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New synthetic methods for hypericum natural products

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New synthetic methods for hypericum natural products

by

Insik Jeon

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

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Ames, Iowa

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TABLE OF CONTENTS

| | |
|--|-----|
| GENERAL INTRODUCTION | 1 |
| CHAPTER 1. Synthesis of papuaforin B and related phloroglucinol natural products | |
| Introduction | 2 |
| Results and Discussion | 12 |
| Experimental | 56 |
| References | 80 |
| CHAPTER 2. Direct syntheses of 7,8-dihydroxycalamenene and mansonone C | |
| Introduction | 84 |
| Results and Discussion | 89 |
| Experimental | 93 |
| References | 113 |
| GENERAL CONCLUSION | 115 |
| ACKNOWLEDGMENTS | 116 |

GENERAL INTRODUCTION

Organic chemistry has served as a solid foundation for interdisciplinary research areas, such as molecular biology and medicinal chemistry. An understanding of the biological activities and structural elucidations of natural products can lead to the development of clinically valuable therapeutic options. The advancements of modern synthetic methodologies allow for more elaborate and concise natural product syntheses.

The theme of this study centers on the synthesis of natural products with particularly challenging structures and interesting biological activities. The synthetic expertise developed here will be applicable to analog syntheses and to other research problems.

CHAPTER 1. SYNTHESIS OF PAPUAFORIN B AND RELATED PHLOROGLUCINOL NATURAL PRODUCTS

Introduction

An understanding of the biological activities and effects of herbal supplements becomes essential for efficacy and safety concerns with the increasing use of dietary supplements. Recently, the antidepressant activity of *Hypericum perforatum*, commonly known as St. John's wort, has drawn much attention.¹⁻⁴ St. John's wort is commonly used as a natural remedy to treat moderate to mild depression. Studies of the constituents of St. John's wort and other plants from the family Guttiferae have disclosed a class of compounds, polycyclic polyprenylated acylphloroglucinols (PPAPs), with fascinating structures and interesting biological activities.

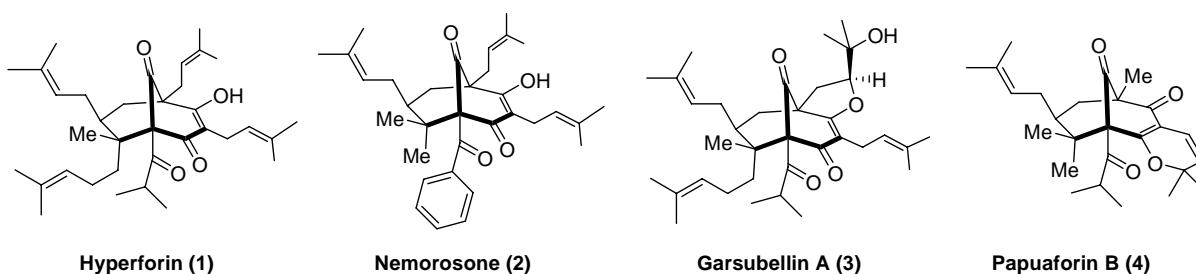


Figure 1. Polycyclic polyprenylated acylphloroglucinol (PPAP) natural products

Hyperforin (1) was first isolated in 1971 from the species *Hypericum perforatum*,⁵ and has drawn substantial attention, because it is thought to be responsible for the antidepressant and antibacterial activities of St. John's wort.⁶⁻¹⁰ Its antidepressant activity is

attributed to a broad inhibitory effect on the synaptosomal uptake of several neurotransmitters, such as serotonin, noradrenaline, dopamine, γ -aminobutyric acid (GABA) and L-glutamate at hyperforin concentrations as low as $IC_{50} = 1.1 \mu\text{g/mL}$.¹¹ A recent report has shown that hyperforin (**1**) inhibits penicillin-resistant and methicillin-resistant *Staphylococcus aureus*, which is resistant to various antibiotics, such as the cephalosporins, erythromycin and clindamycin.¹²

Nemorosone (**2**) is the major constituent of *Clusia* (*Clusiaceae*) species resin,¹³ and is known to possess antimicrobial, cytotoxicity and antioxidant activities.¹⁴⁻¹⁶ Garsubellin A (**3**) was isolated from the wood of *Garcinia subelliptica* (*Guttiferae*) in 1997.¹⁷ Garsubellin A (**3**) enhances choline acetyltransferase (ChAT) activity in P10 rat septal neurons relative to a control by 154% at a 10 μM concentration.¹⁸ Choline acetyltransferase (ChAT) is involved in the biosynthesis of neurotransmitter acetylcholine (ACh) in the nervous system. Taking into account that Alzheimer's disease has been attributed to deficiencies in the levels of acetylcholine (ACh),¹⁹ The ChAT enhancing activity of garsubellin A (**3**) provides potential in developing chemotherapies for Alzheimer's disease. Papuaforin B (**4**) is extracted from *Hypericum papuanum* (Papua New Guinea). Its chemical structure is similar to hyperforin (**1**) with the additional 2,2-dimethyl-2*H*-pyran ring that is probably formed by cyclization of a 3-methylbut-2-enyl side chain with an enolic hydroxyl group.

The biosynthesis of hyperforin (**1**) was proposed using early labeling experiments, which involve acylphloroglucinols and isoprenoid moieties (Figure 2).²⁰ The acylphloroglucinol moiety is generated by a polyketide type biosynthesis beginning with two units of pyruvate. Condensation of malonyl-CoA and acyl-CoA furnishes a tetraketide, which undergoes cyclization to acylphloroglucinol **5**. Enzyme-catalyzed prenylation of **5** using

prenyl pyrophosphate, derived from a non-mevalonate pathway, generates **6** which, upon prenylation and cyclization, would provide hyperforin (**1**).

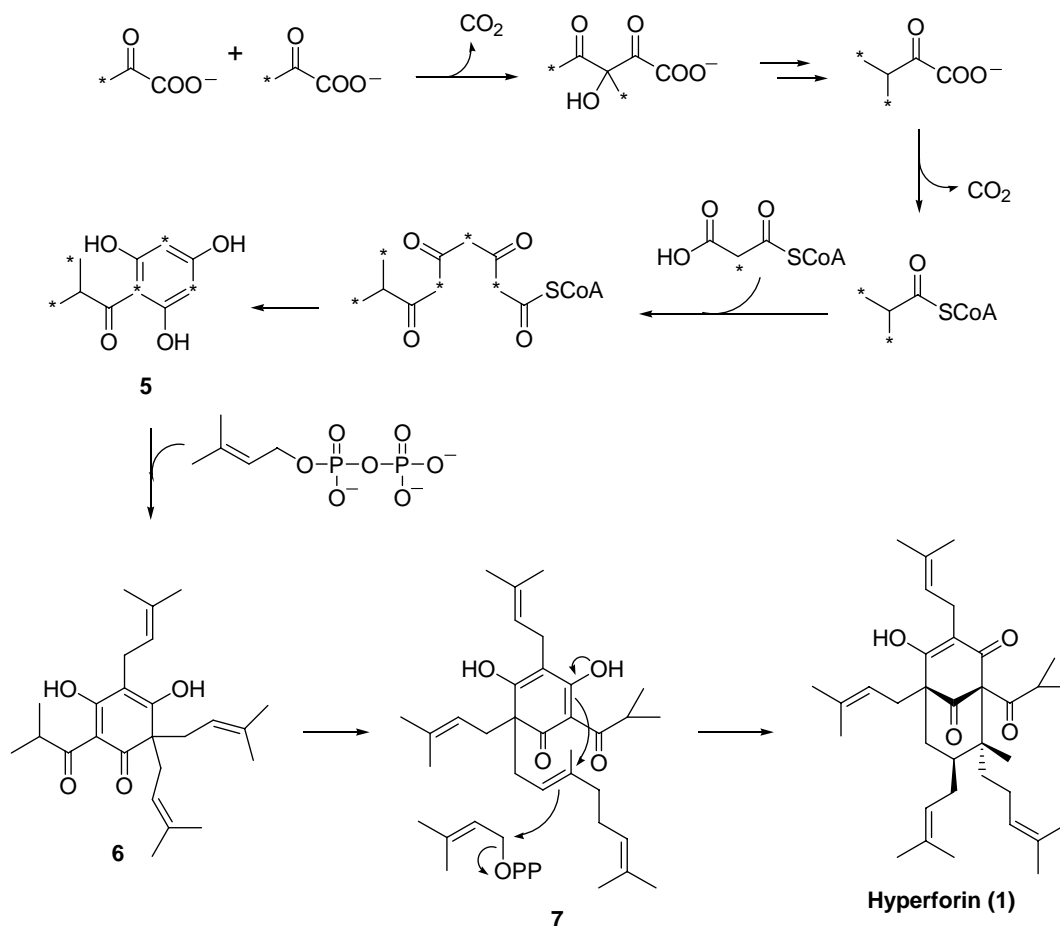
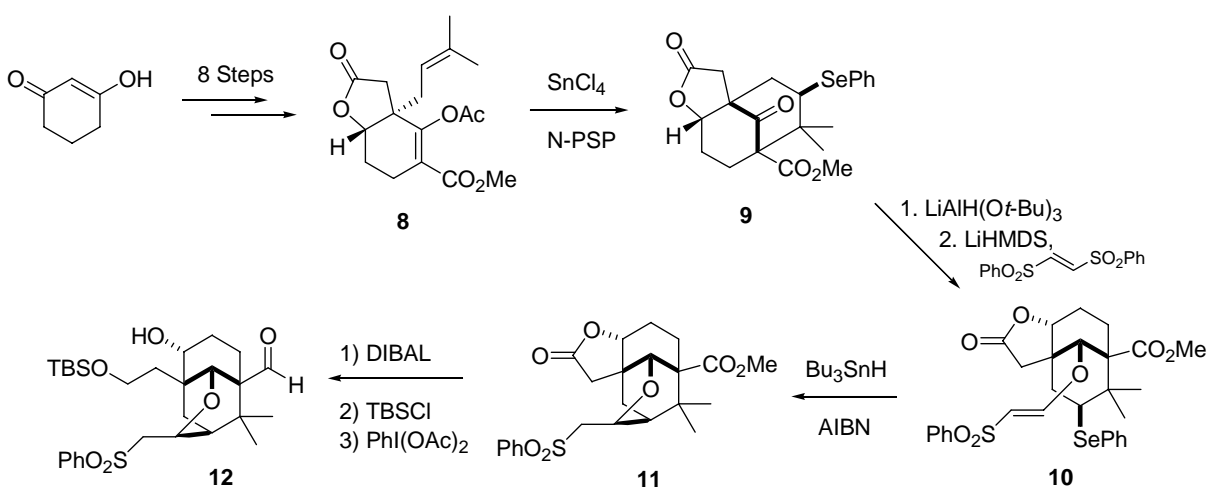


Figure 2. Proposed biosynthesis of Hyperforin (**1**)

In the past decade, the significant biological activity and challenging structure of this class of natural products have drawn many synthetic chemists' attention. However, most studies rely only on the construction of the bicyclic core structure, not surprisingly, because

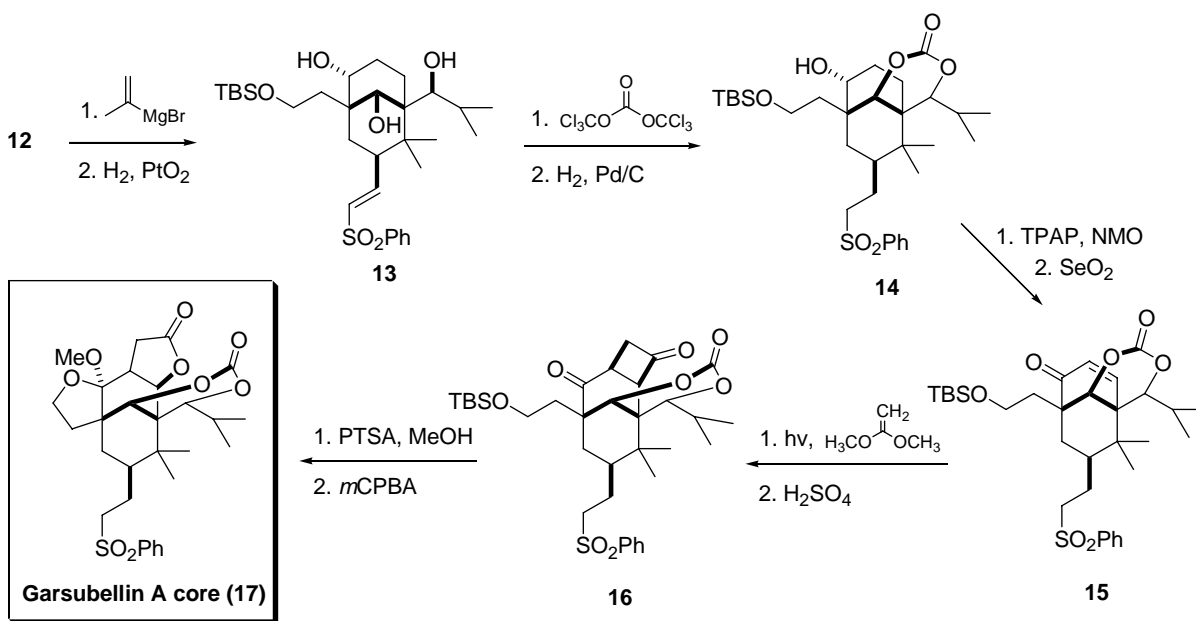
of its synthetically formidable structural features. Indeed, two total syntheses of garsubellin A (**3**) have been reported.^{21,22}

Nicolaou firstly reported a synthetic route to the highly functionalized core structure of garsubellin A (**3**) employing a selenocyclization approach.²³ Initially, the requisite precursor **8** was synthesized from commercially available 1,3-cyclohexanedione in eight steps (Scheme 1). The selenium-mediated cyclization in the presence of *N*-(phenylseleno)phthalimide (N-PSP) and SnCl₄ furnished the selenide **9**. Selective reduction of the bridged ketone of **9** produced a single alcohol, which, upon alkylation with *trans*-1,2-bis(phenylsulfonyl)ethylene, yielded vinylogous sulfone **10**. The construction of tetracycle **11** by the use of *n*-Bu₃SnH and AIBN, followed by the sequence of reactions : reduction, selective monoprotection, and oxidation formed the corresponding aldehyde **12**.



Scheme 1

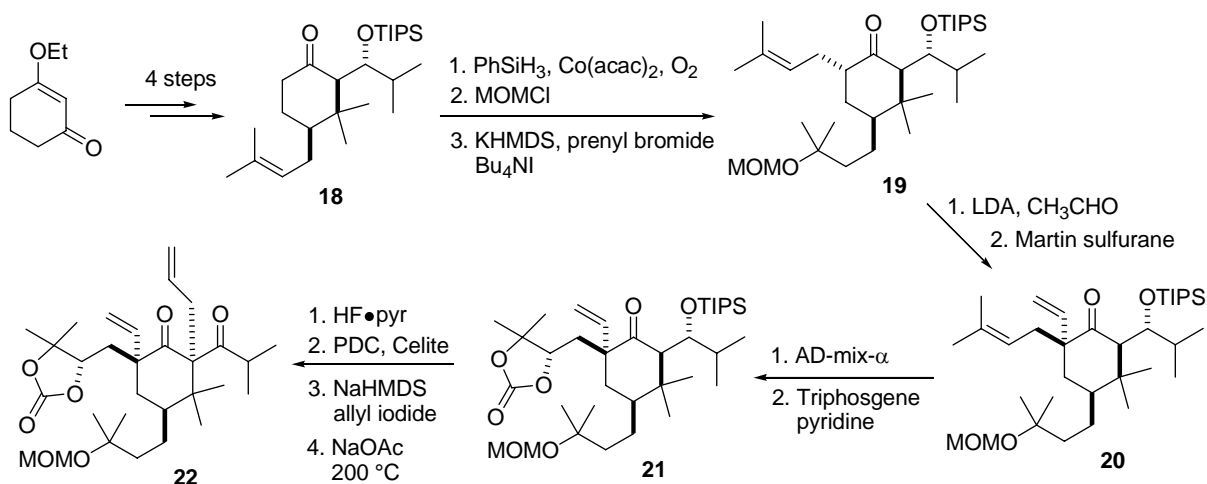
The use of isopropenylmagnesium bromide effected the addition to the aldehyde with concomitant β -elimination of the sulfone side chain. Selective hydrogenation by using H_2/PtO_2 produced isopropyl alcohol **13** (Scheme 2). Subsequently, selective protection of the two free hydroxyls of **13** as a cyclic carbonate, followed by hydrogenation, produced intermediate **14**. After oxidation of the free hydroxyl of **14**, the ensuing conversion of the saturated ketone to an α,β -unsaturated enone was accomplished to give **15**. For completion of the bicyclic core, the regio- and stereoselective [2+2] cycloaddition was employed to give the protected cyclobutanone adduct **16**. Deprotection and subsequent Baeyer-Villiger oxidation completed construction of the fully functionalized bicyclic core (**17**) of garsubellin A (**3**).



Scheme 2

Nicolaou's strategy introduced several interesting synthetic steps, which include biomimetic electrophile-mediated cyclizations of a pendant prenyl group and a novel bicyclic cycloaddition. However, the many steps to the core structure of garsubellin A (**3**) might limit its practical use towards this class of natural products syntheses.

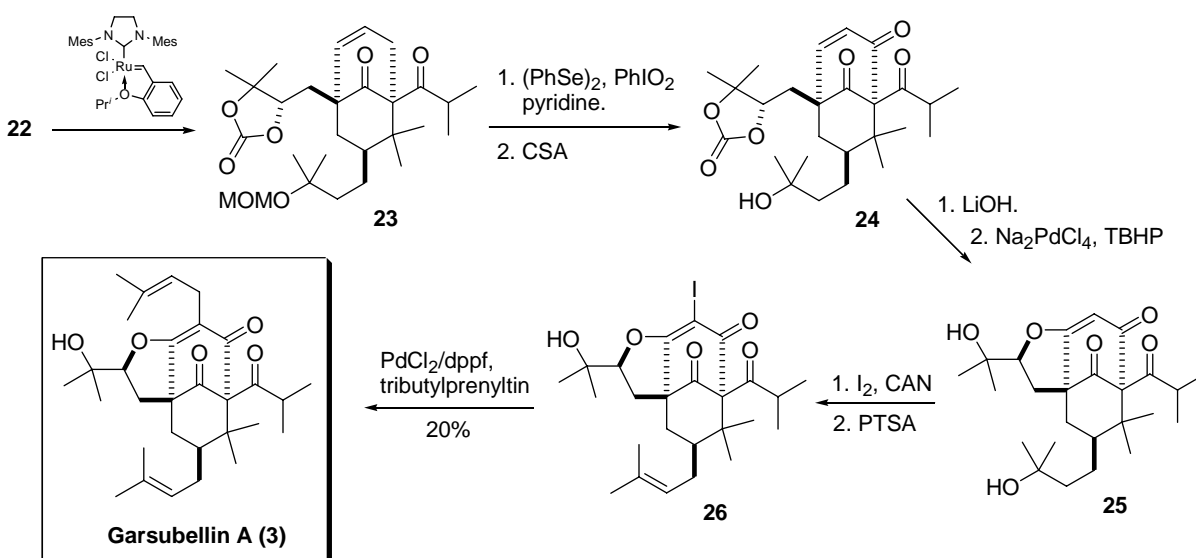
In 2005, Shibasaki first reported the complete total synthesis of Garsubellin A (**3**).²¹ The Shibasaki synthesis began with commercially available 3-ethoxycyclohex-2-enone, which underwent prenylation, methylation, and acid hydrolysis of the vinyl ether to yield an enone (Scheme 3).



Scheme 3

Conjugate addition of an methyl cuprate and *in situ* trapping of the resulting magnesium enolate by isobutyraldehyde gave the *anti*-aldol product, which was protected by TIPS to give **18**. Protection of the prenyl group, followed by addition of an additional prenyl group, gave **19**. Attempted aldol reaction with acetaldehyde occurred at the sterically less

demanding α -carbonyl position, which was then dehydrated to the corresponding olefin **20** using the Martin sulfurane. Highly chemoselective dihydroxylation and protection of the diol furnished carbonate **21**. Cyclization precursor **22** was generated in four straightforward steps from **21**: desilylation, oxidation, *O*-allylation and stereoselective Claisen rearrangement. A ring-closing metathesis reaction of **22** was realized by employing the Hoveyda-Grubbs catalyst²⁴ to construct the crucial bicyclic skeleton of **23** (Scheme 4).



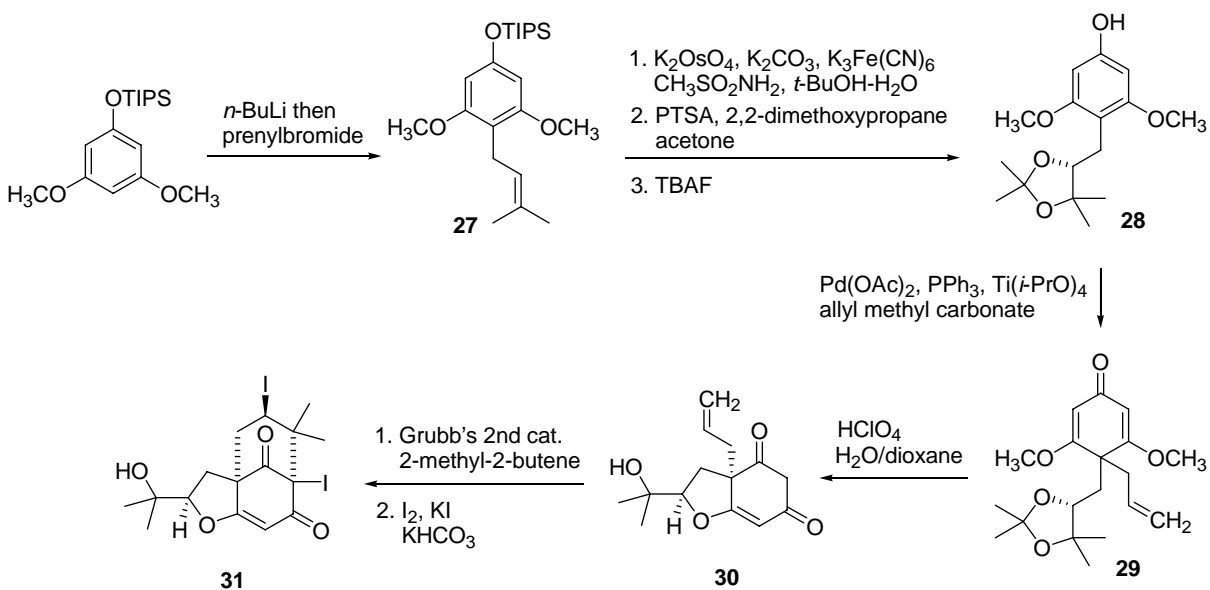
Scheme 4

Allylic oxidation, and subsequent deprotection of the MOM ether using CSA provided the alcohol **24**. Upon hydrolysis of the carbonate, the secondary alcohol underwent Wacker oxidative cyclization to give **25**. In order to secure two prenyl groups, **25** was further functionalized to a vinylic iodide, which was then dehydrated to regenerate the prenyl

group. The total synthesis of garsubellin A (**3**) was completed by Stille coupling of **26** with tributylprenyltin.

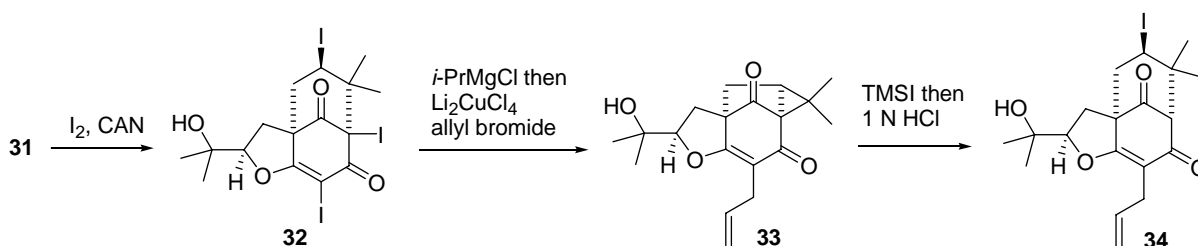
Shibasaki's group completed the total synthesis of the target compound by a reasonably direct synthetic route, except for the low yield of the final step. They also mentioned that this synthesis could be extended to an asymmetric synthesis of garsubellin A (**3**) by early introduction of a catalytic, enantioselective alkylation method developed by Koga.²⁵

A recent report from Danishefsky's group described the complete synthetic effort to garsubellin A (**3**). It involved a unique synthetic approach.²² For the construction of the bicyclic skeleton, they dearomatized a substituted phloroglucinol, a step reminiscent of the biosynthetic pathway to hyperforin (**1**).



Scheme 5

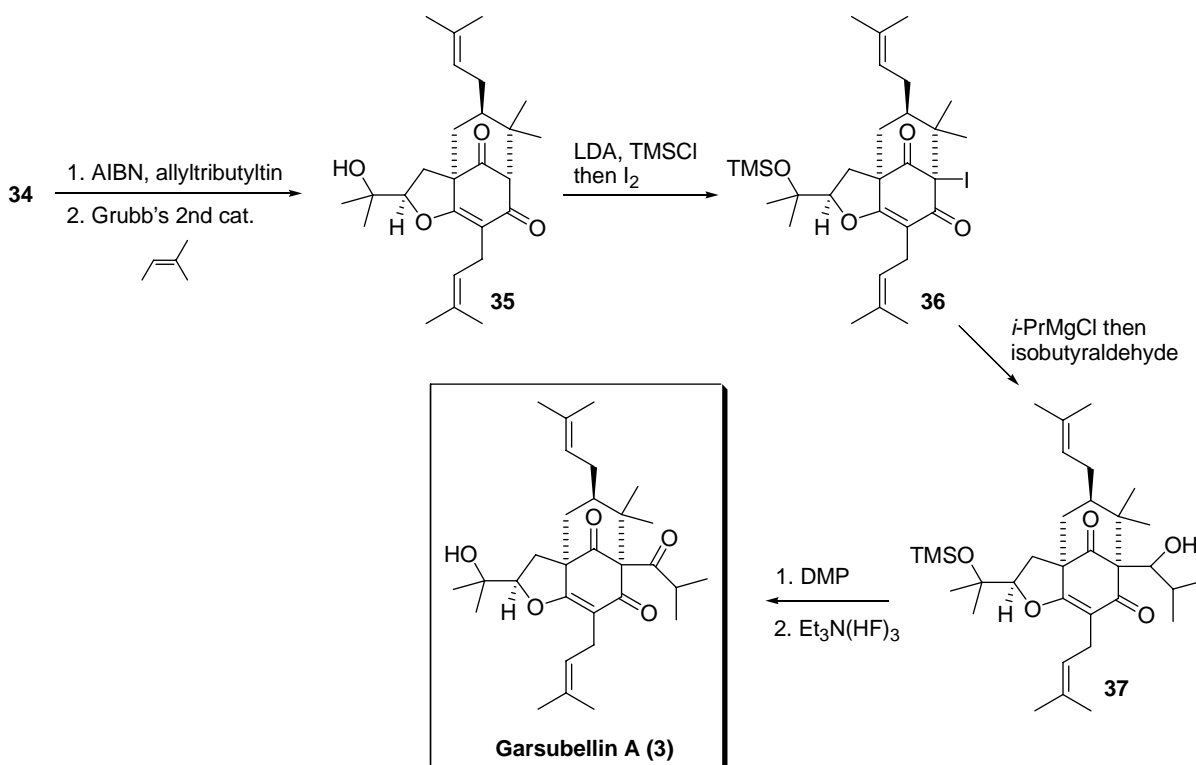
The synthesis commenced with regioselective prenylation of the protected phloroglucinol derivative (Scheme 5). Dihydroxylation of **27**, followed by acetonide formation and desilylation using TBAF, gave phenol **28**. The product **29** was obtained by allylation of **28**, either by direct allylation at the *para* carbon or by *O*-allylation, followed in sequence by rapid *o*-Claisen and Cope-like rearrangements. Upon treatment with aqueous acid, the acetonide group of **29** was removed, and ensuing conjugate addition and hydrolysis provided **30** as a single diastereomer. An olefin cross metathesis reaction converted the allyl group into a prenyl group. Iodocarbocyclization led to **31**, which contained the key bicyclo[3.3.1]nonane ring system.



Scheme 6

Vinylic iodination of **31** using the iodine/CAN system gave triiodinated compound **32**. Metal-halogen exchange using excess isopropylmagnesium chloride with careful temperature control promoted a transannular Wurtz cyclopropanation reaction. Upon allylation of the remaining vinylic Grignard intermediate, **33** was produced, which was then successfully returned to the bicyclo[3.3.1]nonane skeleton by treatment with TMSI. Allyltributyltin-mediated radical allylation introduced an allyl group to the sterically favored *exo* face. The product was subjected to cross metathesis reactions to install two prenyl moieties.

Disilylation of both the tertiary alcohol and bridgehead carbon positions of **35**, followed by iodination, provided **36**. Metal-halogen exchange and subsequent treatment with isobutyraldehyde yielded adduct **37**. Oxidation and deprotection of the TMS ether completed the synthesis of garsubellin A (**3**).



Scheme 7

Danishefsky's synthetic route is direct and efficient, and employed a biomimetic approach in the initial stage. However, given the modest and variable yields of some steps, there is room for improvement. Keeping in mind that this class of natural products contains the bicyclic acyl phloroglucin subunit, the main focus of this study will be placed on finding

an efficient route for the construction of the fully elaborated bicyclo[3.3.1]nonane skeleton, and also its successful application to their total synthesis.

Results and Discussion

The synthetically challenging structure and diverse biological activities of the phloroglucinol-containing natural products prompted a synthetic study to establish a general strategy towards the bicyclic core. This could lead to a total synthesis of this natural product (Figure 3).

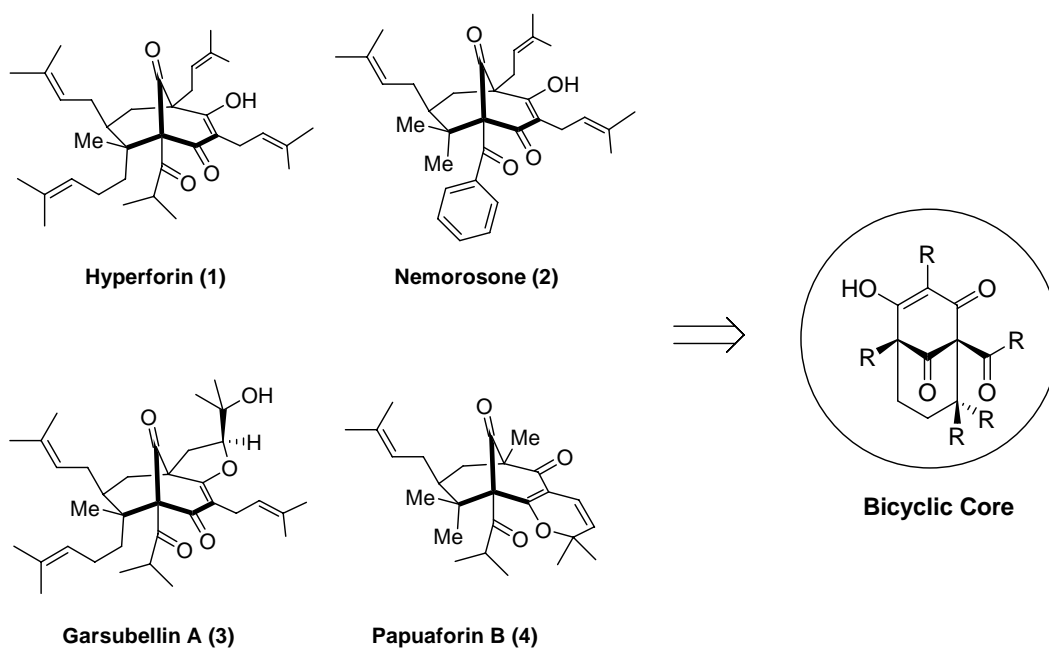
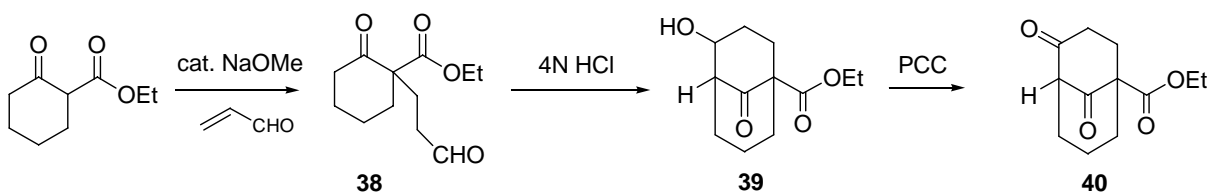


Figure 3. Bicyclic core structure of PPAPs

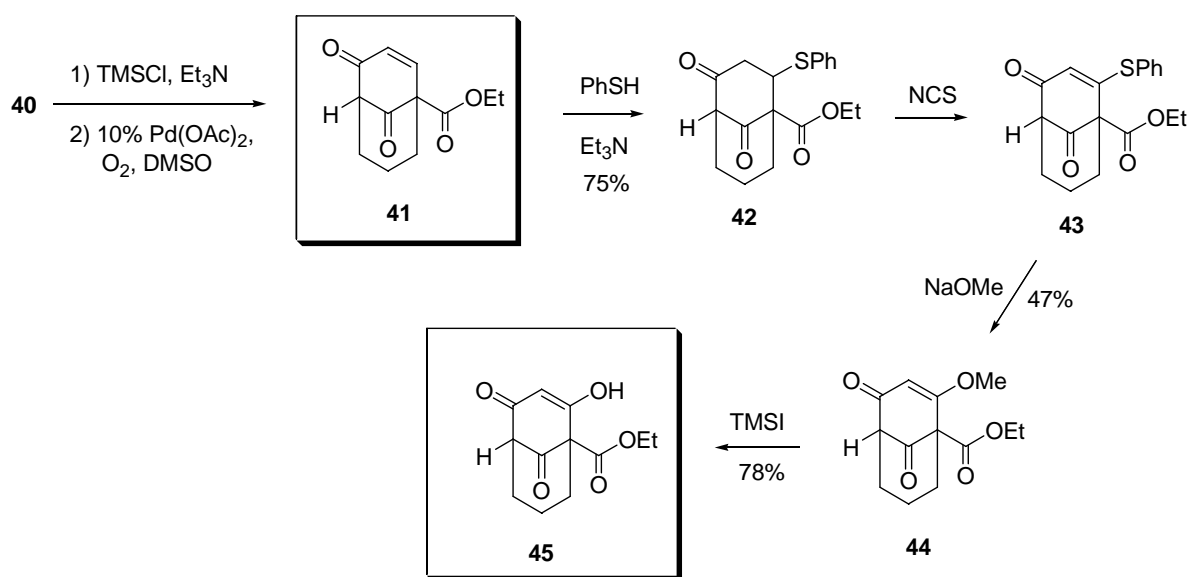
Our initial approach commenced with the Michael addition²⁶ of ethyl 2-cyclohexanone carboxylate with acrolein using a catalytic amount of sodium ethoxide to

produce aldehyde **38** (Scheme 8). Intramolecular aldol condensation of aldehyde **38** to produce alcohol **39** under acidic conditions, followed by oxidation of **39** with pyridinium chlorochromate, produced ketone **40** (72% overall yield from ethyl 2-cyclohexanone carboxylate).



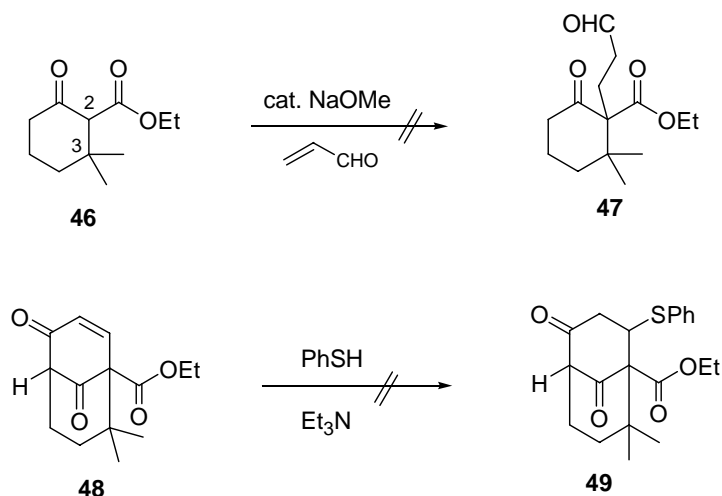
Scheme 8

With ketone **40** in hand, the conversion to enone **41** was achieved using conditions developed by Larock and Kraus²⁷ (Scheme 9). After several attempts, we found an efficient way to construct the enolic bicyclic β -diketone **45** from the key intermediate **41** as depicted in Scheme 9.



Scheme 9

Although this result for the functionalized bicyclo[3.3.1]nonane synthesis was successful, we found some limitations of this synthetic strategy for its practical application towards the more elaborated bicyclic core. According to our preliminary studies, as shown in Scheme 10, the Michael addition of acrolein onto the cyclohexanone carboxylate **46** yielded no desired product. This presumably resulted from the steric hindrance of the geminal dimethyl group of the enolate. The protocol employing the conjugate addition of benzenethiol to the bicyclic enone **41** required a multistep route to produce the desired β -diketone **45** (Scheme 9). Furthermore, benzenethiol did not react with **48** (Scheme 10).



Scheme 10

The synthetic challenge of establishing the bicyclic skeleton in a sterically demanding environment prompted us to find a better synthetic route to overcome these problems. Our second approach to the target molecule relied on the construction of the bicyclic β -diketone compound via cyclization, followed by oxidation, as shown in the retrosynthetic analysis

(Figure 4). After the functionalized bicyclic core is constructed, the β -diketone would be constructed to obtain the target molecule.

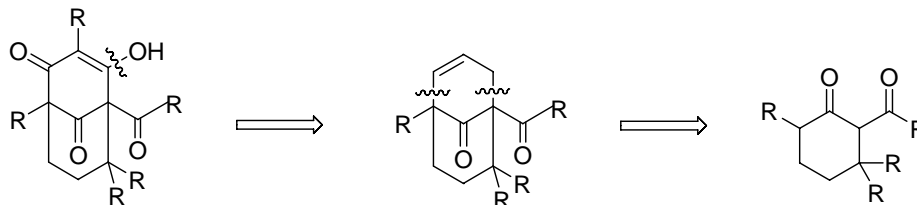
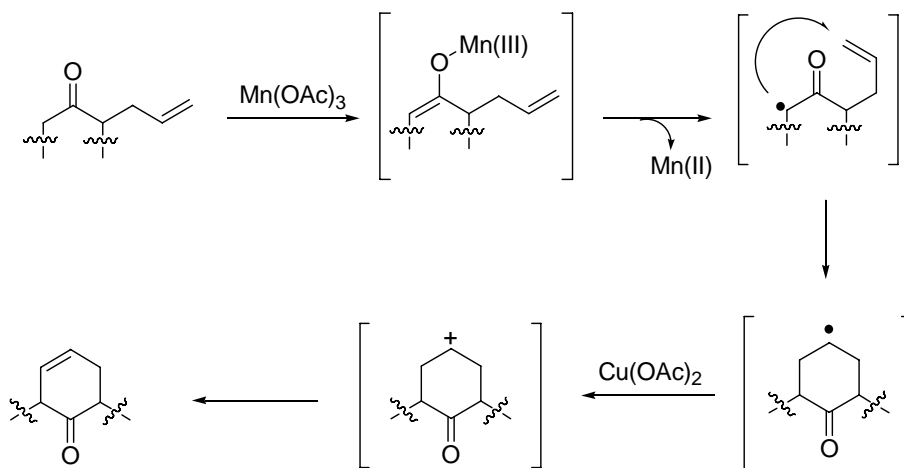


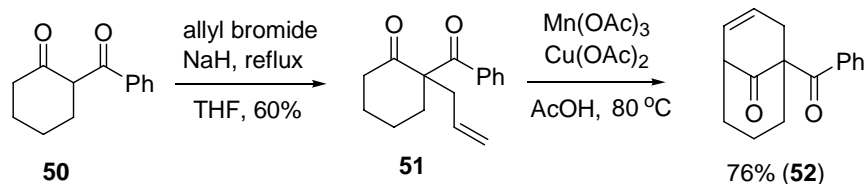
Figure 4. Retrosynthetic analysis

In the course of a program directed towards a successful route for the synthesis of the bicyclic core unit, manganese(III)-mediated oxidative radical cyclizations caught our attention. This methodology has been extensively investigated by Snider and co-workers.²⁸ It requires an alkene moiety to form a bicyclic frame. The allyl-substituted starting compound may be readily accessible (Scheme 11).



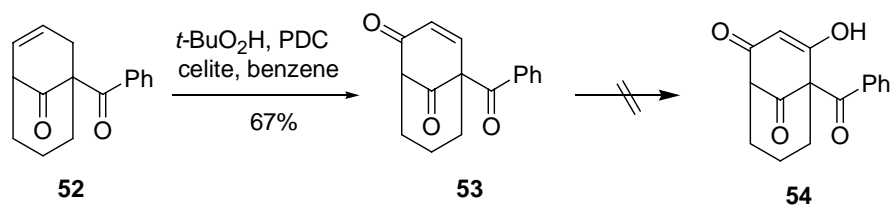
Scheme 11. The oxidative free-radical cyclization mechanism

Manganese(III)-mediated oxidative radical cyclization provides additional benefits. First, the reaction is quite general. Second, it might enable the construction of the bicyclic structure with a handle for introducing the β -diketone functionality.



Scheme 12

Our synthetic route began with the known 2-benzoylcyclohexanone (**50**), since the benzoyl group in compound **50** is present in the natural product nemosorone (**2**) (Scheme 12). Alkylation with allyl bromide and sodium hydride at an elevated temperature yielded allylated compound **51** in 60% yield. With this compound, cyclization using manganic triacetate and cupric acetate according to the method of Snider gave a 76% isolation yield of the desired diketone **52** and a trace amount of the exo-cyclization by-product.



Scheme 13

Cyclized product **52** was then oxidized using PDC/*t*-BuO₂H to generate enone **53** (Scheme 13), a key intermediate for introducing the β -diketone. However, efforts to induce bicyclic β -diketone under a variety of reaction conditions were not successful.

In order to minimize the number of synthetic steps and increase the reactivity of the bicyclic enone, generation of β -halo enone **56** was attempted (Figure 5). The presence of a good leaving group would increase the electrophilicity of enone **56**, thus making it more susceptible to conjugate addition. In essence, the β -bromo enone's electrophilicity would be comparable to an acid chloride. The retrosynthetic analysis depicted in Figure 5 indicates that the β -diketone **55** could be made from β -bromo enone **56**, which could be made from the bicyclic alkene **57**. Employing the synthetic strategy, the key step would be the transformation of the bicyclic olefin **57** to the corresponding β -halo enone **56**, since, to our knowledge, there is no literature precedent for the direct construction of β -bromo enones from disubstituted olefins.

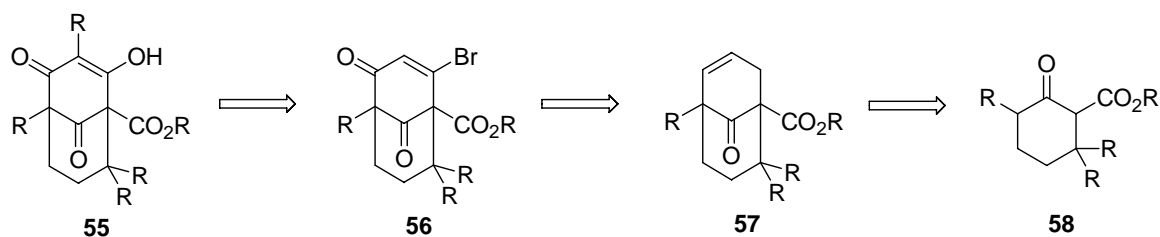
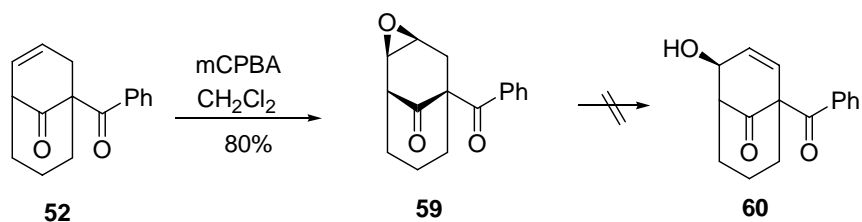


Figure 5. Retrosynthetic Analysis

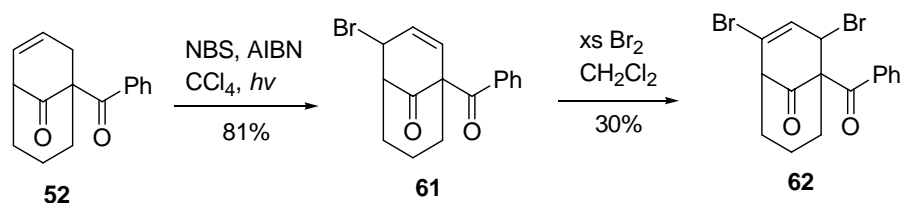
Our synthetic study commenced with previously prepared bicyclic compound **52** (Scheme 13). Epoxidation of **52** using MCPBA in methylene chloride produced epoxide **59**

in an 80% yield. Attempts to transform epoxide **59** to allylic alcohol **60** failed using several epoxide opening conditions, such as LDA, Al(O-*i*-Pr)₃, (PhSe)₂/NaBH₄, DBN/TMSI, DBU/TMSI and DIEA/TMSI.

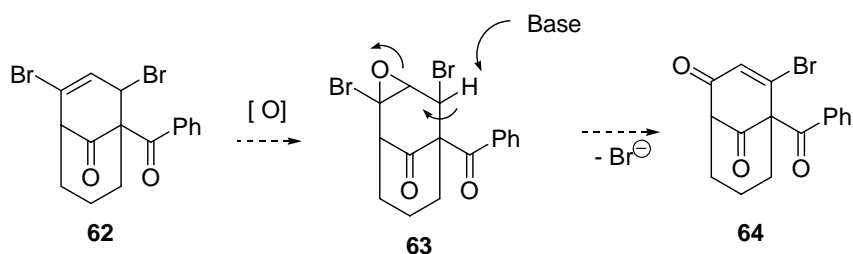


Scheme 13

Instead of using the unexpectedly stable epoxide **59**, we decided to introduce bromine onto the bicyclic compound **52**. An NBS/AIBN-mediated bromination of compound **52** generated the desired allylic bromo compound **61** in good yield. Upon treatment of compound **61** with excess bromine, dibromo compound **62** was produced in moderate yield.

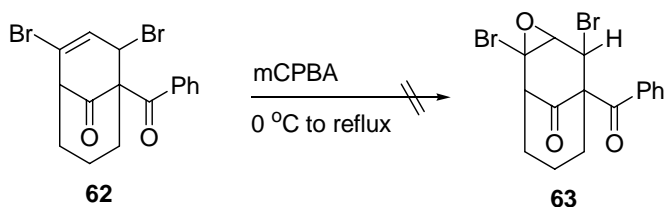


Scheme 14

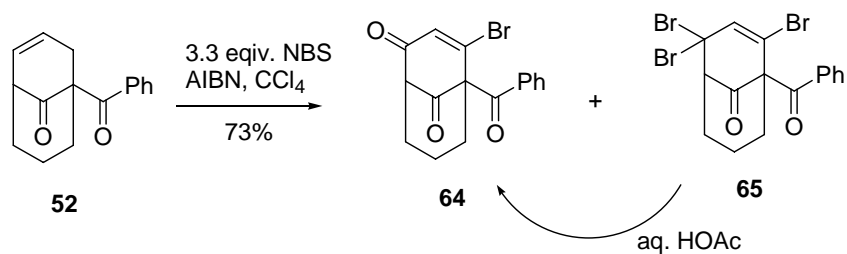


Scheme 15

Attempted epoxidation of dibromide **62** by MCPBA failed (Scheme 16). Based on 1H NMR spectral analysis, it produced a complex mixture with mostly unreacted **62**. We were pleased to find that treatment of **52** with 3.3 equivalents of NBS and a catalytic amount of AIBN gave a mixture of enone **64** and tribromide **65** in a 73% combined yield (Scheme 17). Tribromide **65**, a precursor to **64**, was readily converted into **64** upon treatment with hot aqueous acetic acid. The transformation of diketone **50** to enone **64** was achieved in only three steps with a 33% overall yield.

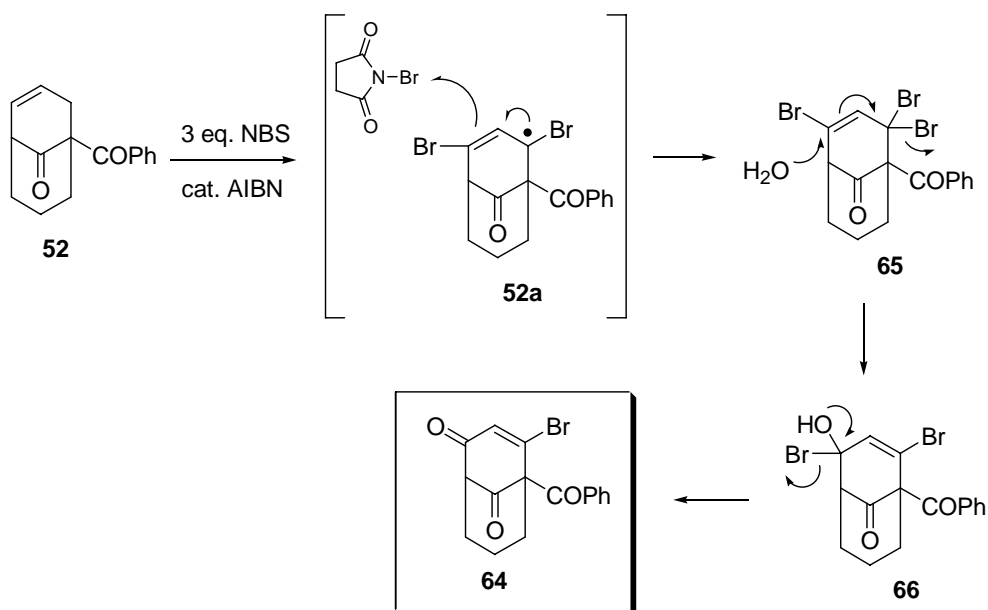


Scheme 16



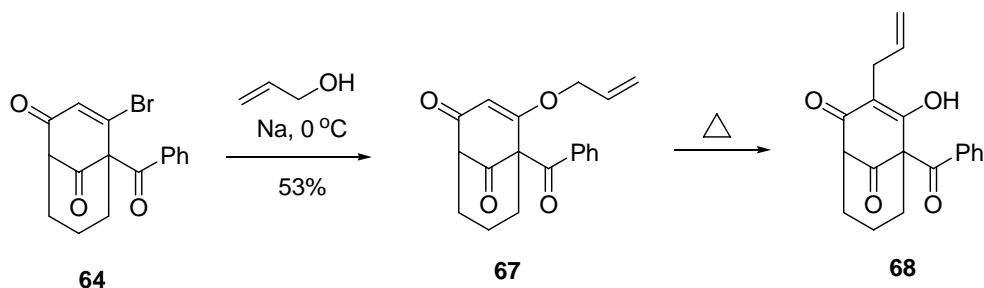
Scheme 17

We believe that compound **52** may undergo tribrominations in the presence of excess NBS, which was then hydrolyzed leading to **64**.

Scheme 18. Plausible mechanism to β -bromo enone **64**

Displacement of β -bromo enone **64** using sodium allyloxide provided **67**, which was then heated in a sealed tube at 170 °C to afford tetraketone **68** via a Claisen rearrangement

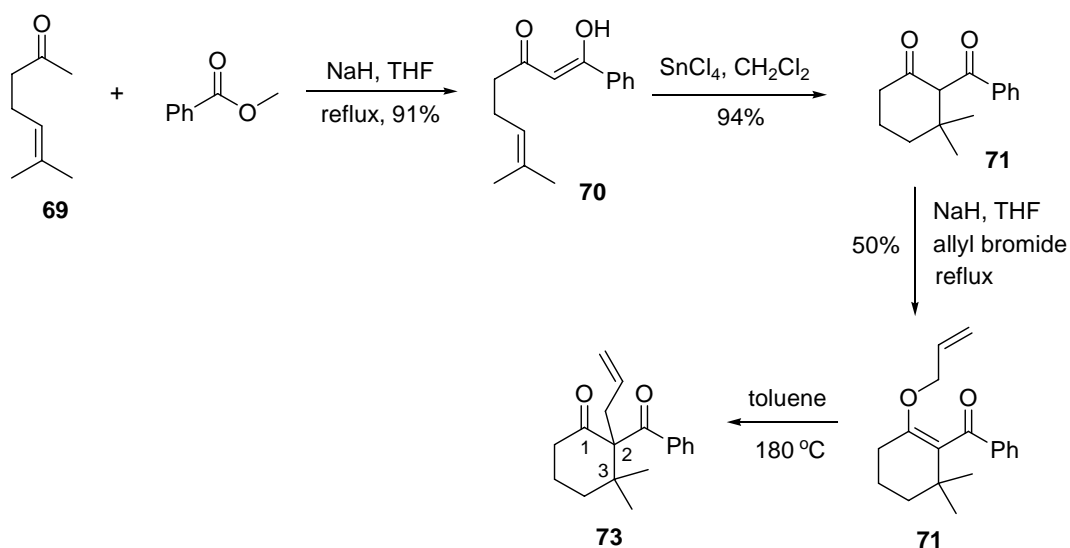
(Scheme 19). The structure assignment of **68** was supported by ^1H and ^{13}C NMR, IR and high resolution mass spectrometry.



Scheme 19

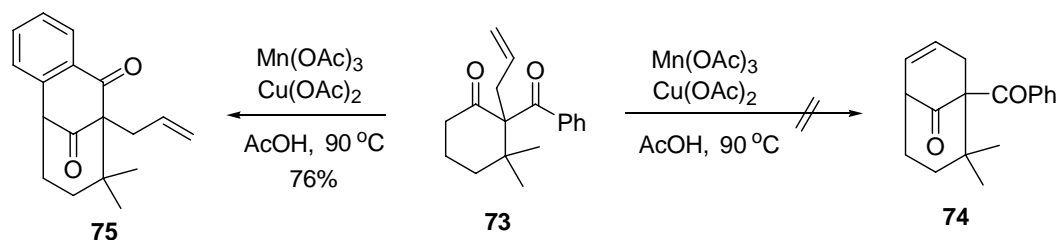
The synthesis of **68** in good overall yield constitutes a useful preparation of analogs of nemorosonone (**2**). The synthetic route is direct and flexible enough to be extended to a synthesis of natural products, such as hyperforin (**1**) and its analogues.

The next objective was the preparation of a more advanced intermediate bearing a geminal dimethyl group at C3. The diketone **73** was synthesized based on Rothberg's protocol in his synthesis of dehydroambliol-A.²⁹ The synthesis began with condensation of 6-methyl-5-hepten-2-one and methyl benzoate to produce diketone **70** (Scheme 20). The Lewis acid-catalyzed cyclization of **70** afforded **71**. Treatment of **71** with sodium hydride and allyl bromide at boiling temperature yielded *O*-allylated product **71** in good yield. Heating at 180 °C in a sealed tube gave the rearranged compound **73**.

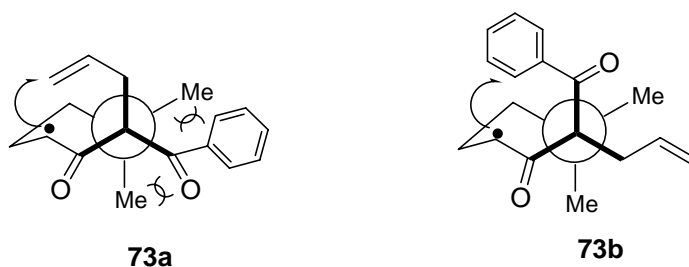


Scheme 20

Contrary to our expectation, the reaction of **73** with Mn(OAc)₃/Cu(OAc)₂ in acetic acid at 90 °C exclusively afforded compound **75**. We did not find any evidence for the formation of **74** (Scheme 20). Although the exclusive formation of **75** could not be explained, it is conceivable that the more favorable conformation of the α -carbonyl radical could be **73b**, which positions the benzoyl group in an axial position. This conformation appeared to have less steric interaction with the geminal dimethyl group (Scheme 21).

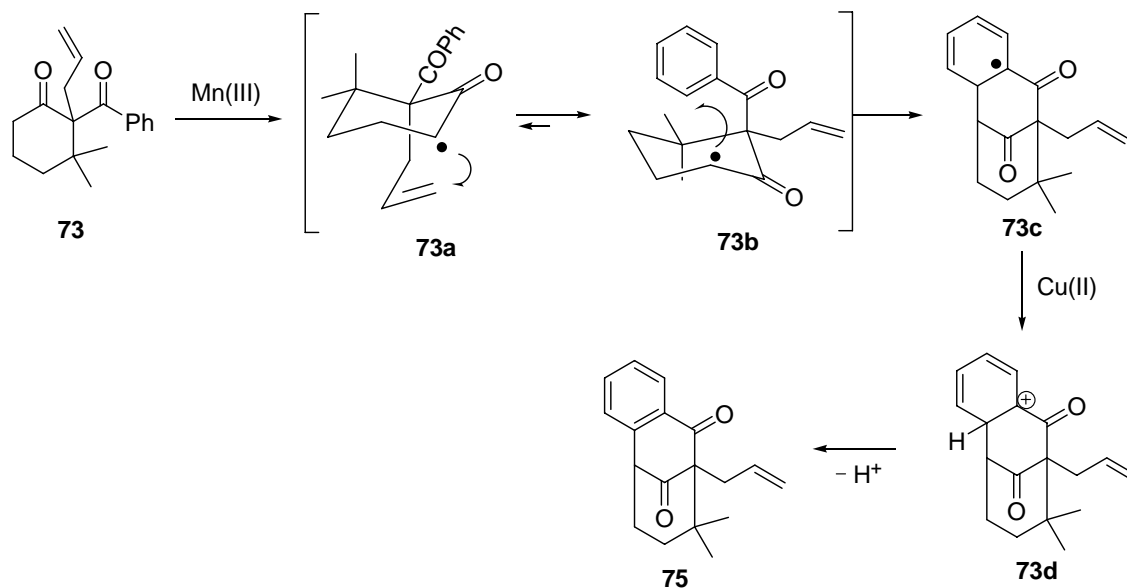


Scheme 20



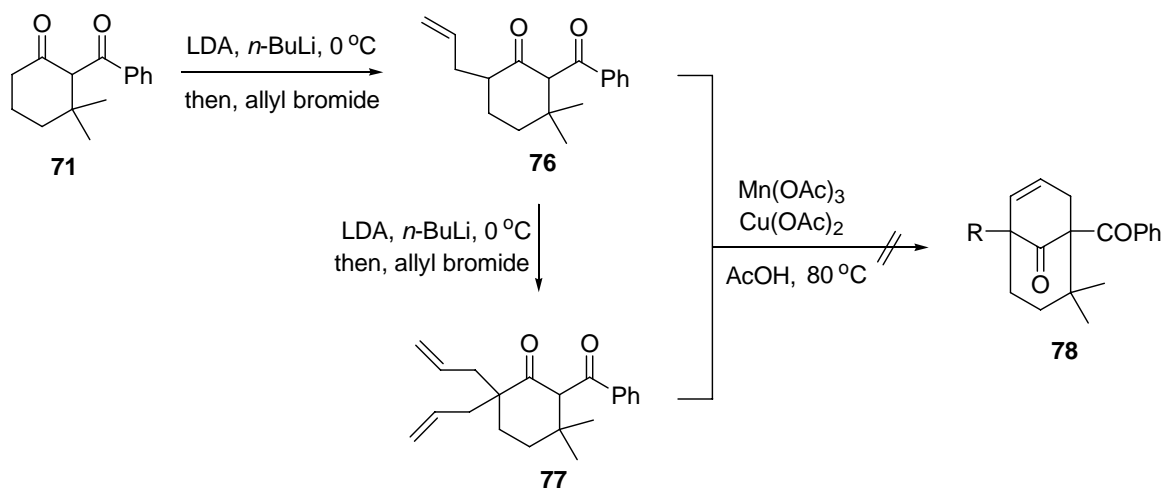
Scheme 21

After *ortho* attack of the α -carbonyl radical on the benzoyl group, the resonance-stabilized α -keto radical adduct **73c** is generated. It is then oxidized by Cu(II), and readily undergoes aromatization to form diketone **75**.



Scheme 22

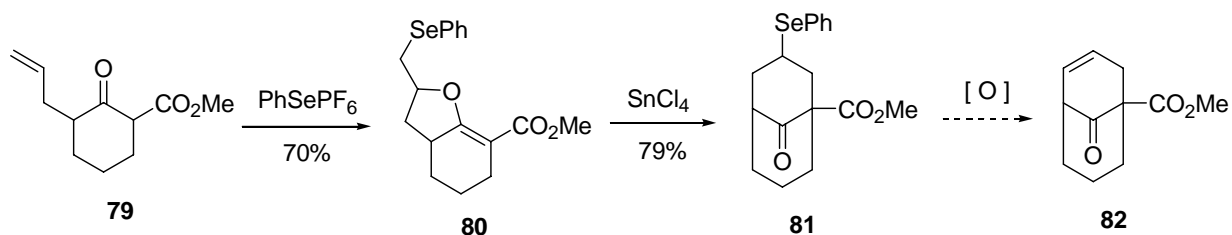
To circumvent the problems associated with the conformational issues, oxidative radical cyclizations using regioisomers of diketone **73**, such as **76** or diallylic diketone **77**, were examined (Scheme 23). LDA-mediated enolation and subsequent dianion formation by adding *n*-butyllithium at 0 °C, followed by treatment with allyl bromide, furnished diketone **76** in a 56% yield. Diallylation product **77** was also obtained in 50% yield by repeating the same conditions. Unfortunately, attempted manganic triacetate-mediated oxidative cyclizations failed. Neither **76**, nor **77**, gave the desired cyclized products. Only starting compounds were recovered.



Scheme 23

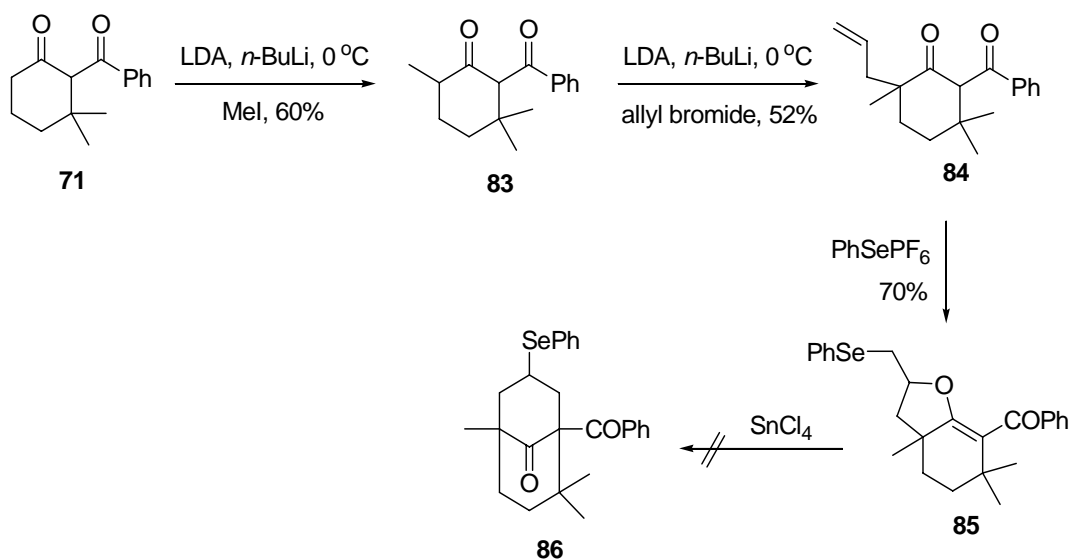
In 1980, Ley and co-workers³⁰ reported a selenium-mediated cyclization reaction (Scheme 24). This protocol interested us as another cyclization method for our system. The reaction furnished oxygen-cyclization compound **80**. Intramolecular rearrangement of **80** under Lewis acid conditions gave the corresponding carbon-cyclized counterpart **81**, which

seemed particularly interesting, since oxidative elimination of the phenylselenenyl group in **81** may provide a bicyclo[3.3.1]nonene unit, a precursor for our key bromination reaction.



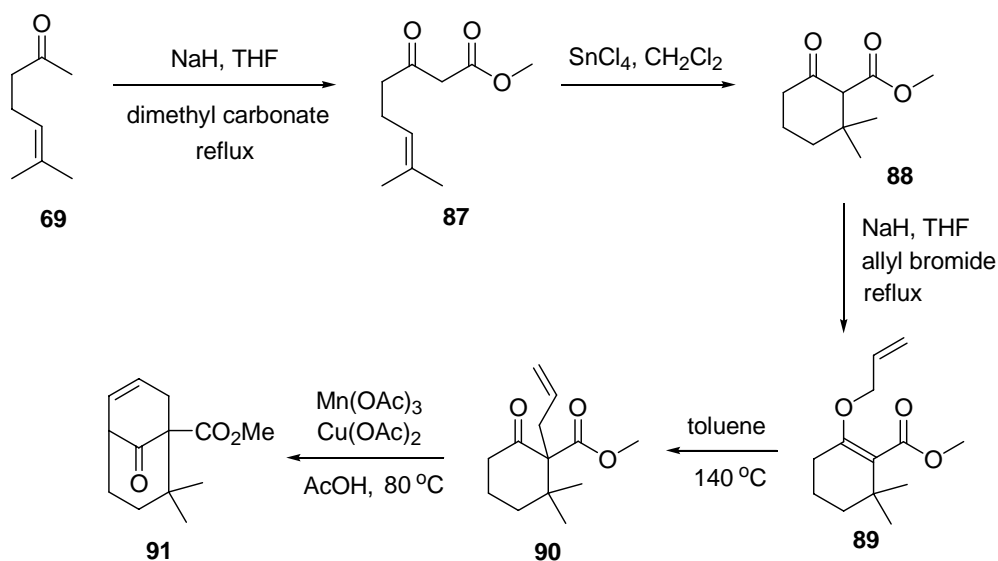
Scheme 24

To investigate the applicability of Ley's protocol to our system, compound **71** was first methylated via the dianion. Subsequent allylation by the same method yielded **84**. Compound **84** was treated with PhSePF₆ at -78 °C and then slowly warmed to room temperature to afford selenide **85** in a 70% yield.



Scheme 25

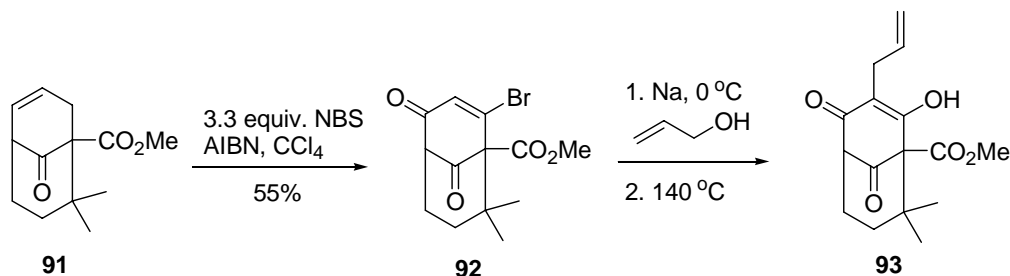
Unfortunately, the attempted carbon-carbon bond forming reactions by the rearrangement of selenide **85** in the presence of SnCl_4 were not successful. The reactions either went back to **84** or remained as **85**. As this disappointing result might be related with the decreased reactivity of the diketone with respect to the approaching electrophile due to the decreased reactivity of the diketone with respect to the approaching electrophile due to the strong steric demand of the geminal dimethyl group, it was felt that the oxidative radical cyclization conditions $[\text{Mn}(\text{OAc})_3/\text{Cu}(\text{OAc})_2]$ might solve this problem. First, the installation of an allyl group onto the sterically hindered system proceeds with ease. Second, aromatic radical cyclizations could be avoidable by changing the benzoyl group to an ester. Recall that PPAPs contain isobutyryl or benzoyl groups at the bridgehead carbon. The ester group could be easily converted either into isobutyryl or benzoyl group.



Scheme 26

The starting material was the known keto ester **90** that was conveniently prepared following Rothberg's account.²⁹ With this keto ester **90** in hand, the manganic triacetate

oxidative cyclization was then examined. To our delight, **91** was obtained without difficulty under the reaction conditions outlined in Scheme 26. Bromination of **91** with 3.5 equiv. of NBS in the presence of molecular sieves directly afforded β -bromo enone **92** in a 55% yield (Scheme 27). In this case, no evidence was found for the tribromide. The ^{13}C NMR spectrum supported the production of one regioisomer. The structure for **92** was assigned based on a comparison of the chemical shift of the bridgehead hydrogen in **92** with that of the bridgehead hydrogen in a model system.³¹ Substitution of bromide **92** with sodium allyloxide, followed by a Claisen rearrangement at 140 °C, produced tetraketone **93**.

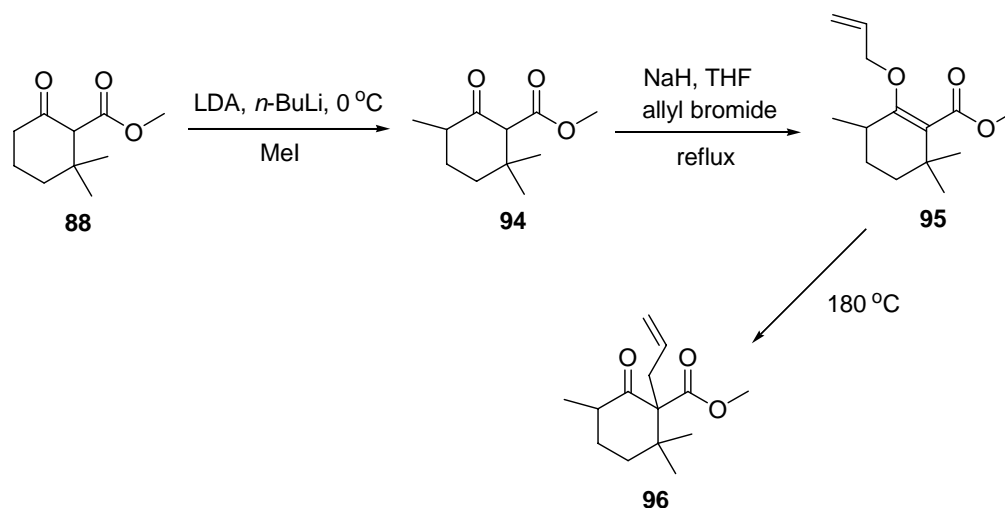


Scheme 27

A concise synthesis of the functionalized bicyclic core subunit of acyl phloroglucinol natural products was achieved in eight steps. In the above sequence of events leading to **93**, the bromination-hydrolysis methodology served the crucial role to transform bicyclic olefins into bicyclic β -diketones. At this point, we must point out that access to the natural products required the extension of this chemistry to more substituted compounds, since this class of natural products contains either a prenyl or a methyl group on the bridgehead position as illustrated in Figure 3.

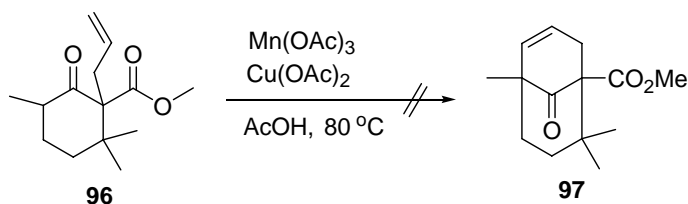
Based on our success, we focused on the application of this synthetic sequence to more heavily substituted compounds bearing two quaternary centers. This will provide a bicyclo[3.3.1]nonane ring system with much closer structural analogy to the natural products.

The synthesis started from previously prepared diketone **88** (Scheme 28). Treatment of diketone **88** with LDA, followed by *n*-butyllithium at 0 °C, gave a dianionic intermediate, which was quenched by iodomethane to give the corresponding diketone **94** in a 61% yield. Allylation using NaH and allyl bromide generated *O*-allylated compound **95**, which then underwent thermal rearrangements to the desired *C*-allylation compound **96** in a 54% yield.



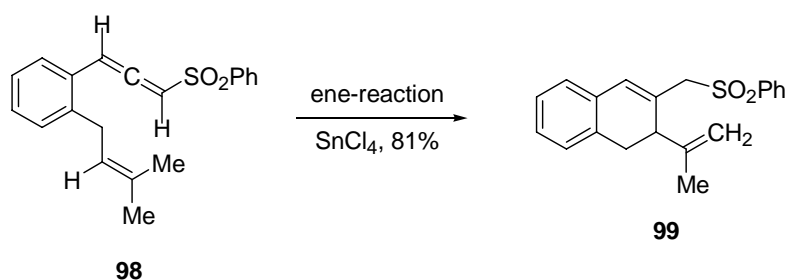
Scheme 28

Intramolecular cyclization of compound **96** was attempted by the use of manganic triacetate and cupric acetate in acetic acid at 80 °C as demonstrated in the Snider protocol.²⁸ Unfortunately, it failed to yield the bicyclo[3.3.1]nonane skeleton **97**. Instead, starting compounds were recovered.



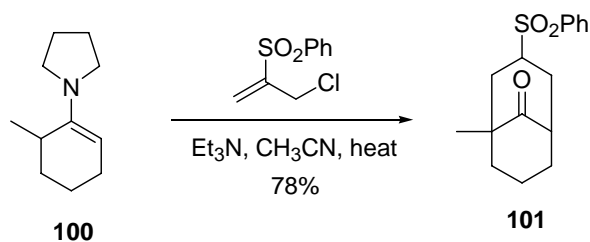
Scheme 29

In the course of searching for an alternative method to construct the bicyclo[3.3.1]nonane skeletal framework, we found that Padwa had developed innovative methodology using sulfones as Michael acceptors (Scheme 30).³²



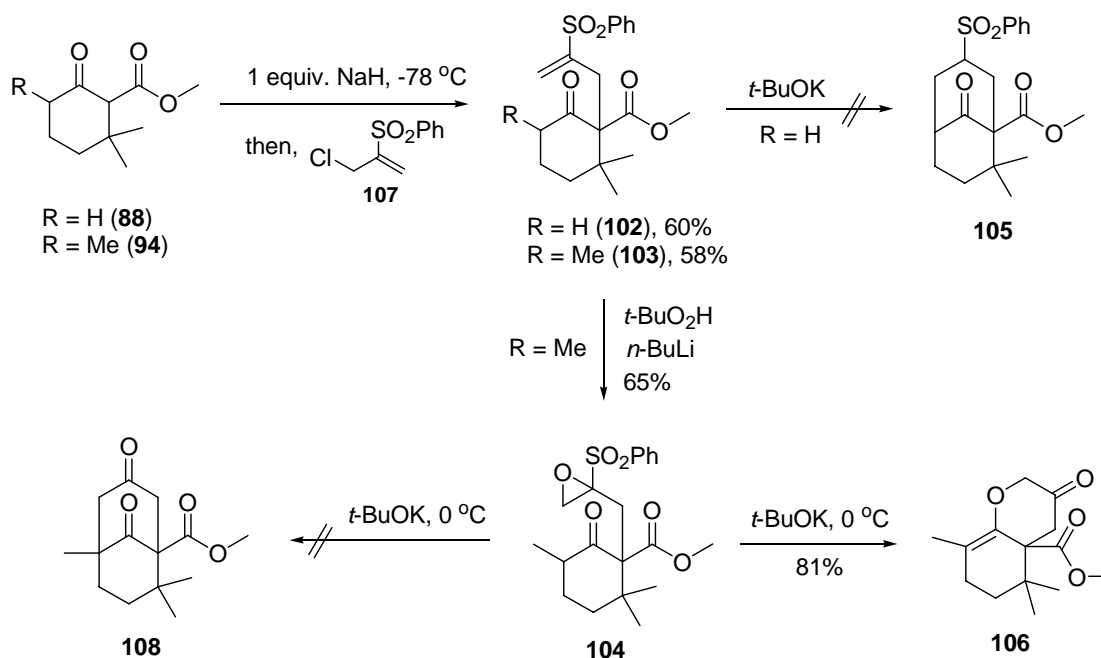
Scheme 30

More interestingly, Anzeveno and co-workers³³ have reported α,α' -annulation of cyclic ketones using 3-chloro-2-phenylsulfonyl-1-propene as a Michael acceptor. It is noteworthy that it forms the bicyclic skeleton in good yield in one step by treatment of an enamine with a vinylic sulfone (Scheme 31). It was envisioned that this vinylic sulfone could permit construction of the functionalized bicyclic skeleton even in a sterically congested system. Based on our literature studies, we applied this chemistry to our cyclization step using 3-chloro-2-phenylsulfonyl-1-propene as Michael acceptor.



Scheme 31

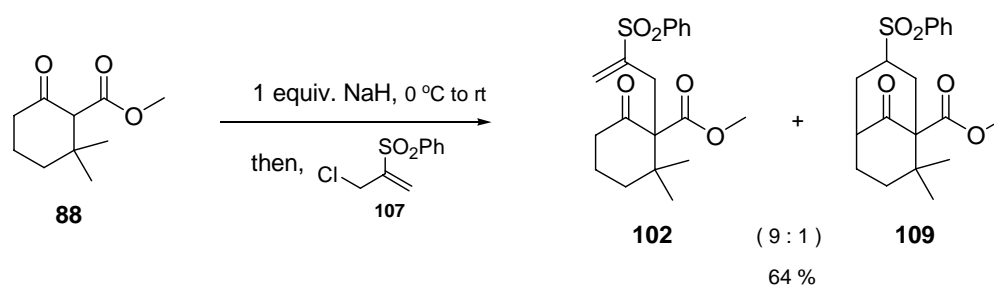
Instead of using enamines as a nucleophile, keto esters **88** and **94** were used, because enamine formation could not be realized from α,α' -disubstituted ketones. Gratifyingly, the Michael addition of diketone **88** onto sulfone **107** in the presence of one equivalent of sodium hydride afforded vinylic sulfone **102** in a 60% yield (Scheme 32).



Scheme 32

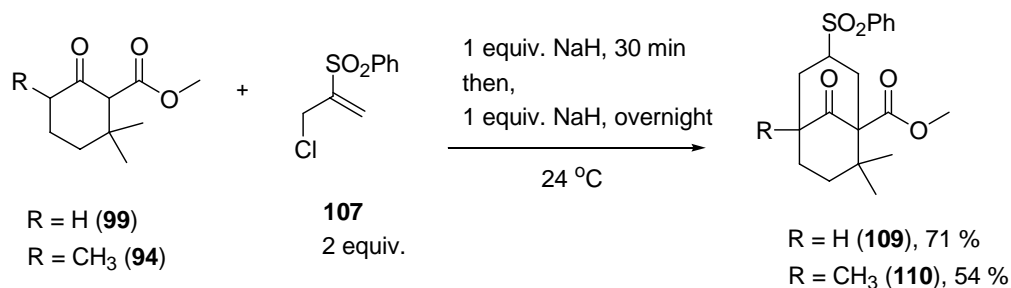
The sulfone **107** seemed to be a more reactive Michael acceptor than acrolein to overcome the steric hindrance of the geminal dimethyl group. Attempted Michael addition

of acrolein with diketone **46** failed. Michael addition of **107** onto the α -methylated keto ester **94** proceeded smoothly to afford **103** in good yield. However, cyclization of **102** with a strong base, such as potassium *tert*-butoxide, was unsuccessful. Further oxidation of compound **103** to epoxide **104**, followed by potassium *tert*-butoxide addition at 0 °C afforded *O*-cyclized product **106**.



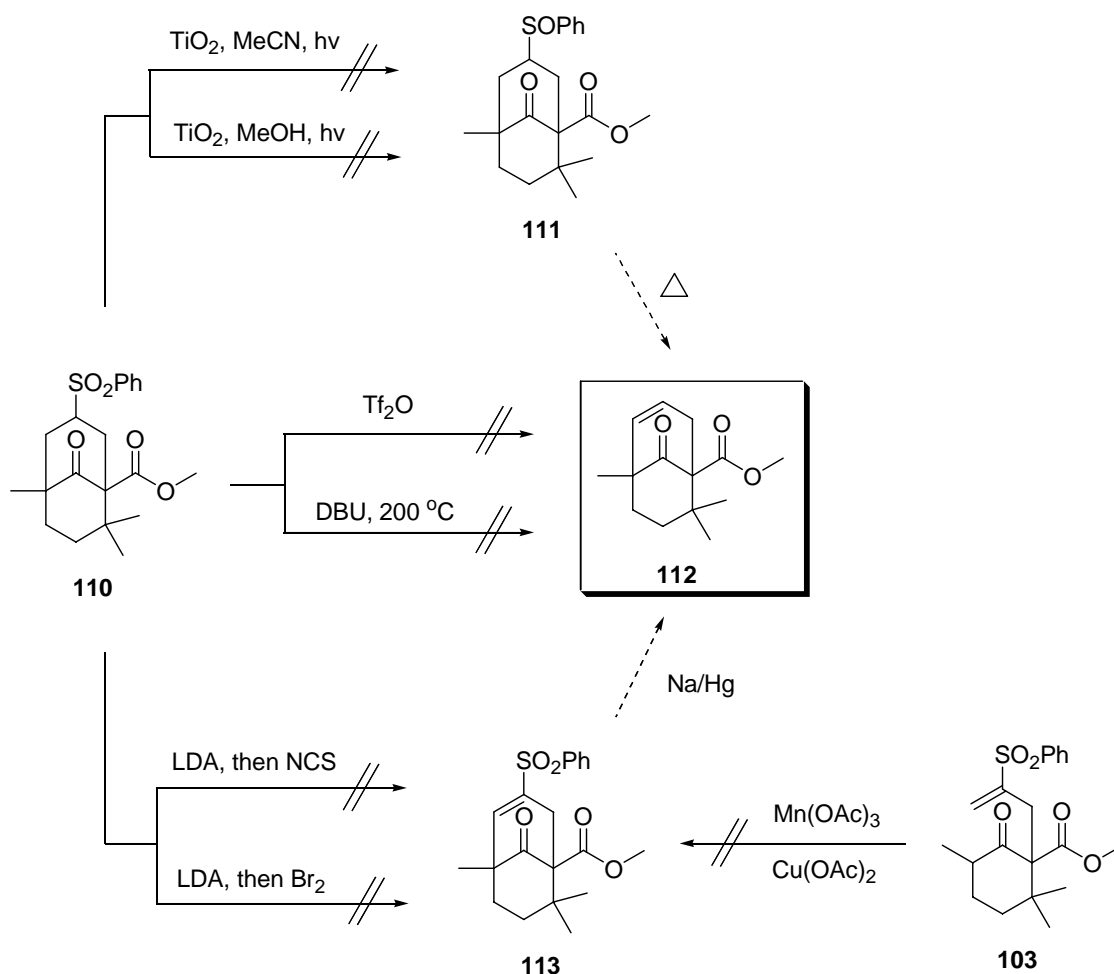
Scheme 33

Subjecting **88** to one equivalent of sodium hydride, followed by treatment with **107** and extending the reaction time to 16 hours at room temperature, produced a small portion of the desired bicyclic sulfone **109**, together with the major sulfone **102** in 64% combined yields.



Scheme 34

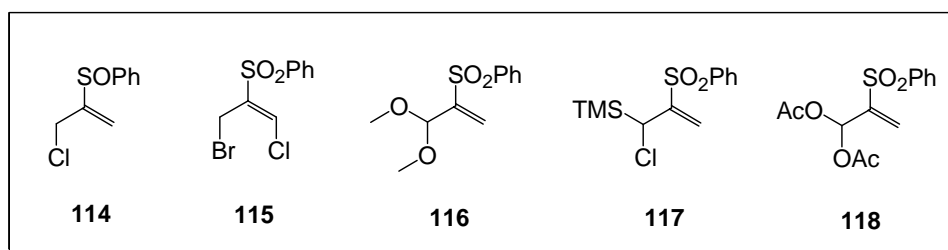
Although **109** was a minor product, it was envisaged that optimization of the conditions might lead to the bicyclic sulfone **109** in one pot or, at least, enhance the product ratio. Surprisingly enough, the use of two equivalents of sulfone **107** and two equivalents of sodium hydride at room temperature gave bicyclic sulfone **109** in good yield as the exclusive product (Scheme 34). This reaction was also successful for the α -methylated diketone **94**, which afforded bicyclic sulfone **110** in a 54% yield.



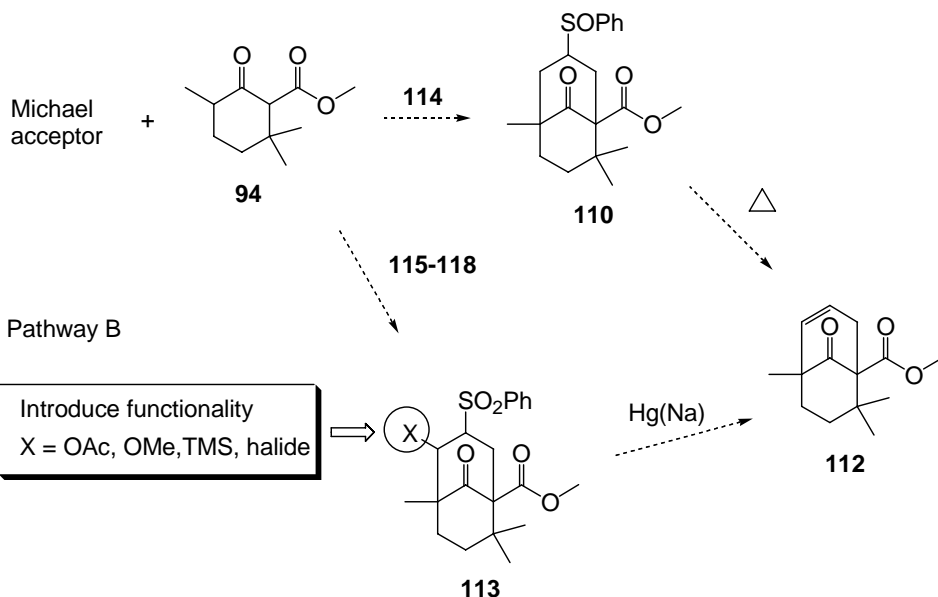
Scheme 35

The next task was conversion of sulfone **110** to the corresponding olefin **112** (Scheme 35). Our initial approach was the base-assisted elimination of sulfones, where the sulfone group acts as a leaving group, since sulfinates are well-known leaving groups.³⁴ Unfortunately, an attempted elimination reaction using DBU at 200 °C failed. Further efforts to produce compound **112** by conversion of sulfone **110** into vinylic sulfone **113** or sulfoxide **111** under a variety of different conditions were also unsuccessful. Taking into account the low basicity of sulfones compared to sulfoxides and the sterically congested bicyclic domain, the unsuccessful outcomes resulted from either functional group interconversions or unexpected heat-assisted desulfonylations.

With these disappointing results, we prepared a series of Michael acceptors based on sulfone **107**, which could lead to compound **112** from either pathway A or B (Scheme 36). The synthesis of compound **110** would be realized via pathway A where sulfoxide **114** is employed. Sulfoxide **110** could act as a leaving group to afford alkene **112**. It is known that the proton affinity of dimethyl sulfoxide is 17 kcal/mol more than that of dimethyl sulfone.³⁵ Pathway B describes an alternative approach to **112** employing various sulfone derivatives **115-118** with the idea of performing two successive Michael additions to form a bridged bicyclic system. Reductive elimination of the sulfone moiety and subsequent liberation of leaving groups (X⁻, MeO⁻, AcO⁻, etc.) will give alkene **112**.



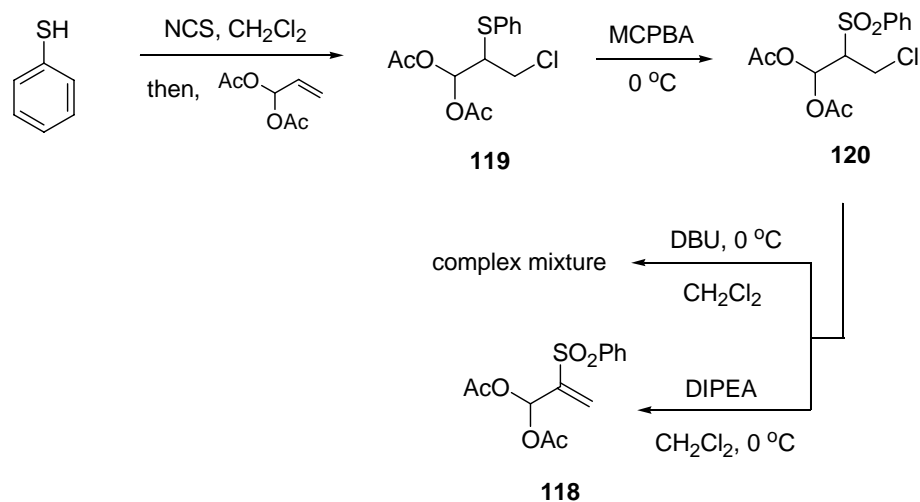
Pathway A



Scheme 36

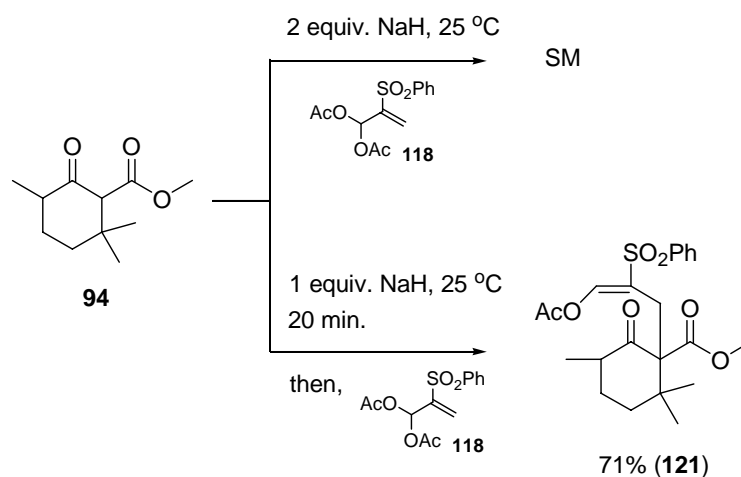
After several screening tests for addition reactions of keto ester **94** and Michael acceptors **114-118**, diacetoxy sulfone **118** showed the most promising results. The synthesis of **118** began with commercially available 3,3-diacetoxypropene. Addition of phenylsulfenyl chloride followed by oxidation of the sulfide with 2 equiv of MCPBA, gave sulfone **120**. DBU-mediated dehydrochlorination of **120** was unsuccessful. It produced a complex mixture. However, the use of diisopropylethylamine (DIPEA) as a substitute for DBU,

sulfone **118** was obtained as the exclusive product. The synthesis of **118** was accomplished in an 80% overall yield on a 50 mmol scale (Scheme 37).



Scheme 37

At first, the attempted Michael addition of diketone **94** with sulfone **118** in the presence of two equivalents of sodium hydride in THF at $25\text{ }^\circ\text{C}$ failed to give the addition product **121**. However, reaction of **94** with exactly one equivalent of sodium hydride, followed by the addition of sulfone **118**, furnished a 71% isolated yield of adduct **121** as one diastereomer based on proton NMR spectral analysis (Scheme 38). Excess sodium hydride seems to promote the decomposition of sulfone **118** before it participates in the addition reaction. The stereochemistry of the methyl group relative to the quaternary center was not established. Once it forms the bicycle[3.3.1]nonane skeleton, the relative stereochemistry of the methyl group would be established. The *E*-stereochemistry of β -acetoxy sulfone **121** was determined by a NOESY experiment.

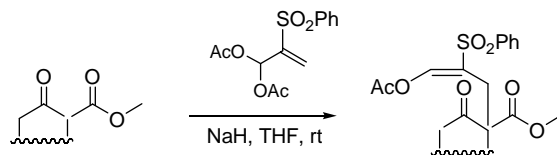


Scheme 38

Similarly, Michael addition reactions to generate β -acetoxy sulfone adducts were also examined to extend and generalize the applicability of **118** to various keto esters (Table 1). Overall reaction yields were good to excellent (70 ~ 100%) as shown in Table 1. In the case of less sterically hindered cyclic keto esters (Table 1, entries 3-6), excellent yields of Michael addition products were obtained. An acyclic keto ester (Table 1, entry 7) also furnished a 70% isolated yield of adduct.

Cyclization of keto sulfone **121** using one equiv of potassium *tert*-butoxide at ambient temperature produced three products, esters **122**, **123** and **124** in 20%, 5% and 50% yields, respectively (Scheme 39). The product **122** was derived from the deacetylation of **123**. In order to enhance the yield of the cyclization products, **121** was converted to pivalate **125** in 80% yield using potassium *tert*-butoxide and pivaloyl chloride at 0 °C.

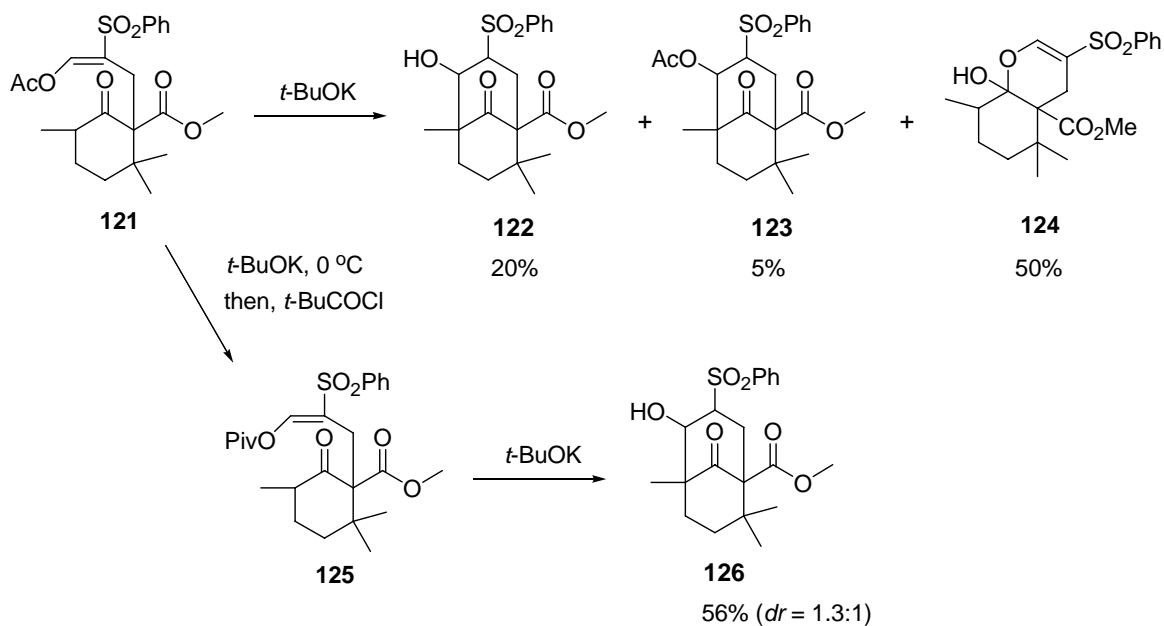
Table 1. Michael addition reactions of 3,3-diacetoxy-2-(phenylsulfonyl)propene and β -keto esters



| entry | substrate | product | yield (%) |
|-------|-----------|---------|-----------------|
| 1 | | | 71 ^a |
| 2 | | | 70 ^a |
| 3 | | | 100 |
| 4 | | | 75 ^b |
| 5 | | | 91 |
| 6 | | | 100 |
| 7 | | | 75 |

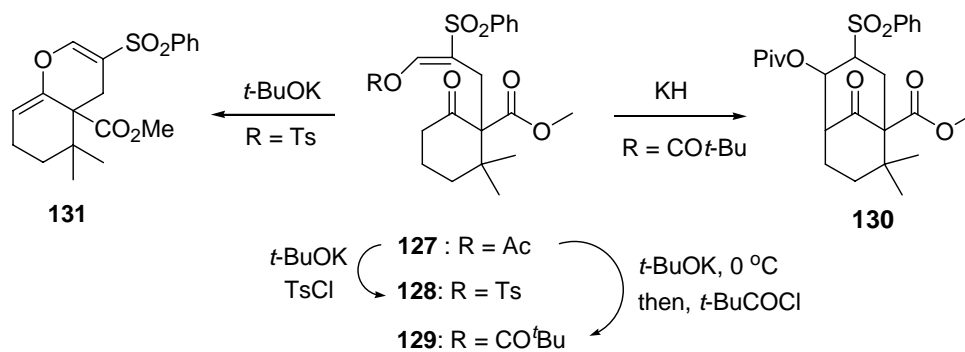
^aAfter the addition of the sulfone, Ac₂O (1 equiv.) was added. ^bUpon completion of the sulfonylations, *t*-BuOK (3 equiv.) was added at 0 °C, followed by addition of pivaloyl chloride (3equiv.).

Reaction of **125** with potassium *tert*-butoxide in THF from 0 °C to room temperature afforded a 56% isolated yield of **126** as a 1.3:1 mixture of diastereomers.



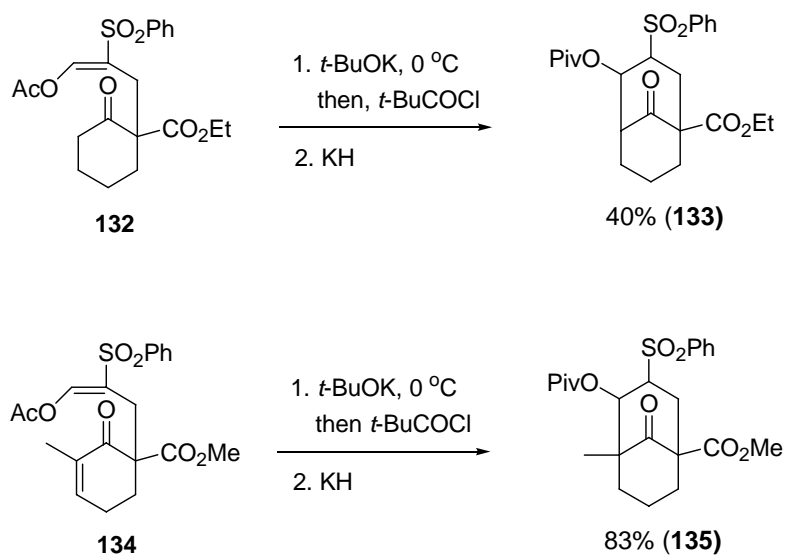
Scheme 39

Base-promoted cyclization of **127** also proved problematic due to the instability associated with the labile acetoxy group under basic conditions. Initially, sulfone **127** was converted into tosylate **128** using potassium *tert*-butoxide and *para*-toluenesulfonyl chloride at 0 °C. Cyclization of **128** with potassium *tert*-butoxide afforded **131** in a 90% yield. After the transformation of sulfone **127** to **129**, pivalate **129** was cyclized to **130** (single diastereomer based on proton NMR spectroscopy) in a 57% yield using KH in THF at 0 °C (Scheme 40).



Scheme 40

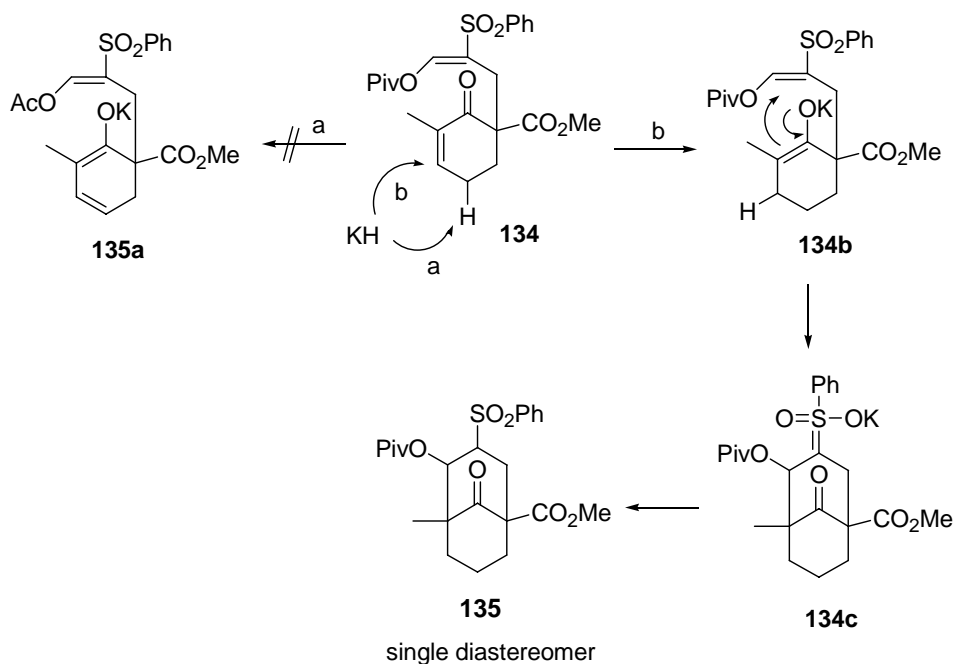
In view of the problems with acetate **121** and tosylate **127**, sulfones **132** and **134** were converted to the corresponding pivalates, which were then exposed to the cyclization conditions using potassium hydride. Both systems cyclized, producing adducts **133** and **135** in 40% and 83% yields, respectively.



Scheme 41

The formation of **135** was an unexpected result. The reaction of the pivalate derived

from **134** with potassium hydride might first undergo a rather unusual hydride addition to the enone system, which subsequently cyclized to generate pivalate **135**. The reaction proceeded very cleanly with generation of **135** in an 83% yield as a single diastereomer based on proton NMR analysis (Scheme 42).

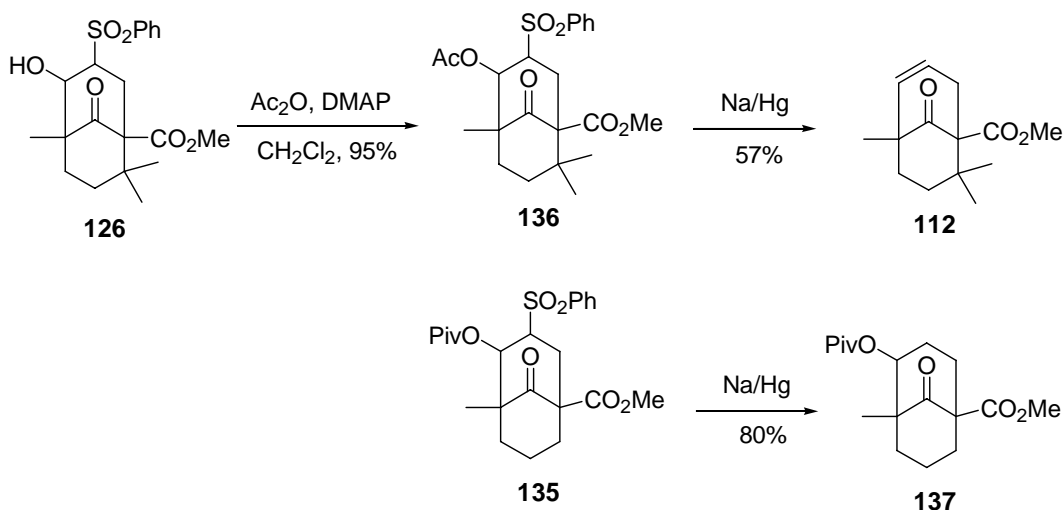


Scheme 42

Acetoxy sulfone **136**, obtained from alcohol **126** in a 95% yield by acetylation with acetic anhydride and DMAP in methylene chloride at 25 °C, was converted into the alkene **112** using sodium amalgam³⁶ in MeOH in 57% yield. Product **112** contained alkyl and acyl functions at bridgehead carbons, a pattern seen in phloroglucinol natural products.

Interestingly, pivalate **135** provided only desulfonated product **137** (Scheme 43). We did not

observe any elimination product. The reaction of diacetoxy sulfone **118** with β -keto esters provides a useful synthetic method for the preparation of complex bicyclic systems.



Scheme 43

The reactions are operationally convenient and amenable to scale up to produce gram quantities of bicyclic compounds. With protocols in hand for the construction of the bicyclic unit, our attention was then directed at retooling the route toward bicyclic β -bromoenone **140**, which could be a key precursor to complete papuaforin B (**4**) synthesis. Retrosynthetic analysis to papuaforin B (**4**) using diacetoxy sulfone **118** was proposed in Figure 5.

Coupling reaction of allylic enone **138** and diacetoxy sulfone **118** could provide the adduct **139**. Potassium hydride mediated cyclization, elimination of sulfone moiety, protection of terminal olefin, and finally bromination using NBS would give the key bicyclic β -bromoenone **140**.

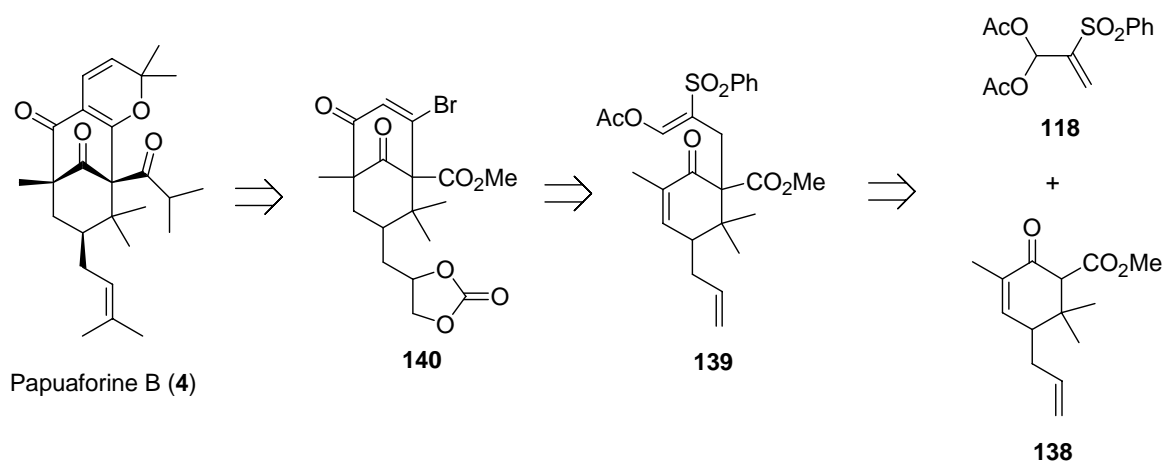
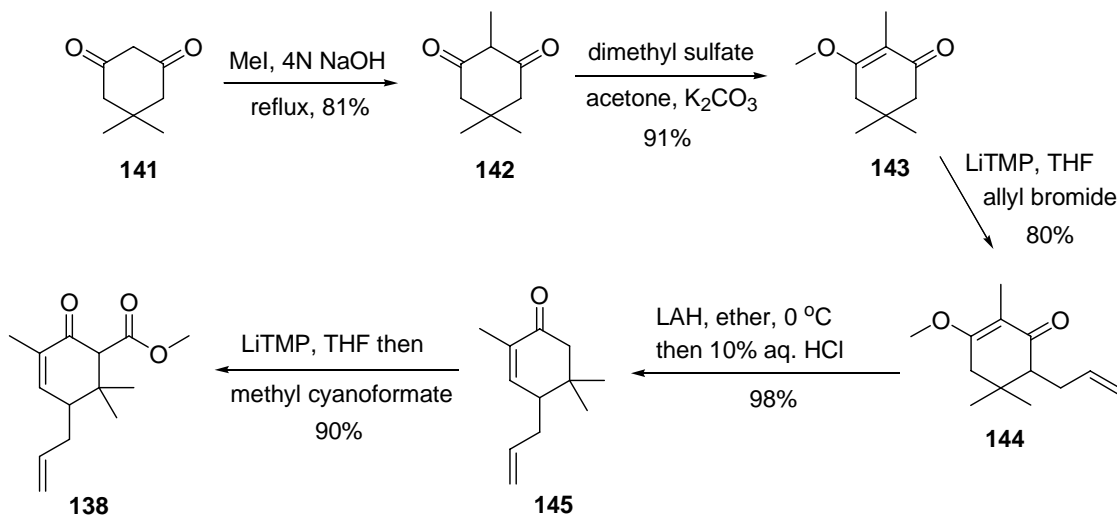


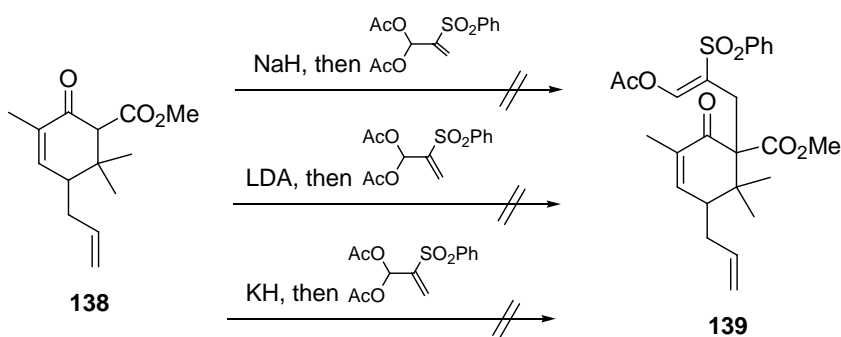
Figure 5. Retrosynthetic analysis of papuaforin B (4)

Synthesis of β -keto ester **138** commenced with *C*-methylation of 5,5-dimethylcyclohexane-1,3-dione using methyl iodide and 4N aqueous NaOH. *O*-Methylation of β -diketone **142**, and subsequent allylation of **143** gave enone **144** in good overall yield.



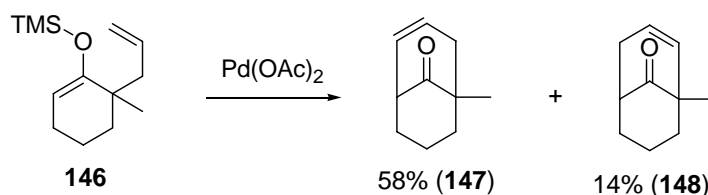
Scheme 44

Reduction of **144** followed by rearrangement under acidic condition provided allylic enone **145** in a 98% yield, which was then converted into β -keto ester **138** by the treatment of the enolate and methyl cyanoformate. β -Keto ester **138** was treated with vinylic sulfone **118** in the presence of NaH. Contrary to our expectation, the desired Michael addition adduct **139** was not obtained. Unreacted **138** was recovered even under conditions utilizing different bases, such as LDA and KH.



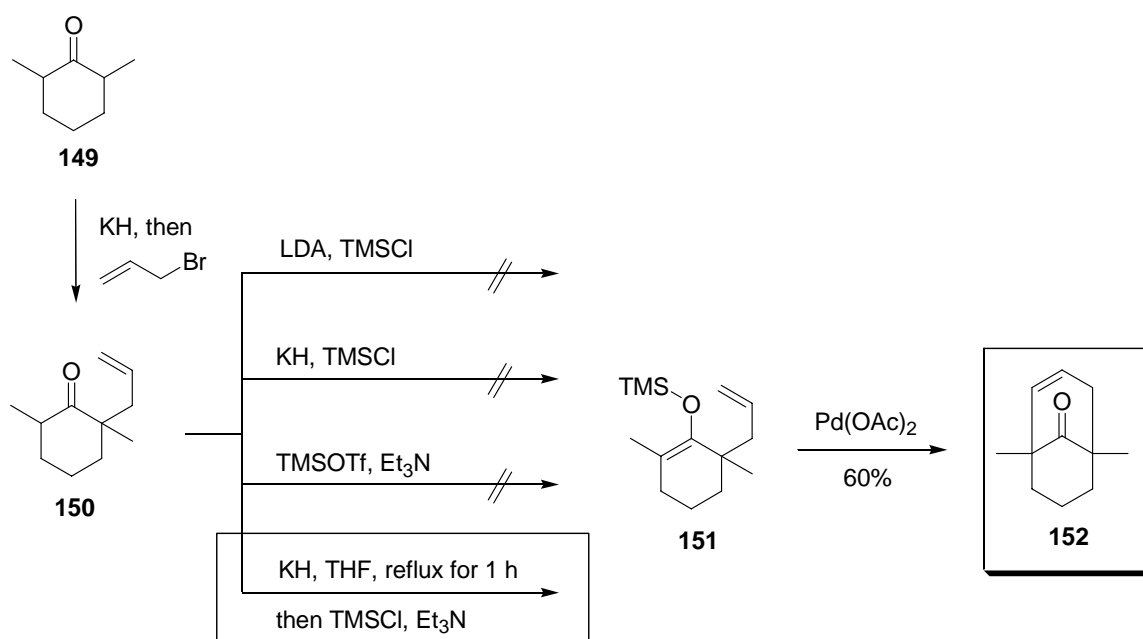
Scheme 45

Kende and co-workers discovered a Pd(II)-mediated intramolecular cycloalkenylation of silyl enol ether **146** (Scheme 46).³⁷ We performed a model study to test its applicability to our system.



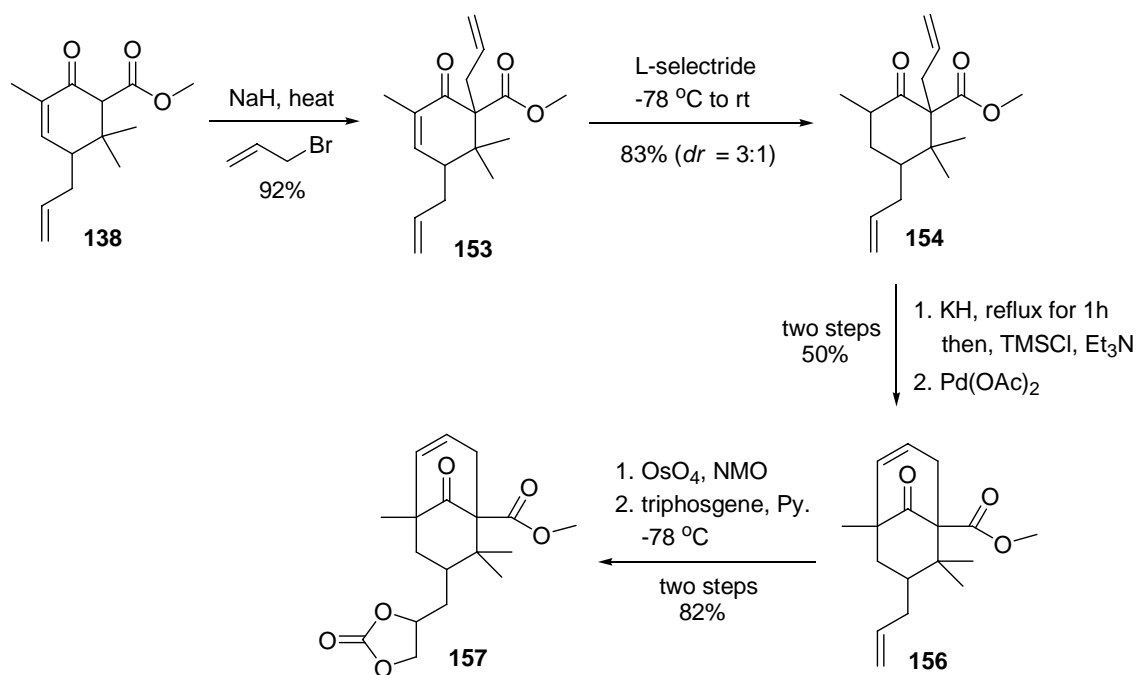
Scheme 46

The synthesis of the model system commenced with allylation of 2,6-dimethylcyclohexanone using KH and allyl bromide (Scheme 47). Due to steric hindrance in ketone **150**, an elevated reaction temperature was necessary to prepare enol silyl ether **151**. The attempted intramolecular cycloalkenylation of **151** using Pd(OAc)₂ following Kende's protocol furnished the desired bicyclo[3.3.1]nonene ring system **152** in a 60% yield.



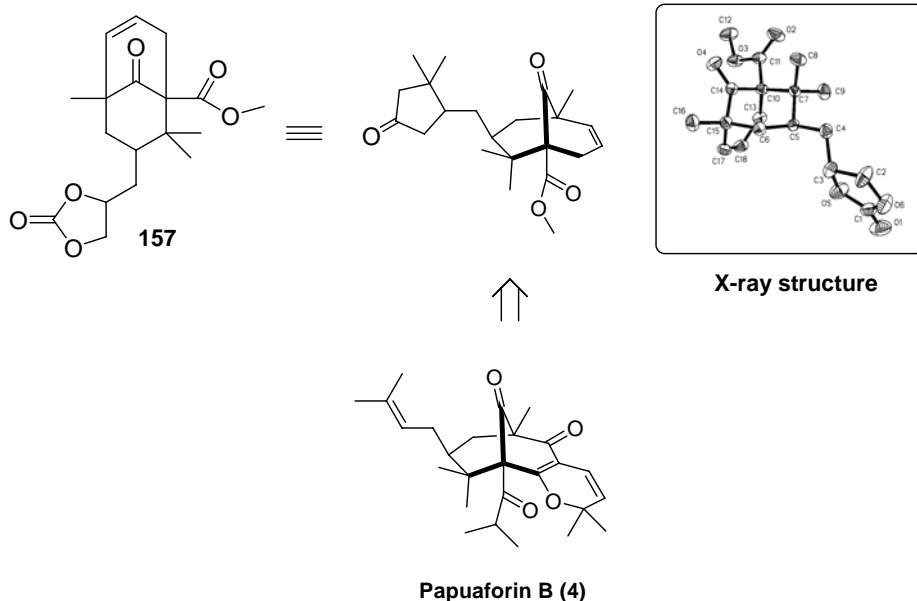
Scheme 47

This successful result encouraged us to apply this method to our real system. Firstly, enone **138** was allylated using NaH and allyl bromide in boiling THF. The allylic enone **153** was then reduced by L-selectride to give ketone **154** as a 3:1 mixture of diastereomers in a 83% yield. The silylation of **154**, followed by the Pd(II)-mediated cycloalkenylation, afforded **156** in a 50% yield.



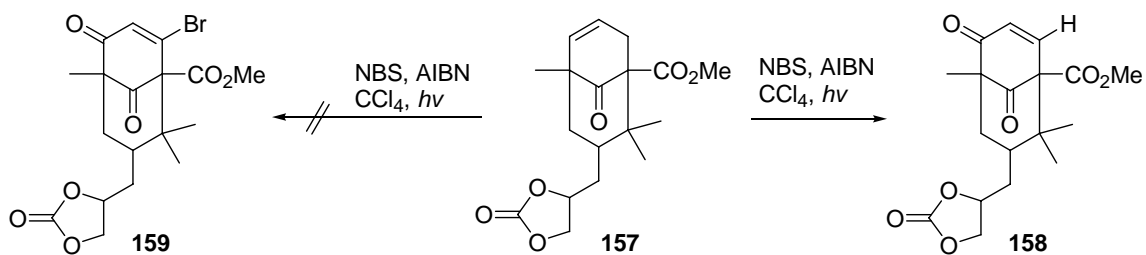
Scheme 48

The terminal olefin in **156** was selectively oxidized to the corresponding diol, which was then protected as a carbonate group with triphosgene in the presence of pyridine at low temperature to yield **157**. At this point, the equatorial stereochemistry of the carbonate side chain of **157** was confirmed by x-ray crystallography as shown in Scheme 49. The fully elaborated bicyclo[3.3.1]nonane skeleton of **157** is stereochemically well matched with papuaforin B (**4**).

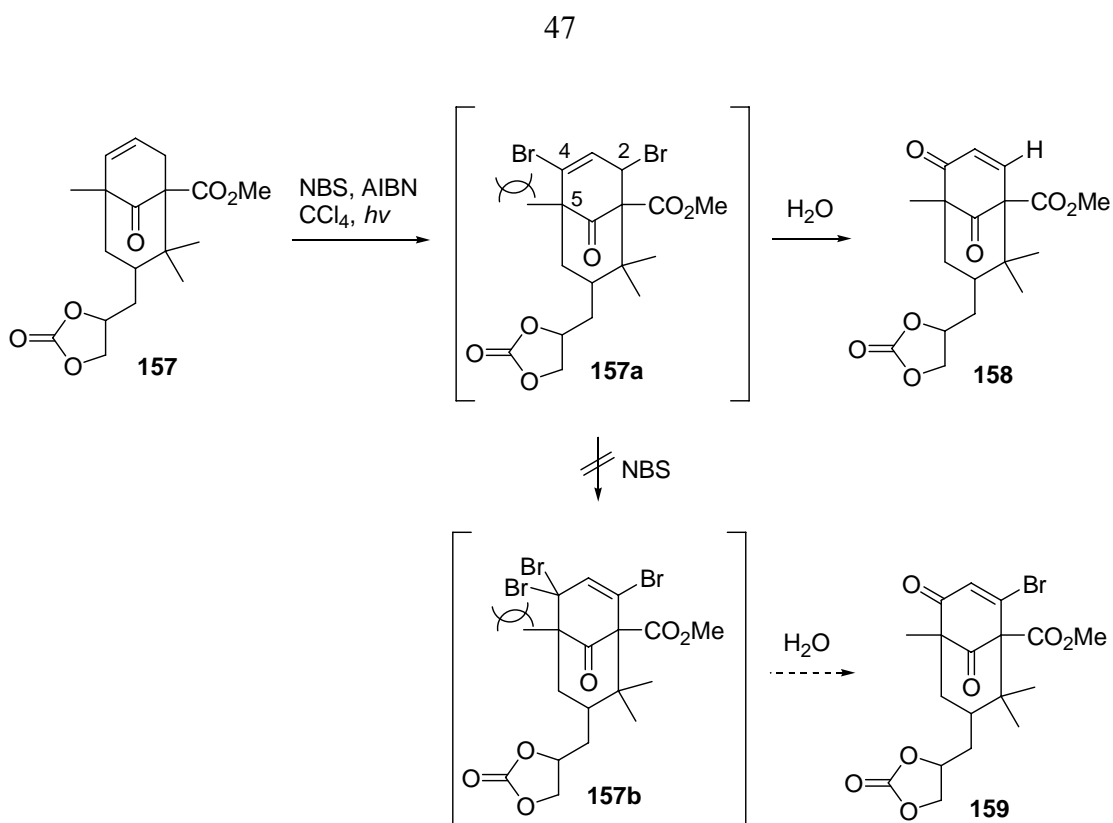


Scheme 49

Unfortunately, bromination of **157** failed to give β -bromo enone **159**. Enone **158** was achieved as the sole product (Scheme 50). The steric hindrance between bromine at C4 and the bridgehead methyl group at C5 of **157a** seemed to prevent a further bromination leading to tribromide **157b** (Scheme 51).



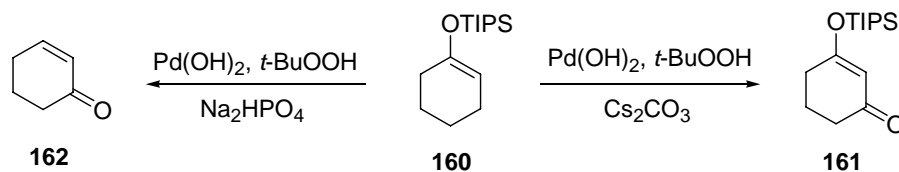
Scheme 50



Scheme 51

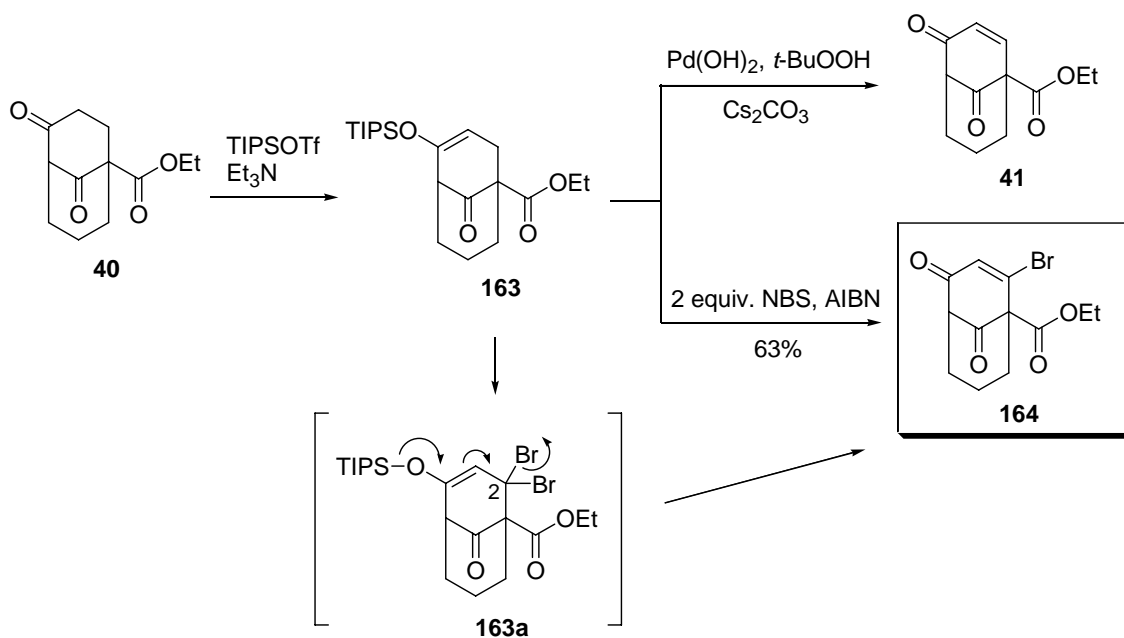
The rapid hydrolysis of **157a** gave enone **158**. In a recent report from Corey's group, an interesting transformation to obtain a β -diketone from a silyl enol ether was described.³⁸

The Pd(OH)₂-catalyzed oxidation of silyl enol ether **160** by *t*-BuOOH produces either β -silyloxy enone **161** or enone **162** depending on the base used (Scheme 52).



Scheme 52

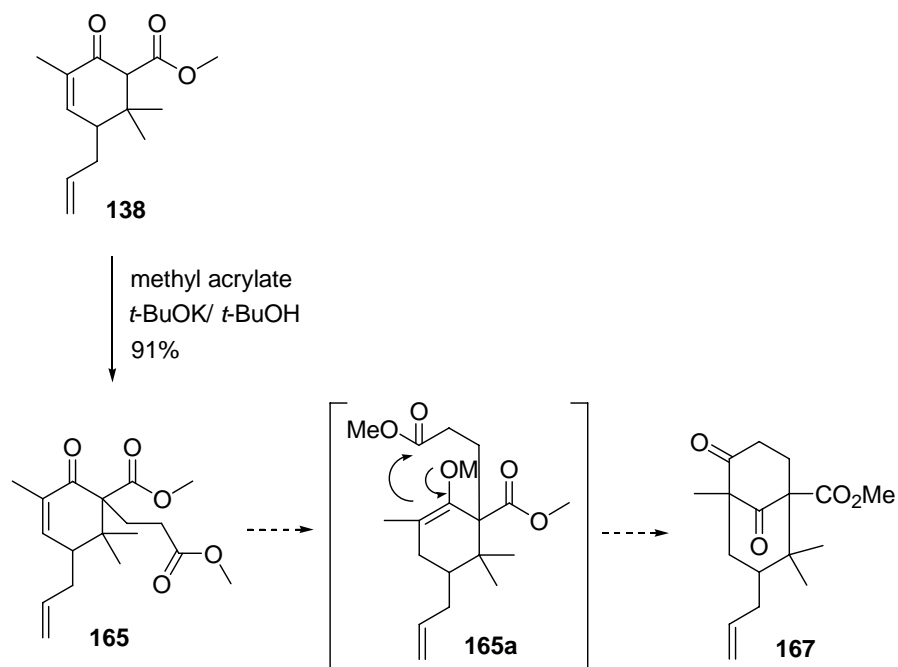
In order to test its applicability to our system, the previously synthesized ketone **40** was first converted to the corresponding silyl enol ether **163** using triisopropylsilyl trifluoromethanesulfonate and triethylamine (Scheme 53). Following Corey's method, treating **163** with Pd(OH)₂ and *t*-BuOOH in the presence of Cs₂CO₃, only generated enone **41**. However, when **163** was exposed to the bromination conditions, the desired β -bromoenone **164** was achieved in a 63% yield, presumably via dibromination at C2, followed by elimination.



Scheme 53

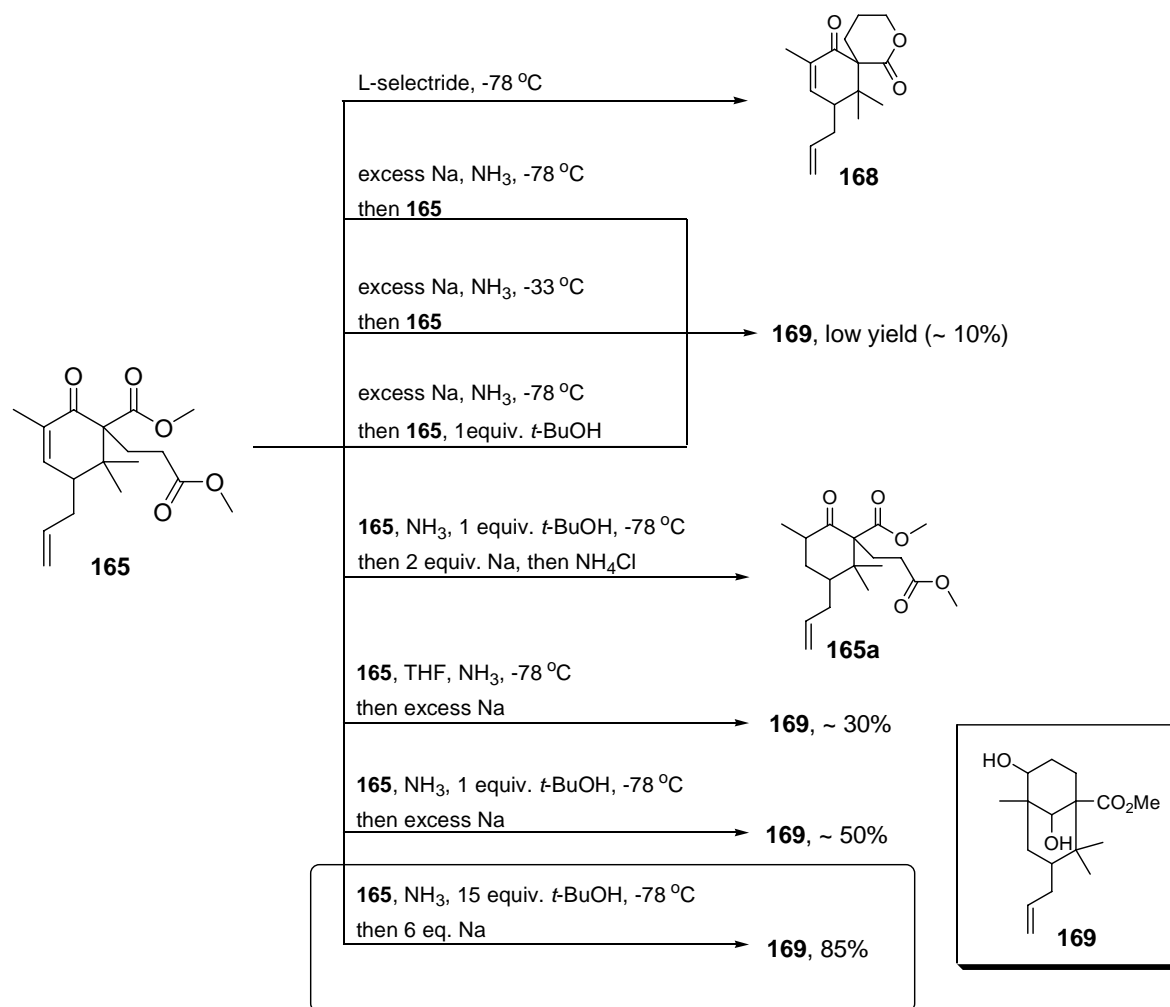
Based on the result shown in Scheme 53, the synthesis of a fully substituted β -bromoenone precursor was started from the Michael addition of **138** using methyl acrylate and *t*-BuOH. With the adduct **165** in hand, we examined cyclization reactions with the idea

of employing the two sequential reactions (Scheme 54). The selective reduction of α,β -enone, followed by intramolecular cyclization, should furnish bicyclic ketone **167**.



Scheme 54

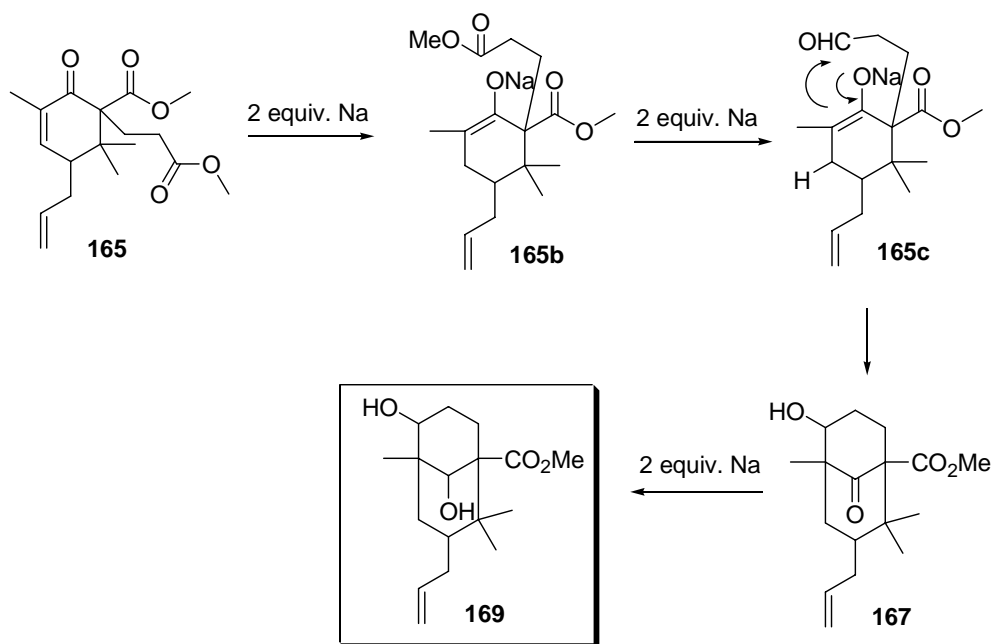
Our first attempt using L-selectride was unsuccessful. It generated the spirocyclization product **168**. However, reduction of **165** using excess Na/NH₃ produced bicyclic diol **169** in about 10% yield (Scheme 55). After many attempts to optimize this step, the reaction yield was improved to 85%.



Scheme 55

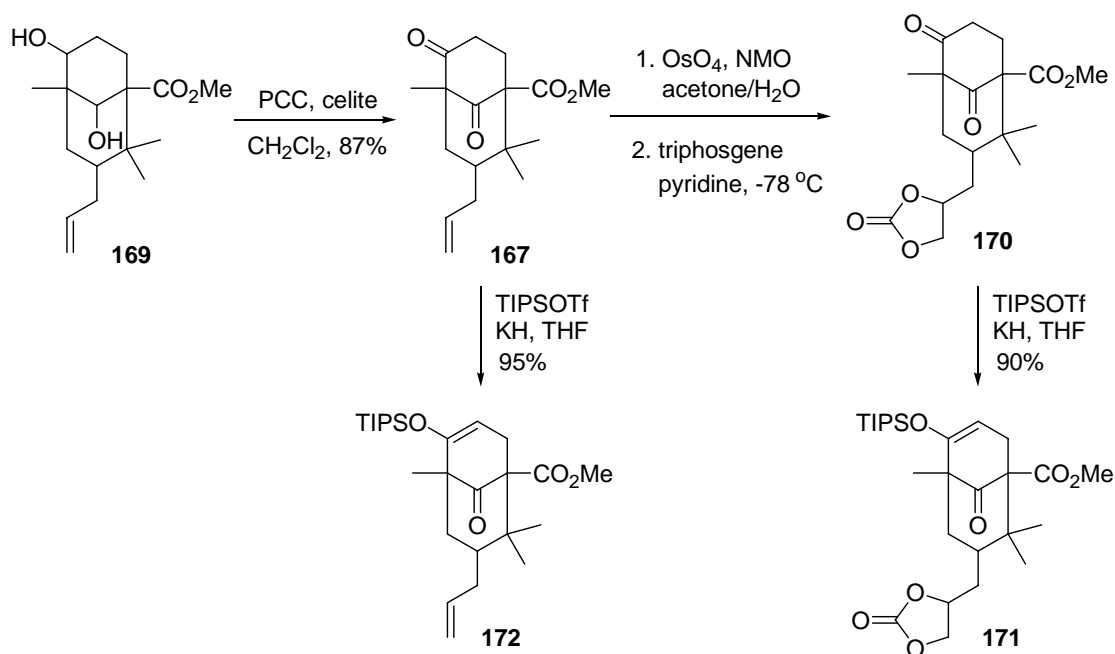
Although the mechanism for this step is still unclear, we postulated that the enone is initially reduced by two equivalents of sodium metal (Scheme 56). The resulting enolate **165b** does not undergo cyclization until the less hindered ester group is reduced to a more reactive aldehyde group. Indeed, the reaction using only two equivalents of sodium metal gave **165a** without generating any cyclization product as shown in Scheme 55. The intramolecular cyclization of **165c**, followed by the third reduction of ketone function in **167**,

gives diol **169**. The sterically congested ester group at the C1 position was not reduced under the conditions. The reaction yields were significantly lower when more or less than six equivalents of sodium metal were used.



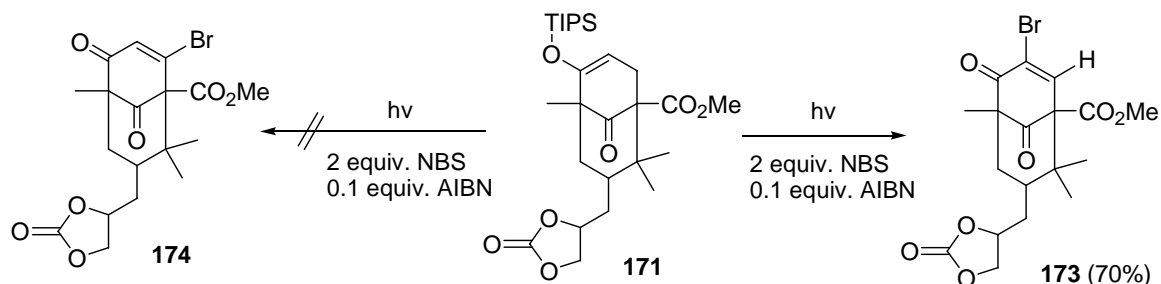
Scheme 56

Bicyclic diol **169** was oxidized using pyridinium chlorochromate to give ketone **167** in an 87% yield (Scheme 57). In order to ensure selectivity during the bromination reaction, the allylic side chain at C7 was converted to a relatively stable carbonate function by dihydroxylation, followed by protection of the diol group. Enol silyl ether formation leading to **171** occurred employing KH and TIPSOTf. Bromoenone precursor **172**, where the allyl group was not protected, was also prepared in the same manner to examine the regioselectivity of the bromination reaction.



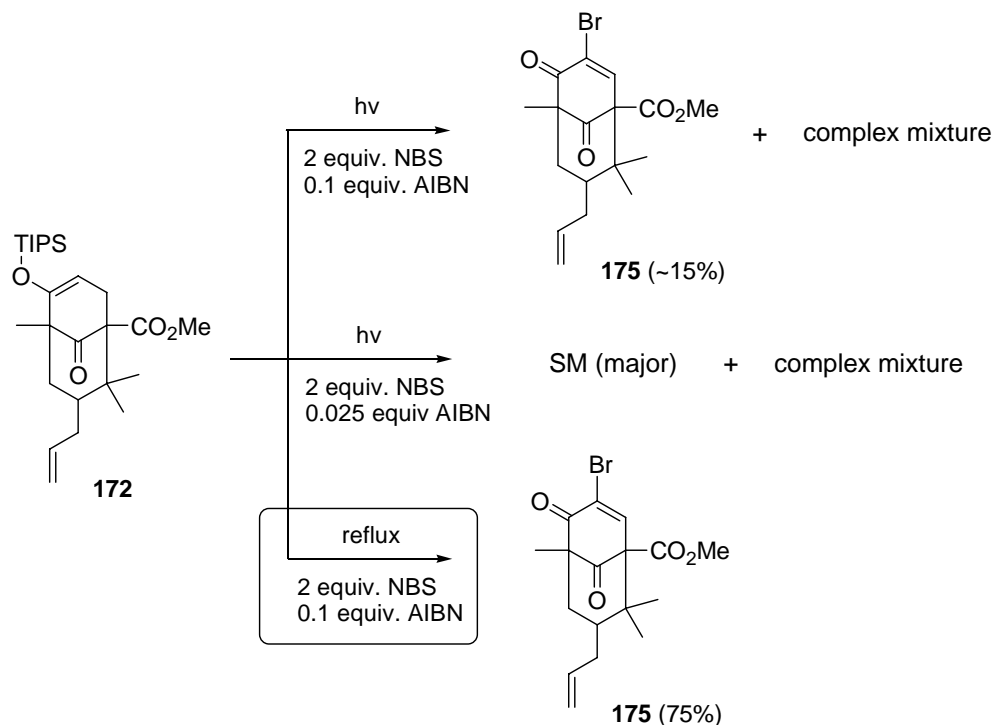
Scheme 57

We first examined the bromination reaction of **171** using two equivalents of NBS (Scheme 58). Surprisingly, it generated α -bromoene **173**, instead of the expected β -bromoene **174**.



Scheme 58

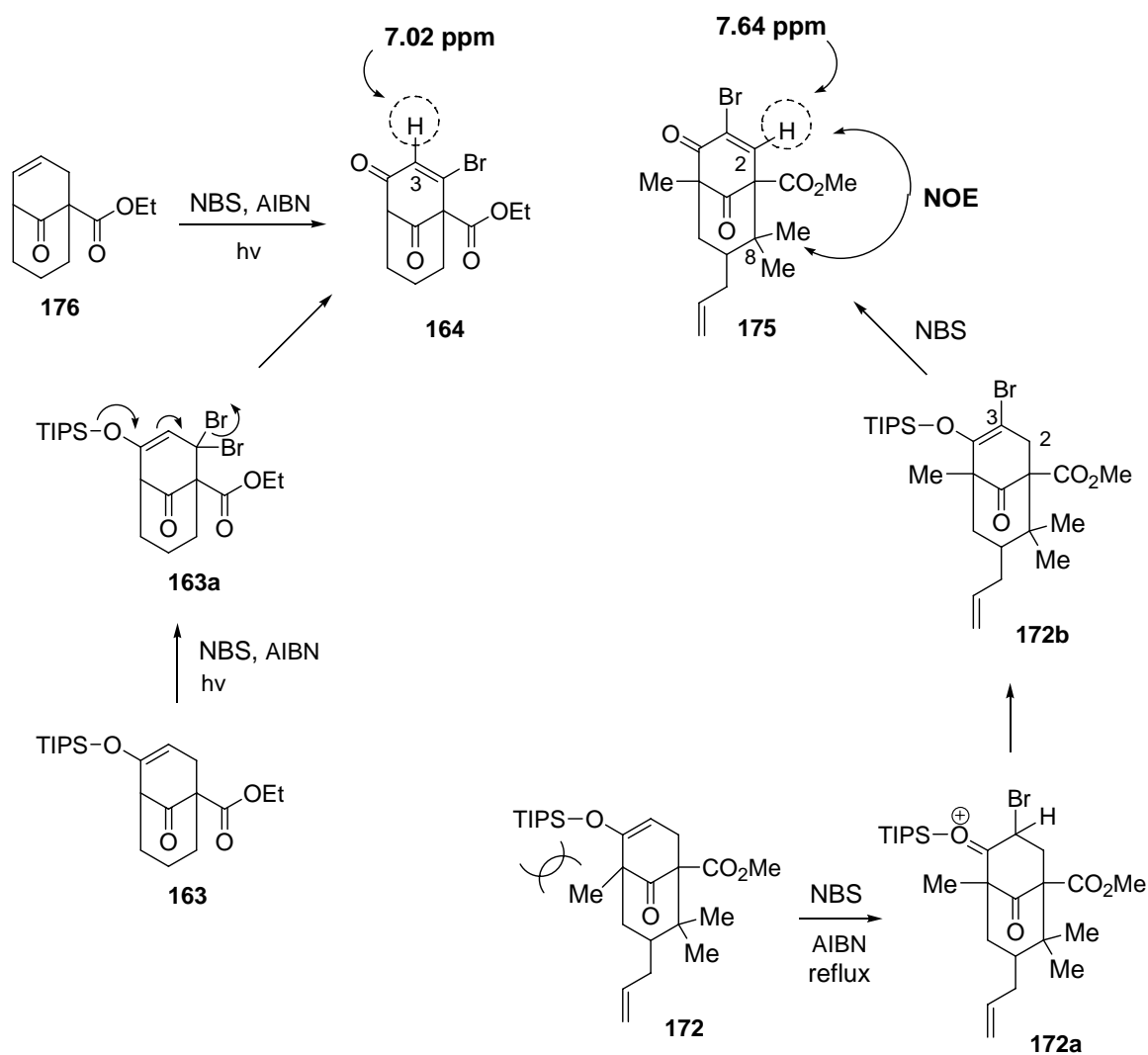
Bromination of **172** also furnished α -bromoenone **175** employing the same reaction conditions. Interestingly, brominations only occurred on the enol silyl ether moiety without affecting the allyl group, and the reaction yield as improved to 75% by boiling (Scheme 59).



Scheme 59

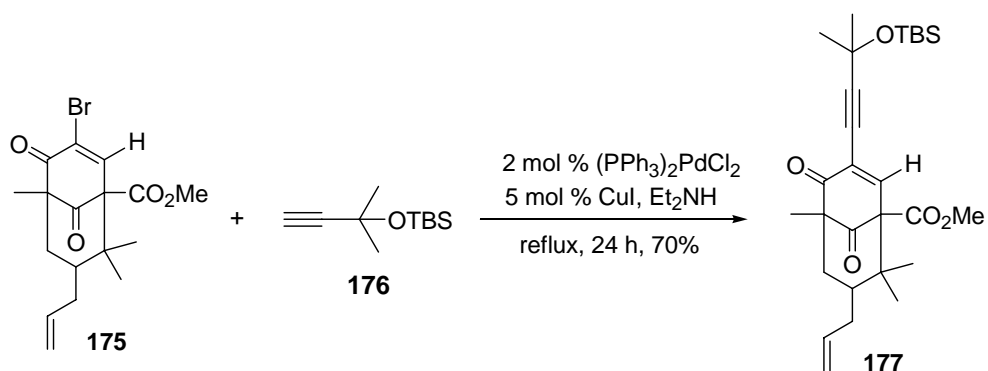
We confirmed the structure of **175** based on ^1H NMR and NOESY spectra (Scheme 60). In the ^1H NMR spectrum, the proton signal at C3 of **164**, obtained either from **176** or **163**, is 7.02 ppm, whereas that of **175** is shifted downfield (7.64 ppm). Furthermore, a notable interaction between the methyl group at C8 and the proton at C2 of **175** was observed in the NOESY experiment, which strongly supports the structure of **175**. The possible mechanism for formation of **175** is shown in Scheme 60. The first bromination may occur at

C3, which leads to intermediate **172b**. The second bromination either at C2 or C3 followed by dehydrobromination forms α -bromoenone **175**.



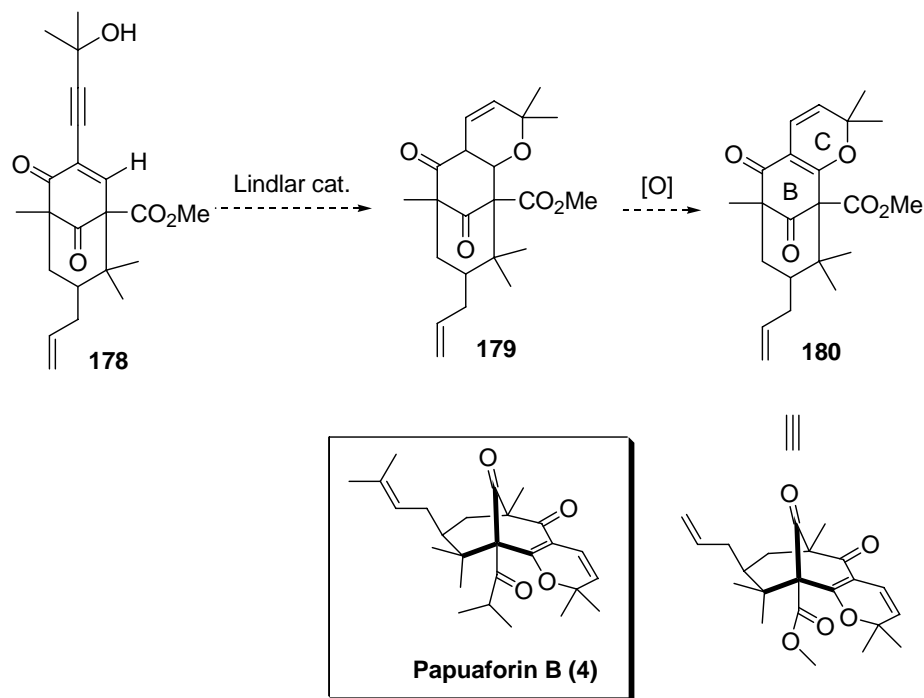
Scheme 60

The bromide **175** was coupled with the TBS-protected acetylene **176** under Hagihara's conditions³⁹ to give **177** in a 70% yield (Scheme 61).



Scheme 61

The selective reduction of the acetylene moiety of **178** to a *cis*-alkene using Lindlar's catalyst, followed by *in situ* Michael addition, would generate **179** (Scheme 62). Upon oxidation of **179**, the synthesis of the fully substituted tricyclic core of papuaforin B (**4**) would be realized.

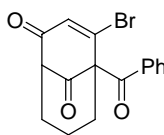


Scheme 62

In conclusion, a concise and efficient synthetic route to the highly functionalized tricyclic core skeleton of papuaforin B (**4**) was examined. In the course of the synthesis, an efficient cyclization method using Na/NH₃ was demonstrated. We also developed a novel bromination method leading to an α -bromoenone that would serve as a handle for construction of the fused pyran ring. Cross-metathesis of the terminal alkene to the prenyl group, and transformation of the ester to an isobutyryl unit at C1 would complete the synthesis of papuaforin B (**4**). Further efforts along this line are in progress.

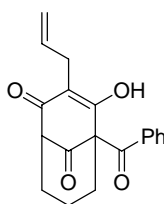
Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Dichloromethane, benzene and diisopropyl amine were distilled over calcium hydride. All experiments were performed under an 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 CDCl₃ (7.27 ppm for ¹H and 77.23 ppm for ¹³C), 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. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.



5-Benzoyl-4-bromobicyclo[3.3.1]non-3-ene-2,9-dione (**64**)

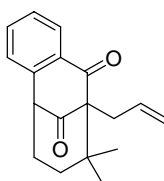
To a solution of 5-benzoylbicyclo[3.3.1]non-2-en-9-one in dry CCl_4 was added dry NBS (3.5 equiv.) and AIBN (0.1 equiv.). The flask was fitted with a reflux condenser and irradiated with a sun lamp. After 1.5 h (monitored by TLC), the mixture was allowed to cool to rt and filtered. The crude material was purified by column chromatography to yield the bromo enone **1** in a 73% yield: ^1H NMR (300 MHz, CDCl_3) δ 7.77 (d, $J = 8.1$ Hz, 2H), 7.55 (t, $J = 7.8$ Hz, 1H), 7.41 (t, $J = 7.8$ Hz, 2H), 7.13 (s, 1H), 3.54 (t, $J = 3.9$ Hz, 1H), 2.44-1.72 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 204.84, 193.70, 192.94, 148.49, 136.07, 135.22, 133.68, 128.86, 128.81, 63.05, 34.60, 33.82, 25.31, 17.54.



3-Allyl-5-benzoyl-4-hydroxybicyclo[3.3.1]non-3-ene-2,9-dione (**68**)

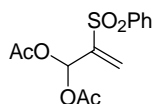
To a solution of allyl alcohol (20 equiv.) at 0°C was added freshly cut sodium metal (1.1 equiv.), bromoenone **64** (1 equiv.) in allyl alcohol was added and the mixture was allowed to stir for 1 h. After aqueous work-up, the crude material was purified by column chromatography. The allyl enol ether was then dissolved in dry toluene and placed in a sealed tube, where it was heated at 170°C for 7 h. Compound was purified by column chromatography: FTIR (thin film) 1682, 1635, 1596, 1569 cm^{-1} ; ^1H NMR (300 MHz,

CDCl₃) δ 7.98 (d, J = 8 Hz, 2H), 7.61 (t, J = 7.5, 1H), 7.50 (t, J = 7.8, 2H), 6.02–5.89 (m, 1H), 5.36–5.20 (m, 2H), 4.57 (t, J = 5.4, 1H), 3.32 (d, J = 6.3, 2H), 2.59–2.50 (m, 1H), 2.40–2.30 (m, 1H), 2.13–2.03 (m, 2H), 1.79–1.67 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 198.27, 164.95, 164.74, 155.23, 135.51, 135.39, 133.87, 129.06, 128.89, 117.84, 111.88, 100.86, 45.24, 28.46, 26.70, 20.51, 18.57; HRMS (EI) m/z calcd for 310.12051, found 310.12098.



9-Allyl-10,10-dimethyltricyclo[7.3.1.02,7]trideca-2(7),3,5-triene-8,13-dione (75)

To a stirred solution of Mn(OAc)₃ dihydrate (2 equiv.) and Cu(OAc)₂ monohydrate (1 equiv.) in degassed glacial acetic acid at rt was added a solution of 2-allyl-2-benzoyl-3,3-dimethylcyclohexanone (1 equiv.) in glacial acetic acid. The mixture was stirred at 90 °C for 16 h. After normal aqueous work-up, the crude material was purified by column chromatography to yield the compound **3** in 76% yield: ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 5.57–5.43 (m, 1H), 5.10–4.88 (m, 2H), 3.82 (t, J = 3.3 Hz, 1H), 2.75–2.58 (m, 2H), 2.45–2.33 (m, 1H), 1.85–1.77 (m, 1H), 1.55–1.44 (m, 1H), 1.29–1.17 (m, 1H), 1.07 (s, 3H), 0.99 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 209.28, 197.50, 141.22, 135.29, 134.92, 134.25, 128.09, 127.78, 126.80, 118.21, 72.89, 53.42, 45.52, 33.54, 31.45, 29.76, 25.60, 22.52.



3,3-Diacetoxy-2-(phenylsulfonyl)propene (118)

To a mechanically stirred suspension of 6.8 g (0.05 mol) of *N*-chlorosuccinimide in 60 mL of dry methylene chloride at room temperature in a 250 mL flask equipped with a pressure-equalizing dropping funnel and an efficient condenser was added about 0.5 g of a total of 5.5 g (0.05 mol) of thiophenol. The mixture was then gently heated on a steam bath for 1 to 2 min until sulfenyl chloride formation commenced as evidenced by the intense orange coloration of the suspension. Once initiated, the remaining thiophenol was added dropwise at a rate sufficient to maintain the solvent at reflux. When the addition was complete (usually about 30 min were required), the homogeneous orange solution was stirred at room temperature for an additional 30 min. The suspension was then cooled to 0 °C and 8.7 g (0.055 mol) of 1,1-diacetoxy-2-propene was added in one portion. The mixture was then maintained at 0 °C until complete decoloration of the sulfenyl chloride suspension was observed (2 h). After warming to room temperature, the colorless suspension was filtered to remove the majority of the succinimide. Concentration of the combined filtrate and wash left a pale yellow oil, which was diluted with 30 mL of hexane to precipitate the remainder of the succinimide. This suspension was let stand 1 h and then filtered, and the filtrate was evaporated to dryness, which was pure enough to be used without further purification: ¹H NMR (300 MHz, CDCl₃) δ 7.53–7.49 (m, 2H), 7.38–7.31 (m, 3H), 7.14 (d, *J* = 3.6 Hz, 1H), 3.84–3.68 (m, 2H), 3.63–3.58 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H).

To a stirred solution of 4.4 g (0.02 mol) of chloro sulfide prepared above in 25 mL of dry methylene chloride, cooled to 0 °C under nitrogen, a solution of 2.2 equiv of *m*-

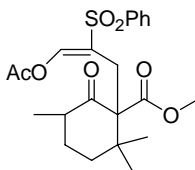
chloroperbenzoic acid in 50 mL of methylene chloride was added dropwise. When the addition was complete, the mixture was stirred an additional 20 min and then filtered to remove the majority of the chlorobenzoic acid, which was washed with 30 mL of methylene chloride. The combined filtrate and wash was diluted with 50 mL of methylene chloride and then washed successively with 10% NaHCO₃ (50 mL), 10% NaHSO₃ (50 mL), 10% NaHCO₃ again (50 mL), and saturated brine and finally dried (MgSO₄), which was pure enough to be used without further purification: ¹H NMR (300 MHz, CDCl₃) δ 7.98–7.94 (m, 2H), 7.76–7.60 (m, 3H), 7.23 (d, *J* = 3.0 Hz, 1H), 4.17–3.94 (m, 2H), 3.88–3.83 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H)

A solution of 1.3 mL (7.5 mmol) of diisopropylethylamine in 50 mL of dry methylene chloride was added dropwise, under a nitrogen atmosphere, to a stirred solution of 2.3 g (6.9 mmol) of chlorosulfone at -10 °C. The reaction temperature was maintained at 0 °C for 2 h, then diluted with 40 mL of methylene chloride, washed with 25 mL each of chilled 1 N HCl, water, and brine, and finally dried over anhydrous magnesium sulfate. Recrystallization with diethylether/hexane gave compound **118** as a white solid: mp 64–67 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.92–7.89 (m, 2H), 7.69–7.54 (m, 3H), 7.39 (s, 1H), 6.75 (s, 1H), 6.36 (s, 1H), 1.96 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.95, 145.84, 139.68, 134.05, 129.53, 129.43, 128.55, 84.90, 20.61; HRMS (EI) *m/z* (M⁺ - CH₃CO₂) calcd for 239.03781, found 239.03830.

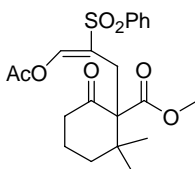
General procedure for Michael addition to **118**

The keto ester (1 mmol) was added dropwise to the solution of sodium hydride (1 mmol) in THF (10 mL). After 20 min, sulfone **7** (1 mmol) was added in one portion and stirred for another 1 h. The resulting mixture was neutralized with AcOH, which was

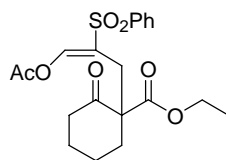
dissolved in 20 ml of ether. The ether layer was washed with brine and dried over anhydrous MgSO_4 . The crude material was purified by column chromatography.



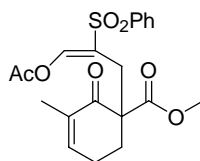
(2E)-1-[3-Acetoxy-2-(benzenesulfonyl)allyl]-2,2,5-trimethyl-6-oxocyclohexanecarboxylic acid methyl ester (121): ^1H NMR (300 MHz, CDCl_3) δ 8.29 (d, $J = 3.3$ Hz, 1H), 7.88 (d, $J = 7.8$ Hz, 2H), 7.67–7.52 (m, 3H), 3.67 (s, 3H), 3.31 (d, $J = 16.8$ Hz, 1H), 2.90 (d, $J = 16.8$ Hz, 1H), 2.23 (s, 3H), 1.87–1.34 (m, 4H), 0.92 (s, 6H), 0.74 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 206.44, 169.59, 166.20, 145.45, 139.58, 133.78, 129.58, 128.27, 123.20, 65.43, 51.43, 42.46, 40.53, 36.20, 30.56, 28.73, 26.28, 25.55, 20.75, 15.27; HRMS (EI) m/z calcd for 436.15558, found 436.15630.



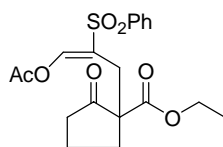
(2E)-1-[3-Acetoxy-2-(benzenesulfonyl)allyl]-2,2-dimethyl-6-oxocyclohexanecarboxylic acid methyl ester (127): ^1H NMR (300 MHz, CDCl_3) δ 8.14 (s, 1H), 7.91 (d $J = 7.5$ Hz, 2H), 7.64–7.51 (m, 3H), 3.46 (s, 3H), 2.65–2.50 (m, 2H), 2.33–1.21 (m, 6H), 2.02 (s, 3H), 0.91 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 207.50, 170.76, 165.72, 142.24, 139.73, 133.47, 129.16, 128.04, 125.55, 66.73, 51.65, 44.17, 39.17, 36.25, 26.72, 26.62, 22.75, 22.53, 20.37; HRMS (EI) m/z calcd for 422.13993, found 422.14080.



(2E)-1-[3-Acetoxy-2-(benzenesulfonyl)allyl]-2-oxocyclohexanecarboxylic acid methyl ester (132); ^1H NMR (300 MHz, CDCl_3) δ 8.47 (s, 1H), 7.87-7.83 (m, 2H), 7.63–7.50 (m, 3H), 4.26-4.17 (m, 2H), 2.90-2.76 (m, 2H), 2.52-1.56 (m, 8H), 2.20 (s, 3H), 1.32-1.24 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 206.27, 170.67, 165.89, 146.91, 139.82, 133.49, 129.30, 128.07, 124.08, 61.69, 59.98, 40.62, 35.11, 28.89, 27.07, 22.39, 20.59, 13.98; HRMS (EI) m/z calcd for 408.12428, found 408.12500.

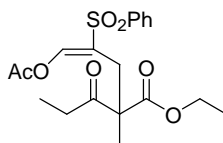


(2E)-1-[3-Acetoxy-2-(benzenesulfonyl)allyl]-3-methyl-2-oxocyclohex-3-enecarboxylic acid methyl ester (134): ^1H NMR (300 MHz, CDCl_3) δ 8.40 (s, 1H), 7.81-7.76 (m, 2H), 7.58–7.43 (m, 3H), 6.57 (br s, 1H), 3.62 (s, 3H), 3.99 (d, $J = 15.6$ Hz, 1H), 2.75 (d, $J = 15.6$ Hz, 1H), 2.45-2.19 (m, 2H), 2.13 (s, 3H), 1.95-1.88 (m, 2H), 1.73 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 194.93, 171.22, 166.06, 146.92, 144.91, 139.65, 134.81, 133.71, 129.46, 128.30, 124.10, 56.08, 52.81, 30.20, 28.93, 23.67, 20.69, 16.84, 14.34.



(2E)-1-[3-Acetoxy-2-(benzenesulfonyl)allyl]-2-oxocyclopentanecarboxylic acid ethyl

ester: ^1H NMR (300 MHz, CDCl_3) δ 8.48 (s, 1H), 7.87-7.83 (m, 2H), 7.64–7.51 (m, 3H), 4.19-4.08 (m, 2H), 3.09 (d, $J = 15.6$ Hz, 1H), 2.63 (d, $J = 15.6$ Hz, 1H), 2.39-2.30 (m, 2H), 2.22 (s, 3H), 2.03-1.91 (m, 2H), 1.21 (t, $J = 6.9$ Hz 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 214.17, 171.14, 166.03, 146.31, 138.85, 133.79, 129.42, 128.49, 124.00, 62.00, 59.04, 37.53, 31.92, 27.70, 20.65, 19.86, 14.11.



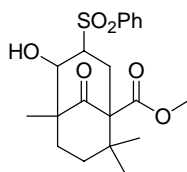
(4E)-5-Acetoxy-4-benzenesulfonyl-2-methyl-2-propionylpent-4-enoic acid ethyl ester: ^1H

NMR (300 MHz, CDCl_3) δ 8.48 (s, 1H), 7.84-7.81 (m, 2H), 7.63–7.49 (m, 3H), 4.28-4.09 (m, 2H), 3.05 (d, $J = 15.6$ Hz, 1H), 2.84 (d $J = 15.6$ Hz, 1H), 2.61-2.2.45 (m, 2H), 2.20 (s, 3H), 1.33 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.06 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 207.45, 172.38, 166.02, 146.66, 139.27, 133.68, 129.38, 128.37, 124.22, 61.95, 58.62, 31.64, 28.75, 20.69, 18.64, 14.08, 8.365.

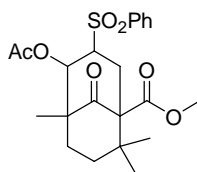
Procedure for cyclizations using *t*-BuOK

To a stirred solution of diketone (1 mmol) in THF (10 mL) was added *t*-BuOK (1 mmol) in one portion at 0 °C. The mixture was stirred overnight at rt and dissolved in 20 ml

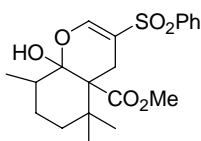
of ether. The ether layer was washed with 10 % aq. HCl, brine and dried over anhydrous MgSO_4 . The crude material was purified by column chromatography.



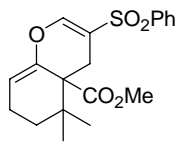
7-Benzenesulfonyl-6-hydroxy-2,2,5-trimethyl-9-oxobicyclo[3.3.1]nonane-1-carboxylic acid methyl ester (122): ^1H NMR (300 MHz, CDCl_3) δ 7.95-7.89 (m, 2H), 7.76-7.54 (m, 3H), 4.52 (d, $J = 10.5$ Hz, 1H), 3.85 (s, 1H), 3.48 (s, 3H), 3.13-3.03 (m, 1H), 2.05-1.25 (m, 6H), 1.12 (s, 6H), 1.04 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 208.94, 170.13, 136.07, 134.92, 129.81, 129.35, 74.31, 66.17, 64.63, 52.29, 51.27, 42.93, 37.81, 29.30, 28.41, 26.48, 25.54, 20.90; HRMS (EI) m/z calcd for 394.14501, found 394.14570.



6-Acetoxy-7-benzenesulfonyl-2,2,5-trimethyl-9-oxobicyclo[3.3.1]nonane-1-carboxylic acid methyl ester (123): ^1H NMR (300 MHz, CDCl_3) δ 7.88-7.83 (m, 2H), 7.71-7.56 (m, 3H), 5.62 (d, $J = 11.4$ Hz, 1H), 3.68 (s, 3H), 3.45-3.33 (m, 1H), 2.76 (dd, $J = 14.7, 4.8$ Hz, 1H), 2.47 (d, $J = 14.4$ Hz, 1H), 2.17-1.96 (m, 2H), 1.77-1.71 (m, 1H), 1.64 (s, 3H), 1.31-1.26 (m, 1H), 1.13 (s, 3H), 1.11 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 209.80, 170.86, 169.78, 139.47, 134.07, 129.50, 128.33, 74.83, 62.99, 61.07, 52.31, 49.84, 43.76, 38.08, 33.74, 26.59, 24.58, 22.87, 20.30, 17.63.



3-Benzenesulfonyl-8a-hydroxy-5,5,8-trimethyl-6,7,8,8a-tetrahydro-4H,5H-chromene-4a-carboxylic acid methyl ester (124): ^1H NMR (300 MHz, CDCl_3) δ 7.88 (m, 2H), 7.62–7.49 (m, 3H), 7.49 (d, $J = 1.8$ Hz, 1H), 6.88 (d, $J = 2.1$ Hz, 1H), 3.19 (s, 3H), 2.82–2.61 (m, 2H), 1.82–1.23 (m, 5H), 1.11–0.89 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.63, 152.20, 140.44, 132.87, 129.11, 127.55, 112.56, 105.36, 52.65, 52.22, 38.37, 36.04, 34.54, 27.70, 27.46, 25.60, 24.99, 13.39; HRMS (EI) m/z calcd for 394.14501, found 380.97603.

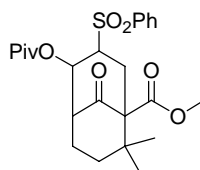


3-Benzenesulfonyl-5,5-dimethyl-6,7-dihydro-4H,5H-chromene-4a-carboxylic acid methyl ester (131): ^1H NMR (300 MHz, CDCl_3) δ 7.88–7.84 (m, 2H), 7.65–7.52 (m, 3H), 7.46 (d, $J = 2.4$ Hz, 1H), 5.59 (t, $J = 4.2$ Hz, 1H), 3.28 (s, 3H), 2.82 (d, $J = 15.6$ Hz, 1H), 2.33 (dd, $J = 15.6, 2.4$ Hz, 1H), 2.17–2.09 (m, 2H), 1.63–1.55 (m, 1H), 1.33–1.28 (m, 1H), 0.98 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.44, 150.63, 147.13, 140.34, 133.15, 129.22, 127.92, 115.84, 109.73, 52.19, 51.04, 35.47, 33.90, 25.63, 24.23, 20.29; HRMS (EI) m/z calcd for 362.11880, found 362.11940.

Procedure for cyclizations using KH

To a stirred solution of potassium hydride (1 mmol) in THF (10 mL) was added the diketone (1 mmol). The mixture was stirred overnight at rt and dissolved in 20 ml of ether.

The ether layer was washed with 10 % aq. HCl, brine and dried over anhydrous MgSO₄. The crude material was purified by column chromatography.



7-Benzenesulfonyl-6-(2,2-dimethylpropionyloxy)-2,2-dimethyl-9-

oxobicyclo[3.3.1]nonane-1-carboxylic acid methyl ester (130): ¹H NMR (300 MHz,

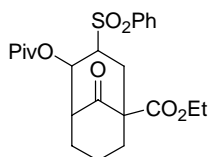
CDCl₃) δ 7.89-7.86 (m, 2H), 7.72-7.56 (m, 3H), 5.40 (d, *J* = 10.8 Hz, 1H), 4.12-4.00 (m, 2H),

3.49-3.39 (m, 1H),), 2.48-1.80 (m, 6H), 1.27-1.21 (m, 1H), 1.15-1.06 (m, 18H); ¹³C NMR

(75 MHz, CDCl₃) δ 209.06, 177.39, 170.00, 138.41, 134.41, 129.68, 128.70, 73.82, 62.92,

61.18, 60.78, 54.22, 44.08, 38.71, 33.95, 28.62, 28.44, 27.00, 24.71, 22.73, 14.14; HRMS

(EI) *m/z* calcd for 478.20253, found 478.20310.



3-Benzenesulfonyl-4-(2,2-dimethylpropionyloxy)-9-oxobicyclo[3.3.1]nonane-1-

carboxylic acid ethyl ester (133): ¹H NMR (300 MHz, CDCl₃) δ 7.94-7.89 (m, 2H), 7.73-

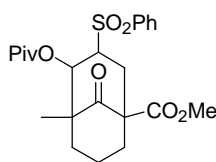
7.57 (m, 3H), 5.54 (dd, *J* = 10.5 Hz, 0.9 Hz, 1H), 4.27-4.11 (m, 3H), 3.46-3.36 (m, 1H), 3.01-

2.75 (m, 2H), 2.32 (br s, 1H), 2.28-1.51 (m, 6H), 1.18 (t, *J* = 10.2 Hz 3H), 1.12 (s, 9H); ¹³C

NMR (75 MHz, CDCl₃) δ 209.27, 177.41, 171.28, 138.23, 134.44, 129.69, 128.82, 73.26,

61.97, 60.19, 56.39, 55.01, 38.73, 38.06, 34.17, 29.03, 26.99, 17.70, 14.23; HRMS (EI) *m/z*

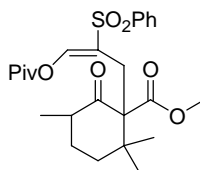
calcd for 450.17123, found 450.17200.



3-Benzenesulfonyl-4-(2,2-dimethylpropionyloxy)-5-methyl-9-oxobicyclo[3.3.1]nonane-1-carboxylic acid methyl ester (135): ^1H NMR (300 MHz, CDCl_3) δ 7.83 (d, $J = 8.4$ Hz, 2H), 7.71–7.54 (m, 3H), 5.51 (d, $J = 1.5$ Hz, 1H), 3.73 (s, 3H), 2.88 (br s, 1H), 2.67 (d, $J = 12.3$ Hz, 1H), 2.49 (dd, $J = 12.3, 1.8$ Hz, 1H), 2.31–1.81 (m, 6H), 1.27 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 207.59, 176.57, 170.40, 136.35, 134.57, 129.64, 129.48, 72.68, 65.73, 58.61, 55.46, 52.67, 39.45, 38.79, 31.21, 28.86, 26.81, 16.53, 15.14; HRMS (EI) m/z calcd for 450.17123, found 450.17190.

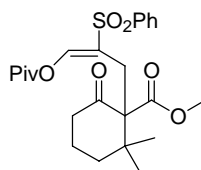
General procedure for pivaloyl group substitution

To a stirred solution of diketone (1 mmol) in THF (10 mL) was added *t*-BuOK (2 mmol) in one portion at 0°C . The reaction temperature was maintained at 0°C for 1 h, then trimethylacetyl chloride (2 mmol) was added. The resulting mixture was neutralized with AcOH, which was dissolved in 20 mL of ether. The ether layer was washed with brine and dried over anhydrous MgSO_4 . The crude material was purified by column chromatography.



(2E)-1-[2-Benzenesulfonyl-3-(2,2-dimethylpropionyloxy)allyl]-2,2,5-trimethyl-6-oxocyclohexanecarboxylic acid methyl ester (125): ^1H NMR (300 MHz, CDCl_3) δ 8.32 (d, $J = 0.9$ Hz, 1H), 7.84 (d, $J = 8.7$ Hz, 2H), 7.62–7.49 (m, 3H), 3.65 (s, 3H), 3.21 (dd, $J = 15.6,$

0.9 Hz, 1H), 2.99 (d, $J = 15.6$ Hz, 1H), 2.04-1.38 (m, 4H), 1.25 (s, 9H), 1.00-0.95 (m, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 207.02, 173.77, 170.68, 147.20, 140.17133.47, 129.30, 128.09, 124.61, 66.63, 51.52, 41.98, 41.23, 39.11, 36.17, 29.92, 27.53, 26.69, 26.26, 25.45, 15.41; HRMS (EI) m/z calcd for 478.20253, found 478.20320.

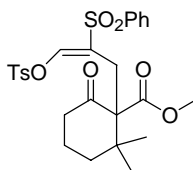


(2E)-1-[2-Benzenesulfonyl-3-(2,2-dimethylpropionyloxy)allyl]-2,2-dimethyl-6-oxocyclohexanecarboxylic acid methyl ester (129): ^1H NMR (300 MHz, CDCl_3) δ 8.36 (s, 1H), 7.91 (d, $J = 7.8$ Hz, 2H), 7.64–7.51 (m, 3H), 3.51 (s, 3H), 3.21-3.10 (m, 1H), 2.88 (dd, $J = 15.9, 1.2$ Hz, 1H), 2.57 (d, $J = 15.9$ Hz, 1H), 2.38-2.32 (m, 1H), 2.11-2.00 (m, 1H), 1.90-1.67 (m, 2H), 1.34-1.28 (m, 1H), 1.21 (s, 9H), 1.10 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 206.40, 174.50, 170.19, 145.62, 140.27, 133.29, 129.10, 128.18, 125.34, 67.25, 51.65, 43.79, 40.02, 39.13, 36.56, 26.74, 24.93, 22.86, 22.49; HRMS (EI) m/z calcd for 464.18688, found 464.18760.

2.6. Procedure for tosyl group substitution

To a stirred solution of **127** (422 mg, 1 mmol) in THF (10 mL) was added *t*-BuOK (224 mg, 2 mmol) in one portion at 0 °C. The reaction temperature was maintained at 0 °C for 1 h, then *p*-toluenesulfonyl chloride (381 mg, 2 mmol) was added. The resulting mixture was neutralized with AcOH, which was dissolved in 20 mL of ether. The ether layer was washed with brine and dried over anhydrous MgSO_4 . The crude material was purified by

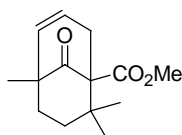
column chromatography.



(2E)-1-[2-Benzenesulfonyl-3-(p-toluenesulfonyloxy)allyl]-2,2-dimethyl-6-oxocyclohexanecarboxylic acid methyl ester (128): ^1H NMR (300 MHz, CDCl_3) δ 7.92-7.39 (m, 10H), 3.49 (s, 3H), 2.49 (s, 3H), 2.09-1.53 (m, 6H), 1.26-1.11 (m, 2H), 0.86 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 207.06, 169.82, 146.56, 143.13, 139.22, 133.60, 131.51, 130.15, 129.14, 128.51, 127.98, 126.70, 66.52, 51.78, 43.93, 38.85, 36.05, 26.50, 26.48, 22.49, 22.42, 21.90; HRMS (EI) m/z calcd for 534.13821, found 534.13900.

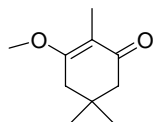
2.7. Procedure for acetoxysulfone elimination

The sulfone **136** (43.6 mg, 0.1 mmol) in methanol (1 mL) and ethyl acetate (0.5 mL) was stirred at 0 °C with 5% sodium amalgam. After 3 h, the mixture was poured into water (5 mL) and extracted with ether three times. The combined organic layer washed with brine and dried over anhydrous MgSO_4 . The crude material was purified by column chromatography.



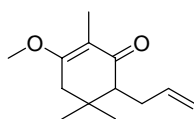
5,8,8-Trimethyl-9-oxobicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (112): ^1H NMR (300 MHz, CDCl_3) δ 5.81 (dt, $J = 9.3, 3.6$ Hz, 1H), 5.29 (d, $J = 9.3$, 1H), 3.71 (s, 3H), 3.13–2.83 (m, 2H), 2.06–1.52 (m, 3H), 1.24–1.167 (m, 1H), 1.11 (s, 3H), 1.09 (s, 6H); ^{13}C

NMR (75 MHz, CDCl₃) δ 210.70, 171.64, 132.74, 127.86, 64.83, 51.86, 46.23, 42.73, 36.89, 36.20, 35.02, 25.46, 25.06, 21.85; HRMS (EI) m/z calcd for 236.14124, found 236.14170.



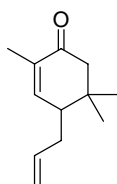
3-Methoxy-2,5,5-trimethylcyclohex-2-enone (**143**)

5,5-Dimethyl-1,3-cyclohexanedione (28 g, 200 mmol) was added to an aqueous NaOH solution (60 mL, 4 M). The solution was placed in an ice bath, followed by addition of iodomethane (25 mL, 400 mmol) via syringe. The ice bath was removed, and the solution was allowed to reflux for 24 h and cooled to room temperature. Excess iodomethane was evaporated, and then 60 mL of 4 M aqueous NaOH was added and extracted with ethyl acetate (2 x 100 mL) to eliminate dimethylated by-product. After the aqueous layer was acidified with 10% HCl, the crystals of **142** were collected. Upon filtration and air-dry, **142** was obtained in 90% purity, which was used for the next step without further purification. The methylated diketone **142** (12.5 g, 81 mmol) was dissolved in acetone (200 mL), and then dimethyl sulfate (6.9 mL, 73 mmol) and potassium carbonate (13.4 g, 97 mmol) was added. The resulting mixture was stirred overnight, and filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide **143** as a white crystal (11.2 g, 91%): mp 55–57 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.80 (s, 3H), 2.41 (d, J = 1.5 Hz, 2H), 2.24 (s, 2H), 1.70 (t, J = 1.5 Hz, 3H), 1.09 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 198.70, 169.97, 113.73, 55.27, 50.27, 38.91, 32.08, 28.73, 7.24.



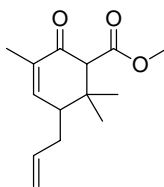
6-Allyl-3-methoxy-2,5,5-trimethylcyclohex-2-enone (144)

To a cooled (-78 °C), stirred solution of 2,2,6,6-tetramethylpiperidine (9.85 mL, 58 mmol) in THF (100 ml) was added *n*-BuLi (23.2 mL of 2.5 M solution in hexane, 58 mmol). The mixture was stirred for 10 min at 0 °C and then cooled to -78 °C followed by the addition of 3-methoxy-2,5,5-trimethylcyclohex-2-enone (8.82 g, 53 mmol) in THF (20 mL). The resulting mixture was stirred for 2 h at -78 °C. After which, allyl bromide (5.02 mL, 58 mmol) in THF (20 mL) was added. The temperature was raised to -15 °C (dry ice, acetone and water) and stirred overnight, at which time the reaction temperature was slowly warmed to room temperature. The solution was diluted with water and extracted with ether. The combined organic layers were washed with water and brine, which was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to provide **144** (8.82 g, 80%): ¹H NMR (300 MHz, CDCl₃) δ 5.94-5.80 (m, 1H), 5.03-4.92 (m, 2H), 3.79 (s, 3H), 2.49-2.27 (m, 4H), 2.11 (dd, *J* = 8.4, 5.1 Hz, 1H), 1.69 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 200.78, 168.00, 137.97, 115.31, 56.47, 55.07, 38.12, 34.83, 31.35, 29.21, 24.82, 7.49; HRMS (EI) *m/z* calcd for 208.14623, found 208.14653.



4-Allyl-2,5,5-trimethylcyclohex-2-enone (145)

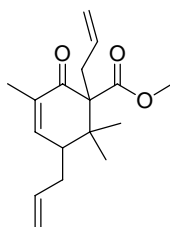
To a cooled (0 °C), stirred solution of lithium aluminum hydride (1.52 g, 40 mmol) in 100 mL of dry ether was slowly added **144** (8.32 g, 40 mmol). The reaction mixture was stirred for 3 h, followed by the addition of a minimum amount of water, and then filtered. After the solvent was evaporated, the alcohol was dissolved in THF (100 mL), and then 10% aqueous HCl (10 mL) was added. The resulting mixture was stirred for 0.5 h, and then diluted with ether (50 mL). The organic phase was separated from the aqueous phase and the aqueous phase was washed three times with 20 mL of ether. The combined organic phase was successively washed with water and brine, which was then dried over MgSO₄ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 1:20) to give **145** (6.99 g, 98%): ¹H NMR (300 MHz, CDCl₃) δ 6.51-6.50 (m, 1H), 5.90-5.77 (m, 1H), 5.17-5.11 (m, 2H), 2.48-2.24 (m, 4H), 1.95-1.75 (m, 4H), 1.09 (s, 3H), 0.88 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 200.06, 146.54, 136.84, 134.47, 117.31, 52.83, 46.30, 37.60, 33.69, 28.93, 21.42, 15.57; HRMS (EI) *m/z* calcd for 178.13577, found 178.13601.



5-Allyl-3,6,6-trimethyl-2-oxocyclohex-3-enecarboxylic acid methyl ester (138)

To a cooled (-78 °C), stirred solution of 2,2,6,6-tetramethylpiperidine (5.6 mL, 33 mmol) in THF (100 mL) was added *n*-BuLi (13.2 mL of 2.5 M solution in hexane, 33 mmol). The mixture was stirred for 10 min at 0 °C and then cooled to -78 °C, followed by the addition of **145** (5.34 g, 30 mmol) in THF (20 mL). The resulting mixture was stirred for 2 h

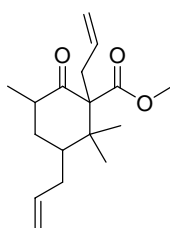
at -78 °C. After which, methyl cyanoformate (2.86 mL, 36 mmol) in THF (10 mL) was added and stirred for 3 h. It was poured into cold 10% aqueous HCl and extracted with ether. The combined organic layers were washed with brine and dried over MgSO₄. After solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide **138** as a mixture of diastereomers (6.38 g, 90%): ¹H NMR (300 MHz, CDCl₃) δ 6.57 (s, 1H), 6.45 (s, 1H), 5.87-5.72 (m, 2H), 5.16-5.08 (m, 4H), 3.73 (s, 3H), 3.66 (s, 3H), 3.36 (s, 1H), 3.17 (s, 1H), 2.69-2.65 (m, 1H), 2.43-2.26 (m, 3H), 1.94-1.83 (m, 2H), 1.78-1.77 (m, 6H), 1.13 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H), 0.93 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 194.87, 169.91, 169.26, 147.68, 145.71, 136.54, 136.40, 134.57, 133.16, 117.85, 117.61, 66.01, 64.85, 52.04, 51.75, 47.64, 43.14, 41.77, 39.50, 33.33, 32.78, 26.34, 25.46, 23.20, 15.86, 15.54, 15.52; HRMS (EI) *m/z* calcd for 236.14124, found 236.14153.



1,5-Diallyl-3,6,6-trimethyl-2-oxocyclohex-3-enecarboxylic acid methyl ester (153)

To a stirred solution of NaH (1 g, 60% in mineral oil, 25 mmol) in THF (50 ml), **138** (5.52 mL, 20 mmol) in THF (10 ml) was slowly added and stirred for 30 min, followed by the addition of allyl bromide (2.16 mL, 25 mmol) in THF (10 mL). The resulting mixture was refluxed overnight, and was cooled to room temperature. It was poured into sat. aqueous NH₄Cl and extracted with ether. The combined organic layers were dried over MgSO₄. After the solvent was removed under reduced pressure, the residue was purified by column

chromatography on silica gel (EtOAc/hexane, 1:20) to provide **153** (5.08 g, 92%): ^1H NMR (300 MHz, CDCl_3) δ 6.37 (s, 1H), 5.86-5.61 (m, 2H), 5.16-5.10 (m, 2H), 4.95-4.87 (m, 2H), 3.72 (s, 3H), 2.92-2.85 (m, 1H), 2.46-2.35 (m, 3H), 1.93-1.81 (m, 1H), 1.77 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.47, 171.26, 142.89, 136.72, 134.69, 133.68, 117.80, 51.66, 42.25, 34.69, 33.71, 23.25, 20.27, 16.18.



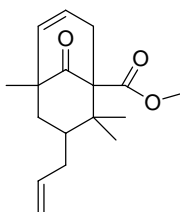
1,3-Diallyl-2,2,5-trimethyl-6-oxo-cyclohexanecarboxylic acid methyl ester (**154**)

To a cooled ($-78\text{ }^\circ\text{C}$), stirred solution of **153** (4.14 g, 15 mmol) in THF (30 ml) was added L-selectride (16.5 mL of 1 M solution in THF, 16.5 mmol). The mixture was stirred for 40 min, and then warmed to room temperature. The resulting mixture was treated with 10% NaOH/30% H_2O_2 (v/v = 25 mL/15 mL) stirred for 3 h. It was diluted with water and extracted with ethyl acetate. The combined organic layers were poured into cold 10% aqueous HCl and extracted with ether. The combined organic layers were washed with 10% aqueous sodium bisulfite and brine, and dried over MgSO_4 . After solvent evaporation, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide **154** as a 3:1 mixture of diastereomers (3.46 g, 83%).

For the major diastereomeric compound (**154a**): ^1H NMR (300 MHz, CDCl_3) δ 5.84-5.71 (m, 1H), 5.59-5.46 (m, 1H), 5.05-4.91 (m, 4H), 3.72 (s, 3H), 3.03-2.97 (m, 1H), 2.51 (dd, $J = 14.1, 9.3$ Hz, 1H), 2.34-2.23 (m, 2H), 2.08-1.95 (m, 2H), 1.76-1.65 (m, 1H), 1.21-

1.16 (m, 1H), 0.99-0.97 (m, 6H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 208.26, 170.88, 137.66, 134.05, 117.55, 116.73, 70.13, 51.60, 42.75, 42.25, 41.32, 36.10, 35.36, 34.79, 23.50, 20.46, 14.86.

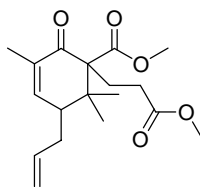
For the minor diastereomeric compound (**154b**): ^1H NMR (300 MHz, CDCl_3) δ 5.86-5.61 (m, 2H), 5.03-4.91 (m, 4H), 3.59 (s, 3H), 3.13-3.04 (m, 1H), 2.68 (dd, $J = 12.6, 4.8$ Hz, 1H), 2.50-2.44 (m, 1H), 2.18 (dd, $J = 12.6, 9.6$ Hz, 1H), 2.04-1.86 (m, 2H), 1.62-1.52 (m, 1H), 1.43-1.39 (m, 1H), 1.36 (s, 3H), 1.02 (d, $J = 6.3$ Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 210.28, 172.93, 138.37, 135.03, 117.73, 116.37, 66.29, 51.54, 46.51, 44.75, 38.38, 35.29, 33.47, 33.04, 27.37, 23.81, 15.19.



7-Allyl-5,8,8-trimethyl-9-oxobicyclo[3.3.1]non-3-ene-1-carboxylic acid methyl ester (156)

To a stirred solution of KH (1.48 g, 30% in mineral oil, 11.1 mmol) in THF (50 ml), **154** (2.06 mL, 7.41 mmol) in THF (10 ml) was slowly added and refluxed for 1 h, after which, the reaction mixture was cooled to room temperature. Triethylamine (3.1 mL, 22.23 mmol) and freshly distilled trimethylsilyl chloride (2.4 mL, 18.53 mmol) were then added, and the reaction was further stirred for 30 min. The resulting solution was diluted with hexane and filtered. After solvent was removed under reduced pressure, the silylated compound was dissolved in CH_3CN (30 mL) followed by the addition of $\text{Pd}(\text{OAc})_2$ (1.66 g, 7.41 mmol). It was stirred overnight, and the solvent was evaporated. The reaction solution

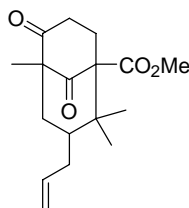
was filtered through a Celite pad, and the solid was washed repeatedly with pentane (100 mL). The combined filtrates are concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide **156** (1.03 g, 50%): ^1H NMR (300 MHz, CDCl_3) δ 5.83-5.60 (m, 2H), 5.33 (dt, $J = 9.6, 1.8$ Hz, 1H), 5.04-4.95 (m, 2H), 3.73 (s, 3H), 3.18-2.83 (m, 2H), 2.35-2.28 (m, 1H), 2.05-1.96 (m, 1H), 1.79-1.67 (m, 2H), 1.40-1.31 (m, 1H), 1.12 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 210.76, 171.79, 137.79, 133.62, 128.13, 116.39, 65.79, 51.94, 46.59, 45.38, 43.18, 39.61, 36.28, 33.48, 23.30, 21.80, 18.36.



5-Allyl-1-(2-methoxycarbonyl-ethyl)-3,6,6-trimethyl-2-oxo-cyclohex-3-enecarboxylic acid methyl ester (165)

Keto ester **138** (2.7 g, 11.4 mmol), *t*-BuOK (256 mg, 2.28 mmol) and *t*-BuOH (1.1 mL) in THF (23 mL) were stirred for 10 min, and then methyl acrylate (2.05 mL, 22.8 mmol) was added. The resulting mixture was stirred overnight, and then diluted with aq. NH_4Cl and extracted with ether (30 mL x 2). The combined organic layers were dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1: 6) to furnish **165** (3.39 g, 91%): ^1H NMR (300 MHz, CDCl_3) δ 6.39 (s, 1H), 5.84-5.70 (m, 1H), 5.14-5.08 (m, 2H), 3.71 (s, 3H), 3.59 (s, 3H), 2.54-2.28 (m, 4H), 2.09-1.74 (m, 6H), 1.03 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.82,

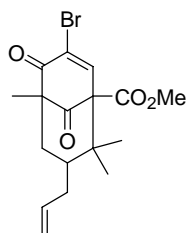
173.97, 171.08, 143.89, 136.54, 133.18, 117.88, 51.73, 51.67, 42.49, 33.59, 30.05, 24.31, 16.12; HRMS (EI) m/z calcd for 322.17802, found 322.17846.



3-Allyl-2,2,5-trimethyl-6,9-dioxobicyclo[3.3.1]nonane-1-carboxylic acid methyl ester (167)

In a 500 mL, 2-necked, round-bottomed flask fitted with a stirrer, and dry ice condenser were placed **165** (3.22 g, 10 mmol), *t*-BuOH (14.4 mL, 150 mmol), and dry THF (50 mL). To the cooled (-78 °C), stirred solution 150 mL of ammonia (NH₃) was collected and then freshly cut sodium (1.38 g, 60 mmol) was portionwise added over 10 min. The resulting mixture was further stirred for 1 h until all the sodium was consumed, and NH₄Cl powder (5 g) was added. The temperature of the bath was allowed to rise gradually to room temperature, and the reaction was stirred overnight to evaporate ammonia. The resulting mixture was diluted with ether, filtered and concentrated *in vacuo*. The diol was dissolved in CH₂Cl₂ (80 mL). PCC (8.62 g, 40 mmol) and Celite (8.62 g) were added, and the resulting solution was stirred for 48 h, and then filtered through a silica gel pad on a sintered-glass funnel. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to furnish **167** (2.16 g, 74%): ¹H NMR (300 MHz, CDCl₃) δ 5.64-5.50 (m, 1H), 4.95-4.90 (m, 2H), 3.67 (s, 3H), 2.55-2.05 (m, 6H), 1.64-1.49 (m, 2H), 1.32-1.23 (m, 1H), 1.11 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 211.17, 208.42, 171.63, 136.61,

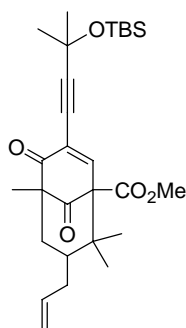
116.88, 64.92, 61.54, 52.02, 46.45, 43.71, 39.88, 39.74, 33.76, 23.45, 21.93, 17.43, 16.86;
HRMS (EI) m/z calcd for 292.16746, found 292.16777.



7-Allyl-3-bromo-5,8,8-trimethyl-4,9-dioxobicyclo[3.3.1]non-2-ene-1-carboxylic acid methyl ester (175)

To a stirred solution of KH (2 g, 30% in mineral oil, 15 mmol, mineral oil was removed with hexane washing prior to use) in THF (20 mL) were added a solution of compound **167** (1.46 g, 5 mmol) and triisopropylsilyl trifluoromethanesulfonate (2.7 mL, 10 mmol) in THF (10 mL), and stirred for 12 h. The reaction mixture was diluted with saturated NaHCO₃ (20 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic phase was successively washed with water, brine, and then dried over anhydrous MgSO₄. After solvent evaporation, the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1: 30) to give the silylated compound. This compound was dissolved in CCl₄ (20 mL), followed by the addition of NBS (3.56 g, 10 mmol) and AIBN (82 mg, 0.5 mmol). The mixture was refluxed for 1 h. After being cooled to room temperature, it was diluted with aqueous NaHCO₃ and extracted with CH₂Cl₂ (20 mL x 2). The combined organic layers were washed with brine and dried over anhydrous MgSO₄. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1: 7) to furnish **175** (1.31 g, 71%): ¹H NMR (300 MHz, CDCl₃) δ 7.64 (s, 1H), 5.67-5.53 (m, 1H), 5.04-4.98 (m, 2H), 3.80 (s, 3H),

2.31-2.25 (m, 1H), 2.02-1.96 (m, 1H), 1.74-1.63 (m, 2H), 1.51-1.41 (m, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 201.65, 191.52, 167.60, 146.37, 136.14, 125.47, 117.66, 71.12, 63.17, 52.99, 44.95, 42.03, 40.41, 34.02, 24.09, 16.69, 16.62; HRMS (EI) m/z calcd for 368.06232, found 368.06285.



7-Allyl-3-[3-(*tert*-butyldimethylsilyloxy)-3-methylbut-1-ynyl]-5,8,8-trimethyl-4,9-dioxobicyclo[3.3.1]non-2-ene-1-carboxylic acid methyl ester (177)

In a 20 mL round-bottomed flask were placed **167** (112.5 mg, 0.304 mmol), bis(triphenylphosphine)palladium dichloride (4.2 mg, 2 mol%), and copper(I) iodide (3 mg, 5 mol%) under an argon atmosphere. To this mixture were added diethylamine (5 mL) and *tert*-butyl-(1,1-dimethylprop-2-ynyloxy)dimethylsilane (121 mg, 0.608 mmol), and the resulting mixture was heated to reflux for 24 h. Excess diethylamine was evaporated under reduced pressure, and the residue was dissolved in ether (15 mL), and the insoluble material was filtered off. The ethereal solution was washed successively with brine, 10% HCl, water, sat. sodium bicarbonate, and finally brine, dried over anhydrous MgSO_4 . The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1: 10) to give **177** (103.5 mg, 70%): ^1H NMR (400 MHz, CDCl_3) δ 7.34 (s, 1H), 5.64-5.55 (m, 1H), 5.03-4.98 (m, 2H), 3.79 (s, 3H), 2.30-2.25 (m, 1H), 1.98 (dd, $J = 13.6, 4.0$ Hz, 1H), 1.77-1.63 (m, 2H), 1.54 (s,

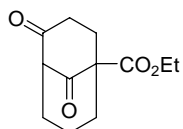
3H), 1.53 (s, 3H), 1.47 (t, $J = 6.8$ Hz, 1H), 1.27 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 0.87 (s, 9H), 0.18 (s, 6H).

References

1. Barnes, J.; Anderson, L. A.; Phillipson, J. D. *J. Pharm. Pharmacol.* **2001**, *53*, 583.
Muller, W. E. *Pharmacol. Res.* **2003**, *47*, 101.
2. Verotta, L. *Phytochem. Rev.* **2002**, *1*, 389.
3. Rodriguez-Landa, J. F.; Contreras, C. M. *Phytomedicine* **2003**, *10*, 688.
4. Salatino, A.; Teixeira, E. W.; Negri, G.; Message, D. *Evidence-Based Complement. Alternat. Med.* **2005**, *2*, 33.
5. Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Poprako, S. A.; Ryabova, I.; Chernov, B. K.; Debrentzeva, N. A.; Aizeman, B. E.; Garagulya, A. D. *Antibiotiki (Moscow)* **1971**, *16*, 510.
6. Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Riabova, I. D. *Antibiotiki* **1971**, *16*, 510.
7. Mennini, T.; Gobbi, M. *Life Sci.* **2004**, *75*, 1021.
8. Adam, P.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Med. Chem.* **2002**, *45*, 4786.
9. (a) Kaehler, S. T.; Sinner, C.; Chatterjee, S. S.; Philippu, A. *Neurosci. Lett.* **1999**, *262*, 199; (b) Muller, W. E.; Singer, A.; Wonnemann, M. *Pharmacopsychiatry* **2001**, *34* (Suppl. 1), S98.
10. Muller, W. E.; Singer, A.; Wonnemann, M.; Hafner, U.; Rolli, M.; Schafer, C. *Pharmacopsychiatry* **1998**, *31* (Suppl. 1), 16.
11. Moore, L. B.; Goodwin, B.; Jones, S. A.; Wisely, G. B.; Serabjit-Singh, C. J.;

- Willson, T. M.; Collins, J. L.; Kliewer, S. A. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7500.
12. Schempp, C. M.; Pelz, K.; Wittmer, A.; Schopf, E.; Simon, J. C. *Lancet* **1999**, *353*, 2129.
13. Lokvam, J.; Braddock, J. F.; Reichardt, P. B.; Clausen, T. P. *Phytochemistry* **2000**, *55*, 29.
14. de Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073.
15. de Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427.
16. Cuesta-Rubio, O.; Frontana-Uribe, B. A.; Ramirez-Apan, T.; Cardenas, J. Z. *Naturforsch. C* **2002**, *57*, 372.
17. Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochemistry* **1998**, *49*, 853.
18. Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947.
19. Roberson, M. R.; Harrell, L. E. *Brain Res. Rev.* **1997**, *25*, 50.
20. Adam, P.; Arigoni, D.; Bacher, A.; Eisenrath, W. *J. Med. Chem.* **2002**, *45*, 4786.
21. Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200.
22. Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048.
23. Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724.
24. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

25. Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829.
26. Horii, Z.; Imanishi, T.; Kim, S.-W.; Ninomiya, I. *Chem. Pharm. Bull.* **1968**, *16*, 1918.
27. Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423.
28. Cole, B. M.; Han, L.; Snider, B. B. *J. Org. Chem.* **1996**, *61*, 7832.
29. Magatti, C. V.; Kaminski, J. J.; Rothberg, I. *J. Org. Chem.* **1991**, *56*, 3102.
30. Jackson, W. P.; Ley, S. V.; Whittle, A. J. *Chem. Commun.* **1980**, *23*, 1173.
31. The model system is shown below



32. (a) Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem.* **2003**, *68*, 6238. (b) Padwa, A.; Ni, Z.; Watterson, S. H. *Pure Appl. Chem.* **1996**, *68*, 831. (c) Padwa, A.; Murphree, S. S. *Rev. Heteroatom Chem.* **1992**, *6*, 241.
33. Anzeveno, P. B.; Matthews, D. P.; Barney, C. L.; Barbuch, R. J. *J. Org. Chem.* **1984**, *49*, 3134.
34. (a) Bordwell, F. G.; Happer, D. A. R.; Cooper, G. D. *Tetrahedron Lett.* **1972**, 2759. (b) Redman, R. P.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1135. (c) Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1914. (d) Hoffman, J. E.; Wallace, T. J.; Schriesheim, A. J. *Am. Chem. Soc.* **1964**, *86*, 1561. (e) Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1898.
35. Buncel, E.; Decouzon, M.; Formento, A.; Gal, J.-F.; Herreros, M.; Li, L.; Maria, P.-

- C.; Koppel, I.; Kurg, R. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 262.
36. Kocienski, P. J.; Lythgoe, B.; Ruston, S. J. *Chem Soc., Perkin Trans. 1* **1978**, 829.
37. Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.*, **1982**, *104*, 5808.
38. Yu, J. Q.; Wu, H. C.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1415.
39. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis.* **1980**, 627.

CHAPTER 2. DIRECT SYNTHESSES OF 7,8-DIHYDROXYCALAMENENE AND MANSONONE C

Introduction

Allylic 1,3-strain has been used in acyclic systems to direct the introduction of new stereogenic centers.¹ The rotation of any alkyl group relative to a double bond is an important conformational event. This becomes even more interesting, when there is a substituent on the double bond *Z* to the allylic center, such as compound **a** (Figure 1). Indeed, conformation **b** is significantly destabilized by allylic 1,3-strain that represents a maximum energy determining the rotational barrier.² Thus, the conformer equilibrium strongly favors conformation **a** in order to avoid allylic 1,3-strain.

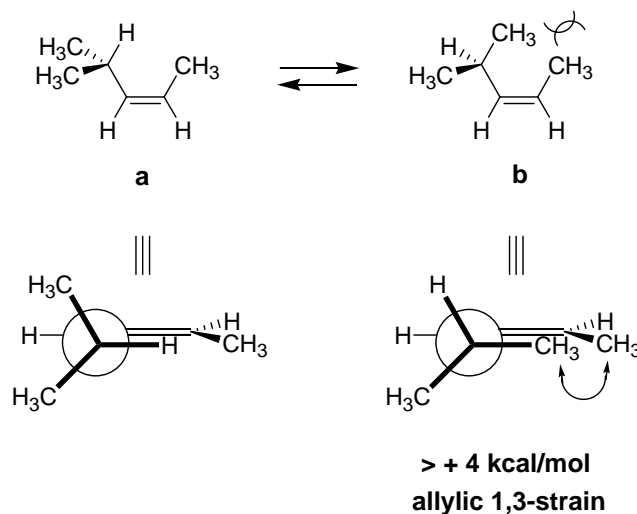
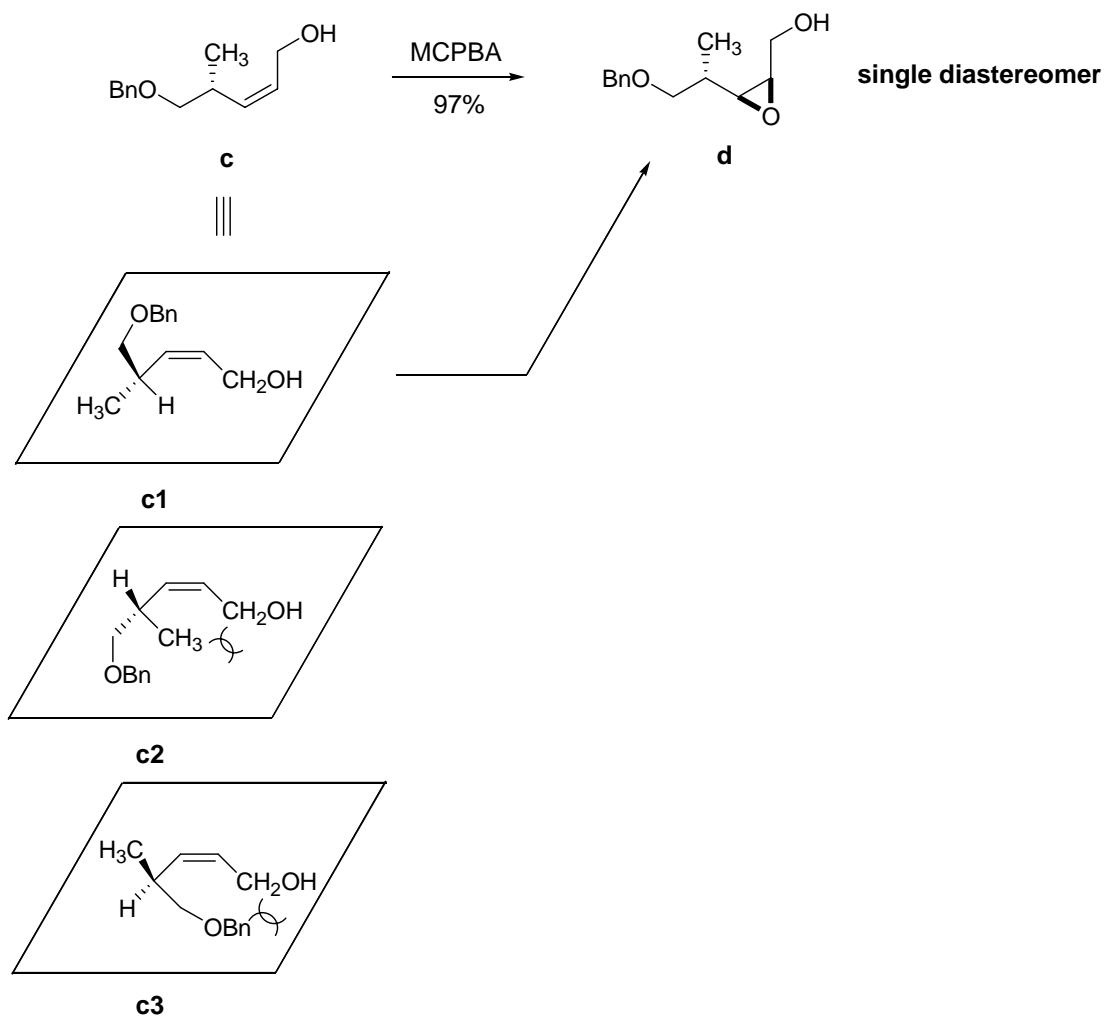


Figure 1. Rotamers of (2*Z*)-4-methylpent-2-ene

Notable examples include diastereoselective epoxidations by Kishi³ and Adam,⁴ and acyclic stereoselective radical reactions by Giese.⁵ The epoxidation of **c** using MCPBA yielded **d** as a single diastereomer (Scheme 1). Because the eclipsed conformations **c2** and **c3** have steric compression by allylic 1,3-strain, only conformer **c1** could participate in the oxidation event. The cooperative effect of the hydroxy group and the ether oxygen also direct the course of the epoxidizing reagent.⁶



Scheme 1

Despite its wide use as useful synthetic tool to direct the stereoselectivity, we are not aware of any application of the allylic 1,3-strain concept to control the relative stereochemistry in disubstituted tetralins. Tetralins, such as **1**, **3** and **4**, have attracted considerable synthetic attention.⁷ 7,8-Dihydroxycalamenene (**1a**) exhibits useful anti-infective activity.⁸ Hydroxycalamenene (**1b**) was isolated from *Hypericum elodeoides*.⁹ Mansonone C (**2**), extracted from the heartwood of *Mansonia altissima*,¹⁰ was found to possess promising antifungal, larvicidal and antioxidant properties.¹¹ 7-Hydroxyerogorgiaene (**3**) and elisapterosin B (**4**) were isolated from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*, and **3** was found to induce 77% growth inhibition for *Mycobacterium tuberculosis* H37Rv at a concentration of 6.25 $\mu\text{g/mL}$.⁷

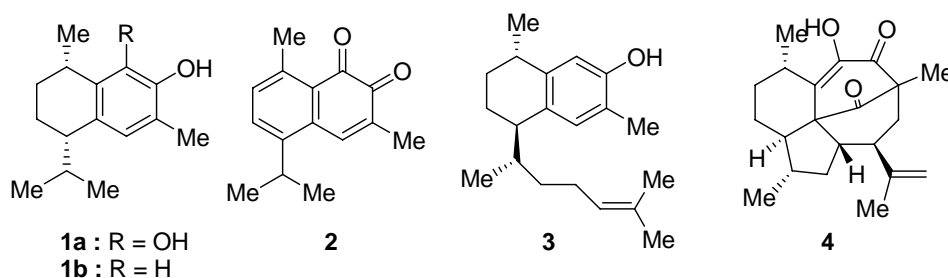
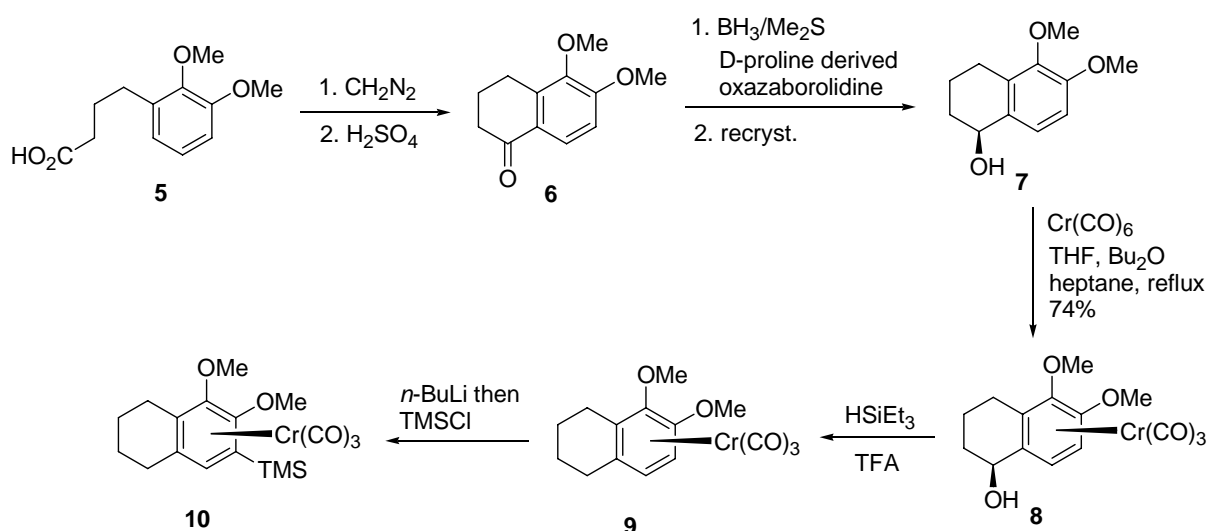


Figure 2. Tetralin-derived products and Mansonone C

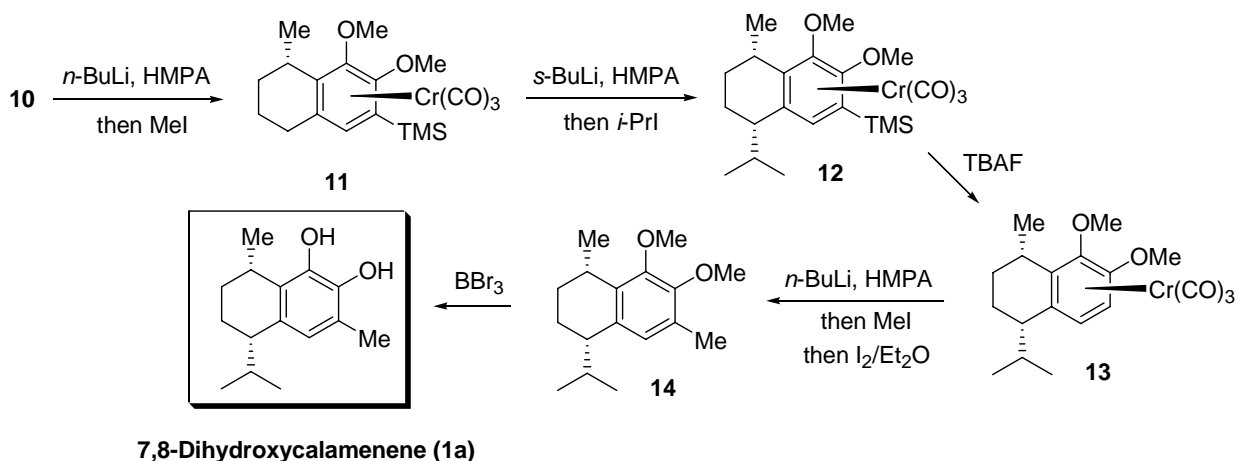
In 1993, Schmalz and co-workers reported a synthesis of **1a** using arene-chromium complexes to introduce the relative stereochemistry (Scheme 2).¹² The synthesis commenced with the reaction of 4-(2,3-dimethoxyphenyl)butyric acid (**5**) and diazomethane, followed by cyclization using sulfuric acid, to obtain tetralone **6**. Enantiomerically pure alcohol **7** was prepared from **6** via borane reduction in the presence of a *D*-proline-derived oxazaboroline catalyst, followed by recrystallization using EtOAc/hexane. Diastereoselective complexation

of **7** with $\text{Cr}(\text{CO})_6$ leading to **8** was accomplished. The $\text{Cr}(\text{CO})_6$ group serves two purposes as follow: (1) enhance the activity at the benzylic position, thus allowing alkylations under mild conditions, and (2) also guarantee the *cis*-configuration of the benzylic substituent by sterically blocking one π -face of the arene. Benzylic dehydration, followed by protection of the acidic *ortho*-methoxy aryl position of **9** as a TMS group, gave **10**.



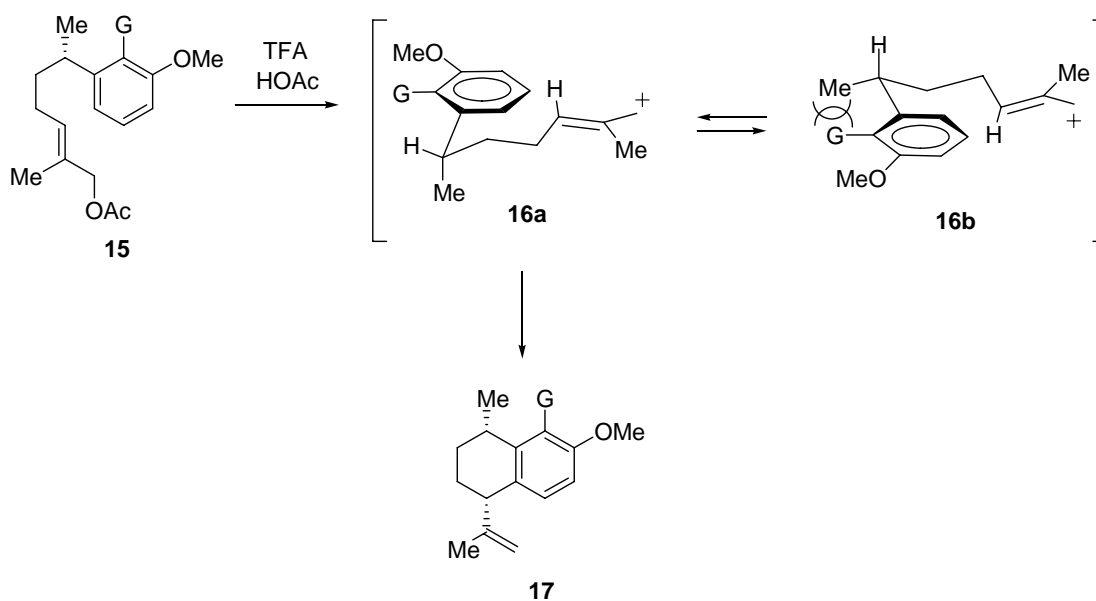
Scheme 2

Benzylic methylation of **10** employing *n*-BuLi in THF/HMPA and methyl iodide followed by *iso*-propylation was accomplished to furnish stereoselective *cis*-disubstituted compound **12** as the sole product. Desilylation, *ortho*-methylation and oxidative decomplexation using iodine gave **14**. Deprotection of the methyl ether group by BBr_3 completed the synthesis of 7,8-dihydroxycalamenene (**1a**).



Scheme 3

Many synthetic approaches to these compounds begin with natural products, such as menthone, wherein the relative stereochemistry has already been established.¹³ Several researchers have noted that attempts to install stereochemistry by epimerization or by cyclization onto the aromatic ring have led to mixtures.^{14,15}

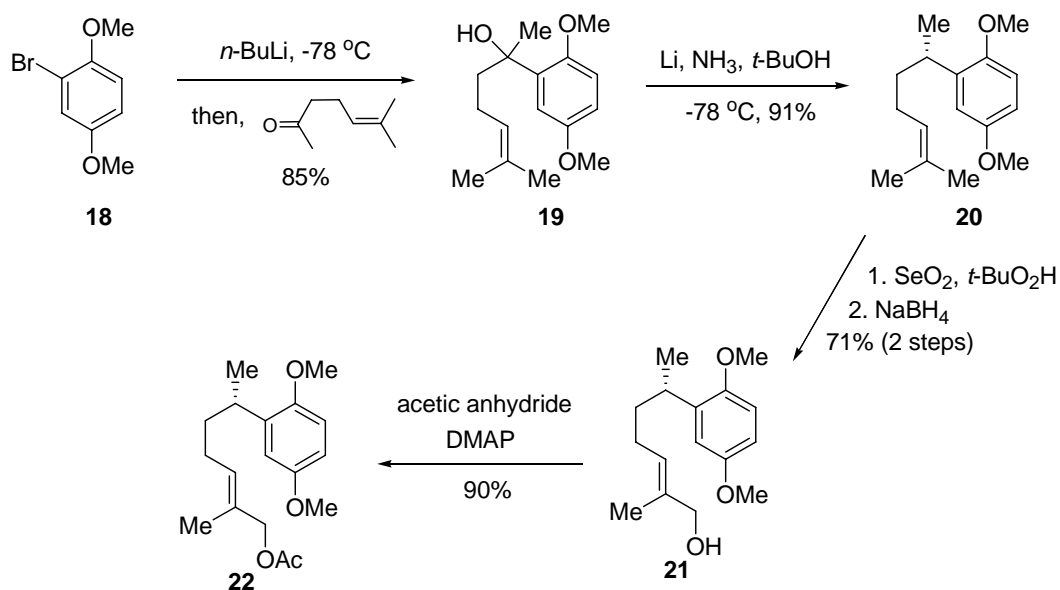


Scheme 4

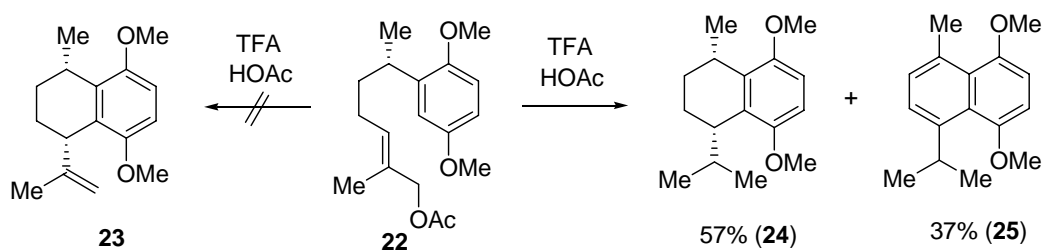
In this study, we exploited a direct, efficient synthetic route to 7,8-dihydroxycalamenene (**1a**) employing the concept of allylic 1,3-strain to direct the relative stereoselectivity. Under the condition of TFA/HOAc, the system such as **15**, wherein allylic strain between G and the methyl group forces the methyl group to be axial as the six-membered ring is being formed, would afford the *cis*-stereoisomer **17**.

Results and Discussion

In order to evaluate the directing effect, we first synthesized allylic acetate **22** (Scheme 5). The synthesis of allylic acetate **22** was achieved starting from the commercially available 2-bromo-1,4-dimethoxybenzene (**18**). Metal-halogen exchange of **18**, followed by the addition of 6-methyl-5-hepten-2-one at low temperature, produced the adduct **19**.

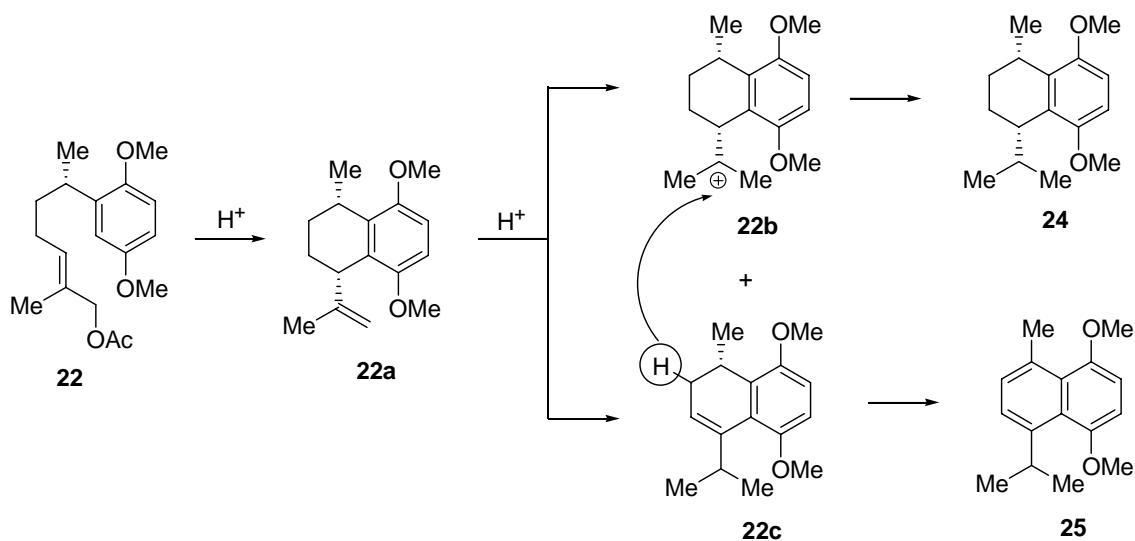


Scheme 5



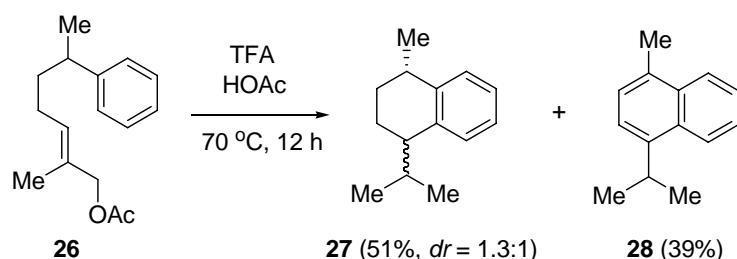
Scheme 6

Dehydration of the resulting benzylic alcohol using Li/NH₃ furnished **20**. Allylic oxidation of **20** by the method of Sharpless¹⁶ yielded an allylic alcohol **21**, which, upon acetylation, afforded **22**. The attempted cyclization of allylic acetate **22** using the conditions of Ma and Zheng¹⁷ afforded tetralin **24** as a single diastereomer in a 51% yield, without any evidence of generating compound **23**, the expected product (Scheme 6). To our surprise, the reaction also produced naphthalene **25** in a 37% yield. We believe that the formation of **24** and **25** result from a novel *cation-mediated disproportionation reaction* (Scheme 7).



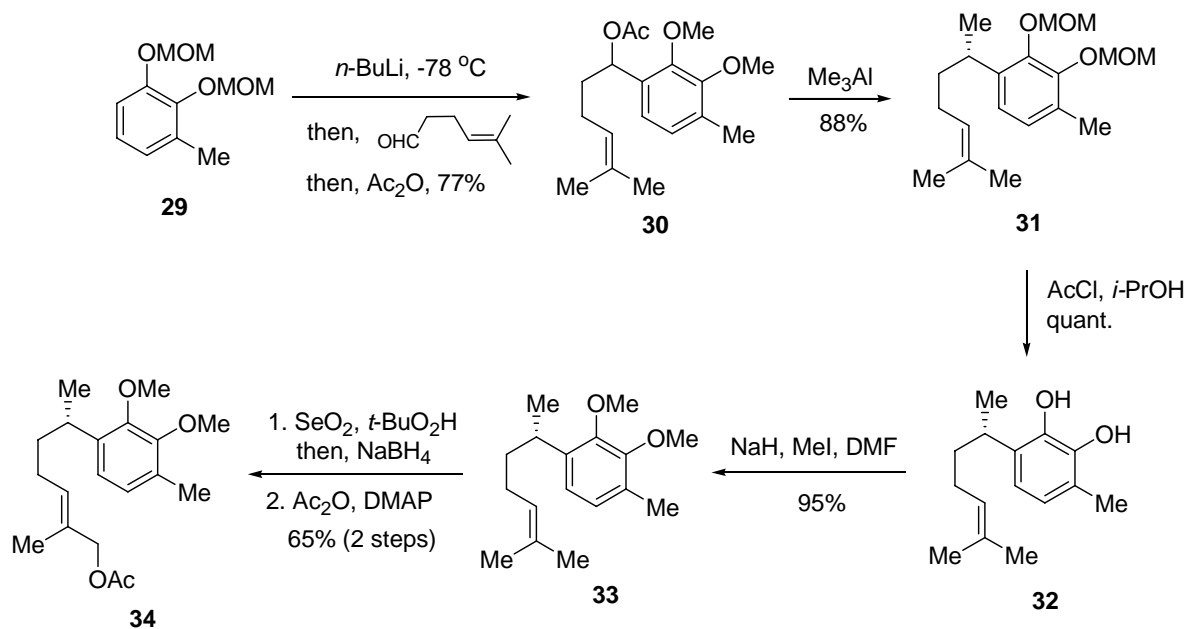
Scheme 7

Accordingly, *in situ* generated cationic intermediate **22b** was reduced by the isomeric intermediate **22c** to give **24**, whereas **22c**, in turn, oxidized to form the aromatized product **25**. Comparison of the ^1H NMR spectrum of **24** with that of the literature compound¹³ showed that the *cis*-stereoisomer was exclusively formed.



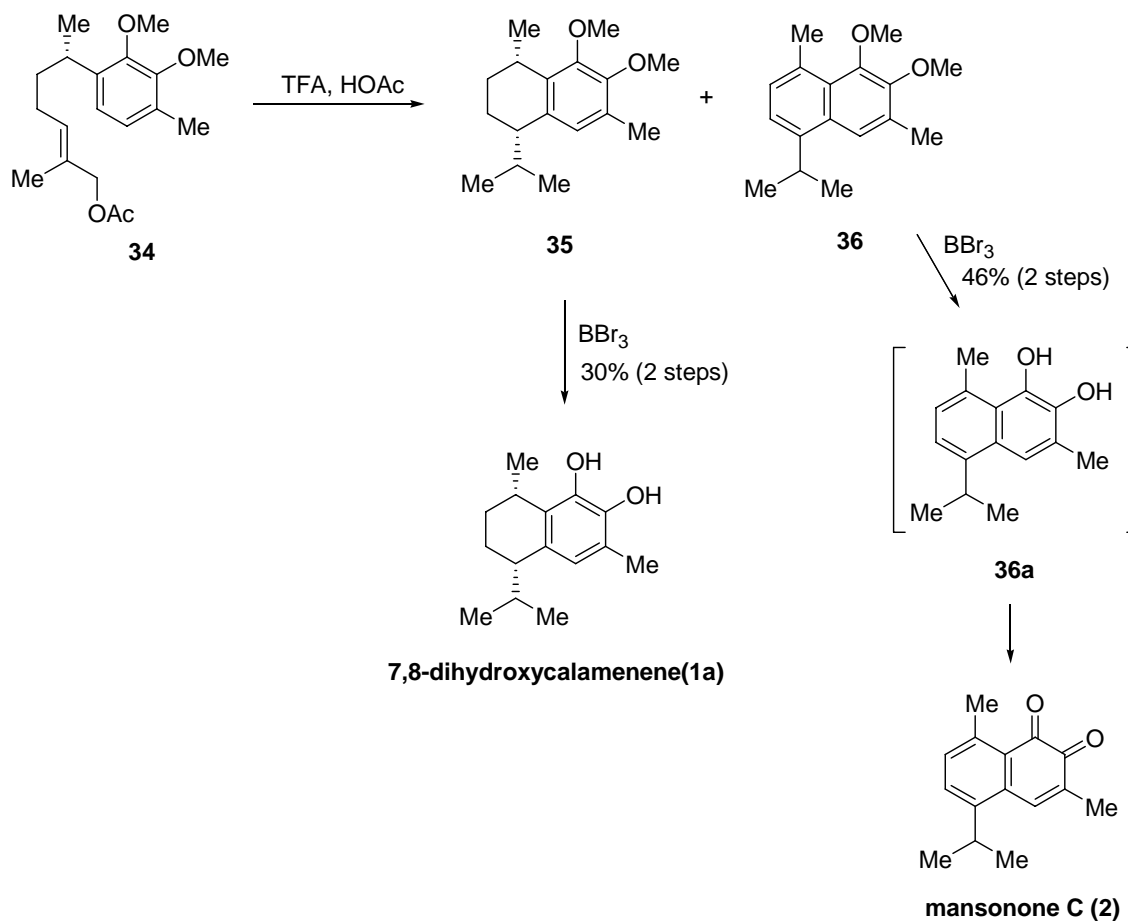
Scheme 8

In support of this allylic 1,3-strain assisted stereoselective cyclization, we have found that cyclization of allylic acetate **26**, which does not contain the directing group G, affords tetralin **27** as a 1.3:1 mixture of diastereomers (Scheme 8). Furthermore, the oxidation product **28** was also isolated in a 39% yield.



Scheme 9

With the stereochemistry of **24** established, we began the synthesis of **1a** by the reaction of the readily available 5-methyl-4-hexen-1-ol¹⁸ with the *ortho*-lithiated 1,2-bis(methoxymethoxy)-3-methylbenzene (Scheme 9). The resulting alkoxide was *in situ* acetylated by the addition of acetic anhydride. The displacement of the acetate to the corresponding methyl group was achieved using Me₃Al to afford **31**. In order to enhance the stability for the acid-mediated cyclization, the MOM protecting groups were converted to more stable methyl ether **33**. It was then oxidized and acetylated employing the same methods used to generate **22**.



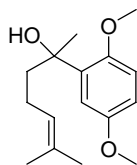
Scheme 10

Cyclization of **34** using trifluoroacetic acid in acetic acid at 70 °C for 12 hours provided an inseparable mixture of **35** and **36** (Scheme 10). Subsequent deprotection of the mixture of **35** and **36** using BBr₃ generated 7,8-dihydroxycalamenene (**1a**). Interestingly, the diol **36a** was not obtained. Instead, it underwent further oxidation under the reaction conditions to furnish mansonone C (**2**), a potent antifungal agent.

The direct synthesis of 7,8-dihydroxycalamenene (**1a**) demonstrates the successful application of allylic strain in the stereoselective synthesis. We are currently applying this synthetic strategy to the synthesis of analog natural products.

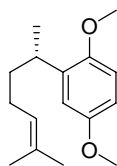
Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Dichloromethane, benzene and diisopropylamine were distilled over calcium hydride. All experiments were performed under an argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Nuclear magnetic resonance experiments were performed with a Bruker 400 MHz instrument. All chemical shifts are reported relative to CDCl₃ (7.27 ppm for ¹H and 77.23 ppm for ¹³C), 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. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.



2-(2,5-Dimethoxyphenyl)-6-methylhept-5-en-2-ol (19)

To a cooled ($-78\text{ }^{\circ}\text{C}$), stirred solution of 1-bromo-2,5-dimethoxybenzene (1.17 g, 10 mmol) in THF (10 mL) was added *n*-BuLi (4.4 mL of 2.5 M solution in hexane, 11 mmol). The mixture was stirred for 30 min, and then 6-methyl-5-hepten-2-one (1.26 g, 10 mmol) in THF (5 mL) was added. The resulting mixture was slowly warmed to room temperature, which was then poured into saturated brine. This was extracted with ether (10 mL x 3). The combined organic layers were dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to afford the title compound (2.25 g, 85%): ^1H NMR (400 MHz, CDCl_3) δ 6.92 (d, $J = 2.8$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 1H), 6.75 (dd, $J = 8.8, 2.8$ Hz, 1H), 5.11-5.07 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 2.04-1.81 (m, 4H), 1.66 (s, 3H), 1.52 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.69, 151.08, 136.29, 131.63, 124.66, 114.04, 112.14, 111.47, 75.21, 55.92, 55.77, 42.08, 27.46, 25.83, 23.48, 17.71; HRMS (EI) m/z calcd for 264.17254, found 264.17286.



2-(1,5-Dimethylhex-4-enyl)-1,4-dimethoxybenzene (20)

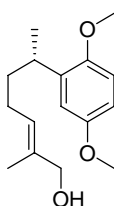
In a 100 mL, 2-necked, round-bottomed flask fitted with a stirrer, and dry ice condenser were placed 2-(2,5-dimethoxyphenyl)-6-methylhept-5-en-2-ol (1.6 g, 6 mmol), *t*-

BuOH (1.1 g, 15 mmol), and dry THF (10 mL). To the cooled (-78 °C), stirred solution 30 mL of ammonia (NH₃) was collected and then freshly cut sodium (0.35 g, 15 mmol) was added over 3-5 min. The resulting mixture was further stirred until all the sodium was consumed, as evidenced by the conversion of the colors to white, and NH₄Cl powder (1 g) was added. The temperature of the bath was allowed to rise gradually to room temperature and the reaction was stirred overnight to evaporate ammonia. The resulting mixture was filtered and concentrated *in vacuo*. After purification by column chromatography (EtOAc/hexane, 1:20), the title compound (1.36 g, 91%) was isolated: ¹H NMR (400 MHz, CDCl₃) δ 6.78 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 2.8 Hz, 1H), 6.68 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.14-5.10 (m, 1H), 3.78 (s, 6H), 3.19-3.14 (m, 1H), 1.96-1.88 (m, 2H), 1.68 (s, 3H), 1.65-1.50 (m, 5H), 1.19 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 153.86, 151.55, 137.47, 131.25, 124.91, 113.70, 111.56, 110.20, 56.18, 55.67, 37.32, 31.97, 26.39, 25.88, 21.20, 17.74; HRMS (EI) *m/z* calcd for 248.17763, found 248.17789.

General procedure for allylic oxidation

In a 100 mL round-bottomed flask, SeO₂ (0.5 mmol) was dispersed in CH₂Cl₂ (25 mL). *t*-BuO₂H (70% in water, 11 mmol) was added dropwise, and the mixture was stirred at room temperature for 10 min. After that time, the mixture was cooled to 0 °C, and then the dimethoxybenzene (5 mmol) in CH₂Cl₂ (10 mL) was slowly added. The reaction was stirred for 36 h, after which time it was poured into NaOH (10% aq.) and extracted with dichloromethane. The organic extracts were washed with water, and then with brine. The solvent was dried over MgSO₄, the solids were filtered, and the mixture was then concentrated on a rotary evaporator. The crude was dissolved in methanol (10 mL) and

cooled to 0 °C, and NaBH₄ (5.5 mmol) was added to reduce the aldehyde by-product. After 1 h, the mixture was poured into water, extracted with ether and then washed with brine. The organic extract was dried over MgSO₄ and concentrated *in vacuo*. After evaporation, the residue was purified by column chromatography on silica gel to give the allylic alcohols (69-71%).



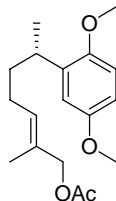
(2E)-6-(2,5-Dimethoxyphenyl)-2-methylhept-2-en-1-ol (21)

¹H NMR (400 MHz, CDCl₃) δ 6.79 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 3.2 Hz, 1H), 6.67 (dd, *J* = 8.8, 3.2 Hz, 1H), 5.38 (t, *J* = 7.3 Hz, 1H), 3.96 (d, *J* = 6.0 Hz, 2H), 3.78 (s, 6H), 3.21-3.15 (m, 1H), 2.02-1.94 (m, 2H), 1.71-1.57 (m, 5H), 1.19 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 153.85, 151.54, 137.25, 134.74, 126.71, 113.78, 111.72, 110.27, 69.22, 56.34, 55.78, 36.82, 31.86, 25.91, 21.34, 13.75; HRMS (EI) *m/z* calcd for 264.17254, found 264.17286.

General procedure for acetylation

To a cooled (0 °C), stirred solution of alcohol (10 mmol) in CH₂Cl₂ (30 mL) was added acetic anhydride (20 mmol) and DMAP (20 mmol). The mixture was stirred for 3 h, and then diluted with aq. NH₄Cl. This was extracted with ether (80 mL x 2). The combined organic layers were dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue

was purified by column chromatography on silica gel to furnish acetylated compounds (80-91%).

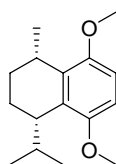


(2E)-6-(2,5-Dimethoxyphenyl)-2-methylhept-2-enyl acetate (22)

^1H NMR (400 MHz, CDCl_3) δ 6.79 (d, $J=8.8$ Hz, 1H), 6.76 (d, $J=3.2$ Hz, 1H), 6.70 (dd, $J=8.8, 3.2$ Hz, 1H), 5.46 (t, $J=6.8$ Hz, 1H), 4.44 (s, 2H), 3.78 (s, 6H), 3.20-3.14 (m, 1H), 2.07 (s, 2H), 2.06-1.94 (m, 2H), 1.73-1.54 (m, 5H), 1.20 (d, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.12, 153.81, 151.50, 137.01, 130.15, 129.91, 113.71, 111.53, 110.26, 70.52, 56.20, 55.72, 36.70, 31.91, 26.04, 21.17, 21.12, 14.01; HRMS (EI) m/z calcd for 306.18311, found 306.18346.

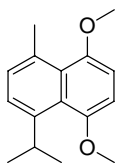
General procedure for cyclization

The allylic acetate (0.5 mmol) in 1 mL of TFA/HOAc (v/v = 3:1) was stirred at 70 °C for 12 h. The reaction mixture was quenched with saturated aq NaCl (10 mL) and extracted with ether (15 mL x 3). The combined organic phases were successively washed with water, saturated NaHCO_3 , and dried over MgSO_4 , which was then concentrated *in vacuo*.



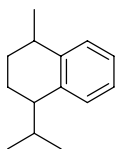
1-Isopropyl-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydronaphthalene (24)

Purification by column chromatography on silica gel gave the compound **24** in 51% yield: ^1H NMR (400 MHz, CDCl_3) δ 6.66 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.22-3.17 (m, 1H), 3.03-2.98 (m, 1H), 2.36-2.28 (m, 1H), 1.86-1.75 (m, 2H), 1.65-1.54 (m, 2H), 1.27 (d, $J = 7.2$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.93, 151.67, 133.32, 131.82, 107.38, 107.17, 55.65, 55.62, 38.48, 30.12, 27.71, 27.26, 21.36, 21.27, 21.15, 18.97; HRMS (EI) m/z calcd for 248.17763, found 248.17803.



1-Isopropyl-5,8-dimethoxy-4-methylnaphthalene (25)

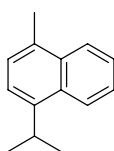
Purification by column chromatography on silica gel gave the compound **25** in 37% yield: ^1H NMR (400 MHz, CDCl_3) δ 7.94 (s, 1H), 7.16 (s, 1H), 6.71-6.66 (m, 2H), 3.97 (s, 3H), 3.88 (s, 3H), 3.08-2.99 (m, 1H), 2.90 (s, 3H), 1.35 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.44, 149.68, 146.04, 135.13, 129.08, 128.04, 124.66, 116.31, 104.23, 103.51, 56.00, 55.96, 34.41, 25.33, 24.15; HRMS (EI) m/z calcd for 244.14633, found 244.14671.



1-Isopropyl-4-methyl-1,2,3,4-tetrahydronaphthalene (27)

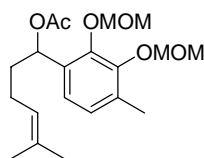
Purification by column chromatography on silica gel gave the compound **27** in 51% yield as a 1.3:1 mixture of diastereomers: ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.11 (m, 4H),

2.94-2.92 (m, 0.6H), 2.85-2.80 (m, 0.4H), 2.77-2.72 (m, 0.5H), 2.68-2.63 (m, 0.6H), 2.32-2.21 (m, 1H), 2.03-1.96 (m, 0.5H), 1.90-1.58 (m, 3H), 1.43-1.36 (m, 0.5H), 1.30 (d, $J = 7.2$ Hz, 1.7H), 1.29 (d, $J = 7.2$ Hz, 1.3H), 1.05 (d, $J = 6.8$ Hz, 1.7H), 1.02 (d, $J = 6.8$ Hz, 1.3H), 0.78 (d, $J = 6.8$ Hz, 1.7H), 0.73 (d, $J = 7.2$ Hz, 1.3H); HRMS (EI) m/z calcd for 188.15650, found 188.15684.



1-Isopropyl-4-methylnaphthalene (28)

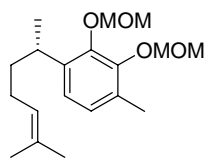
Purification by column chromatography on silica gel gave the compound **28** in 39% yield: ^1H NMR (400 MHz, CDCl_3) δ 8.20-8.17 (m, 1H), 8.07-8.03 (m, 1H), 7.57-7.52 (m, 2H), 7.33 (d, $J = 3.6$ Hz, 2H), 3.80-3.73 (m, 1H), 2.70 (s, 3H), 1.42 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 133.10, 132.24, 131.56, 126.64, 125.51, 125.29, 125.13, 124.00, 121.55, 28.57, 23.85, 19.74; HRMS (EI) m/z calcd for 184.12520, found 184.12540.



1-[2,3-Bis(methoxymethoxy)-4-methylphenyl]-5-methylhex-4-enyl acetate (30)

To a solution of 1,2-bis(methoxymethoxy)-3-methylbenzene (4.3 g, 20 mmol) in dry THF (80 mL) was added *n*-BuLi (8.4 mL of 2.5 M solution in hexane, 21 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature. The mixture was cooled to -78 °C, and then 5-methyl-4-hexen-1-al (2.5 g, 22 mmol) in THF (10 mL) was added. The reaction was stirred

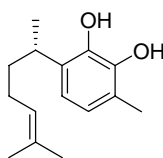
for an additional 1 h at $-78\text{ }^{\circ}\text{C}$, and then slowly warmed to room temperature. The resulting mixture was then cooled to $0\text{ }^{\circ}\text{C}$ and acetic anhydride (2.1 mL, 22 mmol) was added. The mixture was stirred for 1 h, and then diluted with brine (100 mL) and extracted with ether. The combined organic layers were dried over MgSO_4 , filtered and concentrated under reduced pressure. Flash chromatography on silica gel (EtOAc/hexane, 1:4) yielded the title compound (5 g, 77%): ^1H NMR (400 MHz, CDCl_3) δ 7.07 (d, $J = 8.0$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 5.19-5.04 (m, 5H), 4.97-4.92 (m, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 2.78 (d, $J = 4.0$ Hz, 1H), 2.31 (s, 3H), 2.17-2.08 (m, 2H), 1.97-1.88 (m, 1H), 1.83-1.76 (m, 1H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.27, 148.19, 136.89, 132.18, 132.14, 126.86, 124.25, 122.10, 99.79, 99.21, 68.14, 57.80, 57.79, 36.61, 25.94, 25.07, 17.88, 16.67; HRMS (EI) m/z calcd for 324.19367, found 324.19405.



1-(1,5-Dimethylhex-4-enyl)-2,3-bis(methoxymethoxy)-4-methylbenzene (**31**)

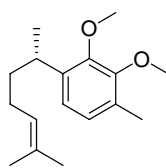
To a solution of 1-[(2,3-bis(methoxymethoxy)-4-methylphenyl]-5-methylhex-4-enyl acetate (2.2 g, 6 mmol) in CH_2Cl_2 (30 mL) was added trimethylaluminum (9.0 mL of 2.0 M solution in hexane, 18 mmol) at $-78\text{ }^{\circ}\text{C}$ under argon. The reaction mixture was warmed to $0\text{ }^{\circ}\text{C}$ over 3 h, quenched with water, and extracted with ether. The organic layer was washed with saturated aq. NaHCO_3 , and brine, dried over MgSO_4 , and evaporated under reduced pressure. The residue was chromatographed on silica gel (EtOAc/hexane, 1:20) to afford the title compound (**31**) (1.7 g, 88%): ^1H NMR (400 MHz, CDCl_3) δ 6.92 (d, $J = 8.0$ Hz, 1H),

6.89 (d, $J = 8.0$ Hz, 1H), 5.13-5.02 (m, 5H), 3.59 (s, 6H), 3.25-3.19 (m, 1H), 2.29 (s, 3H), 2.02-1.83 (m, 2H), 1.76-1.55 (m, 8H), 1.19 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.50, 147.60, 140.06, 129.90, 126.91, 126.49, 124.79, 121.92, 99.50, 99.29, 57.74, 57.68, 38.04, 31.39, 26.43, 25.87, 22.00, 17.80, 16.57; HRMS (EI) m/z calcd for 322.21441, found 322.21491.



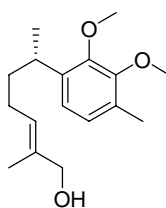
3-(1,5-Dimethylhex-4-enyl)-6-methylbenzene-1,2-diol (32)

To a solution of 1-(1,5-dimethylhex-4-enyl)-2,3-bis(methoxymethoxy)-4-methylbenzene (161 mg, 0.5 mmol) in *i*-PrOH (1.6 mL) was added AcCl (0.18 mL, 2.5 mmol) at 0 °C. The reaction was monitored by TLC to avoid prolonged reaction times. After completion (5 h), H_2O (15 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with H_2O and concentrated to afford a quantitative yield of the title compound, which were used for the next step without further purification: ^1H NMR (400 MHz, CDCl_3) δ 6.71 (d, $J = 8.0$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 5.25-5.17 (m, 3H), 3.01-2.95 (m, 1H), 2.25 (s, 3H), 1.99-1.94 (m, 2H), 1.73 (s, 3H), 1.70-1.63 (m, 2H), 1.57 (s, 3H), 1.27 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.07, 141.12, 132.74, 131.24, 124.97, 122.43, 121.31, 117.92, 37.59, 31.73, 26.16, 25.94, 21.41, 17.94, 15.57; HRMS (EI) m/z calcd for 262.19328, found 262.19376.



1-(1,5-Dimethylhex-4-enyl)-2,3-dimethoxy-4-methylbenzene (33)

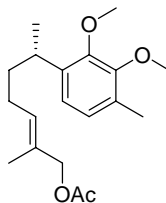
To a solution of 3-(1,5-dimethylhex-4-enyl)-6-methylbenzene-1,2-diol (117 mg, 0.5 mmol) in DMF (3 mL) was added NaH (60 mg of 60% dispersed in mineral oil, 1.5 mmol), and the solution was stirred at room temperature for 30 min, after which MeI (213 mg, 1.5 mmol) was added and the reaction was stirred overnight. It was then diluted with aq. NH_4Cl . This was extracted with ether (10 mL x 2). The combined organic layers were dried over anhydrous MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to furnish the title compound (33) (125 mg, 95%): ^1H NMR (400 MHz, CDCl_3) δ 6.71 (d, $J = 8.0$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 5.25-5.17 (m, 3H), 3.01-2.95 (m, 1H), 2.25 (s, 3H), 1.99-1.94 (m, 2H), 1.73 (s, 3H), 1.70-1.63 (m, 2H), 1.57 (s, 3H), 1.27 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.07, 141.12, 132.74, 131.24, 124.97, 122.43, 121.31, 117.92, 37.59, 31.73, 26.16, 25.94, 21.41, 17.94, 15.57; HRMS (EI) m/z calcd for 262.19328, found 262.19376.



(2E)-6-(2,3-Dimethoxy-4-methylphenyl)-2-methylhept-2-en-1-ol

^1H NMR (400 MHz, CDCl_3) δ 6.89 (d, $J = 8.0$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 5.39 (t, $J = 7.2$ Hz, 1H), 4.01 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.20-3.11 (m, 1H), 2.25 (s, 3H),

2.05-1.89 (m, 2H), 1.71-1.58 (m, 2H), 1.56 (s, 3H), 1.20 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.40, 150.87, 139.05, 134.86, 129.62, 126.68, 125.87, 121.62, 69.25, 60.90, 60.09, 37.36, 31.64, 26.04, 22.48, 15.86, 13.82; HRMS (EI) m/z calcd for 278.18819, found 278.18867.



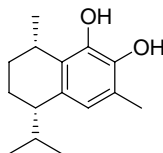
(2E)-6-(2,3-Dimethoxy-4-methylphenyl)-2-methylhept-2-enyl acetate (34)

^1H NMR (400 MHz, CDCl_3) δ 6.88 (d, $J = 8.0$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 5.47 (t, $J = 7.2$ Hz, 1H), 4.44 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.17-3.12 (m, 1H), 2.25 (s, 3H), 2.07 (s, 3H), 2.06-1.91 (m, 2H), 1.70-1.55 (m, 5H), 1.21 (d, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.10, 151.39, 150.92, 138.95, 130.05, 130.00, 129.62, 125.78, 121.51, 70.48, 60.76, 60.01, 37.32, 31.83, 26.24, 22.15, 21.16, 15.82, 14.06; HRMS (EI) m/z calcd for 320.19876, found 320.19919.

Procedure for demethylation

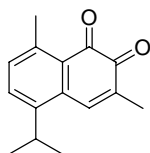
After the cyclization of **17**, allylic acetate (0.5 mmol) in 1 mL of TFA/HOAc (v/v = 3:1) was stirred at 70 °C for 12 h. The reaction mixture was quenched with saturated NaCl (10 mL) and extracted with ether (15 mL x 3). The combined organic phase was successively washed with water, saturated NaHCO_3 , and dried over MgSO_4 . After evaporation, the residue was dissolved in CH_2Cl_2 and cooled to -78 °C with stirring. To this solution, BBr_3 (1 M solution in CH_2Cl_2 , 1 mmol) was added and stirred for 1 h. Meanwhile, the reaction mixture was slowly warmed to room temperature. After this, aq. 10% NaOH solution (2 mL) was

added. The resulting hydrolyzed mixture was then acidified with aq. 10% HCl and extracted with ether. The combined organic layers were dried over anhydrous MgSO_4 and concentrated *in vacuo*.



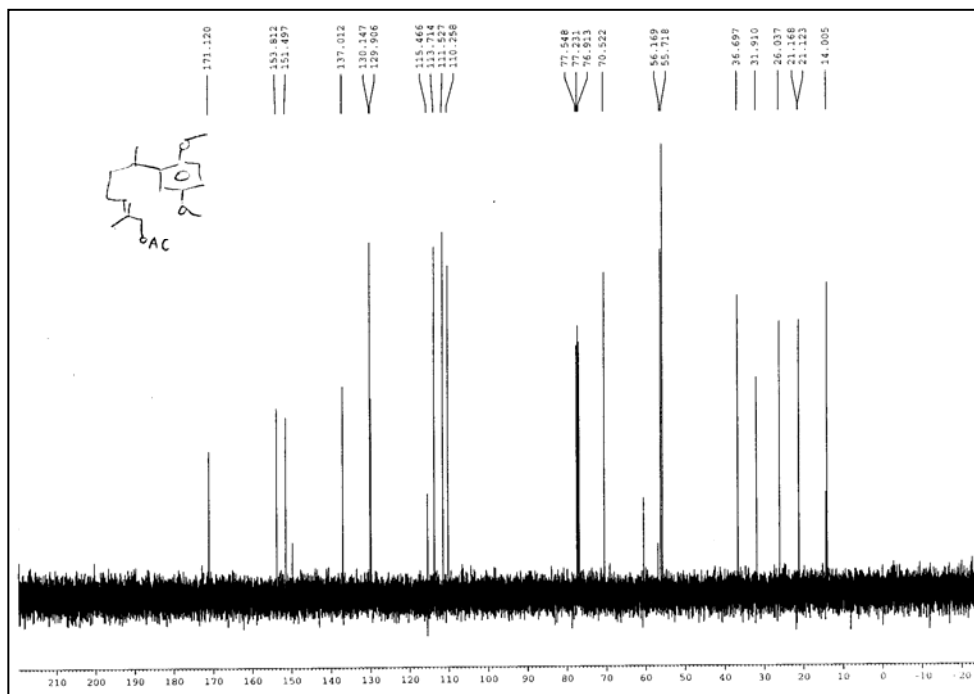
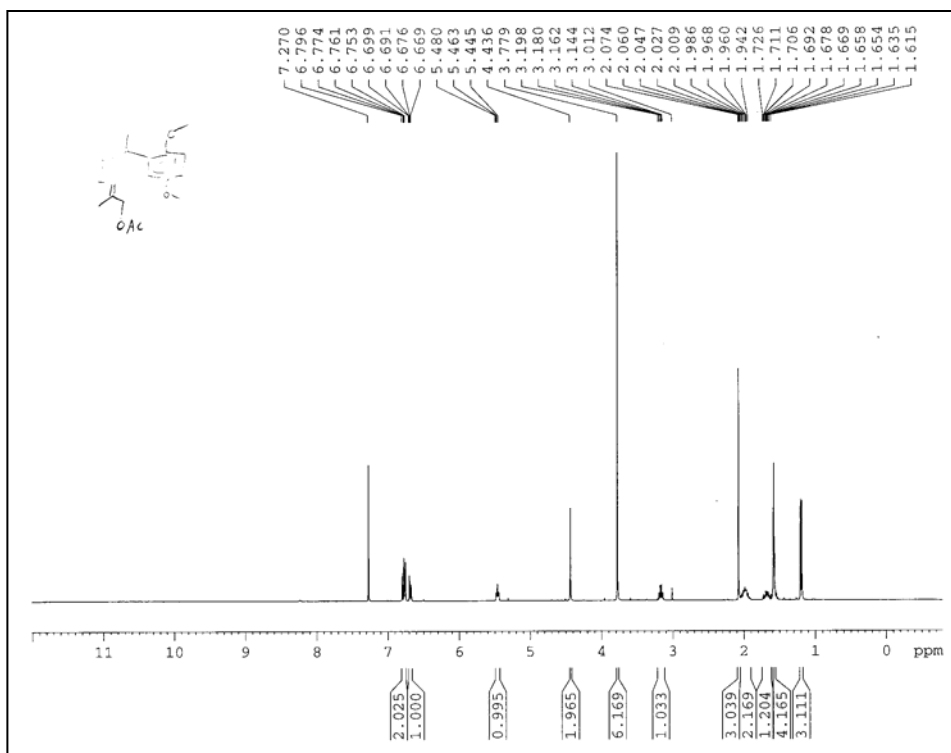
7,8-Dihydroxycalamenene (1a)

Purification by column chromatography on silica gel gave compound **1a** in two steps in a 30% yield: ^1H NMR (400 MHz, CDCl_3) δ 6.64 (s, 1H), 5.09 (s, 1H), 4.74 (s, 1H), 3.08-3.04 (m, 1H), 2.68-2.62 (m, 1H), 2.39-2.32 (m, 1H), 2.23 (s, 3H), 1.78-1.61 (m, 4H), 1.26 (d, $J = 7.2$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.67 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.04, 139.04, 132.37, 127.84, 121.26, 121.00, 42.95, 30.87, 29.02, 27.22, 21.25, 20.72, 17.52, 16.54, 15.87; HRMS (EI) m/z calcd for 234.16198, found 234.16227.

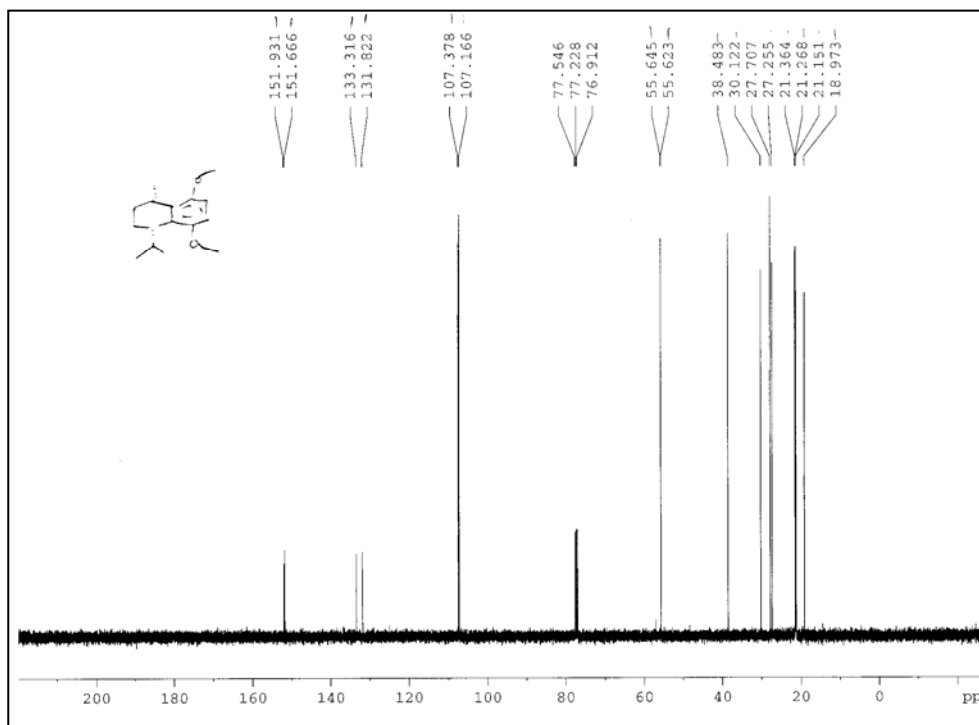
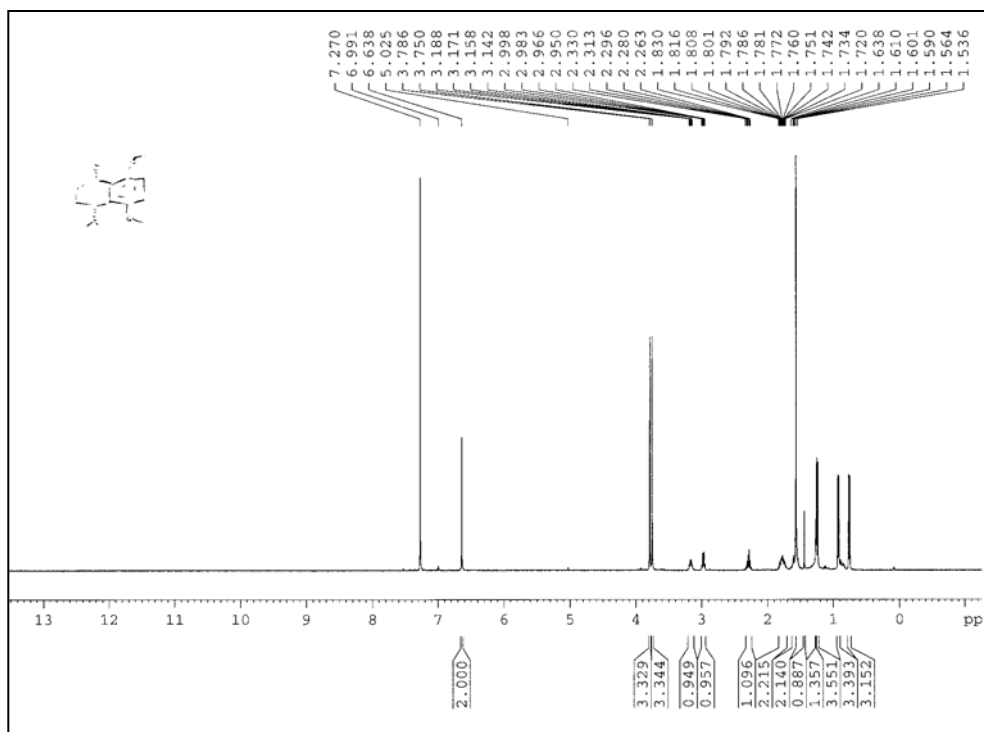


Mansonone C (2)

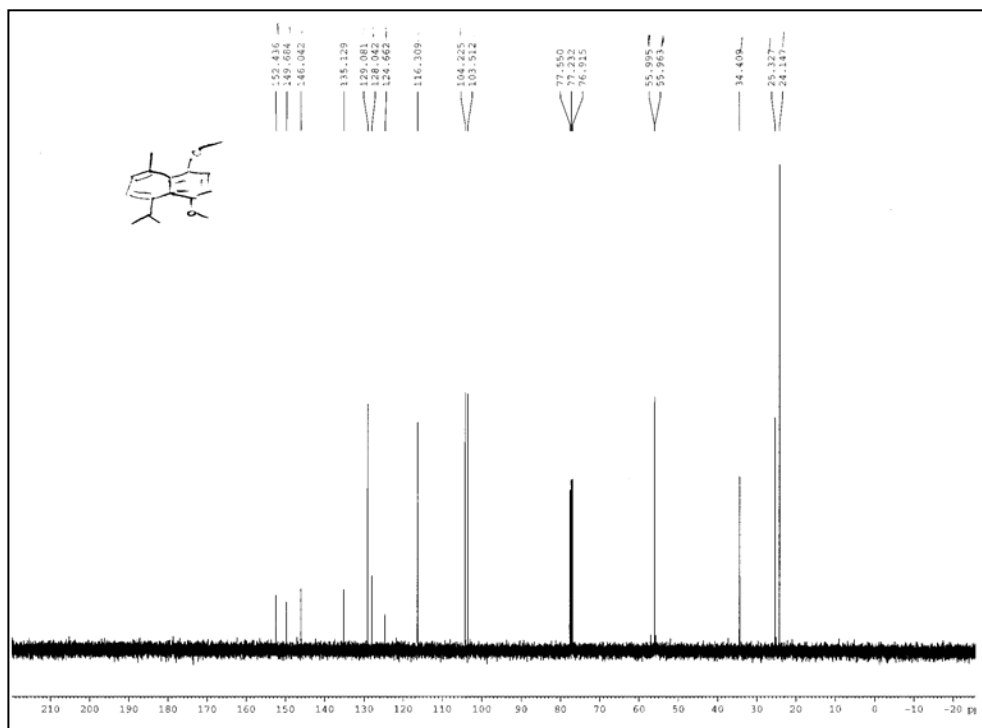
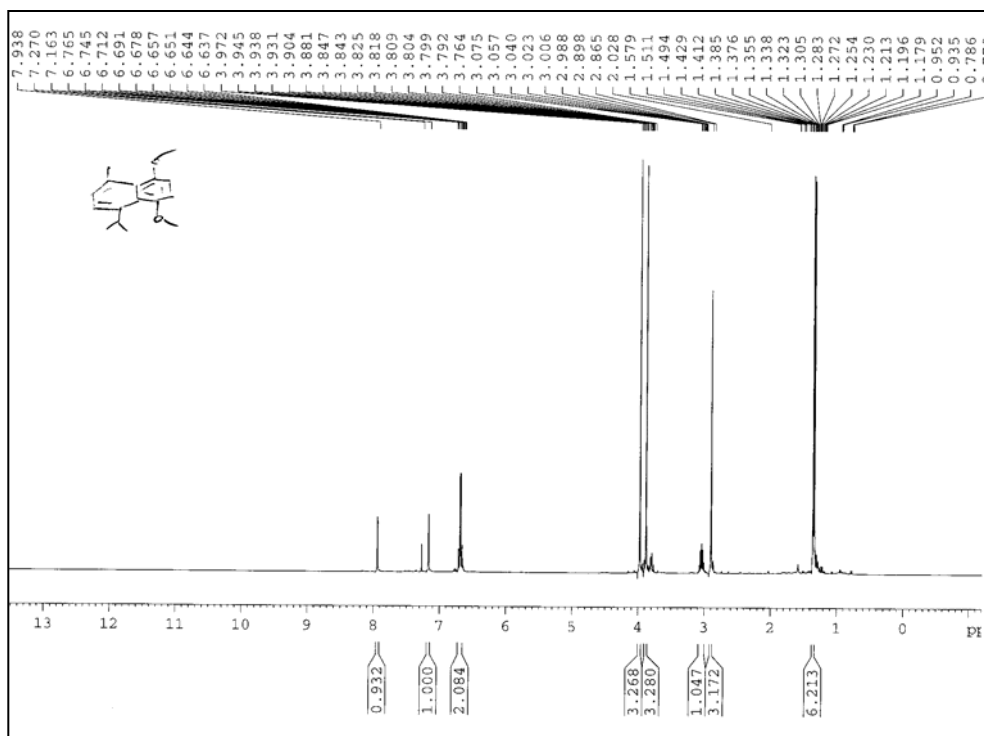
Purification by column chromatography on silica gel gave mansonone C (**2**) in two steps and 46% yield as an orange solid: mp 134–137 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.66 (s, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 1H), 3.43-3.36 (m, 1H), 2.64 (s, 3H), 2.09 (s, 3H), 1.30 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 182.49, 182.18, 145.51, 143.24, 138.23, 135.18, 134.34, 132.63, 132.16, 129.46, 28.49, 23.97, 23.13, 16.25; HRMS (EI) m/z calcd for 228.11503, found 228.11537.



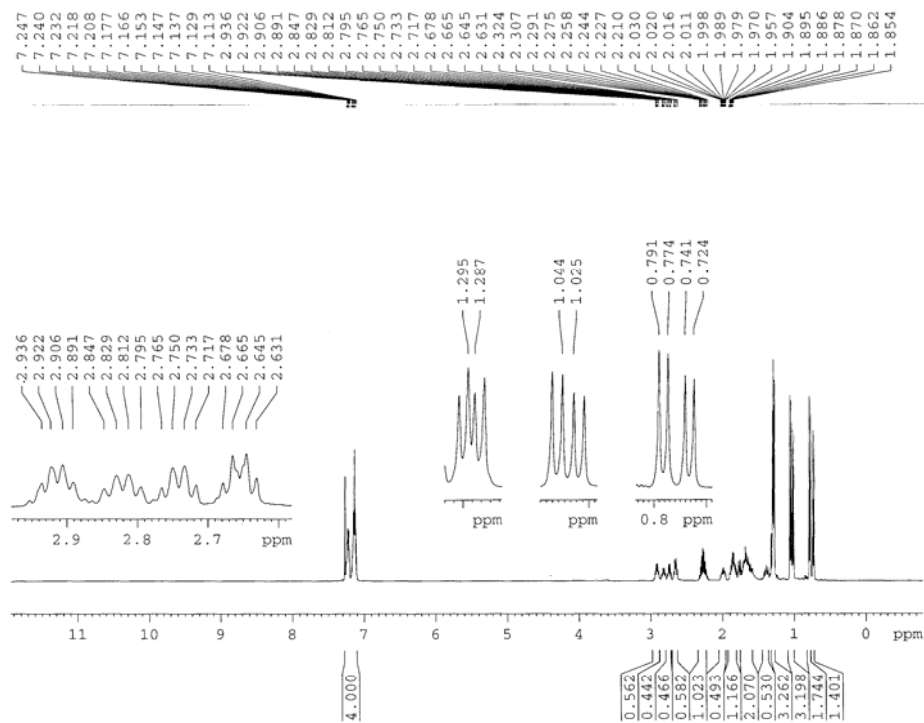
(2E)-6-(2,5-Dimethoxyphenyl)-2-methylhept-2-enyl acetate (22)



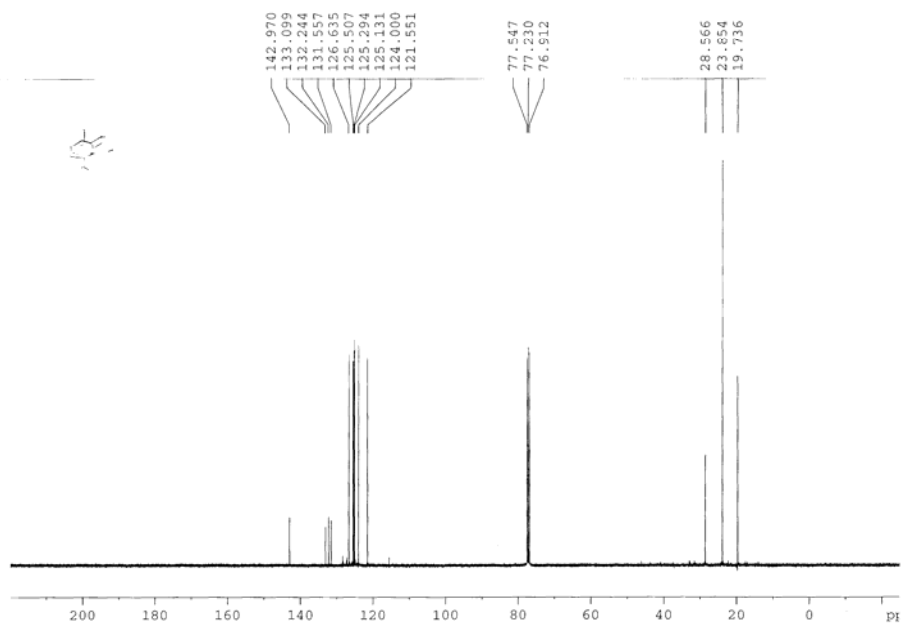
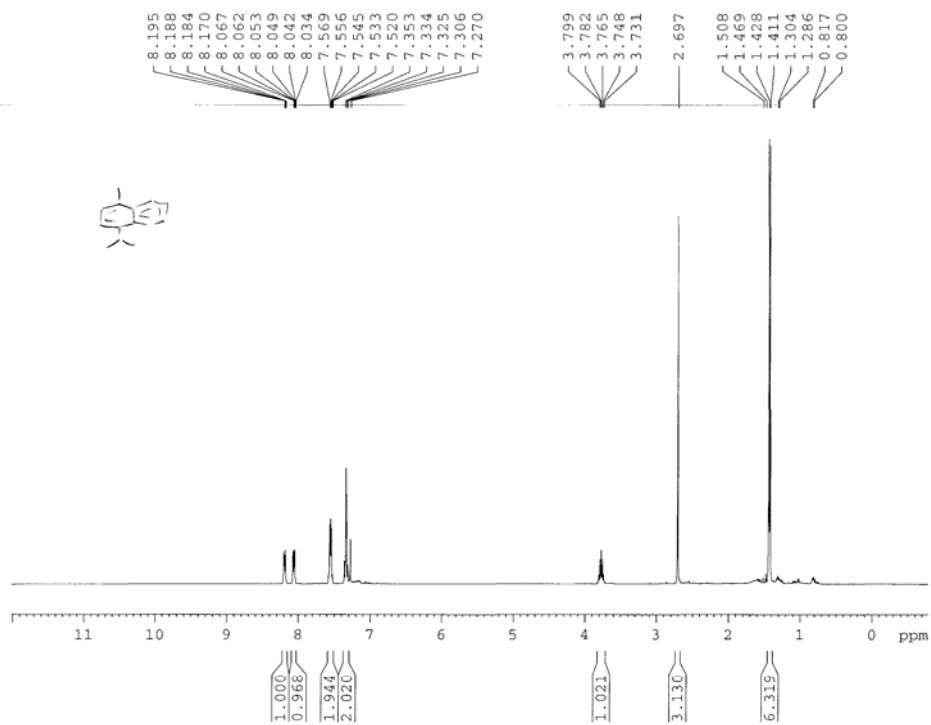
1-Isopropyl-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydronaphthalene (24)



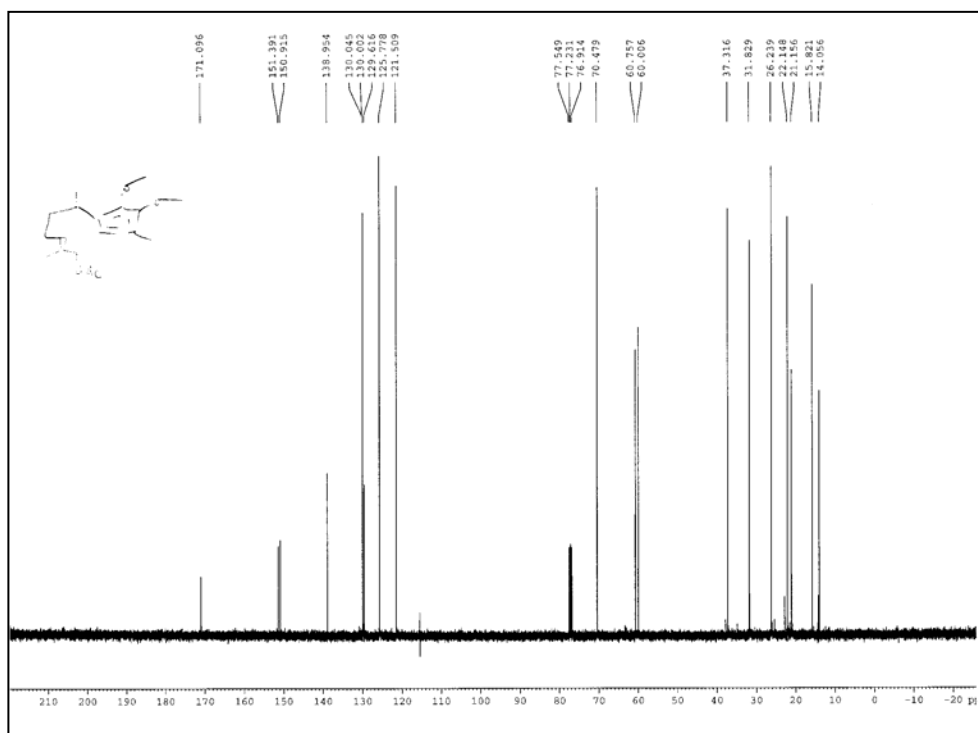
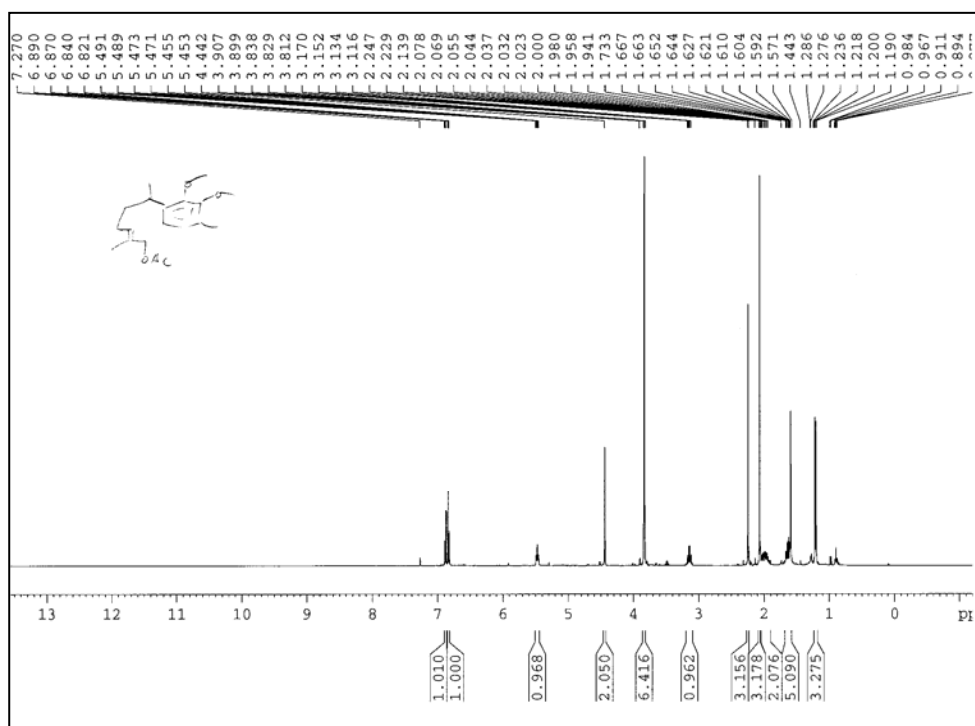
1-Isopropyl-5,8-dimethoxy-4-methylnaphthalene (25)



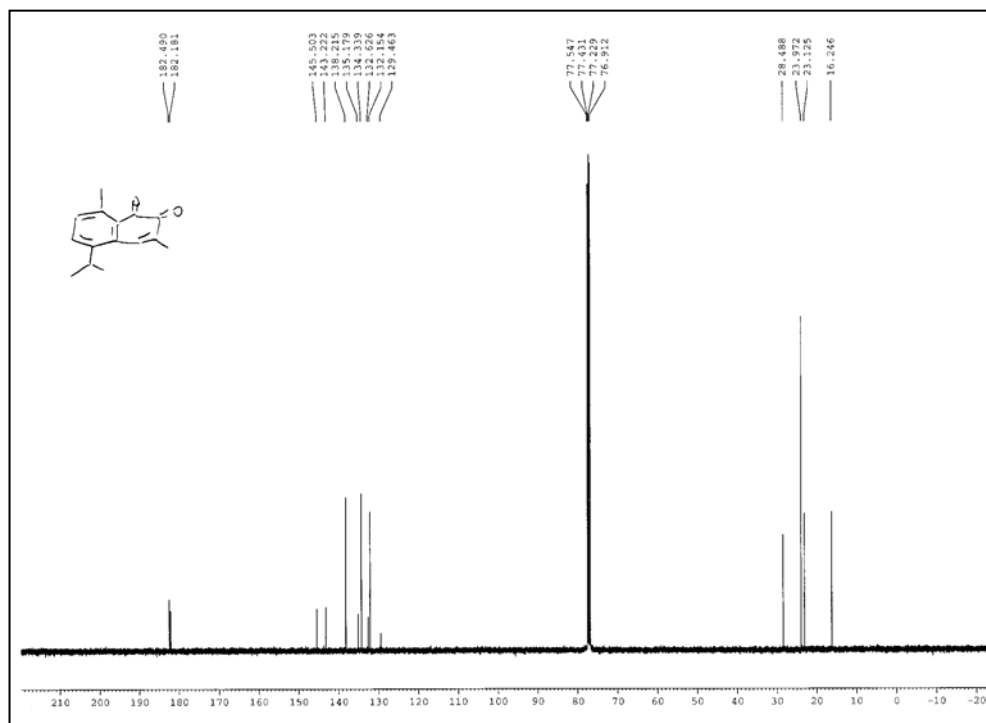
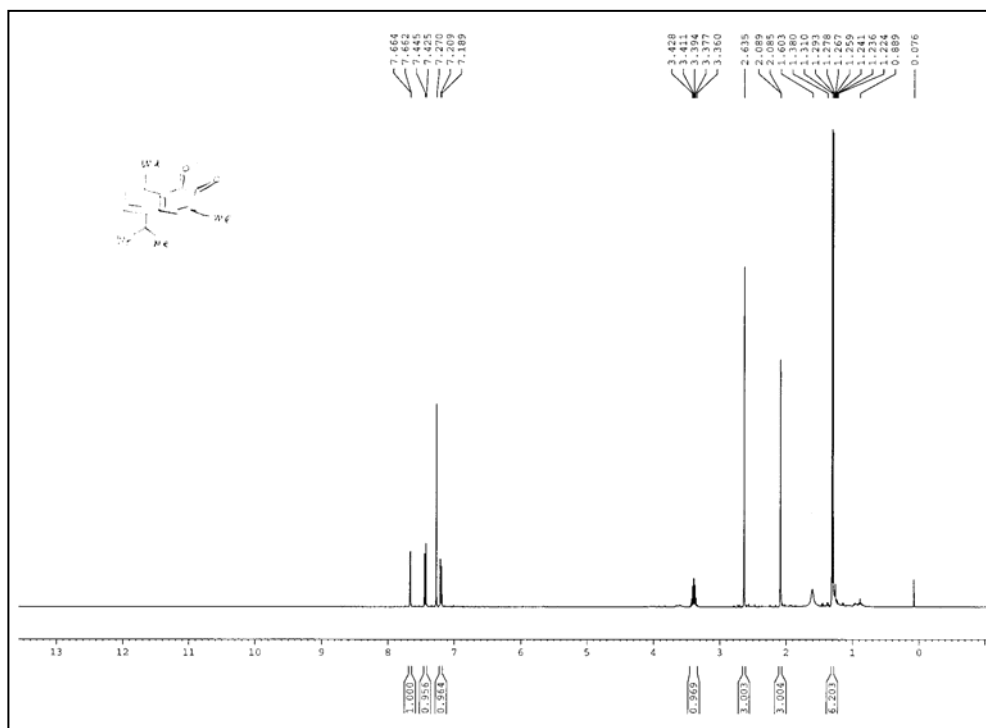
1-Isopropyl-4-methyl-1,2,3,4-tetrahydronaphthalene (27)



1-Isopropyl-4-methylnaphthalene (28)



(2E)-6-(2,3-Dimethoxy-4-methylphenyl)-2-methylhept-2-enyl acetate (34)



Mansonone C (2)

References

1. (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
2. For an early estimate of the steric strain involved in a situation similar to **1b**, see: (a) Packer, J.; Vaughan, J.; Wong, E. *J. Am. Chem. Soc.* **1958**, *80*, 905. (b) Bothner-By, A. A.; Naar-Colin, C.; Gunther, H. *J. Am. Chem. Soc.* **1962**, *84*, 2748.
3. Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343.
4. Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.
5. Giese, B.; Bulliard, M.; Zeitz, H. G. *Synlett* **1991**, 425.
6. Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4347.
7. Erogorgiaene (**3**): Rodriguez, A. D.; Ramirez, C. *J. Nat. Prod.* **2001**, *64*, 100.
Elisapterosin B (**4**): Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390.
8. Wahyouno, S.; Hoffmann, J. J.; Bates, R. B.; McLaughlin, S. P. *Phytochemistry* **1991**, *30*, 2175.
9. Mathela, D. K.; Mathela, C. S.; Dev, V. *J. Ind. Chem. Soc.* **1984**, *61*, 792.
10. Marini Bettòlo, G. B.; Casinovi, C. G.; Galeffi, C. *Tetrahedron Lett.* **1965**, 4857.
11. Tiew, P.; Ioset, J.-R.; Kokpol, U.; Chavasiri, W.; Hostettmann, K. *Phytother. Res.* **2003**, *17*, 190.
12. Schmalz, H. G.; Hollander, J.; Arnold, M.; Duerner, G. *Tetrahedron Lett.* **1993**, *34*, 6259.
13. Serra, S.; Fuganti, C. *Tetrahedron Lett.* **2005**, *46*, 4769.
14. Ramaiah, P.; Rao, A. S. *Synth. Commun.* **1989**, *19*, 931.

15. Beckwith, P. L. M.; Ghisalberti, E. L.; Jefferies, P. R.; Raston, C. L.; White, A. H.
Austr. J. Chem. **1988**, *41*, 351.
16. Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526
17. Ma, S.; Zhang, J. *Tetrahedron.* **2003**, *59*, 6273.
18. Kraus, G. A.; Kim, J. *Org. Lett.*, **2004**, *6*, 3115.

GENERAL CONCLUSIONS

In this dissertation, we have investigated the direct and efficient synthetic route to biologically active natural products.

Chapter 1 describes a concise and efficient synthetic route to the highly functionalized tricyclic core skeleton of papuaforin B. In the course of the synthesis, an efficient cyclization method using Na/NH₃ was demonstrated. Newly developed bromination method leading to an α -bromo enone would serve as a handle for construction of the fused pyran ring of papuaforin B. Further efforts along this line are in progress.

Chapter 2 describes the direct synthesis of 7,8-dihydroxycalamenene, which includes the successful application of allylic strain in the stereoselective synthesis. Interestingly, Mansonone C, a potent antifungal agent, was also obtained as the co-product from the same starting material. Application of this synthetic strategy to the synthesis of analog natural products is in progress.

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