UNIVERSITY OF CALIFORNIA

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Phenylseleno Acrylate As A Novel Ethylene Equivalent for Diels-Alder Reactions

And

An *ortho*-Benzoquinone Cycloaddition Strategy Toward Morphine

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Felix Rene Perez

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ABSTRACT OF THE DISSERTATION

Phenylseleno Acrylate as a Novel Ethylene Equivalent for Diels-Alder Reactions

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Professor Michael E. Jung, Chair

In Chapter 1, a Diels-Alder cycloaddition strategy toward morphine utilizing highly reactive *ortho*-benzoquinones as dienophiles is reported. Various syntheses of the phenanthrene unit of morphine are accomplished. A highly functionalized cycloadduct was synthesized containing the entire framework of morphine including functionality for the final ring closures. A general synthesis of benzofurans via a conjugate addition to *ortho*-benzoquinones has also been developed and an intramolecular addition was investigated as a possible method to access the phenanthrene unit of morphine.

In Chapter 2, phenylseleno acrylate was investigated as a novel ethylene equivalent in the Diels-Alder reaction. Dienes were found to undergo the Diels-Alder reactoin with phenylseleno acrylate to provide phenylseleno ester cycloadducts in excellent yield and with high regioselectivity. The phenylseleno esters were cleaved via a radical reduction to yield the desired ethylene unit. The radical reduction of bicyclo[2.2.2.]octene and bicyclo[2.2.1]heptene cycloadducts produced several side products, which formed due to cyclopropylcarbinyl radical rearrangements.

The dissertation of Felix Rene Perez is approved.

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2013

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Jung, M.E.; Perez, F.; Regan, C.F.; Yi, S.W.; Perron, Q."*Se*-Phenyl Prop-2-eneselenoate: An Ethylene Equivalent for Diels–Alder Reactions" *Angew. Chem. Int. Ed.* **2013**, *53*, 2060-2062.

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Jung, M.E.; Perez, F. "Synthesis of 2-Substituted 7-Hydroxybenzofuran-4-carboxylates via Addition of Silyl Enol Ethers to *o*-Benzoquinone Esters**"** *Org. Lett.* **2009**, *11*, 2165-2167

American Chemical Society, National Conference March 2007, "A New Planar Chiral Ferrocenyl-aminophosphine Ligand for Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of Acetophenone Derivatives" (Poster)

Chapter 1

An *ortho*-Benzoquinone Cycloaddition Strategy Toward Morphine

Introduction

Morphine (Figure 1-1) is a naturally occurring alkaloid obtained from the latex of the opium poppy, *Papaver somniferum*.[1] It is a potent μ-opiod receptor agonist used for the treatment of pain. For millennia, morphine has been used as an analgesic and today is considered the standard to which other analgesics are compared.[2] Morphine was first isolated by Friederich Serturner in 1804, who named it after Morpheus, the god of dreams.[3] However, the structure of morphine remained a mystery for over a hundred years. Robinson was the first to propose the correct structure of morphine in 1925, suggesting a compact T-shaped structure with a bridging D ring.[4] The first total synthesis by Gates in 1952 further established the structure of natural (-)-morphine,[5,6,7] as did X-ray diffraction studies by MacKay and Hodgkin in 1955.[8]

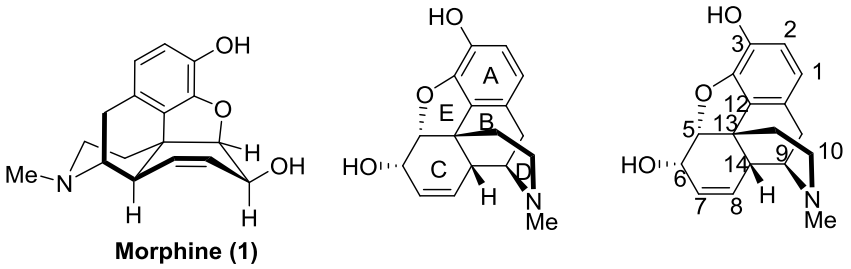


Figure 1-1. Ring and numbering assignments of morphine (**1**).

Numerous alkaloids are produced by the opium poppy (Figure 1-2). Morphine is the most abundant by weight. The effects of these alkaloids vary greatly and have found different uses. The phenanthrenes codeine and thebaine are minor constituents in opium, having analgesic and stimulatory effects, respectively. However, other alkaloids have no effect on the central nervous system. The isoquinolines, noscapine and papaverine, have no analgesic properties, but have found use in cough medicine and vasodilators, respectively.

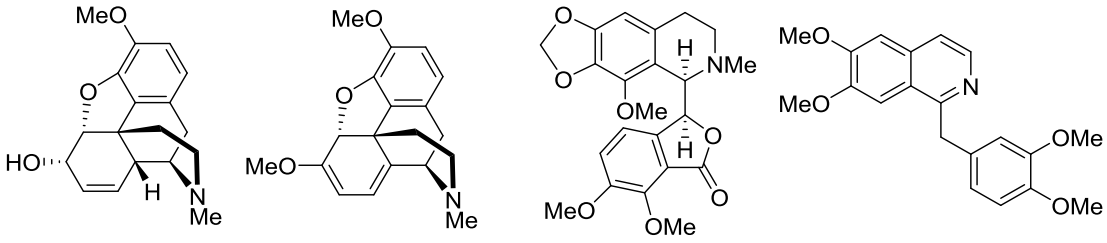
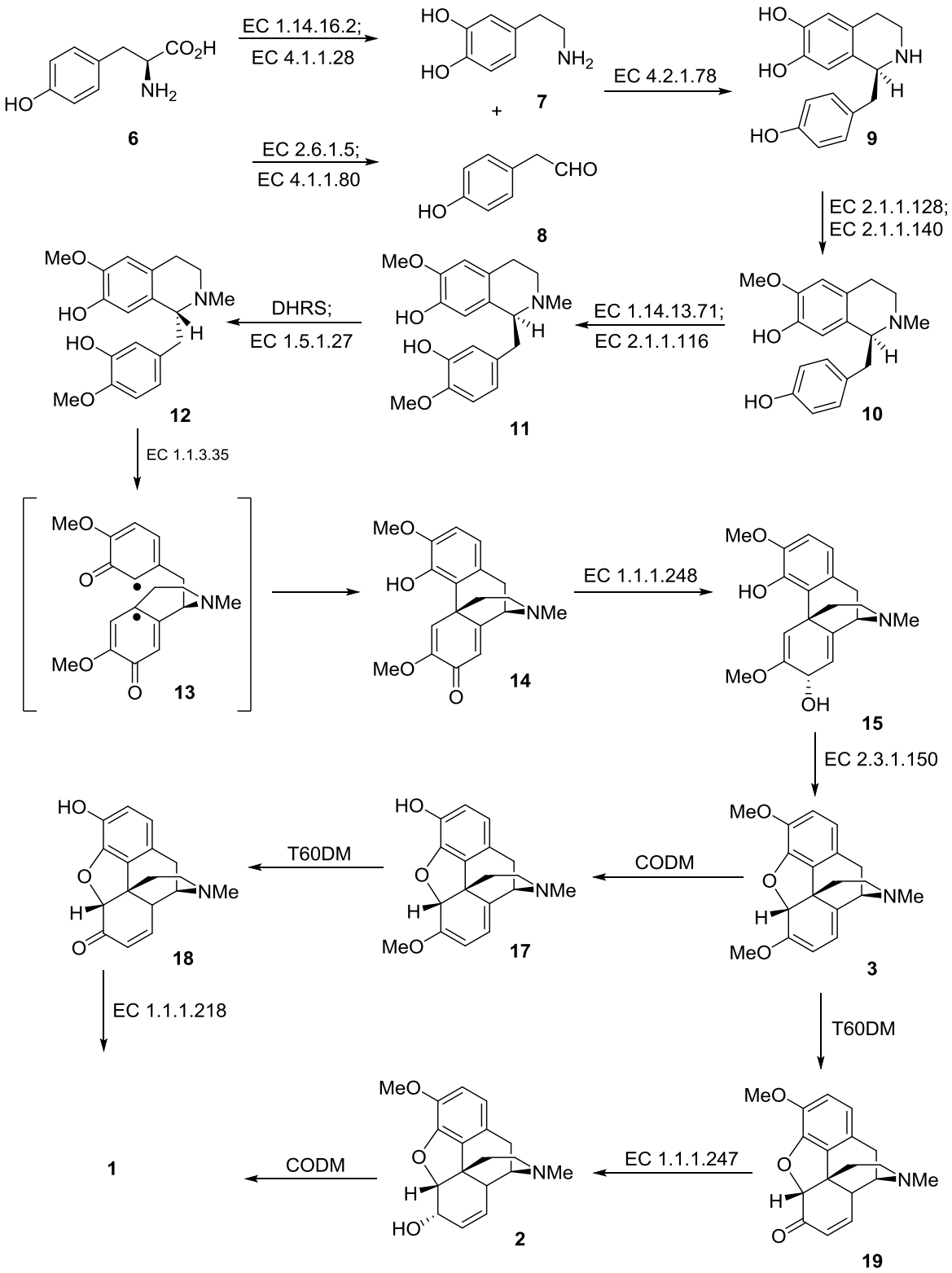


Figure 1-2. Other alkaloids produced by the opium poppy.

The presence of so many different alkaloids has helped elucidate the biosynthetic pathways which produce morphine (Scheme 1-1).[9] The phenolic A ring and allylic alcohol of the C ring immediately suggests that two tyrosine (**6**) units are involved. Two separate pathways convert tyrosine to dopamine (**7**) and phenylacetaldehyde (**8**). An enzyme catalyzed Pictet-Spengler reaction forms ring D, providing (*S*)-norclaurine (**9**). Methylation and oxidation provide (*S*)-reticuline (**11**), an important branch point to a variety of isoquinoline alkaloids. Stereo inversion to (*R*)-reticuline (**12**) is still not well understood. Zenk extracted active 1, 2-dehydroreticuline synthase (DHRS), but was unable to purify the protein due to its unusual instability.[10] However, the reductase has been isolated. The B ring is then formed by ring closure through a diradical intermediate (**13**) to form salutaridine (**14**). Formation of the E ring takes place by capture of an intermediate allyl cation derived from salutaridinol (**15**), forming thebaine (**3**). The final steps from **3** to morphine occur via two pathways. In 2010, Hagel and Facchini succeeded in isolating the enzymes involved with the necessary demethylation steps. Transfection of *E coli.* with genes coding for thebain-6-*O*-demethylase (T6ODM) and codeine-*O*-demethylase (CODM) allowed conversion of thebain into morphine.[11] Elucidating the biosynthesis of morphine may provide selective methods to increase the yields of the other valuable alkaloids present in the opium poppy.



Scheme 1-1. Abbreviated morphine biosynthesis with enzyme commission (EC) numbers.

The compact, pentacyclic morphinan core is a privileged scaffold that has been the subject of many variations (Figure 1-3). Due to a high potential for abuse, morphinan derivatives have been synthesized in the hope of finding an analgesic without the addictive properties of morphine. Heroin, **20**, was one of the first derivatives, marketed as a cough suppressant without the addictive properties of morphine. However, it was found to be more addictive and eventually dominated illicit use. Oxycodone, **21**, has been found to be a less addictive analgesic, but is widely abused as a prescription drug. Enantiomers of the morphinan core have also displayed bioactivity. Dextromethorphan, **22**, was developed as a non-addictive cough suppressant. Modifications of the C ring can dramatically increase the potency of derivatives. Dihydroetorphine, **23**, is more than one-thousand times more potent than morphine and is used to tranquilize large animals. Buprenorphine, **24**, though forty times more potent, is actually used to treat addiction to opiods.

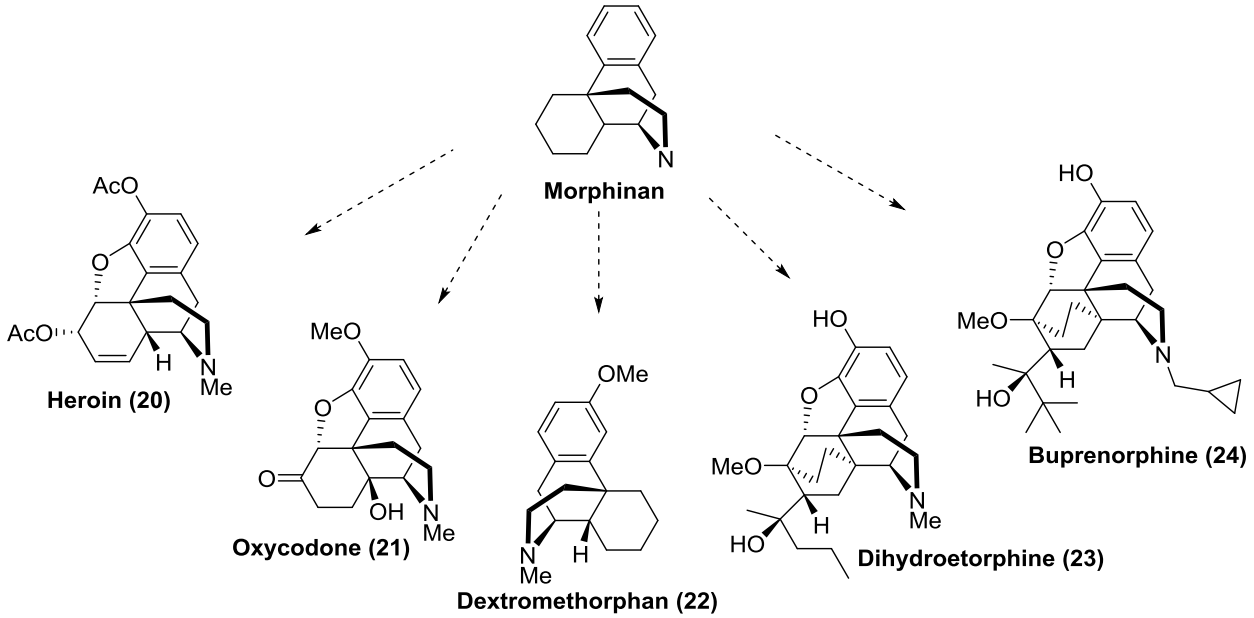


Figure 1-3. Commercial analogs with the morphinan core.

More than sixty years after the Gates synthesis, morphine and its derivatives remain popular targets of total synthesis (Table 1-1).[12] However, no synthesis has been developed that can compete with modern farming. Most efforts end as formal syntheses in codeine, since it can be demethylated to morphine. Other practical reasons for formal syntheses include morphine's amino acid like behavior, making handling difficult. Morphine also oxidizes easily in air due to the electron rich A ring. Though yields have improved greatly since Gates' first synthesis, only Rice's multi-gram synthesis of (-)-dihydrocodeinone has approached commercial viability. Hudlicky has suggested that the difficulty associated with morphine arises from the complete "dissonance" of its connectivity (Figure 1-4). No polarization assignment of morphine can be made that does not assign an incorrect charge to an electronegative atom (e.g., oxygen or nitrogen). In addition, any such assignment will require two like charges be vicinal. According to Hudlicky, these polarization assignments indicate that any strategy toward morphine will "require major tactical maneuvers leading to an increase in the step-count and hence a decrease in practicality."

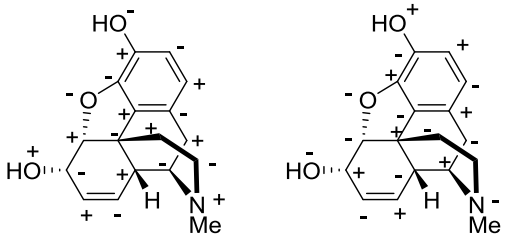


Figure 1-4. Hudlicky's polarization assignments.

Table 1-1. Past total syntheses of morphine and its analogs compiled by Rinner and Hudlicky.[12]

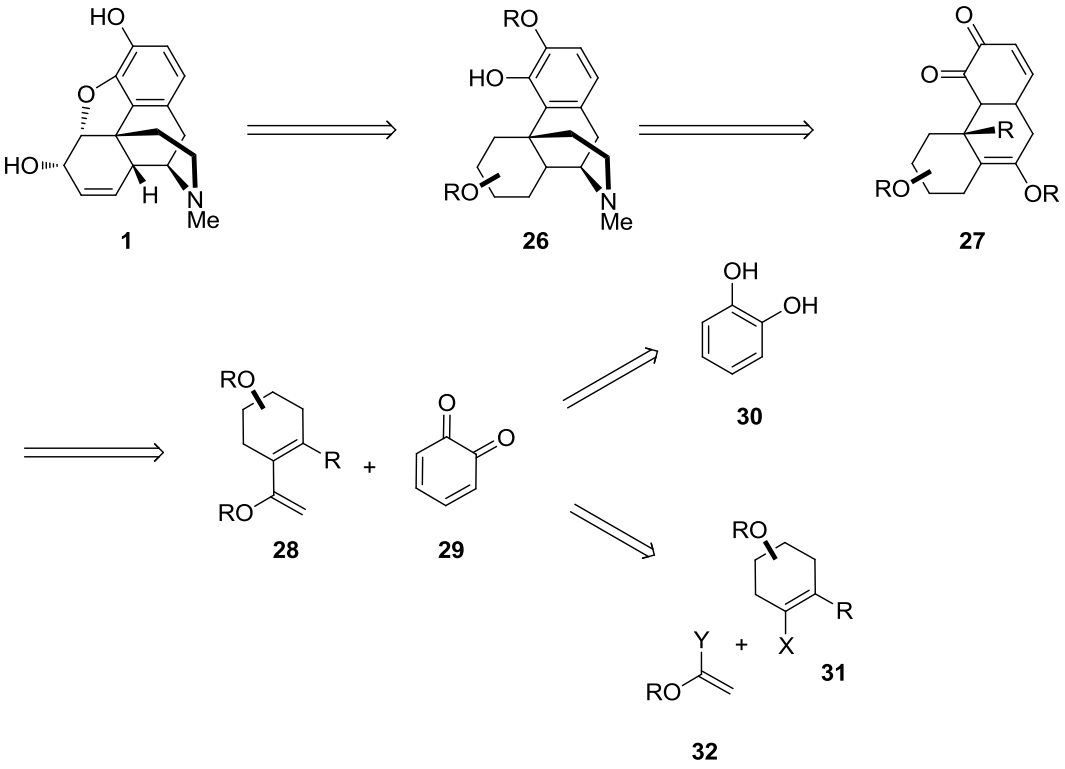
Author	Date	Product	Steps	Yield (%)
Gates[6,7]	1952	(-)-Morphine	31	0.06
Ginsburg[13,14]	1954	(±)-Dihydrothebainone	21	8.9
Grewe[15,16]	1967	(±)-Dihydrothebainone	9	0.81
Rice[17]	1980	(±)-Dihydrocodeinone	14	29.7
Evans[18]	1982	(±)-O-Me-thebainone A	12	16.7
Rapoport[19]	1983	(±)-codeine	26	1.2
Fuchs[20,21]	1988	(±)-codeine	23	1.3
Tius[22]	1992	(±)-Thebainone-A	24	1.1
Parker[23,24]	1992	(±)-Dihydrocodeinone	11	11.1
Overman[25]	1993	Dihydrocodeinone	14	1.9
Mulzer[26]	1996	Dihydrocodeinone	15	9.1
White[27]	1997	Ent-morphine	28	3.0
Mulzer[28]	1997	Dihydrocodeinone	18	5.7
Ogasawara[29,30]	2001	Dihydrocodeinone ethylene ketal	21	1.5
Taber[31]	2002	Morphine	27	0.51
Trost[32,33]	2002	(-)-Codeine	15	6.8
Fukuyama[34]	2006	(±)-morphine	25	6.7
Hudlicky[35]	2007	Ent-codeine	15	0.23
Iorga/Guillou[36]	2008	(±)-codeine	17	0.64
Chida[37]	2008	(±)-dihydroisocodeine	24	3.8
Hudlicky[38]	2009	Codeine	18	0.19
Magnus[39]	2009	(±)-codeine	13	20.1
Stork[40]	2009	(±)-codeine	22	2.0
Fukuyama[41]	2010	(-)-Morphine	18	4.8

Qiu proposed a crude metric for gauging the strategic efficiency of total syntheses (Equation 1-1) by formulating a complexity index (*I*) associated with the core of a natural product.[42] This is computed from the number of chiral centers (*C*), functional groups (*F*) such as heteroatoms, esters, side chains and non-aromatic unsaturations, and rings (*R*). Overlaps (*O*) are defined as functional groups attached only to a chiral center. These are substracted to prevent double counting. In order for a synthesis to be "efficient," the number of steps (N_s) must be less than the complexity index. Morphine and codeine have five stereocenters, five functional groups with one overlap by the alcohol at C6 and five rings. Their complexity index is therefore 14. The biosynthesis of morphine is estimated to require at least 15 enzymatic transformations. Magnus' synthesis of codeine achieves Qiu's definition of efficiency at 13 steps with one of the highest yields.[39] The syntheses of Hudlicky[35] and Trost[32] each take 15 steps, but with poorer yields. Rice's synthesis of dihydrocodeinone[17] (I = 13) takes 14 steps, but achieves a higher yield than Parker's efficient synthesis at 11 steps.[23] Overman's synthesis[25] is just as long as Rice's yet yields only 1.9% product; however, it was the first asymmetric synthesis. Grewe's synthesis of dihydrothebainone[15] (I = 11) is one of the shortest for a synthesis of the morphinan core; however it also has one of the lowest yields. However, Rice claims to have a synthesis of dihydrothebainone that is 13 steps with 37% overall yield.[17] However, the most recent syntheses of codeine by Stork[40] and Metz[43] still take 22 steps. Qiu's crude metric, in combination with past results, suggests that strategies targeting the shortest, high yielding synthesis of morphine or codeine should consider 14 steps as an ideal tradeoff. Any more or less and the overall yield may suffer.

$$Ns < I = C + (F - O) + R$$

Equation 1-1. Qiu's definition of strategic efficiency in synthesis.

The Diels-Alder reaction[44] is one of the most efficient methods to build up complexity and synthesize fused polycycles in organic synthesis.[45] In a single reaction, up to four stereocenters and one cyclohexene ring are created. A possible strategy to synthesize morphine would be to utilize the Diels-Alder reaction to form the phenanthrene ABC ring (**27**) unit of morphine in a single step (Scheme 1-2). An *ortho*-benzoquinone (**29**) would provide the aromatic A ring and act as a dienophile for an electron rich diene **28**. The oxygen at C9 would provide a synthetic handle to close the D ring to **26**.

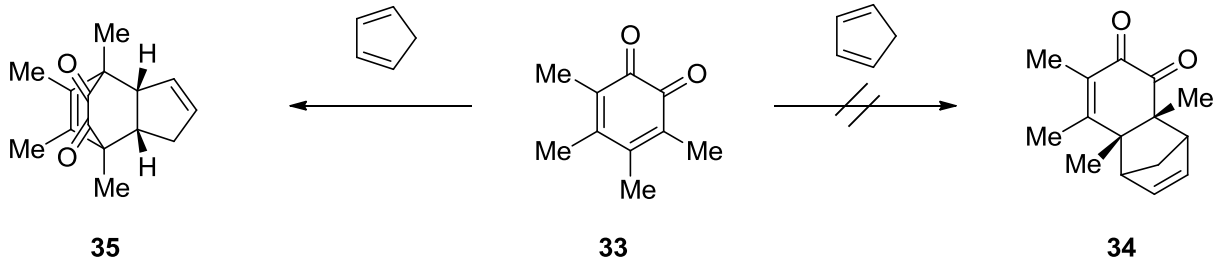


Scheme 1-2. Retrosynthesis of morphine.

Therefore we decided to investigate the use of *ortho*-benzoquinones as dienophiles in the Diels-Alder reaction with electron rich dienes and study whether it could be employed in a synthetic approach toward morphine. We hoped that the *ortho*-benzoquinone could act as a potent dienophile toward a very hindered diene such as **28** where there are substituents on the inside of the diene.

Background

Early reports of the cycloaddition reactions of *o*-benzoquinones were often misleading. Smith and Hac were the first to investigate the Diels-Alder reactions of *o*-benzoquinones with cyclopentadiene (Scheme 1-3).[46] Using tetramethyl *o*-benzoquinone **33**, they obtained a cycloadduct which they assigned as **34**, assuming **33** behaved as a dienophile. Horner and Spietschka[47] later proved that the cycloadduct was actually the oxalylindene **35**. The role of the quinone had been reversed, behaving as a diene in an inverse electron demand Diels-Alder reaction rather than as a dienophile.

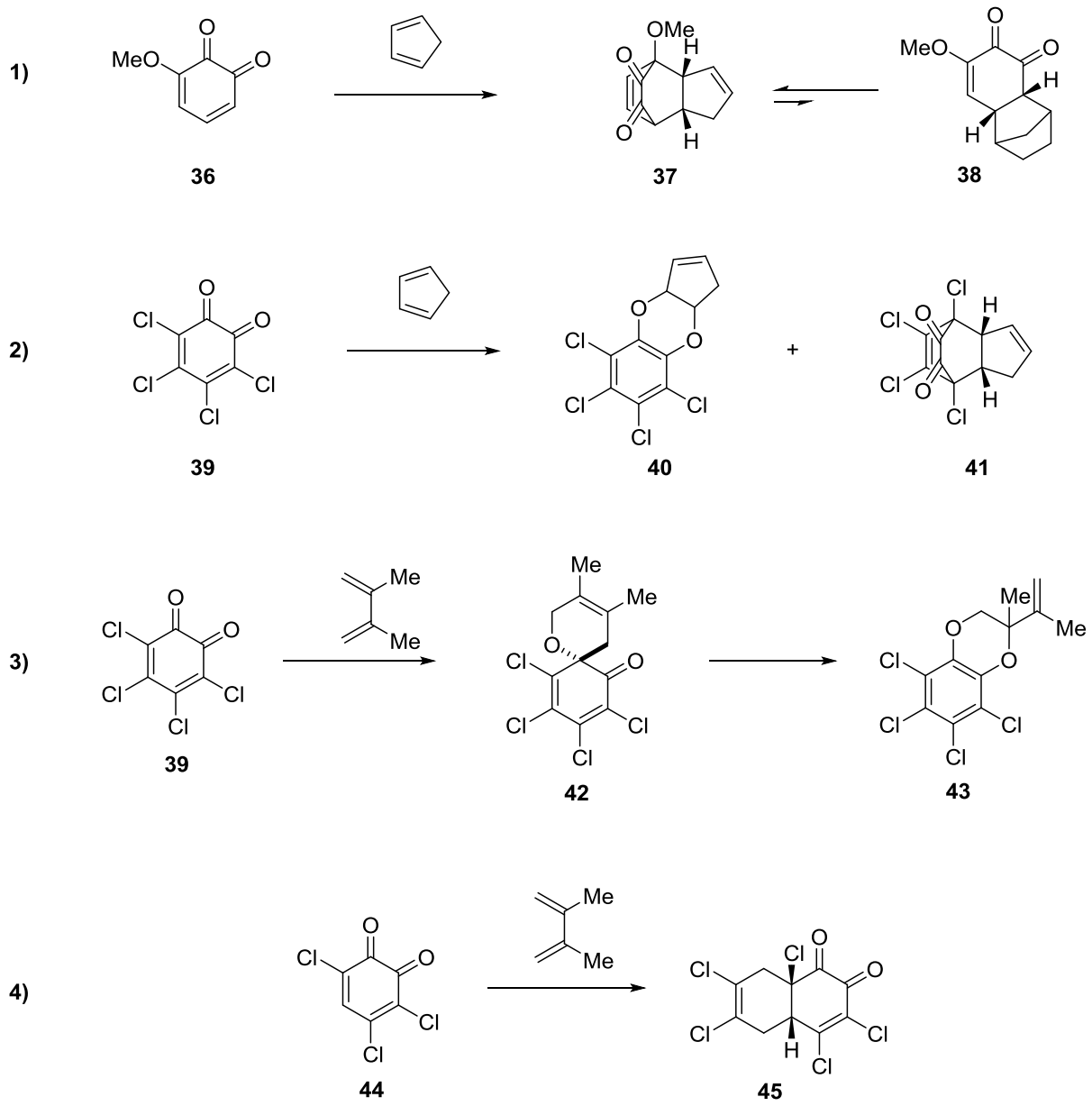


35 **33** **34**

Scheme 1-3. Earliest report of a Diels-Alder reaction with an *o*-benzoquinone.

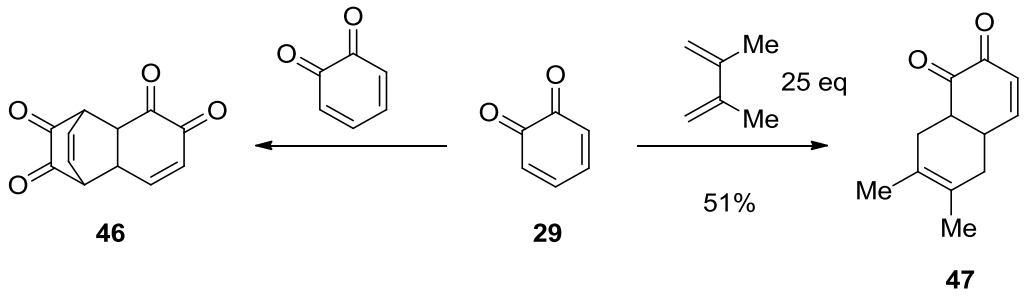
Using ^{1}H NMR, Ansell's pioneering work on the cycloaddition reactions of *o*-benzoquinones proved that a variety of reactivity modes are available (Scheme 1-4).[48,49,50] Ansell showed that 3-methoxy-*o*-benzoquinone **36** participates as a diene in a Diels-Alder reaction with cyclopentadiene providing the cycloadduct **37** which was in thermal equilibrium with the expected normal cycloadduct **38** via a Cope rearrangement (Scheme 1-4, Equation 1). *o*-Benzoquinones can also participate as heterodienes in the Diels-Alder reaction. Reaction of cyclopentadiene with *o*-chloranil **39** provided the dioxolane **40** as the major product, with the oxalylindene **41** being the minor product (Scheme 1-4, Equation 2). The ketone components can themselves behave as heterodienophiles. Dihydropyran **42** was obtained directly from *o*-chloranil and 2,3-dimethyl-1,3-butadiene (Scheme 1-4, Equation 3). This underwent a Claisen rearrangement to give the dioxolane **43**. The same reaction with 3,4,6-trichloro-*o*-benzoquinone

44 gave exclusively the normal cycloadduct **45**, with complete regioselectivity (Scheme 1-4, Equation 4).



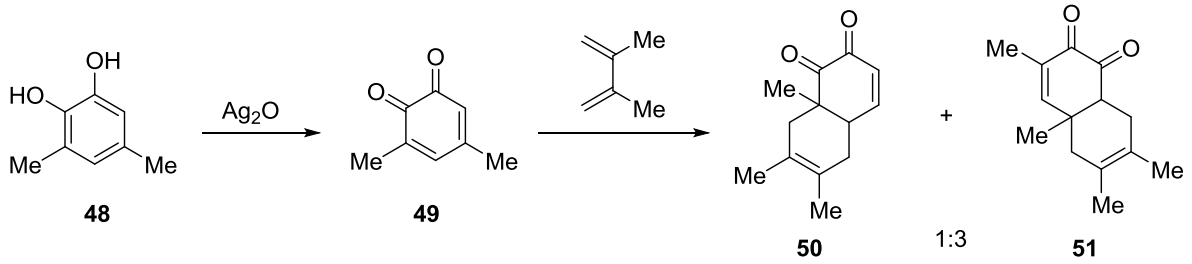
Scheme 1-4. The reactivity modes of *o*-benzoquinones.

Though highly reactive and attractively functionalized, *o*-benzoquinones have not been widely utilized in organic synthesis. The dimerization of *o*-benzoquinones via an inverse electron demand Diels-Alder reaction often predominates, e.g., to give **46** (Scheme 1-5). A large excess of the 1,3-dimethylbutadiene is required in the case of *o*-benzoquinone **29** to give the adduct **47**.



Scheme 1-5. Competitive dimerization of *o*-benzoquinone.

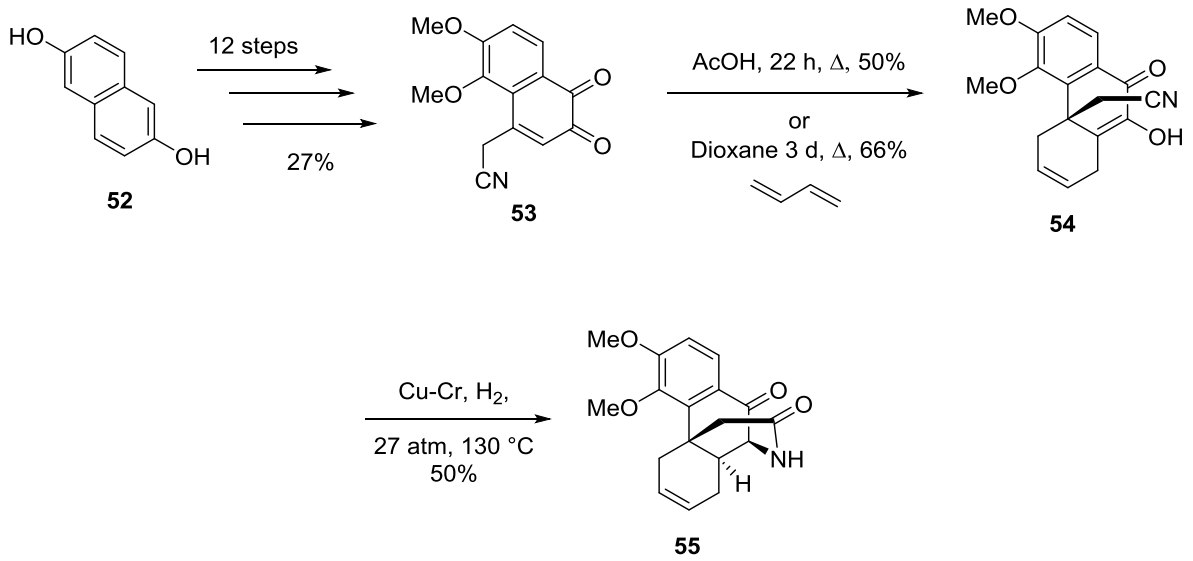
Ansell found that the dimerization can be inhibited by the addition of substituents to the *o*-benzoquinone (Scheme 1-6). Oxidation of 3,5-dimethyl catechol **48** yields the isolable 3,5-dimethyl-*o*-benzoquinone **49**. Although the methyl substitution is effective at suppressing dimerization, the cycloaddition provides a mixture of regioisomers **50** and **51**. However, such substitutions may not be desirable in all syntheses and their removal would require additional transformations.



Scheme 1-6. Regioselectivity of 3,5-dimethyl-*o*-benzoquinone.

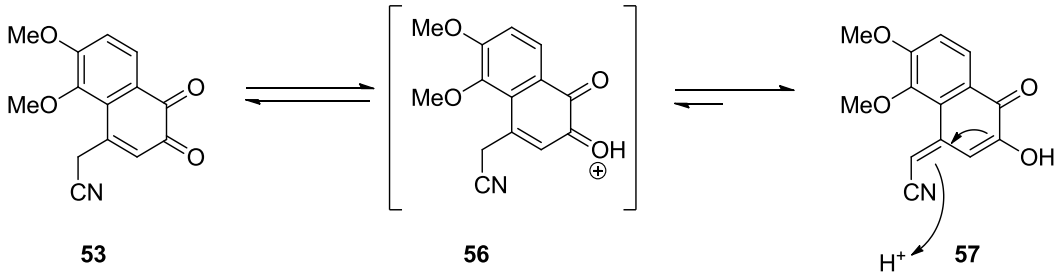
Despite the threat of poor atom economy imposed by reactions with *o*-benzoquinones, there are notable attempts to utilize the *o*-quinone moiety in natural products synthesis. The first total synthesis of morphine by Gates utilized a Diels-Alder cycloaddition strategy with a related *ortho*-naphthoquinone (Scheme 1-7). Starting from 2,6-naphthalenediol **52**, the *o*-naphthoquinone **53** was synthesized and used as a dienophile in a Diels-Alder reaction with 1,3-butadiene. The resulting phenanthrene cycloadduct **54** was obtained. The D ring was then closed during hydrogenation providing the morphinan core **55**. Despite the use of excess diene, only a

50% yield was obtained. The reaction was initially developed using glacial acetic acid as solvent;[5] a subsequent synthesis in 1956 increased the yield to 66% by heating in anhydrous dioxane for three days.[7]



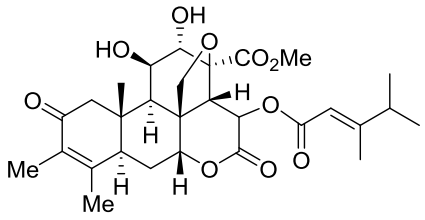
Scheme 1-7. Gates synthesis of morphinan core.

Land, *et al.*, studied the Gates' dienophile **53** and found that the poor dienophilicity was due to rapid tautomerization from **53** to the *para*-naphthoquinone methide **57** (Scheme 1-8).[51] By ^{1}H NMR, **53** was not detected, only the *para*-quinone methide **57** was observed. Computations by Land suggested that the methide **57** was more stable by 7.9 kcal mol^{-1}. Since **57** cannot act as a dienophile in the Diels-Alder reaction, Land hypothesized that the true dienophile was the oxonium species **56**.



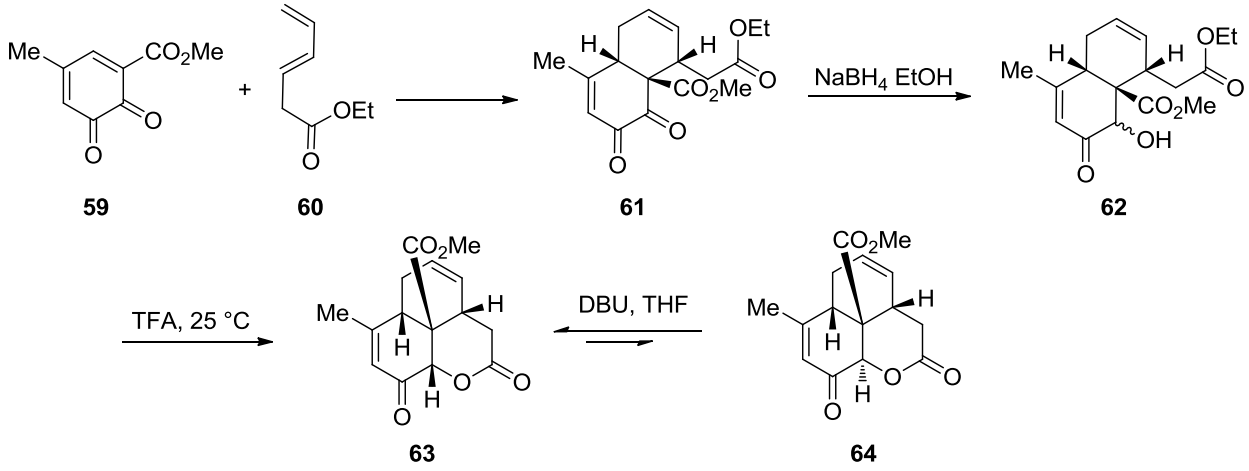
Scheme 1-8. Tautomerization of the Gates' dienophile **53** to the *para*-quinone methide **57**.

Weller and Stirchak[52] studied the synthesis of the quassinoid core of Bruceantin (Figure 1-5) via the cycloadditions of *o*-benzoquinones (Scheme 1-9). The methyl 5-methyl-*o*-benzoquinone ester **59** was generated *in situ* from silver (I) oxide oxidation of the catechol and allowed to react with the diene **60**. The cycloadduct **61** was obtained with complete endo selectivity. Reduction of **61** to the alcohol **62** and trifluoroacetic acid catalyzed cyclization gave a mixture of the lactones **63** and **64** in a 2:1 ratio. However, attempts to isomerize the γ-keto position to the required *trans* stereochemistry were unsuccessful.



Bruceantin (58)

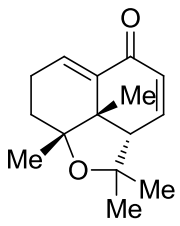
Figure 1-5. Bruceantin (58).



Scheme 1-9. Bruceantin model study.

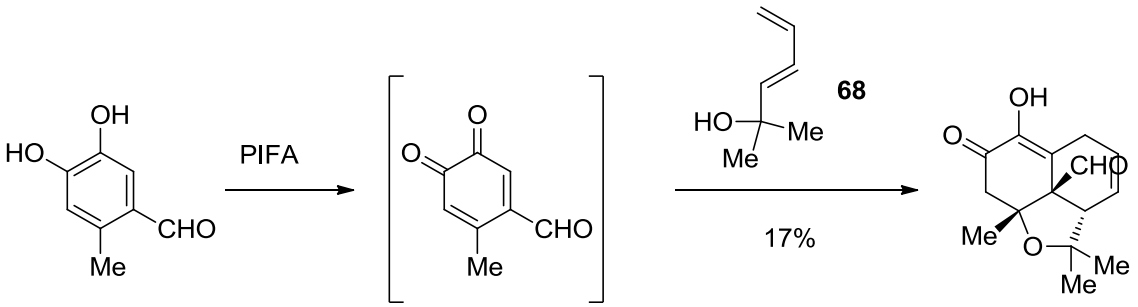
Rodrigo reported an *o*-benzoquinone cycloaddition strategy as a potential route to nardonoxide (Figure 1-6).[53] Using iodobenzene bis(trifluoroacetate) (PIFA), the catechol aldehyde **66** was oxidized *in situ* to the *o*-benzoquinone **67** in the presence of the diene **68**. The tricyclic skeleton of nardonoxide (**69**) was obtained in 17% yield. Again, complete selectivity

was observed for the ortho endo cycloadduct. In addition, the alcohol had undergone an intramolecular oxa-Michael addition to form the tricyclic nardonoxide skeleton.



Nardonoxide (65)

Figure 1-6. Nardonoxide.

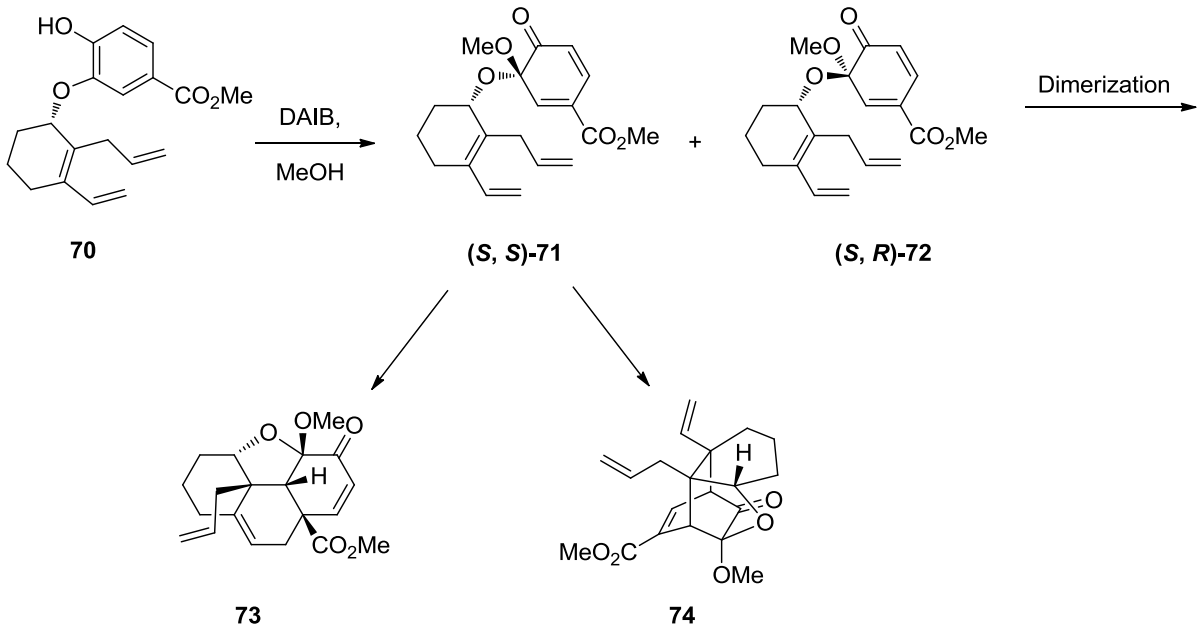


66 **67** **69**

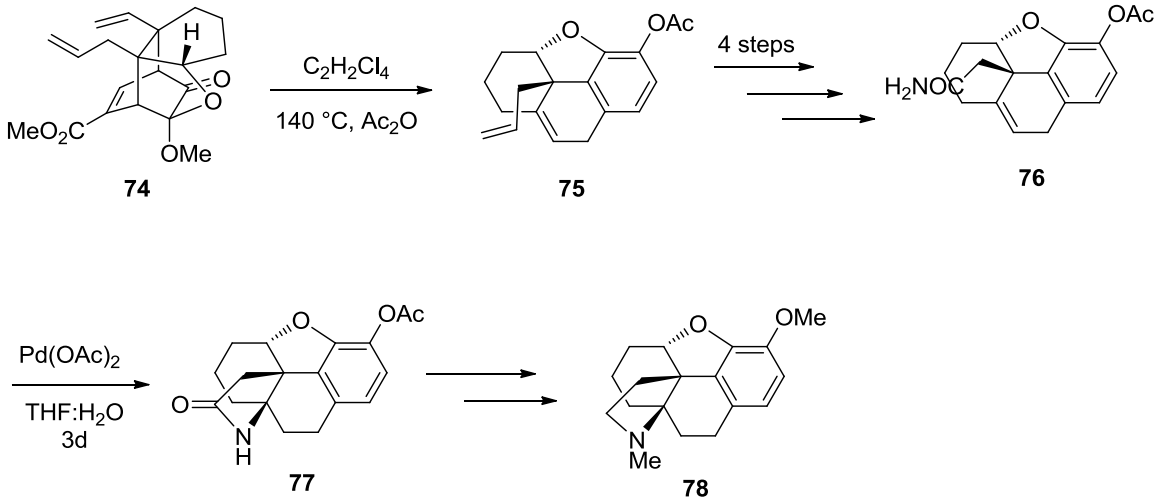
Scheme 1-10. Construction of Nardonoxide core.

No total synthesis of morphine has been reported using an *o*-benzoquinone as an intermediate. However, morphinan analogs have been synthesized using the related masked *ortho*-benzoquinones (MOB) (Scheme 1-11).[54] Rodrigo devised an intramolecular Diels-Alder reaction with MOB ketals. The MOB ketals (***S,S*)-71** and (***S,R***)**-72** can be generated by the oxidative ketalization of the ether **70** using (diacetoxy)iodobenzene. Only the S isomer was found to participate in the intramolecular cycloaddition. It provided the normal demand cycloadduct **73** and the inverse electron demand cycloadduct **74** in a yield of 64%. The other isomer, (***S,R*)-72**, cannot react because the diene cannot assume the required endo conformation and instead underwent a dimerization. The bicyclooctene **74** side product was converted, via a Cope rearrangement (Scheme 1-12), to the desired phenanthrofuran tetracycle **75**. Further

elaboration to the amide **76** allows cyclization of a fifth ring to form **77** and eventual formation of indolinocodeine **78** in 3.6% overall yield in 16 steps.



Scheme 1-11. Synthesis of the phenanthrofuran component of morphine.

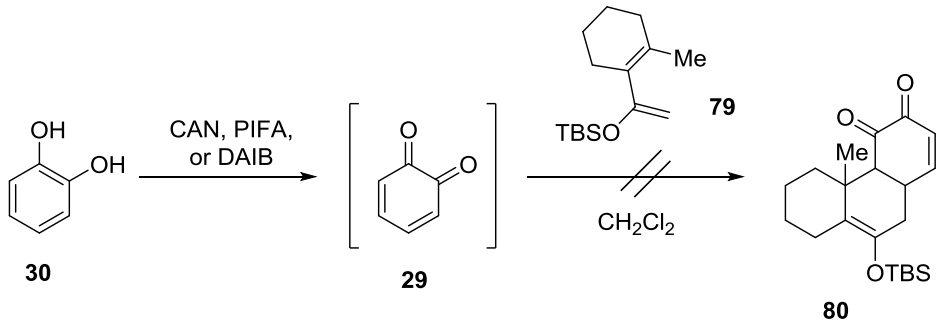


Scheme 1-12. The synthesis of the indolinocodeine **78**.

As mentioned earlier, we decided to investigate the use of substituted *ortho*-benzoquinones as dienophiles in an approach toward morphine. However, our approach would focus on an intermolecular Diels-Alde reaction.

Results and Discussion

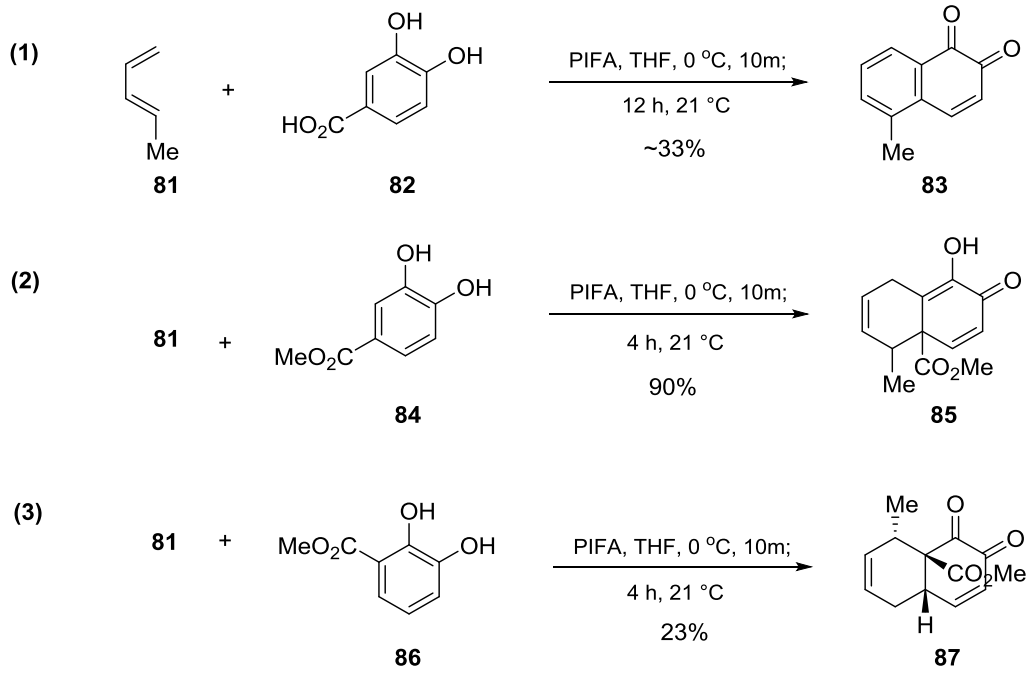
Our initial studies focused on a model for the formation of phenanthrene ABC-ring unit using the silyloxy diene **79** (Scheme 1-13)[55] and *o*-benzoquinone itself. Using dilute solutions of *o*-benzoquinone **29** in methylene chloride (prepared by oxidation of catechol **30** with any of several oxidants), neither the cycloadduct nor its aromatized product were found. There have been few reports using electron rich dienes in Diels-Alder reactions with *o*-benzoquinones.[56,57,58] The most closely related report was by Paquet and Brassard, who found that 1-trimethylsilyloxy-1,3–butadiene did react with 3,6-dichloro-*o*-quinone to yield the expected cycloaddition products.



Scheme 1-13. Initial attempts to form a cycloaddition product.

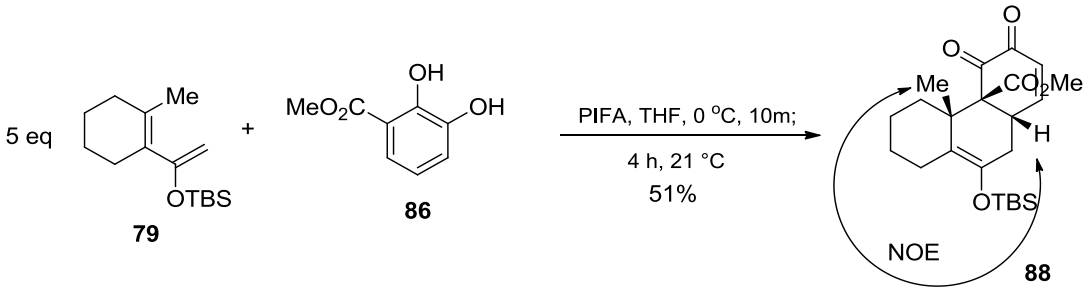
Carboxy substituted *o*-quinones were pursued next, using piperylene as the diene (Scheme 1-15) and 3,4-dihydroxybenzoic acid **82**. The catechol **82** was oxidized with PIFA in the presence of a five molar excess of piperylene in THF (Scheme 1-15, Equation 1). After 12 hours, a red mixture was obtained that yielded a red solid resembling the known *ortho*-naphthoquinone **83** by ^{1}H NMR.[59] The formation of the naphthoquinone involves the *in situ* decarboxylation of the resulting cycloadduct and aromatization to the dihydronaphthalenediol. Further oxidations and rearomatization would then provide the naphthoquinone **83**. Using the catechol methyl ester **84**, the cycloadduct **85** could be obtained in 90% yield using only 5.0 equivalents of the diene (Scheme 1-14, Equation 2). Decreasing the amount of piperylene by half

(2.5 equiv) gave **85** in 73% yield. The regioselectivity was assigned by comparison to the known cycloadduct **85**.[60] Using the isomeric methyl 2,3-dihydroxybenzoate **86** the cycloadduct **87** was obtained in a 23% yield as a single regio- and stereoisomer.



Scheme 1-14. Model studies with piperylene and catechol acids and esters.

The hindered silyloxy diene **79** was reacted with the catechol ester **86** using PIFA as the oxidant to provide the cycloadduct **88** in 51% yield (Scheme 1-15). The endo ortho stereochemistry was proved by 2D-NOESY.



Scheme 1-15. First successful Diels-Alder reaction with the diene **79**.

Further evidence for this structure came from X-ray crystallography (Figure 1-7). The high selectivity for endo ortho cycloaddition products using catechol **86** has been generally

observed and was studied computationally by Pitea.[61] The fact that the very hindered diene, **79**, reacted well indicates that the *o*-benzoquinone ester is a very reactive dienophile, since there is a methyl group on the inside of the diene unit and it is therefore very hindered.

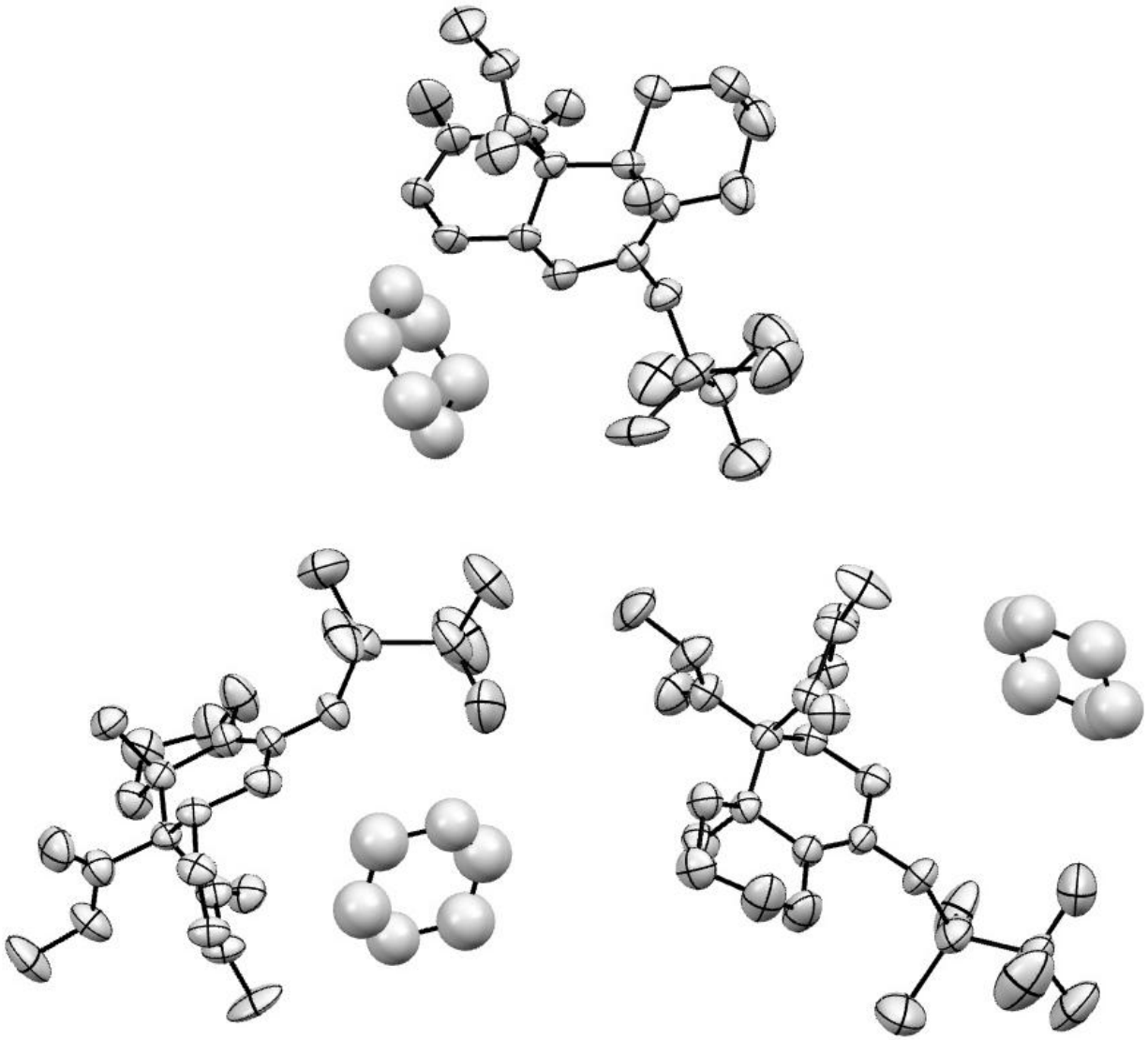
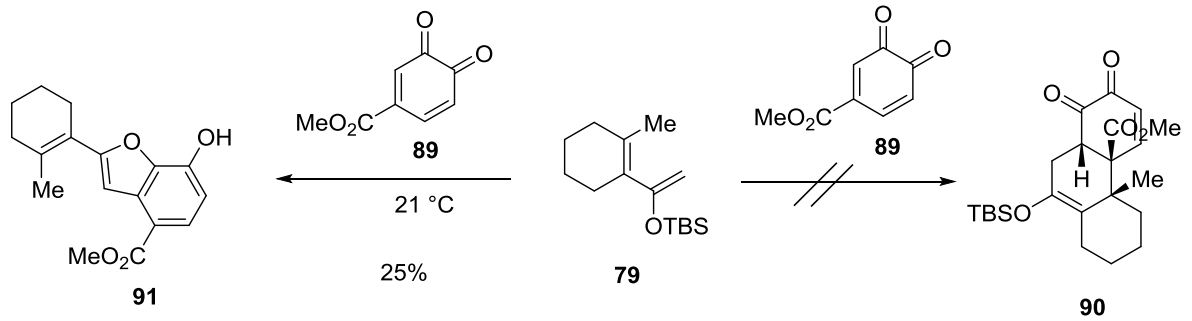


Figure 1-7. Illustratons of the X-ray crystal structure of **88** co-crystallized with cyclohexane.

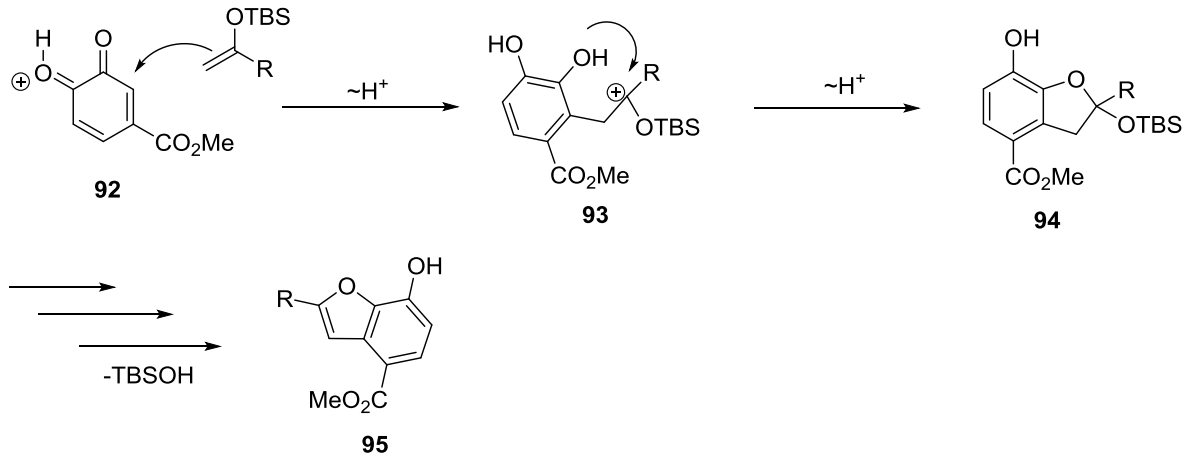
A Diels-Alder reaction of **79** with the *in situ* generated *o*-benzoquinone-4-ester **89** was attempted, but no cycloadduct was isolated (Scheme 1-16). Instead the benzofuran **91** was

isolated in 25% yield. It displayed an intense blue fluorescence under long wave ultraviolet light, a common observation for benzofuans related to **91**.



Scheme 1-16. Formation of benzofuran **91** when using ester **89**.

Mukaiyama *et al*, had reported the trityl perchlorate catalyzed formation of benzofurans from 4-*t*-butyl-*o*-benzoquinone and silyl enol ethers.[62] They proposed a 1,6-addition, which may be occurring in this case also (a likely mechanism is shown in Scheme 1-17).

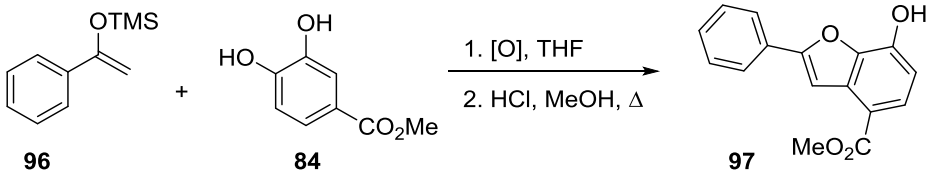


Scheme 1-17. Proposed mechanism for the formation benzofuran **91** from *o*-benzoquinone **92**.

This reaction was developed into a general method for the synthesis of benzofurans. (**Table 1-2**) Trimethylsilyl ethers, such as **96**, were found to effect this reaction most easily, while TBS ethers provided complex mixtures of silylated products. The cyclization to the benzofuran was best performed in refluxing methanol with hydrochloric acid. Using the TMS enol ether **96** as a model, the yield of the benzofuran **97** was at a maximum with four equivalents

of the silyl enol ether **96**. When five equivalents were used, the starting catechol ester **84** was isolated. This could arise from either competition by the silyl enol ether **96** for the oxidant or inhibition of the oxidation by silylation of the catechol **84**. Reactions performed at room temperature gave lower yields of the product **97**. The milder oxidant, diacetoxy iodobenzene (DAIB), gave a poorer yield of the benzofuran in comparison to PIFA.

Table 1-2. Conditions screened for benzofuran synthesis.

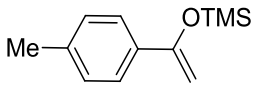
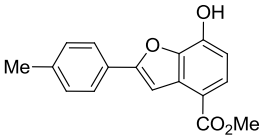
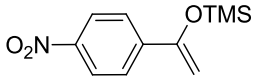
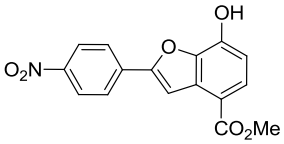
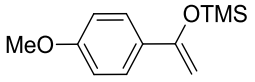
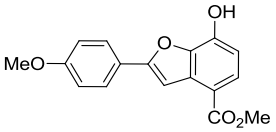
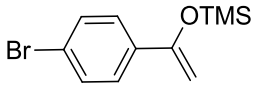
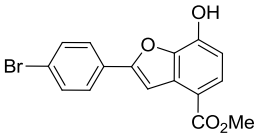
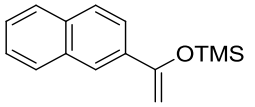
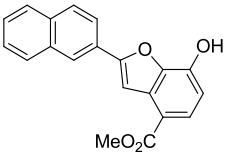
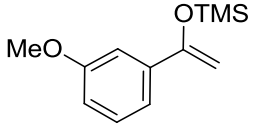
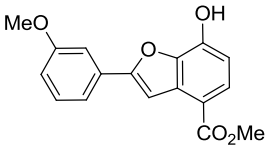
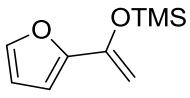
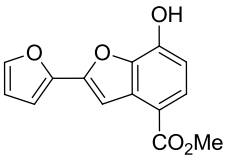


equiv. of 96	conditions	yield [%]
1	1.1 equiv PIFA, 0 ºC, 4 h	22
2	1.1 equiv PIFA, 0 ºC, 4 h	36
4	1.1 equiv PIFA, 0 ºC, 4 h	73
5	1.1 equiv PIFA, 0 ºC, 4 h	63
4	1.1 equiv PIFA, 21 ºC, 4 h	47
4	1.1 equiv DAIB, 0 ºC, 4 h	8.4

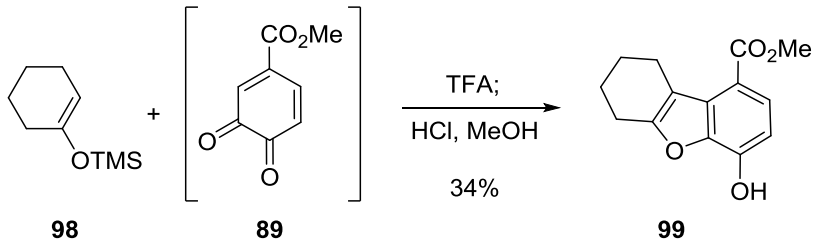
This method was extended to more examples (Table 1-3). Substitution at the para position with methyl and nitro substituents was well tolerated (Entries 1 and 2), providing the benzofurans **97a** and **97b**, both in 74% yield. Substitution by electron donating groups (Entries 3 and **6**) gave the benzofurans **97c** and **97f** in much lower yields (29-33%). This probably is caused by increased α-oxidation of the silyl enol ether. Such oxidations were studied earlier by Moriarty[63] and are well documented.[64] The 4-bromo substituted silyl enol ether **96d** gave a

moderate yield of the benzofuran **97d** (54%),while the silyl enol ether **96g** from 2-acetylfuran gave the furyl product **97g** in 60% yield.

Table 1-3. Scope of benzofuran synthesis.

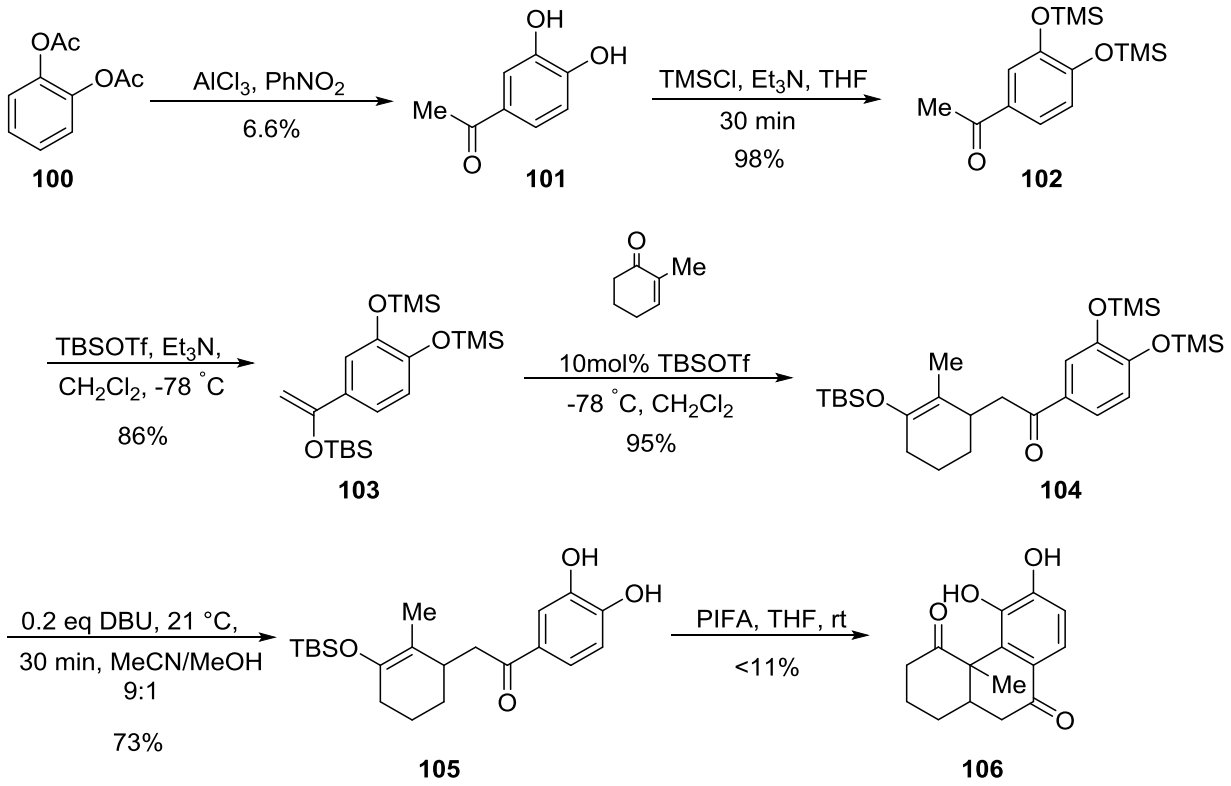
entry	enol ether	product	yield [%]
1	 **96a**	 **97a**	74
2	 **96b**	 **97b**	74
3	 **96c**	 **97c**	29
4	 **96d**	 **97d**	54
5	 **96e**	 **97e**	79
6	 **96f**	 **97f**	33
7	 **96g**	 **97g**	60

The silyl cyclohexenyl ether **98** reacted at room temperature with the *o*-benzoquinone **89** to give the tetrahydrodibenzofuran **99** (Scheme 1-18) in a 34% yield. This was an intriguing result, since the product is analogous to the dibenzofuran AEC tricycle of morphine. Therefore, a synthesis using a tethered silyl enol ether could possibly form the B ring. No instances of such a cyclization are known and a brief investigation of this strategy was undertaken (Scheme 1-19).



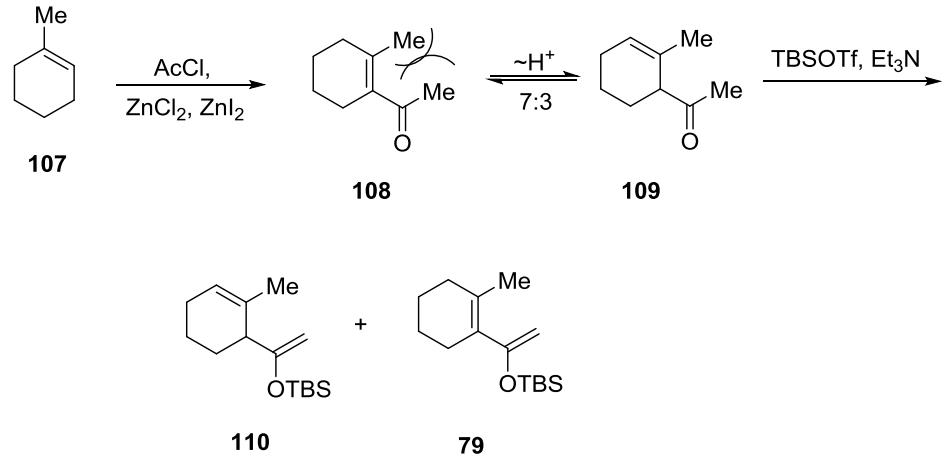
Scheme 1-18. Synthesis of tetrahydrodibenzofuran **99**.

Starting with catechol diacetate **100**, 3,4-dihydroxyacetophenone **101** was synthesized via an aluminum trichloride catalyzed Fries rearrangement.[65] The acetophenone **101** was extremely unstable in solution and oxidized easily. The catechol was protected as the bis(trimethylsilyl) ether **102** in 98% yield and the methyl ketone was converted to the TBS vinyl ether **103** using TBSOTf and triethylamine in 86% yield. The Mukaiyama-Michael addition of **103** to 2-methylcyclohexen-1-one was catalyzed by TBSOTf and was observed to occur quantitatively, providing the 1,4-adduct **104** in 95% yield. A solution of DBU in methanol and acetonitrile was used to cleave the TMS ethers to the catechol **105** in a 73% yield. Oxidation of **105** with PIFA in THF gave the cyclized product **106** in 10-11% yield. Although this intramolecular addition reaction provided the ABC-ring unit of morphine in only five steps, the difficulty of producing the acetophenone **101** combined with the lability of the intermediates made this route impractical.



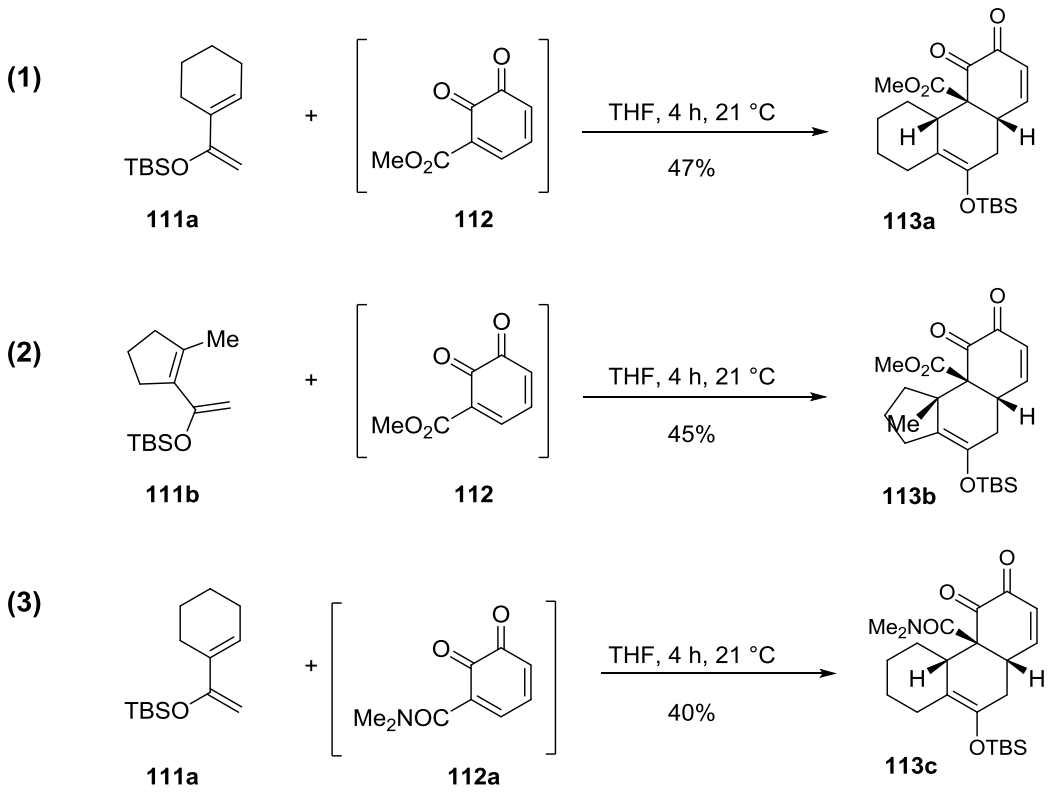
Scheme 1-19. Synthesis of the ABC-ring unit of morphine by an intramolecular addition.

Our focus shifted back to the development of the Diels-Alder strategy. The silyloxy diene **79** used in the prior cycloaddition was actually a mixture of two regioisomers,[66] the conjugated diene **79** and the unconjugated diene **110** (Scheme 1-20). This was a consequence of the Friedel-Crafts acylation of methyl cyclohexene **107**, which was used to generate the methyl ketones **108** and **109**. The steric clashing of the methyl ketone and the β-methyl group causes the two regioisomers to be energetically similar. The decreased abundance of the required diene **79** in the mixture was suspected of contributing to the requirement for an excess of the diene.



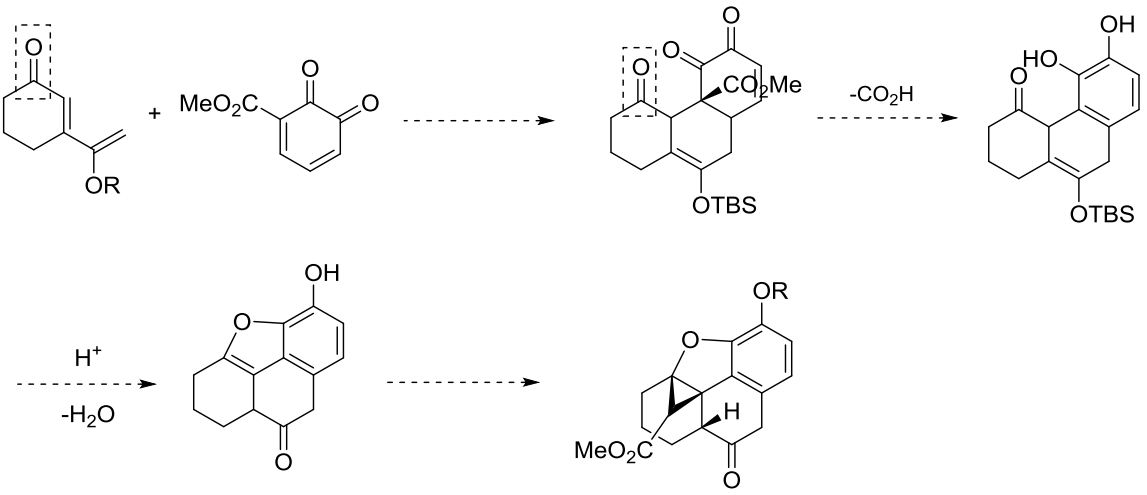
Scheme 1-20. Steric clashing of the methyl ketone and the β-methyl substituent.

To test this, the Diels-Alder reactions were performed using the regioisomerically pure dienes **111a** and **111b**,[67] under the conditions previously developed (Scheme 1-21). Four equivalents of the diene **111a** gave the cycloadduct **113a** (Scheme 1-21, Equation 1). Though the yield was lower than that of the methyl diene, the reaction maintained a similar atom economy, namely that four equivalents of the diene were required in order to produce the cycloadduct in a 47% yield. Using the more hindered methyl cyclopentene **111b**, a 45% yield of the tricycle **113b** was obtained (Scheme 1-21, Equation 2). In both cases, a single isomer is obtained, which has been assigned the ortho endo configuration. Rodrigo has reported the Diels-Alder reactions of *o*-benzoquinones derived from catechol acetophenones and thioesters,[53] but none have been reported for catechol carboxamides. The Diels-Alder reaction of *o*-benzoquinone dimethyl amide (**112a**) provided the cycloadduct **113c** in 40% yield (Scheme 1-21, Equation 3). Thus amides are tolerated in such cycloadditions.



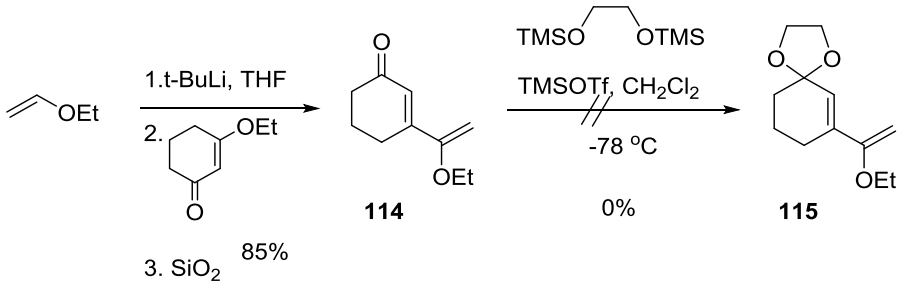
Scheme 1-21. The Diels-Alder reactions of regioisomerically pure dienes.

Substitution on the cyclohexene ring of the diene was explored next (Scheme 1-22). Some synthetic handle would be necessary on the C-ring in order to close the E-ring. A masked keto moiety was pursued, in the hopes that a phenanthrofuran could be generated from the cycloadduct and the bulky side chain introduced later, via a cyclopropanation. Such cyclopropanations have been reported for benzofurans and indoles.[68] This would conveniently provide the two carbons for the D ring and allow direct installation of an N-methyl amide, without having to use an intermediate diene containing an ester or amide.



Scheme 1-22. Phenanthrofuran strategy.

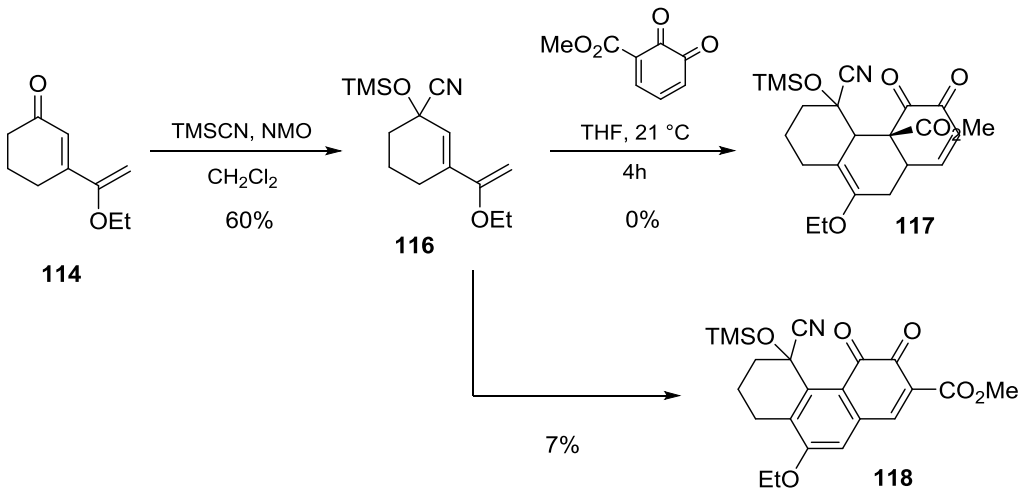
Starting with commercially available 3-ethoxy-2-cyclohexenone, addition of ethoxy vinyl lithium (prepared from ethyl vinyl ether and *t*-butyllithium) and elimination gave the desired 2-(ethoxyvinyl)cyclohexenone **114** in 85% yield (Scheme 1-23).[69] Using the Noyori protocol,[70] attempts to ketalize this substrate with TMSOTf and ethylene glycol bis(trimethylsilyl) ether were unsuccessful.



Scheme 1-23. Attempted synthesis of masked keto diene.

The ketone was masked as the trimethylsilyl cyanohydrin **116**, using TMSCN and catalytic *N*-methylmorpholine-*N*-oxide (Scheme 1-24).[71] Attempted cycloaddition of the diene **116** with the dienophile **112** (obtained using PIFA as an oxidant) did not yield the desired cycloadduct **117**. Instead a red, unstable product was formed. A milder oxidation using silver (I) oxide also provided this red product. The color suggested the formation of a quinone-like moiety.

The material exhibited two aromatic singlets in the ^{1}H NMR spectrum and the presence of two ketones and an ester by ^{13}C NMR. From this information, the structure was assigned as **118**, obtained in an approximately 7% yield. Mass spectrometry also indicated this material contained a mass in agreement with the proposed structure.

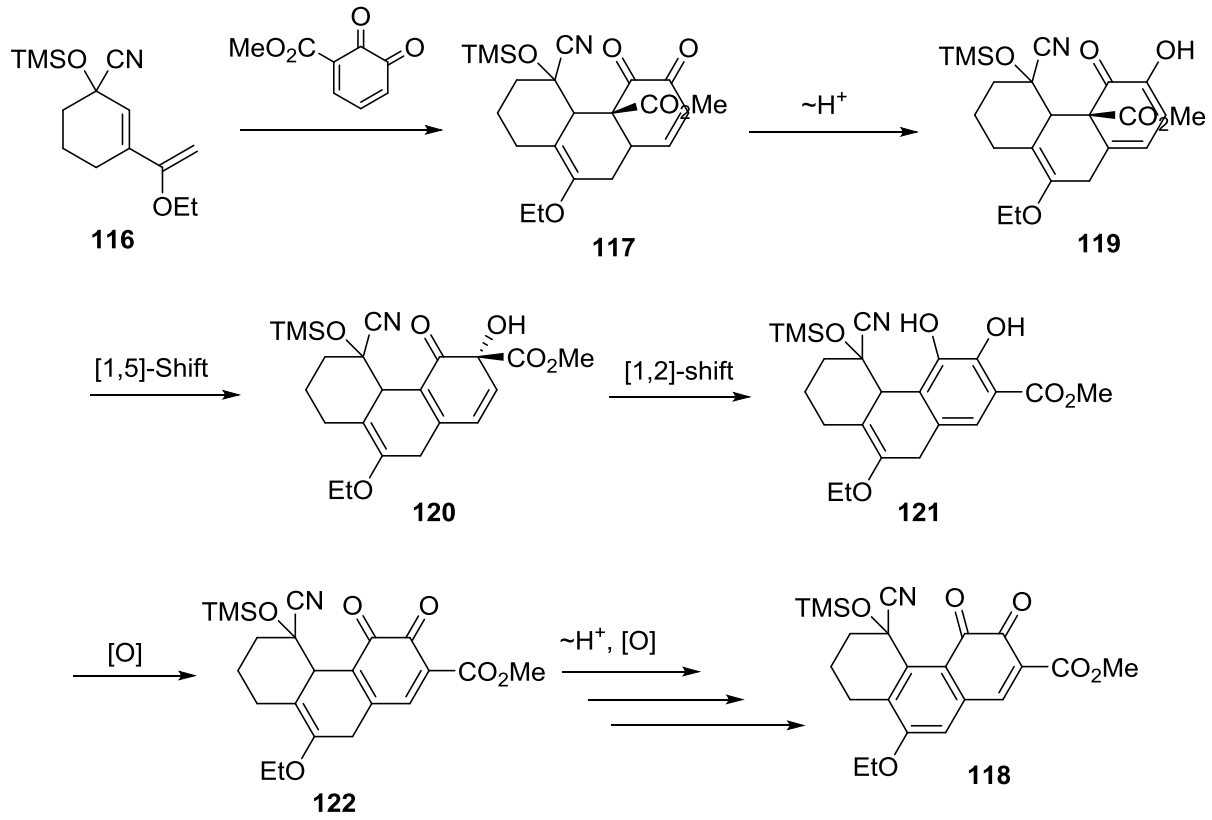


Scheme 1-24. The unexpected formation of **118**.

The proposed structure **118** suggests that the Diels-Alder cycloaddition occurred on the less substituted side of the dienophile to ultimately give **118** and not **117**. However, Pitea, *et al.*,[61] studied the cycloaddition reactions of *o*-benzoquinone esters and found both experimentally and computationally that the Diels-Alder cycloaddition strongly favors addition to the ester bearing side, providing exclusively ortho endo cycloadducts. Rodrigo has found that the Diels-Alder reaction products of *o*-benzoquinone esters can undergo dramatic internal rearrangements resulting in the internal migration of the ester function.[53] An alternative mechanism considering this possibility is proposed (Scheme 1-25).

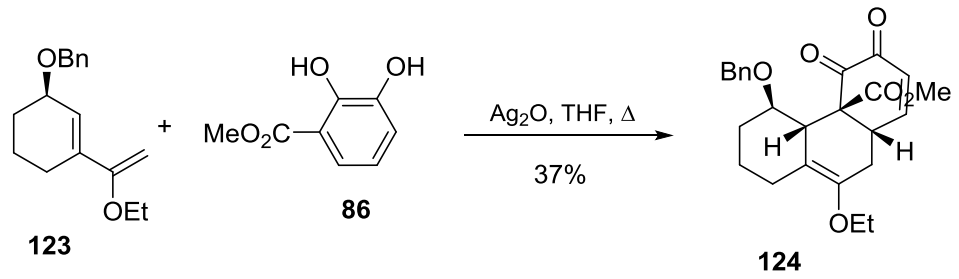
Rodrigo showed that the migration of methyl esters was accomplished by successive alkyl shifts, not by a direct one-step transfer of the ester. The initial cycloadduct **117** undergoes a 1,5-shift from the enol **119** to provide the alcohol **120**, then a 1,2-shift occurs to form the

dihydronaphthalenediol **121**. Successive oxidations and aromatizations would give the *o*-naphthoquinone **118**. However, Rodrigo's conditions involved the use of 10-20 equivalents of trifluoroacetic acid to catalyze the rearrangement. The proposed *o*-naphthoquinone product is formed even when silver (I) oxide was used as the oxidant.



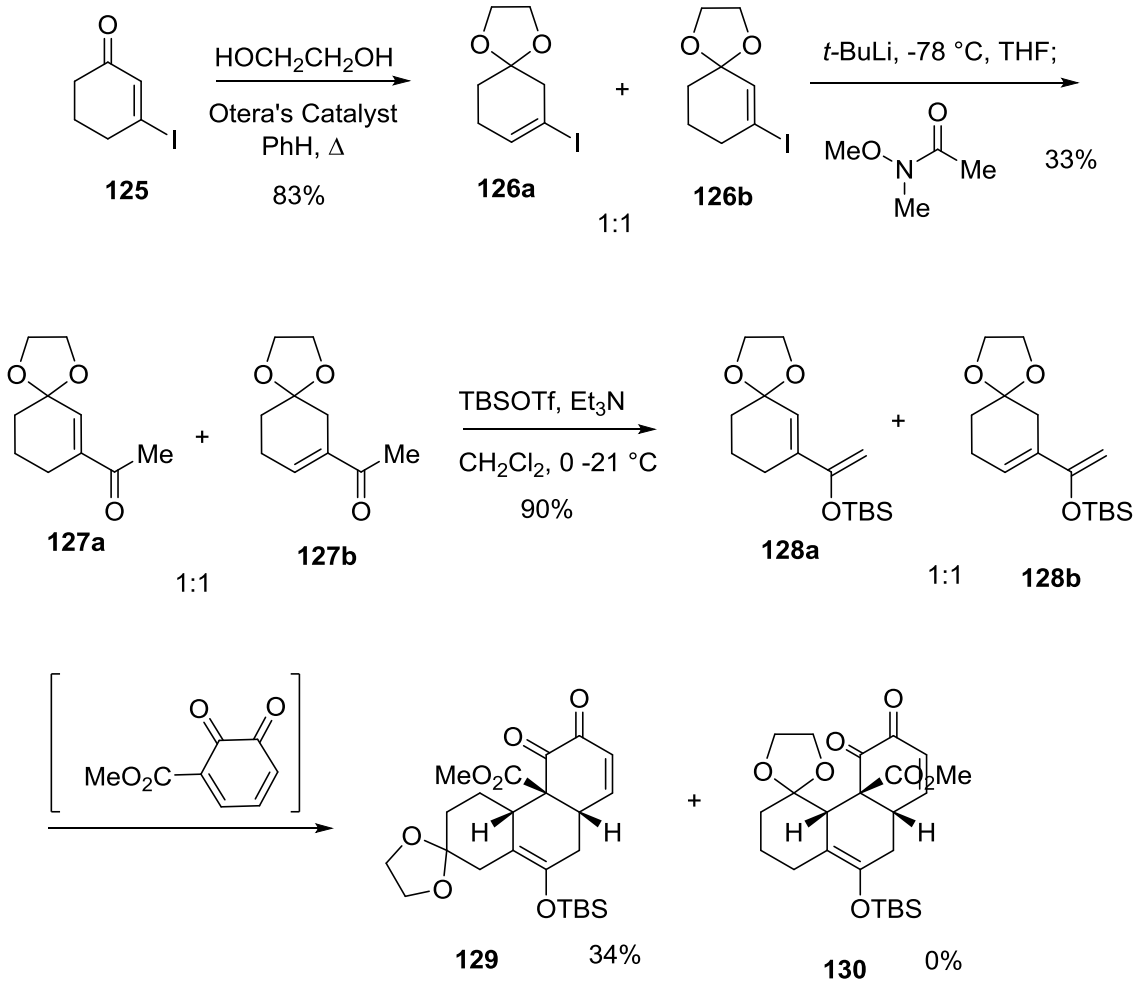
Scheme 1-25. A proposed mechanism for the formation of **118**.

Substitution at the allylic position of the cyclohexenyldiene was investigated (Scheme 1-26). The ethoxy diene **123**, obtained from benzylation of the known alcohol,[72] was subjected to a cycloaddition in refluxing THF using silver (I) oxide as the oxidant of the catechol ester **86**. Analysis of the crude reaction mixture by ^{1}H NMR did not indicate the formation of an *o*-naphthoquinone. The cycloadduct **124** was isolated in 37% yield as a single isomer, with the approach of the dienophile having occurred from the less hindered side of the diene **123** in an endo manner.



Scheme 1-26. The Diels-Alder reaction of benzyl ether **124**.

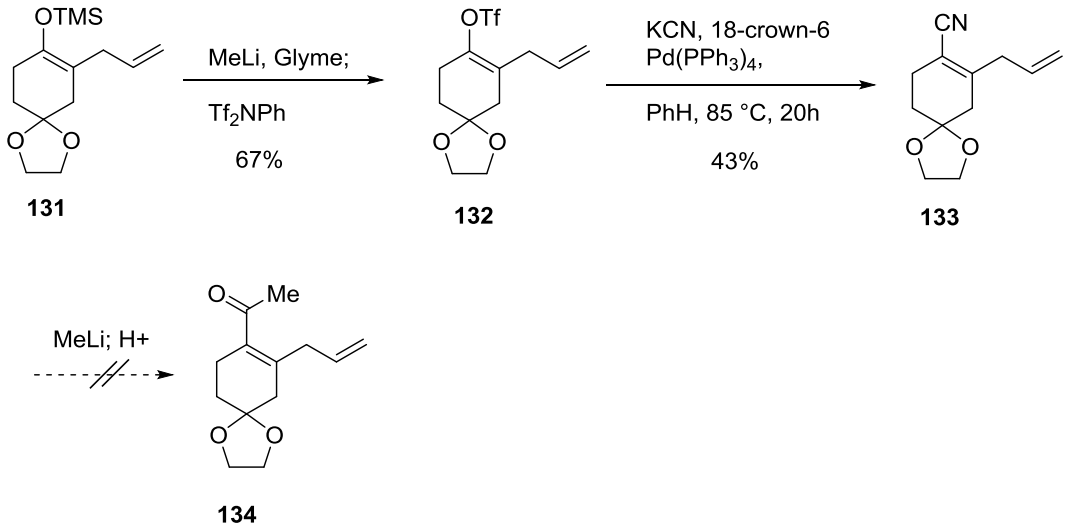
A strategy using an ethylene ketal was pursued as a final attempt to synthesize a phenanthrofuran (Scheme 1-27). Ketalization of the known 3-iodocyclohexen-1-one **125** with Otera's catalyst[73,74] yielded an approximately 1:1 mixture of the regioisomers **126a** and **126b** in 83% yield. Noyori's conditions were also used,[70] but provided similar results at low temperature. Metal halogen exchange and trapping with the Weinreb amide of acetic acid gave the methyl ketones **127a** and **127b** as an inseparable mixture in 33% yield. These were converted to the silyloxy dienes **128a** and **128b** using TBSOTf and triethylamine. The Diels-Alder reaction of the dienes with the ester **112** (prepared by the *in situ* oxidation of the catechol with PIFA) gave only the cycloadduct **129** in 34% yield. The lack of the cycloadduct **130** was demonstrated by the ^{1}H NMR spectrum, which showed the lack of a singlet that would have been present for H_a in the case of cycloadduct **130**. The steric hindrance imposed by the ketal of diene **128a** is thought to be a source of this unfortunate selectivity.



Scheme 1-27. Final attempt to synthesize phenanthrofuran.

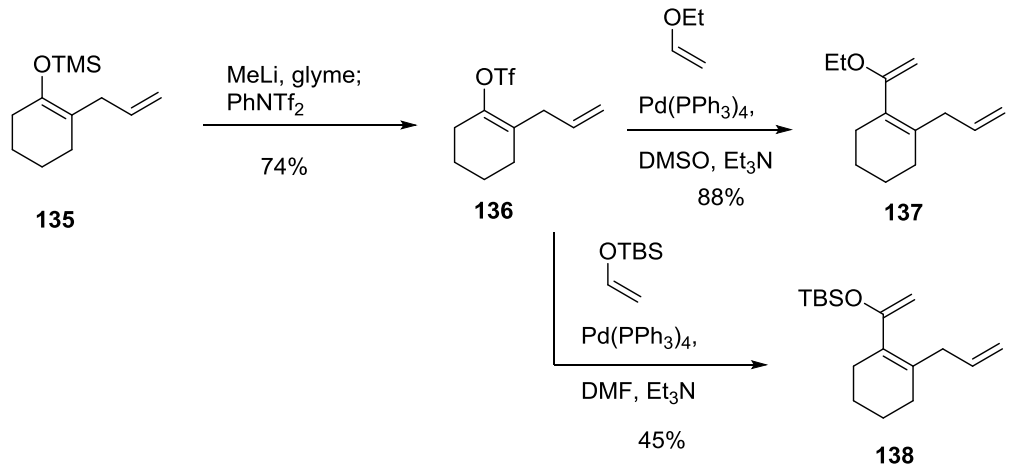
Though intriguing, a cycloadduct such as **129** would require significant elaboration to close the E ring of morphine and install the necessary substituents at C13 to eventually form the bridging D ring. Installing the ketal in closer proximity would be ideal; however, this would require substitution at C13 to be included earlier (Scheme 1-28). The allyl TMS enol ether **131** was cleaved with methyllithium and the resulting enolate was trapped *N*-phenyltriflimide to provide the vinyl triflate **132** in 67% yield. Palladium catalyzed cyanation provided the nitrile **133**. Attempts to form the methyl ketone **134** by addition of methyllithium to the nitrile were not successful. A dark green precipitate formed during the course of the addition of methyllithium, giving rise to unidentified products upon aqueous workup. GC/MS did not indicate the presence

of the methyl ketone. The acidity of the doubly allylic protons was possibly the source of the failure of this reaction.



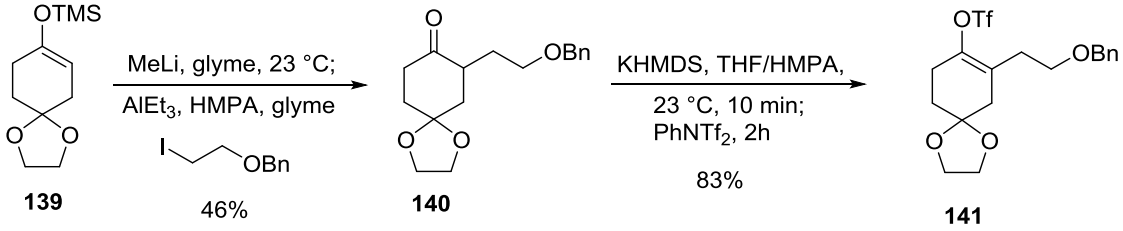
Scheme 1-28. Attempt to access the methyl ketone **134** via the nitrile **133**.

A method of bypassing the enone and forming the desired vinyl ether directly via a Heck vinylation was investigated (Scheme 1-29). Vinylation of the α-position of electron rich olefins has been previously studied.[75,76,77] Vinyl triflates allow α-vinylation to be carried out through an electronically controlled mechanism. The vinyl triflate **136**, prepared in 74% yield by methyllithium cleavage of silyl enol ether **135** and trapping with *N*-phenyltriflimide, was found to undergo palladium catalyzed vinylation with ethyl vinyl ether to give the triene **137** in 88% yield. More surprisingly, the TBS vinyl ether was also found to undergo a coupling reaction into the vinyl triflate **136** to give the triene **138** in 45% yield. However, the reaction had to be conducted in DMF due to the insolubility of the TBS vinyl ether in DMSO. However, these structures proved difficult to handle and indicated that a more stable substitution pattern should be pursued instead of a triene.



Scheme 1-29. Heck vinylation strategy.

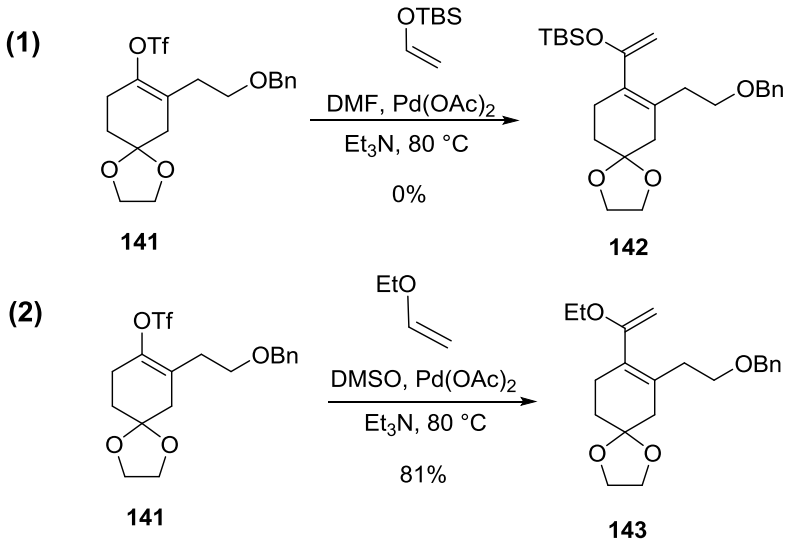
A 2-benzyloxyethyl side chain seemed to be an attractive alternative due to the possibility of an orthogonal method of deprotection (Scheme 1-30). Alkylation of the trimethylsilyl enol ether **139** could be affected in a single step using methyllithium and then triethylaluminum with excess 2-iodoethyl benzyl ether to provide **140** in 46% yield. Very little polyalkylation of **139** was detected. The thermodynamic enolate of **140** was easily formed using KHMDS and trapping with *N*-phenyltriflimide provided the cyclohexenyl triflate **141** in 83% yield.



Scheme 1-30. Benzyloxyethyl side chain and vinyl triflate synthesis.

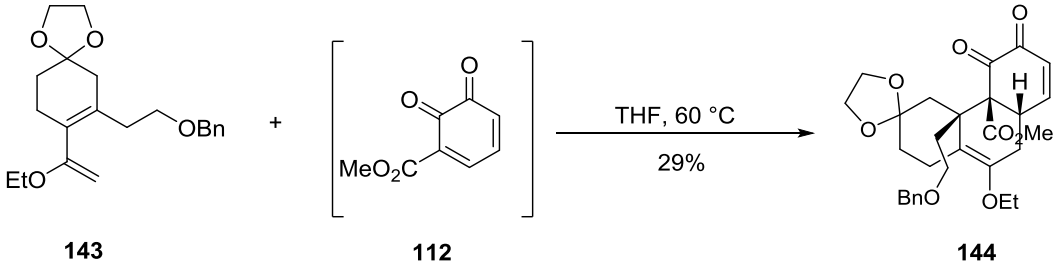
The synthesis of a suitable diene from the cyclohexenyl triflate **141** was studied next. When the vinyl triflate **141** was reacted under the conditions developed for **138**, none of the desired product **142** was formed. Using palladium(II) acetate, only a red solution could be obtained (Scheme 1-31, Equation 1). The same red solution also formed in the absence of the

vinyl triflate **141**. Fortunately, vinylation with ethyl vinyl ether (Scheme 1-31, Equation 2) provide the ethoxy diene **143** in an excellent 81% yield.



Scheme 1-31. The Heck vinylation of cyclohexenyl triflate **141**.

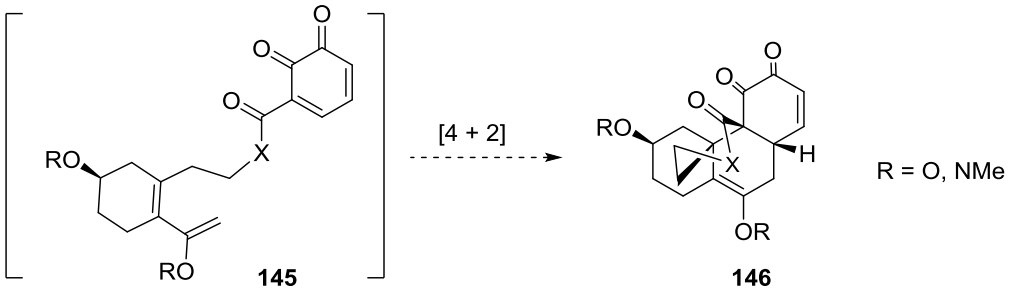
The Diels-Alder reaction between the diene **143** and the dienophile **112** (generated *in situ* from **86** using silver (I) oxide) was successful (Scheme 1-32). The Diels-Alder product **144** was obtained but in a low yield of 29%. Remarkably, this reaction occurs with the very large and hindered benzyloxyethyl side chain on the inside of the diene. The cycloadduct **144** is one of the most functionalized products obtained from a cycloaddition with an *o*-benzoquinone. Nearly the entire framework for morphine is present, except for the *N*-methylamine substituent. The structure of **144** contains all the functionality necessary for transformation into morphine.



Scheme 1-32. Successful Diels-Alder reaction.

Future Work

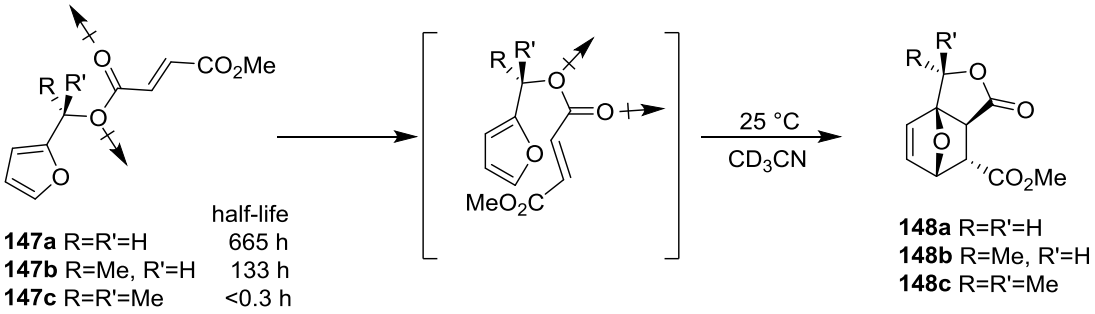
An intramolecular approach would make the *ortho*-benzoquinone cycloaddition strategy more practical since only a 1:1 ratio of diene and dienophile would now be required (Scheme 1-33). The diene could be tethered via the side chain as an ester or an amide, e.g., **145**, to produce a tetracyclic cycloadduct such as **146**. Given the facial selectivity observed for the Diels-Alder cycloaddition product **124** (Scheme 1-26), this strategy could possibly be used in an asymmetric synthesis of morphine via a stereocenter introduced on the eventual C ring of morphine.



Scheme 1-33. Proposed Intramolecular Diels-Alder Cycloaddition.

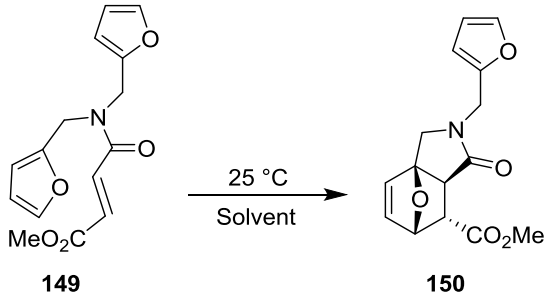
Jung and Gervay have performed numerous studies on the intramolecular Diels-Alder reactions of esters.[78,79,80,81] Their work on the intramolecular cycloadditions of furans tethered to a fumarate dienophile provides important insights into the feasibility of a tethered ester strategy (Scheme 1-34). When the tether is unsubstituted (**147a**, R=R'=H) a sluggish (665 h) cycloaddition providing **148a** was observed. However, increased substitution (**147c**, R=R'=Me) causes a dramatic rate acceleration via the "Thorpe-Ingold" effect to give **148c** in only 20 minutes. Unfortunately such substitutions cannot be used to our advantage for the synthesis of morphine. Increasing the solvent polarity also causes the cycloaddition to occur more quickly. This is due to the stabilization of the more polar *s-cis* ester in the transition state required for the cycloaddition vs the less polar *s-trans* ester o the starting material. When the reaction of **147a**

(R=R'=H) was conducted in DMSO, the cycloaddition occurred 3,200 times faster than when it was conducted in toluene.



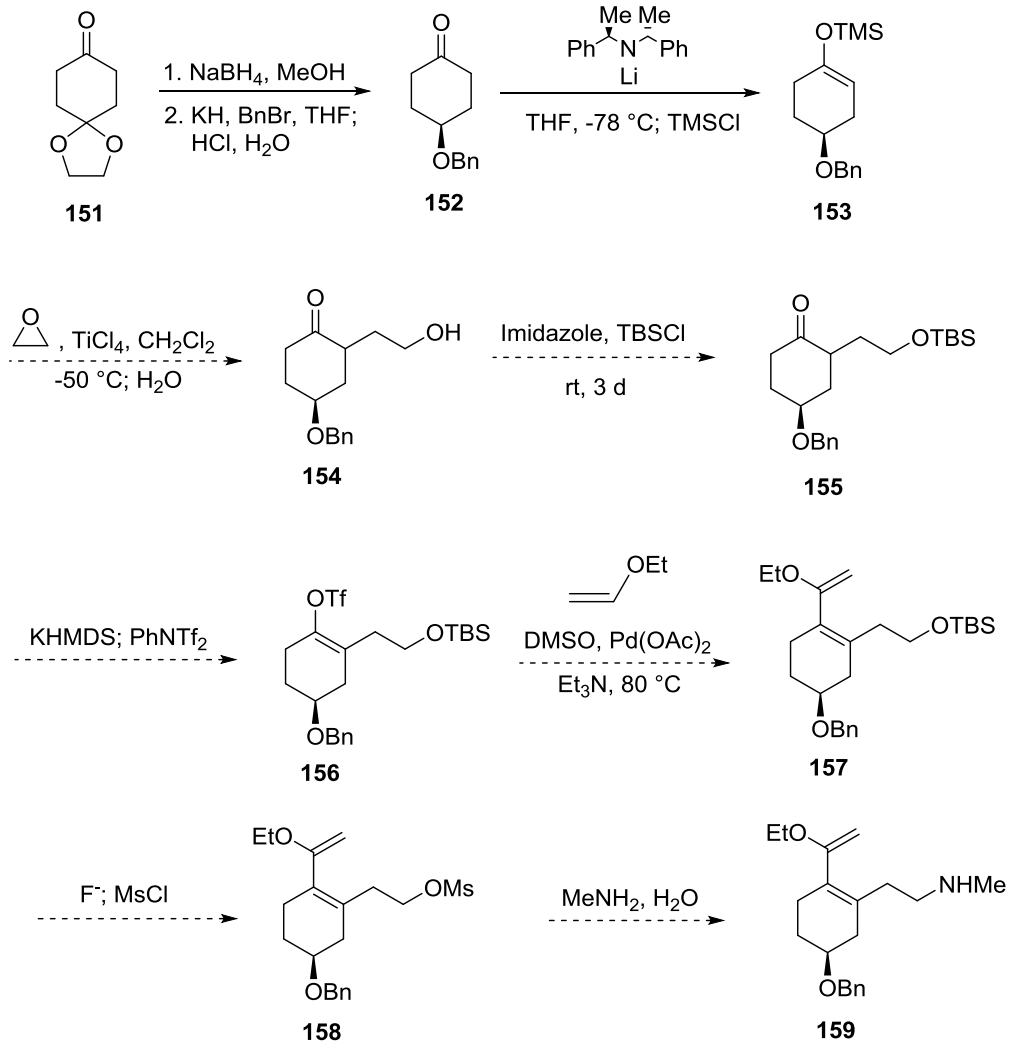
Scheme 1-34. Jung and Gervay's work on the intramolecular Diels-Alder reaction.

Fortunately, amide tethered dienes also undergo the Diels-Alder cycloaddition (Scheme 1-35).[79,82] The intramolecular addition of the furan tethered amide **149** underwent cycloaddition at 25 °C, providing the lactam **150**. The reaction did not display a solvent effect, namely the reaction occurred at the same rate irrespective of solvent. This is likely caused by the lack of a strong dipole effect in tertiary amides. A strategy employing an amide tethered diene would have the best chance of success due to the increased likelihood of forming the necessary *s-cis* transition state.



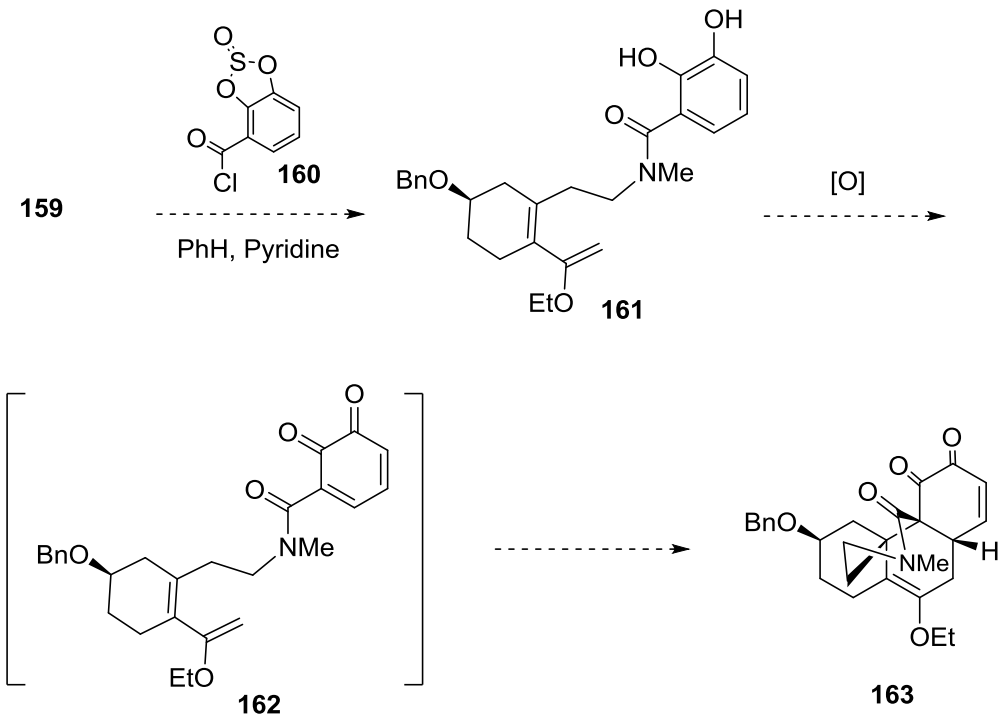
Scheme 1-35. The intramolecular cycloaddition via a tethered amide.

A possible synthesis starting from the commercially available ketone **151** is proposed (Scheme 1-36). The known achiral ketone **152** has been produced in previous reports.[83,84,85] The ketone **152** can be desymmetrized to the silyl enol ether **153** by deprotonation with a chiral lithium amide and trapping of the resulting lithium enolate with trimethylsilyl chloride.[86] Alkylation of **153** with ethylene oxide would provide the cyclohexanone **154**.[87] The cyclohexanone **154** would then be protected as the TBS ether **155** using imidazole and TBSCl.[88] Using the methods developed in our work, the trisubstituted vinyl triflate **156** could be prepared and converted to the electron rich diene **159** via a Heck vinylation with ethyl vinyl ether. Fluoride cleavage of the TBS ether and trapping of the resulting alkoxide as a mesylate would provide the diene **157**. The one-pot conversion of silyl ethers to nonaflates has been previously reported.[89] The mesylate of **158** could then be displaced by methyl amine,[90] to give the ethyl methyl amine **159**. However, the TBS ether **155** could also be used to form tethered esters and the intramolecular Diels-Alder reaction attempted in polar solvents.



Scheme 1-36. Proposed synthesis of the chiral diene **159**.

Tethering the diene is likely to pose another serious challenge (Scheme 1-37). The *N*,*N*-dimethyl-*o*-benzoquinone carboxamide **122a**, used previously in our work (Scheme 1-21, Equation 3), was synthesized by amidation of the benzoyl chloride cyclic sulfite ester **160** with excess dimethyl amine.[91] This is currently the best known method of forming catechol carboxamides and could potentially be used to form the tether necessary to give the product **161**. Oxidation of the tethered catechol would give the *ortho*-benzoquinone intermediate **162** which could then undergo the intramolecular Diels-Alder cycloaddition to provide the cycloadduct **163**. The synthesis at this point theoretically requires 11 steps.



Scheme 1-37. Proposed intramolecular cycloaddition of an *o*-benzoquinone.

Elaboration of a cycloadduct such as **163** to provide morphine would still require several more steps, likely exceeding the target of 14 steps. However, such a synthetic route would provide access to highly functionalized structures more economically from *o*-benzoquinones in an asymmetric manner. And if the intramolecular cycloaddition were not successful, then possibly an asymmetric synthesis could be developed from the chiral dienes **157** and **159** via an intermolecular Diels-Alder reaction.

Conclusion

A potential strategy toward the synthesis of morphine using *o*-benzoquinones as dienophiles in the Diels-Alder reaction has been investigated. Various syntheses of the phenanthrene ABC-ring unit of morphine have been accomplished, with the goal of introducing masked keto groups on the eventual C ring of morphine. Ethylene ketals at C6 and C7 were successfully installed via the Diels-Alder cycloaddition. The ketal at C6 would be the most amenable for further synthetic elaboration to close the E ring of morphine. Attempts to introduce a masked keto function at C5 were problematic. A Diels-Alder reaction is possible as was evidence by the case with the TMS cyanohydrin **116**, however a rearrangement to an *o*-naphthoquinone occurred. An intramolecular 1,4-addition was the only successful method of synthesizing the phenanthrene unit with a keto function at C5.

The Diels-Alder cycloadduct **144** was obtained from the Diels-Alder reaction of the highly hindered diene **143** and *o*-benzoquinone ester **112** as a dienophile. The cycloadduct **144** contains all the necessary functionality to complete a synthesis of morphine, including the two carbons required for the bridging D ring. This cycloadduct was produced in five steps from the commercially available 1,4-cyclohexanedione monoethylene ketal. A highly selective synthesis of the hindered diene was developed via a palladium catalyzed α-vinylation of a vinyl triflate.

In addition to these findings, a method of synthesizing benzofurans via the conjugate addition of trimethylsilyl enol ethers to methyl *o*-benzoquinone-4-carboxylate was developed. The synthesis could be accomplished in a one-pot manner. Most of the benzofuran products obtained from this work displayed a strong blue fluorescence under long wavelength ultraviolet light.

Experimental Section

General: All reactions were carried out under an argon atmosphere unless otherwise specified. Tetrahydrofuran (THF), diethyl ether, toluene, and benzene were distilled from sodium and benzophenone ketyl radical under an argon atmosphere. Dichloromethane (DCM) and triethylamine (TEA) were distilled from calcium hydride under an argon atmosphere. *N*-Phenyltriflimide was purchased from Oakwood Products, Inc. All other solvents or reagents were purified according to literature procedures. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 300, 400 & 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 75, 100 & 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). All Fourier Transform Infrared (FTIR) samples were prepared neat as thin films on a germanium or diamond crystal and spectra were recorded using attenuated total reflectance (ATR) on a JASCO FTIR-4100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Thin-layer chromatography (TLC) was carried out using pre-coated silica gel aluminum backed sheets (EMD Millipore Silica gel 60 F_{254}). Visual detection was performed using ceric ammonium nitrate, *p*-anisaldehyde and potassium permanganate stains or ultraviolet light at 256 nm or 354 nm. Flash chromatography was performed using SilicaFlash™ P60 (60 Å, 40-63 μm) silica gel from SiliCycle Inc. with compressed air.

5-methyl-1,2-naphthoquinone (83): A 25-mL round bottom flask was charged with tetrahydrofuran (THF, 10 ml), 3,4-dihydroxybenzoic acid (250 mg, 1.62 mmol) and piperylene (800 uL, 7.98 mmol). The flask was cooled to 0 °C and iodobenzene bis(trifluoroacetate)[92] (PIFA, 837 mg, 1.95 mmol) was added drop wise as a solution in THF (2.5 ml) over 10 min. Over the next 30 min, the solution became green, then a red color developed. The solution was warmed to 21 °C and stirred overnight at 21 °C. The solution was concentrated to a semi-solid and the residues purified by flash column chromatography (silica gel, ethyl acetate). Naphthoquinone **83**, was obtained as a dark red residue (121 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.98 (bd, *J* = 7.6 Hz, 1H)

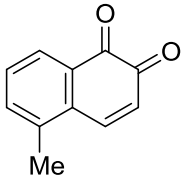
7.76 (d, *J* = 10.8 Hz, 1H)

7.48 (bd, *J* = 7.2, 1H)

7.39 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H)

6.44 (d, *J* = 10.4 Hz, 1H)

2.51 (s, 3H).



Values reported by Ishii: [59] ^{1}H NMR (100 MHz, $CDCl_3$, δ): 7.94 (dd, *J* = 6.8, 1.8 Hz, 1H), 7.74 (d, *J* = 10.0 Hz, 1H), 7.35-7.50 (m, 2H), 6.39 (d, *J* = 10.0 Hz, 1H), 2.48 (s, 3H).

(4*R*,4a*S*) Methyl 8-hydroxy-4-methyl-7-oxo-1,4,4a,7-tetrahydronaphthalene-4a-carboxylate (85): A 10 ml round bottom flask was charged with piperylene (500 μl, 1.23 mmol), methyl 3,4-dihydroxybenzoate[93] (35.6 mg, 0.22 mmol) and THF (5 ml) and the mixture cooled to 0 °C. A solution of PIFA (111 mg, 0.26 mmol, 1 ml THF) was added drop wise over 10 min with stirring. The flask was allowed to warm to 21 °C and stirred for 4 h. A light yellow solution developed, later becoming green. The solution was concentrated and the residue was purified by flash column chromatography (silica gel, 25% ethyl acetate/hexanes) giving **85** as a yellow solid (44.6 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$, δ):

6.89 (d, *J* = 9.9 Hz, 1H),

6.53 (d, *J* = 9.9 Hz, 1H)

6.42 (bs, 1H)

5.79-5.89 (m, 1H)

5.61-5.70 (m, 1H)

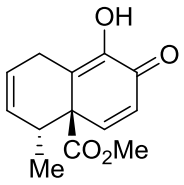
3.68 (s, 3H)

3.34-3.47 (m, 1H)

3.22-3.34 (m, 1H)

2.94-3.09 (m, 1H)

0.75 (d, *J* = 6.9 Hz, 3H).



^{13}C NMR (75 MHz, $CDCl_3$, δ): 180.5, 171.0, 149.8, 145.2, 130.1, 128.6, 125.2, 123.9, 56.7, 53.3, 38.7, 25.8, 15.8.

(4*S*,4a*R*,8a*S*) Methyl 4-methyl-5,6-dioxo-1,4,4a,5,6,8a-hexahydronaphthalene-4a-carboxylate (87): A 25 ml round bottom flask was charged with methyl 2,3-dihydroxybenzoate **86**[94] (84.1 mg, 0.5 mmol), piperylene (189 mg, 2.78 mmol) and THF (10 ml). The flask was cooled to 0 °C and PIFA (240 mg, 0.56 mmol in 7.5 mmol THF) was added drop wise over 10 min. The ice bath was removed and the reaction was allowed to stir at 21 °C for 4 h. The solution was concentrated and the residue was purified by flash column chromatography (silica gel, 25% ethyl acetate/hexanes). The product **87** was obtained as a tan residue (26 mg, 23%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.36 (dd, *J* = 9.6, 6.4 Hz, 1H)

6.27 (d, *J* = 10.0 Hz, 1H)

5.60-5.66 (m, 1H)

5.52-5.59 (m, 1H)

3.69 (s, 3H)

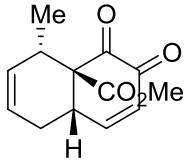
3.31 (dd, *J* = 6.4, 6.4 Hz, 1H)

2.67-2.77 (m, 1H)

2.55-2.65 (m, 1H)

1.60-1.71 (m, 1H)

1.23 (d, *J* = 7.6 Hz, 3H).



^{13}C NMR (100 MHz, $CDCl_3$, δ): 191.0, 183.9, 172.2, 156.2, 130.3, 129.9, 121.9, 65.8, 52.9, 42.5, 36.0, 31.7, 15.6.

(4a*S*,4b*S*,10a*S*) Methyl 9-(1,1-Dimethylethyl)dimethylsilyloxy-4b-methyl-3,4-dioxo-3,4,4a, 4b,5,6,7,8,10,10a-decahydrophenanthrene-4a-carboxylate (88). To a solution of methyl 2,3-dihydroxybenzoate **86** (84 mg, 0.5 mmol) and 1-(1,1-dimethylethyl)dimethylsilyloxy-ethenyl)-2-methylcyclohexene[95] (**79**) (631 mg, 2.5 mmol), was added PIFA (264 mg, 0.55 mmol, 1 ml THF) drop wise over 10 min. A yellow solution formed, the ice bath was removed and the mixture was stirred at 21 °C for 4 h The solution was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (silica gel, 25% ethyl acetate/hexanes) to yield **88** as dark yellow crystals (106.7 mg, 51%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.46 (dd, *J* = 9.5, 6.5 Hz, 1H)

6.28 (d, *J* = 10.0 Hz, 1H)

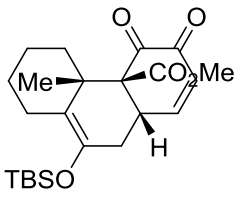
3.69 (s, 3H)

3.65 (ddd, *J* = 12.0, 6.5, 6.5 Hz, 1H)

2.85 (bd, *J* = 15.0 Hz, 1H)

2.53 (ddd, *J* = 17.6, 6.5, 2.5 Hz, 1H)

2.44 (ddd, *J* = 13.5, 13.5, 4.5 Hz, 1H)



1.76-1.83 (m, 1H)

1.64-1.73 (m, 3H)

1.41-1.52 (m, 2H)

1.17 (s, 3H)

1.11-1.16 (m, 1H)

0.90 (s, 9H)

0.089 (s, 3H)

0.030 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 191.1, 185.1, 170.3, 158.2, 136.8, 129.6, 119.6, 70.7, 52.7, 39.1, 38.4, 36.0, 32.6, 25.8, 24.8, 23.7, 23.0, 22.1, 18.1, -3.6, -4.4.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{23}H_{35}O_5Si$ 419.2254found 419.2266.

FTIR (neat): 2951, 2928, 2853, 1748, 1732, 1714 cm^{-1}.

Methyl 7-hydroxy-2-(2-methylcyclohex-1-enyl)benzofuran-4-carboxylate (91). A 25 ml round bottom flask was charged with the diene **79** (2.0 g, 8.00 mmol), methyl 3,4-dihydroxybenzoate **84** (200 mg, 1.20 mmol) and THF (12.5 ml). The solution was cooled to 0 °C and PIFA (563 mg, 1.30 mmol, in 2.5 ml THF) was added drop wise over 5 min. A green solution formed and the reaction was allowed to warm to 21 °C. After stirring for 4 h, the solution became yellow, yielding a fluorescent product by thin layer chromatography. The solution was stirred for 12 h and concentrated. The diene was vacuum distilled (0.1 mm Hg, 100 °C) away to yield yellow solid. Recrystallization from hexanes and ethyl acetate gave **91** as a bright white solid (84 mg, 25%). mp 170-172 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ):

10.92 (s, 1H)

7.72 (d, *J* = 8.4 Hz, 1H)

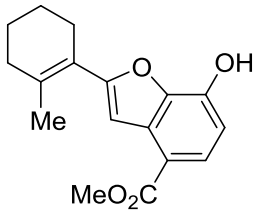
7.07 (s, 1H)

6.78 (d, *J* = 8.4 Hz, 1H)

3.84 (s, 3H)

2.44-2.37 (m, 2H)

2.23-2.15 (m, 2H)



2.00 (s, 3H)

1.72-1.57 (m, 4H).

^{13}C NMR (100 MHz, DMSO-d_6, δ): 166.1, 158.8, 146.9, 141.9, 137.0, 130.9, 128.7, 127.3, 120.8, 112.0, 109.9, 51.5, 32.7, 27.2, 22.15, 22.08, 21.9.

FTIR (neat): 3330, 2932, 2858, 1683 cm^{-1}

General procedure for the synthesis of benzofurans from trimethylsilyl enol ethers: Methyl 7-hydroxy-2-phenylbenzofuran-4-carboxylate (97): The previously reported vinyl trimethylsilyl enol ethers (**96**[96], **96a**,[97] **96b**, **96c**,[98] **96d**,[99] **96e**,[100] **96f**,[101] **96g**[102] and **98**[103]) were prepared by the procedure of Walshe, *et al.*[104] A 25 ml round bottom flask was charged with a solution of methyl 3,4-dihydroxybenzoate **84** (33.7 mg, 0.2 mmol) in THF (2 ml). The flask was cooled to 0 °C and vinyl 1-phenyl-1-trimethylsilyl ether **96** (154.4 mg, 0.80 mmol) was added as a solution in THF (2 ml) and the mixture was stirred for 2 min and cooled to 0 °C. PIFA (86.4 mg, 0.20 mmol) in THF (3 ml) was added dropwise to the solution over 10 min. The solution was stirred at 0 °C for 4 hours, becoming dark yellow, and then was warmed to 21 °C. Hydrochloric acid (1 ml, 4 M in dioxane) and methanol (3 ml) were added and the solution was stirred for 1 h. The solution became nearly water white. The mixture was extracted with diethyl ether (15 ml) and washed with saturated $NaHCO_3$ (3 x 5 ml) and brine (1 x 10 ml) and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated, providing a yellow oil which was purified by flash column chromatography (silica gel 40% diethyl ether/hexanes) to give a white solid. Recrystallization from toluene yielded tan crystals of **97** (39.3 mg, 73%). mp 188-190 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ):

11.12 (s, 1H)

7.99 (d, *J* = 7.5 Hz, 2H)

7.78 (d, *J* = 8.4 Hz, 1H)

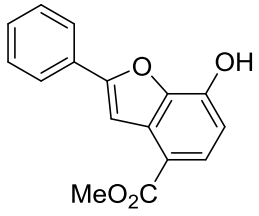
7.73 (s, 1H)

7.53 (m, 2H)

7.46 (m, 1H)

6.86 (d, *J* = 8.4 Hz, 1H)

3.89 (s, 3H).



^{13}C NMR (100 MHz, DMSO-d_6, δ): 166.0, 156.6, 147.1, 142.8, 131.2, 129.3, 129.1, 127.8, 125.0, 112.6, 110.6, 103.1, 51.6. (one low field carbon peak not observed due to overlapping).

FTIR (neat): 3264, 2956, 2924, 2850, 1675 cm^{-1}.

Methyl 7-hydroxy-2-(4-methylphenyl)benzofuran-4-carboxylate (97a). The reaction was conducted with the catechol ester **84** (129 mg, 0.76 mmol) and the silyl ether **96a** (683 mg, 3.1 mmol) according to the general procedure. The residue obtained from the organic extract was purified by flash column chromatography (silica gel, 30 % diethyl ether/hexanes) to provide the product **97a** as a white solid (160 mg, 74%). mp 188-189 °C.

^{1}H NMR (300 MHz, DMSO-d_6, δ):

11.06 (s, 1H)

7.88 (d, *J* = 7.3 Hz, 2H)

7.76 (d, *J* = 8.1 Hz, 1H)

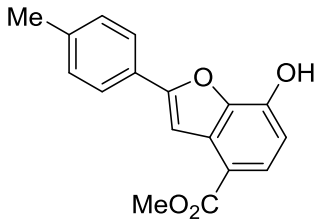
7.65 (s, 1H)

7.34 (d, *J* = 7.3 Hz, 2H)

6.83 (d, *J* = 8.1 Hz, 1H)

3.88 (s, 3H)

2.37 (s, 3H).



^{13}C NMR (75 MHz, DMSO-d_6, δ): 166.0, 156.8, 147.0, 142.6, 139.1, 131.4, 129.7, 127.6, 126.6, 125.0, 112.5, 110.4, 102.3, 51.5, 20.9.

FTIR (neat): 3279, 3016, 2952, 1672 cm^{-1}.

Methyl 7-hydroxy-2-(4-nitrophenyl)benzofuran-4-carboxylate (97b). The reaction was conducted according to the general procedure with the nitrosilyl ether **96b** (1.02 g, 4.3 mmol) and the catechol ester **84** (169 mg, 1.0 mmol). The organic extract was concentrated to a semi-solid residue and purified by flash column chromatography (40%-100% diethyl ether/hexanes). The benzofuran **97b** was obtained as a bright yellow solid (237 mg, 74%). mp 244-245 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ):

11.30 (s, 1H)

8.36 (d, *J* = 8.9 Hz, 2H)

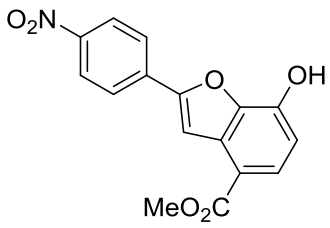
8.25 (d, *J* = 8.9 Hz, 2H)

8.03 (s, 1H)

7.81 (d, *J* = 8.4 Hz, 1H)

6.92 (d, *J* = 8.4 Hz, 1H)

3.90 (s, 3H).



^{13}C NMR (100 MHz, DMSO-d_6, δ): 165.8, 154.1, 147.4, 147.2, 143.5, 135.2, 130.6, 128.7, 128.2, 126.0, 124.4, 113.1, 106.9, 51.7.

FTIR (neat): 3173, 2957, 1673 cm^{-1}.

(Note: This compound did not display blue fluorescence under long wavelength ultraviolet light.)

Methyl 7-hydroxy-2-(4-methoxyphenyl)benzofuran-4-carboxylate (97c). The reaction was conducted with catechol ester **84** (168 mg, 1.0 mmol) and the silyl enol ether **96c** (1.27 g, 4.7 mmol) according to the general procedure. The crude extract was purified by flash column chromatography (20-50% diethyl ether/hexanes) to provide the benzofuran **97c** as a tan solid (86.6 mg, 29%). mp 180-182 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ):

11.04 (s, 1H)

7.92 (d, *J* = 8.8 Hz, 2H)

7.75 (d, *J* = 8.4 Hz, 1H)

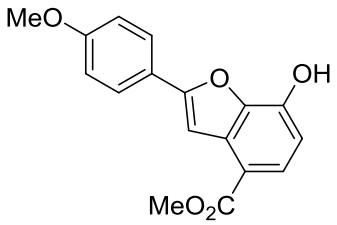
7.57 (s, 1H)

7.09 (d, *J* = 8.8 Hz, 2H)

6.81 (d, *J* = 8.4 Hz, 1H)

3.88 (s, 3H)

3.83 (s, 3H).



^{13}C NMR (100 MHz, DMSO-d_6, δ): 166.1, 160.2, 156.9, 146.9, 142.5, 131.6, 128.7, 126.7, 122.0, 114.6, 112.3, 110.2, 101.3, 55.4, 51.5.

FTIR (neat): 3273, 2951, 2838, 1675 cm^{-1}.

Methyl 2-(4-bromophenyl)-7-hydroxybenzofuran-4-carboxylate (97d). The reaction was conducted according to the general procedure using the catechol ester **84** (168 mg, 1.0 mmol) and the bromo silyl enol **96d** (1.08 g, 4.0 mmol). The crude extract was purified by flash column chromatography (40% diethyl ether/hexanes) to provide the benzofuran **97d** as a tan solid (189 mg, 54%). mp 245-247 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ):

11.14 (s, 1H)

7.95 (d, *J* = 8.6 Hz, 2H)

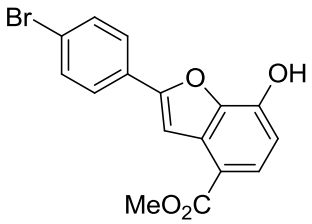
7.80 (s, 1H)

7.78 (d, *J* = 8.4 Hz, 1H)

7.74 (d, *J* = 8.6 Hz, 2H)

6.86 (d, *J* = 8.4 Hz, 1H)

3.89 (s, 3H).



^{13}C NMR (100 MHz, DMSO-d_6, δ) 165.9, 155.4, 147.1, 142.9, 132.1, 131.1, 128.7, 128.5, 127.9, 127.0, 122.5, 112.7, 103.9, 51.6.

FTIR (neat): 3284, 2952, 1677 cm^{-1}.

Methyl 7-hydroxy-2-(naphthalen-2-yl)benzofuran-4-carboxylate (97e). The reaction was conducted according to the general procedure using the catechol ester **84** (168 mg, 1.0 mmol) and the silyl enol ether **96e** (1.18 g, 4.9 mmol). The crude extract was purified by flash column chromatography (25-100% diethyl ether/hexanes) to provide the benzofuran **97e** as a grey solid (253 mg, 79%). mp 217-219 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ):

11.17 (s, 1H)

8.55 (s, 1H)

8.12 (dd, *J* = 8.9, 1.6 Hz, 1H)

8.07 (m, 2H)

7.97 (m, 1H)

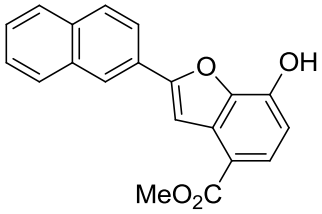
7.88 (s, 1H)

7.80 (d, *J* = 8.4 Hz, 1H)

7.58 (m, 2H)

6.89 (d, *J* = 8.4 Hz, 1H)

3.91 (s, 3H).



^{13}C NMR (100 MHz, DMSO-d_6, δ): 166.0, 156.6, 147.1, 143.0, 133.1, 133.0, 131.3, 128.8, 128.5, 127.8, 127.8, 127.0, 127.0, 126.7, 124.0, 122.9, 112.6, 110.7, 103.8, 51.6.

FTIR (neat): 3246, 2954, 1673 cm^{-1}.

Methyl 7-hydroxy-2-(3-methoxyphenyl)benzofuran-4-carboxylate (97f): The reaction was conducted according to the general procedure using the catechol ester **84** (168 mg, 1.0 mmol) and the silyl enol ether **96f** (889 mg, 4.0 mmol). The crude extract was purified by flash column chromatography (silica gel 30-50% diethyl ether/hexanes) to provide the benzofuran **97f** as a tan solid. (98 mg, 33%). mp 175-177 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ):

11.10 (s, 1H)

7.78 (d, *J* = 8.4 Hz, 1H)

7.76 (s, 1H)

7.57 (bd, *J* = 8.0 Hz, 1H)

7.52 (dd, *J* = 2.5, 1.5 Hz, 1H)

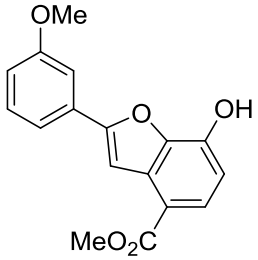
7.45 (dd, *J* = 8.0, 8.0 Hz, 1H)

7.03 (ddd, *J* = 8.2, 2.5, 0.8 Hz, 1H)

6.85 (d, *J* = 8.4 Hz, 1H)

3.89 (s, 3H)

3.87 (s, 3H).



^{13}C NMR (100 MHz, DMSO-d_6, δ): 166.0, 159.8, 156.4, 147.1, 142.8, 131.2, 130.7, 130.3, 128.7, 127.8, 115.3, 112.6, 110.6, 110.0, 103.4, 55.3, 51.6.

Methyl 2-(furan-2-yl)-7-hydroxybenzofuran-4-carboxylate (97g): The reaction was conducted according to the general procedure using the catechol ester **84** (168 mg, 1.0 mmol) and the silyl enol ether **96g** (729 mg, 4.0 mmol). The crude extract was purified by flash column chromatography (30-60 % diethyl ether/hexanes) to provide the benzofuran **97g** as a white solid (155 mg, 60%). mp 190-192 °C.

^{1}H NMR (400 MHz, DMSO-d_6, δ):

11.17 (s, 1H)

7.92 (d, *J* = 1.4 Hz, 1H)

7.78 (d, *J* = 8.4 Hz, 1H)

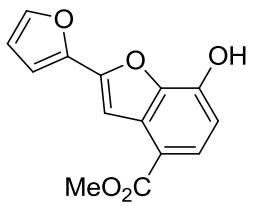
7.43 (s, 1H)

7.08 (d, *J* = 3.2 Hz, 1H)

6.85 (d, *J* = 8.4 Hz, 1H)

6.72 (dd, *J* = 3.2, 1.8 Hz, 1H)

3.87 (s, 1H).



^{13}C NMR (100 MHz, DMSO-d_6, δ): 165.9, 148.7, 147.1, 144.8, 144.6, 142.5, 130.7, 128.7, 128.0, 112.4, 110.8, 109.4, 102.3, 51.6.

FTIR (neat): 3273, 2951, 2838, 1675 cm^{-1}.

Methyl 4-hydroxy-6,7,8,9-tetrahydrodibenzo[*b,d*]furan-1-carboxylate (99). The reaction was conducted according to the general procedure using the catechol ester **84** (168 mg, 1.0 mmol) and the silyl enol ether **98** (704 mg, 4.0 mmol). The crude extract was purified by flash chromatography (silica gel, 20% diethyl ether/hexanes) to give **99** as a bright white solid (83 mg, 34%). mp 138-140 °C.

^{1}H NMR (300 MHz, DMSO-d_6, δ):

10.72 (s, 1H)

7.63 (d, *J* = 8.4 Hz, 1H)

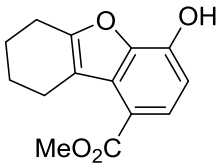
6.72 (d, *J* = 8.4 Hz, 1H)

3.79 (s, 3H)

2.78-2.74 (m, 4H)

1.91-1.78 (m, 2H)

1.78-1.64 (m, 2H).



^{13}C NMR (75 MHz, DMSO-d_6, δ): 166.3, 155.8, 146.5, 142.5, 129.8, 127.2, 113.4, 113.3, 109.2, 51.3, 23.5, 23.4, 22.8, 21.8.

FTIR (neat): 3274, 2951, 2921, 2854, 1678 cm^{-1}.

1-(3,4-Bis((trimethylsilyl)oxy)phenyl)ethanone (102): A 100 ml round bottom flask was charged under argon with 3,4-dihydroxyacetophenone (5.0 g, 32.9 mmol), THF (66 ml) and triethylamine (11.0 g, 109 mmol). Trimethylsilyl chloride (7.9 g, 72.4 mmol) was added drop wise over 30 min to the solution with vigorous stirring, forming a thick white precipitate. The solution was stirred for 5 h at 21 °C then filtered directly through a paper filter, washing with pentane. The filtrate was concentrated *in vacuo*, triturating with pentane. The red oil was diluted with pentane (50 ml) and the precipitate was filtered through a glass fritted funnel, washing with pentane (2 x 10 ml), the filtrate was concentrated *in vacuo* to yield the bis TMS ether **102** as a light red oil (9.52 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.77 (d, *J* = 2.4 Hz, 1H)

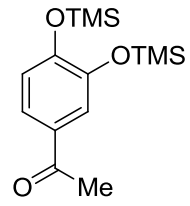
7.34 (d, *J* = 8.4, 2.0 Hz, 1H)

6.77 (d, *J* = 8.4 Hz, 1H)

2.15 (s, 3H)

0.199 (s, 9H)

0.195 (s, 9H).



^{13}C NMR (100 MHz, $CDCl_3$, δ): 194.9, 151.3, 146.9, 132.2, 123.3, 120.8, 120.6, 25.6, -0.002, -0.032.

FTIR (neat): 2959, 1677, 1591, 1570, 1506, 1420, 1357 cm^{-1}.

((4-[1-(1,1-Dimethylethyl)dimethylsilyloxy]vinyl-1,2-phenylene)bis(oxy))bis(trimethyl-silane) (103): A 100 ml round bottom flask was charged under argon with **102** (9.52 g, 32.1 mmol) and THF (50 ml) and cooled to -78 °C. The solution was treated with triethylamine (4.88 g, 48.3 mmol) and TBSOTf (8.5 g, 32.2 mmol) was added drop wise over 10 min. The reaction was stirred for 2 h and then warmed to 21 °C. The reaction mixture was poured into pentane (150 ml), washed with acetonitrile (3 x 25 ml), filtered through paper and concentrated to provide the TBS vinyl ether **103** as a yellow oil (11.4 g, 86%). This was stored at -20 °C.

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.09-7.12 (m, 2H)

6.77 (d, *J* = 8.8 Hz, 1H)

4.74 (d, *J* = 1.6 Hz, 1H)

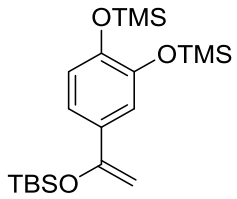
4.30 (d, *J* = 1.6 Hz, 1H)

1.00 (s, 9H)

0.253 (s, 9H)

0.251 (s, 9H)

0.22 (s, 6H).



^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.6, 146.8, 146.0, 131.8, 120.4, 119.0, 118.3, 89.2, 26.3, 18.3, 0.329, -4.612.

1-(3,4-Bis((trimethylsilyl)oxy)phenyl)-2-(3-[(1,1-dimethylethyl)dimethylsilyloxy]-2-methyl-cyclohex-2-en-1-yl)ethanone (104): A 25 ml round bottom flask was charged under argon with a dichloromethane solution (20 ml) of **103** (1.43 g, 2.89 mmol) and 2-methylcyclohexen-1-one (318.2 mg, 2.89 mmol) and the mixture was cooled to -78 °C. Freshly distilled TBSOTf (76.4 mg, 0.289 mmol) was added drop wise to the solution and stirring continued for 2 h. The reaction mixture was quenched with triethylamine and diluted with pentane (50 ml). The solution was filtered through paper, washing with pentane (1 x 5 ml) and concentrated to a yellow oil. The oil was put under vacuum (0.1 mmHg) and heated to 90 °C for 1 h, to provide the practically pure product **104** (1.42 g, 95%), which was stored at -20 °C.

^{1}H NMR (400 MHz, C_6D_6, δ):

7.97 (d, *J* = 2.0 Hz, 1H)

7.59 (dd, *J* = 8.0, 2.0 Hz, 1H)

6.89 (d, *J* = 8.4 Hz, 1H)

3.05-3.10 (m, 1H)

3.05 (dd, *J* = 15.6, 2.4 Hz, 1H)

2.85 (dd, *J* = 16.4, 10.4 Hz, 1H)

1.90-2.05 (m, 1H)

1.78 (bs, 3H)

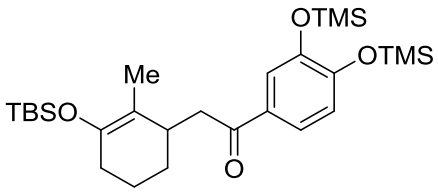
1.58-1.73 (m, 3H)

1.42-1.52 (m, 2H)

1.08 (s, 9H)

0.279 (s, 9H)

0.276 (s, 9H)



0.178 (s, 3H)

0.175 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6, δ): 197.5, 151.3, 147.0, 144.7, 132.6, 123.1, 121.0, 120.7, 113.7, 41.8, 35.8, 30.6, 28.0, 25.8, 20.0, 18.2, 14.7, 0.063, -2.989, -3.816.

2-(3-[(1,1-Dimethylethyl)dimethylsilyloxy]-2-methylcyclohex-2-en-1-yl)-1-(3,4-dihydroxy-phenyl)ethanone (105): A 25 ml round bottomed flask was charged under argon with **104** (587 mg, 1.13 mmol) and a solution of acetonitrile and methanol (10 ml, 9:1). The solution was treated with diazabicycloundecene (DBU, 34 mg, 0.23 mmol) and stirred at 21 °C for 30 min. The solution became dark green. The reaction mixture was extracted with 30 ml dichloromethane, washed with saturated ammonium chloride and brine. The organic phase was dried over anhydrous Na_2SO_4. The crude extract was concentrated *in vacuo* to give a dark residue which was purified by flash column chromatography (silica gel, 40% ethyl acetate/hexanes) to provide tan crystals of **105** (310 mg, 73%). mp 103-105 °C.

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.76 (bd, *J* = 2.0 Hz, 1H)

7.51 (dd, *J* = 8.4, 2.0 Hz, 1H)

6.94 (d, *J* = 8.4 Hz, 1H)

3.07 (dd, *J* = 15.2, 3.2 Hz, 1H)

2.85 (dd, *J* = 15.2, 10.0 Hz, 1H)

2.69-2.77 (m, 1H)

1.98-2.08 (m, 2H)

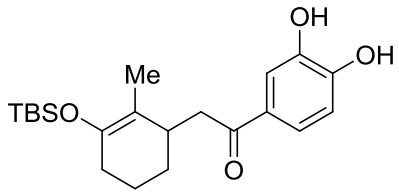
1.63 (s, 3H)

1.52-1.71 (m, 3H)

1.35-1.42 (m, 1H)

-0.953 (s, 9H)

-0.131 (s, 6H).



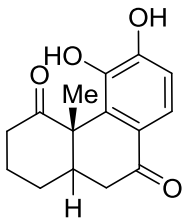
^{13}C NMR (100 MHz, $CDCl_3$, δ): 201.3, 149.8, 145.0, 144.4, 130.2, 123.3, 115.1, 114.6, 113.9, 41.8, 36.2, 30.4, 27.6, 25.9, 19.8, 18.2, 14.8, -3.8.

(4a*S*)-5,6-Dihydroxy-4a-methyl-2,3,10,10a-tetrahydrophenanthrene-4,9(1*H*,4a*H*)-dione (106): A 10 ml round bottom flask was charged under argon with the TBS enol ether **105** (100 mg, 0.27 mmol) and THF (5 ml). The flask was cooled to 0 °C and a solution of PIFA (114 mg, 0.27 mmol, in 1 ml THF) was added drop wise over 10 min; the solution was stirred for 4 h, darkening to a brown color. The solution was concentrated *in vacuo* and the dark residue was purified by flash column chromatography (silica gel, 30% ethyl acetate/dichloromethane) giving a tan residue containing **106** (7.3 mg, 10.5%).

^{1}H NMR (400 MHz, DMSO-d_6, δ):

10.51 (s, 1H)

8.87 (s, 1H)



7.42 (d, *J* = 8.4 Hz, 1H)

6.82 (d, *J* = 8.4 Hz, 1H)

2.91 (dd, *J* = 17.6, 5.2 Hz, 1H)

2.32-2.41 (m, 1H)

2.28 (dd, *J* = 17.2, 2 Hz, 1H)

2.06-2.10 (m, 1H)

1.88-1.93 (m, 1H)

1.47-1.58 (m, 3H)

1.33 (s, 3H)

0.938 (dd, *J* = 14.8, 2.8 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6, δ): 211.8, 194.8, 151.2, 141.3, 133.1, 128.7, 123.3, 113.7, 51.0, 46.6, 40.2, 38.5, 28.3, 27.7, 21.0.

(4a*S*,4b*S*,10a*S*) Methyl 9-[(1,1-dimethylethyl)dimethylsilyloxy)-3,4-dioxo-3,4,4a,4b,5,6,7,8, 10,10a-decahydrophenanthrene-4a-carboxylate (113a). A 25 ml round bottom flask was charged under argon with a solution of the silyl enol ether **111a**[67] (953 mg, 4.00 mmol) and methyl 2,3-dihydroxybenzoate **86** (168 mg, 1.00 mmol) in THF (12 ml). The solution was cooled to 0 °C and a solution of PIFA (473 mg, 1.1 mmol) in THF (10 ml) was added drop wise over 10 min. A yellow solution formed. The reaction was warmed to 21 °C and stirred for 4 h. The orange solution was diluted with ether (100 ml) and washed with water (4 x 125 ml). The organic layer was filtered through a small amount of silica gel, washing with diethyl ether and then concentrated to give a yellow semi-solid residue. Purification of this residue by flash column chromatography (silica gel, 10-40% ethyl acetate/hexanes) gave **113a** as a bright yellow solid (191 mg, 47%), mp 116-118 °C.

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.30 (dd, 1H, *J* = 9.9, 6.0 Hz)

6.32 (d, 1H, *J* = 9.9 Hz)

3.73 (s, 3H)

3.35 (ddd, 1H, *J* = 11.3, 5.7, 5.7 Hz)

2.93 (bd, 1H, *J* = 14.7 Hz)

2.67 (bd, 1H, *J* = 13.1 Hz)

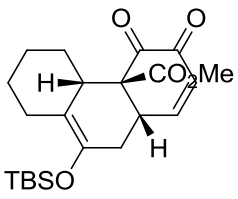
2.47 (bd, 1H, *J* = 12.7 Hz)

2.13 (ddd, 1H, *J* = 12.8, 12.8, 3.7 Hz)

1.70-1.82 (m, 3H)

1.58-1.64 (m, 1H)

1.41-1.43 (m, 1H)



1.25-1.33 (m, 1H)

1.14-1.22 (m, 1H)

0.91 (s, 9H)

0.096 (s, 3H)

0.041 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 191.6, 184.4, 172.4, 155.6, 137.5, 130.4, 115.6, 66.4, 53.0, 42.5, 42.3, 36.2, 26.8, 26.1, 25.8, 25.7, 24.9, 18.1, -3.9, -4.4.

HRMS (ESI-TOF) *m/z*: Calculated for $C_{25}H_{35}NO_5SiNa$ 468.2182 $[M+Na+acetonitrile]^+$; found 468.2167.

FTIR (neat): 2955, 2927, 2854, 1729, 1691, 1250, 1233, 1196 cm^{-1}.

(5a*S*,9a*S*,9b*S*) Methyl 4-[(1,1-dimethylethyl)dimethylsilyloxy]-9b-methyl-8,9-dioxo-2,3,5,5a, 8,9,9a,9b-octahydro-1*H*-cyclopenta[*a*]naphthalene-9a-carboxylate (113b). The TBS enol ether of 1-acetyl-2-methylcyclopentene was prepared by a previously reported procedure.[67] A 25 ml round bottom flask was charged under argon with a solution of the silyl enol ether **111b** (953 mg, 4.00 mmol) and methyl 2,3-dihydroxybenzoate **86** (168 mg, 1.0 mmol) in THF (25 ml). The solution was cooled to 0 °C and a solution of PIFA (473 mg, 1.1 mmol) in THF (10 ml) was added dropwise over 10 min. A yellow solution formed. The reaction was warmed to 21 °C and stirred for 4 h. The red solution was diluted with ether (200 ml) and washed with water (4 x 125 ml). The organic layer was filtered through a small amount of silica gel, washing with diethyl ether and then concentrated to give a red semi-solid residue. Purification of the residue by flash column chromatography (silica gel, 15% ethyl acetate/hexanes) gave **113b** as a bright yellow solid (184 mg, 45%), mp 155-157 °C.

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.49 (dd, *J* = 9.9, 6.5 Hz, 1H)

6.29 (d, *J* = 9.9 Hz, 1H)

3.83 (ddd, *J* = 10.4, 7.0, 7.0 Hz, 1H)

3.70 (s, 3H)

2.53-2.65 (m, 3H)

2.32-2.40 (m, 1H)

1.92-2.00 (m, 1H)

1.75-1.83 (m, 1H)

1.69 (bdd, *J* = 17.8, 10.9 Hz, 1H)

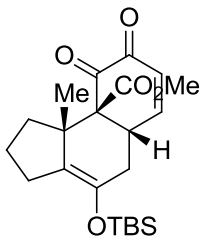
1.28 (ddd, *J* = 12.1, 8.2, 3.4 Hz, 1H)

1.01 (s, 3H)

0.89 (s, 9H)

0.067 (s, 3H)

0.046 (s, 3H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 191.3, 184.5, 170.0, 158.5, 136.3, 129.4, 125.4, 69.4, 53.0, 45.9, 39.9, 35.09, 35.06, 26.8, 25.8, 25.7, 22.5, 18.0, -3.9, -4.0.

HRMS (ESI-TOF) m/z: Calculated $C_{22}H_{33}O_5Si$ $[M+H]^+$ 405.2097; found 405.2108.

FTIR (neat): 2957, 2929, 2888, 2855, 1725, 1711, 1683, 1605, 1199 cm^{-1}.

(4a*S*,4b*S*,10a*S*) *N*,*N*-Dimethyl 9-[(1,1-dimethylethyl)dimethylsilyloxy]-3,4-dioxo-3,4,4a,4b, 5,6,7,8,10,10a-decahydrophenanthrene-4a-carboxamide (113c). A 25 ml round bottom flask was charged under argon with a solution of **111a** (621 mg, 2.61 mmol) and *N*,*N*-dimethyl-2,3-dihydroxybenzamide[91](118 mg, 0.65 mmol) in THF (12 ml). The solution was cooled to 0 °C and a solution of PIFA (308 mg, 0.72 mmol) in THF (10 ml) was added drop wise over 10 min. A yellow solution formed. The reaction was warmed to 21 °C and stirred for 4 h. The orange solution was diluted with diethyl ether (100 ml) and washed with water (4 x 125 ml). The organic layer was filtered through a small amount of silica gel, washing with ether and concentrated to give a yellow semi-solid residue. Purification by flash column chromatography (silica gel, 10-40% ethyl acetate/hexanes) gave **113c** as a bright yellow solid (110 mg, 40%), mp 149-151°C.

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.38-7.44 (m, 1H)

6.24 (d, *J* = 9.4 Hz, 1H)

3.65-3.74 (m, 1H)

2.86-3.04 (m, 7H)

2.62 (bd, *J* = 10.8 Hz, 1H)

2.42 (bd, *J* = 16.6 Hz, 1H)

2.04-2.15 (m, 1H)

1.82 (bd, *J* = 10.9 Hz, 1H)

1.67-1.75 (m, 2H)

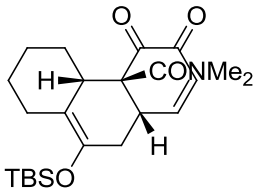
1.50-1.61 (m, 2H)

1.16-1.29 (m, 2H)

0.92 (s, 9H)

0.12 (s, 3H)

0.06 (s, 3H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 197.6, 187.5, 170.5, 158.7, 137.8, 129.5, 115.6, 68.1, 45.4, 43.3, 38.0, 37.8, 35.5, 27.1, 26.3, 25.82, 25.77, 24.9, 18.1, -3.8, -4.5.

HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{36}NO_4Si$ 418.2414 $[M + H]^+$; found 418.2420.

FTIR(neat): 2928, 2854, 1770, 1759, 1673, 1623, 1384, 1360, 1249, 1180, 1147 cm^{-1}.

(The ^{1}H NMR spectrum is broadened due presumably to slow amide rotation.)

3-(1-Ethoxyethenyl)-1-((trimethylsilyl)oxy)cyclohex-2-enecarbonitrile (116): A 25 ml round bottom flask was charged under argon with the ethyl dienone **114**[69](2.0 g, 12.0 mmol), CH_2Cl_2 (15 ml), *N*-methylmorpholine *N*-oxide (422 mg, 3.6 mmol) and TMSCN (1.8g, 18.0 mmol). The solution was stirred at 21 °C overnight. The dark solution was concentrated and the residue was purified by flash column chromatography (silica gel, 0-20% ethyl acetate/hexanes) to give **116** as a clear oil (1.9 g, 60%).

^{1}H-NMR (400 MHz, C_6D_6, δ):

6.58 (bs, 1H)

4.17 (d, *J* = 2.7 Hz, 1H)

3.98 (d, *J* =2.6 Hz, 1H)

3.40 (q, *J* = 7.0 Hz, 2H)

1.85-1.93 (m, 1H)

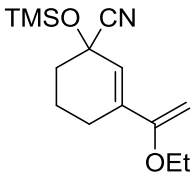
1.84 (dt, *J* = 6.3, 1.7 Hz, 2H)

1.71 (m, 1H)

1.43-1.52 (m, 2H)

1.01 (t, *J* = 7.0 Hz, 3H)

0.23 (s, 9H).



^{13}C NMR (100 MHz, C_6D_6, δ): 158.7, 136.8, 123.7, 121.6, 84.3, 67.6, 62.7, 36.7, 24.2, 18.5, 14.0, 1.28.

GC MS (EI) *m/z*: 265.1 (34% [M]), 236.1 (62%, [M-31]), 219.1 (66%, [M-54]), 73.1 (100%, [M-192.0]).

Methyl 5-cyano-9-ethoxy-3,4-dioxo-5-((trimethylsilyl)oxy)-3,4,5,6,7,8-hexahydrophenanthrene-2-carboxylate (118): A 20 ml round bottom flask was charged with the silyl cyanohydrin **116** (531 mg, 2.00 mmol), methyl 2,3-dihydroxybenzoate **86** (84.1 mg, 0.5 mmol) and dichloromethane. Silver (I) oxide (290 mg, 1.25 mmol) was added in one portion and the solution was stirred overnight at 21 °C. The mixture was filtered through Celite with diethyl ether, concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel, 2-40% ethyl acetate/hexanes) to give **118** as a dark red material (15 mg, 7%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

9.21 (s, 1H)

7.54 (s, 1H)

4.20 (q, *J* = 7.11 Hz, 2H)

3.90 (s, 3H)

2.87 (bdd, *J* = 19.1, 4.5, 4.5, 1H)

2.68 (ddd, *J* = 19.0, 9.5, 5.7 Hz, 1H)

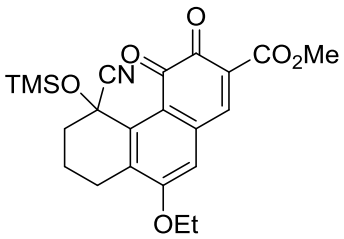
2.58 (bdd, *J* = 12.7, 6.3, 1H)

2.19 (ddd, *J* = 11.6, 11.6, 2.6 Hz, 1H)

1.88-2.00 (m, 2H)

1.47 (t, *J* = 7.1 Hz, 3H)

0.31 (s, 9H).



^{13}C NMR (100 MHz, $CDCl_3$, δ): 178.2, 177.1, 163.5, 159.8, 148.4, 138.2, 135.0, 133.6, 124.7, 124.4, 121.2, 111.1, 68.8, 65.0, 52.4, 38.6, 24.3, 17.9, 14.5, 1.50.

HRMS (ESI-TOF) *m/z*: Calculated for $[M + H]^+$ $C_{22}H_{26}NO_6Si$ 428.1529, found 428.1571.

1-(1-Ethoxyethenyl)-3-(phenylmethoxy)cyclohexene (123): The ethoxy diene alcohol was prepared by a previously reported method.[72] A 100 ml round bottom flask was charged with potassium hydride (817 mg, 7.13 mmol, 35% suspension in mineral oil). The flask was purged with argon and the solid washed with hexanes (3 x 10 ml) then with THF (2 x 10 ml). The flask was cooled to 0 °C and THF (20 ml) was added. The alcohol (600 mg, 3.57 mmol) was added drop wise as a solution in THF (6.0 ml), where upon vigorous bubbling was observed. The reaction was stirred for an additional 20 minutes and then freshly distilled benzyl bromide (671 mg, 3.92 mmol) was added neat. The reaction was complete by TLC after 1.5 hours of stirring. The reaction mixture was quenched with water at 0 °C. The mixture was extracted with a diethyl ether (1 x 100 ml), washed with saturated $NaHCO_3$ (1 x 50 ml) and brine (1 x 50 ml) and dried over anhydrous sodium sulfate. The organic phase was filtered and concentrated *in vacuo* to give a clear yellow oil. The oil was purified by flash column chromatography (basic alumina, 5% ethyl acetate/hexanes). The benzyl ether **123** was obtained as a clear oil (831 mg, 90%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.31-7.40 (m, 4H)

7.24-7.30 (m, 1H)

6.39 (bs, 1H)

4.64 (d, *J* = 12.0 Hz, 1H)

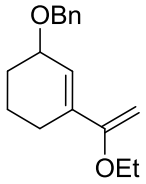
4.60 (d, *J* = 11.9 Hz, 1H)

4.24 (d, *J* = 2.4 Hz, 1H)

4.08-4.12 (m, 1H)

4.07 (d, *J* = 2.4 Hz, 1H)

3.74-3.82 (m, 2H)



2.19-2.27 (m, 1H)

2.08-2.17 (m, 1H)

1.84-1.93 (m, 2H)

1.65-1.73 (m, 1H)

1.57-1.63 (m, 1H)

1.35 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 159.7, 138.9, 135.2, 128.2, 127.6, 127.3, 124.3, 82.6, 72.9, 70.1, 62.7, 28.1, 25.1, 19.5, 14.4.

FTIR (neat): 2931, 1703, 1672, 1586, 1497, 1454 cm^{-1}.

HRMS (ESI-TOF): Calculated $C_{17}H_{23}O_2$ $[M + H]^+$ 259.1680 Found 259.1714.

(4a*S*,4b*S*,5*R*,10a*S*) Methyl 5-(phenylmethoxy)-9-ethoxy-3,4-dioxo-3,4,4a,4b,5,6,7,8,10,10a-decahydrophenanthrene-4a-carboxylate (124): A 3 ml screw cap vial with a stir bar was charged with silver(I) oxide (463 mg, 2.00 mmol), the benzyl ether **123** (260 mg, 1.00 mmol) in THF (2 ml) and methyl 2,3-dihydroxybenzoate **86** (42 mg, 0.25 mmol). The solution was degassed by bubbling with argon for 1 min, then sealed immediately and dipped into a 60 °C oil bath for 12 h with stirring. A thin silver mirror formed. The black mixture was filtered through Celite, washing with ether. The ether filtrate was concentrated to give a red oil and which was purified by flash column chromatography (silica gel, 20-30% ethyl acetate/hexanes) to provide **124** as a dense yellow residue (35 mg, 37%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.16-7.34 (m, 6H)

6.31 (d, *J* = 9.9 Hz, 1H)

4.52 (d, *J* = 11.0 Hz, 1H)

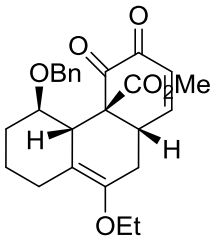
4.33 (ddd, *J* = 10.5, 10.5, 4.0 Hz, 1H)

4.18 (d, *J* = 11.0 Hz, 1H)

3.65-3.74 (m, 1H)

3.51-3.60 (m, 1H)

3.20 (ddd, *J* = 13.5, 5.8, 5.8 Hz, 1H)



3.08 (s, 3H)

3.03 (bd, *J* = 14.8 Hz, 1H)

2.98 (bd, *J* = 10.5 Hz, 1H)

2.53 (bd, *J* = 16.3 Hz, 1H)

2.27 (bd, *J* = 11.6 Hz, 1H)

1.79 (d, *J* = 12.9 Hz, 1H)

1.74-1.90 (m, 1H)

1.56-1.66 (m, 1H)

1.21-1.41 (m, 2H)

1.18 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 192.5, 183.8, 172.7, 152.8, 142.0, 138.5, 130.4, 128.1, 128.1, 127.4, 118.1, 77.7, 70.7, 64.5, 62.5, 52.3, 49.1, 42.9, 32.5, 31.4, 25.1, 22.4, 15.2.

HRMS (ESI-TOF): Calculated for $[M + H]^+$ $C_{25}H_{28}O_6$ 425.1998; found 425.1964.

7-Iodo-1,4-dioxaspiro[4.5]dec-6-ene (126a) and 7-iodo-1,4-dioxaspiro[4.5]dec-7-ene (126b): A 500 ml round bottom flask was charged with 3-iodocyclohexenone[105] (4.96 g, 22.3 mmol), ethylene glycol (28.0 g, 451 mmol), benzene (300 ml) and Otera's catalyst (270 mg, 0.23 mmol). The solution was refluxed for 2 d with a Dean Stark trap. The solution was cooled and washed with sodium thiosulfate (2 x 100 ml) and brine (2 x 100 ml) and dried over sodium sulfate. The organic extract was concentrated and the residue purified by flash column chromatography (silica gel, 10-20% ethyl acetate/hexanes) to give a mixture of **126a** and **126b** as a colorless oil in an approximately 1:1 mixture of regioisomers (4.91 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

6.32-6.36 (m, 0.5H)

6.26-6.28 (m, 0.5H)

3.93-3.99 (m, 4H)

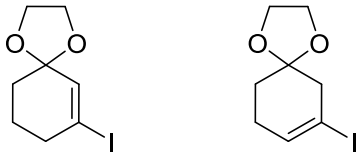
2.73 (m, 1H)

2.51-2.56 (m, 1H)

2.25-2.31 (m, 1H)

1.80-1.83 (m, 2H)

1.75-1.80 (m, 1H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 137.7, 136.5, 107.9, 106.5, 103.8, 91.0, 64.62, 64.58, 49.2, 39.2, 32.6, 30.1, 27.3, 22.9.

LRMS (GC/MS-ESI) *m/z*: 266.0 (<1% [M]), 139.1 (100% [M-126.9]).

1-(1,4-Dioxaspiro[4.5]dec-6-en-7-yl)ethanone (127a) and 1-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)ethan-1-one (127b): A 100 ml round bottom flask was charged with the cyclohexenyl ketals **126a** and **126b** (1.27 g, 4.79 mmol) and THF (24 ml). The solution was cooled with stirring to -78 °C and *t*-butyllithium (5.6 ml, 9.52 ml) was added drop wise over 10 min. The solution was allowed to stir for 15 min, forming a bright yellow precipitate. The Weinreb amide of acetic acid (500 mg, 4.8 mmol) was added neat drop wise over 5 min. The solution was allowed to warm to 21 °C, forming a light yellow solution that darkened over an hour to an orange color. The solution was extracted with diethyl ether (200 ml), washed with saturated sodium thiosulfate (2 x 100 ml) and brine (1 x 100 ml) and dried over magnesium sulfate. The organic extract was filtered and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash column chromatography (silica gel, 10-30% ethyl acetate/hexanes) to yield **127a** and **127b** as a light yellow oil in a 1:1 ratio of regioisomers (291 mg, 33%).

^{1}H NMR (125 MHz, $CDCl_3$, δ):

6.91 (m, 0.5H)

6.45 (dd, *J* = 2.0, 2.0 Hz, 0.5H)

3.96-4.10 (m, 4H)

2.49-2.53 (m, 1H)

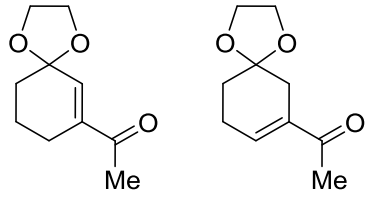
2.45-2.47 (m, 1H)

2.32 (s, 1.5H)

2.31 (s, 1.5H)

2.20-2.26 (m, 1H)

1.74-1.80 (m, 3H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 199.7, 198.4, 142.5, 139.7, 137.8, 136.2, 107.8, 105.9, 65.0, 64.5, 33.4, 33.1, 30.3, 25.6, 25.35, 25.33, 22.9, 20.1.

LRMS (GC/MS-ESI) *m/z*: 8.002 min: 182.1 (25% [M]), 86.1 (100%, [M-96.0]); 8.216 min: 182.1 (20%, [M]), 111.1 (100%, [M-71]).

((1-(1,4-Dioxaspiro[4.5]dec-6-en-7-yl)ethenyl)oxy)[(1,1-dimethylethyl)dimethyl]silane (128a) and ((1-(1,4-Dioxaspiro[4.5]dec-7-en-7-yl)ethenyl)oxy)[(1,1-dimethylethyl)dimethyl] silane (128a): A 25 ml round bottom flask was charged under argon with the methyl ketones **127a** and **127b** (252 mg, 1.38 mmol), dichloromethane (10 ml) and triethylamine (207 mg, 2.07 mmol). The flask was cooled to 0 °C in an ice bath and TBSOTf (365 mg, 1.38 mmol) was added neat drop wise. The solution was allowed to warm to 21 °C and stirred for an hour. The solution was extracted with pentane (100 ml) and washed with saturated $NaHCO_3$ (2 x 50 ml) and brine (1 x 50 ml) and dried over sodium sulfate. The extract was concentrated to give a yellow oil containing practically pure **128a** and **128b** as a 1:1 mixture of regioisomers (368 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

6.25 (bs, 0.5H)

6.05 (bs, 0.5H)

4.47 (d, *J* = 0.8 Hz, 0.5H)

4.31 (d, *J* = 0.8 Hz, 0.5H)

4.27 (bs, 0.5H)

4.17 (bs, 0.5H)

3.95-4.03 (m, 4H)

2.34-2.39 (m, 2H)

2.14-2.18 (m, 1H)

1.76-1.87 (m, 2H)

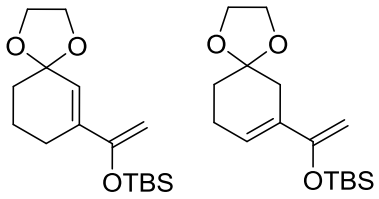
1.70-1.76 (m, 1H)

0.967 (s, 4.5H)

0.960 (s, 4.5H)

0.173 (s, 3H)

0.170 (s, 3H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 155.8, 155.6, 138.2, 131.5, 123.9, 123.6, 108.5, 106.4, 92.6, 89.6, 64.48, 64.47, 35.6, 33.3, 30.5, 25.9, 25.7, 24.8, 24.3, 20.8, 18.29, 18.28, -2.940, -4.665.

Methyl (4a*S*,4b*S*,8a*S*)-10-[(1,1dimethylethyl)dimethylsilyloxy]-5,6-dioxo-4,4a,5,6,8a,9-hexa-hydro-1*H*-spiro[phenanthrene-2,2'-[1,3]dioxolane]-4b(3*H*)-carboxylate (129): A 5 ml screw cap vial was charged with a stir bar, methyl 2,3-dihydroxybenzoate (23.7 mg, 0.141 mmol), THF (1 ml) and the dienes **128a** and **128b** (167 mg, 0.563 mmol) and was then sealed with a septum. The vial was cooled to 0 °C and PIFA (66.2 mg, 0.154 mmol) in 1 ml THF was added drop wise with stirring over 5 min. The solution was allowed to warm to 21 °C and stirred for 4 hours. The reaction was extracted with diethyl ether (10 ml), washed with water (3 x 5 ml) and brine (1 x 5 ml) and dried over anhydrous sodium sulfate. The organic extract was filtered and concentrated *in vacuo* to give a red oil. The oil was purified by flash column chromatography (silica gel, 10-40 % ethyl acetate/hexanes) gave a residue (28 mg, 43%) containing impure **129**. The residue was recrystallized from hexanes to yield **129** as small crystals (22 mg, 34%). mp 170-172 °C.

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.29 (dd, *J* = 10.0, 5.5 Hz, 1H)

6.34 (d, *J* = 10.0 Hz, 1H)

3.94 (m, 4H)

3.74 (s, 3H)

3.42 (ddd, *J* = 10.5, 5.5, 5.5 Hz, 1H)

3.00 (bdd, *J* = 14.8, 3.2 Hz, 1H)

2.73 (bd, *J* = 12.0 Hz, 1H)

2.49 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H)

2.42-2.48 (m, 1H)

1.98 (bd, *J* = 15.2 Hz, 1H)

1.78-1.88 (m, 2H)

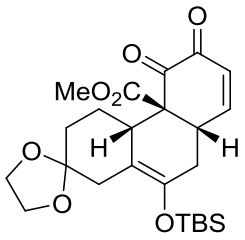
1.51 (ddd, *J* = 13.4, 13.4, 4.0 Hz, 1H)

1.38-1.44 (m, 1H)

0.918 (s, 9H)

0.128 (s, 3H)

0.074 (s, 3H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 191.2, 183.8, 172.1, 155.3, 139.6, 130.6, 112.9, 108.2, 65.8, 64.7, 64.5, 53.2, 41.9, 41.5, 35.8, 35.1, 34.8, 25.7, 24.1, 18.1, -3.927, -4.323.

7-(2-Propenyl)-1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (132): The allyl trimethylsilylenol ether **131** was obtained by a previous literature method.[106] A 100 ml flask was charged with a stir bar and methyllithium (5 ml, 1.6 M in diethyl ether, 8.0 mmol) and was heated to 40 °C under a positive flow of argon until a dry white solid was left. Freshly distilled glyme (20 ml) was added and the mixture was stirred until it was homogeneous and then the temperature was warmed to 21 °C. A solution of **131** (1.8 g, 6.71 mmol) in glyme (5 ml) was added drop wise with stirring to this solution over 5 min. The solution was allowed to stir for 10 min and *N*-phenyltrifluoromethanesulfonimide (2.4 g, 6.71 mmol) was added in one portion and the mixture was allowed to stir for an hour. The dark solution was extracted with hexanes (300 ml), washed with water (2 x 100 ml) and brine (1 x 100 ml) and dried over Na_2SO_4. The organic extract was concentrated *in vacuo* to give an orange oil (1.7 g). The oil was purified by flash column chromatography (silica gel, 20% ethyl acetate/hexnes) to yield **132** as a yellow oil (1.48 g, 67%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.63-5.75 (m, 1H)

5.06-5.15 (m, 2H)

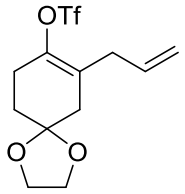
3.92-4.03 (m, 4H)

2.89 (bd, *J* = 6.7 Hz, 2H)

2.56 (bt, *J* = 6.6 Hz, 2H)

2.35 (bs, 2H)

1.89 (bt, *J* = 6.6 Hz, 2H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 142.1, 126.0, 118.1 (q, *J* = 318 Hz), 117.8, 106.6, 64.7, 38.0, 34.8, 31.4, 26.2 (one low field carbon not observed).

7-(2-Propenyl)-1,4-dioxaspiro[4.5]dec-7-ene-8-carbonitrile (133): A 20 ml pressure tube was charged with the vinyl triflate **132** (1.48g, 4.51 mmol), potassium cyanide (587 mg, 9.01 mmol), 18-crown-6 (95.2 mg, 0.36 mmol), benzene (9 ml) and $Pd(PPh_3)_4$ (162 mg, 0.14 mmol). The tube was purged by bubbling with argon for 5 min and then sealed and heated at 80 °C for 24 h. The heterogeneous mixture was cooled to 21 °C and filtered to give a yellow oil (760 mg). The oil was purified by flash column chromatography (silica gel, 1-10% ethyl acetate/hexanes) to give the nitrile **133** as a yellow oil (400 mg, 43%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.66-5.79 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H)

5.07-5.19 (m, 2H)

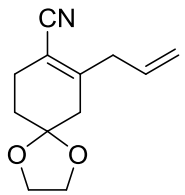
3.97 (s, 4H)

3.09 (d, *J* = 6.8 Hz, 2H)

2.44-2.51 (m, 2H)

2.34-2.38 (bs, 2H)

1.76 (bt, *J* = 6.5 Hz, 2H).

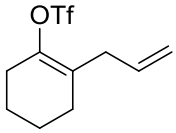


^{13}C NMR (125 MHz, $CDCl_3$, δ): 152.3, 133.0, 118.2, 106.67, 106.66, 64.6, 40.9, 39.4, 30.3, 26.5. (one low field carbon not observed).

LRMS (GC/MS-ESI) *m/z*: 205.0 (10%, [M]), 86.0 (100%, [M-109]).

2-(2-propenyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (136): A 50 ml round bottomed flask was charged with the 2-allyl-1-trimethylsilyloxy cyclohexene ether **135**[107] (1.0 g, 4.76 mmol) and THF (10 ml). The solution was treated drop wise with methyllithium (3 ml, 1.6 M in diethyl ether) over 10 min. The solution was stirred for 30 min and *N*-phenyl(trifluoro-methanesulfonimide) (1.70 g, 4.76 mmol) was added in one portion and the solution was sealed and allowed to stir for 1 h, where upon a dark yellow solution formed. The solution was extracted with hexanes (150 ml), washed with water (2 x 50 ml) and brine (1 x 50 ml), and dried over Na_2SO_4. The organic extract was concentrated to give a pink oil (1.6 g), which was dissolved in pentane and filtered through a small amount of silica gel. The clear solution was concentrated to yield a clear oil containing triflate **136** (950 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$. δ):



5.67-5.77 (m, 1H)

5.06-5.12 (m, 2H)

2.90 (bd, *J* = 6.8 Hz, 2H)

2.31-2.37 (m, 2H)

2.10-2.16 (m, 2H)

1.72-1.78 (m, 2H)

1.58-1.65 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 143.4, 133.7, 128.3, 118.0 (q, *J* = 319 Hz), 117.2, 35.1, 28.3, 27.6, 23.2, 21.7.

FTIR (neat): 2942, 2866, 1408, 1245 cm^{-1}.

1-(2-propenyl)-2-(1-ethoxyethenyl)cyclohex-1-ene (137): A 3 ml screw cap vial with stir bar was charged with allyl vinyl triflate **136** (100mg, mmol), ethyl vinyl ether (133 mg, mmol), triethylamine (75 mg, mmol) and DMSO (400 μl). The solution was degassed for 1 min with bubbling argon and then $Pd(PPh_3)_4$ (75 mg, mmol) was added in one portion. The mixture was degassed for 1 min and then the vial was sealed. The vial was placed on a 65 °C heat mantle and stirred for 10 h. The conversion was >90% by GC/MS (uncorrected). The resulting yellow solution was extracted with pentanes (20 ml), washed with brine (2 x 10 ml) and dried over anhydrous sodium sulfate. After filtering and concentrating *in vacuo*, the diene **137** was obtained as a light yellow oil (63 mg, 88%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.71-5.82 (m, 1H)

4.92-5.04 (m, 2H)

4.04 (d, *J* = 1.5 Hz, 1H)

3.94 (d, *J* = 1.6 Hz, 1H)

3.73 (q, *J* = 7.0 Hz, 2H)

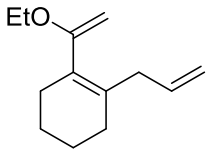
2.85 (bd, *J* = 6.6 Hz, 2H)

2.13-2.19 (m, 2H)

1.97-2.02 (m, 2H)

1.54-1.65 (m, 4H)

1.31 (t, *J* = 7.1 Hz, 3H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 162.3, 137.3, 133.7, 130.6, 115.2, 83.1, 62.7, 39.4, 29.2, 28.6, 22.8, 22.7, 14.5.

LRMS (GC/MS-ESI) *m/z*: 192.2 (30%, [M]), 105.1 (100%, [M-87.1]).

1-1-[(1,1-Dimethylethyl)dimethylsilyloxy]ethenyl-2-(2-propenyl)cyclohexene (138): A 3 ml screw cap vial with stir bar was charged with allyl vinyl triflate **136** (78 mg, 0.289 mmol), TBS vinyl ether (228 mg, 1.44 mmol), Et_3N (58 mg, 0.573 mmol) and DMF (500 μl). The solution was degassed for1 min by bubbling with argon and $Pd(PPh_3)_4$ (17 mg, 0.014 mmol) was added in one portion. The solution was degassed for 1 min with bubbling argon then the vial was sealed and heated to 65 °C for 4 h. The reaction mixture was extracted with pentane (20 ml), washed with saturated $NaHCO_3$ (1 x 10 ml) and water (3 x 10 ml) and dried over sodium sulfate. The extract was filtered through a small amount of basic alumina and concentrated to yield **138** as an orange oil (36 mg, 45%).

^1H NMR (400 MHz, $CDCl_3$, δ):

5.69-5.84 (m, 1H)

4.96-5.05 (m, 2H)

4.29 (s, 1H)

4.17 (s, 1H)

2.96 (d, *J* = 6.6 Hz, 2H)

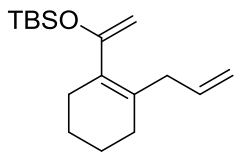
2.11-2.17 (m, 2H)

1.96-2.02 (m, 2H)

1.57-1.60 (m, 4H)

0.922 (s, 9H)

0.139 (s, 6H).



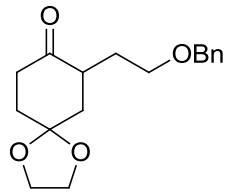
7-(2-Phenylmethoxy)-1,4-dioxaspiro[4.5]decan-8-one (140). A 100-ml round bottom flask was charged with methyllithium (1.6 M in ether, 14 ml, 22.4 mmol) and the silyl enol ether **139** (4.69 g, 20.5 mmol) at 0 ℃. After 1 h, the ice bath was removed and a solution of dimethoxyethane and HMPA was added (50 mL, 10:1, DME:HMPA). The yellow solution was added dropwise over 1h to a solution of triethylaluminum (1.0 M in hexanes, 21 ml, 21 mmol) and benzyl 2-iodoethyl ether[108,109] (13.45 g, 51.3 mmol) in a 10:1 solution of DME and HMPA (50 ml). The solution was allowed to stir for 20 h and was then partitioned between ether (500 ml) and saturated solution of Rochelle's salt (250 ml). The organic layer was washed with water (3x250 ml) and brine (250 ml), dried over magnesium sulfate and concentrated to yield a clear oil. The oil was fractionally distilled, giving **140** (200-205 ℃, 0.1 mm Hg) as a clear oil (2.71 g, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.20-7.40 (m, 5H)

4.49 (d, 1H, *J* = 12.1 Hz)

4.46 (d, 1H, *J* = 12.1 Hz)



3.97-4.05 (4H, m)

3.46-3.54 (2H, m)

2.86 (dddd, 1H, *J* = 13.0, 6.5, 6.5, 6.5 Hz)

2.65 (ddd, 1H, *J* = 14.0, 14.0, 6.4 Hz)

2.37 (ddd, 1H, *J* = 14.0, 5.0, 3.2 Hz)

2.11-2.20 (2H, m)

2.01-2.06 (1H, m)

1.96 (1H, ddd, *J* = 13.5, 13.5, 5.0 Hz)

1.71 (1H, dd, J = 13.2, 13.2 Hz)

1.43-1.49 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 211.4, 138.5, 128.4, 127.6, 127.5, 107.4, 72.9, 67.8, 64.8, 64.6, 43.3, 40.7, 38.3, 34.8, 29.1.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{17}H_{23}O_4$ 291.1596; found 291.1588.

FTIR (neat): 2953, 2888, 2853, 1712, 1454, 1437, 1362, 1307, 1276 cm^{-1}.

7-(2-Phenylmethoxy)-1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (141). A 50-mL round bottom flask was charged, under argon, with the ketone **140** (1.00 g, 3.44 mmol), THF (20 ml) and HMPA (4.4g, 24.6 mmol). A solution of KHMDS (7.0 mL, 3.5 mmol, 0.5 M in toluene) was added drop wise to the solution over 10 min. To the brown solution was added *N*-phenyltriflimide (1.33 g, 3.73 mmol) in one portion and the solution was allowed to stir for 1 h. The solution was extracted with hexanes (500 ml) and washed with saturated bicarbonate (2x250 ml), water (2x250 ml) and brine (250 ml). The organic layer was dried over sodium sulfate and concentrated to afford a yellow oil. The oil was purified by flash column chromatography (silica gel, 5-25% ethyl acetate/hexanes) gave the vinyl triflate **141** as a clear oil (1.21 g, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.29-7.34 (m, 5H)

4.51 (s, 2H)

3.96 (s, 4H)

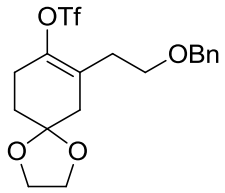
3.56 (t, 2H, *J* = 6.5 Hz)

2.53-2.56 (bt, 2H, *J* = 6.5 Hz)

2.55 (bt, 2H, *J* = 6.5 Hz)

2.43 (bs, 2H)

1.88 (bt, 2H, *J* = 6.7 Hz).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 142.8, 138.2, 128.4, 127.6, 125.9, 118.3 (q, *J* = 319 Hz) 106.5, 72.9, 67.5, 64.7, 38.7, 31.3, 30.9, 26.2 (one low field carbon not observed).

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calculated for $C_{18}H_{21}O_6SF_3Na$ 445.0909; found 445.0906.

FTIR (neat): 2928, 2879, 1409, 1366, 1247, 1203, 1139, 1093 cm^{-1}.

7-(2-Phenylmethoxy)-8-(1-ethoxyethenyl)-1,4-dioxaspiro[4.5]dec-7-ene (143). A 25 ml round bottom flask was charged with the vinyl triflate **141** (900 mg, 2.13 mmol), ethyl vinyl ether (768 mg, 53.3 mmol), triethylamine (431 mg, 4.26 mmol), DMSO (15 ml) and $Pd(OAc)_2$ (72 mg, 0.1 mmol), in that order. Argon was bubbled through the flask for 1 min, then it was sealed and heated at 80 °C for 4 h in an oil bath. The dark reaction mixture was extracted with 50% diethyl ether in hexanes (200 ml) and washed with water (3x 200 ml) and brine (200 ml), dried over anhydrous sodium sulfate and concentrated to give a yellow oil. The oil was purified by flash column chromatography (silica gel, 50% ethyl acetate/hexanes) yielded **143** a clear oil (594 mg, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.32-7.33 (m, 4H)

7.24-7.29 (m, 1H)

4.49 (s, 2H)

4.07 (d, *J* = 1.6 Hz, 1H)

3.95-3.98 (m, 5H)

3.72 (q *J* = 7.0 Hz, 2H)

3.53 (t, *J* = 7.4 Hz, 2H)

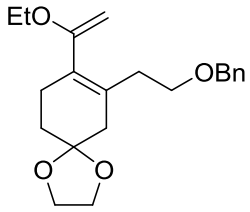
2.48 (t, *J* = 7.3 Hz, 2H)

2.39 (t, *J* = 6.5 Hz, 2H)

2.32 (bs, 2H)

1.75 (t, *J* = 6.7 Hz, 2H)

1.28 (t, *J* = 7.0 Hz, 3H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 161.3, 138.6, 130.7, 130.3, 128.3, 127.6, 127.5, 108.0, 83.8, 72.8, 69.4, 64.4, 62.7, 39.7, 34.8, 31.1, 28.5, 14.5.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{21}H_{29}O_4$ 345.2066; found 345.2053.

FTIR (neat): 2927, 2873, 1607, 1454, 1363, 1276, 1207 cm^{-1}.

(4a'*S*,4b'*S*,8a'*S*) Methyl 4a'-(2-(phenylmethoxy)ethyl)-10'-ethoxy-5',6'-dioxo-2',4',4a',4b',5',6',8a',9'-octahydro-1'*H*-spiro[[1,3]dioxolane-2,3'-phenanthrene]-4b'-carboxylate (144): A 3 ml screw cap vial was charged with silver (I) oxide (37.2 mg, 0.161 mmol), THF (2 ml), the diene **143** (100 mg, 0.290 mmol) and methyl 2,3-dihydroxybenzoate **86** (12.2 mg, 0.073 mmol). The vial was flushed with argon for 1 min then sealed and heated for 12 h at 65 °C. The mixture was filtered through Celite with diethyl ether (20 ml) and concentrated to yield a black oil. The oil was purified by flash column chromatography (50% ethyl acetate/hexanes) gave **144** as a dense yellow residue (11 mg, 29% yield).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.28 (dd, *J* = 10.0, 5.5 Hz, 1H)

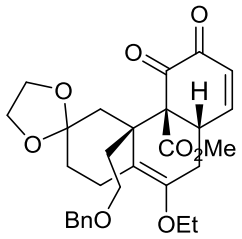
7.27-7.35 (m, 5H)

6.33 (d, *J* = 9.9 Hz, 1H)

4.54 (d, *J* = 11.9 Hz, 1H)

4.45 (d, *J* = 11.8 Hz, 1H)

3.81-3.90 (m, 4H)



3.74 (s, 3H)

3.66-3.71 (m, 1H)

3.50-3.62 (m, 2H)

3.47 (t, *J* = 6.8 Hz, 2H)

3.31-3.42 (m, 2H)

3.15 (bd, *J* = 13.5 Hz, 1H)

2.43-2.53 (m, 2H)

1.86-1.93 (m, 2H)

1.73-1.76 (m, 2H)

1.44 (bdd, *J* = 12.7, 4.5 Hz, 1H)

1.15 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 191.4, 183.9, 171.8, 155.4, 142.3, 138.9, 130.5, 128.3, 127.6, 127.4, 119.2, 108.8, 72.7, 69.2, 65.5, 64.6, 64.2, 63.7, 53.2, 41.7, 37.3, 36.1, 35.4, 34.5, 31.9, 30.1, 15.2.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calculated for $C_{29}H_{34}O_8$ 511.2332; found 511.2326.

FTIR (neat): 2952, 2928, 2853, 1170, 1759, 1715, 1683, 1385, 1249, 1197, 1054 cm^{-1}.

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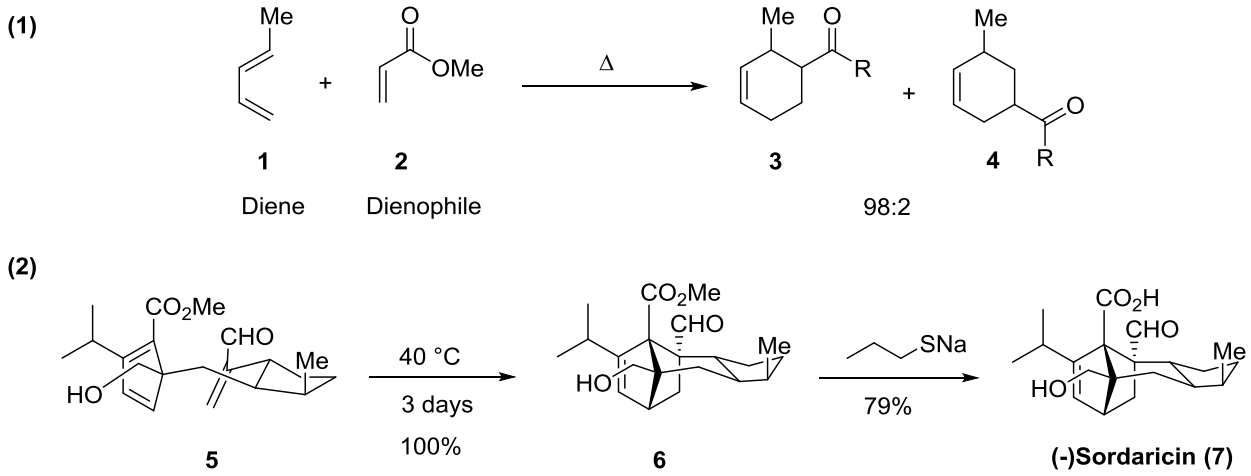
Chapter 2

Phenylseleno Acrylate as an Ethylene Equivalent for Diels-Alder Reactions

Introduction

The Diels-Alder [4+2] cycloaddition is an efficient method for constructing six-membered carbocycles from a diene **1** and a dienophile **2** (Scheme 2-1).[1,2] A variety of dienes and dienophiles have been developed, providing cycloadducts with excellent regio- and stereoselectivity.[3] The Diels-Alder reaction is an attractive method for natural products synthesis. An asymmetric total synthesis of (-)-Sordaricin aglycon, **7**, was achieved recently utilizing an intramolecular Diels-Alder reaction.[4]



Scheme 2-1. The Diels-Alder reaction and its applications.

The reactivity of the components in the Diels-Alder reaction arises from the frontier orbital overlap of the diene and dienophile (Figure 2-1). Reactivity is maximized when the energy difference between the highest-occupied-molecular-orbital (HOMO) of the diene and lowest-unoccupied-molecular-orbital (LUMO) of the dienophile is minimized.[5] The LUMO of the dienophile can be lowered through conjugation, such as with carbonyl functional groups.

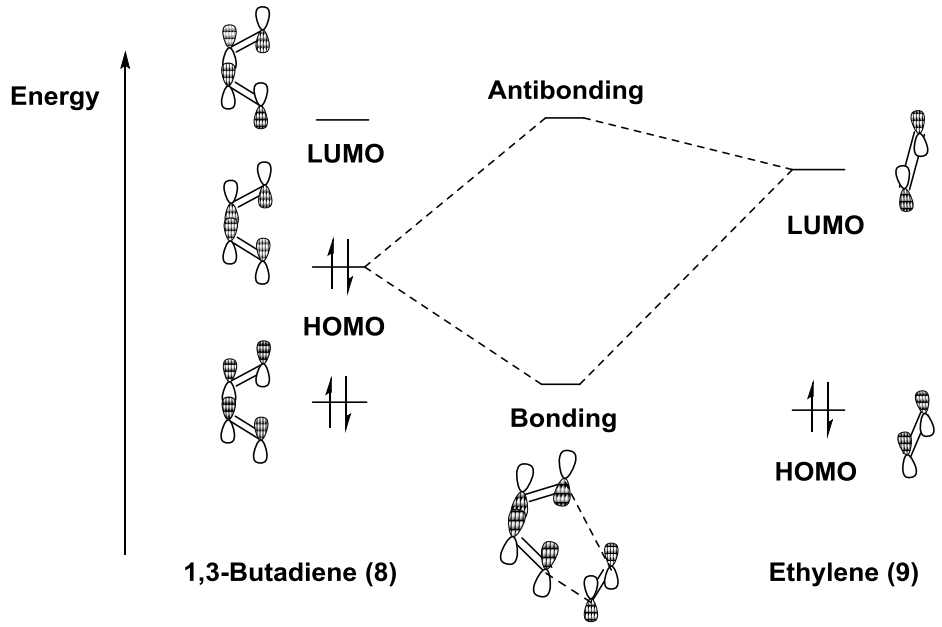
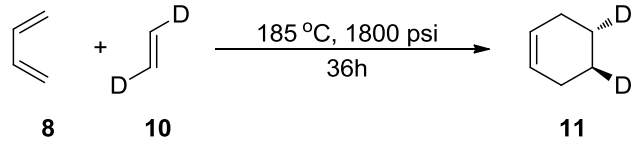


Figure 2-1. Orbital diagram of diene and dienophile.

When the difference between the HOMO and LUMO energies is large, overlap of these orbitals is poor, resulting is little or no reactivity. When using ethylene as a dienophile, high pressure and temperature are necessary for the cycloaddition (Scheme 2-2).[6] Remarkably, Houk observed that a concerted cycloaddition still occurs under such conditions.[7] Using trans-dideuterated ethylene (**4**), the trans-dideuterated cyclohexene (**5**) was obtained and the structure was assigned by ^{1}H NMR.



Scheme 2-2. Concerted Diels-Alder reaction of ethylene and 1,3-butadiene.

However, these forcing conditions restrict the scope of the Diels-Alder reaction. This limitation became important during Jung and Regan's[8] efforts to synthesize the terpenoid core of brasilicardin A, **6** (Figure 2-2**)**.[9] Construction of the C ring (Scheme 2-3) via a Diels-Alder reaction with diene **16** and ethylene would be ideal. The approach of the dienophile would likely occur from the less-hindered β-face of the diene, setting the stereochemistry at C9 and α to the

benzylic ether. The benzyl ether could be cleaved to reveal the alcohol **14** that would direct cyclopropanation to give the cyclopropyl alcohol **13**. However, an efficient method of introducing an ethylene unit was needed.

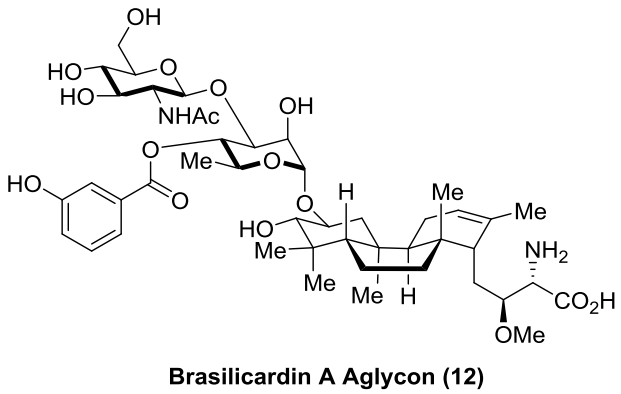
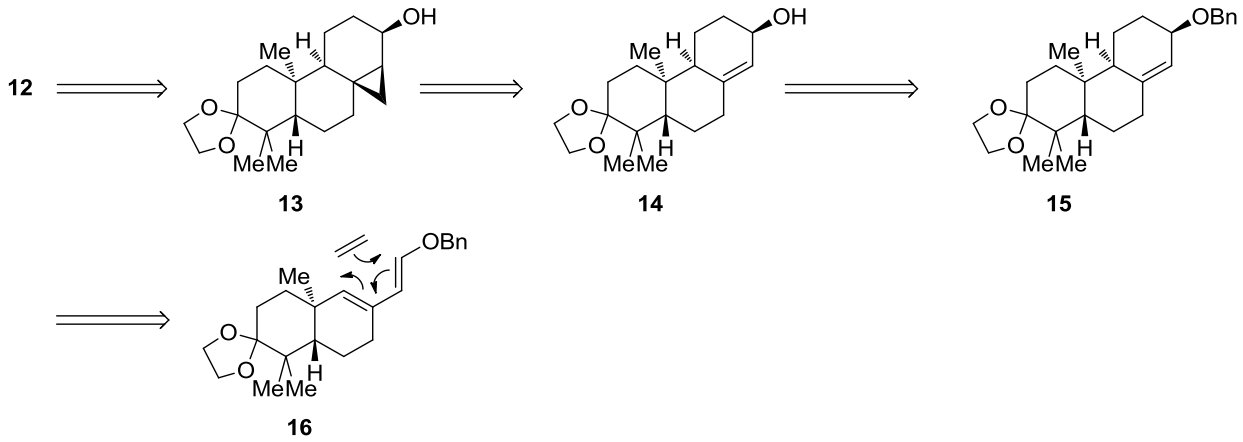


Figure 2-2. Brasilicardin A.

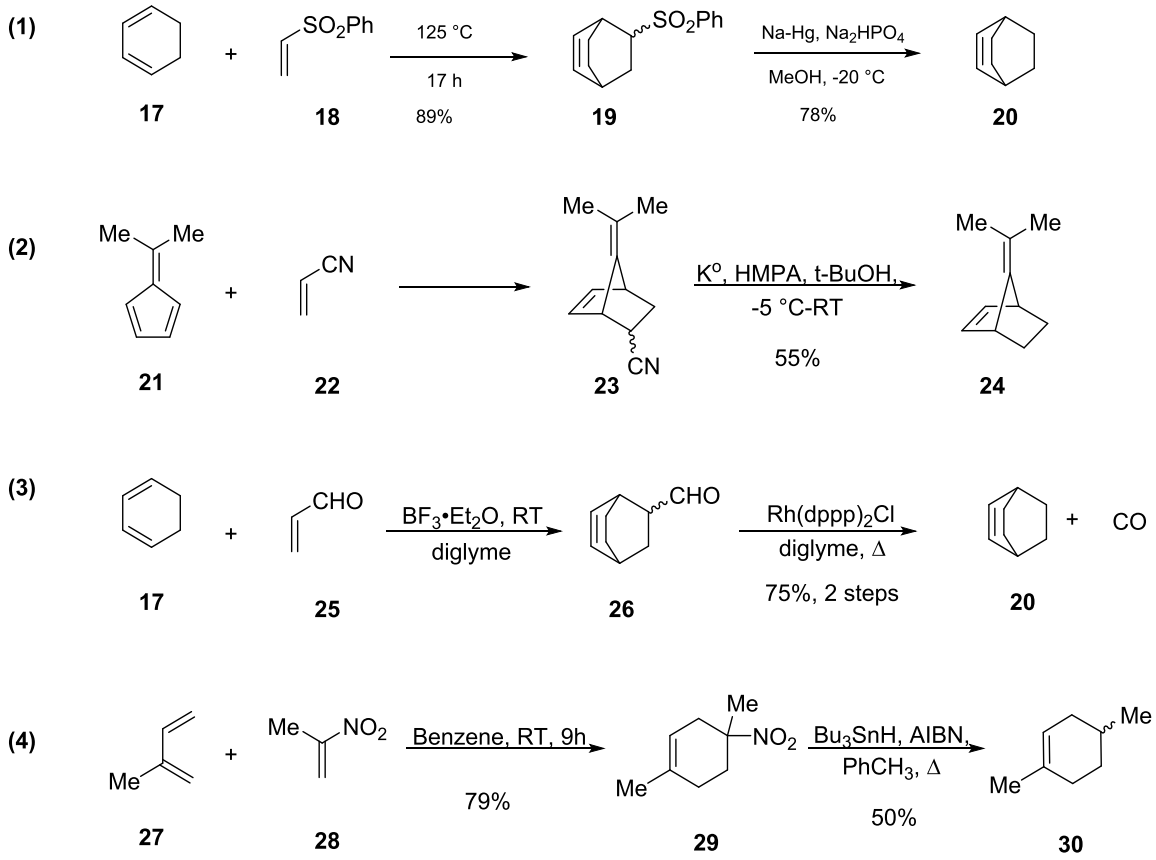


Scheme 2-3. Retrosynthetic Analysis of Brasilicardin A.

Therefore, we began to investigate the known the Diels-Alder reaction of **16** with deinophiles that could serve as possible ethylene equivalents. Our investigations began with the ethylene equivalents that had been developed earlier, but the possibility of developing a new one might also become necessary.

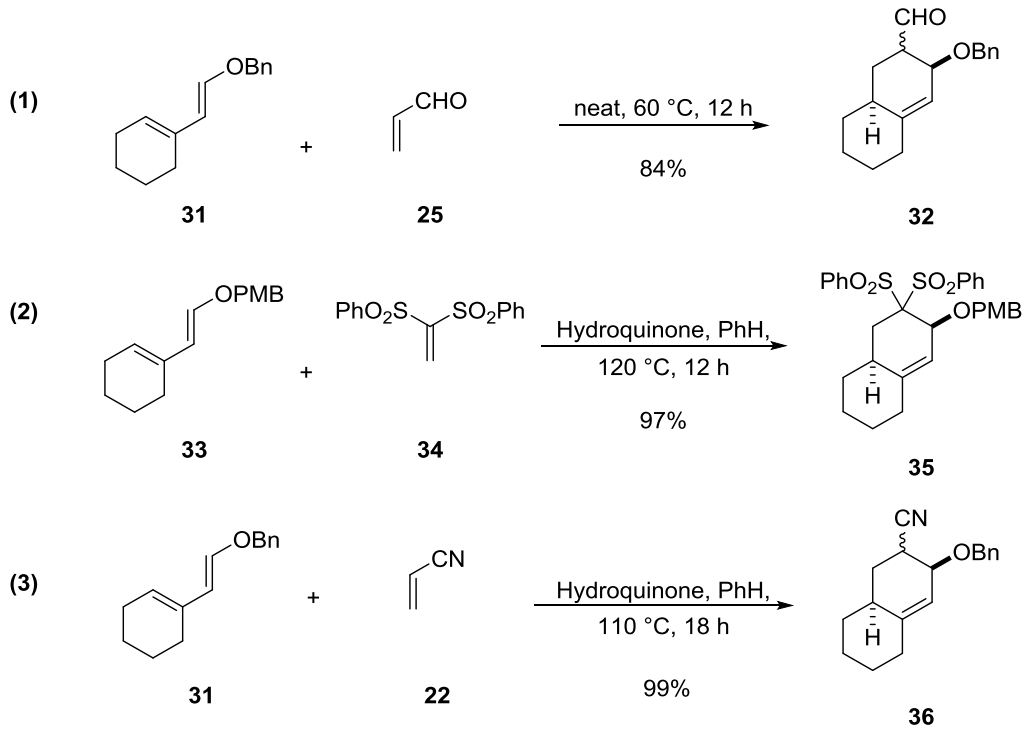
Background

The challenge of introducing an ethylene unit via the Diels-Alder reaction has inspired the development of many possible solutions (Scheme 2-4). Phenyl vinyl sulfone (**18**), developed by Paquette,[10] was one of the earliest ethylene equivalents (Scheme 2-4, Equation 1). Paquette's solution exemplifies the general strategy: the desired olefin is activated with an auxiliary (sulfone, nitrile, aldehyde, etc.) to produce a cycloadduct (**19**). The auxiliary is then removed, in Paquette's case by sodium amalgam reduction of the sulfone, to yield the desired product (**20**). A variety of other ethylene equivalents have been developed over the years, with much variation involving the removal of the activating auxiliary. Mehta and Khan found that cycloadducts obtained from acrylonitrile (**22**), could be decyanated with potassium metal (Scheme 2-4, Equation 2).[11,12] Taarning developed a one pot, catalytic process from acrolein (**25**).[13] The less reactive acrolein **25** was activated by boron trifluoride to provide the cycloadduct **26** which underwent decarbonylation with a catalytic amount of a rhodium catalyst. Nitroethylenes (**28**), developed by Ono, provide cycloadducts (**29**) with good regioselectivity. These undergo radical reduction to the cyclohexene **30**.[14] Other ethylene equivalents include vinyldichloroborane, [15] among others.[16,17]



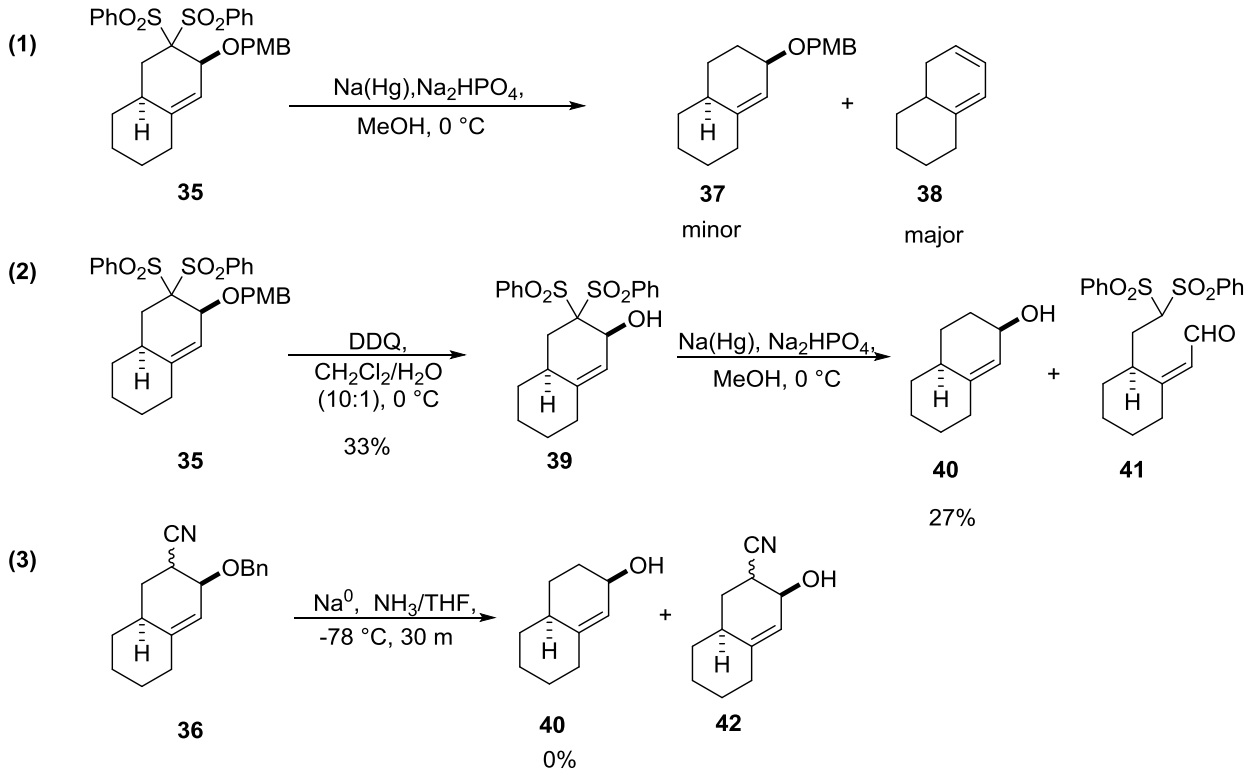
Scheme 2-4. Previous examples of ethylene equivalents.

Many of these ethylene equivalents were used by Jung and Regan in early models for the synthesis of the C ring of brasilicardin A (Scheme 2-5). Using the 1-benzyloxy dienes (**31** and **33**) as analogs of the desired diene (**16**), these ethylene equivalents (**25**, **34**, and **22**) were observed to give the desired products **32**, **35**, and **36** in good to excellent yield. The products were obtained with the desired relative regio- and stereochemistry.



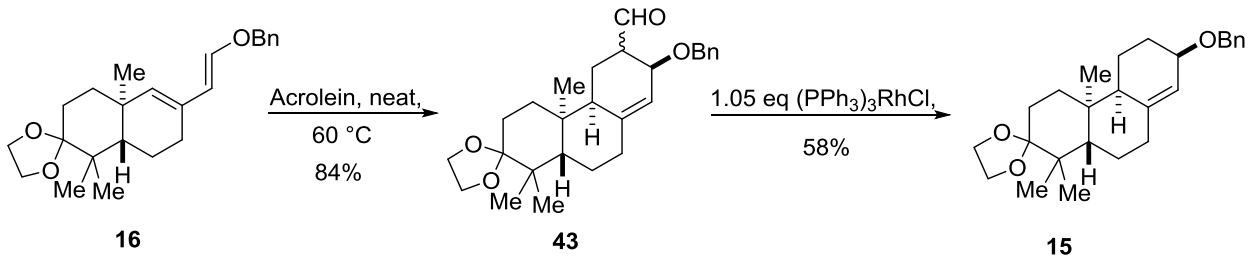
Scheme 2-5. The successful cycloaddition of possible ethylene equivalents.

However, reduction of these products to the allylic ethers proved difficult (Scheme 2-6). The reductive desulfonylation of **35** using sodium amalgam gave only 4% of the desired product **37** with the diene **38** being obtained as the major product (Scheme 2-6, Equation 1). This is caused by the β-elimination of the allylic PMB ether by an intermediate anion generated during the reduction. Cleavage of the PMB ether of **35** with DDQ provided the alcohol **39**. This was resistant to β-elimination during the reduction, providing the desired allylic alcohol **40**, but in poor yield (Scheme 2-6, Equation 2). Observations by ^{1}H NMR showed that an aldehyde, probably **41**, may have formed. This was formed most likely by a competing retro-aldol process. Attempted decyanation of **36**, using sodium in ammonia, gave only the debenzylated product **42**, with none of the desired product **40** having been formed (Scheme 2-6, Equation 3).



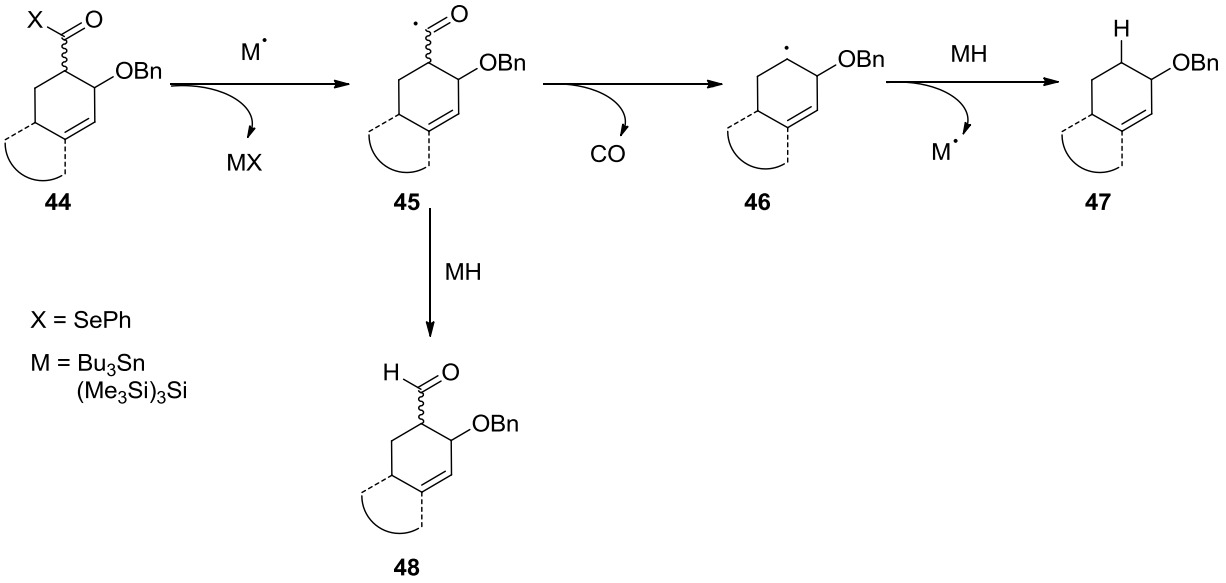
Scheme 2-6. Reduction of the activating auxiliary.

Acrolein was the most successful of the ethylene equivalents used (Scheme 2-7). Cycloaddition with **16** gave **43**, with good facial selectivity. Decarbonylation using Wilkinson's catalyst was successful, providing the allylic ether **15** with no β-elimination. However, no reaction could be achieved under catalytic conditions. The transformation required more than stoichiometric amounts of the rhodium catalyst and so would have been impractical for a total synthesis.



Scheme 2-7. The rhodium catalyzed decarbonylation of the aldehyde **43**.

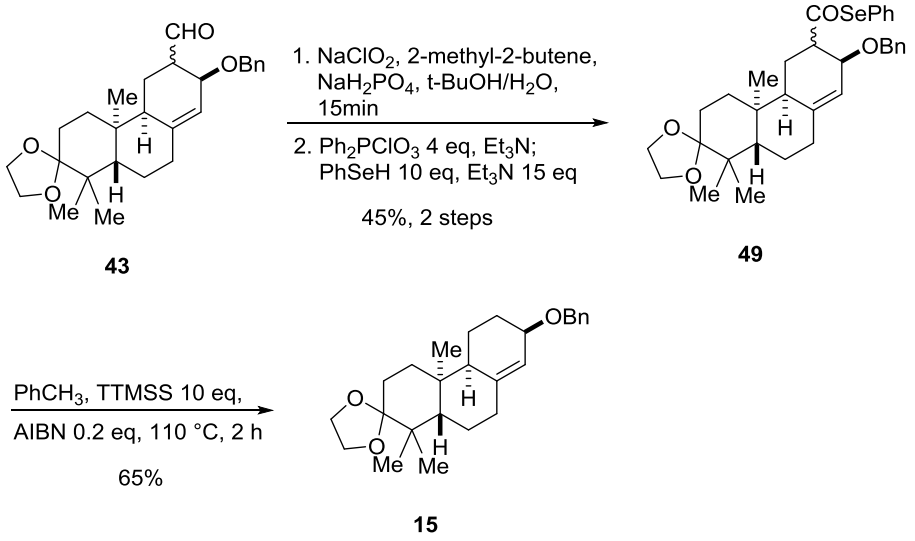
An alternative method of decarbonylation using a radical chain reaction was considered (Scheme 2-8). Seleno esters (**44**) can be cleaved to yield acyl radicals (**45**) by tri-*n*-butyltin hydride or tris(trimethylsilyl)silane (TTMSS).[18,19] However, the resulting acyl radical can either abstract hydrogen to generate an aldehyde (**48**) or decarbonylate to give the secondary carbon radical **46**, which is then trapped by hydrogen to give **47**. Chatgilialoglu studied this competitive process and found that TTMSS could be used to favor the formation of the alkane while the use of Bu_3SnH favored aldehydes. This selectivity arises from the fact that the Si-H bond is 5 kcal mol^{-1} stronger than the Sn-H bond. This increased bond strength results in hydrogen donation taking place 25 times slower than in the case of Bu_3SnH, allowing more opportunity for decarbonylation to generate the alkyl radical.



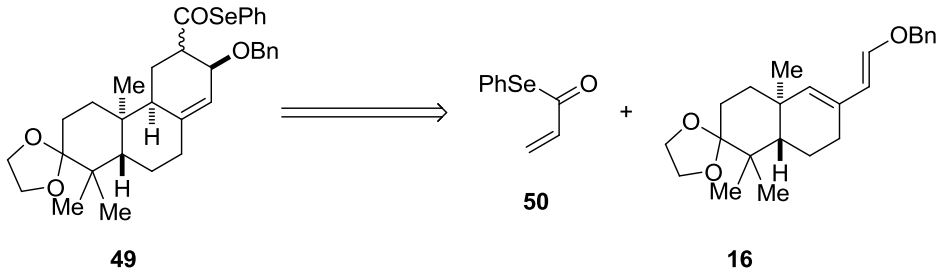
Scheme 2-8. Competing radical reductions pathways.

The seleno ester **49** was synthesized from the aldehyde **43** (Scheme 2-9). The aldehyde **43** was oxidized with hypochlorite and the resulting acid was esterified with benzeneselenol to yield the selenoester **49**. Cleavage of the selenoester with the "super silyl reagent", TTMSS, gave the desired product **15** in 65% yield. However, the low overall yield and poor atom economy

demanded a more direct approach. The known phenylseleno acrylate, **50**,[20] was proposed as a possible ethylene equivalent to allow the faster formation of **49** (Scheme 2-10).



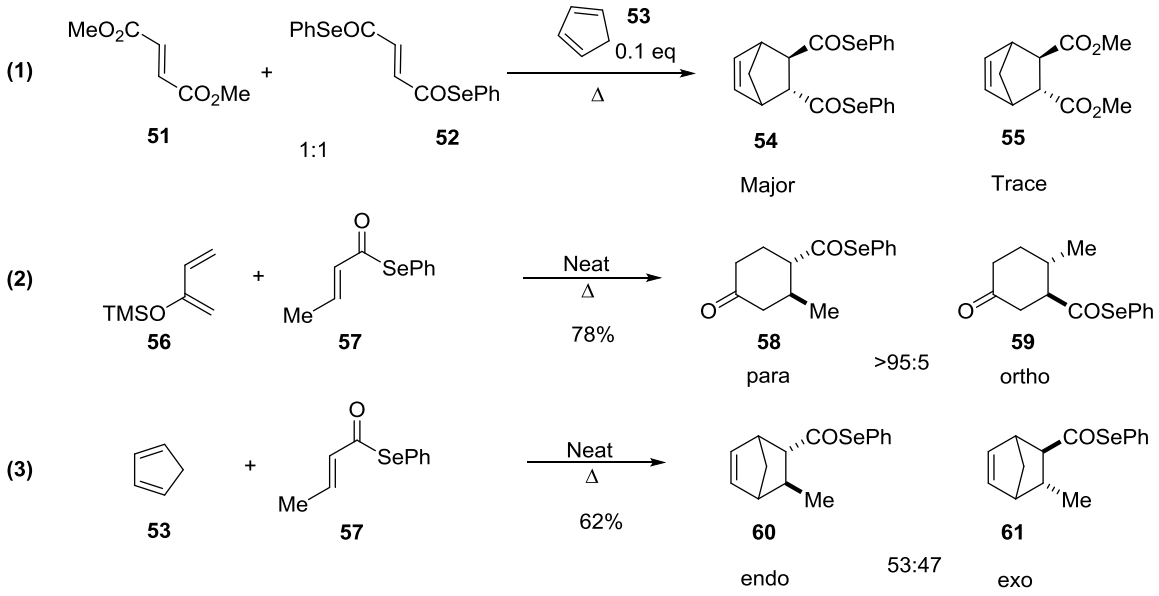
Scheme 2-9. The radical reduction of phenylseleno ester **49**.



Scheme 2-10. Phenylseleno acrylate as a possible dienophile.

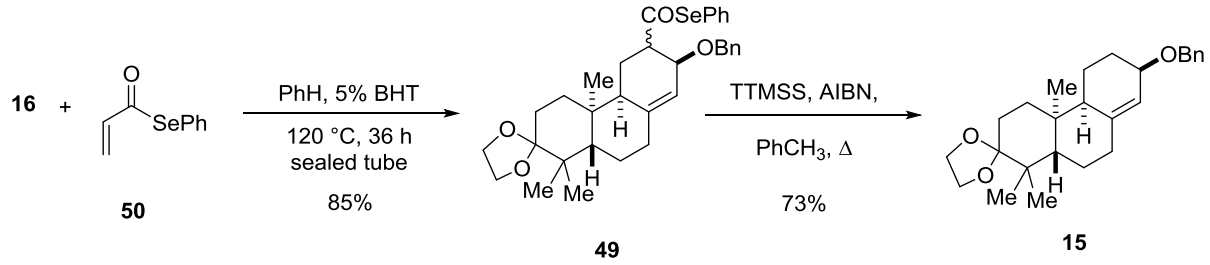
Studies by Hart had found that phenylseleno acrylates were more reactive dienophiles in the Diels-Alder reaction than the analogous methyl acrylates (Scheme 2-11, Equation 1).[21] This was established by competitive reactions using a limiting amount of cyclopentadiene. The reaction of a 1:1 mixture of the fumarate **51** and the seleno analogue **52** with cyclopentadiene **53** gave only a trace of the fumarate cycloadduct **55**. This higher reactivity of the seleno ester is likely the result of the poor orbital overlap of the selenium atom with the carbonyl, resulting in a more ketone-like dienophile, which are known to be more reactive than esters. Excellent regioselectivity was observed for electron-rich dienes under thermal conditions (Scheme 2-11,

Equation 2), providing the "para" 1,4-product **58** as the major isomer. However, poor endo selectivity was observed (Scheme 2-11, Equation 3).



Scheme 2-11. Selenoacrylates as dienophiles.

Jung and Regan were successful in applying this novel ethylene equivalent in the brasilicardin A series (Scheme 2-12). The cycloaddition of the diene **16** with the phenylseleno acrylate **50** proceeded with excellent facial selectivity, providing the cycloadduct **49** in 85% yield. The resulting seleno ester was then reduced using the previously developed procedure to give the allylic ether **15** in 73% yield.

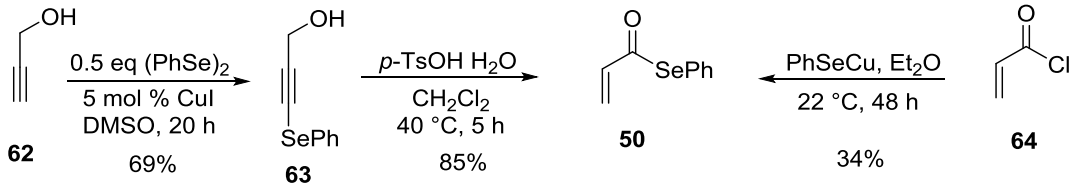


Scheme 2-12. Diels-Alder reaction of phenylseleno acrylate **50** with **16**.

Due to this very positive development, we decided to investigate the generality and scope of this process. The phenylseleno acrylate **50** could potentially serve as a more general ethylene equivalent then the currently known ones.

Results and Discussion

Due to the efficient and mild removal of the selenoester, our studies focused on optimizing conditions and exploring the scope of this new ethylene equivalent **50**. The acrylate was obtained by the Meyer-Schuster rearrangement[22] of the acetylene **63** or the addition of phenylseleno copper[23] to acryloyl chloride **64** (Scheme 2-13). The latter method was found to be more convenient in practice. Similar to other acrylates, **50** polymerized on storage and needed to be freshly distilled before use. However, **50** could be stored with a small amount of 2,6-di-t-butylhydroxytoluene (BHT) at -20 °C for months while still retaining consistent reactivity.

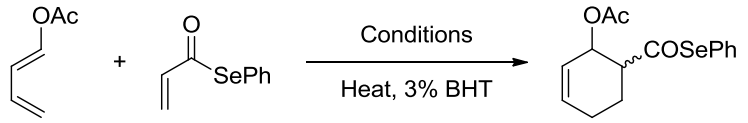


Scheme 2-13. Synthesis of phenylseleno acrylate **50**.

The cycloaddition of butadienyl acetate **65** with **50** was chosen as a model reaction in order to develop conditions mild enough to retain the acetate (Scheme 2-14). No attempt to use such a diene had been attempted prior to this study. Excellent regioselectivity was observed in the formation of the cyclohexene **66**. Heating at higher temperatures, e.g., *o*-xylene (Table 2-1, entry 2), improved the yield. Reactions conducted neat were also successful and were complete within 7 hours (Table 2-1, entry 4). An excess of diene was generally favored due to difficulties in removing the residual phenylseleno acrylate **50** from the resulting products (Table 2-1, entry 8). The yield improved and reactions conducted neat at 80 °C (Table 2-1, entry 5) proceeded in

very good yield. Longer reaction times were not detrimental and experiments conducted in solvents were found to perform as well as reactions performed neat. Reactions performed in toluene (Table 1-1, entry 7) were preferred over reactions performed neat due to the difficulty of degassing the viscous reaction mixtures. The reactions generally gave an approximately 10:1 mixture of isomers, assumed to be the endo and exo isomers respectively.

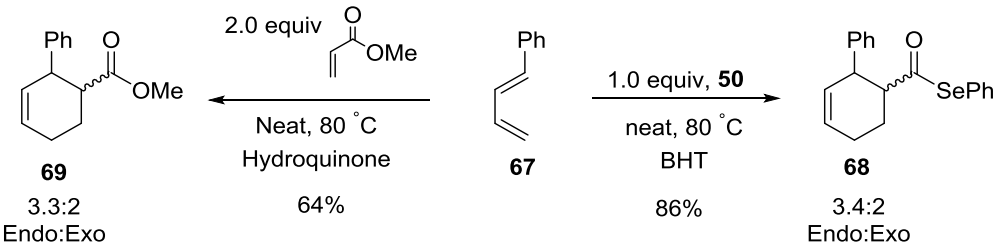
Table 2-1. Conditions screened for the Diels Alder raction of the diene **65**.



65 **50** **66**

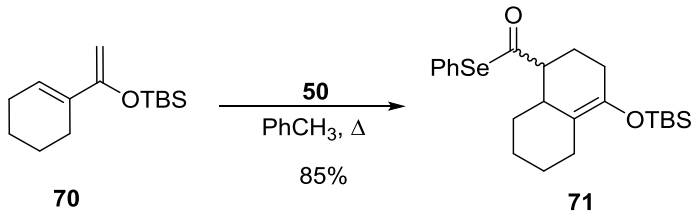
entry	solvent	time	ester equiv.	temp (°C)	yield[%]
1	Benzene	14 h	1.1	85	56%
2	*o*-Xylene	14 h	1.2	120	85%
3	Toluene	14 h	1.2	100	59%
4	Neat	7 h	1.2	120	71%
5	Neat	8 h	0.9	MW 80	88%
6	Neat	12 h	0.9	120	96%
7	Toluene	12 h	0.9	110	91%
8	Benzene	12 h	0.6	120	93%

The reaction of **50** with phenylbutadiene **67** provided the cycloadduct **68** in a 3.4:2 ratio of endo and exo diastereomers (Scheme 2-14). Derivatization to the known methyl ester established that the reaction had a slight endo preference.[24] This was surprisingly similar to Ansell's observation of the reaction of methyl acrylate with **67**, which gave a 3.3:2 mixture of endo:exo products (**69**).[25]



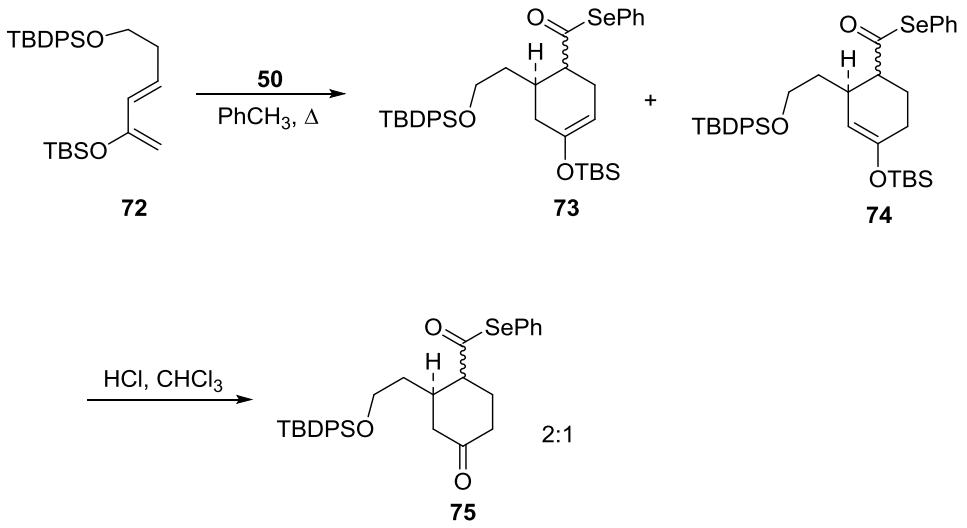
Scheme 2-14. The Diels-Alder reactions of 1-phenyl-1,3-butadiene **67**.

2-Silyloxy dienes were studied in an effort to recover the resulting silyl enol ethers. Hart had conducted a Diels-Alder reaction (Scheme 2-11) with 2-(trimethylsilyloxy)butadiene **56** but intentionally hydrolyzed the resulting silyloxy cyclohexenes. The silyloxy diene **70** reacted well with the dienophile **50** to provide the cyclohexene **71** in an 85% yield (Scheme 2-15).



Scheme 2-15. The Diels-Alder reaction of silyl enol ether **70** with **50**.

When the diene **72** was used, two pairs of diastereomers (**73** and **74**) were obtained (Scheme 2-16) in what appeared to be a 1:1 ratio. An acid-catalyzed alkene isomerizaton was suspected for the formation of **73**, possibly resulting from the high temperatures and traces of acidic benzeneselenol (pKa = 5.9).[26] Desilylation of these compounds gave the ketone **75** as a mixture of two diastereoisomers in a 2:1 ratio.

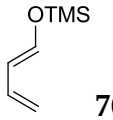
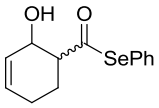
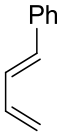
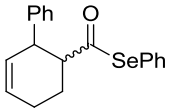
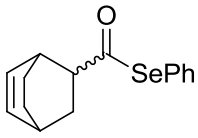
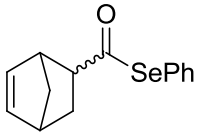
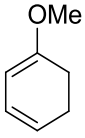
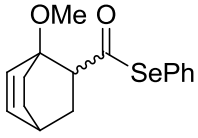
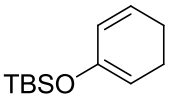
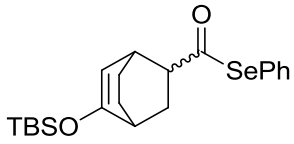
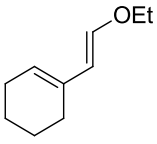
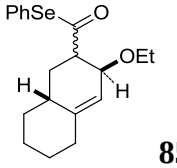


Scheme 2-16. Isomerized Diels-Alder products.

Jung and Ho observed a similar isomerization in the acid promoted double Michael addition of silyloxydienes to 2-methylcyclohexenone, under mixed Lewis acid conditions.[27] Using only trimethylaluminum, the normal Diels-Alder cycloadduct was obtained. The same isomerization was observed in later work by Jung and Guzaev using dimethylaluminum bistriflimide as a catalyst.[28]

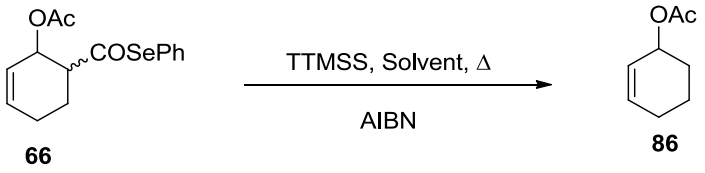
A variety of other dienes (Table 2-2) were also successful in the cycloaddition with **50**. The allylic alcohol **77** (entry 1) was obtained in the reaction of the silyl enol ether **76** with **50** after hydrolysis with citric acid in methanol. At the higher temperatures employed, a slight decrease in endo selectivity was observed for in the Diels-Alder reaction with **67**. Bicyclic systems could be generated with good endo selectivity (entries 3 and 4). More electron rich cyclic dienes (entries 5 and 6) gave products with decreased endo selectivity. The allylic ether **85** (entry 7) was also obtained from the particularly labile ethoxy diene **84** with complete substrate facial stereospecificity, but modest reaction endo/exo stereoselectivity.

Table 2-2. The Diels-Alder products of various dienes and **50**.

entry	diene	product	yield [%];(endo:exo)
1	 **76**	 **77**	91; (2:1)
2	 **67**	 **68**	88; (3:2)
3	 **17**	 **78**	97; (8:1)
4	 **53**	 **79**	91; (4:1)
5	 **80**	 **81**	87; (5:1)
6	 **82**	 **83**	66; (2:1)
7	 **84**	 **85**	81 (3:1)

The radical reduction of **66** was studied; focusing on minimizing the amount of the super silyl reagent needed (Table 2-3). Due to the difficulty of purifying the product **86**, GC/MS was used to screen reaction conditions against a pure sample prepared via a different route.[29] Lower temperatures in the radical reduction generally gave poorer yields (entries 1 and 2) and poor consumption of the ester **66**. Good yields for the reduction could be obtained within an hour in refluxing isooctane (entry 3). Trace amounts of aldehyde were detected by ^{1}H NMR in most cases. The temperature was suspected to be the most important factor; however, the reaction in toluene was unusually low yielding (entry 4). When more reducing agent was used, greater yields were obtained (entries 6 and 7). Isooctane, though unconventional, was investigated because past literature studies suggested that radical decarbonylations occur more rapidly in less polar solvents.[30,31,32] On the Snyder polarity index, toluene has a polarity index of 2.3, whereas isooctane is -0.4.[33]

Table 2-3. A sample of conditions used for the reduction of **66**.

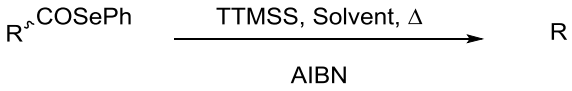


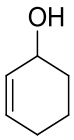
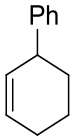
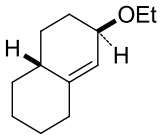
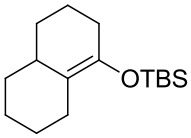
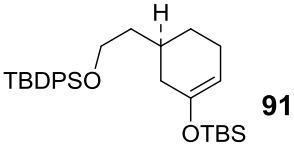
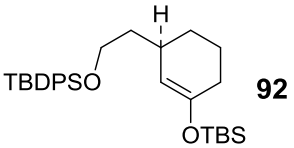
66 **86**

entry	solvent	time	equiv TTMSS	equiv AIBN	temp (°C)	yield(%)
1	Cyclohexane	1 h	1.2	0.2	80	51
2	Benzene	1 h	1.2	0.2	85	51
3	Isooctane	1 h	1.2	0.2	99	78
4	Toluene	1 h	1.2	0.2	110	45
5	Isooctane	1 h	1.5	0.2	99	82
6	Isooctane	1 h	2.0	0.2	99	93
7	Toluene	1 h	2.0	0.2	110	73

The tolerance of other functional groups in the reduction was also investigated (Table 2-4). Due to their volatility and the difficulty in isolating some of these products, many yields were just estimated by ^{1}H NMR (entries 1, 2 and 3) using 2,4,6-triiodophenol as an internal standard. The allylic alcohol **87** and the phenyl cyclohexene **88** (entries 1 and 2) could be obtained in good yield. The remaining material was mostly aldehyde (~5-10%) and complete consumption of the starting esters was observed. In contrast to the prior solvent screen, isooctane and toluene performed similarly for these examples. The fact that the reaction could be performed below 100 °C in good yield was an interesting finding. Given the possibility of isomerization discovered under the Diels-Alder conditions, lower temperatures could possibly prevent isomerizations of silyl enol ethers. The silyl enol ether cycloadducts (**71**, **73**, and **74**) underwent the radical reduction (entries 4 and 5) very well. Approximately 5% of the aldehyde was detected by ^{1}H NMR in these cases and the seleno ester was completely consumed. The remainder of the product was likely lost due to the difficult isolation of these very non-polar reduction products. The reduction of the cycloadduct **85** gave the allylic ether **89** in a 65% yield (entry 3) of the isolated product with an 80% estimated yield by ^{1}H NMR. However, only trace amounts of the aldehyde were detected by ^{1}H NMR and complete consumption of starting material was observed.

Table 2-4. The radical reduction products of the cycloadducts of phenylseleno acrylate **50**.



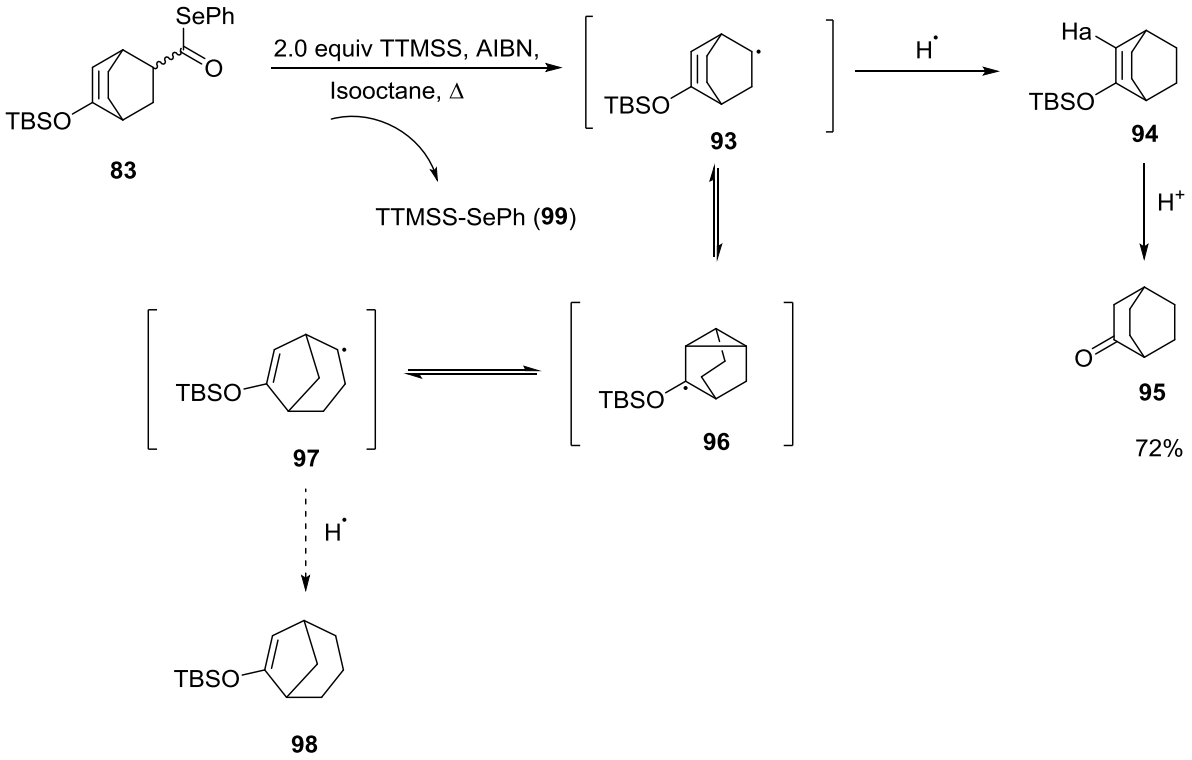
entry	ester	product	yield[%]
1	**77**	 **87**	79 (isooctane)[a] 80 (toluene)[a]
2	**68**	 **88**	>93(isooctane)[a] >99(toluene)[a]
3	**85**	 **89**	80 (isooctane)[a] 65(isooctane) isolated
4	**71**	 **90**	82(isooctane) isolated
5	**73 + 74**	 **91**  **92**	84 (isooctane) isolated

a) Yields estimated by ^{1}H NMR using 2,4,6-triiodophenol as an internal standard.

The radical reductions of the cycloadducts (**78**, **79**, **81**, **83**) posed many more practical challenges than the previous series. The resulting products from this series were often more difficult to study and isolate due to their ability to sublime. Many were unstable to isolation and had a tendency to undergo radical rearrangements. The ability to conduct these reactions on a multigram scale was impeded by the cost of the super silyl reducing agent and the toxicity and

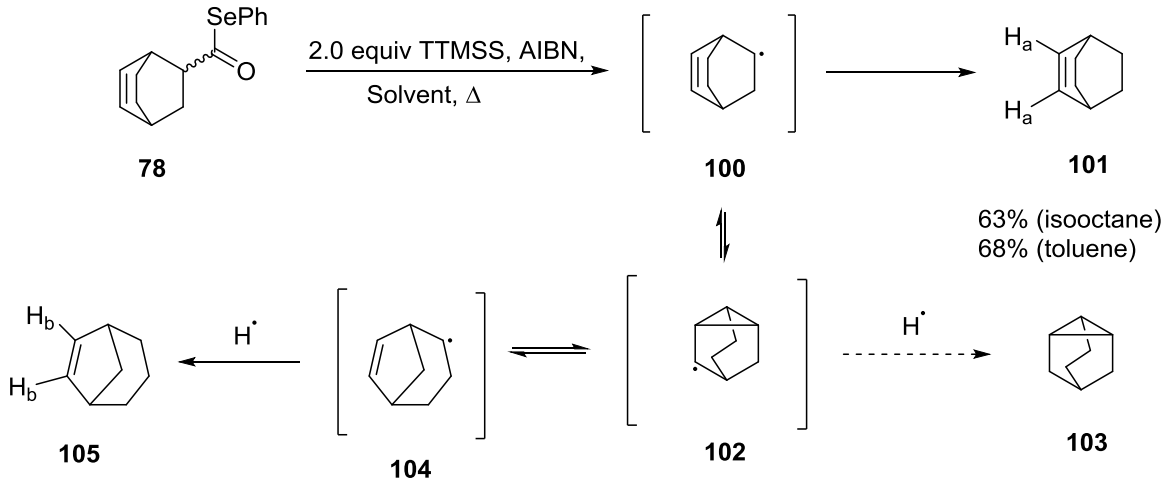
odor associated with the large scale preparation of the phenylseleno acrylate **50**. Each case will be discussed separately in detail.

The radical reduction of **83** produces the radical intermediate **93** (Scheme 2-17). This radical intermedate could abstract hydrogen to form the desired bicyclo[2.2.2]octene product **94** or form the cyclopropylcarbinyl radical **96**, to eventually give the bicyclo[3.2.1]octene **98**. A major olefinic proton (H_a) was detected by ^{1}H NMR of the crude reaction mixture (400 MHz, $CDCl_3$, δ: 5.10 (dd, J = 7.2, 2.0 Hz)). This was attributed to the product **94**. A past study of the analogous TMS enol ether displayed a very similar peak pattern (60 or 100 MHz, CCl_4, δ: 4.98 (dd, J = 7.0, 2.0 Hz)).[34] Attempts to isolate **94** were not successful; it hydrolyzed rapidly to the known bicyclo[2.2.2]octan-2-one **95**.[35] This was isolated and confirmed by ^{1}H and ^{13}C NMR. No starting material was observed at the end of the reaction and only traces of aldehyde were detected in a crude aliquot. Thus, in this case, no radical rearrangement was observed.



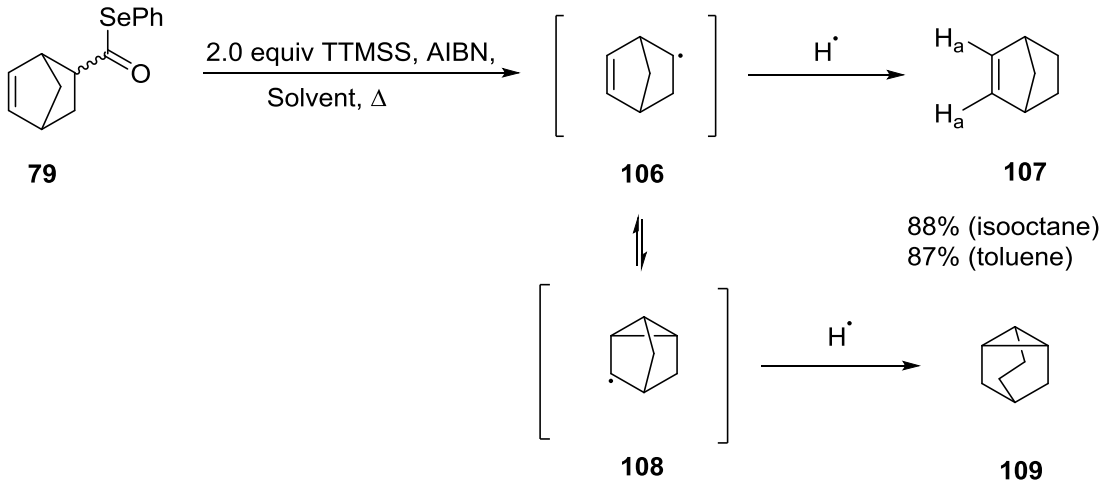
Scheme 2-17. Radical reduction pathways of the ester **83**.

The radical reduction of the cycloadduct **78**, like that of **83**, also proceeded with complete consumption of the selenoester (Scheme 2-18). Traces of two aldehydes (12-13%) were detected by ^{1}H NMR and a new, major olefinic peak was detected, designated as H_a (500 MHz, $CDCl_3$, δ: 6.25 (dd, *J* = 3.7, 3.2 Hz)). This matches the spectrum of bicyclo[2.2.2]oct-2-ene (**101**) reported by Inouye (90 MHz, $CDCl_3$, δ: 6.25 (dd, *J* = 4.5, 3.0 Hz))[36] and that of Powers (500 MHz, $CDCl_3$, δ: 6.23 (dd, 2H)).[35] The yield of **101** was estimated to be 63% in isooctane vs the super silyl phenylselenol ether side product (**99**), which was then checked against a known amount of 2,4,6-triiodophenol after concentration of the reaction mixture (the bicyclooctene **101** evaporated readily as did the other products). Similar results were obtained in either isooctane or toluene. However, the reaction in isooctane provided a larger amount of another olefin, detected by its chemical shift, H_b, (500 MHz, $CDCl_3$, δ: 5.83 (m)), which may be attributed to the bicyclo[3.2.1]oct-5-ene **105** (5.5% yield estimated by ^{1}H NMR) which is similar to the chemical shift of bicyclo[3.2.1]oct-2-ene (20 MHz, $CDCl_3$, δ: 5.85 (m)).[37] This likely arises from the rearrangement the radical **100** to give the cyclopropylcarbinyl radical **102** and its faster rearrangement to **104** followed by radical abstraction of hydrogen to give **105**. The reduction of the tricyclic radical **102** would provide the tricyclo[3.2.1.$0^{2,7}$]octane (**103**) which has been previously prepared and its ^{1}H NMR spectra reported.[37,38] However, the tricycle **103** has not been found in the reaction of **78** with TTMSS in toluene or isooctane since the necessary chemical shifts were not detected in the NMR spectrum.



Scheme 2-18. The radical reduction of the cycloadduct **78**.

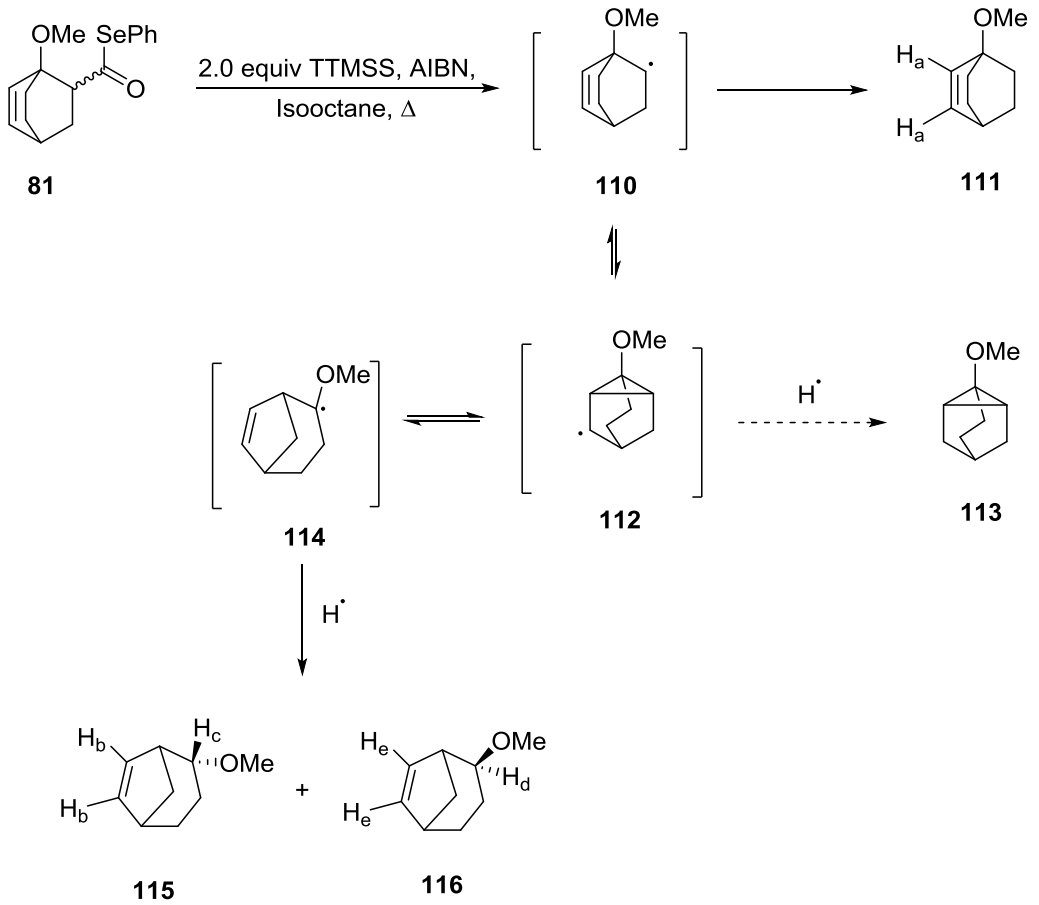
The radical reduction of the cycloadduct **79** gave norbornene **107**, which was immediately detected by its distinctive odor (Scheme 2-19). However, only small amounts of **107** were detected by ^{1}H NMR. Its yield was therefore calculated from the recovered aldehyde (12-13%, ^{1}H NMR, 2,4,6-triiodophenol internal standard), an amount similar to that obtained from the reduction of the cycloadduct **78**. All of the starting ester **79** appeared to be consumed during the course of the reaction. Later, a reaction performed in toluene-d_8 in a closed NMR sample tube again provided a low yield of the expected norbornene **107** (~30% vs TTMSS-SePh). Tricyclo[2.2.1.0^{2,6}]heptane (**109**) was observed by ^{1}H NMR to have been formed in approximately 15-17% yield by ^{1}H NMR. This was surprising since it seemed unlikely that radical rearrangement of **106** (to give **108** and eventually **109**) had occurred since that would be a very endothermic process. However, the presence of **109** is clear from the ^{1}H NMR data.



Scheme 2-19. The radical reduction of **79**.

The radical reduction of the methoxy substituted cycloadduct **81** proceeded with complete consumption of the starting selenoester **81** (Scheme 2-20) and the generation of a small amount of aldehydes (~7% by ^{1}H NMR). The expected reduction product **111** was obtained in approximately 12% yield (estimated by ^{1}H NMR) and matched the previous report by Paquette, *et al.*[39] The major product was another olefin which was detected as an upfield chemical shift (H_b) in the ^{1}H NMR spectrum (Figure 2-3, 400 MHz, $CDCl_3$, δ: (5.87-5.95)). This resembled the chemical shift of the less strained 2-*endo*-bicyclo[3.2.1]oct-6-ene **115**, which has been previously reported by Coxon *et al*[40] Further evidence for this product was obtained by the couplings calculated for the exo-proton (H_c) in **115** (400 MHz, $CDCl_3$, δ: 3.21 (ddd, J = 9.3, 6.1, 2.1 Hz)) which compared favorably to Coxon's studies on the 4-endo-deuterio-2-endo-methoxybicyclo[3.2.1]-oct-6-ene analog (300 MHz, $CDCl_3$, δ: 3.19 (ddd, J = 9.3, 5.6, 2.7 Hz)),[41] which was further downfield than in his previous report (100 MHz, $CDCl_3$, δ: 3.26 (ddd, J = 8, 4, 3 Hz)). The experimental ^{1}H NMR spectrum obtained by Coxon is shown vs the crude aliquot obtained from our studies (Figure 2-4). A third product was obtained during the reduction which was postulated to be the *exo*-methoxy isomer **116**, which has not been reported in the literature

before. Therefore the initially formed radical **110** undergoes facile rearrangement to the cyclopropylcarbinyl radical **112**, which then opens to the bicyclo[3.2.1] radical **114**, stabilized by the methoxy group. The endo and exo isomers **115** and **116** were obtained in 67% yield by ^{1}H NMR (vs 2,4,6-triiodophenol) in an approximately 2.6:1 ratio.



Scheme 2-20. The radical reduction of **81**.

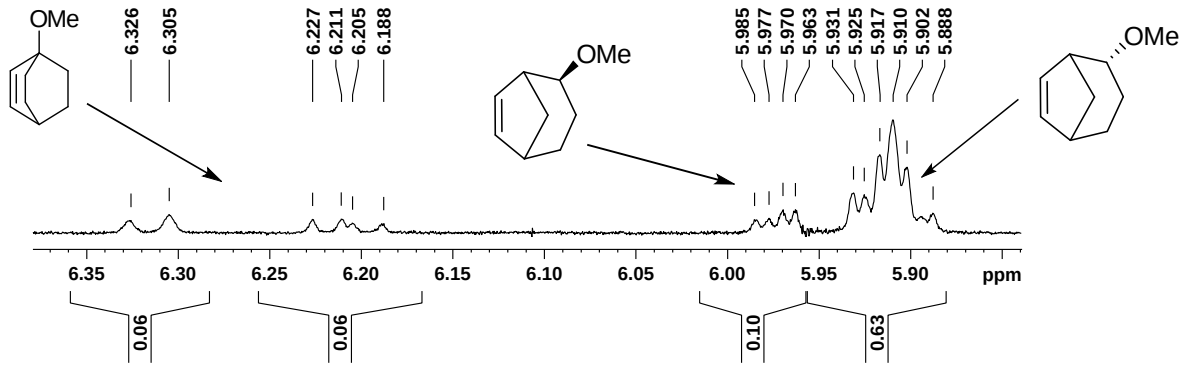


Figure 2-3. [1]H NMR spectrum of the reduction products of **81.**

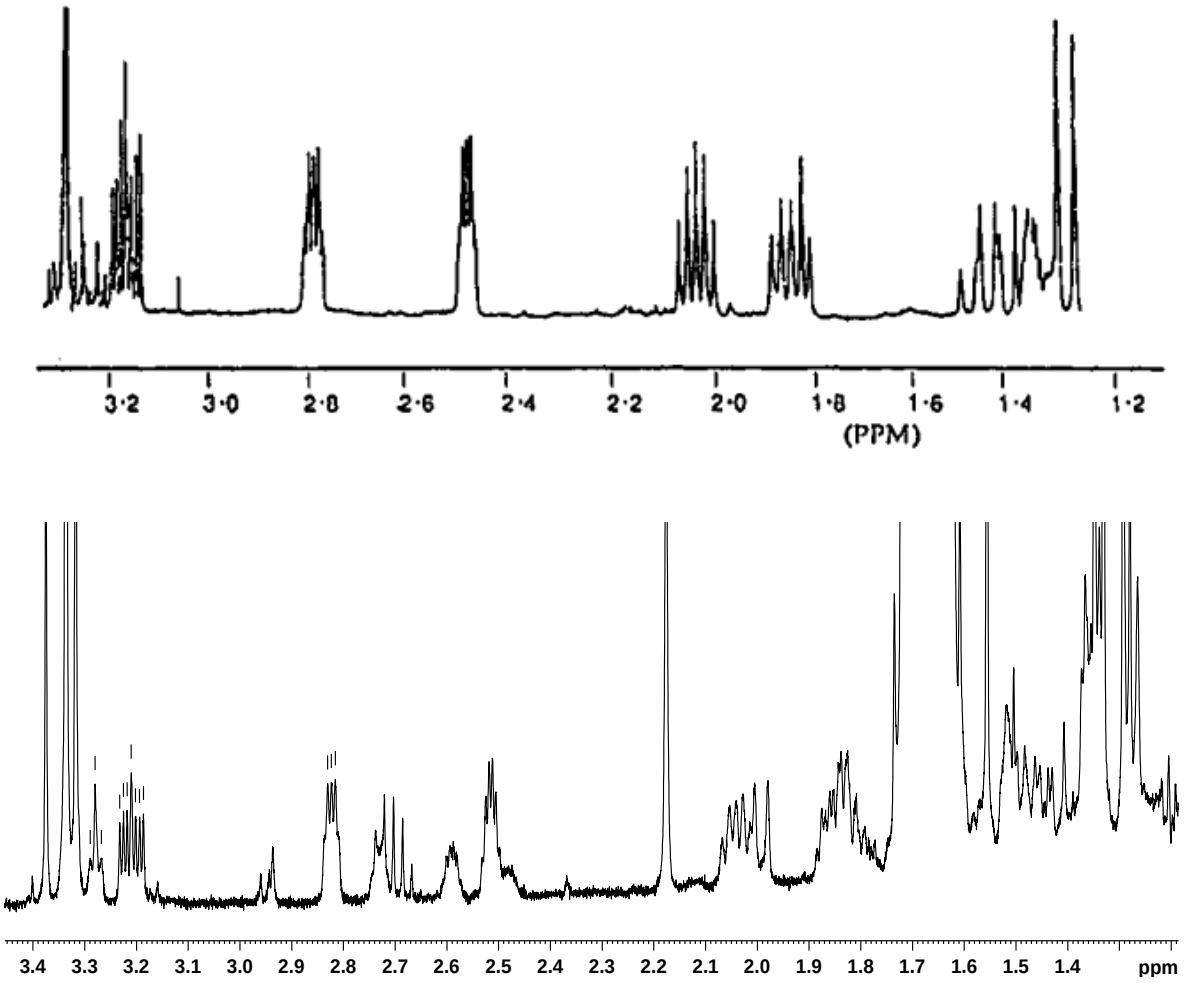


Figure 2-4. [1]H NMR spectrum of **115** obtained by Coxon (top) and **115** from this study (bottom).

The dramatically different behavior observed for the methoxy bicyclo[2.2.2]octene radical **110** when compared to the unsubstituted case, **100**, argued strongly that we should look at these systems computationally. Calculations by Dr. Kendall Houk and his student Lufeng Zhou, indicated that the bicyclo[2.2.2]octene **101** is more stable than the bicyclo[3.2.1]octene **105** by 1.7 kcal mol^{-1} (Figure 2-5). More importantly, the bicyclo[3.2.1]octyl radical **104** is less stable than the bicyclo[2.2.2]octene radical **100** by 2.4 kcal mol^{-1}, which is in line with the observation that little or none of the bicyclo[3.2.1]octene **105** was formed during the radical reduction of **78**, as discussed previously. However, addition of the methoxy substituent to the bridgehead carbon of the bicyclo[2.2.2]octyl radical (**110**) causes the corresponding bicyclo[3.2.1]octyl radical **114** to be more stable by 2.5 kcal mol^{-1}. This is likely due to increased stabilization of the carbon radical by the methoxy substituent. Again, this is in line with our ^1H NMR observations of the reduction of **81**.

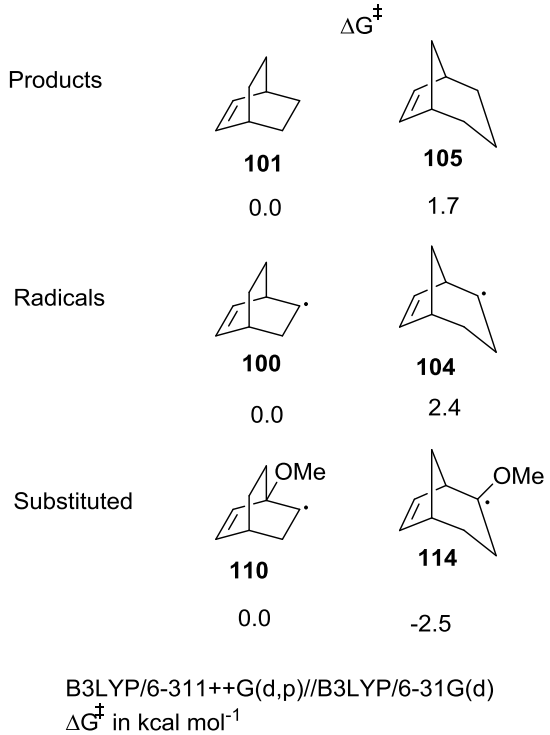
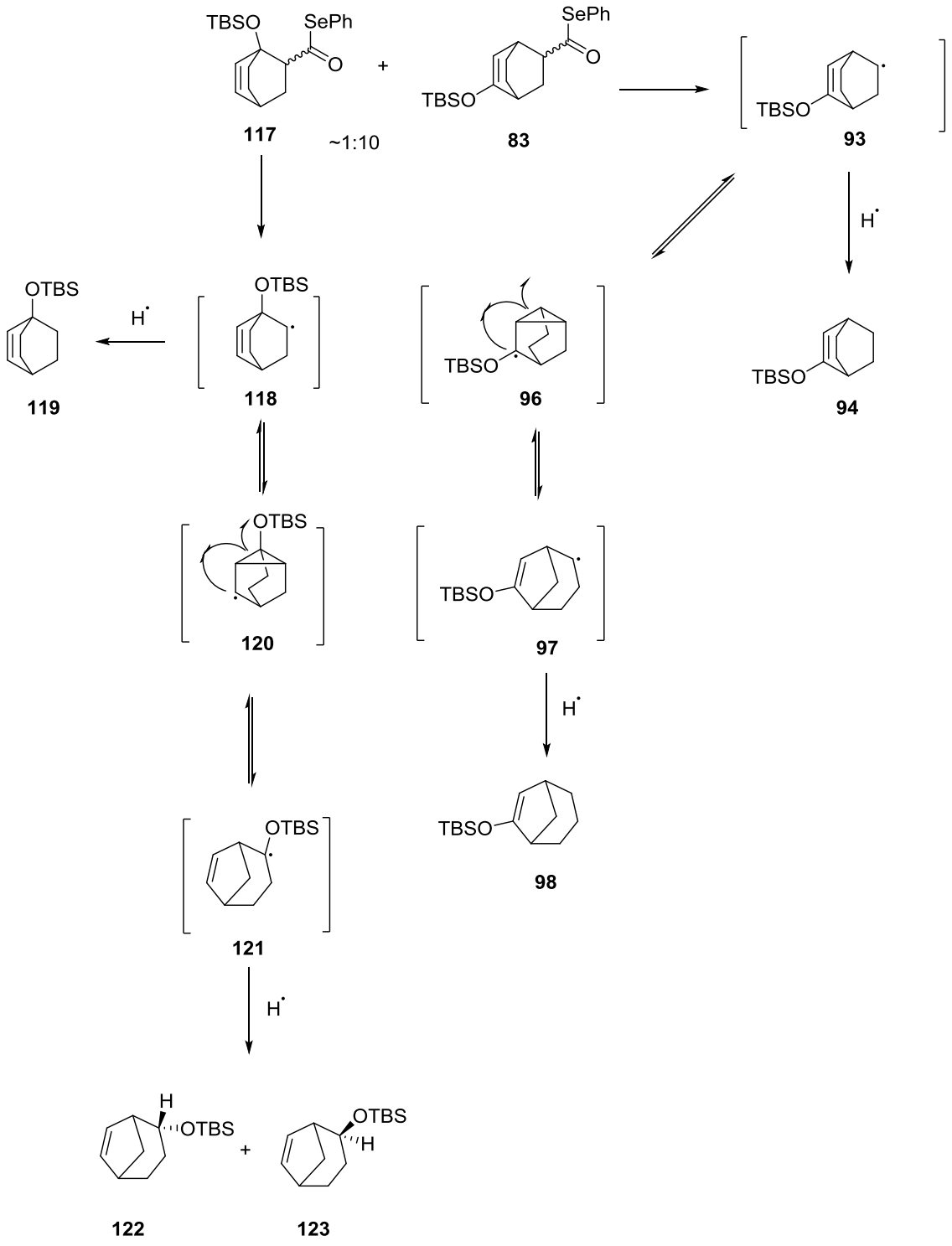


Figure 2-5. Relative stabilities of reduction products and radicals.

When the reduction is performed with a 1:10 mixture of cycloadducts **117** (a minor impurity present at the time) and **83** (Scheme 2-21), many products are obtained as shown by ^{1}H NMR. Complete consumption of the phenylseleno esters **117** and **83** was observed and approximately 5% of a pair of aldehydes were formed (estimated by ^{1}H NMR). The expected direct trapping product **94** was obtained as the major product (>70%) by ^{1}H NMR. A complex mixture of minor olefinic products was obtained (Figure 2-6) as shown by ^{1}H NMR. In light of the results obtained for the methoxy bicyclo[2.2.2]octene **81**, the ^{1}H NMR of this reaction was reexamined and allowed us to propose the mechanism in Scheme 2-21.

The minor chemical shifts in the ^{1}H NMR spectrum displayed remarkably similar characteristics to the prior reduction (Figure 2-4).The direct trapping product of **117** is present (Figure 2-6A) at δ 6.06-6.20 (400 MHz, $CDCl_3$, δ: 6.18 (d, J = 8.8 Hz), 6.09 (dd, J = 8.8, 6.4 Hz)). However, this time, a much more distinctive AB spin system is observed at 5.88-5.93 ppm (Figure 2-6A). This is likely due to the endo bicyclo[3.2.1]octane silyl ether **122**. Further support for this proposal comes from the distinctive upfield chemical shift (δ: 3.63, (ddd, J = 9.4, 6.1, 3.2 Hz)) which has the same distinctive coupling pattern as does the exo proton of the product **115** obtained earlier in this work (Figure 2-6B). In addition, an unidentified isomer, possibly the exo product **123**, may give rise to the chemical shifts at δ 5.96-6.00 and possibly the proton alpha to the *exo*-TBS ether at 3.75 ppm. An additional olefin signal (Figure 2-6C) was observed at 4.59 ppm (dd, J = 2.8, 0.7 Hz), likely corresponding to the rearranged product **98**, which was previously reported by Stothers (however, without any ^{1}H NMR data).[42] The TMS silyl enol ether of bicyclo[2.2.1]heptanone displays an olefinic peak at 4.69 ppm (d, J = 3 Hz).[43] The proposed bicyclo[3.2.1]octenyl silyl ether **98** would likely display a more downfield shift with a similar, small coupling.



Scheme 2-21. The radical reduction of the mixture of **117** and **83**.

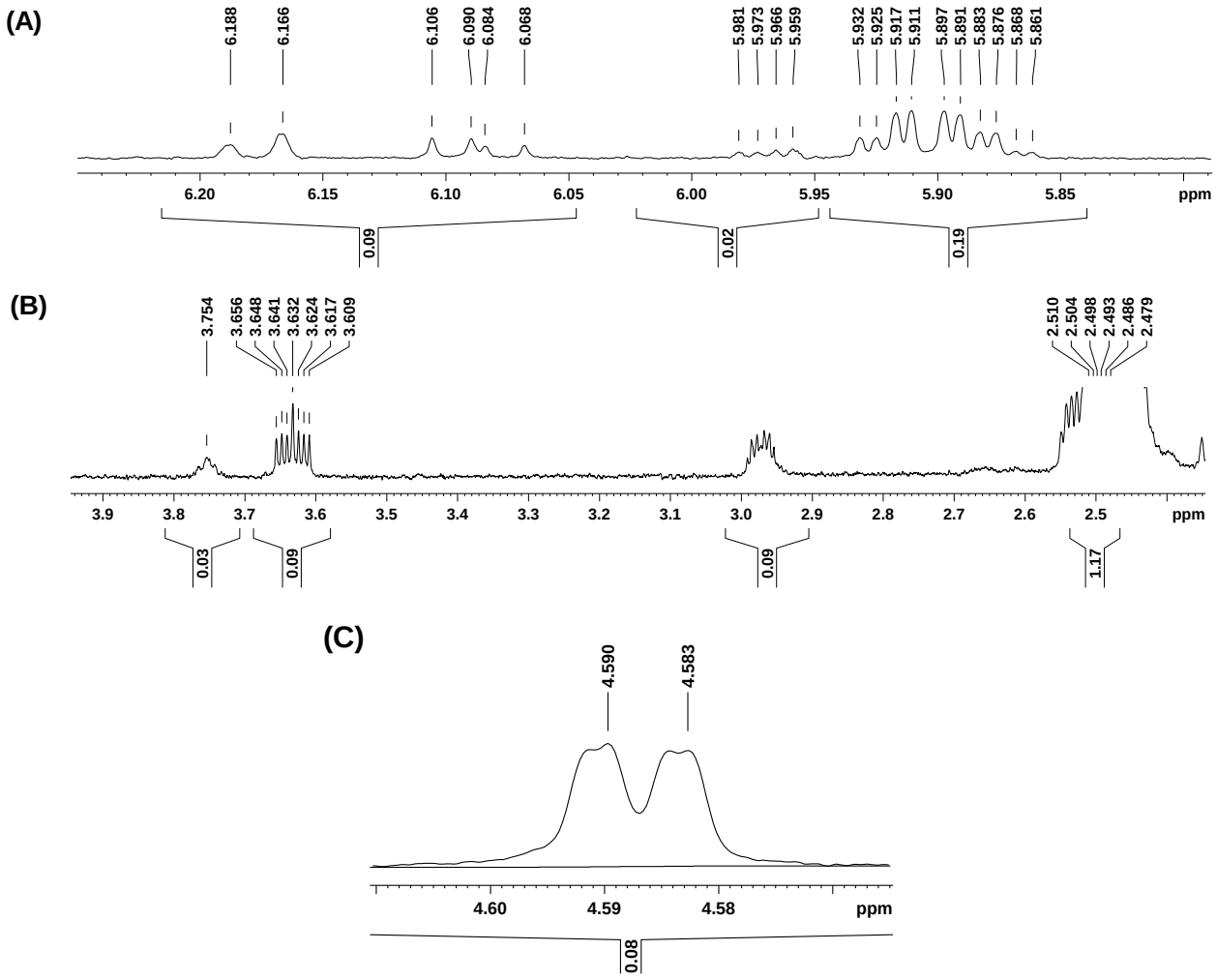
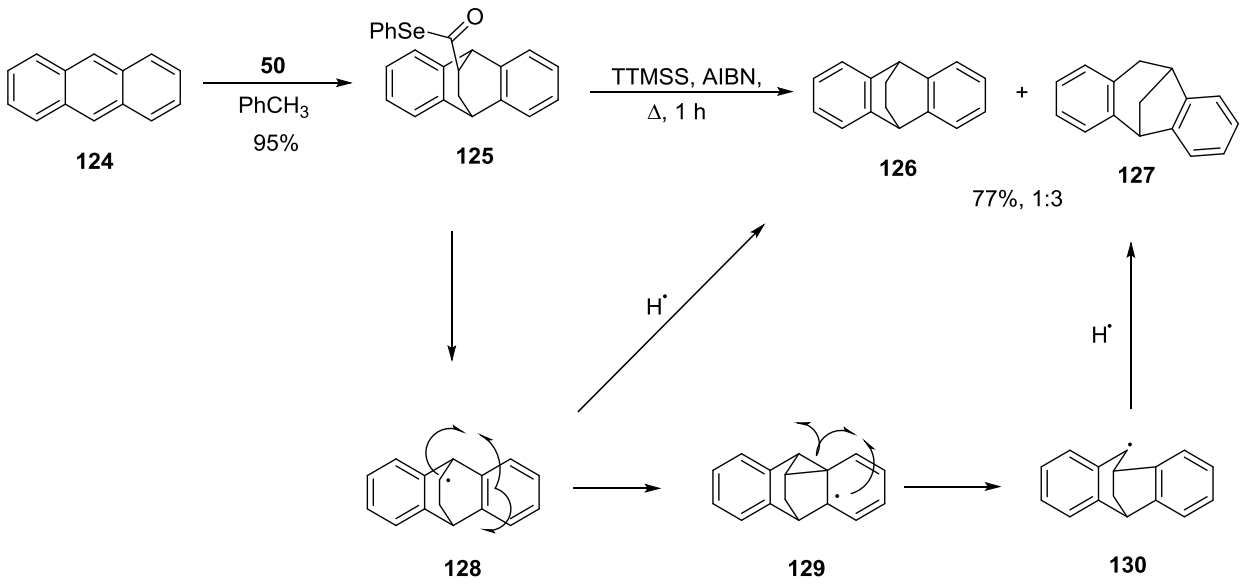


Figure 2-6. The ^{1}H NMR spectrum of the radical reduction of the esters **117** and **83**.

One additional cyclopropylcarbinyl radical rearrangement was also observed in this study (Scheme 2-22). The seleno ester **125** was obtained from the Diels-Alder reaction of **50** with anthracene (**124**). After reduction of **125** two products were obtained, the expected bicyclo[2.2.2]octane **126** and the bicyclo[3.2.1]octane compound **127**. The reason for the formation of these two products is obvious when the intermediate radical **128** is considered. This secondary radical rearranges rapidly to the more stable benzylic radical **130**. This requires dearomatization to give the cyclopropylcarbinyl radical intermediate **129**. This radical rearrangement has been investigated previously by Cristol in his work using chlorine

transfer.[44,45] However, Cristol was only able to obtain the chlorinated bicyclo[3.2.1]octane. Here, the reduction of **125** gave a 1:3 mixture of the direct trapping product **126**, along with the rearranged product **127**.

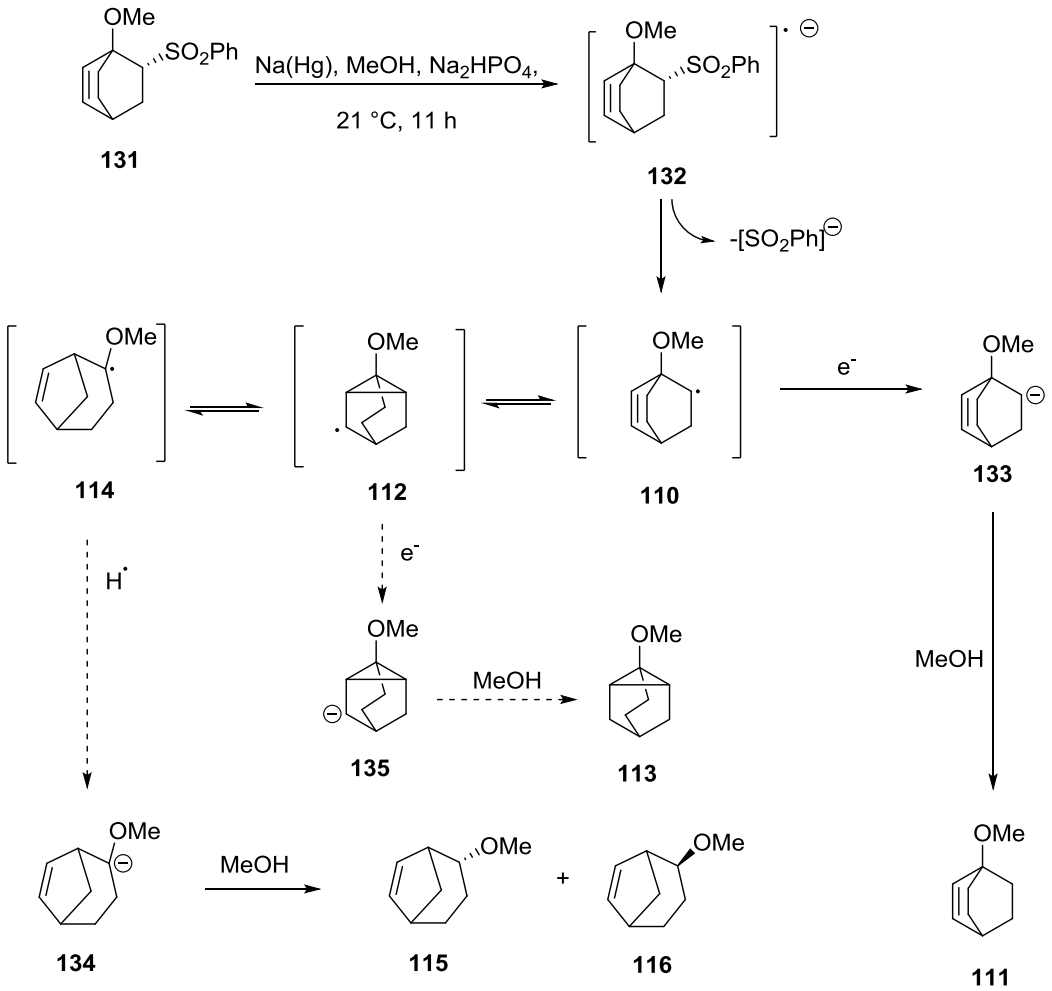


Scheme 2-22. The radical reduction of **125**.

The extent of the cyclopropylcarbinyl rearrangement observed during the reduction of **81** (direct trapping to rearranged, 1:6) was much greater than observed for the reduction of the anthracene cycloadduct **125** (direct trapping to rearranged, 1:3). Such a rearrangement could be used as a probe for reactions that undergo competing pathways. A preliminary case has been investigated by ^{1}H NMR that provided a very interesting result.

The reductive desulfonylation of sulfones with sodium amalgam was discussed earlier as a method of removing the activating auxiliary of Paquette's ethylene equivalent. [10] The reduction of the cycloadduct **131**, previously reported by Paquette, is hypothesized to generate the radical anion **132** as an intermediate which undergoes fragmentation to the sulfinate and the bicyclo[2.2.2]octenyl radical **110** (Scheme 2-23). This carbon radical than rapidly gains an electron, forming the anion **133** and is protonated by solvent to provide the reduction product

111. If the radical intermediate **110** exists, it should be possible to observe some degree of the cyclopropylcarbinyl radical rearrangement discussed earlier in Scheme 2-20 where the radical intermediate **110** is also formed. This would involve the formation of the α-oxyanion **134** which, after protonation, would provide the bicyclo[3.2.1]octenes **115** and **116**.



Scheme 2-23. Desulfonylation of the sulfone **131**.

The reduction of the sulfone cycloadduct **131** was carried out, giving the bicyclo[2.2.2]octene product **111** as reported by Paquette. However, the rearranged endo and exo bicyclo[3.2.1]octenes **115** and **116** were observed by ^{1}H NMR in the isolated product at approximately 2-3% abundance. Although the exo product **116** (400 MHz, C_6D_6, δ: 5.80) is obscured by the ^{13}C satellite peak of the major product **111**, mass spectrometry clearly confirms

the presence of the less abundant exo isomer **116** (GC MS (ESI) *m/z*: 138.1 (15%, $[M]^+$), 106.1(100%, $[M-32]^+$) which has a similar fragmentation pattern to the endo isomer **115** (GC MS (ESI) *m/z*: 138.1 (33%, $[M]^+$, 106.1 (100%, $[M-32]^+$)), namely their radical cations both suffer the loss of neutral methanol. The mass spectrum also matches that obtained from an aliquot of the radical reduction of **81** using C_6D_6 as a solvent at 80 °C. Another important observation was the ratio of **115** and **116** (2.6:1) which was identical to that obtained earlier for the radical reduction of **81**. The more clearly resolved methyl shifts of the endo product **115** (δ 3.07) and the exo product **116** (δ 3.01) were used to determine this ratio.

This result suggests that the radical **110** is an intermediate in the reductive desulfonylation reaction of **131** and that the formation of the carbanion **133** is very fast. If the tricyclo[3.2.1.0]octane anion **135** had formed instead of the radical **112**, then protonation of the anion would occur and the product **113** should have been observed by GC MS. Kirmse has isolated the methoxy tricyclo[3.2.1.0]octane **113** by gas chromatography. [38] However, in our reaction, only the products **111**, **115** and **116** have been observed thus far. Therefore, a radical mechanism is most likely responsible for the formation of **115** and **116** during the desulfonylation of **131**.

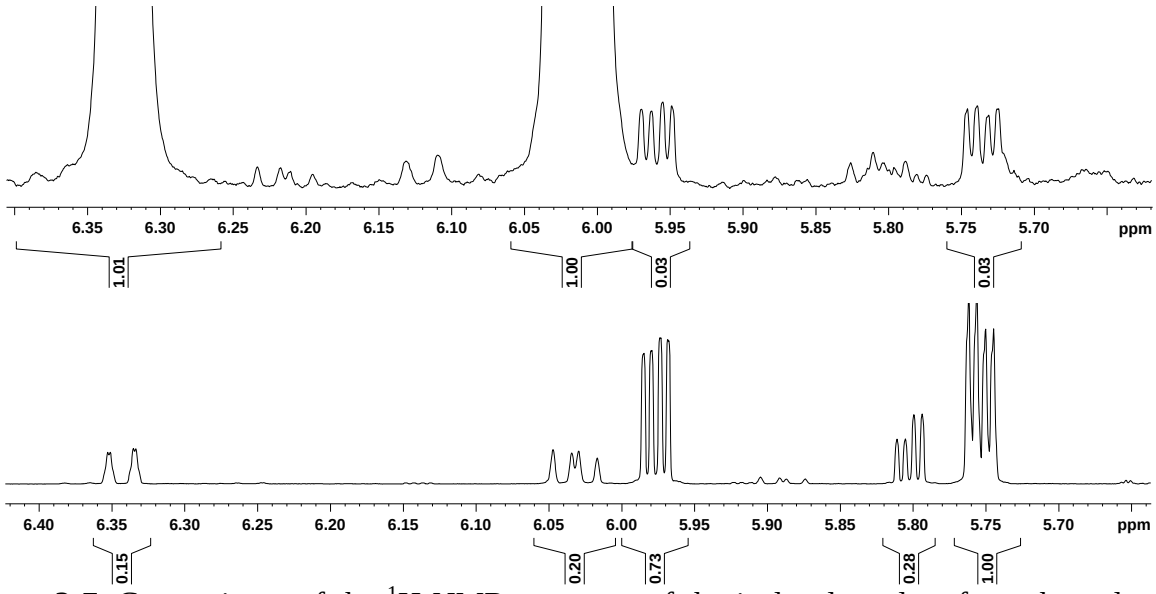


Figure 2-7. Comparison of the ^{1}H NMR spectrum of the isolated product from the reductive desulfonylation of (top) with that obtained from the radical reduction of **81** in C_6D_6 (bottom).

The products obtained from the reduction were noticeably volatile, which was apparent from the strong odor emitted by the isolated product. Future work on this rearrangement should be conducted with the less volatile silyl ethers obtained from the radical reduction of **117** and **83**.

Conclusion

Phenylseleno acrylate has been shown to be an effective and versatile ethylene equivalent for the Diels-Alder reaction. It is a more reactive dienophile than the analogous methyl acrylate and also provides cycloadducts with excellent regioselectivity. Poor endoselectivity is generally observed, but is not important in this application. Isomerization of silyl enol ethers is possible after the cycloaddition, most likely owing to trace amounts of the acidic material benzeneselenol. Most interestingly, the reduction of the seleno ester cycloadducts is mild, tolerating the presence of esters, alcohols, allylic ethers and silyl enol ethers. Ethylene equivalents developed prior to this generally did not show such tolerance as shown during Jung and Regan's studies on the brasilicardin series. However, the intermediate secondary radicals may be susceptible to internal rearrangements, in particular if cyclopropylcarbinyl radicals can possibly form. This was particularly evident for the bicyclo[2.2.2]octene series, which gave varying degrees of the rearranged bicyclo[3.2.1]octene products.

Experimental Section

General: All reactions were carried out under an argon atmosphere unless otherwise specified. Tetrahydrofuran (THF), diethyl ether, toluene, and benzene were distilled from sodium and benzophenone ketyl radical under an argon atmosphere. Dichloromethane (DCM) and triethylamine (TEA) were distilled from calcium hydride under an argon atmosphere. All other solvents or reagents were purified according to literature procedures. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 300, 400 & 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 75, 100 & 125 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift, which are reported in parts per million (ppm, δ). All Fourier Transform Infrared (FTIR) samples were prepared neat as thin films on a germanium or diamond crystal and the spectra were recorded using attenuated total reflectance (ATR) on a JASCO FTIR-4100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Thin-layer chromatography (TLC) was carried out using pre-coated silica gel aluminum backed sheets (EMD Millipore Silica gel 60 F_{254}). Visual detection was performed using ceric ammonium nitrate, *p*-anisaldehyde and potassium permanganate stains or ultraviolet light at 256 nm or 354 nm. Flash chromatography was performed using SilicaFlash™ P60 (60 Å, 40-63 μm) silica gel from SiliCycle Inc. with compressed air.

(*E*)-2-(2-(Ethoxy)ethenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: Ethoxyacetylene was purchased from Aldrich as a 40 wt% solution in hexane. A 25-mL round bottom flask was purged with argon and charged with freshly distilled ethoxyacetylene (3.84 g, 40 wt %, 21.9 mmol) and dichloromethane (10 mL). Chlorobis(cyclopentadienyl)zirconium(IV) hydride (395 mg, 1.53 mmol) was added in one portion and the mixture was sealed and kept under a positive flow of argon. The reaction was stirred at 21 °C for 2 min, then 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.08 g, 24.09 mmol) was added dropwise. After it stirred for 2 h, the dark reaction mixture was diluted with diethyl ether (150 ml) and washed with water (2 x 100 ml), dried over sodium sulfate, filtered and concentrated *in vacuo* to give a dark oil. Short path vacuum distillation yielded the vinyl boronate as a yellow oil (2.69 g, 62%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

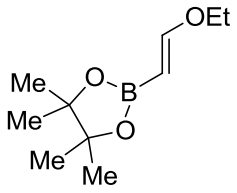
7.04 (d, 1H, *J* = 14.4 Hz)

4.43 (d, 1H, *J* = 14.4 Hz)

3.84 (q, 2H, *J* = 7.1 Hz)

1.29 (t, 3H, *J* = 7.1 Hz)

1.25 (s, 12H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 163.1, 82.7, 64.5, 24.7, 14.5. (One carbon missing due to quadrupole broadening).

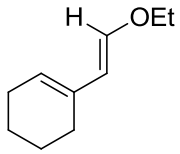
FTIR (neat): 2987, 2929, 1634, 1610, 1373, 1307, 1136, 976 cm^{-1}.

(*E*)-2-(2-(Ethoxy)ethenyl)cyclohex-1-ene (84): The ethoxyethenylboronate (1.39 g, 5.34 mmol) was added to a solution of 1-iodocyclohexene[46] (1.00 g, 4.85 mmol) in THF (15 mL) and water (5 mL). $Pd(PPh_3)_4$ (560 mg, 0.485 mmol) was added and the reaction was stirred for 5 min at 21 °C. Thallium(I) ethoxide (390 uL, 5.34 mmol) was added dropwise via syringe, resulting in a bright orange precipitate. After it stirred for 1 h, the reaction mixture was partitioned between water and pentane and filtered through Celite. The organic phase was washed with water and then brine, then dried over sodium sulfate and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash column chromatography (pentane, basic alumina), to provide the ethoxydiene **84** as a clear, colorless oil (950 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

6.43 (d, 1H, *J* = 12.8 Hz)

5.56 (d, 1H, *J* = 12.8 Hz)



5.48-5.52 (m, 1H)

3.77 (q, 2H, *J* = 7.0 Hz)

2.03-2.11 (m, 4H)

1.62-1.69 (m, 2H)

1.54-1.62 (m, 2H)

1.27 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.8, 132.9, 123.7, 110.2, 65.2, 25.7, 24.8, 22.7, 22.6, 14.9.

6-((Phenylselenyl)carbonyl)cyclohex-2-en-1-yl acetate (66): 1,3-Butadienyl acetate (**65**) was prepared as a mixture of isomers by a previously reported procedure.[47] A 1.5 ml screw cap vial was charged with the phenylseleno acrylate **50** (95 mg, 0.45 mmol), (2,6-di(tert-butyl)-4-methylphenol (BHT, 3 mg, 0.01 mmol) and **65** (70 mg, 0.50 mmol). Argon was gently bubbled through the solution for 1 minute, sealed and heated to 120 °C in an oil bath for 12 h. The dense mixture was subjected directly to flash chromatography (silica gel, 5-10% ethyl acetate/hexanes), yielding a nearly 10:1 mixture of diastereoisomers as a white solid (155 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.46-7.50 (m, 2H)

7.36-7.40 (m, 3H)

6.00-6.04 (m, 0.9H)

5.88-5.92 (m, 1H)

5.61-5.67 (m, 1.1H)

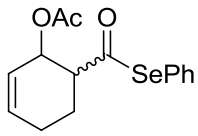
3.00-3.10 (m, 1H)

2.26-2.36 (m, 1H)

2.11-2.20 (m, 1H)

2.04-2.11 (m, 2H)

2.04 (s, 3H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 201.2, 200.0, 170.2, 135.9, 135.8, 135.7, 133.3, 130.6, 129.30, 129.28, 128.91, 128.87, 125.86, 125.7, 125.5, 123.6, 77.3, 77.0, 76.7, 69.3, 69.0, 66.3, 56.1, 55.1, 55.0, 54.8, 50.3, 24.6, 24.3, 23.8, 21.1, 21.0, 19.6.

FTIR (Neat): 3036, 2935, 2836, 1721, 1438, 1374, 1234 cm^{-1}.

***cis*-6-((Phenylselenyl)carbonyl)cyclohex-2-en-1-yl acetate:** A pure sample of the major endo isomer was obtained by recrystallization of **66** from hexanes, yielding a white solid, mp 69-71 °C.

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.46-7.49 (m, 2H)

7.36-7.40 (m, 3H)

6.00-6.04 (m, 1H)

5.88-5.92 (m, 1H)

5.61-5.62 (m, 1H)

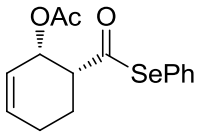
3.00-3.05 (m, 1H)

2.28-2.32 (m, 1H)

2.12-2.17 (m, 1H)

2.04-2.06 (m, 2H)

2.04 (s, 3H).



^{13}C NMR (100 MHz, $CDCl_3$, δ): 200.1, 170.3, 136.0, 133.3, 129.3, 128.9, 125.9, 123.7, 66.4, 55.1, 24.7, 21.0, 19.7.

FTIR (Neat) 3033, 2917, 1723, 1439, 1377, 1237 cm^{-1}.

HRMS-ESI (m/z): $[M + Na]^+$ calculated for $C_{15}H_{16}O_3SeNa$ 347.0163; found, 347.0163.

***Se*-Phenyl 2-hydroxycyclohex-3-enecarboselenoate (77):** 1-(Trimethylsilyloxy)-1,3-butadiene **4b** was prepared according to a previously reported procedure.[48] A 3-ml screw cap vial was charged with **4b** (144 mg, 1.01 mmol), BHT (6.7 mg, 0.03 mmol), toluene (1.5 ml) and the phenylseleno acrylate **50** (193 mg, 0.91 mmol). A small stir bar was added and the mixture was sparged for 2 min with bubbling argon. The vial was sealed immediately and heated in a 110 °C oil bath for 12 h. The mixture was concentrated *in vacuo* and treated with 10% aqueous citric acid and ether for 1 h to cleave the trimethylsilyl ether. The organic phase was washed with brine, dried over sodium sulfate and was concentrated *in vacuo* to a yellow residue. The oil was purified by flash column chromatography (silica gel, 10-20% ethyl acetate/hexanes) gave **77** as a clear oil, as an approximately 2.2:1 mixture of diastereoisomers (234 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.51-7.53 (m, 2H)

7.39-7.41 (m, 3H)

5.91 (m, 0.7H)

5.85-5.88 (m, 0.7H)

5.78-5.80 (m, 0.3H)

5.65-5.68 (m, 0.3H)

4.54-4.59 (m, 1H)

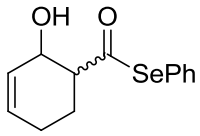
2.94-2.98 (m, 0.7H)

2.83-2.87 (m, 0.3H)

2.44 (d, 0.7H, *J* = 5.9 Hz)

2.33 (d, 0.3H, *J* = 5.3 Hz)

2.23-2.30 (m, 0.7H)



2.01-2.19 (m, 3H)

1.76-1.85 (m, 0.3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 204.3, 203.9, 136.1, 135.9, 131.4, 129.5, 129.4, 129.0, 128.7, 127.2, 125.9, 125.7, 67.9, 64.4, 60.1, 57.5, 25.1, 24.6, 24.6, 20.2.

FTIR (neat): 3416, 3025, 2920, 1713, 1479, 1059, 1018, 960, 913 cm^{-1}.

HRMS-ESI (*m/z*): $[M\text{-}OH]^+$ calculated for $C_{13}H_{13}OSe$ 265.0132; found, 265.0129.

***Se*-Phenyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboselenoate (68):** 1-Phenyl-1,3-butadiene (**67**) was prepared by a previously reported procedure.[49] A 3-ml screw cap vial was charged with **67** (144 mg, 1.11 mmol), BHT (6.6 mg, 0.03 mmol), toluene (1.5 ml) and the phenylseleno acrylate **50** (211 mg, 1.00 mmol). A small stir bar was added and the mixture was purged for 2-minutes with bubbling argon. The vial was sealed immediately and heated in a 110 °C oil bath for 12 h. The reaction mixture was concentrated *in vacuo* togive a dense yellow oil. The oil was purified by flash column chromatography (silica gel, 3-5% ethyl acetate/hexanes) to give **68** as a pale yellow oil, as a 3:2 mixture of diastereoisomers (300 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.29-7.37 (m, 8.5H)

7.20-7.25 (m, 1.5H)

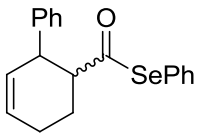
5.95-6.00 (m, 0.6H)

5.85-5.90 (m, 0.4H)

5.76-5.80 (m, 0.6H)

5.64-5.68 (m, 0.4H)

3.97-4.00 (m, 0.6H)



3.78-3.83 (m, 0.4H)

3.23-3.28 (m, 0.6H)

2.93-2.99 (m, 0.4H)

2.35-2.39 (m, 0.6H)

1.89-2.30 (m, 3.4H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 203.5, 202.2, 139.3, 135.8, 130.0, 129.5, 129.3, 129.2, 128.8, 128.7, 128.5, 128.3, 127.94, 127.87, 127.8, 127.14, 127.06, 126.8, 126.5, 126.3, 60.2, 56.6, 44.3, 43.6, 25.6, 24.4, 24.2, 19.6.

FTIR (Neat): 3054, 3026, 2950, 2910, 2876, 2833, 1703, 1600, 1578, 1490, 1476, 1452, 1436, 1012 cm^{-1}.

cis-Se-Phenyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-carboselenoate: A pure sample of the major isomer was obtained after thin layer chromatography of **68** (silica gel, 2.5% diethyl ether/hexanes), followed by recrystallization, giving the endo isomer as a white crystalline solid (144 mg, 42%, mp 38-40 °C).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.25-7.34 (m, 10H)

5.95-5.99 (m, 1H)

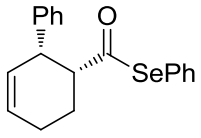
5.76-5.80 (m, 1H)

3.99 (m, 1H)

3.24-3.29 (m, 1H)

2.32-2.37 (m, 1H)

2.16-2.25 (m, 1H)



1.97-2.06 (m, 1H)

1.88-1.94 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 202.2, 139.3, 135.8, 129.9, 129.1, 128.6, 127.93, 127.87, 127.8, 127.1, 126.3, 56.6, 43.6, 24.4, 19.6.

FTIR (Neat): 2854, 2926, 1719, 1680, 1472, 1462, 1359, 1252, 1192 cm^{-1}.

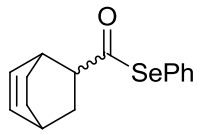
HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{19}H_{19}OSe$ 343.0602; found, 343.0610.

***Se*-Phenyl bicyclo[2.2.2]oct-5-ene-2-carboselenoate (78):** 1,3-Cyclohexadiene **17** was purchased from Aldrich and used without further purification. A 3-ml screw cap vial was charged with **17** (200 mg, 2.50 mmol), BHT (4.3 mg, 0.03 mmol), toluene (1 ml) and the phenylseleno acrylate **50** (227 mg, 1.08 mmol). A small stir bar was added and the mixture was purged for 2 min with bubbling argon. The vial was sealed immediately and heated in a 110 °C oil bath for 12 h. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel, 5% ethyl acetate/hexanes) to give **78** as a 4:1 mixture of diastereomers (113 mg, 36%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.46-7.52 (m, 2H)

7.33-7.39 (m, 3H)



6.32-6.37 (m, 1.2H)

6.19 (dd, 0.8H, *J* = 7.5, 7.5 Hz)

2.95-3.04 (m, 1.8H)

2.78-2.82 (m, 0.2H)

2.59-2.66 (m, 1H)

1.94-1.98 (m, 0.2H)

1.78-1.84 (m, 0.8H)

1.68-1.78 (m, 1H)

1.55-1.65 (m, 1H)

1.46-1.53 (m, 1H)

1.31-1.40 (m, 1H)

1.23-1.30 (m, 1H).

^{13}C NMR (125MHz, $CDCl_3$, δ): 203.1, 202.9, 136.0, 135.9, 135.7, 135.4, 133.3, 131.0, 129.3, 129.21, 129.19, 128.8, 128.6, 126.6, 55.9, 55.5, 53.5, 33.6, 33.2, 30.7, 29.6, 29.5, 28.4, 25.5, 24.9, 24.3, 20.7.

FT-IR (neat): 3059, 2967, 2940, 1718, 1578, 1476, 1439 cm^{-1}.

***Se*-Phenyl bicyclo[2.2.2]oct-5-ene-2-carboselenoate:** The major isomer was obtained from the more polar fraction as a clear viscous oil (192 mg, 61%).

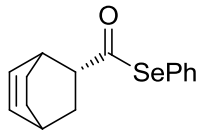
^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.46-7.48 (m, 2H)

7.33-7.35 (m, 3H)

6.33 (dd, 1H, *J* = 7.4, 7.4 Hz)

6.19 (dd, 1H, *J* = 7.3, 7.3 Hz)



2.99-3.04 (m, 2H)

2.63-2.65 (m, 1H)

1.79-1.84 (m, 1H)

1.71-1.76 (m, 1H)

1.58-1.64 (m, 1H)

1.48-1.53 (m, 1H)

1.31-1.38 (m, 1H)

1.23-1.30 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 203.0, 136.0, 135.4, 131.0, 129.2, 128.6, 126.6, 55.9, 33.2, 30.7, 29.5, 25.5, 24.3.

FTIR (neat): 3059, 2967, 2939, 2879, 1717, 1578, 1476, 1438 cm^{-1}.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{17}OSe$ 293.0445; found 293.0440.

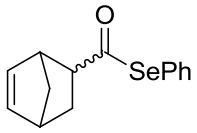
***Se*-Phenyl bicyclo[2.2.1]hept-5-ene-2-carboselenoate (79):** Cyclopentadiene **53** was distilled prior to use. A 3-ml screw cap vial was charged with **53** (182 mg, 2.76 mmol), BHT (9.1 mg, 0.04 mmol), toluene (2.0 ml) and the phenylseleno acrylate **50** (288 mg, 1.36 mmol). A small stir bar was added and the mixture was purged for 2 min with bubbling argon. The vial was sealed immediately and heated in a 110 °C oil bath for 12 h. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, 3% diethyl ether/hexanes) to give the product **78** as a clear oil (172 mg, 45%) as an approximately 1:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.52-7.54 (m, 1H)

7.46-7.49 (m, 1H)

7.34-7.39 (m, 3H)



6.18-6.22 (m, 1H)

6.12 (dd, 0.5H, *J* = 5.6, 3.1 Hz)

6.03 (dd, 0.5H, *J* = 5.6, 2.4 Hz)

3.35-3.92 (m, 1H)

3.17 (m, 0.5H)

2.96 (m, 1H)

2.65 (ddd, 0.5H, *J* = 8.3, 4.4, 1.8 Hz)

1.90-2.01 (m, 1H)

1.47-1.57 (m, 1.5 H)

1.33-1.43 (m, 1.5 H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 203.3, 201.4, 139.0, 138.1, 136.0, 135.5, 132.1, 129.4, 129.3, 128.9, 128.8, 127.0, 126.7, 56.9, 56.2, 49.5, 47.5, 47.1, 46.4, 42.9, 42.0, 30.8, 29.8.

FTIR (neat): 3060, 2974, 2359, 1719, 1578, 1476, 1439, 1334, 996, 733, 688 cm^{-1}.

***Se*-Phenyl bicyclo[2.2.1]hept-5-ene-2-carboselenoate:** The pure endo isomer was recovered from the more polar fraction as a clear oil (173 mg, 46%).

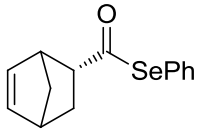
^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.45-7.48 (m, 2H)

7.33-7.37 (m, 3H)

6.21 (dd, 1H, *J* = 5.6, 3.1 Hz)

6.03 (dd, 1H, *J* = 5.6, 2.7 Hz)



3.35-3.39 (m, 2H)

2.94-2.97 (m, 1H)

1.92 (ddd, 1H, *J* = 11.7, 8.8, 3.7 Hz)

1.55 (bd, 1H, *J* = 11.7 Hz)

1.49 (bd, 1H, *J* = 8.4 Hz)

1.33 (bd, 1H, *J* = 8.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 201.3, 138.0, 135.9, 132.0, 129.2, 128.7, 126.6, 56.8, 49.4, 47.0, 42.8, 29.7.

FTIR (neat): 3062, 2871, 2972, 1720, 1470, 1442, 1059, 1025, 993 cm^{-1}.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{15}OSe$ 279.0289; found, 279.0287.

***Se*-Phenyl 1-methoxybicyclo[2.2.2]oct-5-ene-2-carboselenoate (81):** The 1-methoxy-1,3-cyclohexadiene **80** was obtained from Aldrich as a 65% (w/w) solution and used without further purification. A 15-ml screw cap vial was charged with **80** (1.11g, 6.55 mmol), BHT (21.7 mg, 0.1 mmol), toluene (10.0 ml) and the phenyseleno acrylate **50** (694 mg, 3.29 mmol). A small stir bar was added and the mixture was purged for 2 min with bubbling argon. The vial was sealed immediately and heated in a 110 °C oil bath for 12 h. The mixture was concentrated *in vacuo* and the residue was purified flash column chromatography (silica gel, 5-10% ethyl acetate/hexanes) to give **81** as a 4:1 mixture of diastereomers (919 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

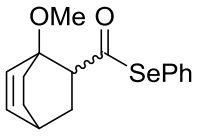
7.47-7.54 (m, 2H)

7.32-7.37 (m, 3H)

6.41 (bd, 0.2H, *J* = 8.9 Hz)

6.37 (bd, 0.8H, *J* = 8.7 Hz)

6.28 (bdd, 0.8H, *J* = 8.8, 6.4 Hz)



6.26 (m, 0.2H)

3.48 (s, 0.4H)

3.42 (s, 2.6H)

3.28 (ddd, 0.8H, *J* = 10.0, 5.3, 1.0 Hz)

3.12 (ddd, 0.2H, *J* = 11.4, 4.9, 2.1 Hz)

2.60-2.63 (m, 0.8H)

2.55-2.58 (m, 0.2H)

1.95-2.10 (m, 1H)

1.87 (ddd, 0.2H, *J* = 12.8, 5.0, 2.3 Hz)

1.72 (ddd, 0.8H, *J* = 5.3, 3.0, 3.0 Hz)

1.69 (ddd, 1H, *J* = 5.3, 3.0, 3.0 Hz)

1.53-1.67(m, 2 H)

1.37-1.44 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 202.8, 201.7, 135.8, 135.7, 134.3, 134.0, 132.9, 132.8, 129.2, 129.1, 128.7, 128.5, 127.6, 127.4, 79.9, 79.1, 59.1, 56.9, 51.8, 51.2, 33.5, 31.7, 29.7, 29.6, 28.4, 25.3, 25.0, 24.9.

FTIR (neat): 3053, 2941, 2867, 1704, 1578, 1476, 1438, 1196, 1112 cm^{-1}.

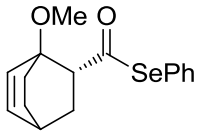
***Se*-Phenyl 1-methoxybicyclo [2.2.2]oct-5-ene-2-carboselenoate:** A small amount of the major product was obtained after preparatory thin layer chromatography of the mixture (5% ethyl acetate/hexanes) providing the endo product as a clear yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.47-7.49 (m, 2H)

7.33-7.34 (m, 3H)

6.37 (bd, 1H, *J* = 8.8 Hz)



6.28 (bdd, 1H, *J* = 8.8, 6.4 Hz)

3.42 (s, 3H)

3.28 (ddd, 1H, *J* = 10.1, 5.3, 0.7 Hz)

2.61 (bs, 1H)

2.00 (ddd, 1H, J = 12.8, 10.2, 2.6 Hz)

1.67-1.73 (m, 1H)

1.61-1.67 (m, 2H)

1.53-1.58 (m, 1H)

1.37-1.44 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 201.7, 135.8, 132.9, 132.8, 129.1, 128.5, 127.4, 79.1, 59.1, 51.2, 33.5, 29.6, 28.4, 25.0.

FTIR (neat): 3052, 2945, 2868, 2830, 1709, 1473, 1438, 1375, 1197, 1116 cm^{-1}.

HRMS-ESI (*m/z*): $[M + Na]^+$ calculated for $C_{16}H_{18}O_2SeNa$ 345.0370; found, 345.0394.

Se-Phenyl 5-[(1,1-dimethylethyl)silyloxy]bicyclo[2.2.2]oct-5-ene-2-carboselenoate (83): The diene **82** was prepared by a previously reported procedure.[50] A 3-ml screw cap vial was charged with **82** (420 mg, 2.0 mmol), BHT (21.7 mg, 0.1 mmol), toluene (2.0 ml) and the phenylseleno acrylate **50** (212 mg, 1.00 mmol). A small stir bar was added and the mixture was purged for 2 min with bubbling argon. The vial was sealed immediately and heated in a 110 °C oil bath for 12 h. The mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (5% diethyl ether/hexanes) to give **83** as a greater than 10:1 mixture of diastereomers as a clear oil (279.8 mg, 66%). The minor isomer had been hydrolyzed greatly during workup to the corresponding ketone.

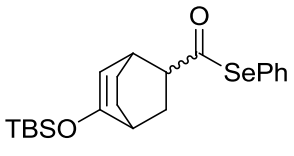
^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.46-7.49 (m, 2H)

7.34- 7.36 (m, 3H)

5.19 (dd, 0.04H, *J* = 7.2, 2.2 Hz)

5.01 (dd, 0.96H, *J* = 7.0, 2.1 Hz)



3.04-3.08 (m, 1H)

2.90-2.94 (m, 1H)

2.41-2.44 (m, 1H)

1.95-2.01 (m, 1H)

1.76 (ddd, 1H, *J* = 12.8, 9.9, 2.7 Hz)

1.56-1.61 (m, 1H)

1.47-1.51 (m, 2H)

1.37-1.43 (m, 1H)

0.92 (s, 9H)

0.14 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 202.6, 157.5, 136.0, 129.2, 128.6, 126.7, 102.1, 56.6, 35.8, 34.2, 30.6, 26.8, 25.7, 25.0, 18.0, -4.36, -4.50.

FT-IR (neat): 3060, 2964, 2948, 2880, 2865, 1718, 1637, 1579, 1471, 1463 cm^{-1}.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{31}O_2SeSi$ 423.1259; found, 423.1258.

***Se*-Phenyl 3-ethoxy-1,2,3,5,6,7,8,8a-octahydronaphthalene-2-carboselenoate (85):** Freshly prepared diene **84** was used. A 3-ml screw cap vial was charged with diene (170 mg, 1.1 mmol), BHT (6 mg, 0.03 mmol), toluene (1.5 ml) and the phenylseleno acrylate **50** (202 mg, 0.95 mmol). The solution was degassed by bubbling argon through it for 2 min. The vial was immediately sealed and heated in an oil bath at 110 °C for 12 h. The mixture was concentrated *in vacuo* to give a yellow oil which was purified by flash column chromatography (silica gel, 1-5% ethyl acetate/hexanes) to give **85** as an approximately 3:2 mixture of diastereomers (280 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.48-7.52 (m, 2H)

7.35-7.39 (m, 3H)

5.64 (bd, 0.6H, *J* = 5.3 Hz)

5.43-5.45 (m, 0.4H)

4.13-4.18 (m, 1H)

3.50-3.73 (m, 2H)

2.98-3.04 (m, 0.4H)

2.77-2.85 (m, 0.6H)

2.18-2.31 (m, 1H)

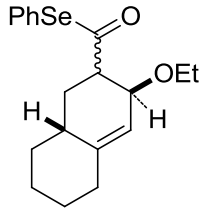
1.70-2.13 (m, 7H)

1.25-1.42 (m, 2H)

1.23 (t, 1.2 H *J* = 7.0 Hz)

1.18 (t, 1.8 H *J* = 7.0 Hz)

1.03-1.16 (m, 1H).



^{13}C NMR (125 MHz, $CDCl_3$, δ): 202.9, 201.3, 146.1, 144.2, 136.0, 135.9, 129.3, 129.2, 128.8, 128.6, 126.5, 126.4, 118.7, 118.3, 74.8, 72.5, 65.3, 64.9, 57.1, 55.2, 37.9, 36.3, 35.4, 34.8, 34.5, 34.3, 30.7, 27.7, 27.2, 27.0, 26.3, 25.8, 15.7, 15.6.

FTIR (neat): 3057, 2927, 2858, 1722, 1476, 1441, 1089, 739, 693 cm^{-1}.

HRMS-ESI (*m/z*): $[M\text{-}OEt]^+$ calculated for $C_{17}H_{19}OSe$ 319.0602; found, 319.0605.

***Se*-Phenyl-4-[(1,1-dimethylethyl)dimethylsilyloxy]-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carboselenoate (71):** The diene **70** was prepared by a previously reported procedure.[51] A 3-ml screw cap vial was charged with **70** (238.4 mg, 1.0 mmol), BHT (7mg, 0.03 mmol), toluene (2.0 ml) and the phenylseleno acrylate **50** (232 mg, 1.1 mmol). The mixture was degassed for 2 min with bubbling argon. The vial was sealed immediately and heated in a 110 °C oil bath for 12 h. The mixture was concentrated to give a dark yellow oil which was purified by flash column chromatography (silica gel, 5- 10% diethyl ether/hexanes) to give **71** as a clear oil in a 1:1 mixture of diastereomers (382 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.48-7.52 (m, 2H)

7.36-7.39 (m, 3H)

2.98-3.04 (m, 0.5H)

2.85-2.93 (m, 1H)

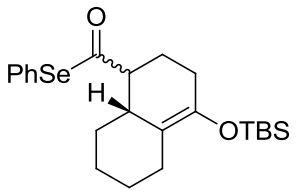
2.43-2.56 (m, 1.5H)

1.98-2.20 (m, 3H)

1.90-2.09 (m, 4H)

1.09-1.53 (m, 4H)

0.939-0.943 (m, 9H)



0.11-0.12 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 204.0, 202.5, 140.8, 140.6, 135.9, 135.8, 132.0, 129.29, 129.27, 129.1, 128.8, 128.7, 126.6, 126.4, 118.4, 117.0, 60.2, 56.2, 40.5, 39.4, 34.1, 29.85, 29.78, 29.6, 27.8, 27.5, 26.8, 26.31, 26.27, 26.0, 25.9, 25.8, 21.4, 18.2, 16.8, -3.8, -3.89, -3.94, -4.1.

FTIR (Neat) 2832, 2922, 2361, 1726, 1714, 1578, 1453 cm^{-1}.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{35}O_2SeSi$ 451.1573; found, 451.1564.

Se-Phenyl 4--[(1,1-dimethylethyl)dimethylsilyloxy]-2-(2--[(1,1-dimethylethyl)diphenylsilyl-oxy]ethyl)cyclohex-3-enecarboselenoate (73) and Se-phenyl 4--[(1,1-dimethylethyl)di-methylsilyloxy]-6--[(1,1-dimethylethyl)diphenylsilyloxy]ethyl)cyclohex-3-enecarboselenoate (74): The diene **72** was prepared by a previously reported procedure.[52] A 5-mL screw cap vial was charged with diene **72** (700 mg, 1.5 mmol), BHT (8 mg, 0.04 mmol), toluene (3 mL), the phenylseleno acrylate **50** (245 mg, 1.2 mmol) and a stir bar. The solution was degassed by bubbling argon through it for 5 min and the vial was sealed immediately and heated to 110 °C in an oil bath for 12 h. The dark yellow solution was concentrated and the residue was purified by column chromatography (silica gel, 1-5% ethyl acetate/hexanes) to give the product, **73** and **74**, as a yellow oil, as a mixture of two diastereomeric pairs of regioisomers (676 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

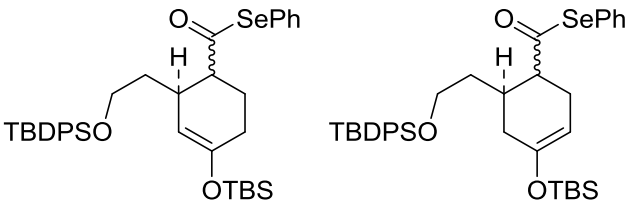
7.66-7.69 (m, 4H)

7.47-7.50 (m, 2H)

7.35-7.42 (m, 9H)

4.98-5.00 (m, 0.2H)

4.81-4.82 (m, 0.8H)



3.70-3.76 (m, 2H)

2.93-3.07 (m, 0.6H)

2.61-2.72 (m, 0.6H)

2.30-2.50 (m, 2H)

1.73-2.01 (m, 4H)

1.56 (m, 0.4H)

1.06-1.08 (m, 9H)

0.90-0.91 (m, 9H)

0.09-0.12 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 203.9, 203.4, 202.3, 202.0, 150.6, 150.1, 149.9, 149.5, 136.06, 136.05, 135.99, 135.9, 135.7, 135.6, 134.0, 133.92, 133.89, 133.86, 133.82, 133.81, 129.7, 129.32, 129.28, 128.80, 128.75, 127.8, 126.7, 126.6, 126.5, 106.6, 106.2, 101.1, 101.0, 61.8, 61.64, 61.62, 61.5, 57.3, 56.9, 55.6, 54.6, 37.9, 36.5, 34.6, 34.3, 33.9, 33.5, 32.9, 32.6, 32.5, 29.8, 28.9, 28.5, 27.0, 26.8, 25.8, 25.7, 24.1, 20.9, 19.4, 19.32, 19.29, 18.1, 18.0, -4.28, -4.30, -4.32, -4.4.

FTIR (neat): 3071, 3052, 2928, 2898, 2857, 1719, 1669, 1579, 1472 cm^{-1}.

***Se*-Phenyl-2-(2-[(1,1-dimethylethyl)dimethylsilyloxy]ethyl)-4-oxocyclohexanecarbo-selenoate (75):** Chloroform (10 mL) was treated with one drop of 37% HCl. A 1 mL aliquot of the organic phase was transferred to a 1.5 mL vial containing 50 mg of the mixture of **73** and **74** and the vial was sealed. The mixture was allowed to stand overnight at 21 °C. The solution was concentrated *in vacuo* and residue was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to give **75** as a clear oil, as a mixture of two diastereomers in an approximately 2:1 ratio (25.4 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.63-7.68 (m, 4H)

7.38-7.50 (m, 11H)

3.79-3.81 (m, 1H)

3.67-3.78 (m, 2H)

3.13-3.16 (m, 0.7H)

2.92-2.97 (m, 0.3H)

2.44-2.66 (m, 3H)

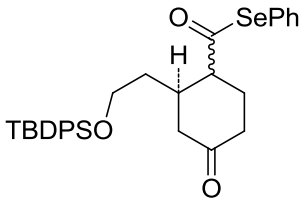
2.20-2.37 (m, 2.8H)

1.95-2.13 (m, 1.5H)

1.76-1.86 (m, 1.2H)

1.51-1.60 (m, 0.5H)

1.06-1.13 (m, 9H).



^{13}C NMR (100 MHz, $CDCl_3$, δ): 210.0, 209.2, 202.8, 202.3, 135.83, 135.77, 135.58, 135.57, 133.59, 133.53, 133.50, 133.49, 129.78, 129.77, 129.76, 129.73, 129.5, 129.1, 127.81, 127.78, 127.77, 127.75, 126.3, 126.0, 61.0, 60.9, 58.1, 54.6, 44.7, 44.5, 39.3, 38.1, 36.9, 36.66, 36.59, 34.6, 27.8, 26.94, 26.92, 26.89, 19.24, 19.18.

7-Ethoxy-1,2,3,4,4a,5,6,7-octahydronaphthalene: A 1.5 mL HPLC vial was charged with seleno ester **85** (130 mg, 0.36 mmol), isooctane (1.0 mml), tris(trimethylsilyl)silane (TTMSS, 179 mg, 0.72 mmol) and azobis(isobutyronitrile) (AIBN, 12 mg, 0.07 mmol). A stream of argon was gently bubbled through the solution for 10 s and the solution was heated to 99 °C in an oil bath for 1 h. The clear solution was concentrated *in vacuo* and the residue purified by flash column chromatography (silica gel, 0-2% diethyl ether/hexanes) to give the octahydronaphthalene as a clear oil (42 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.54 (bd, 1H, *J* = 1.75 Hz)

3.73-3.81 (m, 1H)

3.58-3.64 (m, 1H)

3.49-3.55 (m, 1H)

2.26 (bd, 1H, *J* = 13.5 Hz)

1.92-2.03 (m, 2H)

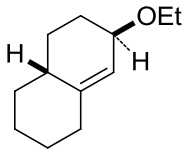
1.77-1.82 (m, 4H)

1.66-1.71 (m, 1H)

1.57-1.64 (m, 1H)

1.31-1.53 (m, 3H)

1.26 (t, 3H, *J* = 7 Hz)



1.15-1.21 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 145.2, 120.1, 72.8, 63.4, 37.7, 35.4, 34.4, 27.3, 26.5, 26.25, 26.20, 15.8.

FTIR (neat): 2970, 2929, 2854, 1445, 1096 cm^{-1}.

3-(2-[(1,1-dimethylethyl)diphenylsilyloxy]ethyl)-(1-[(1,1-dimethylethyl)dimethylsilyloxy] cyclohex-1-ene and 5-(2-[(1,1-dimethylethyl)diphenylsilyloxy]ethyl)-(1-[(1,1-dimethylethyl)-dimethylsilyloxy]cyclohex-1-ene: A 3 ml screw cap vial was charged with the seleno esters **73** and **74** (274 mg, 0.404 mmol), isooctane (1.0 ml), TTMSS (201 mg, 0.808 mmol), AIBN (13.2 mg, 0.08 mmol) and a stir bar. The solution was purged by bubbling argon through it for 1 min and the vial was sealed and heated to 99 °C for one hour. A clear solution developed. The mixture was concentrated and the residue was purified by flash column chromatography (0-2% ethyl acetate/hexanes) to give the products as a clear viscous oil, in an approximately 1:1 mixture of regioisomers (168 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.66-7.68 (m, 4H)

7.36-7.45 (m, 6H)

4.85 (bs, 0.5H)

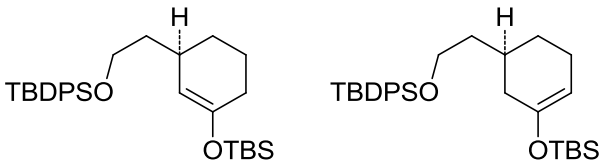
4.77 (bs, 0.5H)

3.70-3.74 (m, 2H)

2.35 (m, 0.5H)

1.80-2.07 (m, 3H)

1.49-1.73 (m, 5.5H)



1.05 (s, 9H)

0.91-0.92 (m, 9H)

0.10-0.12 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, , δ): 150.6, 150.0, 135.6, 134.10, 134.06, 129.53, 129.51, 127.6, 109.3, 103.9, 77.3, 77.0, 76.7, 62.0, 61.9, 39.6, 38.9, 36.5, 31.14, 31.10, 30.0, 28.8, 28.5, 26.9, 25.7, 23.3, 21.6, 19.2, 18.04, 18.02, -4.31, -4.33, -4.42, -4.45.

FTIR (neat): 2955, 2928, 2894, 2857, 1667, 1590, 1487 cm^{-1}.

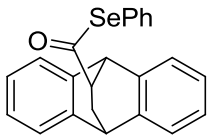
***Se*-Phenyl 9,10-dihydro-9,10-ethanoanthracene-11-carboselenoate (125):** A 25 ml round bottom flask was charged with anthracene (708 mg, 3.98 mmol), BHT (17.5 mg, 0.08 mmol), toluene (5.0 ml), the phenylseleno acrylate **50** (559 mg, 2.65 mmol) and a stir bar. The mixture was purged with argon for 5 min and the vial was sealed with a rubber septum and heated in a 110 °C oil bath for 12 h, becoming a semi-solid mixture. The toluene was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, 10-20% ethyl acetate/hexanes), to provide **88** as a bright white solid (981 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.40-7.43 (m, 2H)

7.27-7.34 (m, 7H)

7.10-7.14 (m, 4H)



4.75 (d, 1H, *J* = 2.4 Hz)

4.38 (bdd, 1H, *J* = 2.6, 2.6 Hz)

3.23 (ddd 1H, *J* = 10.0, 5.1, 2.4 Hz)

2.17 (ddd, 1H, *J* = 12.5, 5.1, 2.6 Hz)

2.07 (1H, ddd, *J* = 12.6, 10.0, 2.7 Hz).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 200.8, 143.8, 143.5, 142.0, 139.0, 135.9, 129.3, 128.8, 126.43, 126.36, 126.3, 126.0, 125.9, 125.4, 123.6, 123.2, 56.3, 47.6, 43.9, 31.2 (one low field carbon not observed).

FTIR (neat): 3069, 3043, 3022, 2948, 1722, 1458, 1437, 1042, 1022 cm^{-1}.

HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{23}H_{18}OSeNa$ 413.0422; found, 413.0424.

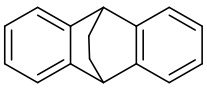
9, 10-Dihydro-9,10-ethanoanthracene (127) and 10,11-dihydro-5*H*-5,10-methanodibenzo-[*a,d*][7]annulene (128): A 15-ml screw cap vial was charged with the phenylseleno ester **88** (200 mg, 0.514 mmol), isooctane (5.0 ml), TTMSS (255 mg, 1.03 mmol), AIBN (11 mg,0.07 mmol), and a stir bar. The suspension was purged with argon for 5 min and the vial was sealed and heated in a 99 °C oil bath for 1 h with vigorous stirring. A transparent solution formed. The solution was concentrated *in vacuo* and the residue purified by flash chromatography (silica gel, 100% hexanes) to give a clear oil containing **89**[39] and **90**[44,45] in an approximately 1:3 ratio (81 mg, 77%).

(89): ^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.26-7.30 (m, 8H)

4.33 (s, 2H)

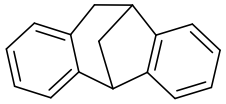
1.72 (s, 4H).



(90): ^{1}H NMR (400 MHz, $CDCl_3$, δ):

6.93-7.16 (m, 8H)

3.90 (d, 1H, *J* = 4.0 Hz)



3.51 (dd, 1H, *J* = 4.0, 4.0 Hz)

3.26 (dd, 1H, *J* = 20.0, 8.0 Hz)

2.76 (d, 1H, *J* = 20 Hz)

2.53-2.58 (m, 1H)

2.14 (d, 1H, *J* = 12.0 Hz).

Mixture: ^{13}C NMR (100 MHz, $CDCl_3$, δ): 150.4, 145.5, 143.9, 143.3, 133.7, 130.3, 126.7, 126.64, 126.56, 125.6, 123.3, 123.2, 121.5, 47.0, 44.1, 41.1, 40.4, 34.3, 26.8.

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