Synthesis of polycyclic natural products

by

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Major Professor

For the Major Program

DEDICATION

To my parents, for all their sacrifices

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GENERAL INTRODUCTION

With the continuous advancements in molecular biology and modern medicine, organic synthesis has become vital to the support and extension of those discoveries. The isolations of new natural products allow for the understanding of their biological activities and therapeutic value. Organic synthesis is employed to aid in the determination of the relationship between structure and function of these natural products. The development of synthetic methodologies in the course of total syntheses is imperative for the expansion of this highly interdisciplinary field of science.

In addition to the practical applications of total syntheses, the structural complexity of natural products represents a worthwhile challenge in itself. The pursuit of concise and efficient syntheses of complex molecules is both gratifying and enjoyable.

CHAPTER I

Synthesis of the Bicylic Core of Hyperforin and Related Natural Products

Introduction

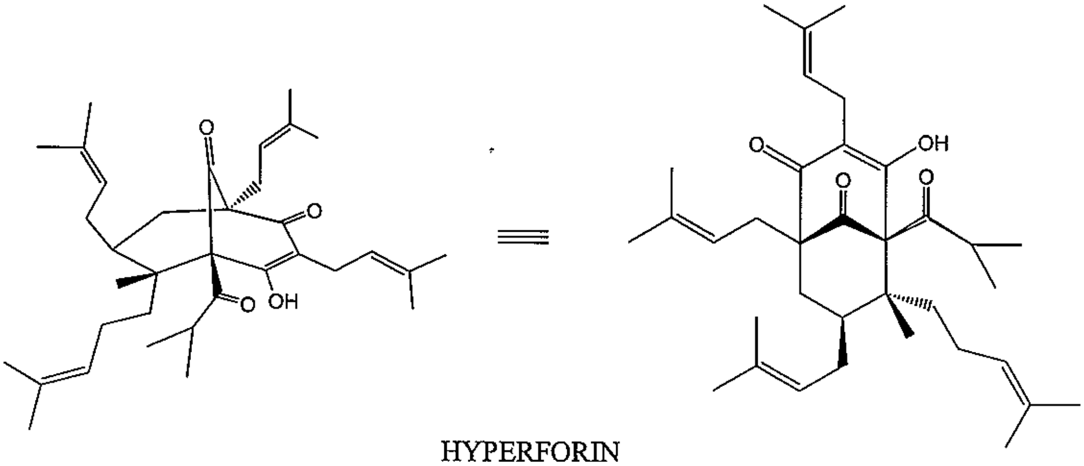
With the increasing use of dietary supplements to treat a wide range of clinical conditions, the understanding of the biological activities and effects of herbal supplements becomes necessary for efficacy and safety concerns. St. John's wort is commonly used as a natural remedy to treat moderate to mild depression. Although it effectively serves its purpose, the mechanism of action and side effects are relatively unknown and have only recently been investigated.

One of the natural products present in the extracts of St. John's wort is hyperforin. Hyperforin has drawn substantial attention recently because it has been suggested to be the main constituent responsible for the antidepressant and antibacterial characteristics of St. John's wort. In the chemistry community it has garnered renewed synthetic interest due to its unique acyl phloroglucin bicyclic structure. The synthetic challenge of hyperforin can be categorized as follows: the generation of a [3.3.1] bicyclic skeleton and the enolic β–diketone moiety.

This chapter details the strategies to construct the bicyclic core subunit of acyl phloroglucin natural products and the progress towards the total synthesis of hyperforin and its related analogs.

Background

The natural product hyperforin was first isolated and characterized[1] in 1971 from the species *Hypericum perforatum* L. The exact structure[2] and stereochemistry[3] were elucidated a few years thereafter.



HYPERFORIN

The extracts of a number of *Hypericum* species were demonstrated as early as 1943 to exhibit antibacterial activity.[4,5] In 1959, Gaind and Ganjoo[6] confirmed those results and identified two compounds as exhibiting activity against a number of gram positive organisms. Recently, hyperforin was shown to inhibit a multi drug resistant[7] strain of *Staphylococcus aureus* and other gram positive bacteria. Growth inhibition was observed for all gram positive bacteria at hyperforin concentrations as low as 0.1 μg/mL. Penicillin resistant and methicillin resistant *Staphlycoccus aureus* were susceptible to hyperforin whereas were resistant to cephalosporins, erythromycin, clindamycin and various other antibiotics. The observed low toxicity *in vitro* in peripheral blood mononuclear cells indicates potential systematic use of hyperforin. On the basis of those results, the natural product's biological activities have attracted renewed interest.

Hyperforin is present up to 5% (dry weight) in the flowers and leaves[8] of St. John's wort, a commonly used botanical dietary supplement. St. John's wort is widely used to treat mild to moderate depression and represents an accepted alternative to synthetic antidepressants. The extracts of St. John's wort have a broad inhibitory effect[9] on the neuronal uptake of not only serotonin, noradrenaline and dopamine, but also of gamma-aminobutyric acid (GABA) and l-glutamate among others. The constituent of St. John's wort that exerts this biological effect has been identified as hyperforin.[10] Although the mechanism of action has not been completely elucidated, it does not act as a competitive inhibitor at the transmitter binding sites of the transporter proteins. Instead, it affects the sodium gradient[11] which leads to an inhibition of uptake. The involvement and role of sodium and calcium ions is inferred from an experiment[12] in which the perfusion of the sodium channel blocker tetrodotoxin inhibited the effect of hyperforin, whereas removal of extracellular calcium increased the effect. The effect of hyperforin on the gradient-driven neurotransmitter transport represents a unique mechanism of action in relation to that of conventional antidepressants.

On a less positive note, hyperforin was identified as a very good ligand for the pregnane X receptor (PXR).[13] PXR is a nuclear receptor that regulates the expression of cytochrome P 450 3A4 monooxygenase, which is an enzyme that is involved in the oxidative metabolism of over half of all pharmacological drugs.[14] Cytochrome P 450 (CYP) enzymes allow for an adaptive response to protect organisms against both endogenous and exogenous toxic chemicals. PXR is responsible for an important class of harmful drug-drug interactions.[15] The activation of PXR by prescription drugs can accelerate the metabolism of other drugs taken concurrently, resulting in a reduction of their clinical effectiveness. Immunosuppressants, HIV protease inhibitors, and various cancer drugs have been clinically observed to be affected by the simultaneous use of St. John's wort. A crystal structure determination of human PXR in complex with hyperforin was recently reported.[16] The substantial evidence provides an explanation[17] of the potential side effects of hyperforin. However, it is worth noting that the researchers who determined the crystal structure of the hyperforin-PXR complex indicated the possible generation of hyperforin analogs that would not activate PXR but still have comparable biological activity. The isoprenyl groups located around the bicyclic core could be replaced with other groups that would alter the shape and conformation, therefore affecting the host-substrate complexation affinity with PXR.

The structure of hyperforin suggests a terpenoid origin.[2] Recently, the biosynthesis[18] of hyperforin (Figure 1) was proposed using isotopomer composition

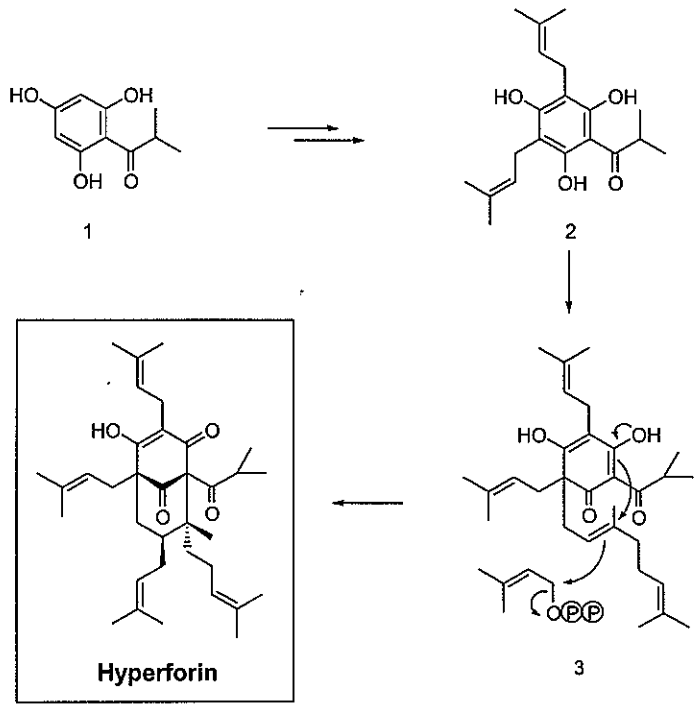


Figure 1. Proposed Biosynthesis of Hyperforin

analysis experiments using ^{13}C-labeled glucose. The proposed biosynthesis involves a phloroglucinol unit and 5 isoprenoid moieties, which are derived via a non-mevalonate pathway (Figure 2).

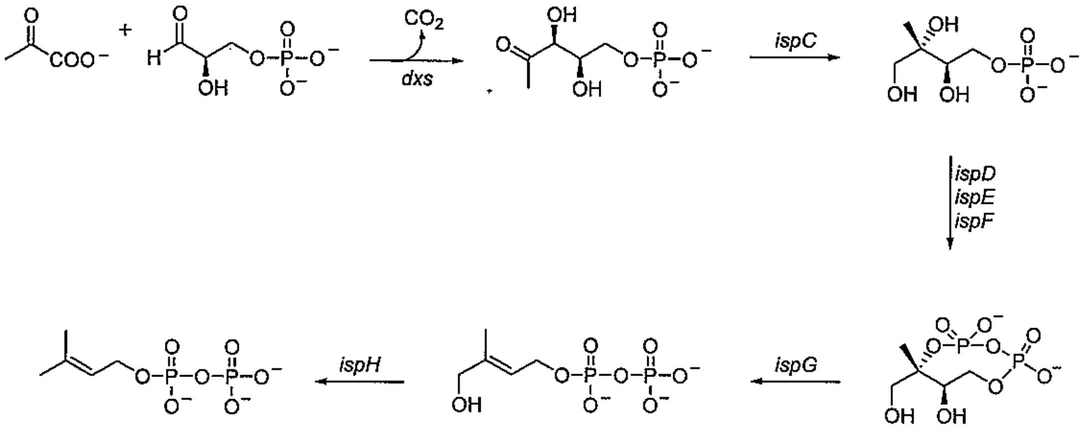


Figure 2. Non-mevalonate Pathway

The acyl phloroglucinol moiety is generated by a polyketide type mechanism beginning with 2 units of pyruvate (Figure 3).

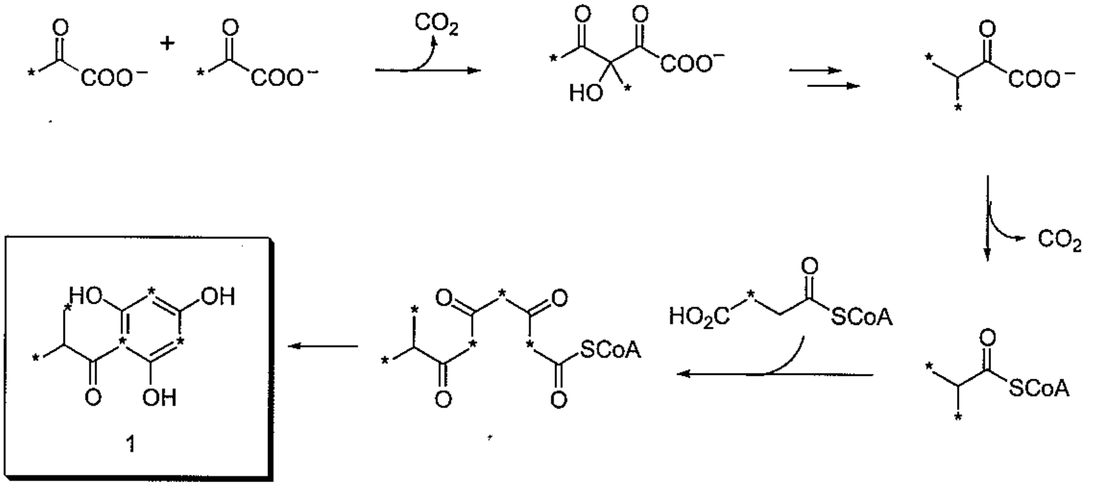
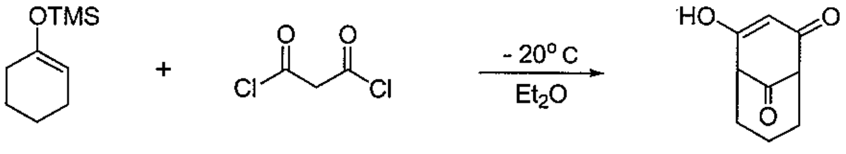


Figure 3. Biosynthesis of the acyl phloroglucinol unit

The construction of the bicyclic structure of hyperforin is dependent on the presence of the isoprenoid moieties. Although the isoprenyl units of hyperforin are necessary as part of the biosynthesis, they might not be for the biological activities; therefore, analogs could possibly reveal biological activity independence of those groups.

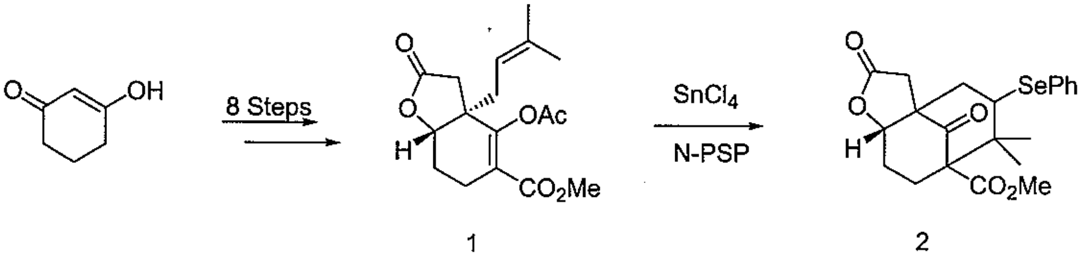
Since the first structure elucidation of hyperforin and related compounds, there have been only a few published reports of synthetic efforts towards the fully funtionalized bicylic core. There have been no total syntheses of hyperforin or any of its related bicyclic phloroglucin natural products.

In 1986 Effenberger and co-workers[19] reported the synthesis of a bicyclic phloroglucin compound in 44% yield from the enol silyl ether of cyclohexanone and malonyl dichloride (Scheme 1). The use of malonyl dichloride allows for the construction of the bicyclic structure and the introduction of the β–diketone functionality directly.



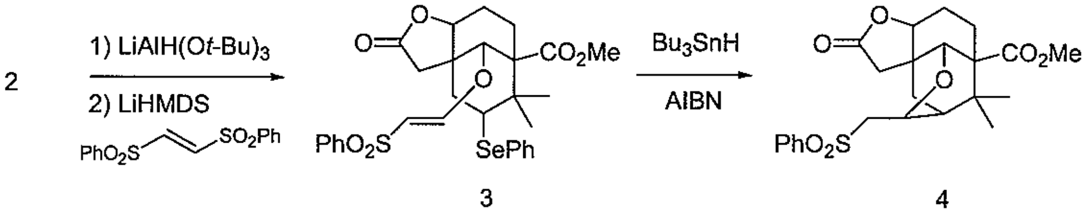
Scheme 1

In 1999, Nicolaou and co-workers[20] reported a synthetic route to a functionalized [3.3.1] bicyclic core of garsubellin A, a natural product analog of hyperforin. The synthesis commenced with commercially available 1,3-cyclohexanedione. In eight steps, bicyclic lactone **1**, which contained the carbon skeleton of the core structure, was constructed. The key cyclization of prenyl lactone **1** was Lewis acid mediated (Scheme 2). The addition of *N*-(phenylseleno)phthalimide (N-PSP) along with $SnCl_4$ functionalized the carbon adjacent to the carbon with two methyl groups in compound **2**.



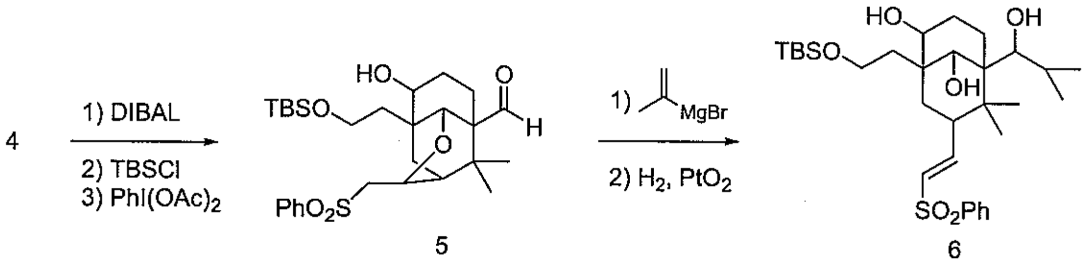
Scheme 2

Selective reduction of the bridged ketone of compound **2** yielded a bridged alcohol, which was subsequently alkylated with *trans*-1,2-bis(phenylsulfonyl)ethylene (Scheme 3). The reaction of Bu_3SnH and AIBN with the vinylogous sulfonate **3** produced tetracycle **4**.



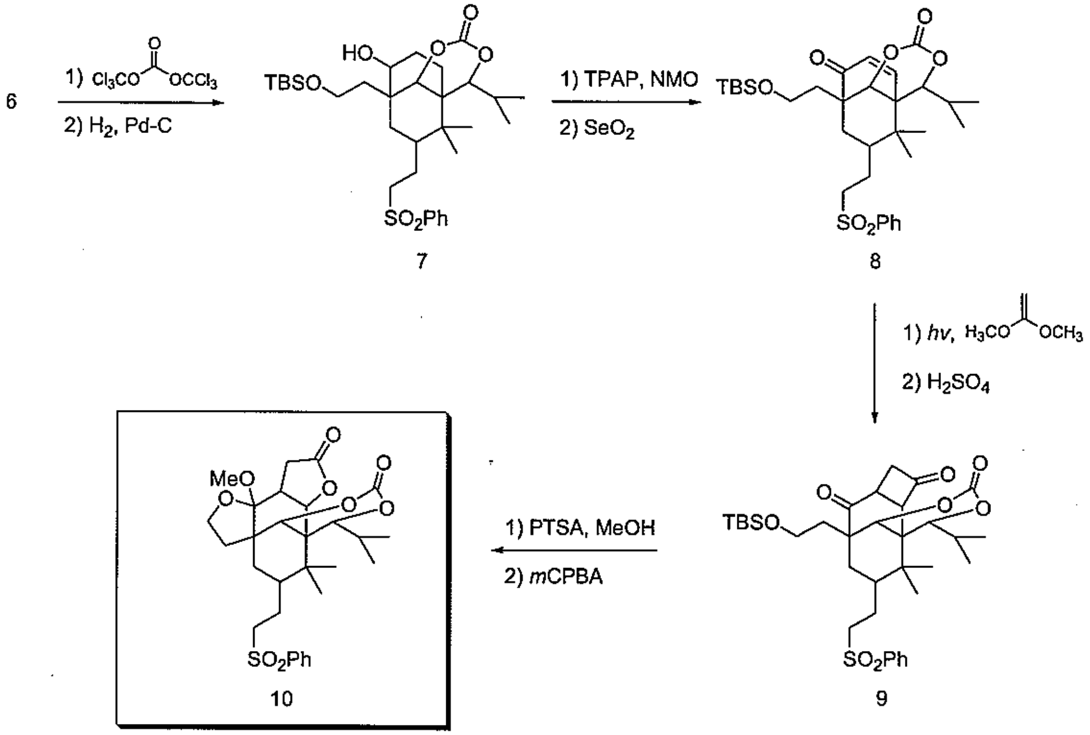
Scheme 3

Reduction with excess DIBAL produced a triol, which was selectively monoprotected with TBSCl. The ensuing oxidation of the hindered primary alcohol with (bisacetoxy)iodobenzene formed aldehyde **5** (Scheme 4). The addition of isopropylmagnesium bromide onto the aldehyde effected simultaneous β-elimination of the sulfone side chain. Selective hydrogenation with hydrogen over platinum oxide produced isopropyl alcohol **6.**



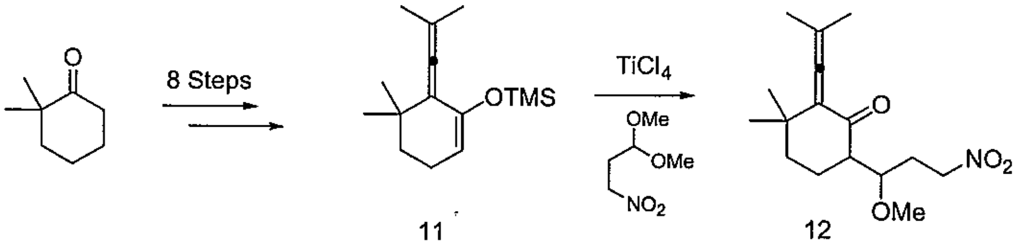
Scheme 4

Two of the hydroxy groups of triol **6** were then protected with triphosgene. The resulting compound was hydrogenated to produce intermediate **7** (Scheme 5). After two further transformations, enone **8** was obtained. To introduce the final functionality of the bicyclic core, a [2+2] photocycloaddition was performed with 1,1-dimethoxyethene. Cyclobutanone **9**, upon treatment with mild acid in methanol and subsequent Baeyer-Villiger oxidation, produced the functionalized [3.3.1] core **10** of garsubellin A. Although this synthetic strategy does contain a novel bicyclic cycloaddition, the large number of steps to the core structure would ultimately limit the utility of the route towards the total synthesis of substituted phloroglucin natural products.



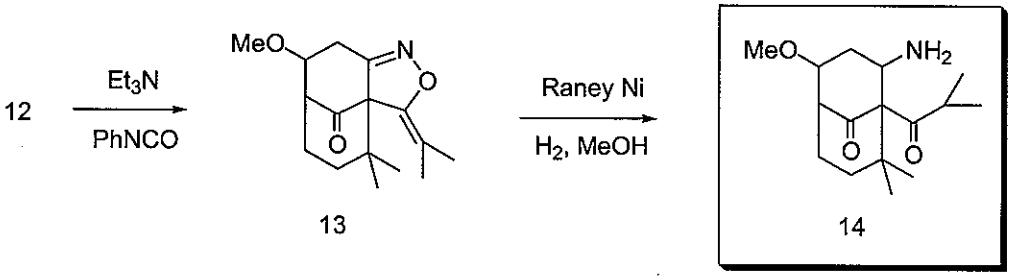
Scheme 5

In 2001, a more direct synthetic approach to the functionalized bicyclic core (**14**) was reported[21] (Scheme 6). The synthesis begins with the conversion of 2,2-dimethyl cyclohexanone to enol silyl ether **11** in eight steps. A Lewis acid-catalyzed Mukaiyama aldol condensation of compound **11** with 3-nitropropanal dimethylacetal produced allenyl cyclochexanone **12**.



Scheme 6

With compound **12** in hand, the key intramolecular nitrile oxide-allene [3+2] cycloaddition was achieved as a single diastereomer **13** in 40% yield (Scheme 7). Subsequent reduction with methanolic Raney nickel produced the functionalized bicyclic core **14**.

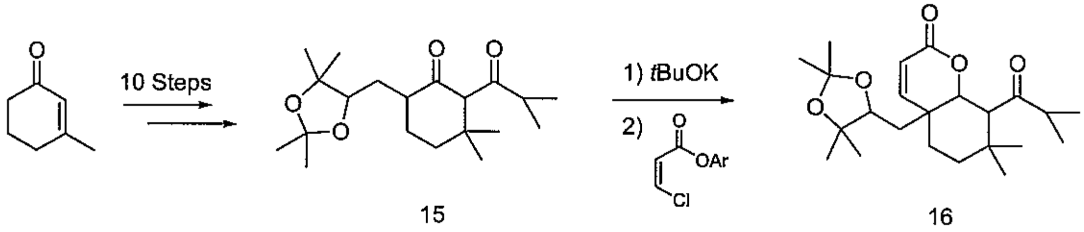


Scheme 7

The synthesis presented utilizes a very unique intramolecular nitrile oxide-allene [3+2] cycloaddition to construct the bicyclic core. The formation of a single diastereomer **13**, from a mixture of two diastereomers that entered the reaction, indicates the need for the nitropropyl group to be axial in order for the cycloaddition to occur.

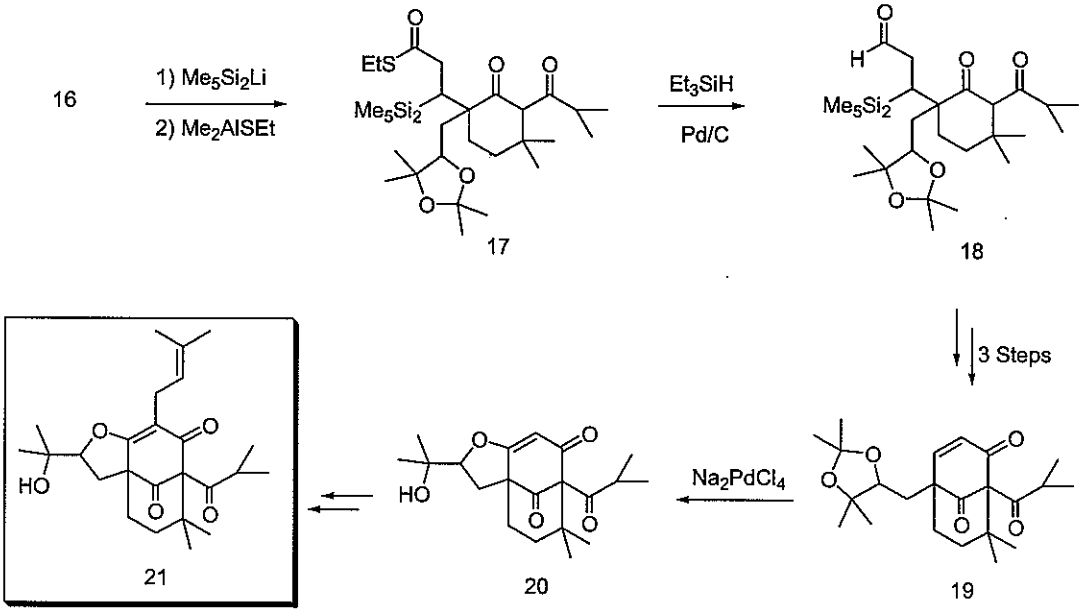
With the inclusion of an additional group located at the carbon alpha to the carbonyl, stereoselectivity could present problems.

Although these two synthetic efforts achieve the construction of the functionalized bicyclic skeleton, the β-diketone moiety is not generated. The most recent synthetic route to the bicyclic core of garsubellin A that addresses this synthetic challenge was reported in 2002 by Shibasaki and co-workers.[22] The synthesis centered upon the Michael addition-elimination of a 3-chloroacrylate compound onto diketone **15** and subsequent Claisen condensation to produce lactone **16** (Scheme 8). The yield of the key cyclization was 20%.



Scheme 8

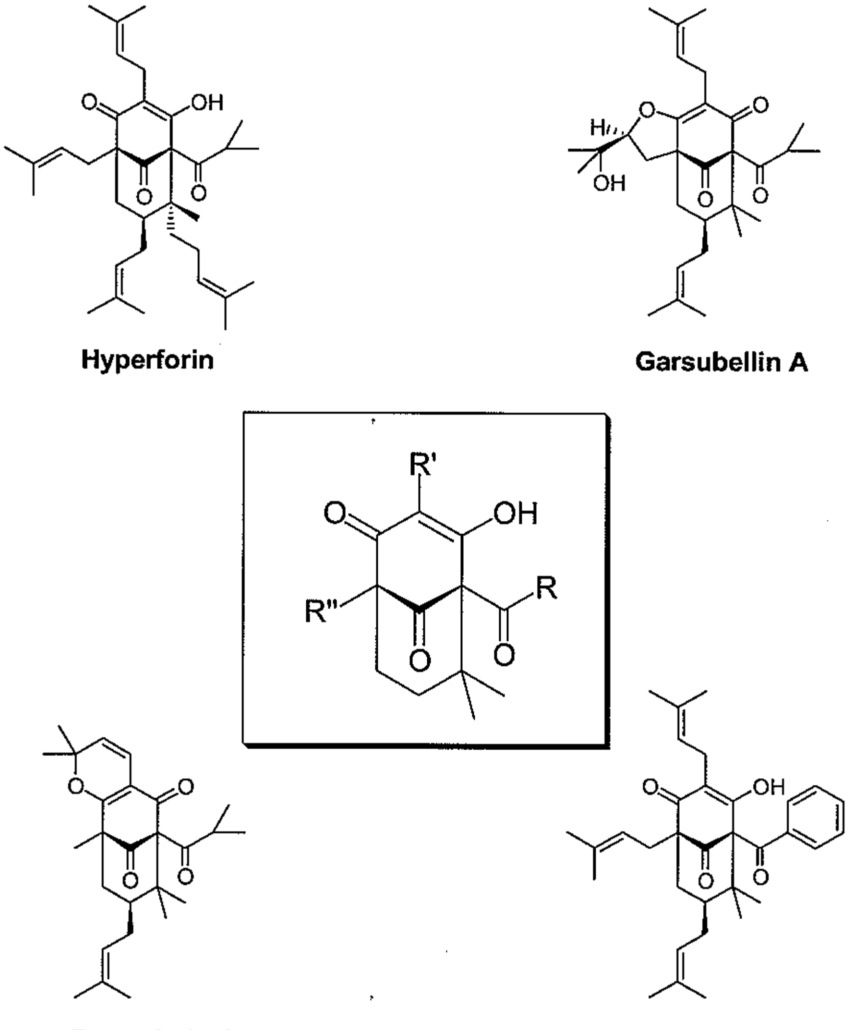
With the construction of lactone **16**, albeit in low yield, the rearrangement was explored by first protecting the olefin of the enone with a silicon atom (Scheme 9). Later deprotection could be facilitated by a modified Tamao oxidation and elimination using *m*CPBA and *tert*-butyl ammonium fluoride. Transformation to the thiol ester **17** was followed by reduction under Fukuyama conditions to the aldehyde **18**. Compound **18** was then treated with base (K_2CO_3/MeOH) and oxidized with Dess-Martin periodinane and subsequent oxidation and elimination of the pentamethyldisilyl group produced enone **19**. Intermediate **19** was subjected to an intramolecular Wacker-type oxidation to produce the tetrahydrofuran ring of the core structure.



Scheme 9

Oxidative vinyl iodide formation, followed by Stille coupling with tributylprenyltin, produced the functionalized bicyclic core of garsubellin A (**21**). To date, this synthesis has the most applicability to the natural product garsubellin A. The use of the intramolecular Wacker-type oxidation limits the synthetic applicability to other oxidized phloroglucinols, such as hyperforin and nemosorone.

The focus of the synthetic strategies will address the concise formation of a functionalized bicyclic intermediate, which can be converted in a few steps to the enolic β-diketone subunit. Keeping in mind various other bicyclic acyl phloroglucin subunit bearing natural products, the route should be general enough to be applicable to their syntheses. Figure 4 displays some natural products that contain the synthetic objective.



Hyperforin

Garsubellin A

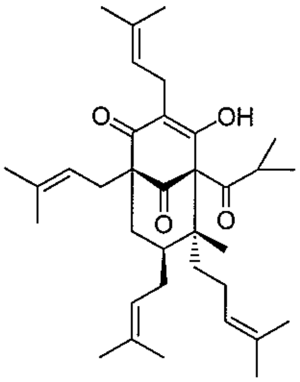
Papuaforin A

Nemorosone

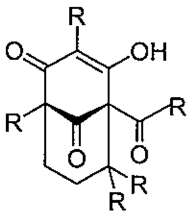
Figure 4. Some Bicyclic Phloroglucin Natural Products

Results and Discussion

Hyperforin's challenging structure and diverse biological activities prompted a synthetic study of the bicyclic phloroglucin core subunit. The general strategy developed would then be applied towards the total synthesis of the natural product hyperforin and related analogs.

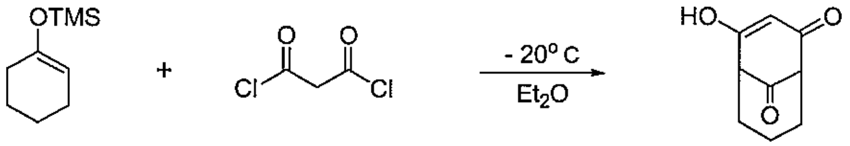


Hyperforin



Bicyclic Core

The initial strategy towards the synthesis of the target molecule relied on a cyclization reaction reported by Effenberger (Scheme 1). The utility of malonyl dichloride allowed for the generation of the bicyclic skeleton and introduction of the enolic β-diketone in one step.



Scheme 1

The success of this remarkable cyclization prompted an investigation of the reaction with α-substituted cyclohexanone enol silyl ethers (Figure 5).

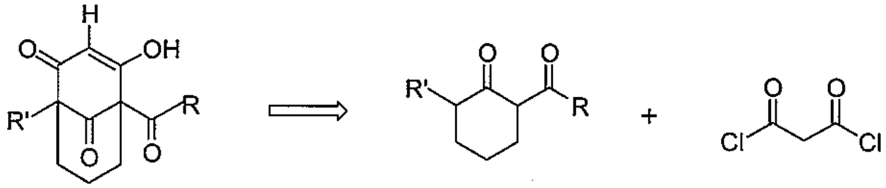
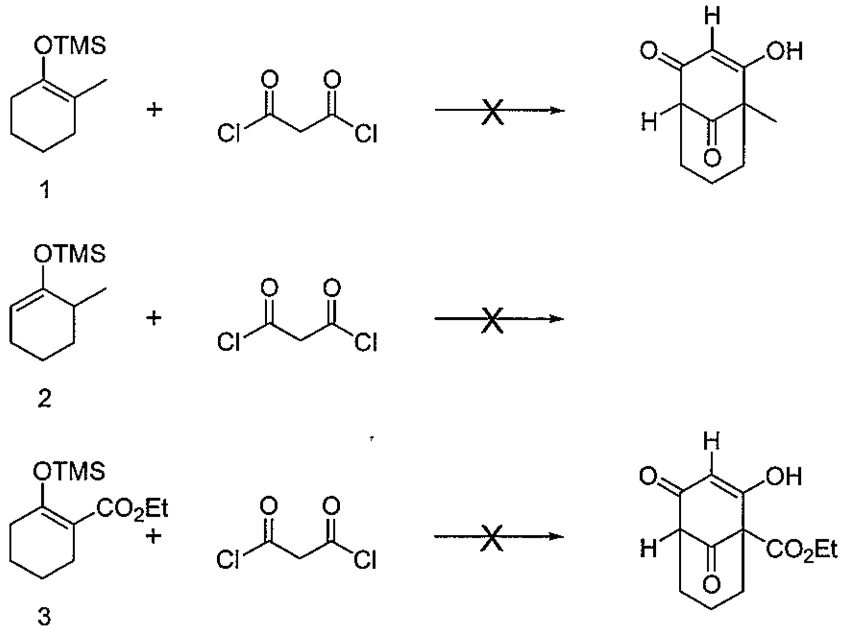


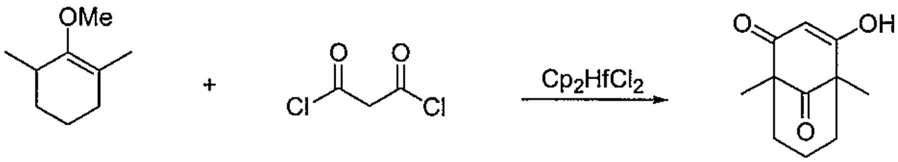
Figure 5. Retrosynthetic Analysis

The exploration began with the reaction of malonyl dichloride with the enol silyl ether of 2-methylcyclohexanone (**1**) under the conditions specified by Effenberger (Scheme 2). However, the reaction yielded only 2-methylcyclohexanone. The kinetic enol silyl ether of 2-methylcyclohexanone (**2**) and compound **3** were also allowed to react with malonyl dichloride and, likewise, did not yield the bicyclic product.



Scheme 2

Altering the temperature did not affect the outcome of the reaction. The addition of Lewis acids, such as $TiCl_4$ and $SnCl_4$, yielded only starting materials. It is of interest to note that Stoltz[23] recently reported the use of bis(cyclopentadienyl)hafnium dichloride to mediate the cyclization of a substituted methyl enol ether with malonyl dichloride in 25% yield (Scheme 3). The use of that specific Lewis acid allowed for the construction of a bicyclic compound with quaternary bridgehead carbons. However, no acyl bridgehead compounds were reported.



Scheme 3

With these disappointing results, attention was focused towards the construction of the bicyclic β-diketone compound through a stepwise approach. The retrosynthetic analysis (Figure 2) indicates that the bicyclic skeleton could be obtained by a Robinson annulation of acrolein onto a substituted cyclohexanone. With the functionalized bicyclic core constructed, the β-diketone transformation would be explored to obtain the target molecule.

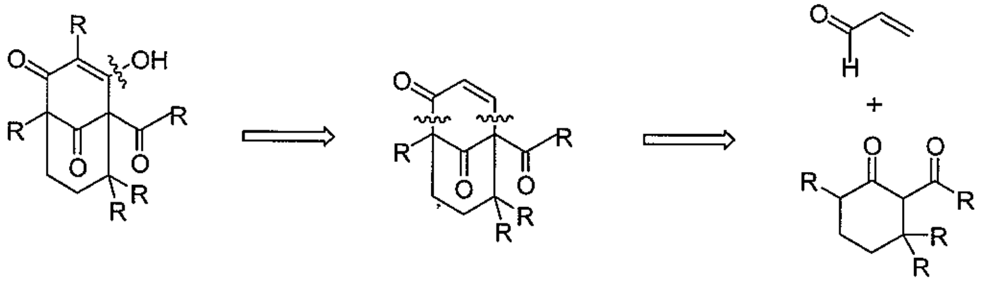
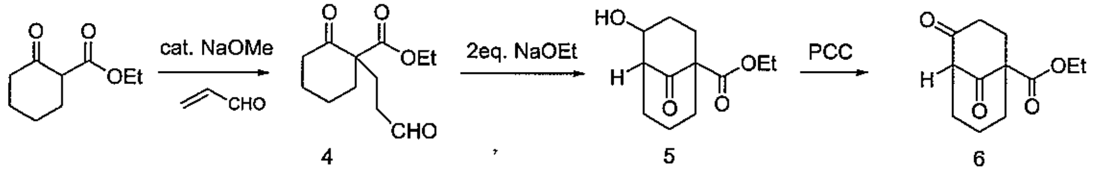


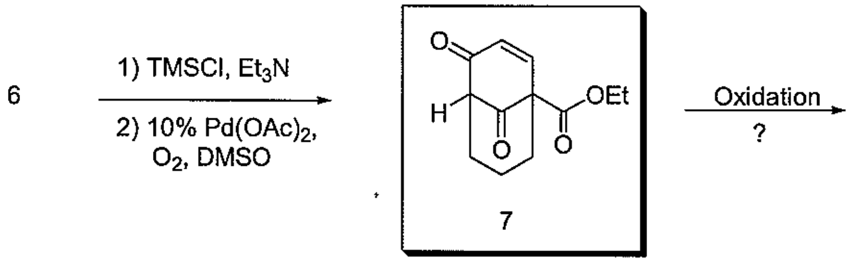
Figure 6. Retrosynthetic Analysis

To begin the synthetic investigation, the Michael addition[24] of ethyl 2-cyclohexanone carboxylate onto acrolein was achieved with catalytic amounts of sodium ethoxide to produce aldehyde **4** (Scheme 4). Two equivalents of sodium ethoxide facilitated the intramolecular aldol condensation of aldehyde **4** to produce alcohol **5**. Acid catalyzed conditions (HCl, AcOH in various solvents) failed to produce compound **5**. The one pot conversion of ethyl 2-cyclohexanone carboxylate to compound **5** was unsuccessful with excess sodium ethoxide. Subsequent oxidation of **5** with pyridinium chlorochromate over Celite produced ketone **6** (72% overall yield from ethyl 2-cyclohexanone carboxylate).



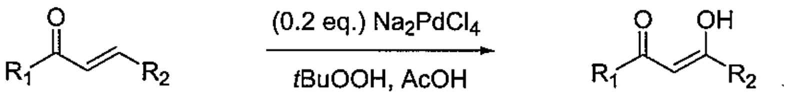
Scheme 4

Conversion to enone **7** was achieved using conditions developed by Larock and Kraus[25] (Scheme 5). With bicyclic enone **7** synthesized, transformation to the enolic β-diketone moiety was explored.



Scheme 5

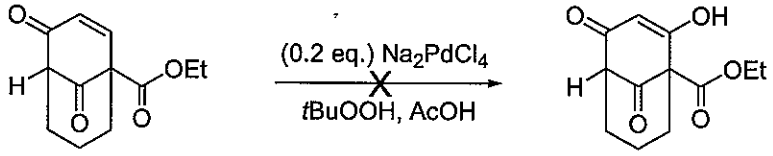
The most direct transformation of α,β-unsaturated carbonyl compounds to β-diketones is the palladium(II)-catalyzed Wacker-type oxidation (Scheme 6) introduced by Tsuji.[26]



Scheme 6

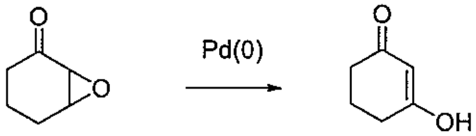
The use of Tsuji's protocol proved to be unsuccessful. Enone **7** when treated with sodium tetrachloropalladate at temperatures up to 110 °C yielded only starting materials

(Scheme 7). The use of classical Wacker oxidation conditions ($PdCl_2$) also failed to yield the β-diketone. There are no literature reports on the direct intermolecular oxidation of cyclic α,β-unsaturated carbonyl compounds to cyclic β-diketones.



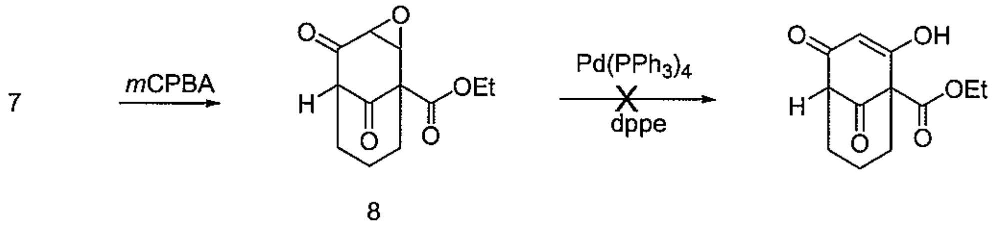
Scheme 7

In view of the unsuccessful attempts to directly convert the bicyclic enone into the desired β-diketone, enone **7** was converted to epoxide **8** with *m*CPBA. Noyori demonstrated[27] that cyclic α,β-epoxyketones can be converted to β-diketones (Scheme 8) with catalytic amounts of $Pd(PPh_3)_4$.



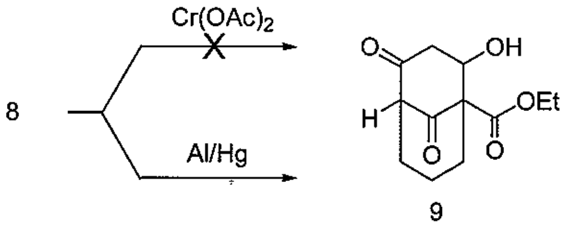
Scheme 8

However, the treatment of bicyclic epoxide **8** with $Pd(PPh_3)_4$ and 1,2-bis(diphenylphosphino)ethane did not produce the desired bicyclic β-diketone (Scheme 9). It is worthwhile to point out that unsuccessful palladium-catalyzed oxidations of complex enones and α,β-epoxyketones to β-diketones have been documented in the literature.[28] The structural generality of these transformations is limited.



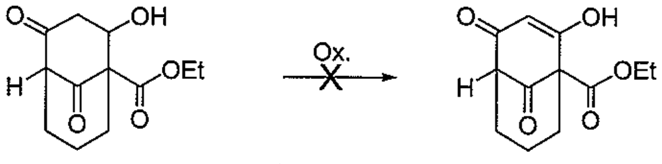
Scheme 9

Since rearrangement of bicyclic epoxyketone **8** failed to yield the target molecule, compound **8** was converted to β-hydroxyketone **9**. Chromium diacetate was first used to facilitate the conversion; however, β-hydroxyketone **9** (Scheme 10) was not formed. The use of aluminum amalgam furnished the desire compound **9** in only 5% yield.



Scheme 10

With β-hydroxy ketone **9** constructed, the oxidation was explored. The use of pyridinium chlorochromate (PCC) degraded the starting material (Scheme 11). Milder conditions, such as the Dess-Martin and Swern oxidations, were also employed, but were unsuccessful.

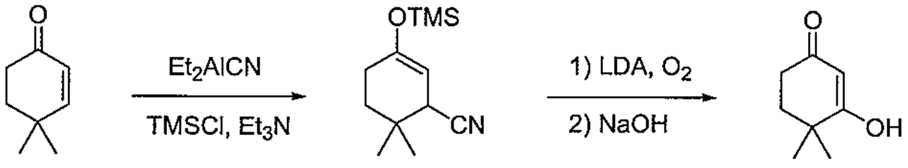


9

Scheme 11

Since oxidative conditions failed to produce the desired compound, the use of an oxygen atom equivalent was investigated. The initial efforts relied upon the conjugate addition of a cyano functional group, which might then be converted to a carbonyl using known conditions. The use of β-cyanoketones as β-diketone equivalents has not been explored in the literature.

The investigation began with the conjugate addition of a cyano group onto 4,4-dimethyl-2-cyclohexenone to make the corresponding cyano silyl enol ether intermediate (Scheme 12). Subsequent treatment under conditions for the conversion of cyanides into ketones yielded 4,4-dimethyl-1,3-cyclohexanedione (**10**) in a 64% yield.

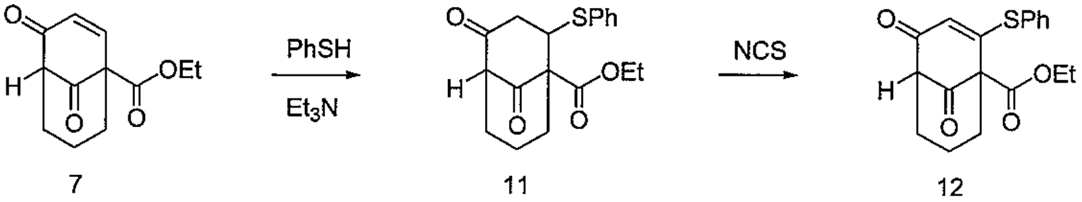


10

Scheme 12

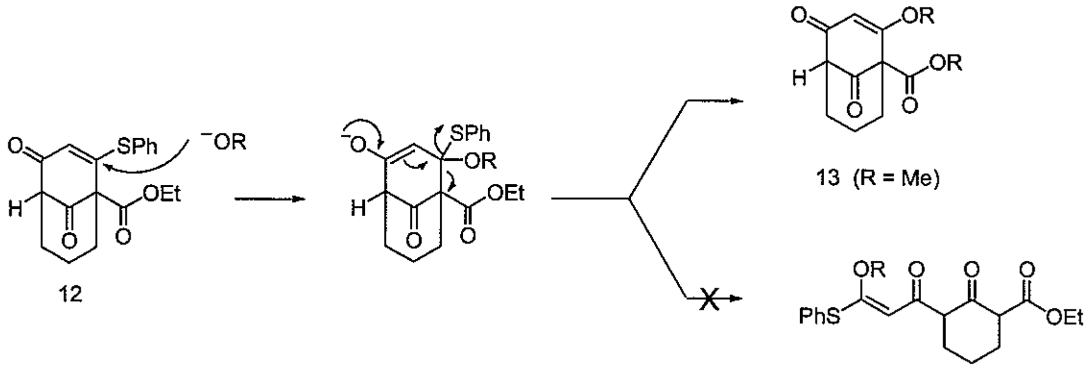
With the successful use of this methodology to produce a cyclic β-diketone, the strategy was applied to a bicyclic system. However, various conditions used to effect the conjugate addition of a cyano group failed with the bicyclic enone **7**.

These unsuccessful attempts prompted the usage of a more nucleophilic oxygen equivalent. Sulfur atoms are very good nucleophiles; therefore, the Michael addition onto bicyclic enone **7** was plausible. Thiophenol was used because the loss of the unsaturation during the conjugate addition could be regenerated by an *n*-chlorosuccinimide mediated Pummerer-type oxidation.[29] The strategy was initiated with triethylamine catalyzed addition of thiophenol onto enone **7** (Scheme 13) to produce ketone **11** in 75% yield.



Scheme 13

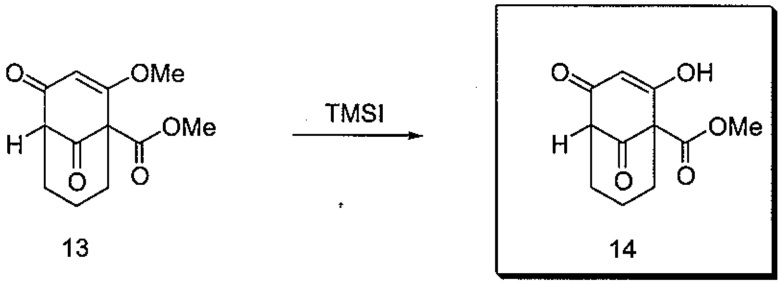
The oxidation of compound **11** with NCS in carbon tetrachloride produced enone **12** as expected. Compound **12** has the same oxidation state as a β-diketone. Substitution of the sulfur moiety by an oxygen moiety would produce the desired bicyclic compound (Scheme 14). However, the use of an alkaline base could enhance the possibility of the bicyclic compound undergoing a retro-condensation reaction at the strained bridgehead.



Scheme 14

The use of potassium trimethylsilanoate (KOTMS), sodium allyloxide, and sodium benzyloxide produced no reaction with enone **12**. Silver nitrate,[30] sulfuric acid[31] or mercuric chloride did not produce the desired β-diketone. Fortunately, sodium methoxide afforded bicyclic enol ether **13**. The displacement of the thiophenyl group with methanol proceeded in 47% yield.

The Reaction of compounds **12** and **13** with aqueous potassium hydroxide converted the bridgehead esters into carboxylic acids. The final transformation to the β-diketone bicyclic core required demethylation of the enol ether of compound **13**. Treating compound **13** with aqueous HCl at various temperatures yielded no reaction. Boron trifluoride diethyl etherate and NaI also did not produce the demethylated product. However, methyl enol ether **13** was treated with iodotrimethylsilane to produce the bicyclic phloroglucin core **14** in 78% yield (Scheme 15).

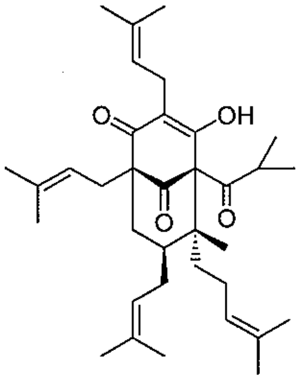


13

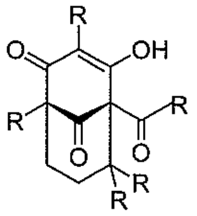
14

Scheme 15

Although the synthesis of the bicyclic core was achieved in eight steps, the model system was unsubstituted. Hyperforin bears many prenyl groups located around the core subunit. In order to make a model system more sterically similar to the natural product, more substituents around the bicyclic core would need to be introduced.



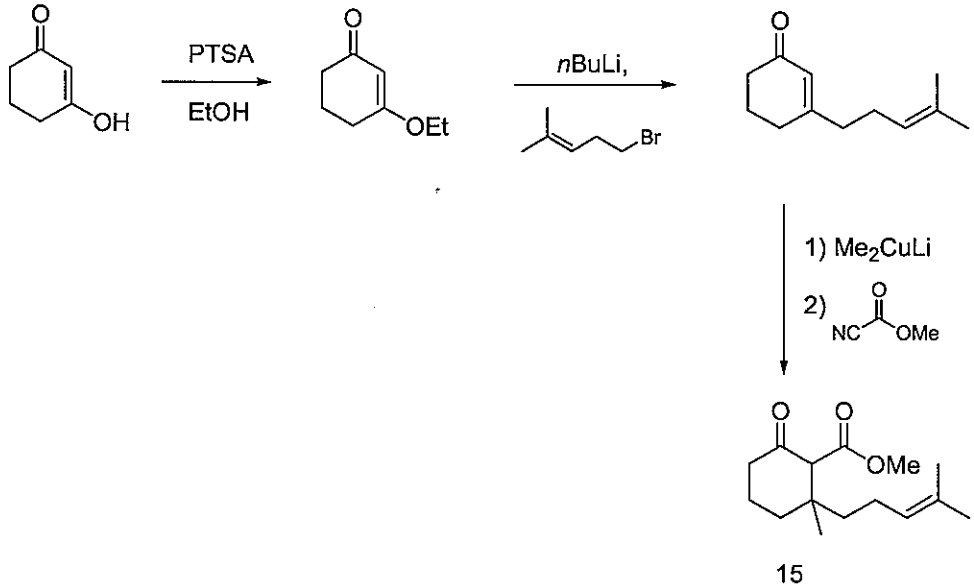
Hyperforin



Bicyclic Core

The use of a more substituted cyclohexanone starting material would introduce the various alkyl groups. Thus, the synthesis began with the alkylation[32] of 1,3-cyclohexanedione by ethanol (Scheme 16). Subsequent treatment with 5-bromo-2-

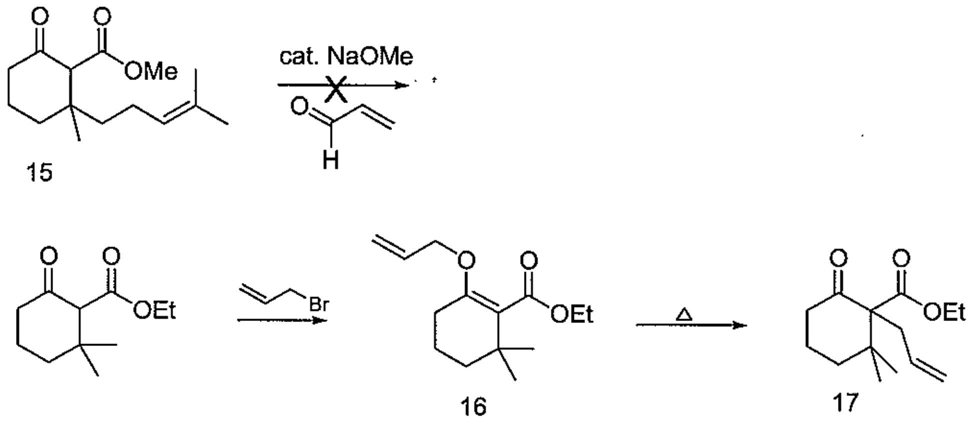
methyl-2-pentene and *n*-butyllithium produced the known isoprenyl cyclohexenone.[33] The conjugate addition of methyl cuprate, followed by the addition of methyl cyanoformate yielded the substituted methyl 2-cyclohexanone carboxylate **15**.



15

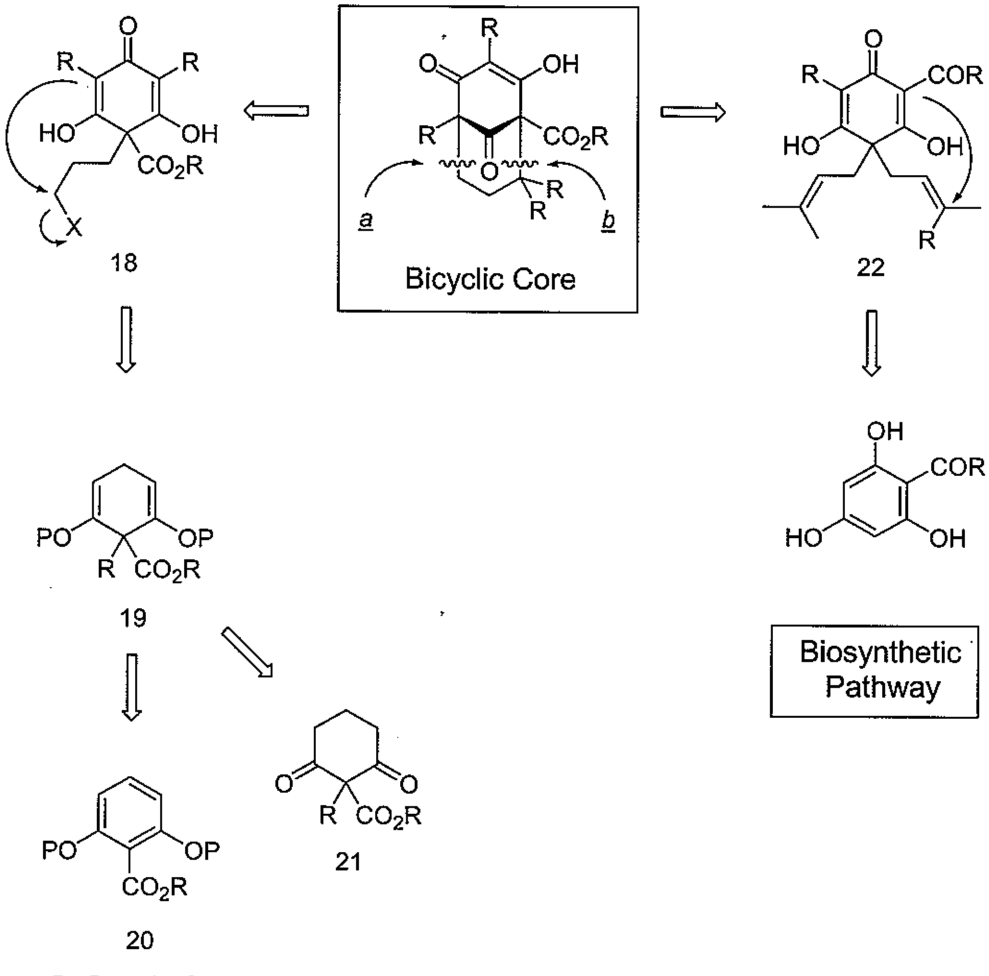
Scheme 16

Substituted compound **15** was then treated with sodium methoxide and acrolein. However, the Michael addition failed (Scheme 17). The presence of the methyl and isoprenyl groups sterically hinders the enolate, resulting in no reaction with acrolein. The steric effects on the alkylation of 3,3-disubstituted cyclohexanone carboxylates is well documented.[31] For example, the allylation of methyl 3,3-dimethyl cyclohexanone carboxlate results in the *O*-allylation affording **16**, and requires a thermal Claisen rearrangement to produce the *C*-allylated compound **17**.



Scheme 17

With the apparent difficulty of generating a bicyclic compound from substituted cyclohexanones, a different approach was developed. The synthetic route (Figure 7) was based on the biosynthetic pathway. The key feature of the strategy emphasizes the symmetrical nature of the bicyclic precursor intermediate. The bicyclic core can be constructed by making the carbon-carbon bond at either quaternary bridgehead carbon. Disconnection _b_ would resemble the biosynthetic pathway, whereas disconnection _a_ utilizes a symmetrical intermediate **18**.

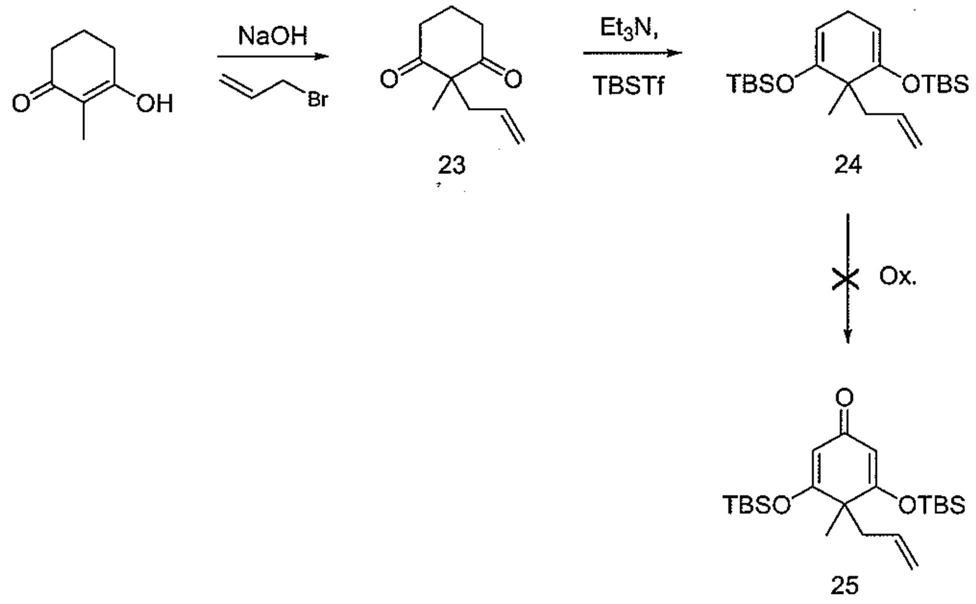


P = Protecting Group

Figure 7. Retrosynthetic Analysis of a Symmetrical Intermediate

The desired conversions would require the alkylation addition of the enolate of compound **18** or **22**. However, the enolate of compound **22** would be much more stable and less nucleophilic than the enolate of compound **18**. Compound **18** could presumably be made by the allylic oxidation of compound **19**. A Birch reduction of benzoate **20** or a bis *O*-alkylation of cyclohexanedione **21** could afford compound **19**.

The synthesis began with the conversion of 2-methyl-1,3-cyclohexanedione into the known 2-allyl-2-methyl-1,3-cyclohexanedione[35] (**23**) with sodium hydroxide and allyl bromide. At this point, the *tert*-butyldimethylsilyl (TBS) group was chosen as the protecting group for the enol ethers (Scheme 18). A durable protecting group was necessary for the subsequent oxidation, but it also had to be easily cleaved afterwards. Compound **24** was produced by treating cyclohexanedione **23** with TBS triflate and triethylamine. The stage was set for the allylic oxidation to produce compound **25**. Various chromium-based oxidants described by Schultz[36] were used to oxidize **24**; however, either starting material was recovered or there was compound degradation during the course of the reaction.



Scheme 18

Since the allylic oxidation failed to give the desired enone **25**, a bis vinyl halide compound **27** was targeted (Figure 8). The halogens at the 2 and 6 positions would be susceptible to substitution, since β-halo-enones are highly reactive.

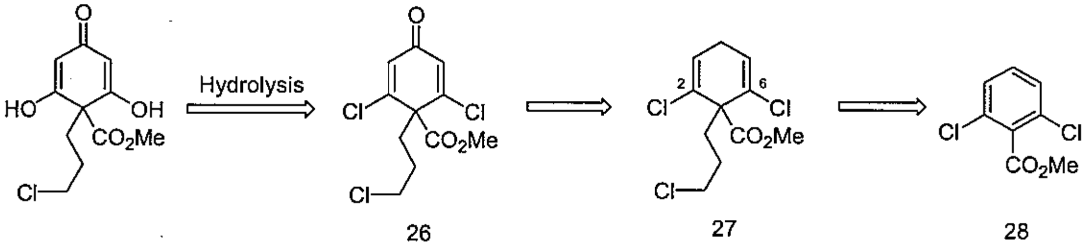
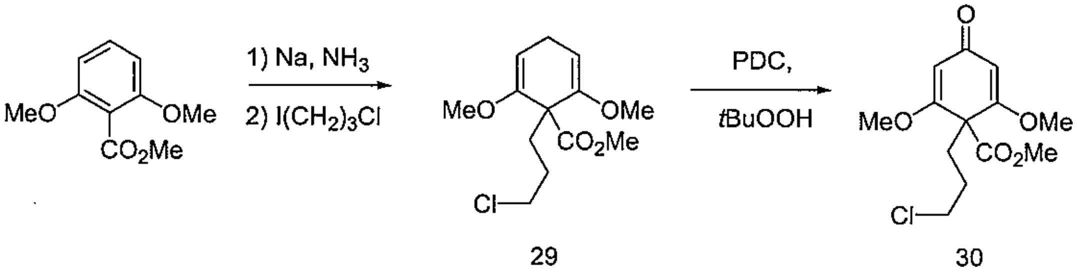


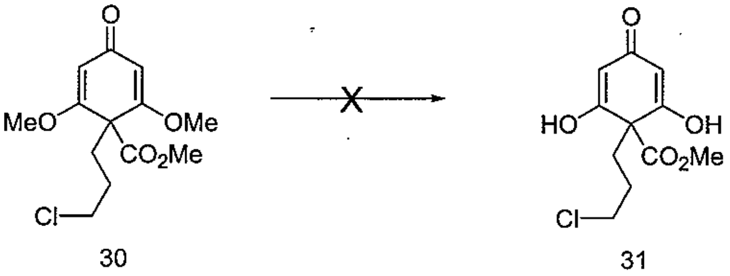
Figure 8

The hydrolysis of compound **26** should yield the desired product. However, methyl 2,6-dichlorobenzoate (**28**) could not be reduced under various Birch conditions. The Birch reduction of aryl halides has not been thoroughly investigated. With the failure of the previous compounds to produce a dienone, a methyl enol ether was chosen. The synthesis (Scheme 19) began with the Birch reduction of methyl 2,6-dimethoxybenzoate, followed by alkylation with 1-chloro-3-iodopropane to produce compound **29**. The allylic oxidation with pyridinium dichromate and *tert*-butyl hydroperoxide produced the best yield (72%) of dienone **30**. Pyridinium chlorochromate and chromium hexacarbonyl produced the product in lower yields.



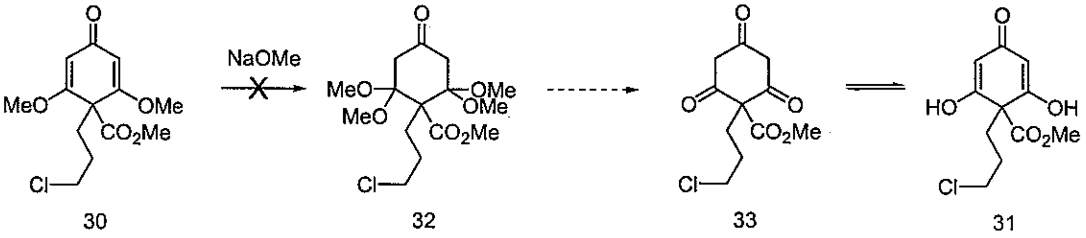
Scheme 19

With the construction of dienone **30**, demethylation and cyclization would yield the bicyclic core. The demethylation of β-methoxyenones should be very straightforward, since they are vinyligous methyl esters (Scheme 20). Unfortunately, under various conditions (HCl, H_2SO_4, HI, PTSA, BF_3•OEt_2, TMSI, AgOTf, $HgCl_2$) only starting materials remained. Even at temperatures of 170 °C with concentrated HCl, compound **30** remained intact. The sturdiness of compound **30** was quite remarkable.



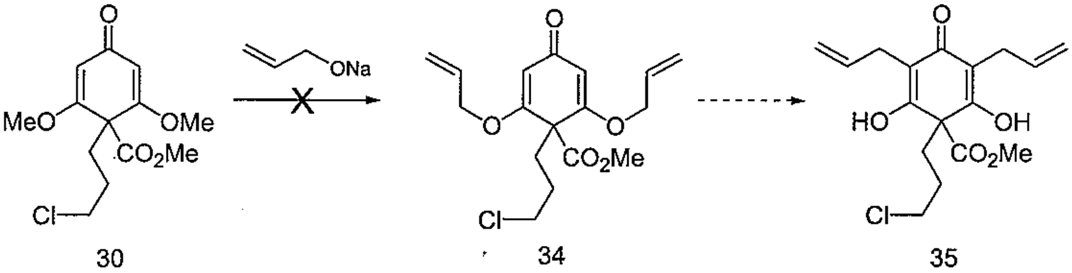
Scheme 20

Since demethylation failed to produce compound **31**, Michael addition of an alkoxide onto compound **30** would have the same effect (Scheme 21). The conjugate addition of sodium methoxide might produce bis-acetal **32**, which upon deprotection would yield the desired product. Unfortunately, the use of sodium methoxide failed to produce the desired conjugate addition.



Scheme 21

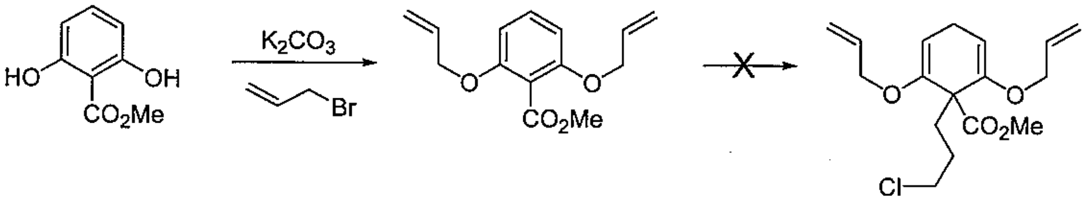
Sodium allyloxide was also used in an attempt to Michael add to enone **30**. With the addition of allyl groups, dealkylation would procede by a thermal Claisen rearrangement (Scheme 22) to produce substituted intermediate **35**, a product that more closely resembles the natural product.



Scheme 22

Unfortunately, compound **30** did not react with sodium allyloxide. Although compound **34** was never prepared by this sequence, the allyl groups could be introduced at an earlier stage before the allylic oxidation.

To prepare compound **34** by a modified strategy, methyl 2,5-dihydroxybenzoate was first treated with potassium carbonate and allyl bromide (Scheme 23) to prepare the diallyl ester **36**. Under Birch conditions, compound **36** failed to give the reduction product **37**. Using lithium instead of sodium did not alter the outcome of the Birch reduction.



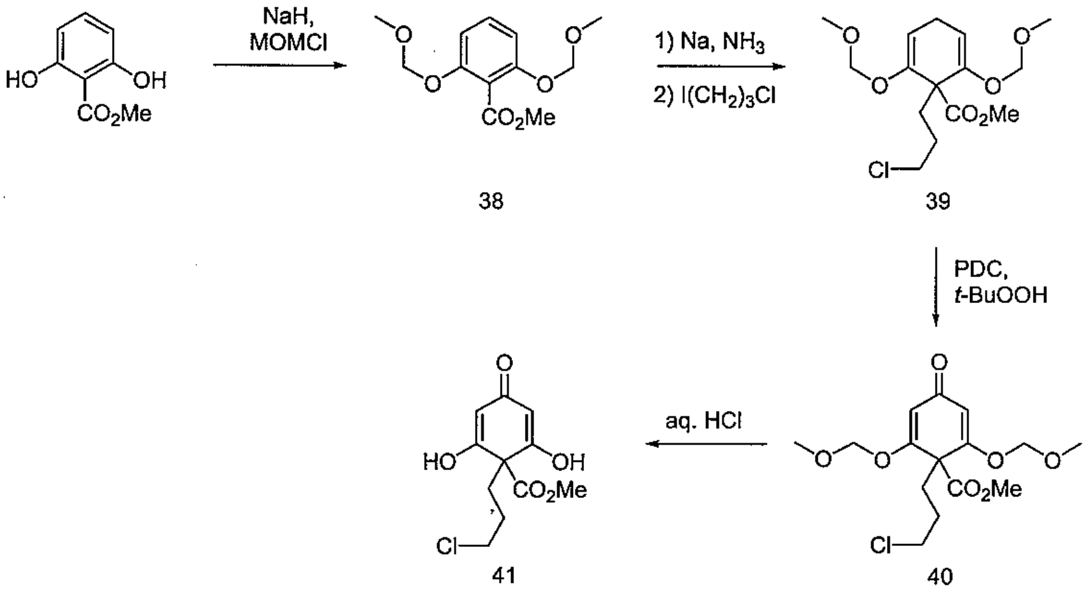
36

37

Scheme 23

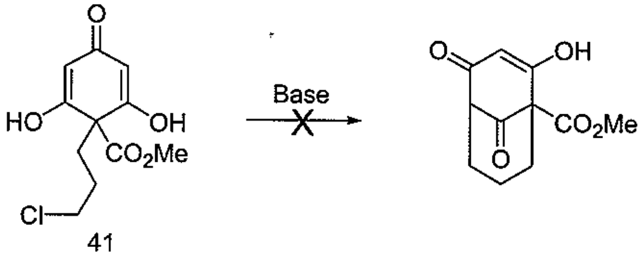
Because of problems encountered during the reduction and dealkylation steps, an alternative protecting group was explored. It seems that the reduction and oxidation steps were specific to the alkyl enol ethers. Methoxymethyl ethers are another alternative to the previously used methyl ethers, since they are sturdy enough to withstand oxidation conditions but labile enough to be easily deprotected. In conjunction with our previous strategy, methoxymethyl (MOM) protecting groups were thus used.

The protection (Scheme 24) of methyl 2,6-dihydroxybenzoate with chloromethyl methyl ether (MOMCl) afforded compound **38**. Subsequent Birch reduction and alkylation produced **39**. Allylic oxidation with PDC and *tert*-butyl hydroperoxide yielded enone **40**. The product was purified by florisil column chromatography. With the construction of compound **40**, the remaining transformations would be the deprotection of the MOM groups and cyclization. To remove the MOM groups, compound **40** was treated with aqueous hydrochloric acid to produce the triketone **41**.



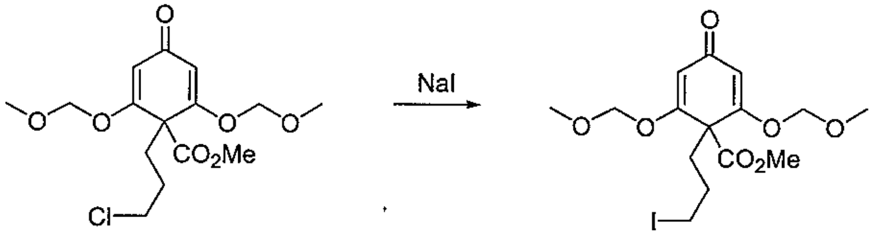
Scheme 24

The cleavage of the MOM groups was successful; however, the triketone formed was very polar and difficult to purify by column chromatography. The enolic protons of tautomer **41** are very acidic. The acidity of the two enolic protons is comparable to carboxylic acids. Treatment of crude compound **41** with mild bases (Scheme 25), such as potassium carbonate and triethylamine, produced messy mixtures that did not contain the desired bicyclic compound.


41

Scheme 25

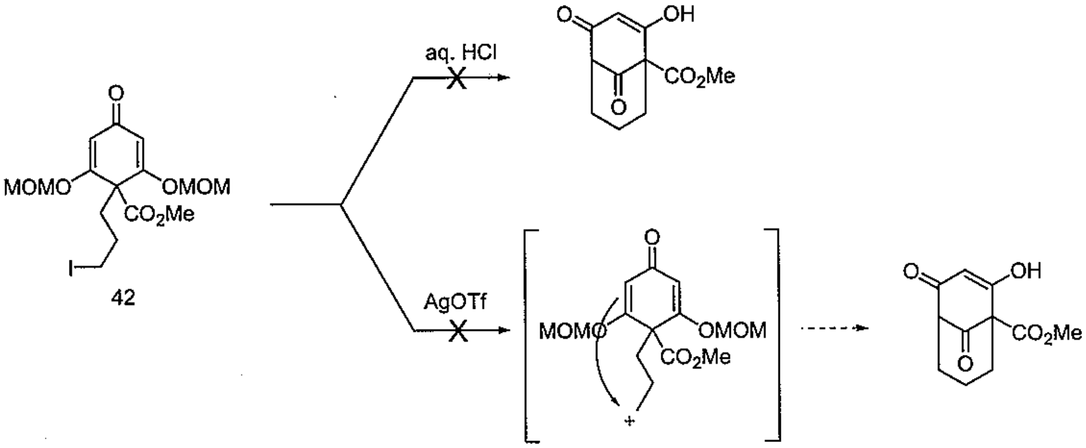
Due to the solubility of intermediate **40**, cyclization to the bicyclic compound was problematic. To circumvent this difficulty, the deprotection and cyclization steps might be effected in a single transformation. In order to explore this possibility, the chloride atom of **40** was first converted (Scheme 26) to a better leaving group to facilitate the cyclization. Compound **40** when treated with sodium iodide in acetone produced compound **42**.


40

42

Scheme 26

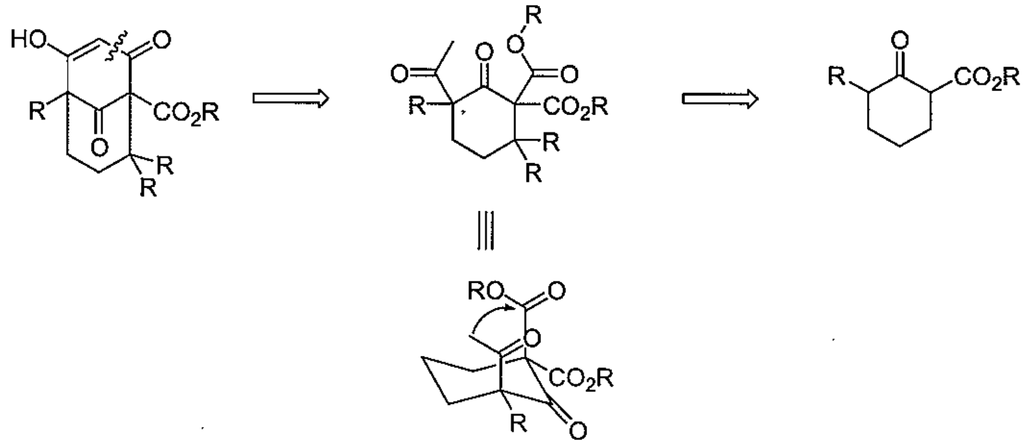
Compound **42** was first treated with aqueous acid to deprotect the MOM enol ethers. Although cleavage of the MOM groups did occur, the cyclization was still unsuccessful (Scheme 27). Instead of cleaving the MOM groups first, a primary carbocation might first be formed from the iodide, with the idea that the enol ethers would be nucleophilic enough to intercept this intermediate.



Scheme 27

The biomimetic synthesis to generate the bicyclic compound from symmetrical intermediate **41** proved to be futile. The cyclization ultimately failed due to the physical properties of triketone **41**. With this in mind, the next strategy to construct the bicyclic compound had an alternative carbon-carbon bond disconnection.

The construction of the bicyclic subunit could be attained from the intramolecular condensation of intermediate **43**, which in turn, could be made from a substituted cyclohexanone intermediate (Figure 9). The generation of the bicyclic compound would also simultaneously establish the desired β-diketone functionality.

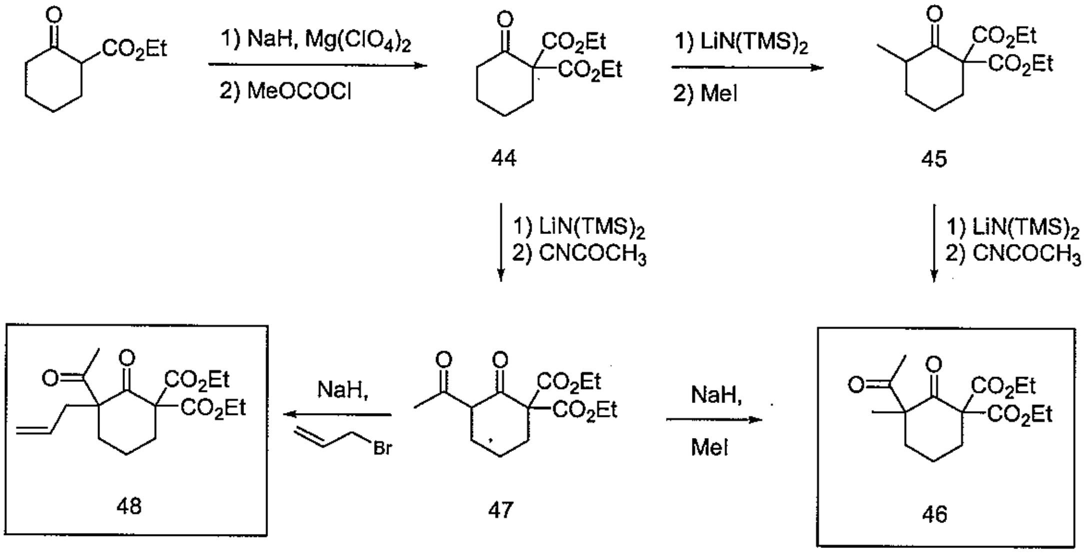


43

Figure 9. Retrosynthetic Analysis

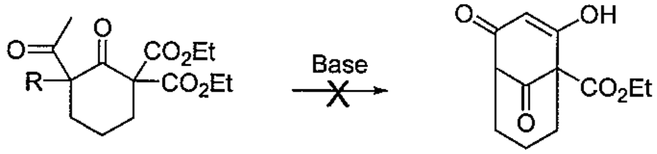
A key element to the success of the condensation of compound **43** is the relative orientation of the methyl ketone and the ester, which would act as the electrophile. In order for the condensation to occur, the ketone and the ester must be in the axial positions. The presence of geminal diesters will ensure that possibility.

The synthesis (Scheme 28) thus began with the generation of diester[16] **44** from ethyl 2-cyclohexanone carboxylate with sodium hydride, magnesium perchlorate, and methyl chloroformate. Subsequent methylation with methyl iodide produced compound **45**. The acylation of **45** with acetyl cyanide produced the bicyclic precursor **46**. The allyl analog **48** was similarly constructed. The acylation of the allyl diester intermediate produced very low yields of **48**. However, when the acylation of **44** preceded the allylation, compound **48** was obtained in high yields. Compound **47** could also be methylated to yield compound **46**.



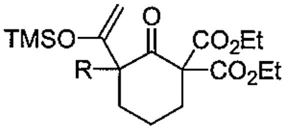
Scheme 28

With the synthesis of compounds **46** and **48**, the key condensation reaction was explored. Sodium hydride was first used (Scheme 29). The reaction was first conducted at 0 °C and then boiled in THF. Surprisingly, only starting material remained with no trace of the desired product. Compound **48** was then treated with triethylamine in toluene. This was also unsuccessful. Other bases, such as potassium *tert*-butoxide, lithium diisopropylamide, and lithium tetramethylpiperidine, also failed to produce the condensation product. The combination of titanium tetrachloride, tributylamine, and TMSCl also did not produce the desired product.



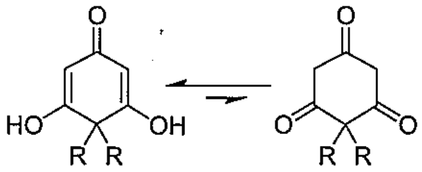
Scheme 29

To increase the electrophilicity of the ester, TMSTf was added along with triethylamine. The TMS group should coordinate with the ester carbonyl, activating it to nucleophilic attack by the enolate of the methyl ketone. Once again, the reaction failed to produce the bicyclic compound. Interestingly, the enol silyl ether **49** of the starting material was not produced under these conditions either.



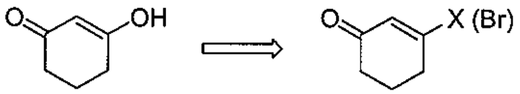
49

Harnessing the oxidized phloroglucin intermediate **50** proved to be difficult. The unpredictable reactions of the densely oxidized bicyclic phloroglucins forced the evaluation of other strategies.



50

Because of these difficulties, the β-diketone functionality should be introduced after the bicyclic formation. The difficulties encountered during the attempted transformation of the bicyclic enone to the β-diketone indicated a need for a flexible method that could be applied towards other phloroglucin natural products. The limitations of conjugate addition to the bicyclic enone required indirect methods to produce the desired β-diketone (Schemes 13 and 14). In order to circumvent these obstacles, the idea of generating a β-bromo enone was studied.



A presence of the bromine atom would increase the electrophilicity of the enone, making it more susceptible to conjugate addition. In essence, the β-bromo enone's electrophilicity would be comparable to acid halides.

The retrosythetic analysis (Figure 10) indicates that the β-diketone bicyclic compound could be made from β-bromo enone **51**, which in turn, could be made from a functionalized bicyclic compound, such as **52**.

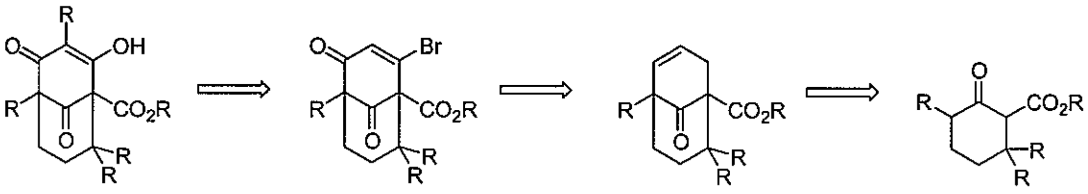


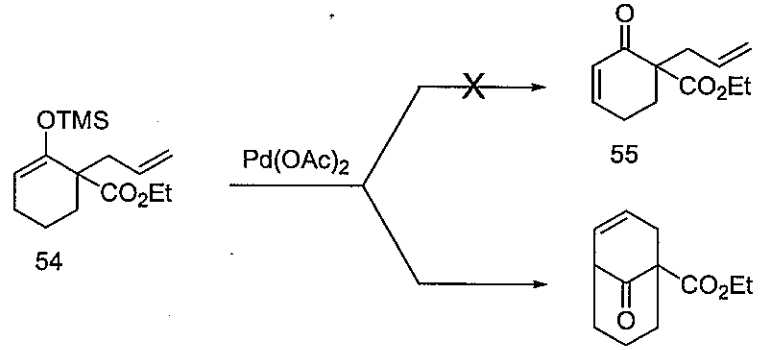
Figure 10. Retrosynthetic Analysis

The key transformation of the strategy is the functionalization of the bicyclic olefin **52**. There is no literature precedence for the direct construction of β-bromo enones from disubstituted olefins. In fact, most β-halo enones (Scheme 30) are made from β-diketones[38] with halogenating reagents, such as oxalyl chloride or phosphorus tribromide.

Scheme 30

Another aspect of this strategy is the construction of the bicyclic compound **52**. The olefin will serve as a handle to functionalize the compound. The starting point of the synthesis might be a substituted cyclohexanone. Compound **53** allows for the incorporation of the alkyl and prenyl groups of the natural product at the onset of the synthetic route.

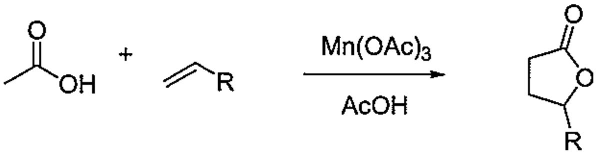
To begin the synthesis, the cyclization to form olefin **52** was investigated. Kende first reported the generation of bicyclic compounds from enol silyl ethers bearing allyl groups[39] using palladium acetate in acetonitrile (Scheme 31). Kende had originally intended to generate enone **55** when unexpectedly, cyclization occurred to produce a bicyclic compound.



Scheme 31

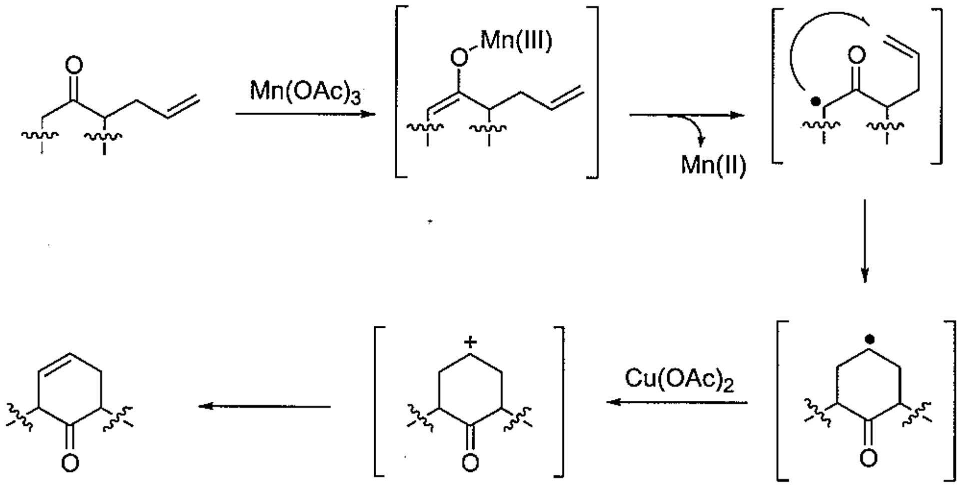
Spiro compounds were also made with these reaction conditions. The use of stoichiometric quantities of palladium was not attractive for our synthetic strategy, since the cyclization step would be fairly early in the synthesis.

An alternative reagent is manganic triacetate, which has been extensively investigated by Snider and co-workers.[40] In 1968 manganese(III) was shown to be a one-electron oxidant[41] in acetic acid. The oxidative addition of acetic acid to alkenes (Scheme 32) has provided the basis for a general approach to oxidative free-radical cyclization.



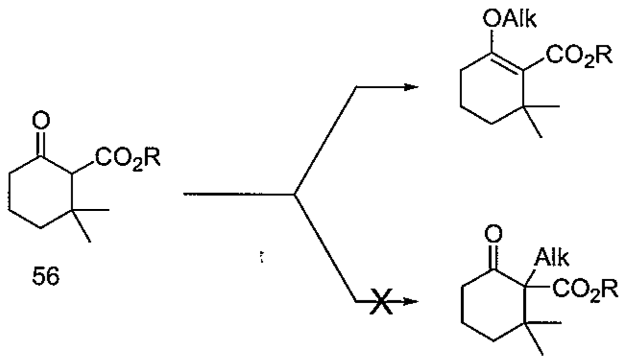
Scheme 32

The mechanism[42] for the manganese reaction involves an enolization of the carbonyl of the substrate and subsequent electron transfer with loss of manganese(II) to produce an α-carbonyl radical (Scheme 33). The enolization is the rate determining step; whereas, the electron transfer is rapid. The attack of the radical onto the alkene is also rapid. Once the cyclization occurs, the secondary radical formed can be oxidized by Mn(III); however, this is slow and can compete with other reactions. Heiba and Dessau[43] demonstrated that Cu(II) oxidizes the radical formed 350 times faster than Mn(III) and that the two reagents are compatible. The use of $Cu(OAc)_2$ promotes oxidative elimination to yield the corresponding olefin.



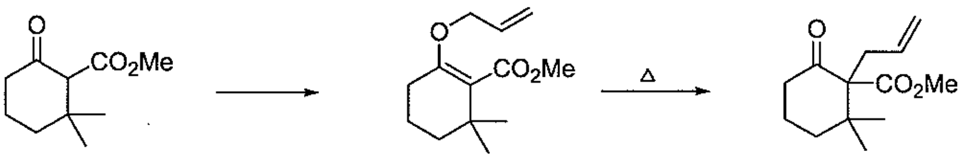
Scheme 33. The Oxidative Free-radical Cyclization Mechanism

Manganese(III) mediated oxidative free-radical cyclization might serve a couple of purposes. First, it might enable the construction of the bicyclic structure with a handle for the β-diketone functionality. Secondly, the generality of the reaction allows for various substituted substrates to undergo the cyclization. Recall that the alkylation of 3,3-disubstituted cyclohexanone carboxylates, such as **56**, is problematic due to the steric hindrance of the enolate. The alkylation can occur on either the 2-carbon or the enolate oxygen depending on the electrophile (Scheme 34). The presence of substituents at the 3-carbon will increase the likelihood of *O*-alkylation occurring.



Scheme 34

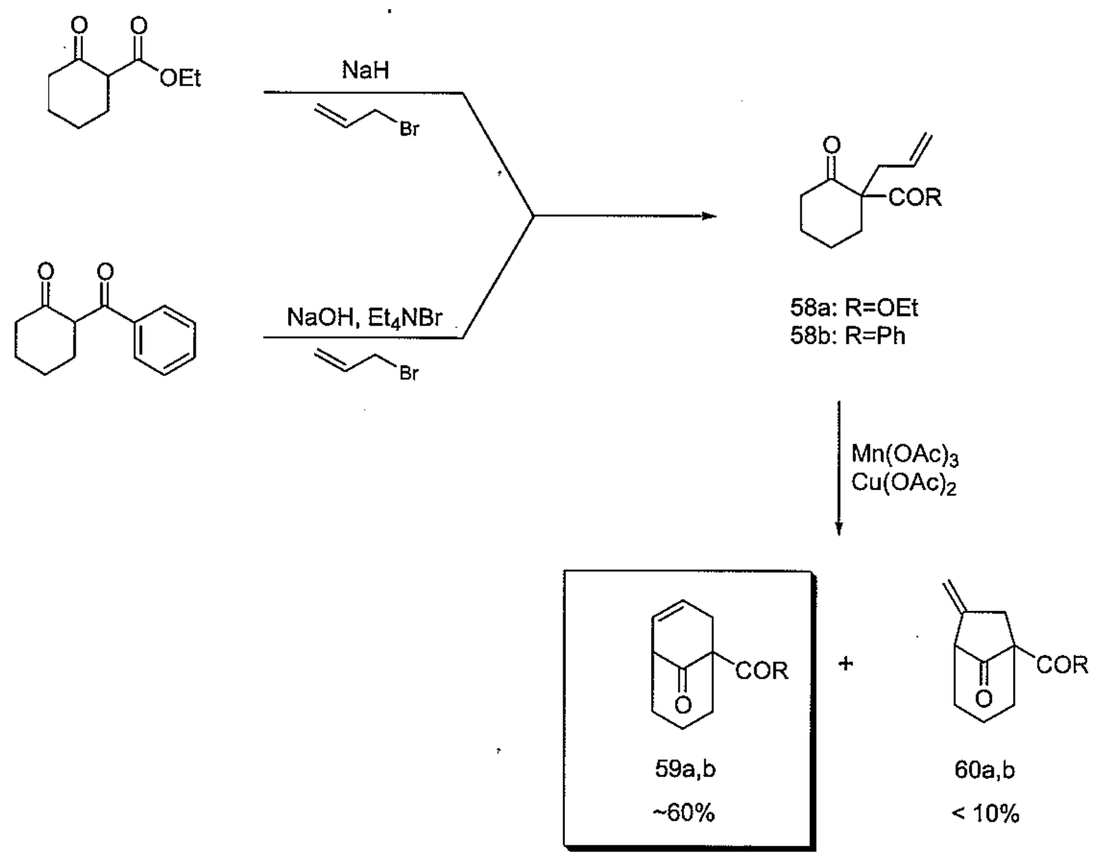
However, an *O*-allylated product can be thermally rearranged (Scheme 35) to the *C*-allylated compound as demonstrated by Rothberg.[34] This will enable the strategy to be expanded to more complex systems.



Scheme 35

The synthesis began with the allylation of 2-substituted cyclohexanones. The allylation of ethyl 2-cyclohexanone carboxylate with sodium hydride and allyl bromide produced compound **58a** in 72% yield. When the same reaction conditions were applied to 2-benzoylcyclohexanone, the yield of compound **58b** was very poor (30%). Using phase transfer conditions[44] of sodium hydroxide, tetraethylammonium bromide and allyl bromide, compound **58b** was produced in a 65% yield (Scheme 36). The use of various 2-substituted cyclohexanones was to explore the cyclization's scope and limitations with regard to the functionality of the side chain carbonyl. It is worthwhile to investigate the differences that an ester might have in relation to a ketone. Furthermore, the bulky benzoyl group in compound **58b** is present in the natural product nemosorone.

Once the allylated compounds were constructed, the cyclization with manganic acetate and copper acetate was explored. The reaction was performed in acetic acid and heated at 80 °C for 18 hours. The oxidative radical cyclization produced 60% of the desired bicyclic olefin **59** and less than 10% of the exo-cyclization product **60**.

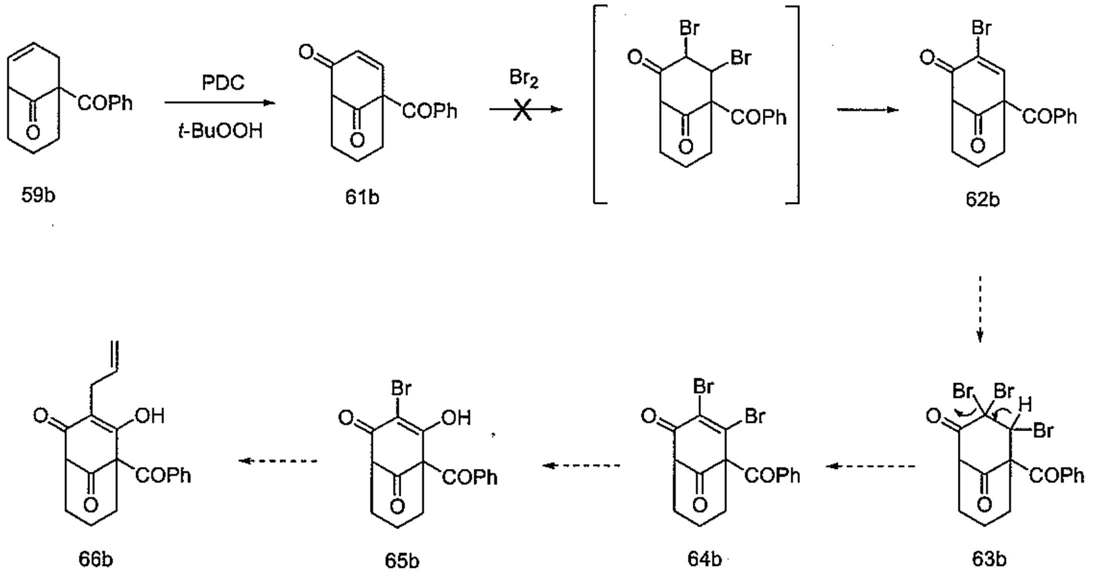


Scheme 36

With bicyclic olefin **59** in hand, the exploration of the β-diketone transformation was undertaken. The initial strategy relied upon the conversion of an enone into a β-bromo enone. Allylic oxidation of olefin **59b** with dry chromium trioxide in 3,5-dimethylpyrazole failed to produce the desired enone. The use of pyridinium dichromate and *tert*-butyl hydroperoxide gave enone **61b** in 80% yield.

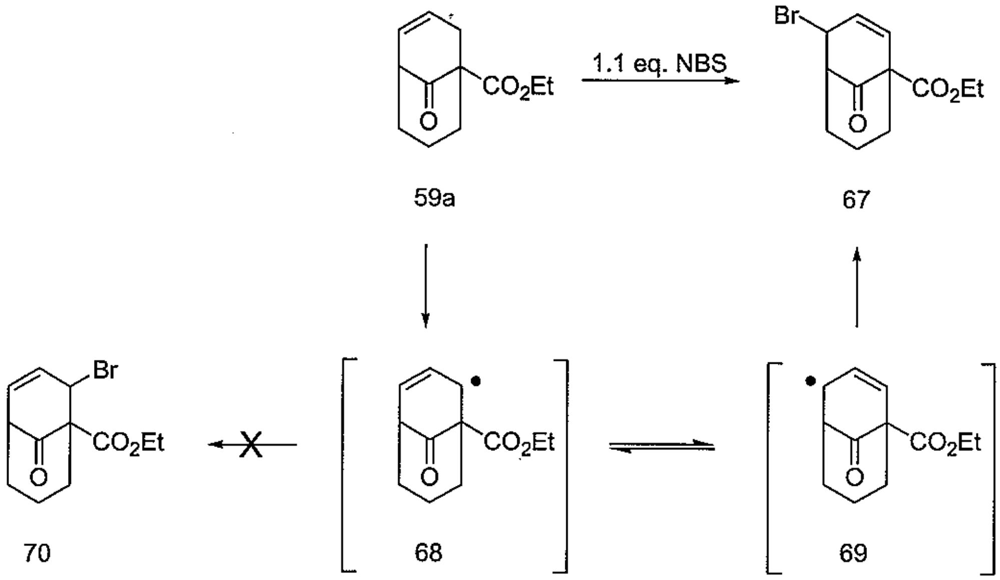
The bicyclic enone **61b** would now be subjected to bromination conditions to produce α-bromo enone **61b** via the dibromide intermediate (Scheme 37). The propensity for the β-elimination of α,β-dibromo ketones should produce the desired compound **62b**. Addition of another equivalent of bromine should produce the tribromide **63b**. An elimination of an α-bromide should produce an α,β-dibromo enone, which upon treatment under hydrolytic conditions should yield a β-diketone **65b**. Compound **65b** could presumably then be allylated to produce the desired bicyclic compound **66b**.

Unfortunately, the bromination reaction of compound **61b** did not produce the expected α-bromo enone or the dibromide intermediate. Instead, it produced a mixture of uncharacterizable products.



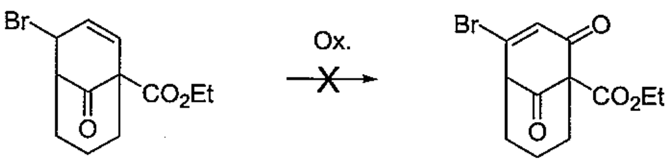
Scheme 37

With these disappointing results, the strategy to construct the β-bromo enone shifted towards a different pathway. The allylic bromination (Scheme 38) of the bicyclic olefin **59a** with NBS produced a single regioisomeric allyl bromide **67**. Proton NMR spectroscopic assignment of the bridgehead hydrogen ruled out isomer **70**.



Scheme 38

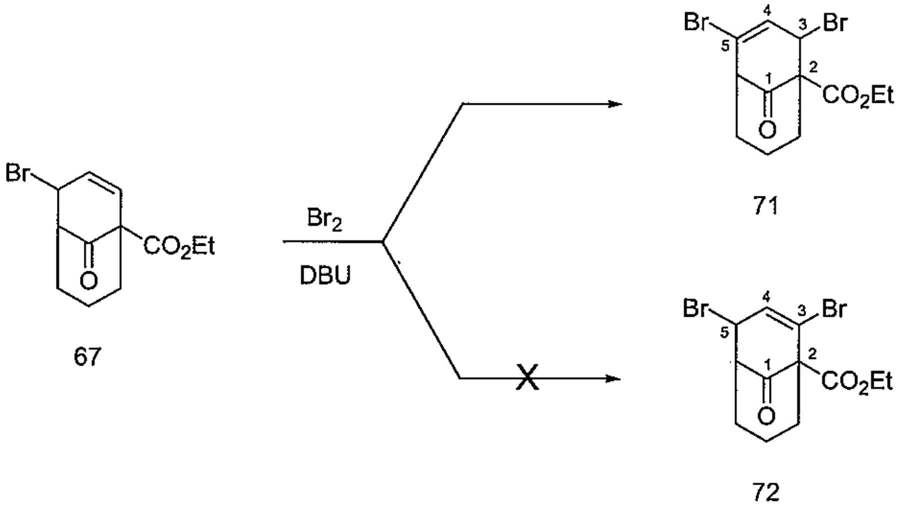
The bridgehead proton of regioisomer **70** should have a similar splitting pattern and a slight change in chemical shift compared to the analogous proton in olefin **59a**. The ^{1}H NMR spectrum of **67** shows the peak corresponding to the bridgehead proton with a drastically different splitting pattern and significant change in chemical shift. The addition of the bromide radical would occur at the less hindered site of the molecule. To produce compound **70**, the bromine radical would have to add to the allylic radical at the more congested site. The allylic bromide **67** was then subjected to various allylic oxidation conditions to produce the β-bromo enone. Unfortunately, the allylic oxidation of compound **67** was not successful (Scheme 39).



67

Scheme 39

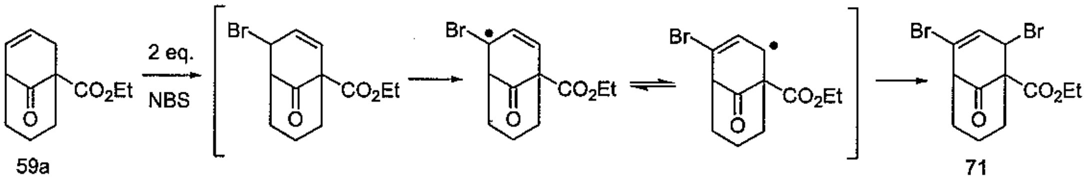
The inability to oxidize bromide **67** redirected attempts to synthesize carbonyl equivalents. Allylic halides can be converted to carbonyls via the Kornblum[45] oxidation with dimethyl sulfoxide and other known reagents. This transformation with enone **67** would require a dibromide intermediate **71** in order to generate the desired bromo enone. Bromide **67** was treated with 1.1 equivalents of bromine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to produce **71**.



Scheme 40

The structure of the product from this reaction was assigned by ^{1}H NMR spectroscopy. The vinylic proton at C-4 and the proton at C-3 in **71** are doublets with coupling constants of 3.0 Hz. The splitting patterns and coupling constants indicate that they are coupled to only one proton. Regioisomer **72** should couple with two protons and have a different splitting pattern.

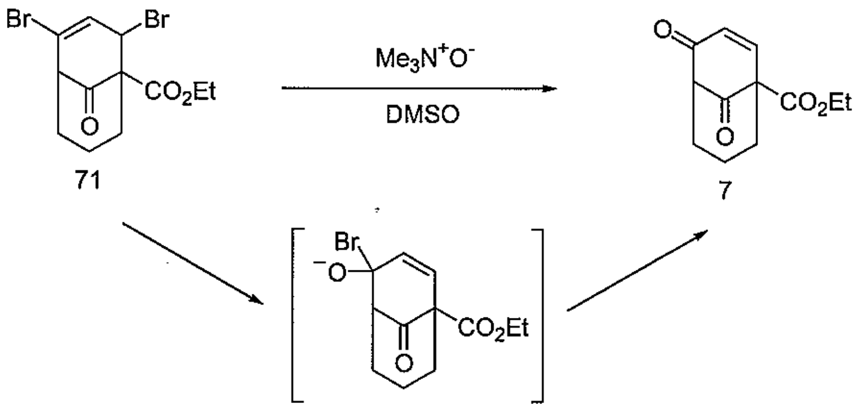
Compound **71** was prepared in two steps from the bicyclic olefin. Since both steps were brominating steps, an attempt was made to generate the dibromide in one step. The bicyclic olefin **59a** was treated with 2 equivalents of NBS and catalytic amounts of AIBN (Scheme 41). The product formed was the expected dibromide **71** in an 82% yield.



Scheme 41

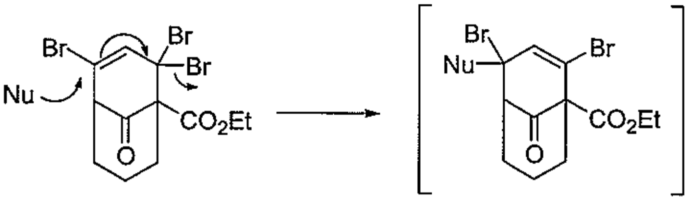
The specificity of the regiochemistry is rationalized as follows. The first bromination occurs as before on the least hindered side of the molecule. The second bromination occurs on the carbon not bearing the bromine atom, due to the stability of the allylic radical intermediate.

With compound **71** in hand, various attempts to oxidize this compound were made. The Kornblum oxidation conditions with DMSO did not affect the starting material, even at elevated temperatures. Treating dibromide **71** with pyridine-N-oxide, alumina (Al_2O_3) and formic acid with triethylamine also did not produce the desired product. The next attempt used a variation of the Kornblum oxidation. Trimethylamine-N-oxide[46] in DMSO was used to transform the dibromide intermediate (Scheme 42). Surprisingly, enone **7** was formed.



Scheme 42

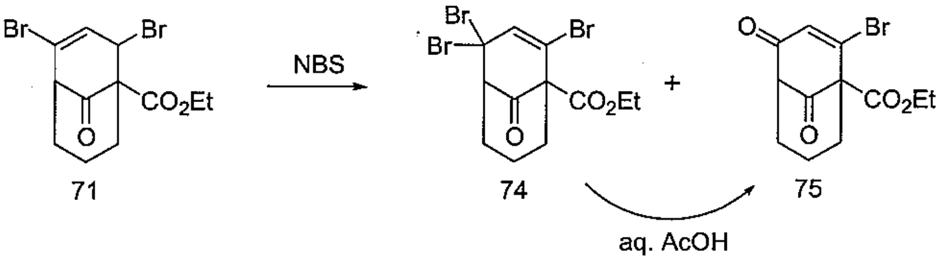
The formation of enone **7** indicated the inclination of the dibromide intermediate to undergo nucleophilic displacement. The nucleophilic addition of an oxygen atom from either DMSO or trimethylamine-N-oxide apparently displaced the allylic bromide creating an allylic bromohydrin which readily converted to the enone. With this insight, a strategy to produce the β-bromo enone could be based on a tribromide intermediate (Scheme 43) where the allylic position contains two bromine atoms, one for the elimination and the other might become the β-bromide of the enone.



73

Scheme 43

To prepare the tribromide intermediate **73**, dibromide **71** was treated with one equivalent of NBS. Tribromide **74** was formed (Scheme 43), but surprisingly, the desired β-bromo enone **75** was also produced in a one to one ratio with compound **74.** Tribromide **74** was converted to compound **75** by heating in aqueous acetic acid to result in an overall yield of 95% of β-bromo enone **75** from the dibromide **71.**



Scheme 43

The structure assignment of compound **75** was based on the ^{1}H NMR spectrum and mechanistic considerations. The chemical shift of the bridgehead proton of **75** was similar to that of the same proton from the bicyclic enone **7** (3.51 and 3.45 ppm respectively). If the proton in question were next to the vinylic bromide isomer, the chemical shift should be considerably different. Mechanistically, the nucleophilic substitution should be from the less hindered side, opposite the ethyl ester. The resulting product formed (**75**) should have the carbonyl adjacent to the tertiary bridgehead carbon instead of adjacent to the quaternary bridgehead carbon. This was supported by the previous generation of enone **7** and its structure (Figure 11). The lack of regioisomer **7a** implies the strong preference of nucleophilic addition from the less sterically congested side.

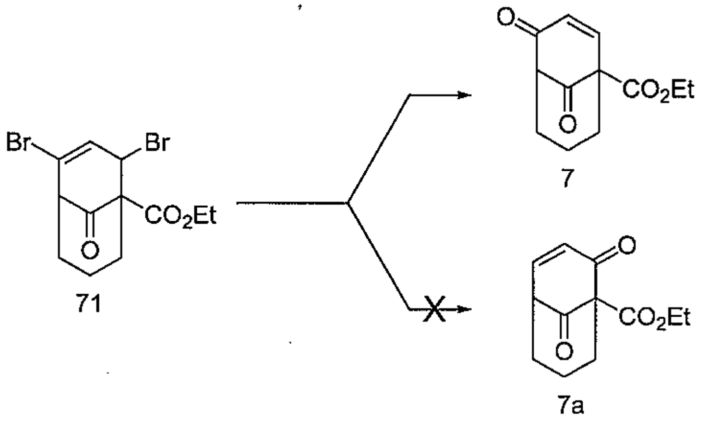


Figure 11. Hydrolysis of the dibromide intermediate

The *in situ* conversion of compound **74** to **75** indicates the rapid rate of hydrolysis of the tribromide intermediate. The addition can occur by possibly two routes (Figure 12). In the first possible pathway, the ionization of compound **74** leads to an allylic carbocation intermediate. Since the nucleophilic addition likely occurs on the less hindered side, the resulting bromohydrin would produce compound **75**. An alternate mechanism would involve a tribromide isomer **76**. S_N2' displacement of an allylic bromide would generate the bromohydrin, which would then lead to a desired β-bromo enone **75.**

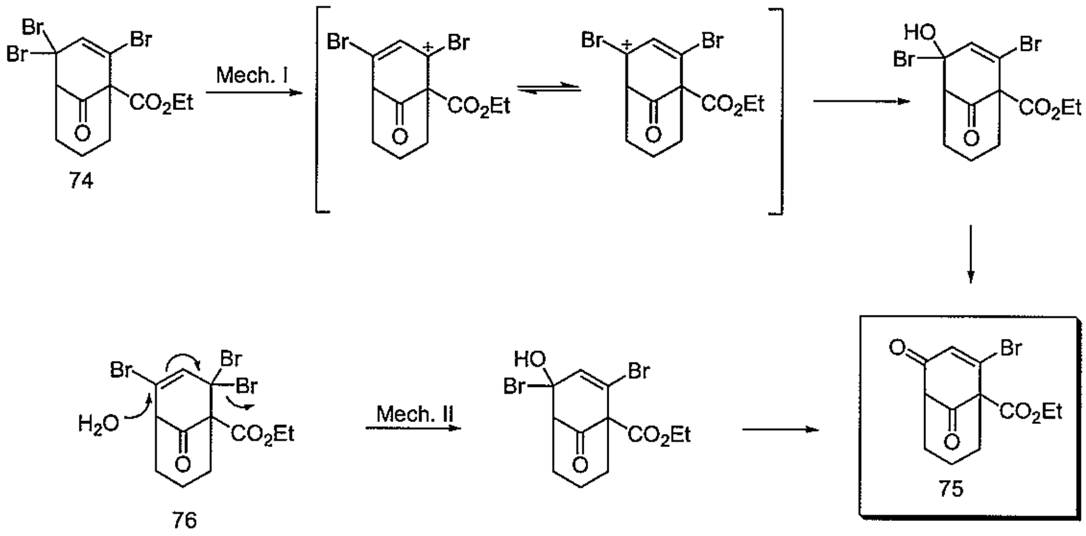


Figure 12. Mechanisms of Hydrolysis

However, the probability of the isomer **76** being the tribromide compound is unlikely (Figure 13). The formation of the tribromide **76** involves the allylic radicals **77** and **78**. Since both radicals seem to have similar electronic and inductive effects, the addition should be more dependent on steric effects. The conclusion can be made that the tribromide compound would be that of isomer **74** rather than **76**.

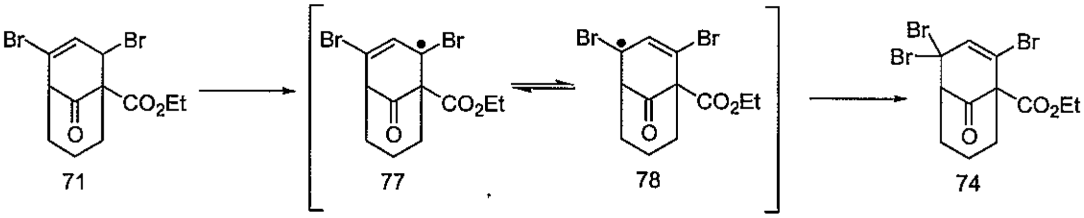
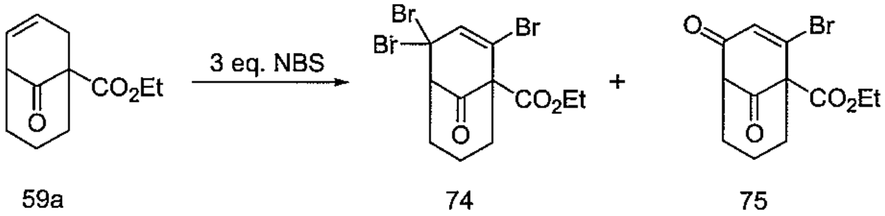


Figure 13. Bromination of the dibromide intermediate

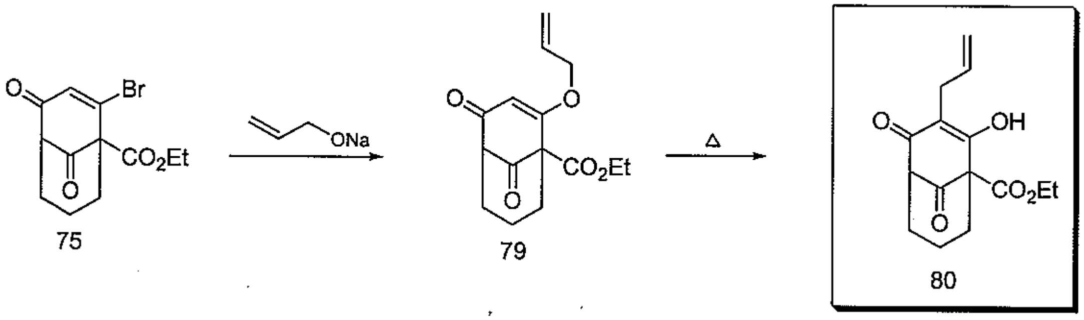
Interestingly, olefin **59a** can be converted directly (Scheme 44) to tribromide **74** and β-bromo enone **75** when treated with three equivalents of NBS. However, the total yields of compound **75** are low (~50%) compared to the two-step sequence.



Scheme 44

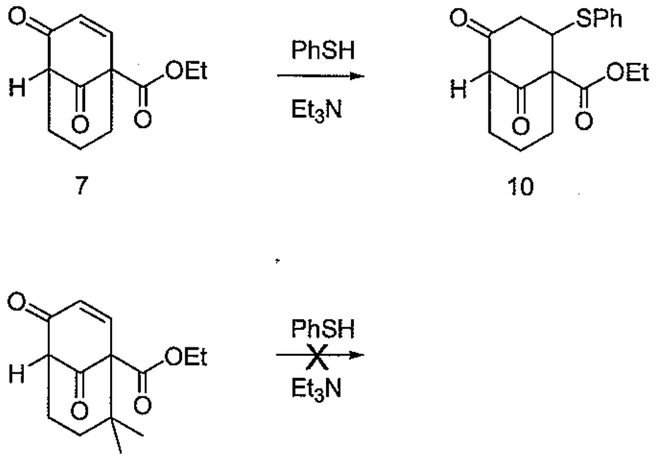
With the attainment of compound **75**, the next goal was to displace the bromide ion with an oxygen nucleophile. The addition of sodium allyloxide (Scheme 45) produced the allyl enol ether **79**. Heating in a sealed tube at 140 °C facilitated the Claisen rearrangement to produce the desire bicyclic β-diketone subunit **80** in 45% isolated yield. The crude yield of the β-diketone compound before purification was over

80%; however, after column chromatography, the isolated yield was much lower. The retention time on the column was indicative of the polarity of the molecule.



Scheme 45

With the successful synthesis of the bicyclic β-diketone **80**, the strategy was applied to a more complex system. Although the bromination-hydrolysis methodology could be extendable to more substituted systems, a previous observation (Figure 14) was a cause for concern. The addition of thiophenoxide onto bicyclic enone **7** occurred smoothly with high yields. However, with the presence of a geminal dimethyl group (**7a**), the addition did not occur.



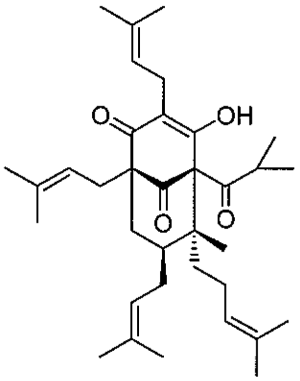
7

10

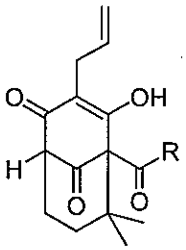
7a

Figure 14. Steric hinderance of conjugate addition

The presence of the additional groups increased the steric hinderance, preventing the addition. In order to generalize the synthetic strategy, the synthesis of the bicyclic β-diketone core containing a geminal dimethyl group was investigated.

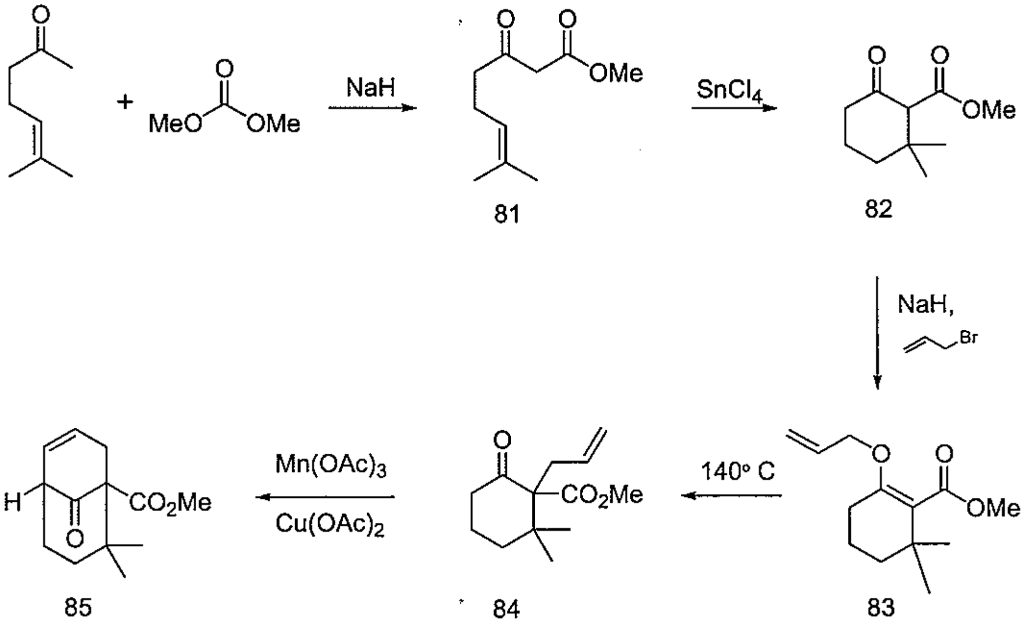


Hyperforin



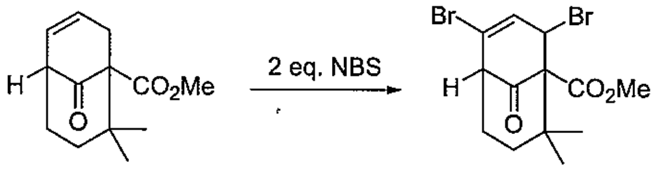
Bicyclic Core

The synthesis began with the construction of the substituted cyclohexanone. The condensation of 6-methyl-5-hepten-2-one and dimethyl carbonate produced keto ester **81** in 85% yield (Scheme 46). The Lewis acid catalyzed cyclization[47] of keto ester **81** formed the keto ester **82**. Treatment of **82** with sodium hydride and allyl bromide yielded the *O*-allylated product **83**, which was isolated and purified. Heating at 140 °C in a sealed tube afforded the rearranged compound **84**. The manganic triacetate oxidative cyclization was then performed to yield the bicyclic olefin **85**.



Scheme 46

The two-step bromination procedure in the previous work garnered higher yields of the bicyclic β-bromo enone versus the one-step procedure. Treatment of olefin **85** with 2 equivalents of NBS (Scheme 47) produced the expected dibromide **86** in a 60% yield.

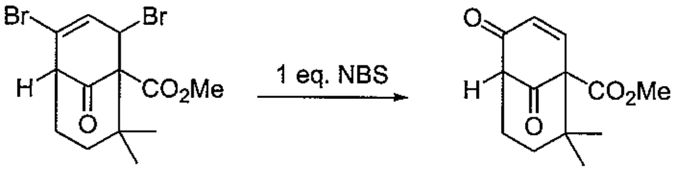


85

86

Scheme 47

When dibromide **86** was treated with one equivalent of NBS, enone **87** formed unexpectedly (Scheme 48). The rate of hydrolysis was in competition with the rate of bromination.



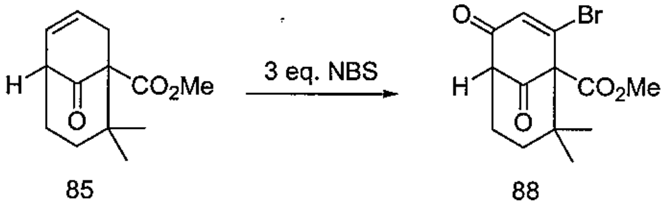
86

87

Scheme 48

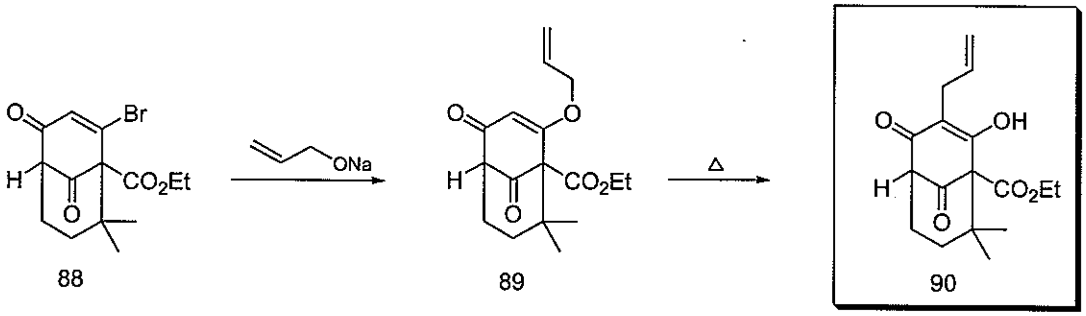
In the previous synthesis without the geminal dimethyl group, the rate of bromination of the dibromide compound was faster than the hydrolysis. With compound **86**, the rate of hydrolysis was faster; therefore, enone **87** was produced exclusively.

Because of these unanticipated results, the next attempt at producing the β-bromo enone was the one step brominating procedure (Scheme 48). The reaction was carried out in dry NBS, AIBN, carbon tetrachloride, and crushed molecular sieves, which were used to prevent the hydrolysis. The hydrolysis did occur, but not on the dibromide. It occurred on the tribromide to produce the desired bicyclic β-bromo enone **88** in a 55% yield from the bicyclic olefin. There was no presence of the tribromide compound in the products obtained. Enone **87** was also isolated from the reaction mixture in less than 10% yield.



Scheme 48

With the construction of compound **88**, the model system was close to completion. The addition of sodium allyloxide (Scheme 49) onto the β-bromo enone produced the allyl enol ether **89**. Subsequent heating produced the bicyclic β-diketone subunit **90**.



Scheme 49

In summary, a concise synthesis of the functionalized bicyclic core subunit of acyl phloroglucin natural products was achieved in eight steps. In the course of this synthesis, the bromination-hydrolysis methodology was investigated to transform bicyclic olefins into bicyclic β-diketones. The generality of this transformation strategy was demonstrated on two related bicyclic systems. The strategic route explored and developed can be applied towards the total synthesis of this class of natural products.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, benzene and diisopropylamide were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.26 ppm for ^1H and 77.06 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m=multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.

2-Oxo-1-(3-oxo-propyl)-cyclohexanecarboxylic acid ethyl ester (**4**)

Sodium metal (0.068g, 3 mmol), freshly cut and washed with hexanes, was added to 200 mL of absolute ethanol and the solution was cooled to -78 °C. A mixture of ethyl 2-cyclohexanone carboxylate (10g, 58 mmol) and acrolein (4.0g, 71 mmol) in 30 mL of ethanol was added dropwise slowly. The solution was stirred at -78 °C for 30 minutes and then at room temperature for an additional 30 minutes. The mixture was neutralized with glacial acetic acid and the solvent was removed by vacuum. The residue was dissolved in ether and washed with water, saturated aqueous $NaHCO_3$, dried, and concentrated in vacuo. Crude compound was used further without purification. ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 4.19 (q, $J = 9$ Hz, 2H), 2.55-1.39 (m, 12H), 1.28 (t, $J = 6$ Hz, 3H); HRMS (EI) m/z calcd for 226.1205, found 226.1209.

4,9-Dioxo-bicyclo[3.3.1]nonane-1-carboxylic acid ethyl ester (**6**)

Sodium metal (2.0g, 88.4 mmol), freshly cut and washed with hexanes, was added to 350 mL of absolute ethanol and the solution was cooled to -78 °C. Aldehyde **4** (10g, 44.2 mmol), dissolved in 20 mL of ethanol, was added dropwise. The solution was kept in the refrigerator for 24 hours. The solution was quenched with 10% HCl followed by removal of the solvents. The residue was diluted with ether and washed with brine, dried, and concentrated. The crude alcohol **5** was then dissolved in 100 mL of CH_2Cl_2 and added to a mixture of PCC (12.4g, 58 mmol) and Celite (12.4g) in 200 mL of CH_2Cl_2 at room temperature. After 4 hours, the solvent was removed and the brown residue was dissolved in ether, filtered through Celite, dried, and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, $J = 6$ Hz, 2H), 3.16 (t, $J = 3$ Hz, 1H), 2.89-2.81

(m, 1H), 2.74-2.68 (m, 1H), 2.60-2.4 (m, 3H), 2.06-2.17 (m, 2H), 1.95-1.88 (m, 1H), 1.79-1.61 (m, 2H), 1.32 (t, *J* = 3 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 209.28, 207.11, 172.50, 62.83, 62.01, 57.94, 39.99, 38.47, 35.03, 25.37, 19.04, 14.41; HRMS (EI) m/z calcd for 224.1049, found 224.1053.

4,9-Dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (7)

To ketone **6** (2.0g, 9 mmol) in 90 mL of acetonitrile was added Et_3N (1.13g, 11.2 mmol), TMSCl (1.21g, 11.2 mmol), and NaI (1.68g, 11.2 mmol) at room temperature. After stirring overnight, the solvent was removed by vacuum and dissolved in dry pentane. The solution was filtered and concentrated in vacuo. (Crude enol silyl ether) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (t, *J* = 3 Hz, 1H), 4.23 (q, *J* = 6 Hz, 2H), 3.21 (d, *J* = 12 Hz, 1H), 2.80 (s, 1H), 2.39-1.64 (m, 7H), 1.29 (t, *J* = 6 Hz, 3H), 0.19 (s, 9H). The crude enol silyl ether in 50 mL of DMSO was added to a solution of 20 mL of DMSO and $Pd(OAc)_2$ (0.20g, 0.9 mmol) at room temperature. Oxygen was bubbled through the mixture for 30 minutes and the solution was heated at 80 °C for 16 hours. After cooling to room temperature, the mixture was added saturated ammonium chloride solution and filtered through Celite. The organic layer was extracted with ether, dried, concentrated and purified by column chromatography to afford **7** in a 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 9 Hz, 1H), 6.57 (d, J = 9 Hz, 1H), 4.29 (q, J = 6 Hz, 2H), 3.38 (t, J = 3 Hz, 1H), 2.52 (dt, J = 12, 6 Hz, 1H), 2.23-2.18 (m, 1H), 2.09-1.95 (m, 2H), 1.79-1.54 (m, 2H), 1.30 (t, J = 6 Hz, 3H); HRMS (EI) m/z calcd for 222.0892, found 222.0895.

5,10-Dioxo-3-oxa-tricyclo[4.3.1.02,4]decane-1-carboxylic acid ethyl ester (**8**)

To enone **7** (0.50g, 2.25 mmol), dissolved in 30 mL of methanol at 0 °C, was added 30% H_2O_2 (76.6 g, 6.75 mmol) and a catalytic amount of aqueous 20% NaOH (0.001g, 0.017 mmol). After 15 minutes, the solution was added ice water and extracted with dichloromethane, dried, concentrated and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (q, J = 6 Hz, 2H), 3.76 (d, J = 3 Hz, 1H), 3.67 (d, J = 3 Hz, 1H), 3.15 (t, J = 3 Hz, 1H), 2.61-2.51 (m, 1H) 2.41-2.29 (m, 2H), 2.10-1.99 (m, 1H), 1.81-1.69 (m, 2H), 1.36 (t, J = 6 Hz, 3H).

2-Hydroxy-4,9-dioxo-bicyclo[3.3.1]nonane-1-carboxylic acid ethyl ester (**9**)

To epoxy ketone **8** (70mg, 0.29 mmol), dissolved in 10 mL of (2:1) THF:H_2O. Aluminum amalgam, made from aluminum foil (0.125g, 4.6 mmol) and 1% HgCl (1.1g, 4.6 mmol) solution in water was added. The mixture was stirred at room temperature for 1 hour and filtered through cotton and washed with THF. The solution was concentrated and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (q, J = 6 Hz, 2H), 3.77 (s, 1H), 3.09 (d, J = 9 Hz, 1H), 2.84 (dd, J = 21, 9 Hz, 1H), 2.62 (dd, J = 18, 3 Hz, 1H), 2.16-1.41 (m, 6H), 1.21 (t, J = 6 Hz, 3H).

4,4-dimethyl-1,3-cyclohexadione (**10**)

To 4,4-dimethyl-2-cyclohexenone (1g, 8.0 mmol) in 100 mL of dry toluene at 0 °C was added 1.0 M Et_2AlCN (12.0 mL, 12.0 mmol). After 30 minutes, Et_3N (3.26g, 32.0 mmol) and TMSCl (1.75g, 16.0 mmol) were added and the mixture was stirred for 1 hour at room temperature and then added saturated aqueous $NaHCO_3$ slowly. The organic layer was extracted with ether, dried and concentrated. Cyano enol silyl ether: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74-4.73 (m, 1H), 3.06-3.04 (m, 1H), 2.12-1.41 (m, 4H), 1.15 (s, 3H), 1.09 (s, 3H), 0.20 (s, 9H). The crude enol silyl ether (0.5g, 2.6 mmol) was dissolved in 5 mL of THF and added to LDA, made from *i*-Pr_2NH (0.31, 3.12 mmol) and 2.5 M *n*-BuLi (1.23g, 3.12 mmol) in 20 mL of THF, at -78 °C. Oxygen was bubbled through the solution for 30 minutes and the mixture was warmed to 0 °C followed by the addition of 1 M $SnCl_2$ (1.15g, 5.12 mmol) in 2 M HCl. After 10 minutes at room temperature, the solution was diluted with water, extracted with ether, dried, concentrated and purified by column chromatography to afford compound **10** in a 64% yield. The product was spectrally identical to the commercial material.

4,9-Dioxo-2-phenylsulfanyl-bicyclo[3.3.1]nonane-1-carboxylic acid ethyl ester (**11**)

To enone **7** (2.0g, 9 mmol) in 100 mL of CH_2Cl_2 was added Et_3N (0.91g, 0.9 mmol) at 0 °C, followed by thiophenol (1.19g, 10.8 mmol) dropwise. The mixture was stirred at 0 °C for 3 hours and quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, washed with brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.22 (m, 5H), 4.20 (m, 2H), 3.36 (m, 1H), 3.21-1.51 (m, 9H), 1.26 (t, J = 6 Hz, 3H); HRMS (EI) m/z calcd for 332.1082, found 332.1084.

4,9-Dioxo-2-phenylsulfanyl-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (**12**)

To enone **11** (1.0g, 3 mmol) in 30 mL of CCl_4 at 0 °C, was slowly added NCS (0.48g, 3.6 mmol). The mixture was kept at 0 °C for 5 hours and then filtered, concentrated and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.41 (m, 5H), 5.95 (s, 1H), 4.42-4.30 (m, 2H), 3.57 (t, $J = 3$ Hz, 1H), 2.61-1.61 (m, 6H), 1.41-130 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 192.47, 187.05, 168.52, 135.99, 131.07, 130.62, 126.47, 68.34, 65.73, 62.53, 61.70, 34.52, 33.16, 25.75, 18.09, 14.24; HRMS (EI) m/z calcd for 330.0926, found 330.0931.

2-Methoxy-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (**13**)

To a fresh solution of sodium metal (0.24g, 10.5 mmol) in 15 mL of methanol at 25°C, was added compound **12** (0.5g, 1.5 mmol) in 5 mL of methanol. The solution was boiled for 2 hours and then cooled to 0 °C. The mixture was quenched with saturated aqueous ammonium chloride, concentrated, diluted with water and extracted with ethyl acetate. The organic layers were dried, concentrated in vacuo and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (s, 1H), 3.79 (s, 3H), 3.72 (s, 3h), 3.53 (t, $J = 3$ Hz, 1H), 2.43 (dt, $J = 12, 3$ Hz, 1H), 2.29-2.25 (m, 1H), 2.11-2.08 (m, 1H), 1.97-1.92 (m, 1H), 1.75-1.69 (m, 2H).

2-Hydroxy-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (**14**)

To methyl enol ether **13** (0.057g, 0.24 mmol) in 3 mL of acetonitrile at 0 °C, was added TMSI (0.15g, 0.72 mmol) dropwise and the reaction mixture was warmed to room temperature. After 3 hours, the mixture was added 25% aqueous sodium thiosulfate and extracted with CH_2Cl_2, dried, concentrated and purified by preparative TLC. ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (s, 1H), 3.71 (s, 3H), 3.58 (t, *J* = 6 Hz, 1H), 2.61-2.48 (dt, *J* = 15, 3 Hz, 1H), 2.41-2.30 (m, 1H), 2.20-2.10 (m, 1H), 2.05-1.92 (m, 1H), 1.81-1.69 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.28, 166.94, 161.46, 156.09, 112.77, 91.15, 52.93, 43.85, 29.92, 26.50, 19.19; FTIR (thin film) 3447, 1734, 1674, 1567, 1265 cm^{-1}; HRMS (EI) m/z calcd for 224.0685, found 224.0691.

2-Methyl-2-(4-methyl-pent-3-enyl)-6-oxo-cyclohexanecarboxylic acid ethyl ester **(15)**

To 1.4 M MeLi (38.5 mL, 54 mmol) and CuI (5.14g, 65 mmol) in 200 mL of ether at -78 °C, was added compound **14** (4g, 22.5 mmol) in 10 mL of ether. After 1 hour, methyl cyanoformate (3.06g, 104 mmol) in 5 mL of ether was added. The solution was stirred for 4 hours at -78 °C, and added saturated aqueous ammonium chloride, extracted with ether, dried, concentrated, and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (m, 1H), 3.71 (s, 3H), 3.28 (s, 1H), 2.75-2.62 (m, 1H), 2.33-1.30 (m, 9H), 1.68 (s, 3H), 1.59 (s, 3H), 1.08 (s, 3H).

6-Allyl-1,5-bis-(tert-butyl-dimethyl-silanyloxy)-6-methyl-cyclohexa-1,4-diene **(24)**

To diketone **23** (0.5g, 3.0 mmol) in 30 mL of CH_2Cl_2 was added Et_3N (0.915g, 9 mmol) then TBSTf (2.4g, 9 mmol) at room temperature. After the reaction was completed, water was added to the mixture and was then extracted with CH_2Cl_2, dried, and purified by column chromatoghraphy. ^1H NMR (300 MHz, $CDCl_3$) δ 5.71-5.59 (m, 1H), 4.99-4.87 (m, 2H), 4.71 (t, *J* = 3 Hz, 2H), 2.64 (t, *J* = 3 Hz, 2H), 2.30 (d, *J* = 6 Hz, 2H), 1.21 (s, 3H), 0.94 (s, 9H), 0.16 (s, 6H).

1-(3-Chloro-propyl)-2,6-dimethoxy-cyclohexa-2,5-dienecarboxylic acid methyl ester (**29**)

Liquid ammonia (100 mL) was collected in a three-neck flask at -78 °C containing methyl-2,6-dimethoxybenzoate (1g, 5.1 mmol) and *t*-BuOH (0.38g, 5.1 mmol). Freshly cut sodium metal (0.3g, 12.75 mmol) was added. When the dark blue color remained for more than 5 minutes, 1-chloro-3-iodopropane (1.12g, 5.5 mmol) was added and the solution turned a faint yellow. The mixture was warmed to room temperature and saturated aqueous ammonium chloride was added slowly. The ammonia was allowed to evaporate overnight. The residue was diluted with brine and extracted with ether, dried and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (t, $J = 3$ Hz, 2H), 3.67 (s, 3H), 3.50 (s, 6H), 3.46 (t, $J = 6$ Hz, 2 H), 2.86 (qt, $J = 15$, 3 Hz, 2 H), 2.10-2.05 (m, 2 H), 1.55-1.48 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.08, 152.09, 93.68, 54.90, 54.64, 52.82,45.31, 28.89, 28.07, 24.19.

1-(3-Chloro-propyl)-2,6-dimethoxy-4-oxo-cyclohexa-2,5-dienecarboxylic acid methyl ester (**30**)

To diene **29** (0.6g, 1.66 mmol) in 20 mL of CH_2Cl_2 was added Celite (2.54g), PDC (2.54g, 6.64 mmol) and then 78% *t*-BuOOH (0.77g, 6.64 mmol) at room temperature. After 4 hours the mixture was filtered through Celite, concentrated in vacuo and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.59 (s, 2H), 3.71 (s, 3H), 3.68 (s, 6H), 3.48-3.44 (t, $J = 6$ Hz, 2H), 2.37-2.32 (m, 2H), 1.52-1.47 (m, 2H).

2,6-Bis-allyloxy-benzoic acid methyl ester (**36**)

Methyl 2,6-dihydroxybenzoate (0.3g, 1.8 mmol) in 20 mL of acetone at room temperature was added K_2CO_3 (0.74g, 5.4 mmol) followed by allyl bromide (0.65g, 5.4 mmol). The mixture was stirred overnight and filtered. The solvent was concentrated and the residue was dissolved in ether. The organic layer was washed twice with saturated aqueous $NaHCO_3$, brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, *J* = 6 Hz, 1H), 6.52 (d, *J* = 6 Hz, 2H), 6.01-5.92 (m, 2H), 5.39 (d, *J* = 12 Hz, 2H), 5.24 (d, *J* = 12 Hz, 2H), 4.54 (d, *J* = 6 Hz, 4H), 3.89 (s, 3H).

2,6-Bis-methoxy-benzoic acid methyl ester (**38**)

Methyl 2,6-dihydroxybenzoate (2g, 11.9 mmol) in 10 mL of THF was added slowly to a solution of NaH (0.14g, 47.8 mmol) in 100 mL of THF at room temperature. After the mixture was stirred for 1 hour, MOMCl (1.4g, 35.7 mmol) was added dropwise. The mixture was stirred overnight and quenched with saturated aqueous ammonium chloride slowly. The organic layer was extracted with ether, washed with brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, *J* = 6 Hz, 1H), 6.81 (d, *J* = 6 Hz, 2H), 5.17 (s, 4H), 3.92 (s, 3H), 3.47 (s, 6H).

1-(3-Chloropropyl)-2,6-bis-methoxymethoxy-cyclohexa-2,5-dienecarboxylic acid methyl ester (**39**)

Liquid ammonia (100 mL) was collected in a three-neck flask at -78 °C containing compound **38** (2g, 7.8 mmol) and *t*-BuOH (0.58g, 7.8 mmol). Freshly cut sodium metal (0.45g, 19.5 mmol) was added. When the dark blue color remained for more than 5 minutes, 1-chloro-3-iodopropane (1.6g, 7.8 mmol) was added and the solution turned faint yellow. The mixture was warmed to room temperature and saturated aqueous ammonium chloride was added slowly. The ammonia was allowed to evaporate overnight. The residue was diluted with brine and extracted with ether, dried and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (t, J = 6 Hz, 2H), 4.95 (dd, J = 15, 9 Hz, 4H), 3.70 (s, 3H), 3.53 (t, J = 6 Hz, 2H), 3.37 (s, 6H), 2.99-2.78 (m, 2H), 2.20-2.15 (m, 2H), 1.68-1.61 (m, 2H).

1-(3-Chloro-propyl)-2,6-bis-methoxymethoxy-4-oxo-cyclohexa-2,5-dienecarboxylic acid methyl ester **(40)**

To diene **39** (1g, 3.0 mmol) in 30 mL of CH_2Cl_2 was added Celite (4.5g), PDC (4.5g, 12 mmol) and then 78% *t*-BuOOH (1.38g, 12 mmol) at room temperature. After 4 hours the mixture was filtered through Celite, concentrated in vacuo and purified by column chromatography packed with Florisil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (s, 2H), 5.08 (q, J = 2Hz, 4H), 3.73 (s, 3H), 3.51 (t, J = 2Hz, 2 H), 3.41 (s, 6H), 2.45-2.40 (m, 2H), 1.55-1.53 (m, 2H).

1-(3-Chloro-propyl)-2,6-dihydroxy-4-oxo-cyclohexa-2,5-dienecarboxylic acid methyl ester **(41)**

To dienone **40** (60 mg, 0.17 mmol) in 2 mL of THF was added 1 mL of 6M HCl at room temperature. After 1 hour, the solution was neutralized, diluted with water and extracted with ethyl acetate, dried and concentrated. The crude product showed, by ^{1}H

NMR, an absence of the MOM groups; however, the compound could not be purified. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 1H), 3.71 (s, 1H), 3.51-3.44 (m, 2H), 2.39-2.33 (m, 2H), 1.54-1.42 (m, 2H).

1-(3-Iodo-propyl)-2,6-bis-methoxymethoxy-4-oxo-cyclohexa-2,5-dienecarboxylic acid methyl ester (**42**)

To dienone **40** (0.06g, 0.17 mmol) in 2 mL of acetone was added NaI (0.052g, 0.34 mmol) at room temperature. After 30 minutes, the solution was filtered and concentrated, and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (s, 2H), 3.71 (s, 6H), 3.70 (s, 3H), 3.10 (t, $J = 6$ Hz, 2H), 2.34-2.28 (m, 2H), 1.57-1.48 (m, 2H).

2-Oxo-cyclohexane-1,1-dicarboxylic acid diethyl ester (**44**)

To ethyl 2-cyclohexanone carboxylate (2.0g, 11.75 mmol) in 10 mL of THF is added dropwise to a suspension of NaH (0.34g, 14.1 mmol) in 100 mL of THF, followed by $Mg(ClO_4)$ (3.15g, 14.1 mmol). The mixture became very dense and was diluted with THF. After 20 minutes, $ClCO_2Et$ (1.4g, 13 mmol) is added slowly. The solution was boiled for 15 minutes and then cooled to room temperature. Aqueous sulfuric acid (1%) was added to the solution, followed by ether extraction. The organic layer was dried, concentrated and purified by distillation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, $J = 6$ Hz, 4H), 2.58 (t, $J = 6$ Hz, 1H) 2.26-2.21 (m, 1H), 1.89-1.84 (m, 4H), 1.70-1.64 (m, 2H), 1.27 (t, $J = 6$ Hz, 6H).

3-Methyl-2-oxo-cyclohexane-1,1-dicarboxylic acid diethyl ester (**45**)

To ketone **44** (1g, 4.13 mmol) dissolved in 20 mL of DMF at -30 °C, was added 1.0M LiHMDS (5.4mL, 5.4 mmol). The solution was stirred at -30 °C for 1 hour, after which, was added MeI (0.88g, 6.2 mmol) in 2 mL of DMF. After 2 hours at -30 °C, saturated aqueous ammonium chloride was added and the solution was warmed to room temperature. The mixture was diluted with water and extracted with ethyl acetate, washed with brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33-4.11 (m, 4H), 2.80-2.71 (m, 1H), 2.67-2.60 (m, 1H), 2.26 (dt, J = 15, 3 Hz, 1H), 2.09-2.02 (m, 1H), 1.86-1.80 (m, 1H), 1.65-1.35 (m, 2H), 1.31-1.22 (m, 6H), 1.10-1.05 (d, J = 15 Hz, 3H).

3-Acetyl-3-methyl-2-oxo-cyclohexane-1,1-dicarboxylic acid diethyl ester (**46**)

To ketone **45** (0.5g, 1.95 mmol) in 20 mL of THF was added 1.0 M LiHMDS (2.53 mL, 2.54 mmol) at -78 °C. After 1 hour at -78 °C, acetyl cyanide (0.18g, 2.54 mmol) in 1 mL of THF was added. After two hours, saturated aqueous ammonium chloride was added and the solution was warmed to room temperature. The mixture was diluted with water and extracted with ethyl acetate, washed with brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30-4.11 (m, 4H), 2.56-2.46 (m, 2H), 2.39-2.28 (m, 1H), 2.19 (s, 3H), 1.82-1.69 (m, 2H), 1.48-1.39 (m, 1H), 1.36 (s, 3H), 1.31-1.21 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 204.00, 202.07, 167.90, 167.78, 69.86, 64.37, 62.58, 62.52, 34.70, 32.42, 25.70, 23.73, 18.85, 14.18, 14.05; HRMS (EI) m/z calcd for 298.1416, found 298.1420.

3-Acetyl-2-oxo-cyclohexane-1,1-dicarboxylic acid diethyl ester (**47**)

To ketone **44** (0.5, 2 mmol) in 20 mL of THF was added 1.0 M LiHMDS (2.7mL, 2.6 mmol) at -78 °C. After 1 hour at -78 °C, acetyl cyanide (0.19g, 2.6 mmol) in 1 mL of THF was added. After two hours, saturated aqueous ammonium chloride was added and the solution was warmed to room temperature. The mixture was diluted with water and extracted with ethyl acetate, washed with brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (q, *J* = 6 Hz, 4H), 3.82 (t, *J* = 3 Hz, 2H) 2.37 (t, *J* = 3 Hz, 2H), 2.33-2.30 (m, 2H), 2.14 (s, 3H), 1.68-1.52 (m, 2H), 1.27 (t, *J* = 6 Hz, 3H).

3-Acetyl-3-allyl-2-oxo-cyclohexane-1,1-dicarboxylic acid diethyl ester (**48**)

To NaH (0.054g, 2.3 mmol) in 10 mL of DMF at 0 °C, was added dione **47** (0.5g, 1.76 mmol) in 1 mL of THF. After 15 minutes, allyl bromide (0.24g, 1.9 mmol) in 1 mL of THF was added slowly, and the solution was stirred overnight at room temperature. The mixture was added saturated aqueous ammonium chloride, and the solution was warmed to room temperature. The mixture was diluted with water and extracted with ethyl acetate, washed with brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51-5.39 (m, 1H), 5.11-5.06 (m, 2H), 4.31-4.09 (m, 4H), 2.85-2.78 (m, 1H), 2.54-2.45 (m, 3H), 2.31-2.21 (m, 1H), 2.19 (s, 3H), 1.79-1.69 (m, 2 H), 1.51-1.38 (m, 1H), 1.32-1.20 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.61, 201.12, 167.89, 167.76, 131.99, 119.73, 70.05, 67.72, 62.61, 62.51, 41.13, 31.91, 31.07, 25.82, 18.65, 14.18, 14.04; HRMS (EI) m/z calcd for 324.1573, found 324.1579.

2-Allyl-2-benzoyl-cyclohexanone (**58b**)

To 2-benzoyl cyclohexanone (10g, 50 mmol) and allyl bromide (12.8g, 75 mmol) in 400 mL of chloroform at room temperature, was added an aqueous solution of NaOH (4g, 100 mmol) and tetraethylammonium bromide (10.7g, 50 mmol). The mixture was stirred for 12 hours and extracted with chloroform, washed with water, dried, concentrated and purified by column chromatography to afford **58b** in 65% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 6 Hz, 2H), 7.55 (t, *J* = 6 Hz, 1H), 7.43 (t, *J* = 6 Hz, 2H), 5.66-5.52 (m, 1H), 5.02-4.90 (m, 2H), 2.92-2.82 (m, 2H), 2.69-2.61 (m, 1H), 2.46-2.41 (m, 1H), 2.21-2.01 (m, 2H), 1.91-1.65 (m, 3H), 1.49-1.35 (m, 1H).

5-Benzoyl-bicyclo[3.3.1]non-2-en-9-one (**59b**):

Allyl ketone **58b** (3g, 12.4 mmol) in 75 mL of degassed acetic acid at room temperature, was added $Mn(OAc)_3•2H_20$ (8.3g, 31 mmol) and $Cu(OAc)_2•H_20$ (2.7g, 13.6 mmol). The dark brown mixture was heated for 16 hours at 80 °C, the solution gradually turned dark green. After cooling to room temperature, the solution was diluted with water and extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried, concentrated and purified by column chromatography to afford **59b** in 60% yield. The exocyclic product (**60b**) was obtained in ~10% yield (multiplet at 4.99-5.14 ppm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 6Hz, 2H), 7.49 (t, *J* = 6 Hz, 1H), 7.41 (t, *J* = 6Hz, 2H), 6.05 (dt, *J* = 9, 3 Hz, 1H), 5.86-5.79 (m, 1H), 3.26 (bd, *J* = 18 Hz, 1H), 3.06 (m, 1H), 2.65 (m, 1H), 2.28-2.18 (m, 2H), 2.11-1.99 (m, 3H), 1.81-1.71 (m 1H).

5-Benzoyl-bicyclo[3.3.1]non-3-ene-2,9-dione (**61b**)

To olefin **59b** (0.55g, 2.3 mmol) in 50 mL of benzene, was added Celite (3.45g), PDC (3.45g, 9.16 mmol) and then 78% *t*-BuOOH (1.06g, 9.16 mmol) at room temperature. After four hours the mixture was filtered through Celite, concentrated in vacuo and purified by column chromatography to afford **61b** in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 6 Hz, 2H), 7.55 (t, *J* = 6 Hz, 1H), 7.40 (t, *J* = 6 Hz, 2H), 7.02 (d, *J* = 9 Hz, 1H), 6.65 (d, *J* = 9 Hz, 1H), 3.54 (t, *J* = 3 Hz, 1H), 2.64 (dt, *J* = 12, 6 Hz, 1H), 2.31-2.26 (m, 1H), 2.16-2.06 (m, 2H), 1.92-1.65 (m, 2H).

4-Bromo-9-oxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (**67**)

To a solution of olefin **59a** (0.6g, 2.9 mmol) in 25 mL of CCl_4, was added AIBN (0.05g, 0.29 mmol) and NBS (0.57g, 3.2 mmol). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 30 minutes (monitored by TLC), the mixture was allowed to cool to room temperature and filtered. The crude material was purified by column chromatography to yield **67** in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 9, 6 Hz, 1H), 5.79 (d, *J* = 9 Hz, 1H), 4.98 (d, *J* = 3 Hz, 1H), 4.28 (q, *J* = 6 Hz, 2H), 3.13 (bs, 1H), 2.32 (dt, *J* = 12, 3 Hz, 1H), 2.21-2.09 (m, 1H), 2.01-1.61 (m, 4H), 1.33 (t, *J* = 6 Hz, 3H).

2,4-Dibromo-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid ethyl ester (**71**)

To a solution of olefin **59a** (0.6g, 2.9 mmol) in 30 mL of CCl_4, was added AIBN (0.05g, 0.29 mmol) and NBS (1.13g, 6.4 mmol). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 30 minutes (monitored by TLC), the mixture was allowed to cool to room temperature and filtered. The crude material was purified by column chromatography to yield **71** in 82% yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.72 (1H, dd, *J* = 12.0, 3.0 Hz), 5.67 (1H, d, *J* = 12.0 Hz), 3.74 (3H, s), 3.48-3.51 (1H, m) , 2.42-2.50 (1H, m), 2.08 (1H, tt, *J* = 12.0, 3.0 Hz), 1.85 (1H, dt, *J* = 12.0, 3.0 Hz), 1.31 (3H, s), 1.10-1.20 (1H, m), 1.05 (3H, s); ^{13}C NMR (300 MHz, CDCl$_3$) δ 201.5, 168.5, 137.1, 124.6, 65.5, 63.5, 63.1, 52.7, 44.4, 34.2, 30.9, 25.9, 22.9.

2,4,4-Tribromo-9-oxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (**74**) and 2-Bromo-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (**75**)

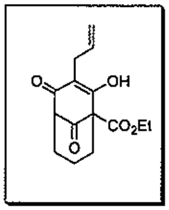
To a solution of olefin **71** (0.24g, 0.66 mmol) in 20 mL of CCl$_4$, was added AIBN (0.011g, 0.066 mmol) and NBS (0.15g, 0.825 mmol). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 30 minutes (monitored by TLC), the mixture was allowed to cool to room temperature and filtered. A 1:1 mixture of **74** and **75** were obtained. The crude residue was diluted with water and added aqueous acetic acid and refluxed. Then 50 % aqueous AcOH was added and the mixture was boiled for 2 hours. After aqueous workup, enone **75** was purified by column chromatography in 95% isolated yield. The conversion of olefin **59a** to compound **75** in one step required 3.5 eq. of NBS and 0.3 eq. of AIBN. (**74**): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.18 (1H, s), 4.24-4.35 (2H, m), 3.56-3.58 (m, 1H), 2.56-2.63 (m, 1H), 1.60-2.31 (m, 5H), 1.30 (t, *J* = 9.0 Hz, 3H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 200.1, 167.7, 139.3, 120.4, 66.4, 63.7, 62.5, 58.9, 36.9, 34.8, 17.2, 14.2. (**75**): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.02 (s, 1H), 4.32 (q, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 3.0 Hz, 1H), 2.36-1.61 (m, 6H), 1.35 (t, *J* = 9.0 Hz, 3H); ^{13}C

NMR (300 MHz, $CDCl_3$) δ 201.5, 193.5, 167.3, 146.3, 137.1, 68.6, 62.7, 61.8, 33.7, 32.9, 17.8, 14.2.

2-Allyloxy-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (**79**)

To 10 mL of allyl alcohol at 0 °C, was added freshly cut sodium metal (0.005g, 0.2 mmol). Enone **75** (0.05g, 0.167 mmol) in 1 mL of allyl alcohol was added and the mixture was allowed to stir for 1 hour. The solution was diluted with saturated aqueous ammonium chloride, extracted with ethyl acetate, dried, concentrated and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 5.98-5.85 (m, 1H), 5.90 (s, 1H), 5.40-5.33 (m, 2H), 4.54-4.48 (m, 2H), 4.35-4.23 (m, 2H), 3.32 (t, *J* = 3 Hz, 1H), 2.31-2.18 (m, 3H), 2.02-1.91 (m, 1H), 1.85-1.63 (m, 2H), 1.28 (t, *J* = 6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.63, 194.18, 171.78, 167.70, 130.38, 119.63, 107.86, 70.83, 65.07, 62.05, 61.43, 33.40, 33.27, 18.37, 14.29.

3-Allyl-2-hydroxy-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid ethyl ester (**80**)



Allyl enol ether **79** (0.015g, 0.054 mmol) was dissolved in 1 mL of dry toluene and placed in a sealed tube, where it was heated at 140 °C for 7 hours. After cooling to room temperature, the compound was concentrated and purified by preparative TLC (product very polar: R_f = 0.1 with [1:1] hexanes: ethyl acetate). The crude yield was >80%. However, the isolated yield was 45%. FTIR (film) 1733, 1710, 1678, 1572 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98-5.90 (m, 1H), 5.35-5.21 (m, 2H), 4.18 (q, J = 9.0 Hz, 2H), 3.53 (t, J = 4.5 Hz, 1H), 3.33 (d, J = 6 Hz, 2H), 2.51-2.31 (m, 2H), 2.14-1.95 (m, 2H) 1.79-1.73 (m, 2H) 1.27 (t, J = 4.5 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.7, 164.9, 164.5, 154.0, 135.4, 118.01, 110.9, 101.0, 61.8, 43.8, 28.5, 26.5, 20.7, 19.2, 14.4; HRMS (EI) m/z calcd for 278.1154, found 278.1161.

7-Methyl-3-oxo-oct-6-enoic acid methyl ester (**81**)

To sodium hydride (3.5g, 87.12 mmol) in 100 mL of THF, was added dimethyl carbonate (7.15g, 79.2 mmol) at room temperature. 6-methyl-5-hepten-2-one (5g, 39.6 mmol) in 15 mL of THF was added dropwise at intervals. The mixture was refluxed for 2 hours and stirred at room temperature for 12 hours. The excess NaH was quenched with methanol, and the mixture was acidified with 10% aqueous HCl, extracted with ether, washed with saturated aqueous $NaHCO_3$, brine, dried, and concentrated. Vacuum distillation afforded **81** in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (m, 1H), 3.73 (s, 3H), 3.44 (s, 2H), 2.55 (t, J = 9 Hz, 2H), 2.27 (q, J = 6 Hz, 2H), 1.67 (s, 3H), 1.61 (s, 3H).

2,2-Dimethyl-6-oxo-cyclohexanecarboxylic acid ethyl ester (**82**)

To compound **81** (3g, 16.3 mmol) in 100 mL of CH_2Cl_2 at 0 °C, was slowly added $SnCl_4$ (6.4g, 24.5 mmol). After 12 hours at room temperature, the mixture was diluted with ether, washed twice with 5% HCl, once with water, dried, concentrated and purified by column chromatography or distillation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (m, 3H), 3.19 (s, 1H), 2.70-2.61 (m, 1H), 2.34-2.25 (m, 1H), 1.98-1.72 (m, 2H), 1.60-1.45 (m, 2H), 1.10 (s, 3H), 1.02 (s, 3H).

2-Allyloxy-6,6-dimethyl-cyclohex-1-enecarboxylic acid ethyl ester (**83**)

To compound **82** (2g, 10.87 mmol) in 10 mL of THF was added to a suspension of NaH (0.39g, 16.3 mmol) in 100 mL of THF at room temperature. After 1 hour, allyl bromide (1.98g, 16.3 mmol) in 5 mL of THF was added to the mixture and heated at 60 °C for 18 hours. The reaction was quenched slowly with water and diluted with saturated aqueous ammonium chloride, extracted with ether, washed with brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91–5.82 (m, 1H), 5.33-5.14 (m, 2H), 4.26 (dt, *J* = 6 Hz, 3 Hz, 2H), 3.73 (s, 3H), 2.18 (t, *J* = 6 Hz, 2H), 1.78-1.70 (m, 2H), 1.49-1.41 (m, 2H), 1.12 (s, 6H).

1-Allyl-2,2-dimethyl-6-oxo-cyclohexanecarboxylic acid ethyl ester (**84**)

Enol **83** (2g, 8.4 mmol) was dissolved in 5 mL of dry toluene and heated at 140 °C in a sealed tube for 3 hours. After concentration, the residue was purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88-5.71 (m, 1H), 5.04-4.94 (m, 2H), 3.65 (s, 3H), 2.91-2.79 (m, 1H), 2.71-2.60 (m, 1H), 2.41-2.31 (m, 2H), 1.90-1.81 (m, 3H), 1.53-1.45 (m, 1H), 1.28 (s, 3H), 1.38 (s, 3H).

8,8-Dimethyl-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (**85**)

To allyl ketone **84** (2g, 8.4 mmol) in 75 mL of degassed acetic acid at room temperature, was added $Mn(OAc)_3{\bullet}2H_20$ (5g, 18.5 mmol) and $Cu(OAc)_2{\bullet}H_20$ (1.85g, 9.3

mmol). The dark brown mixture was heated for 16 hours at 80 °C, the solution gradually turned green. After cooling to room temperature, the solution was diluted with water and extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried, concentrated and purified by column chromatography to afford **85** in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82-5.78 (1H, m), 5.57-5.51 (1H, m), 3.65 (3H, s), 3.07-2.81 (3H, m), 2.06-1.97 (2H, m), 1.57-1.53 (1H, m), 1.19-1.10 (1H, m), 1.07 (3H, s), 1.03 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 209.8, 171.2, 129.5, 127.0, 64.8, 51.9, 46.7, 42.8, 36.2, 33.4, 28.5, 25.6, 25.0.

2,4-Dibromo-8,8-dimethyl-9-oxo-bicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (**86**)

To a solution of olefin **85** (0.5g, 2.25 mmol) in 20 mL of CCl_4, was added AIBN (0.038g, 0.23 mmol) and NBS (0.88g, 4.95 mmol). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 30 minutes (monitored by TLC), the mixture was allowed to cool to room temperature and filtered. The crude material was purified by column chromatography to yield **86** in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (dd, J = 12.0, 3.0 Hz, 1H), 5.67 (d, J = 12.0 Hz, 1H), 3.74 (s, 3H), 3.48-3.51 (m, 1H) , 2.42-2.50 (m, 1H), 2.08 (tt, J = 12.0, 3.0 Hz, 1H), 1.85 (dt, J = 12.0, 3.0 Hz, 1H), 1.31 (s, 3H), 1.10-1.20 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.5, 168.5, 137.1, 124.6, 65.5, 63.5, 63.1, 52.7, 44.4, 34.2, 30.9, 25.9, 22.9.

8,8-Dimethyl-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid methyl ester (**87**)

To a solution of olefin **86** (0.05g, 0.13 mmol) in 3 mL of CCl_4, was added AIBN (0.002g, 0.013 mmol) and NBS (0.026g, 0.145 mmol). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 30 minutes (monitored by TLC), the mixture was allowed to cool to room temperature and filtered. The crude material was purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 12.0 Hz, 1H) 6.52 (dd, J = 9.0 Hz, 1H), 3.78 (s, 3H), 3.37 (t, J = 3.0 Hz, 1H), 2.16-2.27 (m, 1H), 1.95-2.02 (m, 1H), 1.81 (dt, J = 12.0, 3.0 Hz, 1H), 1.37 (s, 3H), 1.27-1.34 (m, 1H), 1.11 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.2, 197.4, 168.3, 148.2, 131.9, 68.4, 62.3, 52.8, 42.2, 34.7, 27.8, 26.4, 22.9.

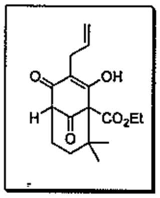
2-Bromo-8,8-dimethyl-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid methyl ester (**88**)

To a solution of olefin **85** (0.611g, 2.75 mmol) in 3 mL of CCl_4 and crushed molecular sieves, was added AIBN (0.14g, 0.83 mmol) and dry NBS (1.73g, 9.6 mmol). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 1 hour (monitored by TLC), the mixture was allowed to cool to room temperature and filtered. The crude material was purified by column chromatography to yield directly **88** in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 3.79 (s, 3H), 3.36-3.38 (m, 1H), 2.47-2.49 (m, 1H), 2.15-2.23 (m, 1H), 1.98-2.03 (m, 1H), 1.48 (s, 3H), 1.36-1.45 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.8, 193.5, 166.7, 146.1, 137.5, 74.0, 60.6, 52.5, 42.7, 34.7, 28.4, 26.7, 22.2.

2-Allyloxy-8,8-dimethyl-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid methyl ester (**89**)

To 5 mL of allyl alcohol at 0 °C, was added freshly cut sodium metal (0.004g, 0.15 mmol). Enone **88** (0.04g, 0.127 mmol) in 0.5 mL of allyl alcohol was added and the mixture was allowed to stir for 1 hour. The solution was diluted with saturated aqueous ammonium chloride, extracted with ethyl acetate, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95-5.86 (m, 1H), 5.87 (s, 1H), 5.40-5.31 (m, 2H), 4.61-4.42 (m, 2H), 3.71 (s, 3H) 3.29-3.27 (m, 1H), 2.17-1.73 (m, 3H), 1.38-1.28 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 207.60, 194.19, 172.83, 167.08, 130.43, 119.43, 107.98, 71.84, 70.71, 60.69, 52.37, 42.39, 35.60, 28.30, 26.60, 21.83.

3-Allyl-2-hydroxy-8,8-dimethyl-4,9-dioxo-bicyclo[3.3.1]non-2-ene-1-carboxylic acid methyl ester (**90**)



Allyl enol ether **89** (0.03g, 0.10 mmol) was dissolved in 2 mL of dry toluene and placed in a sealed tube, where it was heated at 140 °C for 7 hours. After cooling to room temperature, the compound was concentrated and purified by preparative TLC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94-5.89 (m, 1H), 5.37-5.27 (m, 2H), 3.67 (s, 3H), 3.35-3.33 (m, 1H), 3.31-3.28 (m, 2H), 2.20-2.16 (m, 1H), 2.01-1.94 (m, 1H), 1.72-1.64 (m, 1H), 1.39-

1.30 (m, 1H), 1.25 (s, 3H), 1.19 (s, 3H); FT-IR (film) 1737, 1701, 1650, 1572 cm^{-1}; HRMS (EI) m/z calcd for 292.1311, found 292.1316.

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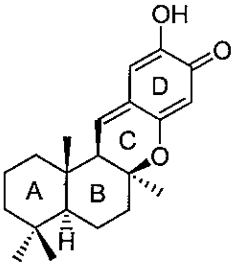
CHAPTER II

Synthesis of the BCD rings of Puupehenone

Introduction

The ability of pathogens to genetically mutate allows for variations in their mechanisms of action and/or resistance to known treatments. The resulting effect is a continuous need for new and different biologically active compounds. With their unique and broad biodiversity, the oceans have produced unusual metabolites that possess varied and distinctive biological activities. One of these metabolites is the sesquiterpene puupehenone.



Puupehenone

The tetracyclic structure of this marine natural product contains a highly reactive quinone methide functionality, which engenders the formation of numerous related analogs. The synthesis of the BCD rings of puupehenone will be discussed in this chapter.

Background

Puupehenone (**1**) was first isolated[1] by Scheuer and co-workers from the sponge *Chondrosia chucalla* off the coast of Hâwaii. This naturally occurring quinone methide has since been found in many sponge specimens, such as *Heteronema*, *Hyrtios*, and *Strongylophora*[2] in tropical waters around the world. There are many puupehenone-derived metabolites (Figure 1) as a consequence of the reactive quinone methide moiety of the natural product. 15-Cyanopuupehenone[3] (**2**), 20-methoxy-puupehenone[4] (**3**), puupehedione[5] (**4**), hyrtenone[10] (**5**), dimer dipuupehedione[6] (**6**) and others also have been isolated. All of these compounds display a wide range of biological activities such as, antitumor,[7] antiviral,[8] antituberculosis[9] and lipoxygenase[10] inhibition.

Recently, extensive evaluations of biological activity have been focused on marine natural products, such as puupehenone. In 2000, Hamann and co-workers[9] reported the effective inhibition of *Mycobacterium tuberculosis* growth with puupehenone and its derivatives. Tuberculosis has emerged as a global emergency with estimates of two billion[11] people world-wide being infected. Immunodepression diseases, such as AIDs, increase[12] the incidence of tuberculosis by enabling latent infections to clinically progress. The increase of tuberculosis has resulted in the identification of drug-resistant strains[13] of *M. tuberculosis*. Resistance to the current antituberculosis therapy is a growing problem. Even with intensive treatment, multi-drug-resistant strains of *M. tuberculosis* are 50-80% fatal.

Puupehenone induced 99% inhibition of the causative pathogen *M. tuberculosis's* growth and shows an MIC of 12.5 μg/mL and IC_{50} value of 2.0 μg/mL. The high percentage of inhibition is only matched by heteronemin, a sclarin-type sesterterpene, and is higher than other natural products, such as, massetolide, viscosin, litosterol, kahalalide and pseudoteroxazole. 15-Cyanopuupehenone (**2**) has a growth inhibitory percentage of 90%, whereas the puupehenone derivatives without the quinone methide moiety (**4**, **6**) exhibit little if any inhibition at all.

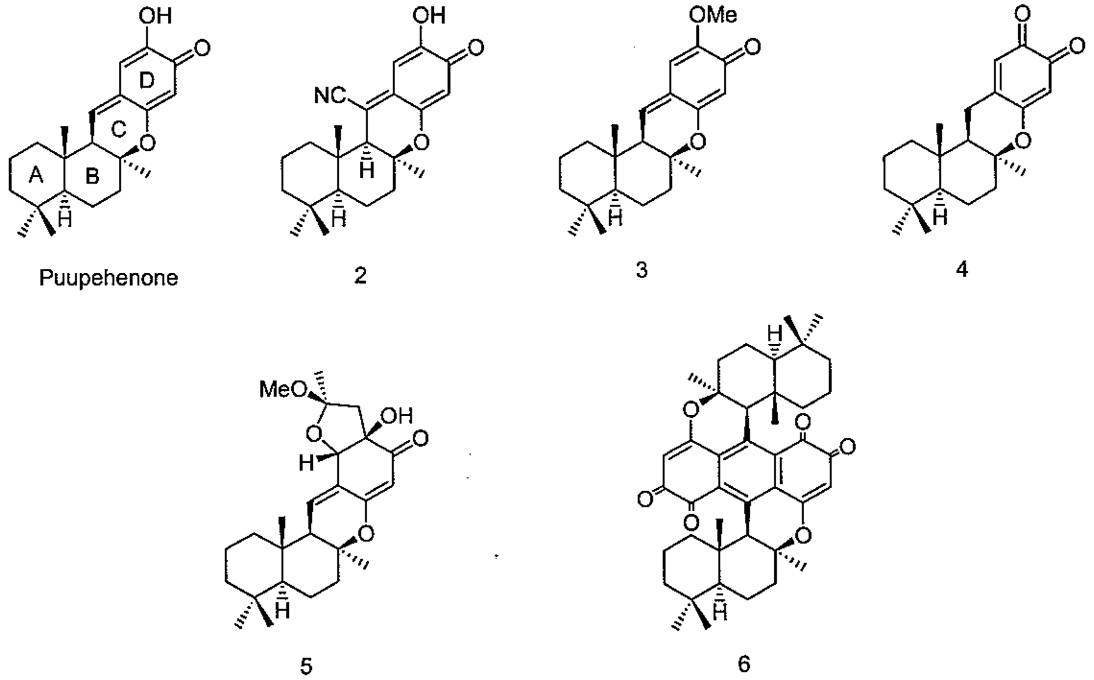


Figure 1. Puupehenone and its derivatives

The authors of the study concluded the necessity of the quinone methide functionality for *M. tuberculosis* inhibition. The emergence of puupehenones as a good candidate for antituberculosis activity has renewed interest in the natural product and other related shikimate sesquiterpenes.

Recently, puupehenone and other sponge derived terpenoids were reported[10] to inhibit various lipoxygenases. The lipoxygenases (LO) are a class of iron-containing enzymes widely occurring in plants and animals that are implicated in the biosynthesis of inflammatory regulators[14] which promote human diseases such as, allergy, arthritis, asthma and cancer cell proliferation.[15] Only a few natural products have been investigated as LO inhibitors. Boswelic acid derivatives from frankincense, hinokitiol, hexamethoxyflavone from orange peel, resveratrol from grapes, and nordihydroguaiaretic acid (NGDA) from the creosote bush are known plant derived LO inhibitors. Very few microorganism derived inhibitors are known. LO inhibitors can be classified into two distinct groups. The first group of compounds acts as redox agents that reduce the iron site. Redox agents reduce ferric lipoxygenase to the inactive ferrous form. Puupehenone acts as a redox inhibitor by the interconversion of the quinone methide (**1**) and *ortho*-quinone (7) moieties (Figure 2).

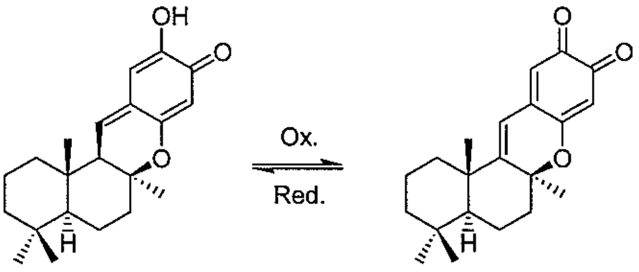


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Figure 2. Redox relationship between puupehenone and puupehedione

The other groups are competitive or allosteric inhibitors binding to the active site of the enzyme. Hyrtenone (**5**), which was isolated during the course of the study, is a non-redox inhibitor of lipoxygenase. The activity of hyrtenone and puupehenone indicates that the quinone methide moiety is not completely necessary for this specific biological activity. This conclusion allows for different analogs of the marine natural product to be targeted.

Another study reported in 1999 further illustrates the point that the tetracyclic structure of puupehenone can be varied and not sacrifice biological activity. In fact, the biological activity can increase by a remarkable magnitude. Barrero and co-workers[16] synthesized monoterpenic analogs (Figure 3) of puupehenone and conducted biological studies in comparison with sesquiterpene derivatives.

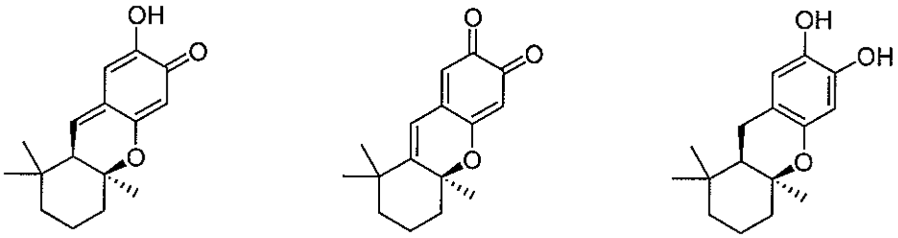

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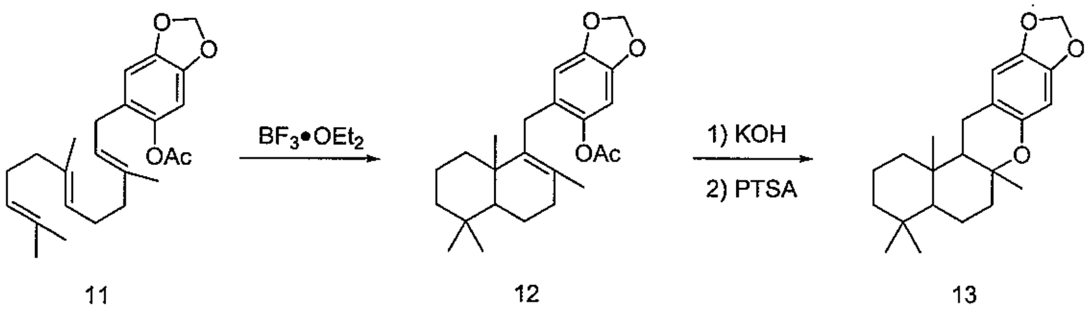
Figure 3. Monoterpenic analogs

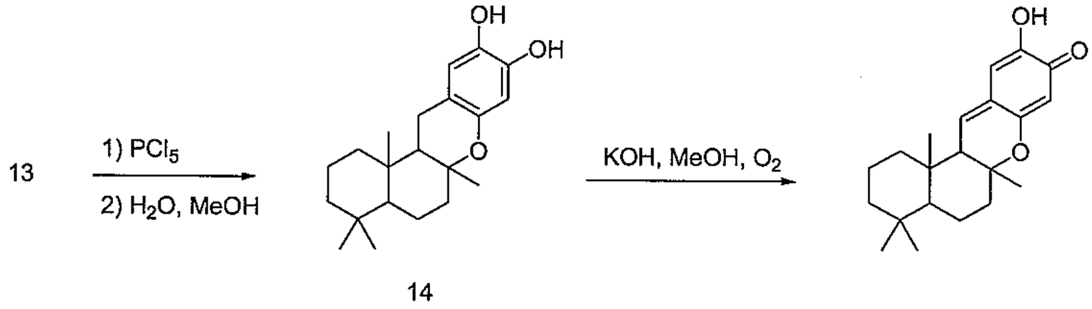
The antitumor activity of the monoterpenic compounds **9** and **10** were assayed against cell lines P-388, A-549, HT-29 and MEL-28. Compound **9** showed an increase in activity by a magnitude of four as compared to its tetracyclic derivative. Analog **10** had similar activities as its tetracyclic derivative. The study supports the notion that the structural constituent responsible for biological activities of these marine natural products is the quinone methide moiety and its related functionalities. These preliminary studies provide strong support for the beneficial efforts towards understanding marine sesquiterpenes and the structural implications for biological activities.

Although puupehenone's structure was first determined in 1979, it has received little synthetic attention. There have been three reports describing the syntheses of puupehenone. Trammel first synthesized[17] the natural product utilizing a biosynthetic cationic cyclization (Scheme 1). Triene **11** was obtained from the alkylation of the lithium salt of sesamol with farnesyl bromide, followed by acetylation with acetic anhydride. Treatment of compound **11** with a Lewis acid effected the construction of the drimane unit. To assemble the benzopyran unit, compound **12** was hydrolyzed with methanolic potassium hydroxide to expose the phenol which upon addition of *para*-toluene sulfonic acid produced the compound **13**.



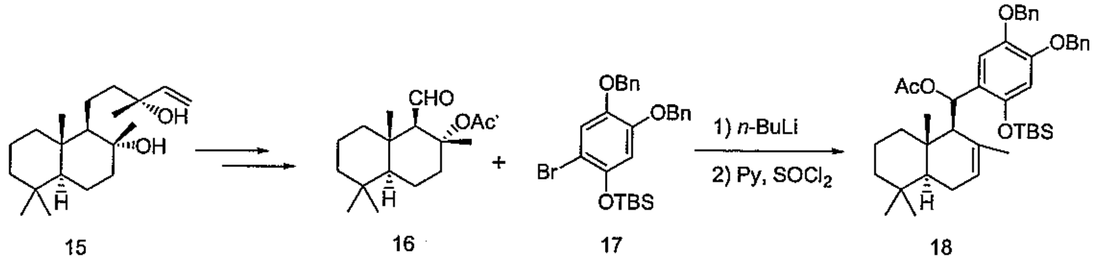
Scheme 1

A mixture (2.4:1) of cis- and trans-fused isomers was obtained with the cis-ring juncture being the major isomer. Deprotection (Scheme 2) of the *ortho*-hydroxy groups of compound **13** produced catechol **14**. Subsequent aerobic oxidation in the presence of KOH produced puupehenone.



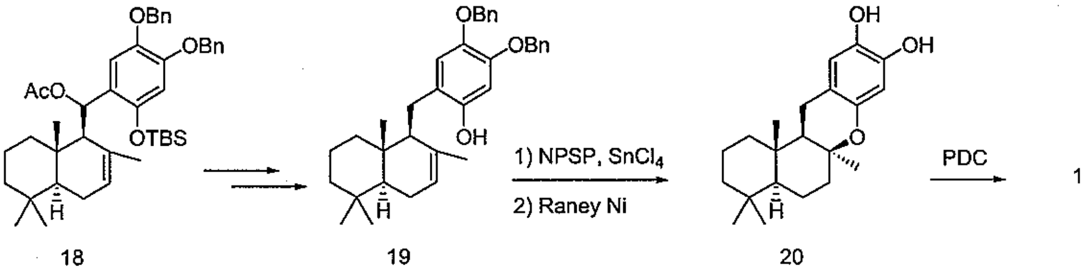
Scheme 2

In 1997, Barrero reported the enantiospecific synthesis[18] of (+)-puupehenone. Aldehyde **16** was previously made from the same authors from (-)-sclareol (Scheme 3). The addition of the lithium salt of aryl bromide **17**, which was made in five steps from 3,4-dihydroxybenzaldehyde, followed by dehydration, produced the complete skeleton (**18**) of puupehenone.



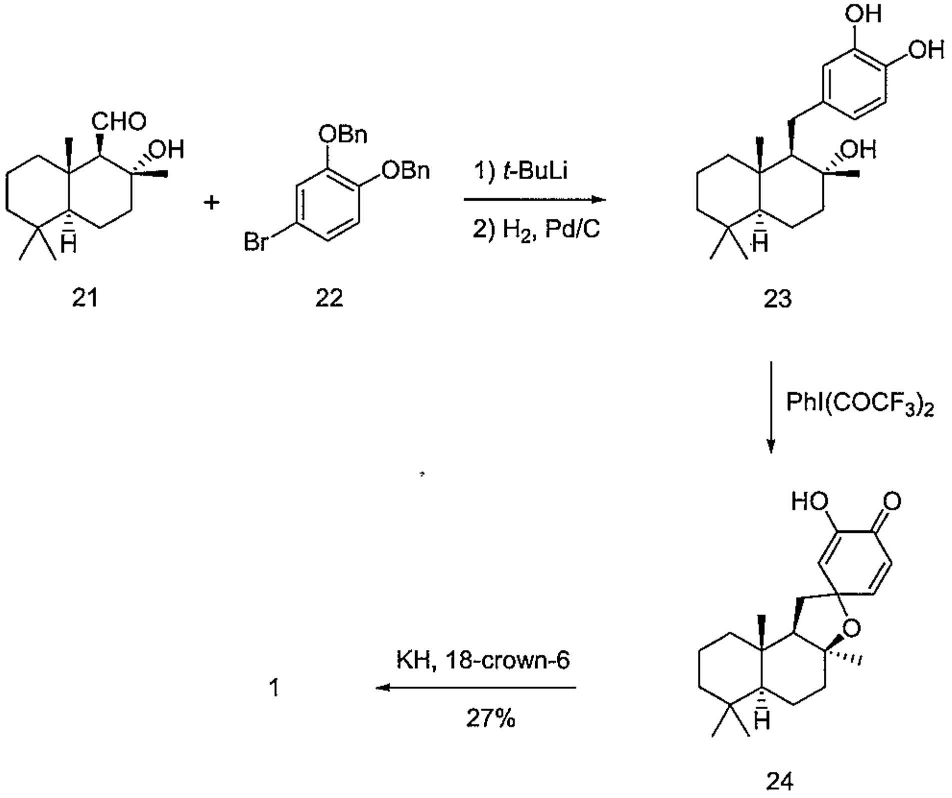
Scheme 3

Compound **18** was then treated with *tert*-butylammonium fluoride to cleave the TBS group and simultaneously eliminated the acetoxy group to produce an *ortho*-quinone methide intermediate, which was then reduced by sodium borohydride to the phenolic compound **19** (Scheme 4). Cyclization was facilitated by *N*-(phenylseleno)phthalimide and tin tetrachloride. Hydrogenation over Raney Ni afforded compound **20**, which underwent oxidation with pyridinium dichlorochromate to yield (+)-puupehenone.



Scheme 4

These two previous syntheses constructed the benzopyran moiety with a phenolic oxygen with the corresponding olefin. A third synthesis[19] reported recently, constructs the ring by an oxidative cyclization strategy. Also starting with drimanic aldehyde **21**, again made from (-)-sclareol, the addition of the lithium salt of compound **22**, followed by hydrogenation, yielded intermediate **23** (Scheme 5). The key aspect of this synthetic strategy was the oxidative cyclization promoted by hypervalent iodide. Catechol **23** was treated with [bis(triflouroacetoxy)iodo]benzene and spirocycle **24** was obtained in 64% yield. The 5-exo-trig spiroannulation mechanism was favored over the desired benzopyran construction. Spirocycle **24** then undergoes rearrangement to the benzopyran intermediate when heated in dioxane, potassium hydride and 18-crown-6. However, the benzopyran compound was not obtained, instead *in situ* oxidation provided (+)-puupehenone directly, albeit in only 27% yield.

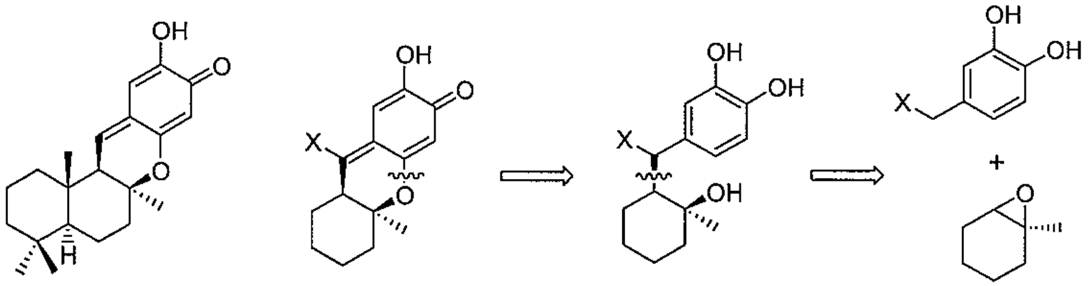


Scheme 5

Although the latter two total syntheses of puupehenone introduce interesting and novel chemical transformations, the numerous steps to the drimane aldehyde and low yields for the key cyclizations indicate a need for more direct and concise syntheses.

Results and Discussion

With Barrero's disclosure of the increased biological activity of the monoterpenic analogs of puupehenone, synthetic efforts were focused on the construction of tricyclic compound **2**. The retrosynthetic analysis (Figure 4) shows the possible disconnection of the carbon-oxygen bond in compound **2** by an oxidative cyclization reaction. The carbon-carbon bond in intermediate **3** could be generated from a nucleophilic epoxide ring-opening.

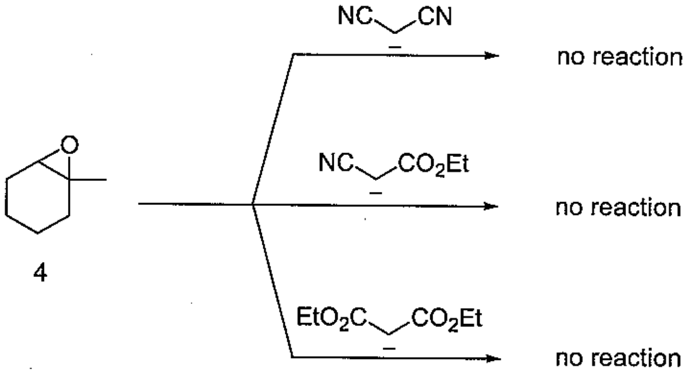


Puupehenone (1) 2 3

Figure 4. Retrosynthetic Analysis

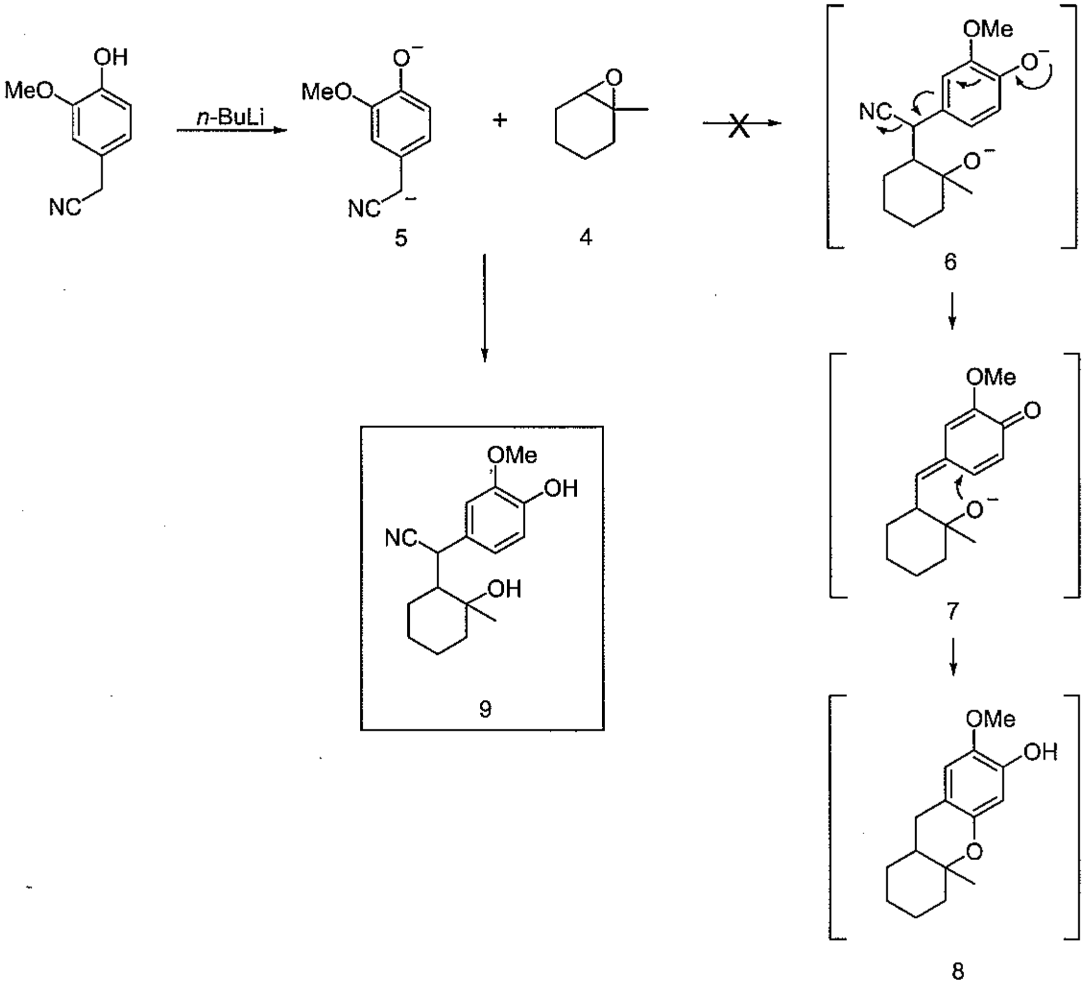
The presence of an additional functional group (X) would serve two purposes. First, the nucleophilic ring-opening of epoxides with carbon nucleophiles is quite limited in the literature.[20] A group that would enhance the selectivity of the benzylic nucleophile would be selected to aid in the reaction. Another purpose of the group would be to allow the introduction of additional functionalities, bearing in mind the class of natural products containing various derivatives at the benzylic position.

The synthesis began with the ring opening of epoxide **4** with various nucleophiles (Scheme 6). Lithiated acetonitriles[21] have been reported to be excellent nucleophiles for such transformations. The reaction of epoxide **4** and various malonyl derived anions yielded only starting materials under various conditions.



Scheme 6

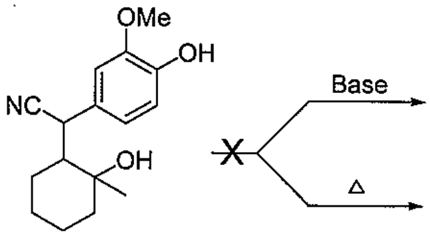
With the disappointing results of these reactions, phenylacetonitrile was next investigated. Commercially available 4-hydroxy-3-methoxyphenylacetonitrile (Scheme 7) was treated with two equivalents of base to generate dianion **5**, which upon addition of epoxide **4** produced a ring-opening product. It was envisioned that the intermediate **6** formed after the ring-opening could potentially eliminate the cyano group to generate a quinone methide intermediate **7**, which would set the stage for the subsequent cyclization to form benzopyran **8**.



Scheme 7

However, the oxidative cyclization product **8** was not produced; the reaction afforded only compound **9** in 70% yields. With construction of the bicyclic intermediate **9**, the aryl-oxygen bond connection was investigated.

Initial attempts to afford the benzopyran compound involved base catalyzed cyclization. However, with various bases (Et_3N, *t*-BuOK, $NaHCO_3$) the cyclization did not occur (Scheme 8). Cyclization was also unsuccessful when compound **9** was heated at various temperatures.



9

Scheme 8

One of the previously reported syntheses of the natural product puupehenone utilized hypervalent iodide (Figure 5) as the oxidation reagent for the cyclization. The oxidation produced an unexpected spiroannulated product.

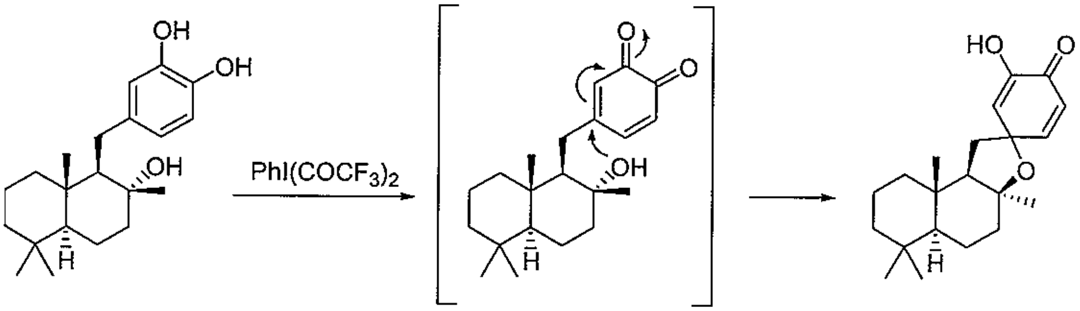
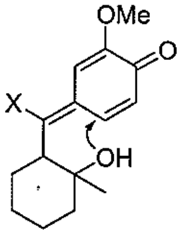


Figure 5. Oxidation Cyclization via Hypervalent Iodide

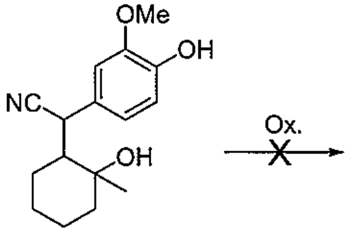
Cyclization would occur via a conjugate addition onto an *ortho*-quinone intermediate. The oxidative cyclization regiochemistry of catechol derivative **23** was exclusively 5-exo-trig spiroannulation. In order to avoid the spiroannulated product, a quinone methide oxidative intermediate **10** would be desired.



10

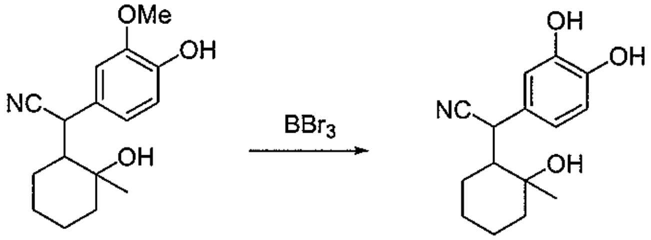
The quinone methide intermediate could allow for the possibility of cyclization forming only benzopyran products and not spiroannulated products. The presence of the cyano group would increase the possibility of the desired quinone methide formation over the *ortho*-quinone tautomer due to the increase in acidity of the benzylic proton.

The oxidation of compound **9** was investigated with these factors in mind. Under different oxidative conditions ($AgNO_3$, AgO, Ag_2O, DDQ), only starting materials were recovered (Scheme 9).


9'

Scheme 9

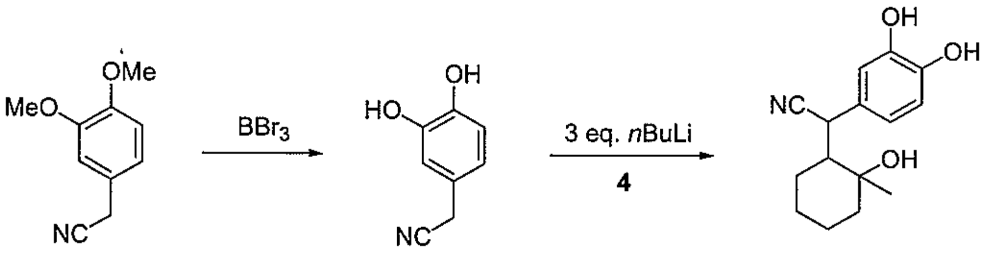
With the unsuccessful attempts at oxidation of compound **9**, the demethylated derivative was synthesized in order to affect the desired oxidation. Using BBr_3, demethylation occurred to afford catechol **10** in poor yield (35%) with the majority of the starting material decomposing (Scheme 10).


9

11

Scheme 10

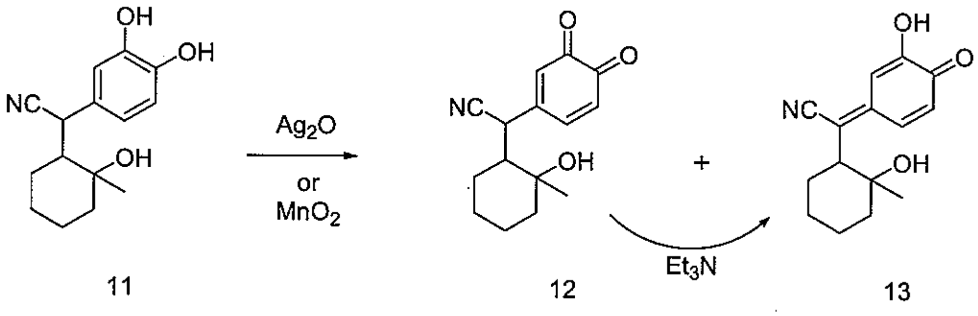
The poor yield of the demethylation of compound **9** required an alternative route to produce **11**. Since decomposition of compound **9** was the key factor determining the yield of catechol **11**, demethylation should be performed before the epoxide ring-opening step. Treatment of 3,4-dimethoxy phenylacetonitrile with BBr_3 (Scheme 11) afforded the demethylated product in a 75% yield. The trianion of 3,4-dihydroxyphenylacetonitrile was generated with three equivalents of *n*-butyl lithium. The ring-opening of epoxide **4** with the trianion produced compound **11** in a 65% yield.



11

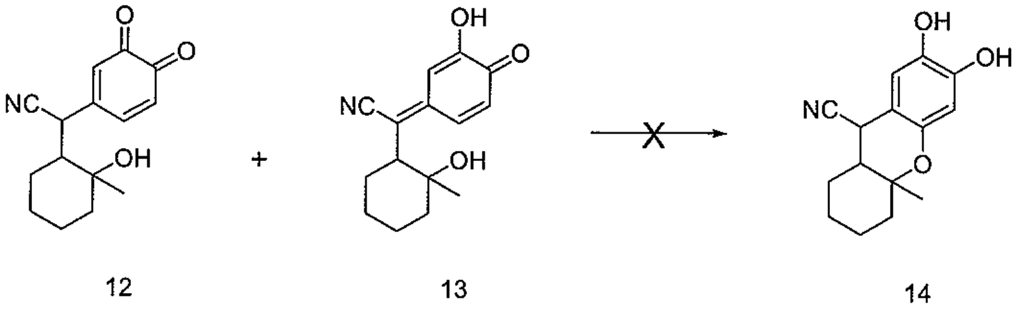
Scheme 11

With catechol **11** in hand, treatment with silver(I) oxide or manganese dioxide produced a mixture of unstable oxidative products (Scheme 12). By ^1H NMR spectroscopy, the structures were determined to be *ortho*-quinone **12** and quinone methide **13** tautomers in equal amounts. The *ortho*-quinone tautomer could be tautomerized to the quinone methide, by the addition of triethyl amine at room temperature. Unfortunately, the mixture could not be separated or purified due to decomposition on silica gel.



Scheme 12

The crude materials were subjected to cyclization conditions (Scheme 13). Acid catalyzed conditions, such as BF_3•OEt_2, $ZnBr_2$, and PTSA, eliminated the tertiary alcohol to form a tetrasubstituted olefin. Base catalyzed conditions (*t*-BuOK, NaOMe, NaH) either afforded only starting materials or in the case of *t*-BuOK, also gave an elimination product.



Scheme 13

The propensity of the tertiary alcohol to eliminate and form the extended conjugated product prevented the cyclization of intermediates **12** and **13**. Using the lability of the alcohol, the cyclization could occur with the oxygen from the shikimate unit, instead of from the drimane (Figure 5). Acid catalyzed cyclization of compound **16** could allow for the formation of the carbon-oxygen bond.

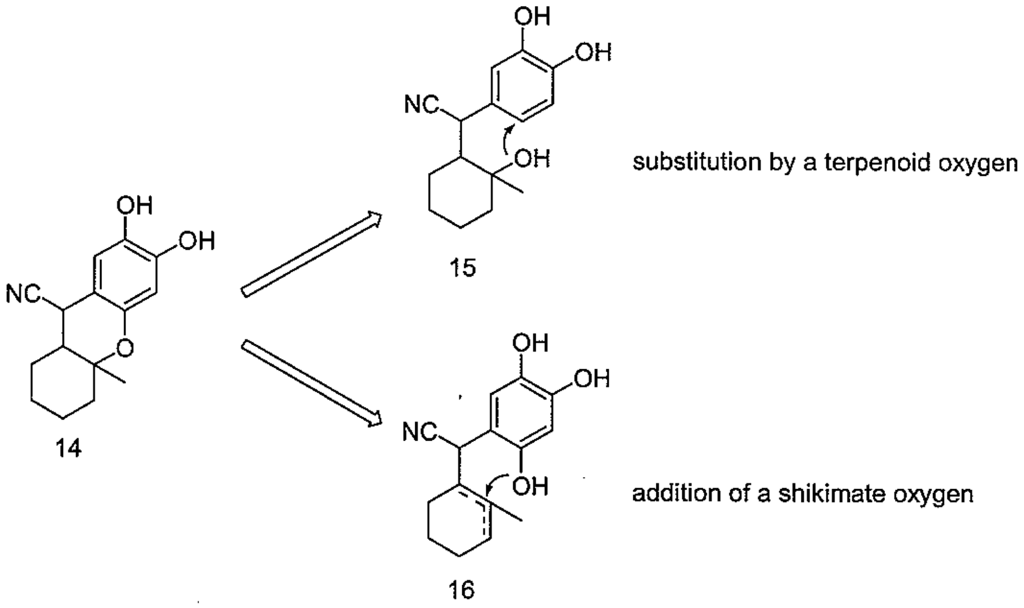
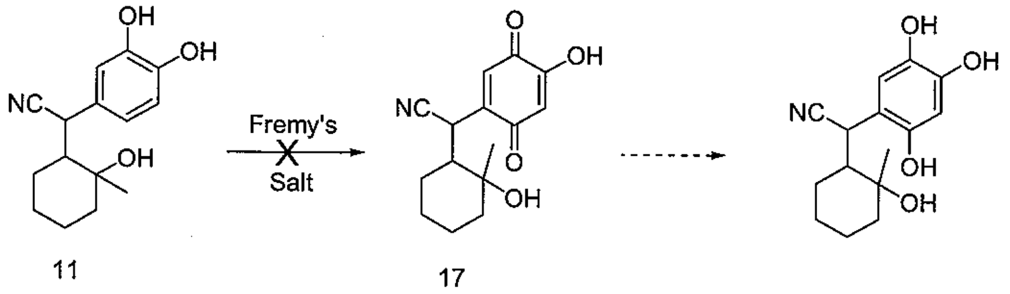


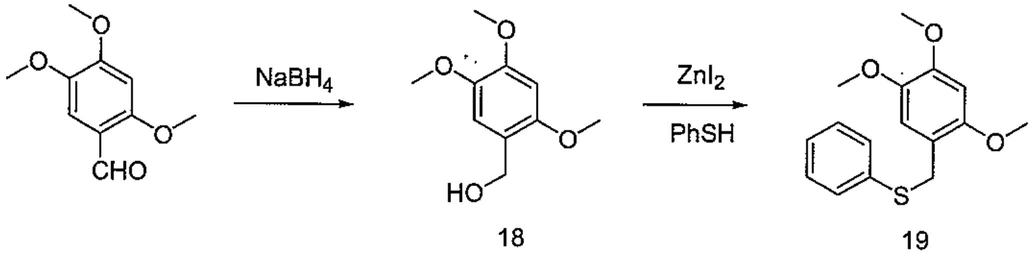
Figure 5

Compound **16** might be made by the oxidation of catechol **11** with Fremy's salt [$(KSO_3)_2NO$]. However, the desired oxidative product was not obtained. The reaction with Fremy's salt produced inconsistent results under various conditions (Scheme 14). In THF at 0 °C, the reaction afforded only starting materials; however, in acetic acid and water, elimination of the tertiary alcohol was observed with no further oxidation. The use of potassium dihydrogenphosphate as a buffer in conjunction with Fremy's salt gave decomposition of starting materials.



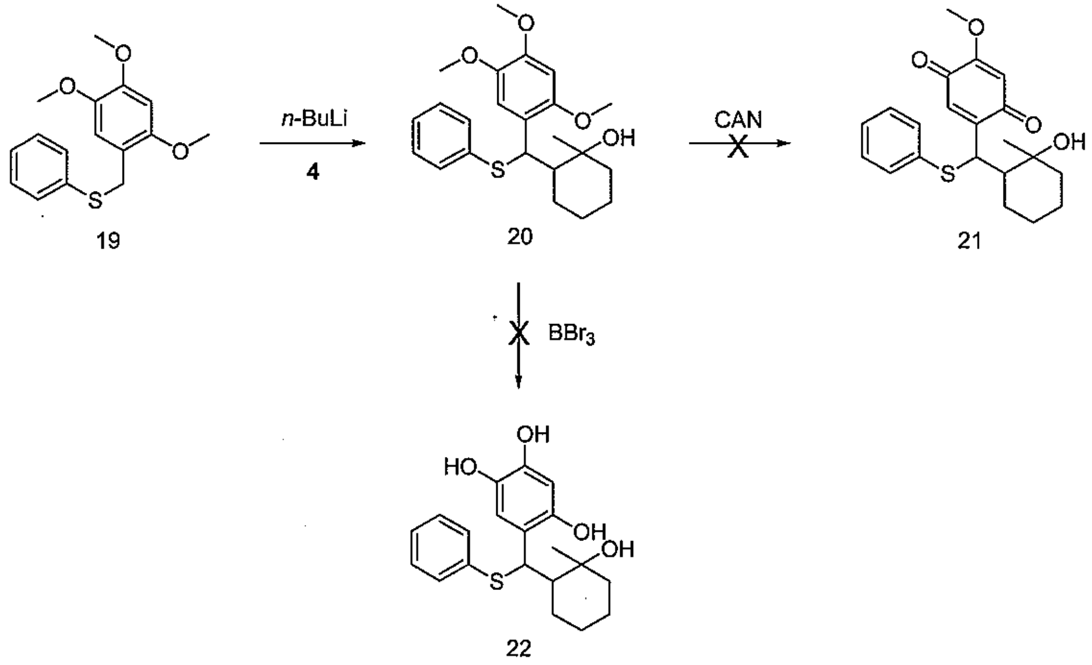
Scheme 14

The difficulty in obtaining a trihydroxy compound prompted the usage of a different handle at the benzylic position. A thiophenyl group was chosen as a replacement for the cyano group. The construction of compound **19** (Scheme 15) began with the reduction of 2,4,5-trimethoxybenzaldehyde and subsequent substitution with thiophenol catalyzed by zinc iodide.[22]



Scheme 15

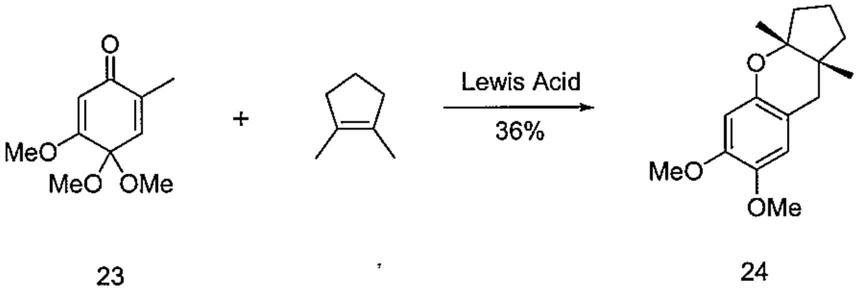
Epoxide **4** was then treated with lithiated compound **19** produce the expected ring-opening product compound **20** (Scheme 16). With construction of intermediate **20**, the oxidative cyclization was investigated. The *para*-methoxy group of compound **20** could potentially be oxidatively demethylated to yield *para*-benzoquinone **21**. However, oxidation with ceric ammonium nitrate decomposed the starting materials. The next approach involved the demethylation of compound **20** with boron tribromide. Once again, the decomposition of starting materials was observed. The fragility of compound **20** was evident under these conditions.



Scheme 16

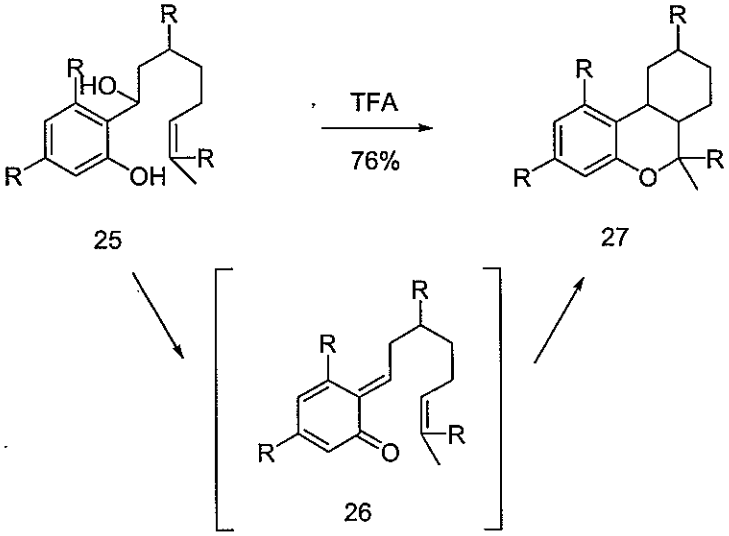
With these disappointing results, the strategy to construct the tricyclic quinone methide was revised. The construction of a benzopyran from a heteroatom Diels-Alder reaction was reported by Buchi in the synthesis[23] of gymnitrol (Scheme 17). Quinoketal

23 when treated with $BF_3{\bullet}OEt_2$ yielded an *ortho*-quinone methide intermediate, which was trapped with 1,2-dimethylcyclopentene to afford benzopyran **24**.



Scheme 17

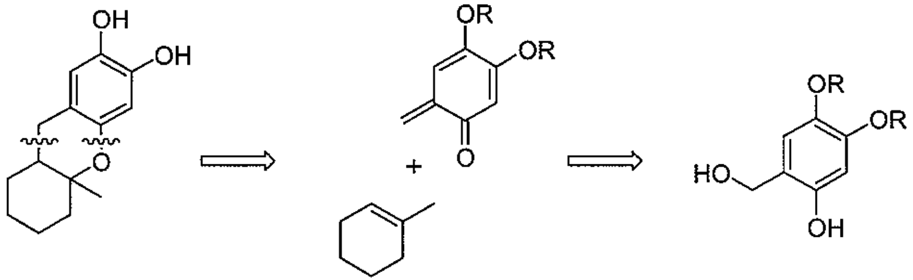
Recently, Tius and co-workers[24] utilized an intramolecular Diels-Alder reaction to construct the benzopyran moiety of canniboid natural products (Scheme 18). Benzylic alcohol **25** when treated with trifluoroacetic acid yielded tricyclic compound **27** in a 76% yield.



Scheme 18

The acid catalyzed dehydration of benzyl alcohol **25** was facilitated by the presence of the *ortho*-hydroxy group. Reaction intermediate **26** was an *ortho*-quinone methide, which readily underwent a [4+2] cycloaddition to give benzopyran **27**. The generation and trapping of *ortho*-quinone methides by various methods have been reported.[25]

To synthesize the targeted benzopyran moiety **28**, an intermolecular heteroatom Diels-Alder reaction might construct both carbon-carbon and carbon-oxygen bonds (Figure 6). The precursor needed for the Diels-Alder reaction would be phenol **29**. The *ortho*-hydroxy groups of phenol **24** might need to be protected selectively to ensure the generation of an *ortho*-quinone methide and not the possible *para*-quinone methide intermediate.

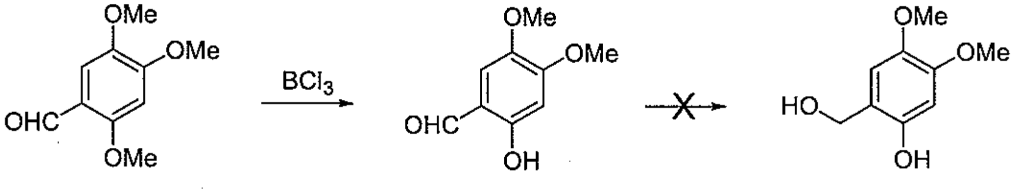


28

29

Figure 6. Retrosynthetic Analysis of Diels-Alder strategy

The synthesis began with the attempted construction of phenol **31**. Starting with commercially available 1,3,4-trimethoxybenzaldehyde, selective demethylation with boron trichloride afforded compound **30** in 85% yield (Scheme 19). However, reduction of aldehyde **30** was unsuccessful with numerous attempts using sodium borohydride and lithium aluminum hydride under various solvents and temperatures as described in the literature.[25]

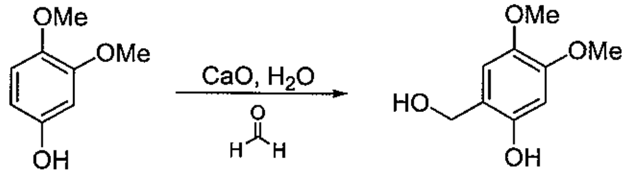


30

31

Scheme 19

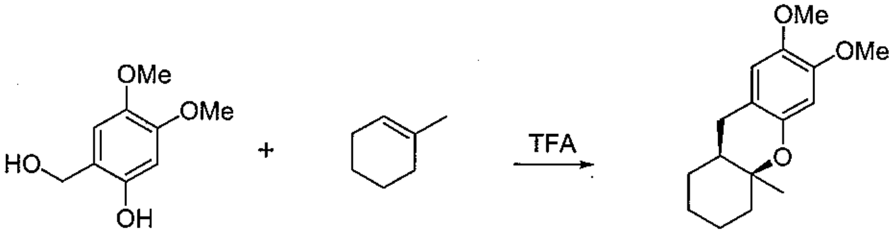
The reduction produced uncharacterizable and inseparable oligomers. The presence of the alkoxy groups at the *ortho* and *para* positions enhances the dehydration to form various byproducts. With the problematic synthesis of compound **31** under these conditions, an alternative route was explored. Hydroxymethylation of phenols under basic[27] and acidic[28] conditions are known to selectively occur ortho to the hydroxy group. When 3,4-dimethoxyphenol was treated with calcium oxide (Scheme 20) in water and formalin, the desired compound **31** was produced.



31

Scheme 20

Benzyl acohol **31** was unstable to silica gel column chromatography and readily decomposed at room temperature. Once made, compound **31** was added to 1-methylcyclohexene and treated with trifluoroacetic acid (Scheme 21). After heating, the reaction afforded the tricyclic benzopyran **32** in 45% yields over two steps from 3,4-dimethoxyphenol.

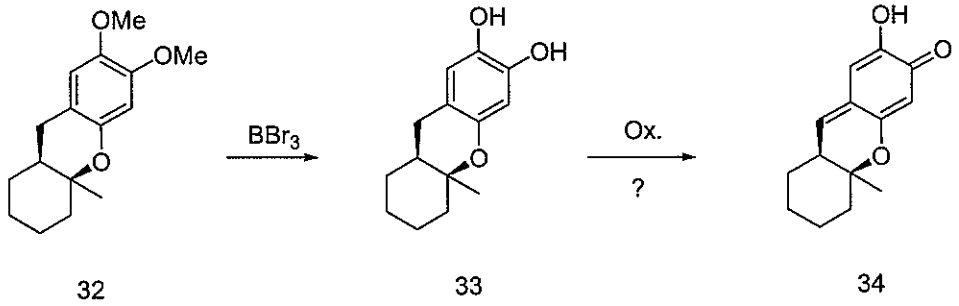


31

32

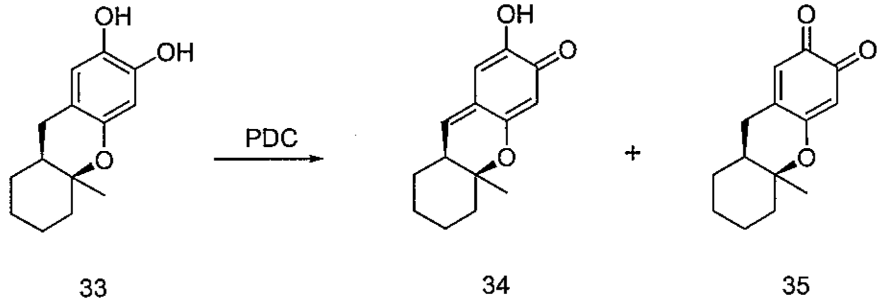
Scheme 21

The [4+2] cycloaddition generated both the carbon-carbon and carbon-oxygen bonds with a cis ring juncture, which was determined by a NOESY experiment. With the construction of benzopyran **32**, demethylation (Scheme 22) with boron tribromide afforded catechol **33** in 60% yields. With the dihydroxy compound synthesized, the final oxidation to the quinone methide was investigated.



Scheme 22

The previous syntheses of the monoterpenic analogs indicated a variety of oxidants could effect the generation of the quinone methide moiety. The use of PDC afforded an inseparable mixture of the desired quinone methide **34** and *ortho*-quinone **35** (Scheme 23).



Scheme 23

Methoxy-substituted intermediate **36** can only form the desired quinone methide **37** (Figure 7). The selective protection of catechol **33** would be difficult. The methoxy group in compound **36** would need to be introduced prior to the Diels-Alder reaction.

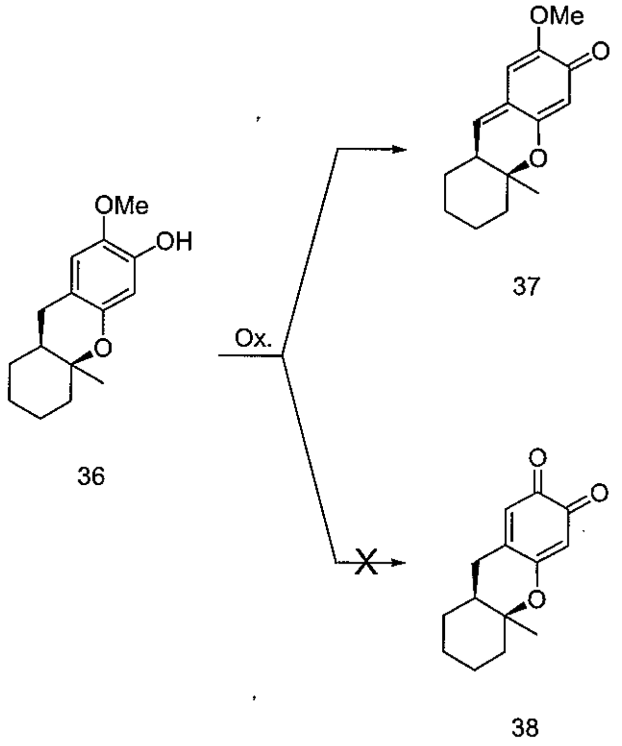
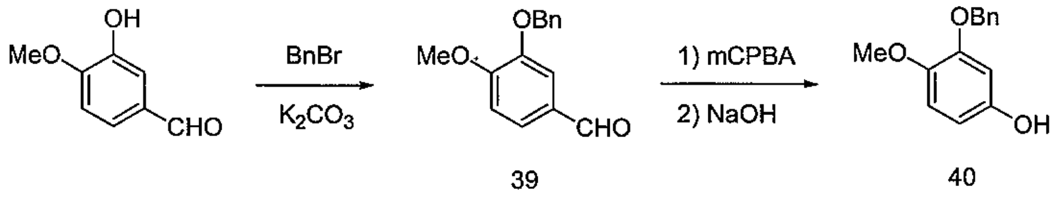


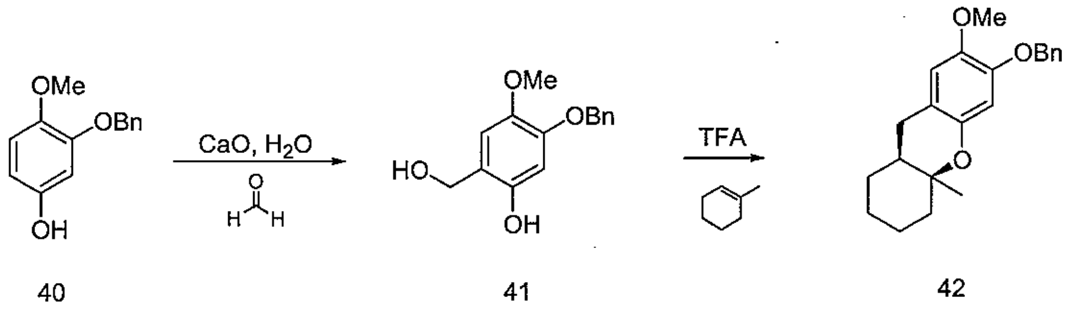
Figure 7. Quinone methide oxidation

The synthesis of compound **36** began with the benzylation of isovanillin with benzyl bromide and potassium carbonate in ethanol (Scheme 24). The protection afforded benzaldehyde **39** in quantitative yields. The Baeyer-Villiger oxidation of benzaldehyde **39**, followed by hydrolysis with aqueous sodium hydroxide, produced the selectively protected phenol **40** in a 80% yield.



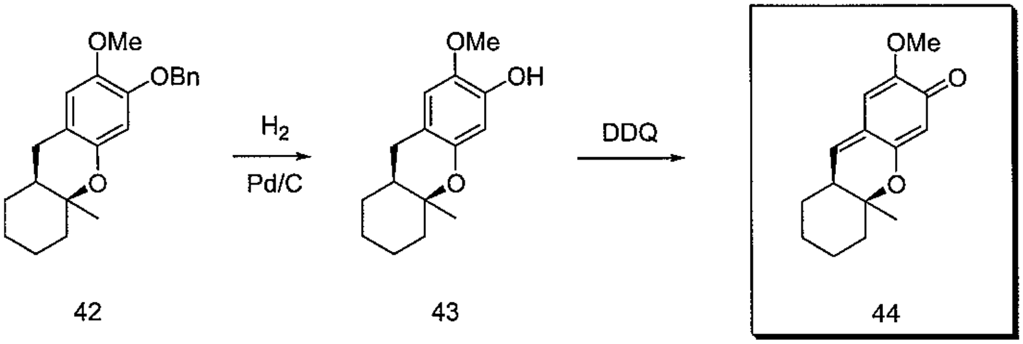
Scheme 24

After the construction of compound **40**, the hydroxymethylation with formalin and calcium oxide provided benzyl alcohol **41** (Scheme 25). The key Diels-Alder reaction afforded benzopyran **42** in a 40% yield.



Scheme 25

Catalytic hydrogenation of compound **42** produced compound **43** in quantitative yield (Scheme 26). The oxidation of compound **43** was then investigated. The use of silver(I) oxide has been reported by Winstein[29] and others[30] to generate quinone methides. However, when compound **43** was treated with silver(I) oxide, an inseparable mixture of uncharacterized products was obtained. Trammel observed polymeric products with silver oxide oxidation.[17] The use of pyridinium dichlorochromate did not produce the desired quinone methide **44**. Compound **43**, when treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the desired product in 95% isolated yield. The structure of **44** was confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and UV spectrometry.



Scheme 26

In summary, the synthesis of the quinone methide BCD rings of puuphenone was achieved using an intermolecular heteroatom Diels-Alder reaction. The reaction proceeded through an *ortho*-quinone methide intermediate, which was produced from the dehydration of an *ortho*-hydroxy benzyl alcohol derivative.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, benzene and diisopropylamide were distilled over calcium hydride. All experiments were performed under argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.26 ppm for ^1H and 77.06 ppm for ^{13}C), unless otherwise noted. Coupling constants (J) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m=multiplet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer and low resolution mass spectra were performed with a Finnegan 4023 mass spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.

1-Methyl-7-oxa-bicyclo[4.1.0]heptane (**4**)

To 1-methyl-1-cyclohexene (10g, 0.1 mmol) in 300 mL of water at room temperature, was added $NaHCO_3$ (13g, 0.15 mol) and *m*CPBA (23.3g, 0.13 mol). The mixture was stirred at room temperature for 3 hours, monitored by TLC, and then filtered and extracted with CH_2Cl_2, dried, concentrated and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 2.85 (d, $J = 3$ Hz, 1H), 1.82-1.74 (m, 3H), 1.60-1.53 (m, 1H), 1.35-1.26 (m, 2H), 1.20 (s, 3H), 1.19-1.08 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 59.66, 5.64, 30.01, 24.89, 24.13, 20.18, 19.81.

(4-Hydroxy-3-methoxyphenyl)-(2-hydroxy-2-methylcyclohexyl)-acetonitrile (**9**)

To 4-hydroxy-3-methoxy phenylacetonitrile (1g, 6.12 mmol) in 200 mL of THF at -78 °C, was added 2.5 M *n*-BuLi (5.6 mL, 14.1 mmol) dropwise. After 30 minutes, epoxide **4** (0.83g, 7.4 mmol) in 2 mL of THF was slowly added and the mixture was slowly warmed to room temperature. The mixture was added saturated aqueous ammonium chloride after the starting materials were consumed (monitored by TLC). The organic layer was extracted with ethyl acetate, washed with brine, dried, concentrated and purified by column chromatography (inseparable mixture of 2 stereoisomers). ^1H NMR (300 MHz, $CDCl_3$) δ 6.84-6.78 (m, 2H), 6.71 (d, $J = 6$ Hz, 1H), 4.43 (s, 1H), 3.84 (s, 3H), 1.64-1.01 (m, 9H), 1.36 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 145.67, 145.17, 127.18, 122.65, 120.53, 110.63, 110.35, 72.78, 56.11, 52.36, 42.78, 35.68, 28.31, 25.65, 23.75, 21.53.

3,4-Dihydroxy phenylacetonitrile

To 3,4-dimethoxy phenylacetonitrile (1g, 3.5 mmol) in 40 mL of CH_2Cl_2 at -78 °C, was added slowly 1.0 M boron tribromide (11.4 mL, 11.6 mmol). After 30 minutes at -78 °C, the mixture was warmed to room temperature and stirred for 4 hours. The solution was diluted with CH_2Cl_2 and water was slowly added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated $NaHCO_3$, brine, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (bd, J = 6 Hz, 2H), 6.73 (d, J = 6 Hz, 1H), 3.63 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.04, 143.36, 122.60, 120.67, 115.89, 115.09, 23.00.

(3,4-Dihydroxy-phenyl)-(2-hydroxy-2-methyl-cyclohexyl)-acetonitrile (**11**)

To 3,4-dihydroxy phenylacetonitrile (0.5g, 3.35 mmol) in 35 mL of THF at -78 °C, was added 2.5 M *n*-BuLi (4.7 mL, 11.7 mmol) dropwise. After 30 minutes, epoxide **4** (0.45g, 4.0 mmol) in 2 mL of THF was slowly added and the mixture was slowly warmed to room temperature. The mixture was added saturated aqueous ammonium chloride after the starting materials were consumed (monitored by TLC). The organic layer was extracted with ethyl acetate, washed with brine, dried, concentrated and purified by column chromatography. The product was insoluble in $CDCl_3$. ^{1}H NMR (300 MHz, CD_3COCD_3) δ 6.87-6.68 (m, 2H), 4.48 (s, 1H), 1.77-1.00 (m, 9H), 1.41 (s, 3H); ^{13}C NMR (300 MHz, CD_3COCD_3) δ 145.00, 144.65, 129.33, 128.48, 119.07, 115.61, 114.97, 71.56, 54.71, 43.20, 35.03, 25.88, 24.98, 23.81, 21.25.

(3,4-Dioxo-cyclohexa-1,5-dienyl)-(2-hydroxy-2-methyl-cyclohexyl)-acetonitrile (**12**) and (2-Hydroxy-2-methyl-cyclohexyl)-(3-hydroxy-4-oxo-cyclohexa-2,5-dienylidene)-acetonitrile (**13**)

To compound **11** (0.1g, 0.38 mmol) in 10 mL of THF at room temperature, was added Ag_2O (0.89g, 3.8 mmol). After 3 hours the mixture was filtered through Celite and concentrated. The crude products were a 1:1 mixture of isomers **12** and **13**. The crude mixture in 10 mL of THF at room temperature was added Et_3N (0.15g, 1.52 mmol). After 2 hours, saturated aqueous ammonium chloride was added to the solution, and the mixture was extracted with ethyl acetate, dried and concentrated to afford **13**. **12**: ^1H NMR (300 MHz, CD_3COCD_3) δ 7.91 (dd, J = 12 Hz, 1H), 6.92 (d, J = 3 Hz, 1H), 6.43 (d, J = 6 Hz, 1H), 3.10 (m, 1H), 1.91-1.33 (m, 8H), 1.31 (s, 3H). **13**: ^1H NMR (300 MHz, CD_3COCD_3) δ 7.76 (dd, J = 9 Hz, 1H), 7.08 (d, J = 1Hz, 1H), 6.61 (d, J = 12 Hz, 1H), 3.71-3.51 (m, 1H), 3.00 (m, 1H), 1.90-1.35 (m, 8H), 1.28 (s, 3H).

(2,4,5-Trimethoxyphenyl)-methanol (**18**)

To 2,4,5-trimethoxybenzaldehyde (1g, 5.1 mmol) in 50 mL of EtOH at room temperature, was slowly added $NaBH_4$ (0.29g, 7.7 mmol). After 2 hours, ethanol was removed by vacuum and the mixture was diluted with CH_2Cl_2, and water was slowly added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried and concentrated. The crude product was used without purification. ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.51 (s, 1H), 4.60 (s, 2H), 3.87 (s, 3H), 3.82 (s, 6H).

1,2,4-Trimethoxy-5-phenylsulfanylmethyl-benzene (**19**)

To benzyl alcohol **18** (1g, 5.0 mmol) in 50 mL of dichloroethane at room temperature, was added ZnI_2 (0.84g, 2.5 mmol) followed by thiophenol (0.67g, 6.05 mmol) slowly. After 30 minutes, the solution turned light blue and was added water, extracted with CH_2Cl_2, dried, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 4 H), 7.19 (t, $J = 6$ Hz, 1H), 6.82 (s, 1H), 6.69 (s, 1H), 4.12 (s, 2H), 3.82 (s, 6H), 3.66 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 152.09, 149.92, 143.31, 137.56, 129.60, 128.98, 128.48, 126.07, 116.92, 115.43, 98.47, 56.26, 56.08, 55.69.

1-Methyl-2-[phenylsulfanyl-(2,4,5-trimethoxy-phenyl)-methyl]-cyclohexanol (**20**)

To compound **19** (0.4g, 1.4 mmol) in 20 mL of THF at -78 °C, was added 2.5 M *n*-BuLi (0.67mL, 1.68 mmol) dropwise. After 30 minutes, epoxide **4** (0.2g, 1.82 mmol) in 1 mL of THF was slowly added and the mixture was slowly warmed to room temperature. The mixture was added saturated aqueous ammonium chloride after the starting materials were consumed (monitored by TLC). The organic layer was extracted with ethyl acetate, washed with brine, dried, concentrated and purified by column chromatography. The product was insoluble in $CDCl_3$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.18-7.06 (m, 5H), 6.42 (s, 1H), 4.96 (d, $J = 3$ Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 2.14-2.05 (m, 1H), 1.87-1.11 (m, 8H), 1.35 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 149.83, 148.57, 143.40,, 136.02, 131.17, 128.69, 126.46, 123.43, 112.92, 97.52, 73.99, 56.72, 56.69, 56.31, 54.51, 46.88, 43.27, 27.26, 26.65, 24.27, 21.95.

2-Hydroxy-4,5-dimethoxy-benzaldehyde (**30**)

To 2,4,5-trimethoxy benzaldehyde (1g, 5.1 mmol) in 50L of CH_2Cl_2 at 0 °C, was added dropwise 1.0 M BCl_3 (7.6 mL, 7.65 mmol). The mixture was stirred overnight and was added water slowly, extracted with CH_2Cl_2, dried, concentrated and purified by column chromatography. The compound was spectrally identical to the commercially available material.

2-Hydroxymethyl-4,5-dimethoxy-phenol (**31**)

To 3,4-dimethoxy phenol (1.0g, 6.5 mmol) in 20 mL of water at room temperature, was added 37% formalin (1.4 mL, 13.4 mmol) and followed by calcium oxide (0.18g, 3.3 mmol). After an hour (monitored by TLC), saturated aqueous ammonium chloride was added and the organic layer was extracted with ether, dried, concentrated and used without purification. ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.51 (s, 1H), 4.80 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H).

6,7-Dimethoxy-4a-methyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (**32**)

To crude compound **31** (0.6g, 3.26 mmol) in 40 mL of $CHCl_3$ at 0 °C, was added 1-methyl-1-cyclohexene (0.47g, 4.9 mmol) followed by dropwise addition of trifluoroacetic acid (0.45g, 3.91 mmol). The mixture was boiled for 3 hours (monitored by TLC). After cooling to room temperature, the solution was diluted with water and extracted with CH_2Cl_2, dried, concentrated and purified by column chromatography (product was very nonpolar) to afford benzopyran **32** in 45 % yields (from 3,4-dimethoxy phenol). The cis-ring juncture was assigned by NOESY spectroscopy. ^1H NMR (300

MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.38 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.03 (dd, J = 12, 6 Hz, 1H, 2.25 (d, J = 18 Hz, 1H), 1.94-1.90 (m, 1H), 1.67-1.24 (m, 8H), 1.19 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.44, 146.91, 142.82, 112.79, 110.31, 101.25, 74.93, 56.63, 55.99, 38.72, 37.21, 29.21, 28.68, 25.84, 25.58, 21.94.

<u>10a-Methyl-5,7,8,8a,9,10a-hexahydro-6H-xanthene-2,3-diol</u> (**33**)

To compound **32** (0.05g, 0.19 mmol) in 5 mL of CH_2Cl_2 at -78 °C, was added slowly 1.0 M boron tribromide (0.57 mL, 0.57 mmol). After 30 minutes at -78 °C, the mixture was warmed to room temperature and stirred for 4 hours (monitored by TLC). The solution was diluted with CH_2Cl_2 and slowly added water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated $NaHCO_3$, brine, dried, concentrated and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.37 (s, 1H), 3.00 (dd, J = 15, 6 Hz, 1H), 2.21 (d, J = 18 Hz, 1H), 1.91- 1.10 (m, 9H), 1.21 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.22, 142.94, 137.02, 116.21, 111.87, 104.34, 74.91, 38.65, 37.14, 29.05, 28.62, 25.81, 25.56, 21.90; HRMS (EI) m/z calcd for 234.1256, found 234.1259.

<u>2-Hydroxy-10a-methyl-5,6,7,8,8a,10a-hexahydro-xanthen-3-one</u> (**34**)

To compound **33** (0.02g, 0.085 mmol) in 2 mL of CH_2Cl_2 at room temperature was added PDC (0.05g, 0.13 mmol). After 4 hours (monitored by TLC), the mixture was filtered through Celite and concentrated to afford a mixture of products. ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 1.5 Hz, 1H), 6.35 (s, 1H), 5.95 (d, J = 3 Hz, 1 H), 2.18-2.10

(m, 1H), 1.98-1.21 (m, 6H), 1.19 (s, 3H); HRMS (EI) m/z calcd for 232.1010, found 232.1102.

3-Benzyloxy-4-methoxy-benzaldehyde (**39**)

To isovanillin (1.0g, 6.6 mmol) in 75 mL of EtOH at room temperature, was added K_2CO_3 (1.1g, 7.9 mmol) and benzyl bromide (1.18g, 6.93 mmol). The mixture was stirred for 24 hours, filtered and concentrated. The residue was dissolved in ether and washed with cold 10% NaOH (2X), the aqueous layer was acidified with 10% HCl and extracted with ether, dried, concentrated and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.45-7.28 (m, 7H), 6.96 (d, $J = 9$ Hz, 1H), 5.15 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 190.99, 155.27, 148.92, 136.55, 130.22, 128.85, 128.33, 127.71, 127.07, 111.59, 111.03, 71.04, 56.37.

3-Benzyloxy-4-methoxy-phenol (**40**)

To benzaldehyde **39** (1g, 4.13 mmol) in 60 mL of CH_2Cl_2 at 0 °C, was added *m*CPBA (1.43g, 4.26 mmol). After 4 hours at room temperature, the mixture was filtered and the organic layer was washed with $NaHCO_3$, brine and concentrated. The residue was taken up in 10 mL of ethanol and added 10% NaOH (40 mL). The solution was heated at 60 °C for 15 minutes and then cooled to room temperature. The solution was then acidified with 10% HCl and extracted with ether, dried, concentrated and purified by column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 6.74 (d, $J = 9$ Hz, 1H), 6.46 (d, $J = 1$ Hz, 1H), 6.35 (dd, $J = 9, 3$ Hz, 1H), 5.05 (s, 2H), 3.81 (s, 3H);

^{13}C NMR (300 MHz, CDCl$_3$) δ 150.51, 149.31, 143.78, 137.08, 128.76, 128.09, 127.54, 113.71, 106.91, 103.16, 71.08, 57.15.

5-Benzyloxy-2-hydroxymethyl-4-methoxy-phenol (**41**)

To compound **40** (0.8g, 3.5 mmol) in 20 mL of water at room temperature was added 37% formalin (0.77g, 7.35 mmol) followed by calcium oxide (0.098g, 1.75 mmol). After an hour (monitored by TLC), saturated aqueous ammonium chloride was added and the organic layer was extracted with ether, dried, concentrated and used without purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43-7.30 (m, 5H), 6.56 (s, 1H), 6.51 (s, 1H), 5.10 (s, 2H), 4.76 (s, 2H), 3.82 (s, 3H).

6-Benzyloxy-7-methoxy-4a-methyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (**42**)

To crude compound **41** (0.4g, 1.53 mmol) in 20 mL of CHCl$_3$ at 0 °C, was added 1-methyl-1-cyclohexene (0.22g, 2.3 mmol) followed by dropwise addition of trifluoroacetic acid (0.035g, 1.84 mmol). The mixture was boiled for 3 hours (monitored by TLC). After cooling to room temperature, the solution was diluted with water and extracted with CH$_2$Cl$_2$, dried, concentrated and purified by column chromatography (product was very nonpolar) to afford benzopyran **42** in 40% yield (from **40**). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50-7.28 (m, 5H), 6.57 (s, 1H), 6.43 (s, 1H), 5.08 (s, 2H), 3.82 (s, 3H), 3.04 (dd, J = 15, 6 Hz, 1H), 2.26 (d, J = 15 Hz, 1H), 1.98-1.25 (m, 9H), 1.19 (s, 3H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 148.02, 147.10, 143.48, 137.53, 128.70, 127.94, 127.61, 113.93, 111.17, 103.49, 74.88, 71.07, 57.06, 38.69, 37.20, 29.23, 28.67, 25.82, 25.57, 21.92

2-Methoxy-10a-methyl-5,7,8,8a,9,10a-hexahydro-6H-xanthen-3-ol (**43**)

To compound **42** (0.1g, 0.3 mmol) in 5 mL of THF at room temperature was added Pd/C (0.032g, 0.03 mmol). The flask was flushed with hydrogen gas for 5 minutes and capped with a large balloon. After 1 hour (monitored by TLC), the mixture was filtered through Celite, concentrated and purified by column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.41 (s, 1H), 3.81 (s, 3H), 3.03 (dd, $J = 15, 6$ Hz, 1H), 2.24 (d, $J = 18$ Hz, 1H), 1.94-1.25 (m, 9H), 1.20 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.50, 144.97, 140.76, 112.05, 110.35, 103.79, 74.75, 56.70, 38.67, 37.19, 29.34, 28.64, 25.84, 25.52, 21.89; HRMS (EI) m/z calcd for 248.1412, found 232.1418.

2-Methoxy-10a-methyl-5,6,7,8,8a,10a-hexahydro-xanthen-3-one (**44**)

To compound **43** (0.02g, 0.08 mmol), in 5 mL of dioxane at room temperature was added DDQ (0.022g, 0.096 mmol). After 2 hours (monitored by TLC), the mixture was filtered through Celite, concentrated and purified by column chromatography to afford **44** in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (bs, 1H), 6.46 (s, 1H), 6.18 (s, 1H), 3.89 (s, 3H), 2.22 (dd, $J = 12, 3$ Hz, 1H), 2.05-2.00 (m, 1H), 1.75-1.30 (m, 8H), 1.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 195.61, 156.35, 153.59, 142.01, 111.47, 106.76, 103.71, 79.77, 56.52, 52.50, 37.09, 26.85, 24.80, 24.16, 21.65; UV (CH_2Cl_2) λ_{max} 240, 272, 335 nm; HRMS (EI) m/z calcd for 246.1256, found 232.1258.

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