQ in 1,4-dioxane at 100 °C resulted in mixed results. When an *n*-propyl, allyl, or propargyl group was present at the C4 position, reaction with DDQ resulted in decomposition and the desired C4-substituted isocoumarins (**2.9.41**) were not observed. Dienones **2.9.40A** and **2.9.40C**, on the other hand, yielded isocoumarins **2.9.41A** and **2.9.41C** in 43% and 33%, respectively. This can be rationalized by examination of the mechanism of DDQ oxidation shown in Scheme 2.9.4. Represented in Figure 2.9.2, **2.9.40B, D,** and **E** all contain methylene and methine groups that can undergo hydrogen atom abstraction to give stable radical cations (marked with * in Figure 2.9.2). Compared to **2.7.7**, dienone **2.9.40A** contains the same number of stablilizing groups, thus less opportunity for competing reactivity or hydrogen atom migration. On the other hand, when treated with DDQ, **2.9.40B, D,** and **E** could

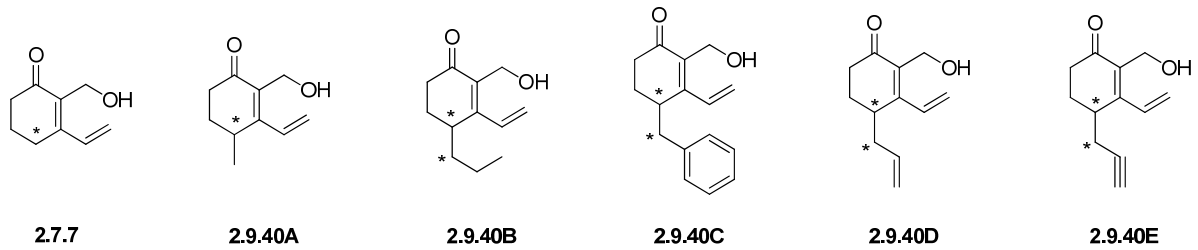


Figure 2.9.2

produce radical cation species that would be susceptible to migration or competing reactivity. Thus, decomposition of these substrates is likely due to these factors. The reaction of benzyl derivative **2.9.40C** gives the C4-sustituted isocoumarin in 33% yield, perhaps due to the inability of migration or competing reactivity.

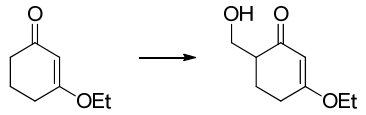
To conclude, a novel method for the generation of 8-hydroxyisocoumarins via a one-pot aromatization-cyclization-oxidation reaction by DDQ has been developed and some a mechanism has been proposed to account for this reactivity. The introduction of simple C3 and C4 substituents has been explored and the limitations of C4 substitution have been evaluated.

2.10 Summary and Conclusions

A novel approach to the synthesis of highly-functionalized 6-hydroxy and 8-hydroxy isochromenes and isocoumarins has been developed. Simple and versatile starting materials allow for the functionalization of the intermediates. A 6-*endo*-dig intramolecular cyclization of enynones **2.5.4** and **2.7.9** is featured, which installs the vinyl enol ether linkage present in the isochromene and isocoumarin skeleton. A novel method for the synthesis of 8-hydroxyisocoumarins has also been developed.

2.11 Experimental Section

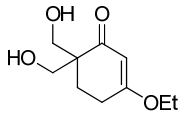
General Procedures: All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all extractive workups consisted of the following procedure: to the quenched reaction was added Et_2O and the aqueous layer was extracted with two portions of Et_2O. The combined extractive extracts were washed with water, brine, and dried over anhydrous sodium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 100 torr to a constant weight, afforded a crude residue which was purified by flash chromatography using silica gel 60 (230-400 mesh ASTM) and reagent grade petroleum ether (pet ether), Et_2O, and EtOAc. ^1H and ^{13}C NMR spectra were recorded on Bruker AVB-400 and DRX-500 MHz spectrometers with ^{13}C operating frequencies of 100 MHz and 125 MHz, respectively. Proton NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference. Carbon NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 77.23) as an internal reference.



2.5.7 **2.5.5**

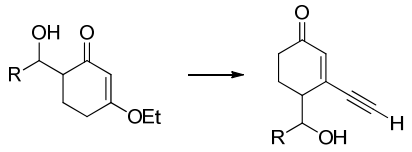
Preparation of 3-ethoxy-6-(hydroxymethyl)cyclohex-2-enone (2.5.5): To a solution of diisopropylamine (33 mL, 0.23 mol) dissolved in 250 mL THF at -78 °C was added *n*-butyllithium (93.6 mL, 0.23 mol) over a 5-min.period. The resulting mixture was allowed to rise to 0 °C over 30-min. A solution of **2.5.7** (30.00 g, 0.21 mol) dissolved in 50 mL of THF was added using a cannula to the reaction mixture over a 5-min.period and the resulting mixture was stirred at 0 °C for an additional 30-min. Solid paraformaldehyde (9.50 g, 0.32 mol) was added to the reaction mixture in one portion and the reaction was kept at 0 °C for 15-min., at which time the reaction was quenched with ammonium chloride (50 mL). Standard extractive workup,

followed by silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 16.3 g (89% brsm, 61% conversion) of **2.5.7** as a dark red oil which was homogeneous by TLC analysis [R_f (**2.5.7**) = 0.31, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.24 (s, 1H), 3.91 (septet, *J* = 7.1 Hz, 2H), 3.76-3-82 (m, 1H), 3.70 (bs, 1H), 3.52 (bs, 1H), 2.49-2.56 (m, 1H), 2.37-2.44 (m, 2H), 1.90-1.98 (m, 1H), 1.75 (dq, *J* = 12.7, 5.0 Hz, 1H), 1.36 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 202.5, 178.5, 102.6, 64.7, 63.7, 46.9, 28.8, 24.1, 14.2.



2.5.8

3-ethoxy-6,6-bis(hydroxymethyl)cyclohex-2-enone (2.5.8) was generated when the above aldol reaction (preparation of **2.5.5**) was carried out under extended reaction time. Silica gel chromatography (elution with 100% EtOAc) gave variable yields of **2.5.8** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.5.8**) = 0.62, 100% acetone] ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.17 (s, 1H), 4.12 bs, 2H), 3.79 (q, *J* = 6.9 Hz, 2H), 3.63 (d, *J* = 11.2 Hz, 2H), 3.51 (d, *J* = 11.2 Hz, 2H), 2.38 (t, *J* = 6.3 Hz, 2H), 1.76 (t, *J* = 6.3 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 204.2, 178.6, 102.2, 64.8, 62.9, 49.9, 25.8, 24.6, 14.2.

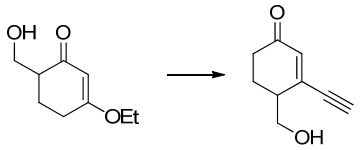


2.5.5
2.6.1A-D

2.5.4
2.6.8

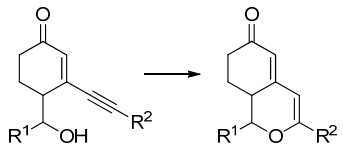
General Procedure A: To a solution of TMS-acetylene (2.5 equiv., ~50 mmol) in 75 mL of THF at -78 °C was added *n*-butyllithium (2.5 *M*, 2.2 equiv., ~44 mmol) over a 2-min.period. The resulting mixture was stirred at -78 °C for 30-min., and then warmed to 0 °C over a 30-min.period. The resulting solution was cooled to -78 °C and a solution of **2.5.5** or **2.6.1** (1.0 equiv., ~20 mmol) dissolved in 20 mL of THF was then added via cannulation over a 5-

min.period. The resulting reaction mixture was stirred at -78 °C for 1h. The reaction mixture was quenched by the addition of water (20 mL), followed by the portion-wise addition of aqueous 6 *M* HCl (50 mL). After warming the resulting solution to rt, and stirring for 30-min., the resulting solution was subjected to standard extractive workup to yield the crude TMS-enynone, which was used in the next step without further purification or characterization. To a solution of crude TMS-enynone dissolved in 150 mL of THF at rt was added TBAF-trihydrate (2.5 equiv., ~50 mmol) in a single portion. The resulting solution was stirred for 5-min. Standard extractive workup yielded the crude enynone, which was purified by silica gel chromatography.



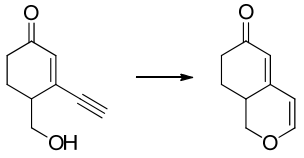
2.5.5 **2.5.4**

Preparation of 3-ethynyl-4-(hydroxymethyl)cyclohex-2-enone (2.5.4): 2.5.5 (3.50 g, 21 mmol) was reacted according to general procedure A, but was warmed to 0 °C after the addition of **2.5.5** to the solution of lithium (trimethylsilyl)acetylide. Silica gel chromatography (elution with pet ether/EtOAc = 1.1) gave 2.54 g (82%) of **2.5.4** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.5.4**) = 0.26, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.31 (s, 1H), 3.91 (s, 2H), 3.62 (s, 1H), 2.32-2.66 (m, 5H) 2.10-2.19, (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.9, 143.0, 135.9, 88.9, 81.5, 63.8, 41.6, 35.7, 25.1.



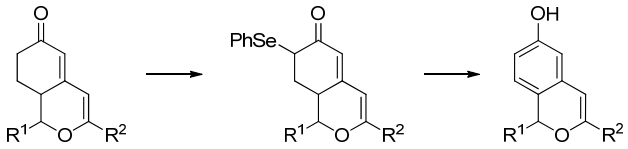
General Procedure B: To a solution of enynone (~15 mmol) and ethanethiol (1.2, equiv., ~18 mmol) in 100 mL of DCM at 0 °C was added BF_3-Et_2O (1.5 equiv., ~33 mmol) over a 2-min. period. The resulting solution was stirred at rt for 6 h. The reaction mixture was diluted

with Et_2O (100 mL) and 50 mL H_2O (100 mL) and stired vigorously at rt for 5-min. Standard extractive workup gave the crude pyran.



2.5.4 **2.5.1**

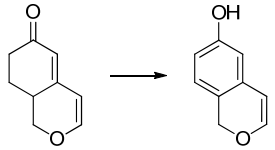
Preparation of 8,8a-dihydro-1H-isochromen-6(7H)-one (2.5.1): 2.5.4 (2.20 g, 15 mmol) was reacted according to general procedure B. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4.1) gave 1.8 g (82%) of **2.5.1** as a red oil which was homogeneous by TLC analysis [R_f (**2.5.1**) = 0.26, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.81 (d, *J* = 5.7 Hz, 1H), 5.72 (s, 1H), 5.56 (d, *J* = 5.7 Hz, 1H), 4.34 (dd, *J* = 5.4, 10.8 Hz, 1H), 3.65 (dd, *J* = 13.3, 11.4 Hz, 1H), 2.80-2.89 (m, 1H), 2.54-2.61 (m, 1H), 2.44-2.50 (m, 1H), 1.99-2.03 (m, 1H), 1.55-1.63 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.7, 153.0, 152.8, 119.2, 104.7, 70.4, 37.3, 34.1, 25.4.



General Procedure C: To a solution of pyran (~3 mmol) in THF (20 mL) was added PhSeCl (4.5 mmol) in one portion. The reaction mixture was stirred until TLC analysis indicated the consumption of the starting pyran. Standard ethereal workup gave a crude α-phenylselenide, which was used directly in the next step without purification or characterization.

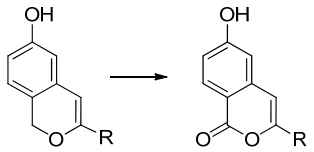
To a solution of phenylselenide in EtOAc (20 mL) at rt was added a solution of hydrogen peroxide (30% in water, 9 mmol). The resulting solution was stirred at rt for 30-min., at which time Et_2O (20 mL) was added to the reaction mixture. The organic layer was washed with water (5 mL), saturated aqueous $NaHCO_3$ (5 mL), water (4x5 mL), and brine (5 mL). The crude

isochromene was obtained by drying over anhydrous sodium sulfate and concentration under reduced pressure.

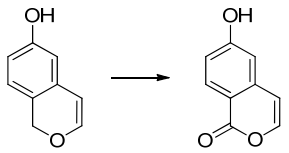


2.5.1 **2.5.2**

Preparation of 1H-isochromen-6-ol (2.5.2): 2.5.1 (650 mg, 4.3 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 505 mg (78%) of **2.5.2** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.5.2**) = 0.26, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.87 (d, *J* = 8.0 Hz, 1H), 6.60-6.66 (m, 2H), 6.47 (s, 1H), 5.74 (d, *J* = 5.6 Hz, 1H), 5.00 (s, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 155.9, 146.9, 132.1, 125.4, 120.6, 113.2, 110.2, 105.5, 68.0.

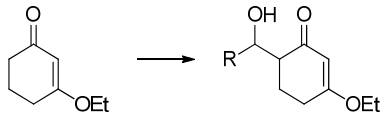


General Procedure D: To a solution of isochromene (~ 0.5-2 mmol) in 1,4-dioxane (~6-15 mL) at rt was added DDQ (2.0 equiv.) in one portion. The resulting suspension was allowed to stir at rt until TLC analysis indicated consumption of the starting isochromene. To the reaction mixture was added Et_2O (20 mL). The reaction mixture was washed with H_2O (4x4 mL) and brine (5 mL). The crude isocoumarin was obtained by drying over anhydrous sodium sulfate and concentration under reduced pressure.



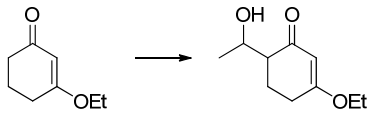
2.5.2 **2.5.3**

Preparation of 6-hydroxy-1H-isochromen-1-one (2.5.3): 2.5.2 (79 mg, 0.5 mmol) was reacted according to general procedure D. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 79 mg (91%) of **2.5.3** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.5.3**) = 0.23, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 9.72 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 5.6 Hz, 1H), 7.06 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.57 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 163.4, 161.4, 149.9, 139.4, 132.0, 117.6, 114.2, 110.4, 106.8.



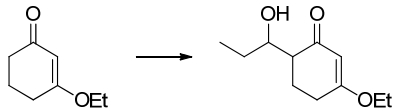
2.5.7 **2.6.1**

General Procedure E: To a solution of **2.5.7** (29 mmol) in THF (50 mL) at -78 °C was added dropwise a solution of LDA (1.8M, 35 mmol). The resulting solution was stirred at -78 °C for 30-min., at which time the corresponding aldehyde (41 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred at -78 °C for an additional hour. The reaction was quenched by the addition of ammonium chloride (10 mL). Standard extractive workup, followed by silica gel chromatography gave both diastereomers of **2.6.1**. **NP** indicates the more nonpolar diastereomer and **P** indicates the more polar diastereomer by silica gel chromatography.



2.5.7 **2.6.1A**

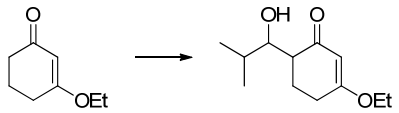
Preparation of 3-ethoxy-6-(1-hydroxyethyl)cyclohex-2-enone (2.6.1A): 2.5.7 (4.00 g, 29 mmol) was reacted with acetaldehyde according to general procedure E. Purification using silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 4.7 g (89% combined yield) of **2.6.1A** as two components as yellow oils which by TLC analysis [R_f (**2.6.1A-NP**) = 0.31, 1.1, pet ether/EtOAc; R_f (**2.6.1A-P**) = 0.22, 1.1, pet ether/EtOAc]: **2.6.1A-NP** ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.34 (s, 1H), 5.07 (s, 1H), 3.90-3.95 (m, 2H), 2.28-2.60 (m, 3H) 2.00-2.09 (m, 2H), 1.57-1.61 (m, 1H), 1.33-1.38 (m, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 203.0, 178.4, 102.6, 68.2, 64.5, 51.2, 28.8, 23.5, 20.1, 14.1. **2.6.1A-P** ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.36 (s, 1H), 4.18-4.25 (m, 1H), 3.85-3.94 (m, 2H), 3.26 (d, *J* = 10.1 Hz. 1H), 2.34-2.58 (m, 3H), 1.81-2.02 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.8, 178.3, 103.3, 67.1, 64.7, 50.9, 29.1, 22.2, 19.3, 14.3.



2.5.7 **2.6.1B**

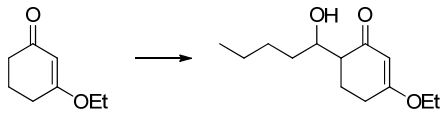
Preparation of 3-ethoxy-6-(1-hydroxypropyl)cyclohex-2-enone (2.6.1B): 2.5.7 (4.00 g, 29 mmol) was reacted with propionaldehyde according to general procedure E and silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 5.5 g (97% combined yield) of **2.6.1A** as two components as yellow oils which by TLC analysis [R_f (**2.6.1B-NP**) = 0.47, 1.1, pet ether/EtOAc; R_f (**2.6.1B-P**) = 0.36, 1.1, pet ether/EtOAc]: **2.6.1B-NP** ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.35 (s, 1H), 4.87 (s, 1H), 3.93 (m, 2H), 3.79 (m, 1H), 2.50 (m, 1H), 2.42 (m, 1H), 2.21 (m, 1H), 2.03 (m, 1H), 1.68 (m, 2H), 1.45 (m, 1H), 1.38 (t, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 203.3, 178.3, 102.5, 72.8, 64.5, 49.1, 28.8, 26.2, 23.4, 14.1,

9.1. **2.6.1B-P** ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.35 (d, *J* = 7.4 Hz, 1H), 4.04-4.14 (m, 1H), 3.85-4.00 (m, 2H), 2.32-2.56 (m, 6H), 1.90-2.04 (m, 2H), 1.37 (t, *J* = 8.2 Hz, 3H), 1.00 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.6, 178.1, 103.2, 71.6, 64.5, 50.0, 28.1, 26.2, 21.4, 14.4, 10.9.



2.5.7 **2.6.1C**

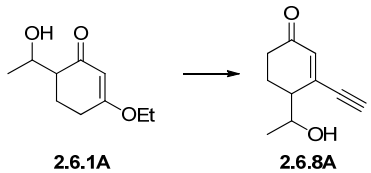
Preparation of 3-ethoxy-6-(1-hydroxy-2-methylpropyl)cyclohex-2-enone (2.6.1C): (4.00 g, 29 mmol) was reacted with isobutyraldehyde according to general procedure E. Purification using silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 5.63 g (95% combined yield) of **2.6.1C** as two components as yellow oils which by TLC analysis [R_f (**2.6.1C-NP**) = 0.61, 1.1, pet ether/EtOAc; R_f (**2.6.1C-P**) = 0.42, 1.1, pet ether/EtOAc]: **2.6.1C-NP** ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.33 (s, 1H), 4.73 (s, 1H), 3.85-3.95 (m, 2H), 3.55-3.67 (m, 2H), 2.43-2.41 (m, 1H), 2.31-2.39 (m, 1H), 2.20-2.28 (m, 1H), 1.93-2.00 (m, 1H), 1.73-1.81 (m, 1H), 1.60-1.69 (m, 1H), 1.35 (t, *J* = 6.2 Hz, 3H), 1.03 (d, *J* = 6.0, 3H), 1.03 (d, *J* = 6.0, 3H), 0.89 (d, *J* = 6.0, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 203.6, 178.0, 102.4, 75.7, 64.4, 47.7, 29.3, 28.6, 23.5, 20.0, 14.3, 14.0. **2.6.1C-P** ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.39 (s, 1H), 3.81-3.99 (m, 4H), 2.41-2.53 (m, 1H), 2.37-2.45 (m, 1H), 2.21-2.32 (m, 1H), 1.99-2.09 (m, 2H), 1.67-1.76 (m, 1H), 1.37 (t, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.6, 177.9, 103.2, 74.6, 64.4, 48.2, 30.1, 28.8, 20.1, 19.7, 19.1, 14.2.



2.5.7 **2.6.1D**

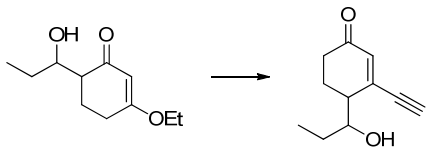
Preparation of 3-ethoxy-6-(1-hydroxypentyl)cyclohex-2-enone (2.6.1D): 2.5.7 (4.00 g, 29 mmol) was reacted with pentanal according to general procedure E and silica gel

chromatography (elution with pet ether/EtOAc = 1:1) gave 6.1 g (95% combined yield) of **2.6.1D** as two components as yellow oils which by TLC analysis [R_f (**2.6.1D-NP**) = 0.56, 1.1, pet ether/EtOAc; R_f (**2.6.1D-P**) = 0.47, 1.1, pet ether/EtOAc]: **2.6.1D-NP**: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.24 (s, 1H), 4.84 (s, 1H), 3.90-3.96 (m, 2H), 3.83 (bt, 1H), 2.37-2.57 (m, 2H), 2.16-2.22 (m, 1H), 2.00-2.07 (m, 1H), 1.29-1.75 (m, 9H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 203.2, 178.2, 102.5, 71.7, 64.5, 49.9, 33.5, 28.8, 27.1, 23.6, 22.8, 14.0, 14.0. **2.6.1D-P**: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.37 (s, 2H), 4.16 (bs, 1H), 3.82-3.90 (m, 2H), 2.72 (d, *J* = 5.9 Hz, 1H, 2.32-2.58 (m, 3H), 1.90-2.03 (m, 2H), 1.48-1.57 (m, 2H), 1.27-1.45 (m, 8H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.6, 178.2, 103.2, 70.2, 64.5, 50.3, 33.0, 29.0, 28.6, 22.8, 21.3, 14.2, 14.2.



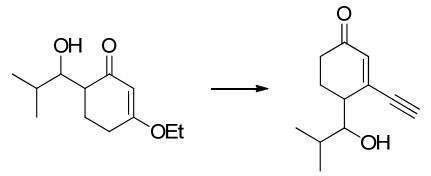
2.6.1A **2.6.8A**

Preparation of 3-ethynyl-4-(1-hydroxyethyl)cyclohex-2-enone (2.6.8A): 2.6.1A (4.10 g, 22 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 3.0 g (82%) of **2.6.8A** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.6.8A**) = 0.32, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.34 (s, 1H), 4.43 (pentet, *J* = 5.8 Hz, 1H), 3.64 (s, 1H), 2.56-2.71 (m, 2H), 2.37 (dq, *J* = 17.2, 5.1, 1H), 2.17-2.23 (m, 1H), 1.89-1.96 (m, 2H), 1.25 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.9, 143.1, 136.0, 89.2, 82.0, 69.3, 45.3, 36.2, 23.0, 19.7.



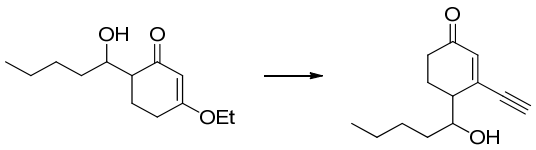
2.6.1B **2.6.8B**

Preparation of 3-ethynyl-4-(1-hydroxypropyl)cyclohex-2-enone (2.6.8B): 2.6.1B (3.90 g, 20 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 3.13 g (89%) of **2.6.8B** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.6.8B**) = 0.36, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.35 (s, 1H), 4.01-4.12 (m, 1H), 3.62 (s, 1H), 2.59-2.73 (m, 2H), 2.36 (dq, *J* = 17.2, 5.1, 1H), 2.17-2.27 (m, 1H), 1.87-1.95 (m, 2H), 1.62 (s, 1H), 1.47-1.54 (m, 1H), 1.03 (t, *J* = 7.3, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.9, 143.9, 136.1, 89.0, 82.1, 75.3, 44.7, 36.2, 26.9, 24.0, 11.0.



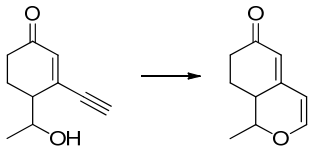
2.6.1C **2.6.8C**

Preparation of 3-ethynyl-4-(1-hydroxy-2-methylpropyl)cyclohex-2-enone (2.6.8C): 2.6.1C (4.40 g, 21 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 3.63 g (91%) of **2.6.8C** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.6.8C**) = 0.44, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.33 (s, 1H), 3.60-3.69 (m, 2H), 2.57-2.73 (m, 2H), 2.34 (dt, *J* = 17.6, 6.1 Hz, 1H), 2.11-2.20 (m, 1H), 1.90-1.99 (m, 1H), 0.98 (dd, *J* = 15.6, 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.1, 144.1, 135.8, 89.2, 83.3, 79.6, 42.5, 35.2, 31.8, 26.5, 20.1, 17.6.



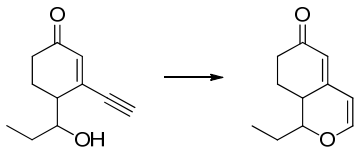
2.6.1D 2.6.8D

Preparation of 3-ethynyl-4-(1-hydroxypentyl)cyclohex-2-enone (2.6.8D): 2.6.1D (4.50 g, 20 mmol) was reacted according to general procedure A. Purification using silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 3.75 g (92%) of **2.6.8D** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.6.8D**) = 0.46, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.35 (s, 1H), 4.11-4.22 (m, 1H), 3.62 (s, 1H), 2.57-2.73 (m, 2H), 2.35 (dq, *J* = 17.1, 5.1 Hz, 1H), 2.20-2.27 (m, 1H), 1.63-1.99 (m, 2H), 1.47-1.55 (m, 2H), 1.31-1.39 (m, 2H), 0.92 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.2, 143.3, 136.0, 89.2, 82.0, 73.4, 44.9, 36.3, 33.3, 28.8, 23.6, 22.7, 14.2.



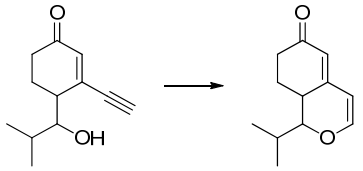
2.6.8A 2.6.10A

Preparation of 1-methyl-8,8a-dihydro-1H-isochromen-6(7H)-one (2.6.10A): 2.6.8A (1.80 g, 11 mmol) was reacted according to general procedure B. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4.1) gave 1.4 g (77%) of **2.6.10A** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.10A**) = 0.33, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.84 (d, *J* = 5.4 Hz, 1H), 5.71 (s, 1H), 5.53 (d, *J* = 5.4 Hz, 1H), 3.60-3.67 (m, 1H), 2.51-2.60 (m, 2H), 2.41 (dt, *J* = 14.7, 4.9 Hz, 1H), 2.05-2.13 (m, 1H), 1.86-1.95 (m, 1H), 1.50-1.73 (m, 2H), 1.05 (t, *J* =7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.6, 153.8, 153.6, 119.3, 104.8, 81.6, 37.8, 37.4, 25.7, 24.8.



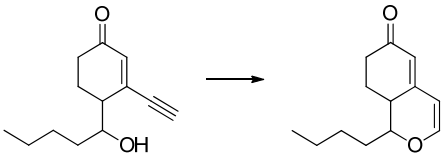
2.6.8B **2.6.10B**

Preparation of 1-ethyl-8,8a-dihydro-1H-isochromen-6(7H)-one (2.6.10B): 2.6.8B (2.40 g, 13 mmol) was reacted according to general procedure B. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.15 g (89%) of **2.6.10B** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.10B**) = 0.41, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.81 (d, *J* = 5.6 Hz, 1H), 5.71 (s, 1H), 5.54 (d, *J* = 5.6 Hz, 1H), 3.80 (sextet, *J* = 5.9 Hz, 1H), 2.35-2.60 (m, 2H), 2.10-2.18- (m, 1H), 1.53-1.59 (m, 1H), 1.44 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.7, 153.4, 153.4, 119.2, 105.0, 77.4, 40.3, 37.4, 25.8, 18.7.



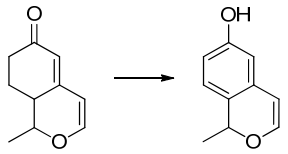
2.6.8C **2.6.10C**

Preparation of 1-isopropyl-8,8a-dihydro-1H-isochromen-6(7H)-one (2.6.10C): 2.6.8C (1.70 g, 9 mmol) was reacted according to general procedure B. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.17 g (69%) of **2.6.10C** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.10C**) = 0.49, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.80 (d, *J* = 5.5 Hz, 1H), 5.71 (s, 1H), 5.50 (d, *J* = 5.6 Hz, 1H), 3.58 (d, *J* = 12.2 Hz, 1H), 2.59-2.71 (m, 1H), 2.50-2.59 (m, 1H), 2.41 (dt, *J* = 14.4, 5.0 Hz, 1H), 2.01-2.10 (m, 2H), 1.56 (dq, *J* = 12.8, 4.5 Hz, 1H), 1.10 (d, *J* = 7.0 Hz, 1H), 0.97 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.6, 154.4, 153.8, 199.2, 104.6, 84.5, 37.4, 36.2, 27.9, 25.3, 20.0, 14.2.



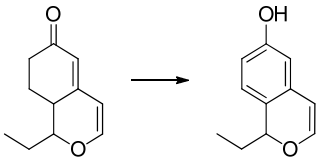
2.6.8D 2.6.10D

Preparation of 1-butyl-8,8a-dihydro-1H-isochromen-6(7H)-one (2.6.10D): 2.6.8D (2.0 g, 10 mmol) was reacted according to general procedure B. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.83 g (91%) of **2.6.10D** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.10D**) = 0.54, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.82 (d, *J* = 5.6 Hz, 1H), 5.69 (s, 1H), 5.2 (d, *J* = 5.6 Hz, 1H), 3.62-3.69 (m, 1H), 2.49-2.56 (m, 2H), 2.40 (dt, *J* = 14.4, 5.0 Hz, 1H), 2.09-2.18 (m, 1H), 1.75-1.83 (m, 1H), 1.52-1.61 (m, 2H), 1.31-1.39 (m, 1H), 0.93 (t, 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.6, 153.8, 153.5, 119.2, 104.9, 80.7, 38.3, 37.4, 31.6, 26.6, 25.8, 22.8, 14.2.



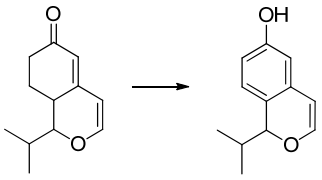
2.6.10A 2.6.11A

Preparation of 1-methyl-1H-isochromen-6-ol (2.6.11A): 2.6.10A (710 mg, 4.3 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 631 mg (90%) of **2.6.11A** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.11A**) = 0.35, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.86 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.54 (d, *J* = 5.6 Hz, 1H), 6.46 (s, 1H), 5.88 (bs, 1H), 5.69 (d, *J* = 5.6 Hz, 1H), 5.18 (q, *J* = 6.4 Hz, 1H), 1.58 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 155.6, 145.6, 131.6, 125.2, 124.9, 113.4, 110.3, 105.0, 73.7, 20.0.



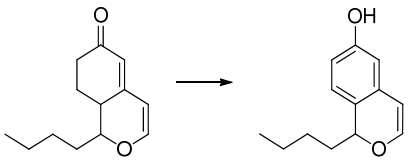
2.6.10B 2.6.11B

Preparation of 1-ethyl-1H-isochromen-6-ol (2.6.11B): 2.6.10B (562 mg, 3.2 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 512 mg (92%) of **2.6.11B** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.11B**) = 0.38, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.83 (d, *J* = 8.1 Hz, 1H), 6.62 (dd, *J* = 2.1, 8.0 Hz, 1H), 6.52 (d, *J* = 5.7 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 5.65 (d, *J* = 5.7 Hz, 1H), 5.45 (bs, 1H), 4.97 (dd, *J* = 5.2, 7.7 Hz, 1H), 2.00 (m, 2H), 1.71-1.80 (m, 2H), 1,01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 155.5, 145.1, 131.5, 125.6, 124.1, 113.1, 110.3, 104.4, 78.8, 27.4, 10.1.



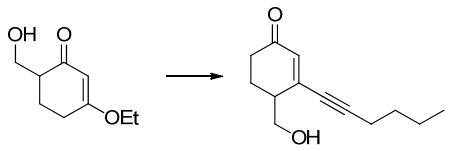
2.6.10C 2.6.11C

Preparation of 1-isopropyl-1H-isochromen-6-ol (2.6.11C): 2.6.10C (450 mg, 2.3 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 303 mg (69%) of **2.6.11C** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.11C**) = 0.41, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.80 (d, *J* = 8.1 Hz, 1H), 6.61 (dd, *J* = 2.1, 8.0 Hz, 1H), 6.53 (d, *J* = 5.7 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 5.61 (d, *J* = 5.7 Hz, 1H), 5.53 (bs, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 2.21 (sextet, *J* = 6.7 Hz, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 155.4, 145.3, 131.6, 126.9, 122.8, 112.9, 110.2, 104.3, 82.9, 31.9, 19.2, 18.3.



2.6.10D **2.6.11D**

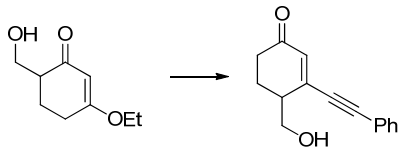
Preparation of 1-butyl-1H-isochromen-6-ol (2.6.11D): 2.6.10D (733 mg, 3.6 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 662 mg (91%) of **2.6.11D** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.11D**) = 0.41, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.84 (d, *J* = 8.0 Hz, 1H), 6.62 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.51 (d, *J* = 5.6 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 5.67 (d, *J* = 5.7 Hz, 1H), 5.44 (bs, 1H), 5.05 (dd, *J* = 4.9, 8.2 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 1H), 1.92-2.01 (m, 1H), 1.66-1.73 (m, 1H), 1.45-1.50 (m, 1H), 1.33-1.41 (m, 2H), 1.26-1.32 (m, 1H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 155.4, 145.1, 131.4, 125.5, 124.4, 113.2, 110.3, 104.5, 76.9, 34.1, 27.8, 22.8, 14.3.



2.5.5 **2.6.12-Hex**

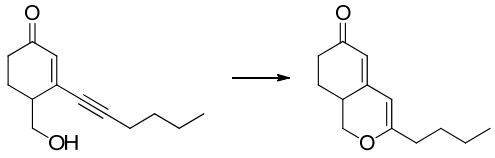
Preparation of 3-(hex-1-yn-1-yl)-4-(hydroxymethyl)cyclohex-2-enone (2.6.12-Hex): To a solution of 1-hexyne (5.6 mL, 48 mmol) in 75 mL of THF at -78 °C was added *n*-butyllithium (17.0 mL, 2.5 *M*, ~43 mmol) over a 2-min. period. The resulting mixture was stirred at -78 °C for 30-min., and then warmed to 0 °C over a 30-min. period. To the resulting solution was added a solution of **2.5.5** (3.30 g, 19 mmol) dissolved in 20 mL of THF via cannulation over a 5-min. period. The resulting reaction mixture was stirred at 0 °C for 1h. The reaction mixture was quenched by the addition of water (20 mL), followed by the portion-wise addition of aqueous 6 *M* HCl (50 mL). After warming the resulting solution to rt, and stirring for 30-min., the resulting

solution was subjected to standard extractive workup. Silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 3.2 g (80%) of **2.6.12-Hex** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.6.12-Hex**) = 0.30, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.19 (s, 1H), 3.82-3.91 (m, 3H), 2.50-2.59 (m, 2H), 2.33-2.41 (m, 3H), 1.95-2.19 (m, 2H), 1.50-1.59 (m, 2H), 1.33-1.41 (m, 2H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.5, 145.5, 133.4, 104.2, 79.4, 63.7, 42.1, 35.4, 30.5, 24.9, 22.1, 19.7, 13.7.



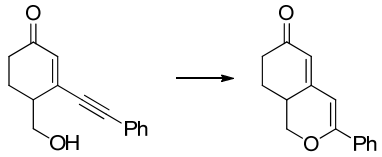
2.5.5 **2.6.12-Ph**

Preparation of 4-(hydroxymethyl)-3-(phenylethynyl)cyclohex-2-enone (2.6.12-Ph): To a solution of phenylacetylene (5.2 mL, 47 mmol) in 75 mL of THF at -78 °C was added *n*-butyllithium (16.5 mL, 2.5 *M*, ~42 mmol) over a 2-min. period. The resulting mixture was stirred at -78 °C for 30-min., and then warmed to 0 °C over a 30-min. period. To the resulting solution was added a solution of **2.5.5** (3.20 g, 19 mmol) dissolved in 20 mL of THF via cannulation over a 5-min. period. The resulting reaction mixture was stirred at -0 °C for 1h. The reaction mixture was quenched by the addition of water (20 mL), followed by the portion-wise addition of aqueous 6 *M* HCl (50 mL). After warming the resulting solution to rt, and stirring for 30-min., the resulting solution was subjected to standard extractive workup. Silica gel chromatography (elution with pet ether/EtOAc = 1:1) gave 3.0 g (72%) of **2.6.12-Ph** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.6.12-Ph**) = 0.42, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.43-7.49 (m, 2H), 7.30-7.39 (m, 3H), 6.33 (s, 1H), 3.89-4.04 (m, 2H), 2.53-2.85 (m, 3H), 2.35-2.43 (m, 1H), 2.09-2.16 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.1, 144.2, 134.1, 132.2, 129.9, 128.8, 121.9, 101.5, 87.5, 64.0, 41.9, 35.7, 25.2.



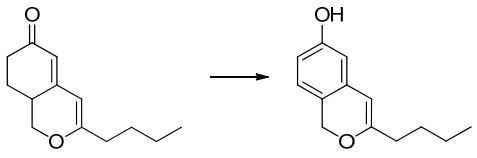
2.6.12-Hex **2.6.12-HexB**

Preparation of 2.6.12-Hex (752 mg, 3.7 mmol) was reacted according to general procedure B. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4.1) gave 660 mg (88%) of **2.6.12-HexB** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.13-HexB**) = 0.44, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.63 (s, 1H), 5.41 (s, 1H), 4.32 (dd, *J* = 10.7, 5.4 Hz, 1H), 3.61 (dd, *J* = 13.3, 11.0 Hz, 1H), 2.75 (m, 1H), 2.48-2.55 (m, 1H), 2.37-2.45 (m, 1H), 2.19 (t, *J* = 7.1 Hz, 2H), 2.05-2.13 (m, 1H), 1.47-1.55 (m, 3H), 1.33 (sextet, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.7, 167.0, 154.9, 117.3, 101.0, 70.7, 37.2, 34.4, 33.7, 29.0, 25.2, 22.4, 14.0.



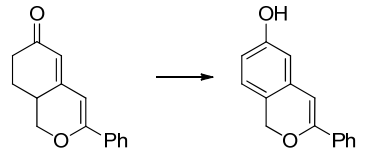
2.6.12-Ph **2.6.12-PhB**

Preparation of 2.6.12-Ph (890 mg, 3.9 mmol) was reacted according to general procedure B. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 540 mg (61%) of **2.6.12-PhB** as a red oil which was homogeneous by TLC analysis [R_f (**2.6.12-PhB**) = 0.42, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.63-7.76 (m, 2H), 7.38-7.46 (m, 3H), 6.18 (s, 1H), 5.84 (s, 1H), 4.55 (dd, *J* = 10.7, 5.3 Hz, 1H), 3.61 (dd, *J* = 13.0, 11.8 Hz, 1H), 2.84-2.91 (m, 1H), 2.55-2.64 (m, 1H), 2.48 (dt, *J* = 14.3, 4.9 Hz, 1H), 2.01-2.12 (m, 1H), 1.64 (dt, *J* = 13.4, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.7, 160.4, 154.5, 133.7, 130.6, 128.8, 126.0, 119.3, 100.7, 71.0, 37.3, 34.1, 25.3.



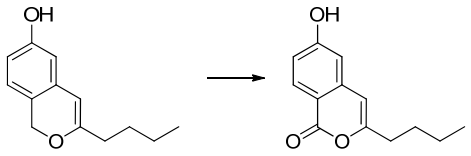
2.6.12-Hex 2.6.13-Hex

Preparation of 3-butyl-1H-isochromen-6-ol (2.6.13-Hex): 2.6.12-Hex (415 mg, 2.0 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 342 mg (82%) of **2.6.13-Hex** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.6.13-Hex**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.87 (d, *J* = 6.9 Hz, 1H), 6.56 (d, *J* = 6.9 Hz, 1H), 6.42 (s, 1H), 5.58 (s, 1H), 4.98 (s, 2H), 4.81 (bs, 1H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.50-1.58 (m, 2H), 1.31-1.40 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 159.8, 155.7, 133.9, 125.0, 120.0, 112.2, 109.5, 100.9, 68.7, 33.6, 29.4, 22.5, 14.1.



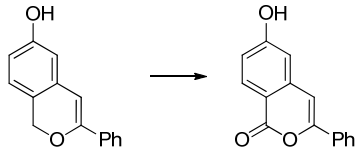
2.6.12-Ph 2.6.13-Ph

Preparation of 3-phenyl-1H-isochromen-6-ol (2.6.13-Ph): 2.6.12-Ph (620 mg, 2.7 mmol) was reacted according to general procedure C. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 569 mg (93%) of **2.6.13-Ph** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.6.13-Ph**) = 0.39, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.73 (d, *J* = 7.1 Hz, 2H), 7.31-7.40 (m, 3H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.60 (s, 1H), 6.39 (s, 1H), 5.17 (s, 2H), 4.81 (bs, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 155.9, 154.7, 134.4, 133.7, 130.4, 129.2, 128.6, 125.4, 125.1, 120.7, 113.2, 110.6, 101.2, 69.0.



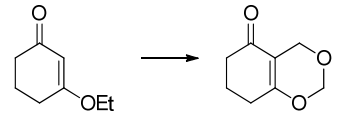
2.6.13-Hex **2.6.14-Hex**

Preparation of 3-butyl-6-hydroxy-1H-isochromen-1-one (2.6.14-Hex): 2.6.13-Hex (109 mg, 0.5 mmol) was reacted according to general procedure D. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 83 mg (71%) of **2.6.14-Hex** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.6.14-Hex**) = 0.50, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.13 (d, *J* = 8.7 Hz, 1H), 8.00 (bs, 1H), 7.02 (dd, *J* = 1.7, 8.7 Hz, 1H), 6.82 (d, *J* = 1.9 Hz, 1H), 6.20 (s, 1H), 2.50 (t, *J* = 7.6 Hz, 2H), 1.65 (pentet, *J* = 7.6 Hz, 2H), 1.37 (pentet, *J* = 7.5 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 164.3, 162.8, 158.9, 140.6, 132.3, 117.2, 112.7, 110.0, 103.5, 33.3, 29.1, 22.3, 14.0.



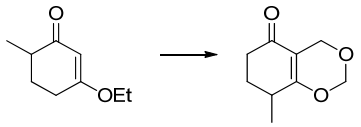
2.6.13-Ph **2.6.14-Ph**

Preparation of 3-phenyl-6-hydroxy-1H-isochromen-1-one (2.6.14-Ph): 2.6.13-Ph (160 mg, 0.7 mmol) was reacted according to general procedure D. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 134 mg (79%) of **2.6.14-Ph** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.6.14-Ph**) = 0.44, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, CH_3OH) δ 8.06 (d, *J* = 8.7 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.40-7.50 (m, 3H), 7.10 (s, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (100 MHz, CH_3OH) δ 164.2, 163.1, 153.7, 140.5, 132.2, 131.6, 129.8, 128.8, 125.0, 117.4, 112.0, 110.5, 102.1.



1.9.6 **2.7.12**

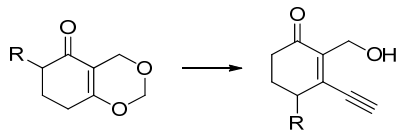
Preparation of 7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.7.12): To a solution of **1.9.6** (30.8 g, 0.22 mol) and 1,3,5-trioxane (42.0 g, 0.47 mol) in DCM (300 mL) at 0 °C was added dropwise BF_3-Et_2O (53 mL, 0.42 mmol) over 5-min. The resulting solution was stirred at rt for 16h, at which time it was filtered through a short pad of Celite, which was rinsed with two 50 mL portions of DCM. The resulting solution was cooled to 0 °C and slowly quenched by the addition of saturated $NaHCO_3$ (100 mL). Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 33.7 g (97%) of **2.7.12** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.7.12**) = 0.37, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.10 (s, 2H), 4.39 (s, 2H), 2.33-2.40 (m, 2H), 2.27-2.35 (m, 2H), 1.90-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.5, 170.5, 112.0, 91.6, 63.0, 36.7, 27.8, 20.8.



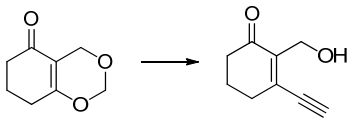
1.9.19 **2.7.17**

Preparation of 8-methyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.7.17): To a solution of **1.9.19** (1.20 g, 8 mol) and 1,3,5-trioxane (1.35 g, 16 mmol) in DCM (15 mL) at 0 °C was added dropwise BF_3-Et_2O (2.1 mL, 16 mmol) over 5-min. The resulting solution was stirred at rt for 16h, at which time it was filtered through a short pad of Celite, which was rinsed with two 10 mL portions of DCM. The resulting solution was cooled to 0 °C and slowly quenched by the addition of saturated $NaHCO_3$ (5 mL). Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 1.15 g (88%) of **2.7.17** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.7.17**) = 0.46, 1:1, pet ether/EtOAc]: ^{1}H NMR

(400 MHz, $CHCl_3$) δ 5.10-5.16 (m, 1H), 5.03-5.12 (m, 1H), 4.43 (s, 2H), 2.55-2.62 (m, 1H), 2.40-2.49 (m, 1H), 2.27-2.36 (m, 1H), 2.03-2.10 (m, 1H), 1.66-1.73 (m, 1H), 1.18-1.25 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.4, 173.4, 111.0, 91.6, 63.0, 34.6, 32.4, 28.8, 16.5.



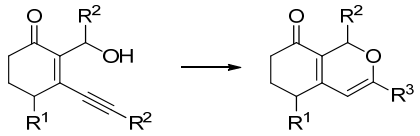
General Procedure F: To a solution of TMS-acetylene (1.4 equiv., ~21 mmol) in 50 mL of THF at -78 °C was added *n*-butyllithium (1.2 equiv., 2.5 *M*, ~18 mmol) over a 2-min. period. The resulting mixture was stirred at -78 °C for 30-min., and then warmed to 0 °C over a 30-min. period. A solution of **2.7.12** or **2.8.6** (1.0 equiv., ~15 mmol) dissolved in 15 mL of THF was then added via cannulation over a 5-min. period. The resulting reaction mixture was stirred at 0 °C for 1h. The reaction mixture was quenched by the addition of water (10 mL), followed by the portion-wise addition of aqueous 6*M* HCl (40 mL). The resulting solution was subjected to standard extractive workup to yield the crude TMS-enynone, which was used in the next step without further purification or characterization. To a solution of crude TMS-enynone dissolved in 100 mL of THF at rt was added TBAF-trihydrate (1.5 equiv., ~23 mmol) in a single portion. The resulting solution was stirred for 5-min. Standard extractive workup yielded the crude enynone.



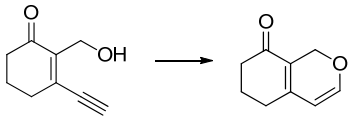
2.7.12 **2.7.8**

Preparation of 3-ethynyl-2-(hydroxymethyl)cyclohex-2-enone (2.7.8): 2.7.12 (4.20 g, 27 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2.1) gave 2.92 g (73%) of **2.7.8** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.7.8**) = 0.35, 1:1, pet ether/EtOAc]: ^1H NMR

(400 MHz, $CHCl_3$) δ 4.53 (d, *J* = 5.5 Hz, 2H), 3.81 (s, 1H), 2.87 (bt, *J* = 6.2 Hz, 1H), 2.54 (t, *J* = 5.8 Hz, 2H), 2.54 (t, *J* = 6.2 Hz, 2H), 2.49 (t, *J* = 5.8 Hz, 2H), 2.04 (pentet, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.0, 142.1, 139.1, 92.3, 80.9, 59.9, 38.0, 31.2, 23.3.

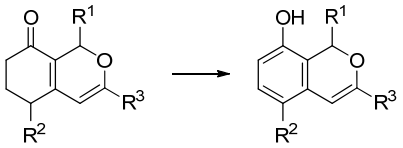


General Procedure G: To a solution of enynone (~7 mmol) in either DCM or DCE (40 mL) heated to a vigorous reflux was added MsOH (2 equiv., ~14 mmol) in one portion. The resulting solution was stirred at reflux for 15-min. The reaction mixture was cooled to rt and diluted with Et_2O (60 mL) and filtered through a short pad of silica. The silica is flushed with three 15 mL portions of EtOAc. The organic portions were combined and concentration under reduced pressure gave pyran, which was immediately purified by silica gel chromatography, concentrated almost completely, and stored in the remaining column solvent until further use.

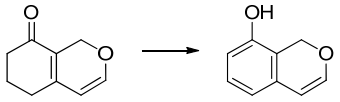


2.7.8 **2.7.9**

Preparation of 6,7-dihydro-1H-isochromen-8(5H)-one (2.7.9): 2.7.8 (1.00 g, 6.7 mmol) was reacted according to general procedure G using DCM. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 785 mg (79%) of **2.7.9** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.7.9**) = 0.52, 4:1, pet ether/EtOAc]: ^1H NMR (400 MHz, $CHCl_3$) δ 6.74 (d, *J* = 5.1 Hz, 1H), 5.29 (d, *J* = 5.1 Hz, 1H), 4.83 (s, 2H), 2.29-2.42 (m, 4H), 1.93-2.01 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.0, 153.1, 150.5, 117.5, 105.3, 63.3, 37.5, 28.1, 22.4.

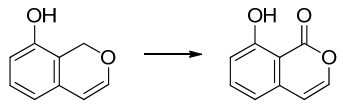


General Procedure H: To a solution of pyran (~3 mmol) in THF (8 mL) at -78 °C was added dropwise a solution of LDA (1.8 *M*, 3.6 mmol). The resulting solution was stirred at -78 °C for 1h, at which time PhSeCl (4.2 mmol) in THF (1 mL) was added rapidly in one portion and the reaction mixture was stirred at -78 °C for 30-min. Standard ethereal workup gave the crude α-phenylselenide, which was used directly in the next step without purification or characterization. To a solution of phenylselenide in EtOAc (20 mL) at rt was added a solution of hydrogen peroxide (30% in water, 9 mmol). The resulting solution was stirred at rt for 30-min., at which time Et_2O (20 mL) was added to the reaction mixture. The organic layer was washed with water (5 mL), 10% aqueous $NaHCO_3$ (5 mL), four portions of water (5 mL), and brine (5 mL). The crude isochromene was obtained by drying over anhydrous sodium sulfate and concentration under reduced pressure.



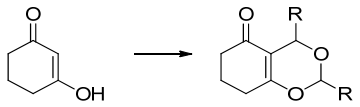
2.7.9 **2.7.19**

Preparation of 1H-isochromen-8-ol (2.7.19): 2.7.9 (650 mg, 4 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 595 mg (93%) of **2.7.19** as a red oil which was homogeneous by TLC analysis [R_f (**2.7.19**) = 0.37, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.03 (t, *J* = 7.8 Hz, 1H), 6.56 (m, 3H), 5.73 (d, *J* = 5.6 Hz, 1H), 5.17 (s, 2H), 4.80 (s, 1H); ^{13}C NMR (100 MHz, acetone) δ 152.1, 146.2, 131.9, 128.6, 114.9, 114.3, 114.2, 105.1, 62.7.



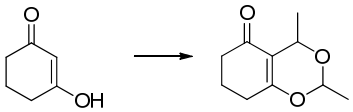
2.7.19 2.7.20

Preparation of 8-hydroxy-1H-isochromen-1-one (2.7.20): 2.7.19 (145 mg, 10 mmol) was reacted according to general procedure D. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 146 mg (92%) of **2.5.3** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.5.3)** = 0.43, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, acetone) δ 11.0 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 5.6 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.4, 161.9, 144.1, 137.6, 136.9, 110.1, 110.0, 108.6, 107.5.



2.7.11 2.8.1

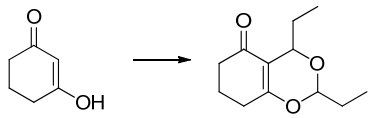
General Procedure I: To a solution of **2.7.11** (~45 mmol) and an aldehyde (3 equiv., ~135 mmol) in DCM (125 mL) at 0 ^oC was added dropwise BF_3-Et_2O (2 equiv., ~90 mmol) over a 5-min. period. The resulting solution was stirred at rt for 5-7h, at which time it was cooled to 0 °C and quenched by the addition of saturated $NaHCO_3$ (20 mL). Standard extractive workup gave the corresponding substituted 1,3-dioxin vinylogous ester **2.8.1**.



2.7.1 2.8.1A

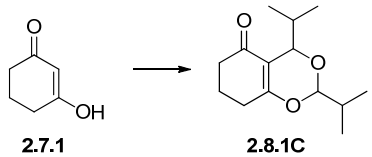
Preparation of 2,4-dimethyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.1A): 2.7.1 (5.00 g, 45 mmol) was reacted with acetaldehyde according to general procedure I. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 6.5 g (81%) of **2.8.1A** as a clear colorless oil which was homogeneous by TLC analysis but consisted

of a mixture of two diastereomers by ^{1}H and ^{13}C NMR analysis [R_f (**2.8.1A**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.26 (q, *J* = 5.1 Hz) and 5.03 (q, *J* = 5.1 Hz) (1H), 4.66-4.79 (m, 1H), 2.41 (t, *J* = 6.0 Hz, 2H), 2.36 (t, *J* = 6.7 Hz, 2H), 1.99 (pentet, *J* = 6.3 Hz, 2H), 1.38-1.53 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.1, 170.9 + 169.9, 116.7 + 115.5, 97.1 + 91.9, 70.5 + 67.6, 37.2 + 37.1, 28.1 + 28.0, 20.8, 20.3 + 20.1, 19.9 + 19.8.



2.7.1 **2.8.1B**

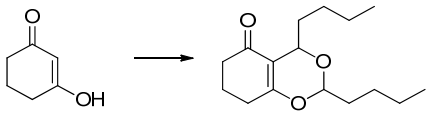
Preparation of 2,4-diethyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.1B): **2.7.1** (5.00 g, 45 mmol) was reacted with propionaldehyde according to general procedure I and silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 8.7 g (93%) of **2.8.1B** as a clear colorless oil which was homogeneous by TLC analysis analysis but consisted of a mixture of two diastereomers by ^{1}H and ^{13}C NMR analysis [R_f (**2.8.1B**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.00 (t, *J* = 5.1 Hz) and 4.81 (t, *J* = 4.9 Hz) (1H), 4.60 (d, *J* = 6.2 Hz) and 4.45 (d, *J* = 10.7 Hz) (1H), 2.25-2.56 (m, 6H), 1.90-2.01 (m, 2H), 1.73-1.84 (m, 2H), 0.97-1.10 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.6 + 196.5, 172.3 + 170.4, 117.6 + 115.1, 100.7, 95.6, 74.6, 73.0, 37.3 + 37.1, 28.4 + 28.1, 27.3 + 27.1, 26.0 + 25.8, 20.9, 20.2 + 20.1.



2.7.1 **2.8.1C**

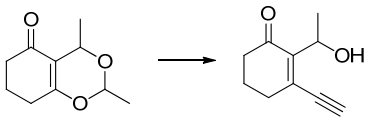
Preparation of 2,4-diisopropyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.1C): **2.7.1** (5.00 g, 45 mmol) was reacted with isobutyraldehyde according to general procedure I. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 9.2 g (86%) of **2.8.1C** as a clear colorless oil which was homogeneous by TLC analysis

analysis but consisted of a mixture of two diastereomers by ^{1}H and ^{13}C NMR analysis [R_f (**2.8.1C**) = 0.55, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.92 (d, *J* = 5.0 Hz) and 4.59 (d, *J* = 4.2 Hz) (1H), 4.53 (s) and 4.36 (d, *J* = 7.0 Hz) (1H), 2.21-2.50 (m, 4H), 1.89-1.99 (m, 4H) 0.64-1.09 (m, 12H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.2 + 196.0, 172.5 + 170.3, 114.9 + 113.7, 102.6 + 99.3, 77.3 + 74.9, 37.4 + 37.2, 32.2 + 32.1, 29.2, 28.5, 20.6 + 20.2, 19.5, 19.1 + 19.0, 16.9 + 16.5, 16.4 + 16.3, 14.6.



2.7.1 **2.8.1D**

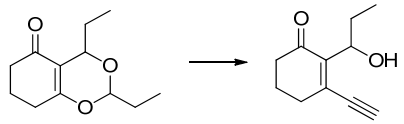
Preparation of 2,4-dibutyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.1D): **2.7.1** (5.00 g, 45 mmol) was reacted with pentanal according to general procedure I. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 10.3 g (87%) of **2.8.1D** as a clear colorless oil which was homogeneous by TLC analysis but consisted of a mixture of two diastereomers by ^{1}H and ^{13}C NMR analysis [R_f (**2.8.1D**) = 0.58, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.07 (t, *J* = 5.1 Hz) and 4.84 (t, *J* = 5.1 Hz)(1H), 4.61 (d, *J* = 7.2 Hz) and 4.54 (d, *J* = 10.2 Hz)(1H), 2.28-2.47 (m, 4H), 1.68-2.07 (m, 4H), 1.24-1.54 (m, 8H), 0.82-0.99 (m, 6H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.4, 171.7 + 170.1, 115.7 + 115.2, 100.1 + 94.8, 74.1 + 71.7, 37.4 + 37.2, 33.8 + 33.6, 32.8 + 32.7, 28.4 + 28.2, 27.7 + 27.0, 25.8 + 25.7, 22.8 + 22.5, 22.6 + 22.5, 20.9 + 20.2, 14.2 +14.2, 14.0 + 14.0.



2.8.1A **2.8.2A**

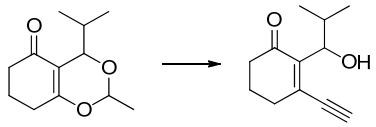
Preparation of 3-ethynyl-2-(1-hydroxyethyl)cyclohex-2-enone (2.8.2A): 2.8.1A (4.40 g, 24 mmol) was reacted according to general procedure F. Purification using silica gel

chromatography (elution with pet ether/EtOAc = 2:1) gave 3.49 (88%) of **2.8.2A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.2A**) = 0.38, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.87-4.99 (m, 1H), 3.94 (d, *J* = 11.4 Hz, 1H), 3.83 (s, 1H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.47 (t, *J* = 6.2 Hz, 2H), 1.95-2.06 (m, 3H), 1.42 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.4, 144.7, 137.1, 93.2, 80.8, 68.8, 38.7, 31.1, 23.2, 22.2.



2.8.1B **2.8.2B**

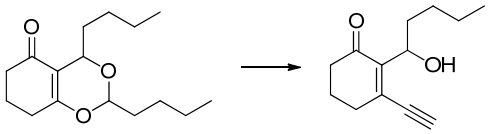
Preparation of 3-ethynyl-2-(1-hydroxypropyl)cyclohex-2-enone (2.8.2B): 2.8.1B (4.90 g, 23 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 3.69 g (86%) of **2.8.2B** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.2B**) = 0.47, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.55-4.69 (m, 2H), 3.80 (s, 1H), 3.74 (d, *J* = 11.4 Hz, 1H), 2.54 (t, *J* = 6.0 Hz, 2H), 2.47 (t, *J* = 6.2 Hz, 2H), 1.93-2.04 (m, 2H), 1.73-1.85 (m, 1H), 1.63-1.72 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.7, 143.8, 138.0, 92.8, 81.1, 74.4, 38.8, 31.3, 30.3, 22.3, 10.8.



2.8.1C **2.8.2C**

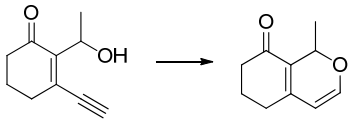
Preparation of 3-ethynyl-2-(1-hydroxy-2-methylpropyl)cyclohex-2-enone (2.8.2C): 2.8.1C (4.10 g, 20 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 3.57 g (96%) of **2.8.2C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.2C**) = 0.50, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.35 (t, *J* = 9.5 Hz, 1H), 3.79 (s, 1H), 3.64 (d, *J* =

11.4 Hz, 1H), 2.55 (t, *J* = 5.8 Hz, 2H), 2.47 (t, *J* = 6.7 Hz, 2H), 1.85-2.07 (m, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.9, 143.3, 138.9, 92.7, 81.5, 78.7, 38.9, 34.4, 31.5, 22.3, 16.6, 16.5.



2.8.1D **2.8.2D**

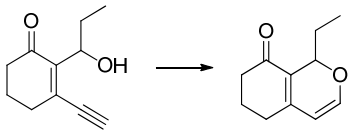
Preparation of 3-ethynyl-2-(1-hydroxypentyl)cyclohex-2-enone (2.8.2D): 2.8.1D (4.30 g, 16 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 2.95 g (89%) of **2.8.2D** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.2D**) = 0.53, 2:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.65-4.76 (m, 1H), 3.81 (s, 1H), 3.73 (d, *J* = 11.4 Hz, 1H), 2.53 (t, *J* = 5.9 Hz, 2H), 2.46 (t, *J* = 6.2 Hz, 2H), 1.97-2.05 (m, 2H), 1.75-1.82 (m, 1H), 1.55-1.64 (m, 1H), 1.40-1.50 (m, 1H), 1.25-1.33 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.7, 144.2, 137.7, 92.8, 81.1, 72.9, 38.9, 37.0, 31.3, 28.3, 22.6, 22.3, 14.2.



2.8.2A **2.8.3A**

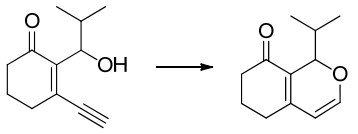
Preparation of 1-methyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.3A): 2.8.2A (1.60 g, 9.8 mmol) was reacted according to general procedure G in DCE, except that the cyclization was performed at rt for 24 hours. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.07 g (67%) of **2.8.3A** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.3A**) = 0.38, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.63 (d, *J* = 5.4 Hz, 1H), 5.43 (q, *J* = 6.4 Hz, 1H), 5.21 (d, *J* = 5.4 Hz, 1H), 2.29-2.47 (m, 5H), 1.95-

2.06 (m, 2H), 1.28 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.0, 150.7, 148.4, 122.5, 103.6, 69.9, 37.8, 28.3, 22.4, 18.8.



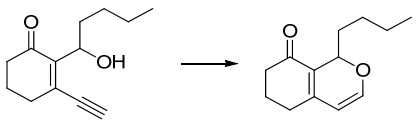
2.8.2B **2.8.3B**

Preparation of 1-ethyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.3B): 2.8.2B (1.30 g, 7.3 mmol) was reacted according to general procedure G in DCE, except that the cyclization was performed at rt for 24 hours. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.0 g (51%) of **2.8.3B** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.3B**) = 0.38, 4:1 pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.65 (d, *J* = 5.4 Hz, 1H), 5.18-5.25 (m, 2H), 2.29-2.48 (m, 4H), 1.98-2.05 (m, 2H), 1.79-1.91 (m, 1H), 1.39-1.47 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.1, 150.9, 148.9, 121.6, 104.0, 74.8, 37.8, 28.4, 25.9, 22.4, 9.84.



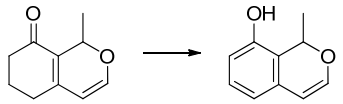
2.8.2C **2.8.3C**

Preparation of 1-isopropyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.3C): 2.8.2C (1.10 g, 5.7 mmol) was reacted according to general procedure G in DCE, except that the cyclization was performed at rt for 24 hours. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 760 mg (69%) of **2.8.3C** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.3C**) = 0.41, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.70 (d, *J* = 5.4 Hz, 1H), 5.19 (d, *J* = 5.4 Hz, 1H), 5.09 (d, *J* = 7.3 Hz, 1H), 2.26-2.57 (m, 4H), 1.91-2.17 (m, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.5, 151.8, 149.4, 120.3, 104.1, 78.1, 37.9, 31.5, 28.7, 22.2, 18.4, 18.1.



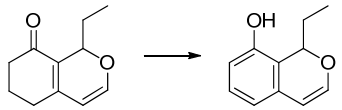
2.8.2D 2.8.3D

Preparation of 1-butyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.3D): 2.8.2D (1.30 g, 6.3 mmol) was reacted according to general procedure G in DCE, except that the cyclization was performed at rt for 24 hours. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 900 mg (69%) of **2.8.3D** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.3D**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.64 (d, *J* = 5.4 Hz, 1H), 5.21-5.33 (m, 1H), 5.21 (d, *J* = 5.4 Hz, 1H), 2.28-2.49 (m, 5H), 1.77-2.08 (m, 4H), 1.21-1.50 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 196.1, 150.8, 148.7, 121.8, 104.0, 73.6, 37.8, 32.4, 28.4, 27.5, 22.7, 22.4, 14.2.



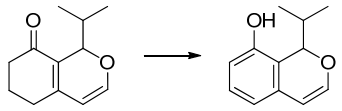
2.8.3A 2.8.4A

Preparation of 1-methyl-1H-isochromen-8-ol (2.8.4A): 2.8.3A (523 mg, 3 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 479 mg (93%) of **2.8.4A** as a red oil which was homogeneous by TLC analysis [R_f (**2.8.4A**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.04 (t, *J* = 7.8 Hz, 1H), 6.57 (t, *J* = 6.9 Hz, 2H), 6.45 (d, *J* = 5.7 Hz, 1H) 5.60-5.72 (m, 3H), 1.48 (d, *J* = 4.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 150.5, 143.7, 130.4, 128.5, 119.3, 116.3, 114.1, 103.8, 69.2, 19.7.



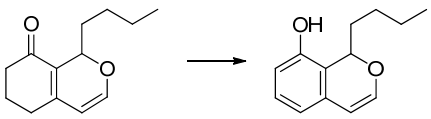
2.8.3B 2.8.4B

Preparation of 1-ethyl-1H-isochromen-8-ol (2.8.4B): 2.8.3B (379 mg, 2 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 350 mg (93%) of **2.8.4B** as a red oil which was homogeneous by TLC analysis [R_f (**2.8.4B**) = 0.42, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.05 (t, *J* = 7.7 Hz, 1H), 6.57 (m, 2H), 6.4 (d, *J* = 5.7 Hz, 1H), 5.71 (d, *J* = 5.7 Hz), 5.45 (dd, *J* = 9.2, 4.0 Hz, 1H), 5.07 (s, 1H), 1.99-2.07 (m, 1H), 1.55-1.66 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 150.6, 143.9, 130.9, 128.5, 118.4, 116.5, 114.1, 104.3, 74.3, 26.8, 10.4.



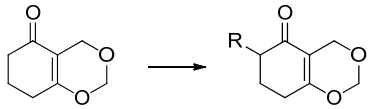
2.8.3C 2.8.4C

Preparation of 1-isopropyl-1H-isochromen-8-ol (2.8.4C): 2.8.3C (451 mg, 2 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 415 mg (93%) of **2.8.4C** as a red oil which was homogeneous by TLC analysis [R_f (**2.8.4C**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.06 (t, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 6.1 Hz, 1H), 5.70 (d, *J* = 5.7 Hz, 1H), 5.24 (d, *J* = 7.2 Hz, 1H), 5.19 (bs, 1H), 2.31 (sextet, *J* = 6.9 Hz, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CHCl_3$) δ 151.3, 144.7, 131.4, 128.6, 117.0, 116.4, 114.2, 104.7, 77.8, 32.3, 18.8, 18.7.



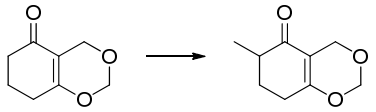
2.8.3D **2.8.4D**

Preparation of 1-butyl-1H-isochromen-8-ol (2.8.4D): 2.8.3D (610 mg, 3 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 550 mg (91%) of **2.8.4D** as a red oil which was homogeneous by TLC analysis [R_f (**2.8.4D**) = 0.50, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.05 (t, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 6.7 Hz, 1H), 6.49 (d, *J* = 5.7 Hz, 1H), 5.74 (d, *J* = 5.78 Hz, 1H), 5.70 (bs, 1H), 5.57 (dd, *J* = 9.7, 2.6 Hz, 1H), 2.08-2.17 (m, 2H), 1.29-1.64 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 150.7, 143.6, 130.8, 128.5, 118.8, 116.4, 114.2, 104.6, 73.1, 32.2, 28.0, 22.7, 14.3.



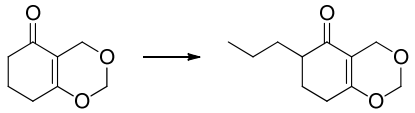
2.7.12 **2.8.6**

General Procedure J: To a solution of **2.7.12** (~25 mmol) in THF (50 mL) at -78 °C was added dropwise a solution of LDA (1.8M, 1.2 equiv., 30 mmol) over a 5-min. period. The resulting solution was stirred at -78 °C for 30-min., at which time a corresponding alkylating agent (1.4, equiv., ~35 mmol) in THF (10 mL) was added dropwise over 1-min. The resulting solution was allowed to stir at -78 °C for 1h, then warmed to -30 °C over 30-min., then stirred at -30 °C for 1h. The reaction was then quenched by the addition of saturated NH_4Cl (10 mL). Standard extractive workup, followed by silica gel chromatography gave crude **2.8.6**.



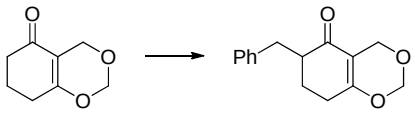
2.7.12 2.8.6A

Preparation of 6-methyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.6A): **2.7.12** (4.10 g, 27 mmol) was reacted with iodomethane according to general procedure J. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 4.16 g (93%) of **2.8.6A** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.8.6A**) = 0.32, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.18 (d, *J* = 5.4 Hz, 1H), 5.07 (d, *J* = 5.4 Hz, 1H), 4.43 (dq, *J* = 14.8, 9.7 Hz, 2H), 2.27-2.55 (m, 3H), 1.98-2.09 (m, 1H), 1.66-1.79 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.7, 169.5, 111.1, 91.5, 63.1, 40.0, 28.8, 27.1, 15.3.



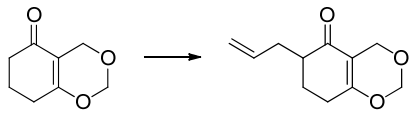
2.7.12 2.8.6B

Preparation of 6-propyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.6B): **2.7.12** (4.20 g, 27 mmol) was reacted with *n*-propyl iodide according to general procedure J, but the temperature was increased from -30 °C to rt until no further reaction was observed by TLC analysis. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.4 g (61% brsm, 73% conversion,) of **2.8.6B** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.8.6B**) = 0.47, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.16 (d, *J* = 5.4 Hz, 1H), 5.09 (d, *J* = 5.4 Hz, 1H), 4.43 (s, 2H), 2.33-2.48 (m, 2H), 2.16-2.27 (m, 1H), 2.04-2.13 (m, 1H), 1.71-1.82 (m, 2H), 1.30-1.39 (m, 3H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 198.4, 169.2, 111.2, 91.4, 63.0, 44.7, 31.6, 26.6, 25.7, 20.3, 14.2.



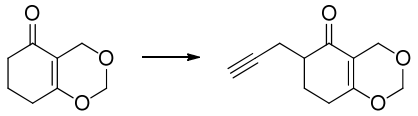
2.7.12 **2.8.6C**

Preparation of 6-benzyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.6C): **2.7.12** (4.10 g, 27 mmol) was reacted with benzylbromide according to general procedure J. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 5.93 g (91%) of **2.8.6C** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.8.6C**) = 0.38, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.23-7.33 (m, 2H), 7.10-7.20 (m, 3H), 5.18 (d, *J* = 5.4 Hz, 1H), 5.08 (d, *J* = 5.4 Hz, 1H), 4.46 (dq, *J* = 14.6, 6.1 Hz, 2H), 3.37 (dq, *J* =9.6, 8.4 Hz, 1H), 2.40-2.52 (m, 2H), 2.34-2.43 (m, 2H), 1.87-1.99 (m, 1H), 1.59-1.70 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 197.0, 169.7, 140.1, 129.6, 128.6, 126.3, 111.3, 91.6, 63.1, 46.9, 35.7, 27.0, 25.2.



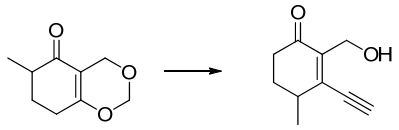
2.7.12 **2.8.6D**

Preparation of 6-allyl-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.6D): **2.7.12** (4.20 g, 27 mmol) was reacted with allyl bromide according to general procedure J. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 4.91 g (93%) of **2.8.6D** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.8.6D**) = 0.44, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.76 (septet, *J* = 7.4, 1H), 5.18 (d, *J* = 5.4 Hz, 1H), 5.02-5.12 (m, 3H), 4.44 (dd, *J* = 15.0, 3.8 Hz, 2H), 2.60-2.71 (m, 1H), 2.41-2.49 (m, 2H), 2.22-2.35 (m, 1H), 2.05-2.16 (m, 2H), 1.68-1.81 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 197.2, 169.6, 136.3, 116.9. 111.3, 91.5, 63.0, 44.5, 34.0, 26.9, 25.4.



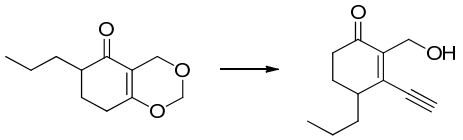
2.7.12 2.8.6E

Preparation of 6-(prop-2-yn-1-yl)-7,8-dihydro-4H-benzo[d][1,3]dioxin-5(6H)-one (2.8.6E): 2.7.12 (4.10 g, 27 mmol) was reacted with propargyl bromide according to general procedure J. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 4.68 g (90%) of **2.8.6E** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.8.6E**) = 0.32, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.21 (d, *J* = 5.4, 1H), 5.07 (d, *J* = 5.4, 1H), 4.43 (q, *J* = 17.4 Hz, 2H), 2.71-2.83 (m, 1H), 2.36-2.60 (m, 2H), 2.25-2.36 (m, 2H), 1.80-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.5, 170.1, 111.2, 91.6, 82.3, 70.2, 62.9, 43.9, 27.3, 25.7, 19.1.



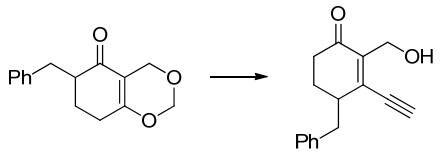
2.8.6A 2.8.5A

Preparation of 3-ethynyl-2-(hydroxymethyl)-4-methylcyclohex-2-enone (2.8.5A): 2.8.6A (3.7 mg, 22 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 3.34 g (92%) of **2.8.5A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.5A**) = 0.35, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.49 (d, *J* = 5.4, Hz, 2H), 3.83 (s, 1H), 2.90-3.02 (m, 1H), 2.50-2.65 (m, 2H) 2.37-2.48 (m, 1H), 2.10-2.21 (m, 1H), 1.69-1.79 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.8, 144.1, 141.4, 93.4, 80.1, 59.9, 35.8, 34.4, 29.8, 19.1.



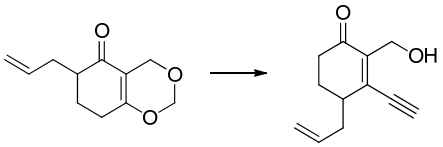
2.8.6B 2.8.5B

Preparation of 3-ethynyl-2-(hydroxymethyl)-4-propylcyclohex-2-enone (2.8.5B): **2.8.6B** (2.80 g, 14 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.45 g (89%) of **2.8.5B** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.5B**) = 0.45, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.50 (s, 2H), 3.84 (s, 1H), 2.95 (bs, 1H), 2.44-2.53 (m, 2H), 2.34-2.41 (m, 1H), 2.06-2.15 (m, 1H), 1.79-1.88 (m, 2H), 1.43-1.50 (m, 2H), 1.30-1.39 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.0, 143.7, 141.7, 93.2, 80.4, 60.3, 39.2, 35.3, 34.6, 26.1, 20.6, 14.2.



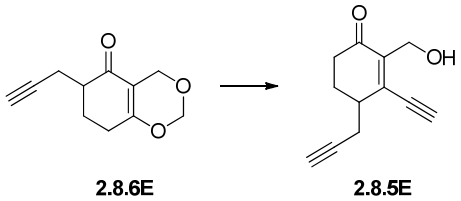
2.8.6C 2.8.5C

Preparation of 4-benzyl-3-ethynyl-2-(hydroxymethyl)cyclohex-2-enone (2.8.5C): **2.8.6C** (4.15 g, 17 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 3.36 g (82%) of **2.8.5C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.5C**) = 0.48, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.29-7.39 (m, 2H), 7.16-7.23 (m, 3H), 4.57 (d, *J* = 6.0 Hz, 2H), 3.93 (s, 1H), 3.39 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.95 (bs, 1H), 2.69-2.81 (m, 1H), 2.49-2.70 (m, 2H), 2.30-2.39 (m, 1H), 1.92-2.02 (m, 1H), 1.69-1.78 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.7, 142.4, 142.4, 139.3, 129.2, 128.8, 126.8, 93.8, 80.3, 60.2, 41.4, 38.7, 35.1, 25.5.



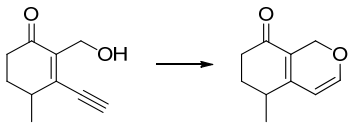
2.8.6D 2.8.5D

Preparation of 4-allyl-3-ethynyl-2-(hydroxymethyl)cyclohex-2-enone (2.8.5D): **2.8.6D** (3.30 g, 17 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.93 g (91%) of **2.8.5D** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.5D**) = 0.48, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.77 (sextet, *J* = 9.3 Hz, 1H), 5.09-5.16 (m, 2H), 4.50 (d, *J* = 14.6, 2H), 2.95 (t, *J* = 6.5 Hz, 1H), 2.57-2.64 (m, 1H), 2.50-2.61 (m, 2H), 2.33-2.41 (m, 1H), 2.22-2.31 (m, 1H), 2.06-2.13 (m, 1H), 1.80-1.89 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.7, 142.5, 142.2, 135.5, 117.9, 93.7, 80.1, 59.9, 39.0, 37.0, 35.4, 25.9.



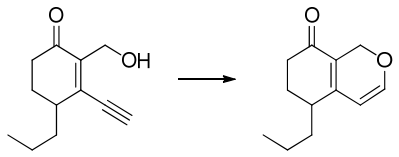
2.8.6E 2.8.5E

Preparation of 3-ethynyl-2-(hydroxymethyl)-4-(prop-2-yn-1-yl)cyclohex-2-enone (2.8.5E): **2.8.6E** (3.10 g, 16 mmol) was reacted according to general procedure F. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 2.6 g (85%) of **2.8.5E** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.5E**) = 0.35, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.52 (d, *J* = 5.8 Hz, 2H), 3.87 (s, 1H), 2.90 (bs, 1H), 2.73-2.81 (m, 1H), 2.58-2.73 (m, 2H), 2.39-2.56 (m, 2H), 2.23-2.32 (m, 1H), 2.02-2.10 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 199.5, 142.9, 140.3, 93.9, 81.3, 79.4, 71.2, 60.3, 38.4, 35.9, 26.5, 22.9.



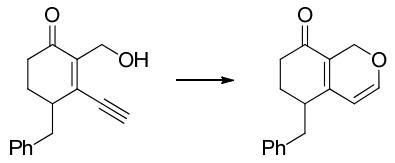
2.8.5A 2.8.7A

Preparation of 5-methyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.7A): 2.8.5A (1.50 g, 9 mmol) was reacted according to general procedure G in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.16 g (78%) of **2.8.7A** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.7A**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.80 (d, *J* = 5.5 Hz, 1H), 5.40 (d, *J* = 5.5 Hz, 1H), 4.84 (dd, *J* = 3.2, 16.3, Hz, 2H), 2.41-2.56 (m, 2H), 2.28-2.36 (m, 1H), 2.09-2.18 (m, 1H), 1.70-1.78 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.8, 153.3, 153.6, 116.7, 104.0, 63.3, 34.9, 31.7, 29.8, 18.3.



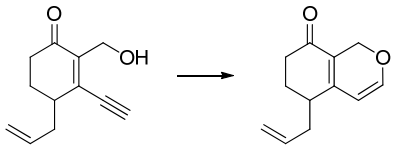
2.8.5B 2.8.7B

Preparation of 5-propyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.7B): 2.8.5B (1.10 g, 6 mmol) was reacted according to general procedure G in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 910 mg (83%) of **2.8.7B** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.7B**) = 0.11, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.77 (d, *J* = 5.5 Hz, 1H), 5.37 (d, *J* = 5.5 Hz, 1H), 4.83 (s, 2H), 2.42-2.53 (m, 1H), 2.23-2.31 (m, 2H), 2.01-2.11 (m, 1H), 1.83-1.92 (m, 1H), 1.29-1.61 (m, 4H), 0.94 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.8, 154.1, 153.3, 116.9, 104.6, 63.3, 36.6, 34.1, 34.0, 26.0, 20.9, 14.3.



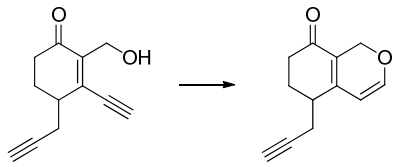
2.8.5C 2.8.7C

Preparation of 5-benzyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.7C): 2.8.5C (1.20 g, 5 mmol) was reacted according to general procedure G in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.01mg (85%) of **2.8.7C** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.7C**) = 0.42, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.29 (t, *J* = 7.3 Hz, 2H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 6.76 (d, *J* = 5.4 Hz, 1H), 5.33 (d, *J* = 5.4 Hz, 1H), 4.84 (q, *J* = 10.8 Hz, 2H), 2.97 (dd, *J* = 4.1, 13.1 Hz, 1H), 2.39-2.69 (m, 3H), 2.27 (dt, *J* = 4.8, 17.4 Hz, 1H), 1.88-1.96 (m, 1H), 1.70-1.81 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.5, 153.5, 153.0, 139.5, 129.2, 128.8, 126.8, 117.3, 104.6, 63.4, 38.7, 38.3, 33.8, 25.6.



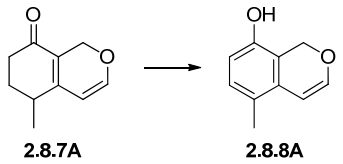
2.8.5D 2.8.7D

Preparation of 5-allyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.7D): 2.8.5D (1.6 mg, 7 mmol) was reacted according to general procedure G in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.42 g (90%) of **2.8.7D** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.7D**) = 0.12, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.80 (d, *J* = 6.8 Hz, 1H), 5.71-5.82 (m, 1H), 5.42 (d, *J* = 5.5 Hz, 1H), 5.13 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 1H), 4.86 (s, 2H), 2.20-2.55 (m, 5H), 2.01-2.09 (m, 1H), 1.88-1.95 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 192.7, 153.5, 152.9, 135.9, 117.7, 117.4, 104.3, 63.3, 36.5, 36.4, 34.2, 26.0.



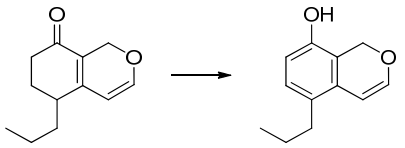
2.8.5E 2.8.7E

Preparation of 5-(prop-2-yn-1-yl)-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.7E): 2.8.5E (1.70 g, 7 mmol) was reacted according to general procedure G in DCE. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.54 g (91%) of **2.8.7E** as a clear yellow oil which was homogeneous by TLC analysis [R_f (**2.8.7E**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.82 (d, *J* = 5.2 Hz, 1H), 5.44 (d, *J* = 5.2 Hz, 1H), 4.84 (s, 2H), 2.20-2.64 (m, 4H), 1.93-2.24 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.2, 153.8, 151.1, 117.7, 103.7, 81.7, 70.9, 63.3, 36.0, 34.4, 26.7, 22.0.



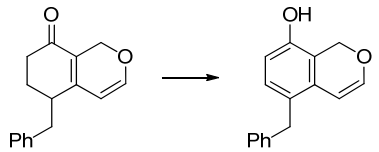
2.8.7A 2.8.8A

Preparation of 5-methyl-1H-isochromen-8-ol (2.8.8A): 2.8.7A (740 mg, 5 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 670 mg (92%) of **2.8.8A** as a red oil which was homogeneous by TLC analysis [R_f (**2.8.8A**) = 0.30, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.89 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 5.8 Hz, 1H), 6.50 (d, *J* = 8.2 Hz, 1H), 5.89 (d, *J* = 5.9 Hz, 1H), 5.24 (bs, 1H), 5.18 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 148.7, 146.3, 129.9, 129.9, 123.4, 114.6, 113.9, 102.9, 63.2, 17.9.



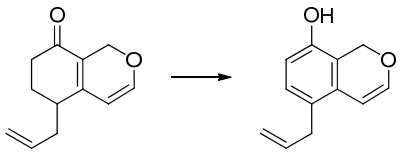
2.8.7B 2.8.8B

Preparation of 5-propyl-1H-isochromen-8-ol (2.8.8B): 2.8.7B (440 mg, 2 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 370 mg (85%) of **2.8.8B** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.8B**) = 0.36, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.88 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 5.9 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 5.89 (d, *J* = 5.9 Hz, 1H), 5.16 (s, 2H), 4.74 (bs, 1H), 2.50 (t, *J* = 7.9 Hz, 2H), 1.50-1.63 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 148.6, 146.4, 129.5, 129.3, 128.3, 114.8, 113.8, 102.6, 63.2, 34.0, 24.4, 14.2.



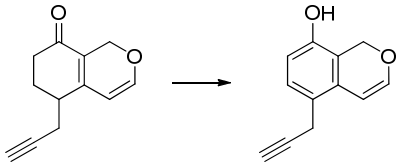
2.8.7C 2.8.8C

Preparation of 5-benzyl-1H-isochromen-8-ol (2.8.8C): 2.8.7C (490 mg, 2 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 390 mg (80%) of **2.8.8C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.8C**) = 0.42, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.90-7.15 (m, 5H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.38 (d, *J* = 6.0 Hz, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 5.65 (d, *J* = 6.0 Hz, 1H), 4.98 (s, 2H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 149.3, 146.8, 141.2, 131.1, 130.3, 128.8, 128.7, 128.6, 128.3, 126.2, 114.1, 102.7, 63.3, 37.7.



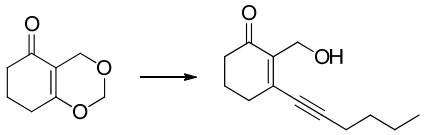
2.8.7D 2.8.8D

Preparation of 5-allyl-1H-isochromen-8-ol (2.8.8D): 2.8.7D (517 mg, 3 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 510 mg (90%) of **2.8.8D** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.8D**) = 0.35, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.89 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 5.9 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 5.86-5.94 (m, 1H), 5.87 (d, *J* = 5.9 Hz, 1H), 5.16 (s, 2H), 5.05 (d, *J* = 10 Hz, 1H), 4.99 (d, *J* = 16.9 Hz, 1H), 4.89 (bs, 1H), 3.30 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 149.1, 146.7, 137.3, 130.0, 129.5, 125.3, 115.8, 114.8, 114.0, 102.5, 63.2, 36.2.



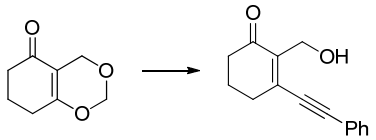
2.8.7E 2.8.8E

Preparation of 5-(prop-2-yn-1-yl)-1H-isochromen-8-ol (2.8.8E): 2.8.7E (600 mg, 3 mmol) was reacted according to general procedure H. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 535 mg (92%) of **2.8.8E** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.8E**) = 0.25, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.13 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 5.8 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.88 (d, *J* = 5.8 Hz, 1H), 5.16 (s, 2H), 5.09 (bs, 1H), 3.46 (s, 2H), 2.18 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 149.6, 147.1, 129.6, 128.7, 121.3, 114.8, 114.0, 101.8, 82.2, 70.8, 63.1, 21.5.



2.7.12 **2.8.10-Hex**

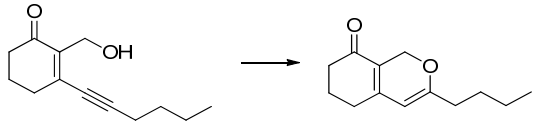
Preparation of 3-(hex-1-yn-1-yl)-2-(hydroxymethyl)cyclohex-2-enone (2.8.10-Hex): To a solution of 1-hexyne (4.4 mL, 38 mmol) in 75 mL of THF at -78 °C was added *n*-butyllithium (13.1 mL, 2.5 *M*, ~33 mmol) over a 2-min.period. The resulting mixture was stirred at -78 °C for 30-min., and then warmed to 0 °C over a 30-min.period. To the resulting solution was added a solution of **2.7.12** (4.20 g, 27 mmol) dissolved in 20 mL of THF via cannulation over a 5-min. period. The resulting reaction mixture was stirred at 0 °C for 1h. The reaction mixture was quenched by the addition of water (20 mL), followed by the portion-wise addition of aqueous 6 *M* HCl (50 mL). After warming the resulting solution to rt, and stirring for 30-min., the resulting solution was subjected to standard extractive workup. Silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 5.02 g (89%) of **2.8.10-Hex** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.8.10-Hex**) = 0.55, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 4.42 (s, 2H), 3.13 (bs, 1H), 2.35-2.43 (m, 6H), 1.90-1.99 (m, 2H), 1.43-1.52 (m, 2H), 1.32-1.40 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.0, 141.5, 139.8, 107.6, 78.9, 59.9, 38.0, 31.8, 30.5, 22.4, 21.1, 19.8, 13.7.



2.7.12 **2.8.10-Ph**

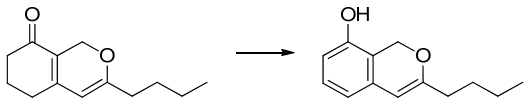
Preparation of 2-(hydroxymethyl)-3-(phenylethynyl)cyclohex-2-enone (2.8.10-Ph): To a solution of phenylacetylene (2.2 mL, 20 mmol) in 50 mL of THF at -78 °C was added *n*-butyllithium (6.9 mL, 2.5 *M*, 17 mmol) over a 2-min. period. The resulting mixture was stirred at -78 °C for 30-min., and then warmed to 0 °C over a 30-min. period. To the resulting solution was

added a solution of **2.7.12** (2.20 g, 14 mmol) dissolved in 10 mL of THF via cannulation over a 5-min. period. The resulting reaction mixture was stirred at 0 °C for 1h. The reaction mixture was quenched by the addition of water (20 mL), followed by the portion-wise addition of aqueous 6 *M* HCl (30 mL). After warming the resulting solution to rt, and stirring for 30-min., the resulting solution was subjected to standard extractive workup. Silica gel chromatography (elution with pet ether/EtOAc = 2:1) gave 2.37 g (73%) of **2.8.10-Ph** as a yellow oil which was homogeneous by TLC analysis [R_f (**2.8.10-Ph**) = 0.57, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.43-7.52 (m, 2H), 7.30-7.41 (m, 3H), 4.62 (s, 2H), 3.03 (bs, 1H), 2.64 (t, *J* = 5.7 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.07 (pentet, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.2, 140.3, 140.2, 132.1, 129.9, 128.8, 122.1, 104.9, 86.9, 60.5, 38.1, 31.5, 22.5.



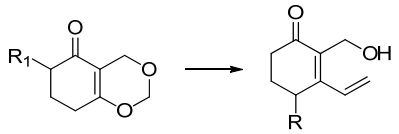
2.8.10-Hex **2.8.11**

Preparation of 3-butyl-6,7-dihydro-1H-isochromen-8(5H)-one (2.8.11): 2.8.10-Hex (1.40 g, 7 mmol) was reacted according to general procedure G in DCE, except that the cyclization was performed at rt for 24 hours. Silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 284 mg (45% brsm, 55% conversion) of **2.8.11** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.11**) = 0.45, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.14 (s, 1H), 4.84 (s, 2H), 2.35 (t, *J* = 6.4 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.15 (t, *J* = 6.2 Hz, 2H), 1.95 (pentet, *J* = 7.6 Hz, 2H), 1.49 (pentet, *J* = 7.5 Hz, 2H), 1.32 (sextet, *J* = 7.5 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 195.5, 167.6, 152.5, 115.6, 101.6, 64.2, 37.6, 33.9, 29.2, 28.3, 22.5, 22.4, 14.0.

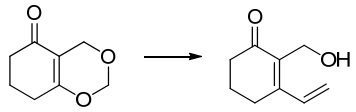


2.8.11 2.8.12

Preparation of 3-butyl-1H-isochromen-8-ol (2.8.12): 2.8.11 (540 mg, 3 mmol) was reacted according to general procedure G. Purification using silica gel chromatography (elution with pet ether/EtOAc = 6:1) gave 470 mg (88%) of **2.8.12** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.8.12**) = 0.43, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.03 (t, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 2H), 5.60 (s, 1H), 5.17 (s, 2H), 4.78 (bs, 1H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.49-1.58 (m, 2H), 1.31-1.40 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 159.3, 150.4, 133.9, 128.6, 115.6, 113.6, 113.2, 100.6, 63.5, 33.6, 29.3, 22.5, 14.0.



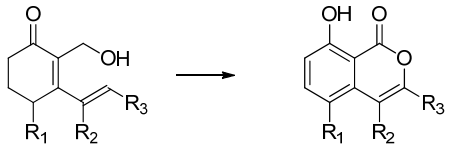
General Procedure K: To a solution of 1,3-dioxin vinylogous ester (~13 mmol) in THF (50 mL) at 0 °C is added a solution of vinylmagnesium bromide (1.0*M,* 1.5 equiv., 20 mmol). The resulting reaction mixture is warmed to rt and stirred at rt for an additional 1h. After cooling to 0 °C, H_2O (20 mL) is added, followed by portionwise addition of 6*M* HCl (30 mL). The resulting solution is allowed to rise to rt and stirred for an additional 1h. Standard extractive workup gave the crude enone.



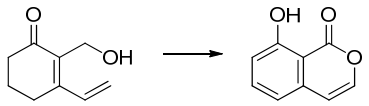
2.7.12 2.7.7

Preparation of 2-(hydroxymethyl)-3-vinylcyclohex-2-enone (2.7.7): 2.7.12 (2.50 g, 16 mmol) was reacted according to general procedure K. Purification using silica gel

chromatography (elution with pet ether/EtOAc = 1:1) gave 2.05 g (82%) of **2.7.7** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.7.7**) = 0.30, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.00 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.76 (d, *J* = 17.4 Hz, 1H), 5.56 (d, *J* = 11.0 Hz, 1H), 4.49 (s, 2H), 2.73 (bs, 1H), 2.57 (t, *J* = 6.0 Hz, 2H), 2.48 (t, *J* = 6.0 Hz, 2H), 2.04 m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.3, 153.4, 134.7, 133.9, 122.5, 55.6, 33.8, 25.8, 21.7.



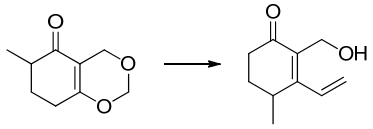
General Procedure L for Isocoumarin Formation: To a solution of dienone (~5 mmol) in 1,4-dioxane (~10 mL) at rt was added DDQ (4 equiv., ~20 mmol) in one portion. The resulting solution was stirred at 110°C until reaction completion. The reaction mixture was diluted with Et_2O (50 mL) and the supernatant was decanted. The remaining solid was rinsed with Et_2O (3 x 10 mL). The combined organic extractions were washed with H_2O (5 x 5 mL), brine (5 mL), and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave the crude isocoumarin.



2.7.7 **2.7.20**

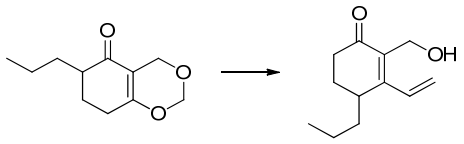
Preparation of 8-hydroxy-1H-isochromen-1-one (2.7.20): 2.7.7 (560 mg, 4 mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 486 mg (81%) of **2.7.20** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.7.20**) = 0.43, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, acetone) δ 11.0 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 5.6 Hz, 1H), 7.01 (d, *J* = 8.3 Hz,

1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.4, 161.9, 144.1, 137.6, 136.9, 110.1, 110.0, 108.6, 107.5.



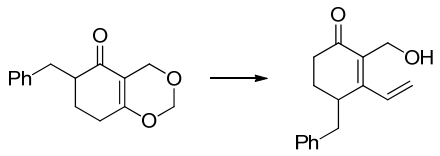
2.8.6A **2.9.40A**

Preparation of 2-(hydroxymethyl)-4-methyl-3-vinylcyclohex-2-enone (2.9.40A): **2.8.6A** (1.70 g, 10 mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.57 g (93%) of **2.9.40A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.40A**) = 0.36, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.84 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.74(d, *J* = 17.4 Hz, 1H), 5.62 (d, *J* = 11.0 Hz, 1H), 4.44 (s, 2H), 2.95 (bs, 1H), 2.76 (bs, 1H), 2.56-2.65 (m, 1H), 2.39-2.48 (m, 1H), 2.09-2.19 (m, 1H), 1.82-1.90 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.6, 158.7, 133.7, 133.0, 126.7, 55.5, 32.7, 28.8, 28.5, 18.4.



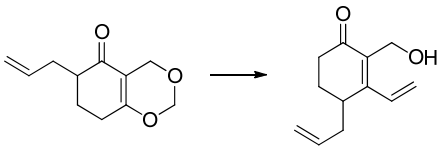
2.8.6B **2.9.40B**

Preparation of 2-(hydroxymethyl)-4-propyl-3-vinylcyclohex-2-enone (2.9.40B): **2.8.6B** (1.20 g, 6mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.1 g (89%) of **2.9.40B** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.40B**) = 0.42, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.84 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.72(d, *J* = 17.4 Hz, 1H), 5.57 (d, *J* = 11.0 Hz, 1H), 4.42 (s, 2H), 2.68-2.95 (m, 2H), 2.48-2.57 (m, 1H), 2.31-2.39 (m, 1H), 1.97-2.06 (m, 2H), 1.28-1.60 (m, 3H), 0.90-0.99 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.0, 157.2, 132.7, 132.0, 121.3, 55.1, 32.7, 32.5, 31.7, 23.1, 20.5, 13.0.



2.8.6C 2.9.40C

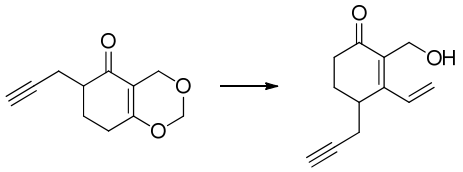
Preparation of 2-(hydroxymethyl)-4-benzyl-3-vinylcyclohex-2-enone (2.9.40C): **2.8.6C** (1.50 g, 6 mmol) was reacted according to general procedure L Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.29 g (88%) of **2.9.40C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.40**) = 0.39, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.30-7.38 (m, 2H), 7.20-7.27 (m, 3H), 6.93 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.91 (d, *J* = 17.4 Hz, 1H), 5.69 (d, *J* = 11.0 Hz, 1H), 4.42-4.52 (s, 2H), 2.97-3.08 (m, 2H), 2.66-2.73 (m, 3H), 2.39-2.48 (m, 1H), 1.57-2.00 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.9, 156.9, 140.0, 134.6, 133.1, 128.9, 128.9, 126.8, 122.8, 37.7, 36.2, 32.8, 23.7, 21.2.



2.8.6D 2.9.40D

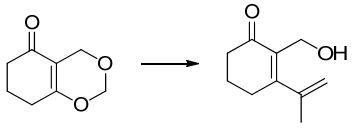
Preparation of 2-(hydroxymethyl)-4-allyl-3-vinylcyclohex-2-enone (2.9.40D): 2.8.6D (1.60 g, 8 mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.49 g (94%) of **2.9.40D** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.40D**) = 0.39, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.82 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.70-5.78 (m, 1H), 5.69 (d, *J* = 17.4 Hz, 1H), 5.54 (d, *J* = 11.0 Hz, 1H), 5.05 (d, *J* = 8.0 Hz, 1H), 5.01 (s, 1H), 4.35 (s, 2H), 3.05 (bs, 1H), 2.72-2.80 (m, 1H), 2.43-2.52 (m, 1H), 2.28-2.35 (m, 2H), 2.15-2.23

(m, 1H), 1.94-2.02 (m, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.8, 157.2, 136.5, 134.4, 133.0, 122.7, 117.2, 55.9, 36.0, 33.9, 32.7, 24.2.



2.8.6E **2.9.40E**

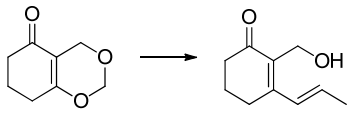
Preparation of 2-(hydroxymethyl)-4-(prop-2-yn-1-yl)-3-vinylcyclohex-2-enone (2.9.40E): 2.8.6E (1.80 g, 9 mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 1.46 g (82%) of **2.9.40E** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.40E**) = 0.36, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.84 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.76 (d, *J* = 17.4 Hz, 1H), 5.62 (d, *J* = 11.0 Hz, 1H), 4.41 (s, 2H), 2.94-3.02 (m, 1H), 1.94-2.77 (m, 8H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.3, 155.1, 134.9, 132.6, 122.9, 82.1, 70.9, 55.8, 33.6, 32.8, 24.9, 21.7.



2.7.12 **2.9.35**

Preparation of 2-(hydroxymethyl)-3-(prop-1-en-2-yl)cyclohex-2-enone (2.9.35): To a suspension of Mg metal (1.00 g, 40 mmol), 2-bromopropene (360 μL, 4 mmol) and an I_2 crystal in THF (30 mL) was dropwise added a solution of 2-bromopropene (3.3 mL, 36 mmol) in THF (10 mL) at such a rate as to maintain a gentle reflux. Once the Mg is consumed, the solution of propenyl magnesium bromide was cannulated to a solution of **2.7.12** (3.00 g, 19 mmol) in THF (10 mL) at 0 °C. The resulting reaction mixture is allowed to rise to rt and stirred at rt for an additional 1h. After cooling to 0 °C, H_2O is added, followed by 6*M* HCl (15 mL). The resulting

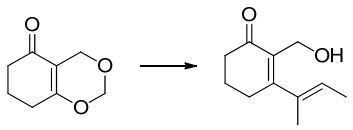
solution is allowed to rise to rt and stirred for an additional 1h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 1:1), gave 2.3 g (71%) of **2.9.35** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.35**) = 0.38, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.08 (s, 1H), 4.84 (s, 1H), 4.32 (s, 2H), 2.45 (t, *J* = 6.3 Hz, 4H), 1.97-2.06 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 200.9, 162.4, 143.4, 132.9, 114.6, 57.8, 37.8, 29.9, 22.3, 21.7.



2.7.12 **2.9.37**

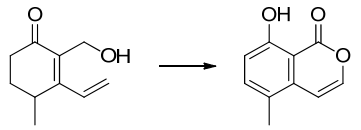
Preparation of 2-(hydroxymethyl)-3-(prop-1-en-1-yl)cyclohex-2-enone (2.9.37): To a suspension of Li metal (222 mg, 37 mmol), 1-bromopropene (310 μL, 4 mmol, ~1:1 E:Z mixture) and an I_2 crystal in THF (30 mL) was dropwise added a solution of 1-bromopropene (2.8 mL, 33 mol) in THF (10 mL) at such a rate as to maintain a gentle reflux. Once the Li is consumed, the solution of 1-propenyl lithium was cannulated to a solution of **2.7.12** (2.70 g, 18 mmol) in THF (10 mL) at 0 °C. The resulting reaction mixture is allowed to rise to rt and stirred at rt for an additional 1h. After cooling to 0 °C, H_2O is added, followed by 6*M* HCl (15 mL). The resulting solution is allowed to rise to rt and stirred for an additional 1h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 1:1), gave 2.0 g (68%) of **2.9.37** as a clear colorless oil of two components (**NP**: nonpolar component; **P**: polar component) by TLC analysis [R_f (**2.9.37NP**) = 0.29, 1:1, pet ether/EtOAc, R_f (**2.9.37P**) = 0.38, 1:1, pet ether/EtOAc]. **NP** ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.02 (d, *J* = 11.7 Hz, 1H), 5.71-5.80 (m, 1H), 4.24 (s, 2H), 3.01-3.09 (m, 1H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.37 (t, *J* = 6.4 Hz, 2H), 1.93-2.00 (m, 2H), 1.59 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.6, 156.0, 134.0, 130.1, 128.2, 59.1, 38.2, 31.1, 22.5, 15.4. **P** ^{1}H NMR (400 MHz, $CHCl_3$) δ 6.68 (d, *J* = 15.5Hz,

1H), 6.28 (m, 1H), 4.41 (s, 2H), 2.92-3.01 (m, 1H), 2.44-2.52 (m, 2H), 2.35-2.42 (m, 2H), 1.89-1.95 (m, 2H), 1.88 (d, *J* = 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.4, 153.8, 135.9, 132.9, 128.8, 56.0, 37.9, 26.5, 21.9, 19.6.



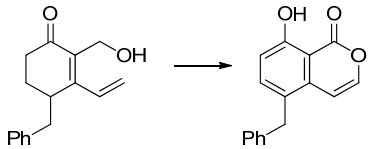
2.7.12 **2.9.39**

Preparation of 3-(but-2-en-2-yl)-2-(hydroxymethyl)cyclohex-2-enone (2.9.39): To a suspension of Li metal (205 mg, 34 mmol), 2-bromo-2-butene (350 μL, 3 mmol, ~3:1 E:Z mixture) and an I_2 crystal in THF (30 mL) was dropwise added a solution of 2-bromo-2-butene (3.1 mL, 30 mmol) in THF (10 mL) at such a rate as to maintain a gentle reflux. Once the Li is consumed, the solution of 2-butenyl lithium was cannulated to a solution of **2.7.12** (2.50 g, 16 mol) in THF (10 mL) at 0 °C. The resulting reaction mixture is allowed to rise to rt and stirred at rt for an additional 1h. After cooling to 0 °C, H_2O is added, followed by 6*M* HCl (15 mL). The resulting solution is allowed to rise to rt and stirred for an additional 1h. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/EtOAc = 1:1), gave 2.2 g (75%) of **2.9.39** as a clear colorless oil which was homogeneous by TLC analysis but consisted of two components by ^{1}H and ^{13}C NMR analysis [R_f (**2.9.39**) = 0.44, 1:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.23-5.31 (m, 1H), 4.17 + 4.06 (s, 2H), 3.06 (bs, 1H), 2.28-2.42 (m, 4H), 1.87-1.99 (m, 2H), 1.73 + 1.68 (s, 2H), 1.59 (d, *J* = 6.7 Hz) + 1.36 (d, *J* = 6.6 Hz)(3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.4, 161.2, 135.2, 133.4, 121.5, 58.8, 38.1, 38.0, 29.7, 22.6, 22.4.



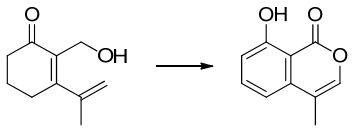
2.9.40 2.9.41

Preparation of 8-hydroxy-5-methyl-1H-isochromen-1-one (2.9.41A): 2.9.40A (606 mg, 4 mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 277 mg (43%) of **2.9.41 A** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.41A**) = 0.49, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 10.98 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 6.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.7, 160.1, 143.7, 138.9, 134.7, 123.3, 115.6, 107.4, 105.6, 17.9.



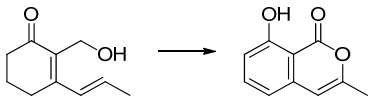
2.9.40 2.9.41

Preparation of 8-hydroxy-5-benzyl-1H-isochromen-1-one (2.9.41C): 2.9.40C (710 mg, 3 mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 248 mg (33%) of **2.9.41C** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.41C**) = 0.53, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.63 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 6.8 Hz, 1H), 7.42 (t, *J* = 6.8 Hz, 2H), 7.21 (d, *J* = 5.6 Hz, 1H), 7.10 (d, *J* = 6.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 3.63 (s, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.4, 164.6, 145.6, 140.2, 138.1, 137.7, 133.5, 130.3, 128.9, 124.8, 114.9, 108.1, 106.2, 67.3.



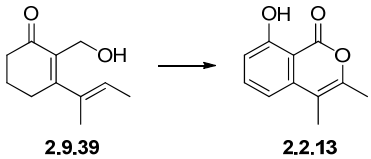
2.9.35 2.9.36

Preparation of 8-hydroxy-4-methyl-1H-isochromen-1-one (2.9.36): 2.9.35 (508 mg, 3 mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 329 mg (61%) of **2.9.36** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.36**) = 0.46, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.3 (s, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.8, 162.2, 140.5, 138.2, 137.5, 116.0, 114.6, 113.6, 106.8, 13.4.



2.9.37 2.9.38

Preparation of 8-hydroxy-3-methyl-1H-isochromen-1-one (2.9.38): 2.9.37 (690 mg, 4 mmol) was reacted according to general procedure L. Purification using silica gel chromatography (elution with pet ether/EtOAc = 4:1) gave 402 mg (55%) of **2.9.38** as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.9.38**) = 0.49, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.0 (s, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.27 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.4, 161.2, 153.5, 137.6, 136.9, 114.8, 114.2, 105.3, 104.3, 19.0.



2.9.39 2.2.13

Preparation of 8-hydroxy-3,4-dimethyl-1H-isochromen-1-one (2.2.13): 2.9.39 (510 mg, 3 mmol) was reacted according to general procedure L. Purification using silica gel

chromatography (elution with pet ether/EtOAc = 4:1) gave 411 mg (76%) of **2.2.13**as a clear colorless oil which was homogeneous by TLC analysis [R_f (**2.2.13**) = 0.49, 4:1, pet ether/EtOAc]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 11.30 (s, 1H), 7.61 (t, *J* = 8.1 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 166.8, 162.1, 149.8, 139.3, 137.4, 114.6, 113.1, 109.4, 106.1, 17.3, 12.7.

2.12 References and Notes

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