PROGRESS TOWARD THE TOTAL SYNTHESIS OF GARSUBELLIN A AND STRUCTURALLY RELATED PHLOROGLUCIN NATURAL PRODUCTS

Thesis by

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Abstract

Progress toward the polyprenylated phloroglucin garsubellin A is presented. A highly diastereoselective single-step cyclization reaction provides access to the bicyclo[3.3.1]nonane core of this natural product. Further elaboration to a more functionalized analog involves a sequential Claisen rearrangement/Grubbs olefin cross metathesis strategy. Additionally, the feasibility of this strategy toward the preparation of the bis-quaternary carbon array found at the bridgehead positions of the phloroglucinol natural products is demonstrated. Enantioselective strategies and model studies will also be discussed.

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I. Introduction

Alzheimer's disease affects over four million Americans and is the most common form of dementia. It afflicts 47% of people over the age of 85, currently the fastest-growing group with respect to the rest of the population. In the next 50 years, it is expected that the number of people suffering from Alzheimer's disease will more than triple.[1] These statistics necessitate the expedient development of an effective therapeutic. The dementia associated with neurodegenerative diseases such as Alzheimer's has been attributed to deficiencies in levels of the neurotransmitter acetylcholine (ACh).[2] Thus, inducers of the enzyme choline acetyltransferase (ChAT), which is responsible for the biosyntheis of ACh, may be potential Alzheimer's therapeutics.[3] It has been shown that a neural growth factor (NGF) has been able to induce ChAT activity and also promote the survival of cholinergic neurons *in vitro*. Oral administration of NGF is ineffective, however, because it is a high molecular weight protein that cannot pass through the blood-brain barrier and it is readily metabolized by enzymes in the digestive organs.[4] Such drawbacks have inspired the search for small molecule neurotrophic factors as an alternative treatment. One such biologically active molecule is garsubellin A (**1**), a polyprenylated phloroglucin isolated from the wood of *Garcinia subelliptica*.[5] Preliminary studies have shown that garsubellin A increases *in vitro* ChAT activity in rat septal neurons by 154% at a 10 mM concentration, and due to this biological activity, it has been targeted as a potential treatment for Alzheimer's disease.[5]

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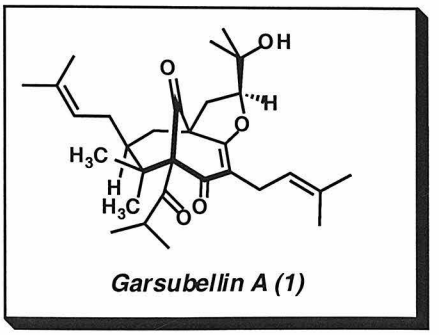
[1] Alzheimer's Association. Alzheimer's Vital Statistics. (http://www.alz.org/research/current/stats.htm)
[2] *Fundamental Neuroscience*; Zigmond, M. J., Bloom, F. E., Landis, S. C., Roberts, J. L., Squire, L. R., Eds.; Academic Press: San Diego, 1999; pp 216-219.
[3] Auld, D. S.; Mennicken, F.; Day, J. C.; Quirion, R. *J. Neurochemistry* **2001**, *77*, 253.
[4] Yabe, T.; Yamada, H.; Shimomura, M.; Miyaoka, H.; Yamada, Y. *J. Nat. Prod.* **2000**, *63*, 433.
[5] Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947.

Figure 1. Garsubellin A (1)



Garsubellin A (1)

Structurally, garsubellin A is characterized by a highly oxygenated and densely functionalized bicyclic core fused to a tetrahydrofuran ring and appended by prenyl side chains (Figure 1). As shown in Figure 2, the [3.3.1] bicyclic core present in garsubellin A is also an important structural feature in a variety of natural products. These bicyclic phloroglucinol derivatives have emerged as an important and reasonably large class of natural products. There are now well over 50 natural products that belong to this family, and the number of newly isolated compounds with related structures has been steadily increasing over the past few years. More than 30 years have passed since the isolation of hyperforin (**2**) from St. John's Wort (*Hypericum perforatum*) and its subsequent structure elucidation.[6] The common architecture of these natural products suggests a potential biosynthetic link to the phloroglucinol substructure. Recently, Eisenreich and coworkers elucidated a biosynthetic pathway for the production of hyperforin that involved elaboration of a polyketide-derived phloroglucinol subunit by nonmevalonate-produced isoprenoid units.[7]

In addition to garsubellin A, a number of these phloroglucinol-derived natural products exhibit a wide range of biological activity. For example, hyperforin not only accounts for the antidepressive effects of St. John's Wort (acting as a seratonin reuptake

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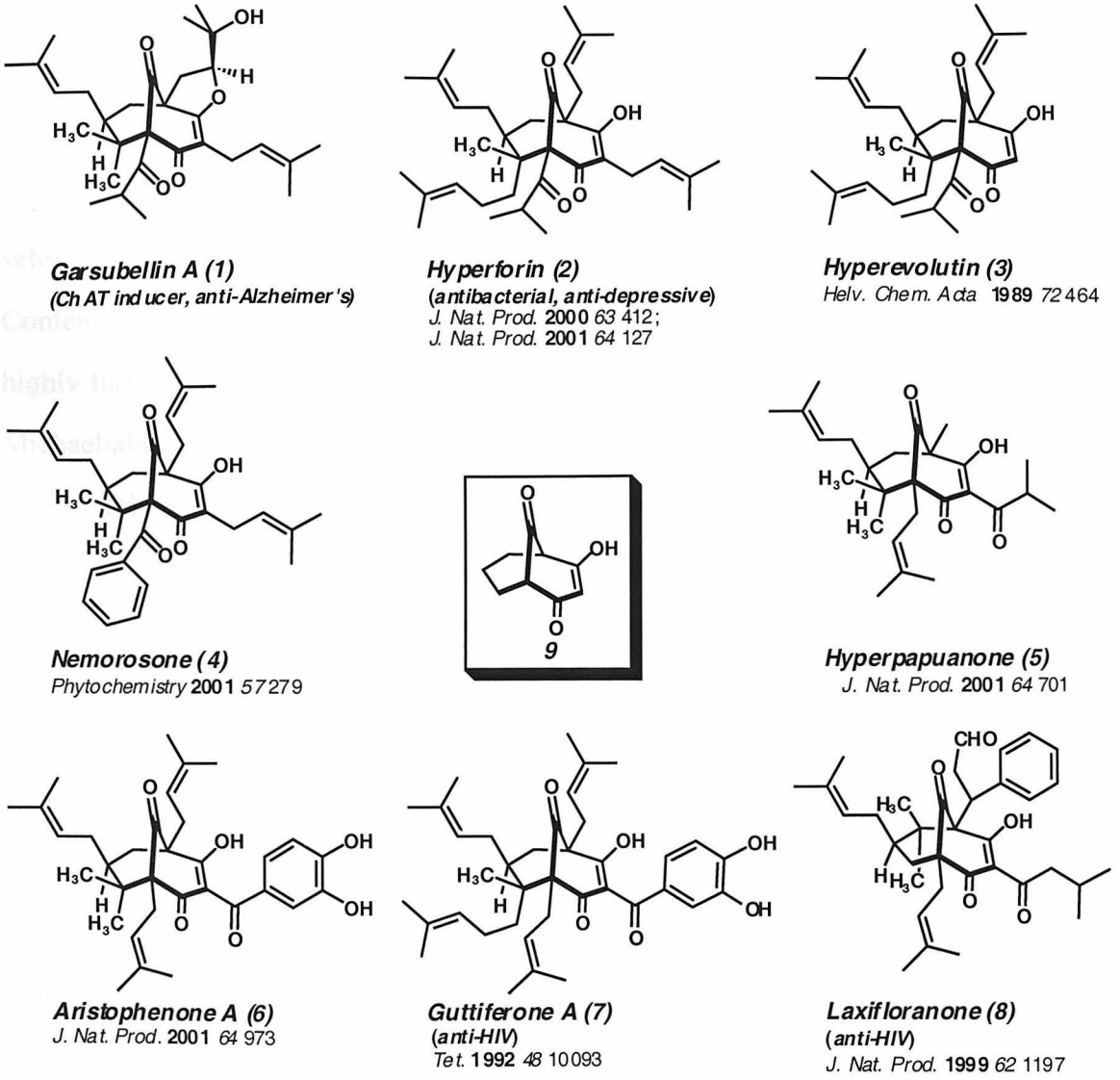
[6](a) Brystov, N.S.; Chernov, B.K.; Dobrynin, N.V.; Kolosov, M.N. *Tetrahedron Lett.* **1975**, *16*, 2791; (b) Revised configuration: Brondz, I.; Greibrokk, T.; Groth, P.A.; Aasen, A.J. *Tetrahedron Lett.* **1982**, *23*, 1299; (c) Absolute configuration: Brondz, I.; Greibrokk, T.; *Acta Chem. Scand. A* **1983**, *37*, 263.
[7]Adam, P.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Med. Chem.* **2002**, *45*, 4786.

inhibitor), but also has been shown to display cytostatic and antibacterial activity (including inhibition of multidrug resistant *Staphylococcus aureus* strains).[8]

Figure 2. Representative Phloroglucin Natural Products Containing a Bicyclo[3.3.1]nonane-1,3,5-trione Core



In 2002, researchers in Italy found that the antidepressive activity of hyperforin was dependent on the enolizable β-diketone moiety of the structure. Analogs lacking this functionality (masked by etherification, acylation, or quaternization of the central carbon)

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[8](a) Antidepressive effects: Cervo, L.; Rozio, M.; Ekalle-Soppo, C.B.; Guiso, G.; Morazzoni, P.; Caccia, S. *Psychopharmacology* **2002**, *164*, 423; (b) Tumor inhibition: Schempp, C.M.; Kirkin, V.; Simon-Haarhaus, B.; Kersten, A.; Kiss, J.; Termeer, C.C.; Gilb, B.; Kaufmann, T.; Borner, C.; Sleeman, J.P.; Simon, J.C. *Oncogene* **2002**, *21*, 1242; (c) Schempp, C.M.; Pelz, K.; Wittmer, A.; Schopf, E.; Simon, J.C. *Lancet* **1999**, *353*, 2129.

had diminished activity (>10-fold less active) in their assays.[9] These results highlight the critical natural of structure-activity relationships in the phloroglucin series and underscore the importance of synthetic access to a wide range of analogs.

Despite the isolation of hyperforin almost 30 years ago, this class of natural products has received relatively little attention from the synthetic community. Prior to our own work, only a single approach to any of these phloroglucin natural products had appeared in the literature. In 1999, Nicolaou *et al.*[10] published their development of a selenium mediated cyclization to furnish the bicyclic core of garsubellin A. Contemporary with our own work, Shibasaki *et al.*[11] published a route to access the a highly functionalized model system of garsubellin A in which they employed a stepwise Michael/aldol cyclization sequence. Other groups have focused on different members of this natural product class: Young *et al.* have developed a novel intramolecular allene-nitrile oxide cycloaddition en route to the core of hyperevolutin (**3**)[12] and Kraus *et al.* have recently published the synthesis of model systems for both hyperforin (**2**) and nemorosone (**4**) featuring a manganic acetate-mediated cyclization.[13] All of these approaches, while successful in accessing the core phloroglucin framework, are stepwise processes and the products resulting from the cyclization event all require further adjustment in oxidation state relative to the natural product of interest.

Described herein is an approach to garsubellin A featuring the construction of the highly oxygenated [3.3.1] bicyclic core in a single, diastereoselective cyclization reaction and the development of methodology to achieve this a transformation.[14] Importantly,

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[9]Verotta, L.; Appendino, G.; Belloro, E.; Bianchi, F.; Sterner, O.; Lovati, M.; Bombardelli, E. *J. Nat. Prod.* **2002**, *65*, 433.

[10](a) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724; (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807.

[11](a) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859; (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621.

[12]Young, D.G.J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134.

[13]Kraus, G.A.; Nguyen, T.H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659.

[14]Spessard, S.J.; Stoltz, B.M. *Org. Lett.* **2002**, *4*, 1943.

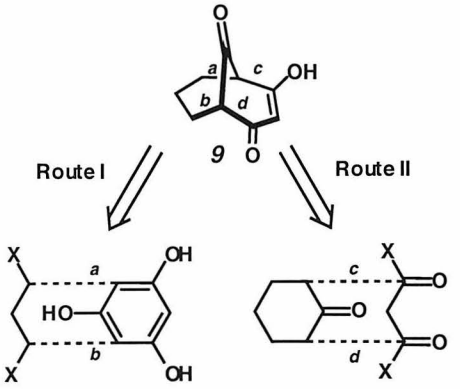
development of such methodology may prove useful to access a wide variety of structually similar natural prodcuts.

II. Retrosynthesis

General Strategy

Retrosynthetically, there are two limiting strategies to consider for convergent 2-bond disconnections of bicyclic core **9**, as illustrated by Route I and Route II (Figure 3). Disconnecting bonds ***a*** and ***b*** in Route I provides a phloroglucinol piece as a bis-nucleophile and a three carbon unit to serve as a electrophile. Alternatively, breaking bonds ***c*** and ***d*** in Route II results in a cyclohexanone bis-nucleophile and a 1,3-dicarbonyl bis-electrophile. Although Route I represents a more likely 'biomimetic' pathway, Route II provides a much more rational entry into this synthesis in that it allows for the possibility of a single reaction to form the bicycle, as well as a greater degree of stereocontrol.[12]

Figure 3. Two possible disconnections of bicyclic core 9.

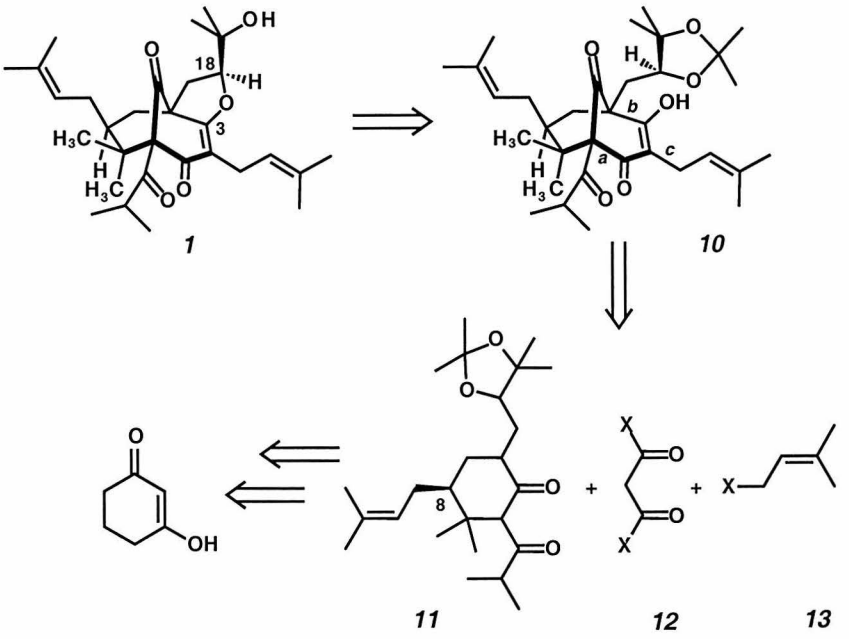


Retrosynthesis of Garsubellin A

Upon examination, garsubellin A (**1**) reveals an array of interesting functionality and stereocenters. Disconnection of the C(3) / C(18) tetrahydrofuran linkage and protection of the resulting diol exposes the bicyclo[3.3.1]nonane-1,3,5-trione core (**10**) of garsubellin A (Scheme 1). Breaking bonds ***a***, ***b***, and ***c*** yields three pieces: a functionalized

cyclohexanone system (**11**), a dielectrophile (**12**), and a prenyl fragment (**13**). It was anticipated that the stereochemistry about the core ring structure would arise via remote induction from the C(8) stereocenter, thus allowing for an eventual asymmetric synthesis based on a single stereogenic center. Functionalized cyclohexanones such as **11** should be readily available from a cyclohexanedione precursor via Stork-Danheiser chemistry. Thus, the synthesis of garsubellin A was undertaken in such a way as to construct **11** enantioselectively and to develop the cyclization chemistry that represents the key step in this synthesis.

Scheme 1. Retrosynthesis of Garsubellin A (1)



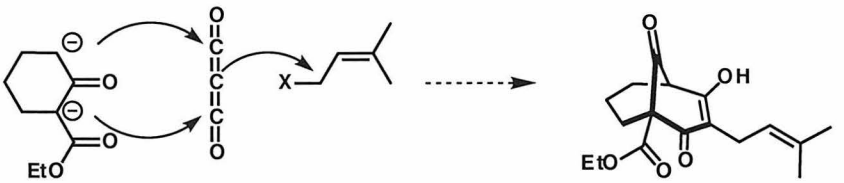
III. Development of a General Route to Highly Oxygenated Bicyclo [3.3.1] Ring Systems

As mentioned above, previously reported efforts toward the total synthesis of garsubellin A have similarly focused on the bicyclic core system.[10-13] Indeed, many methods exist for the synthesis of [3.3.1] bicycles, but they are multi-step procedures

and/or yield a product with the incorrect oxidation state for the desired target.[15] A considerable effort was undertaken in our laboratory to develop a reliable reaction to access this core system in a one-step procedure. Additionally, the development of such methodology was expected to have broad implications for the preparation of a number of bicyclic phloroglucinol natural products (Figure 2) and synthetic analogs.

The initial synthetic plan to access the desired bicyclic core is outlined in Scheme 2. It was hoped that the dianion derived from a β-keto ester (**14**) would react with a dielectrophile such as carbon suboxide (C_3O_2) to yield a [3.3.1] bicycle (**15**) with all the carbons in the necessary oxidation states. In addition, the middle carbon of C_3O_2 is nucleophilic, allowing the possibility of trapping it with an electrophile, such as prenyl bromide, in a 3-component coupling reaction.

Scheme 2. Three-Component Coupling Strategy



14 *13* *15*

Model studies were undertaken with **14** as the dianion[16] and C_3O_2,[17] but due to the highly reactive nature of dianions and the unidentifiable complex mixture of products that resulted under these conditions, this was soon determined to be an undesirable choice. In order to simplify the reaction conditions, a silyl enol ether was employed as a type of 'masked' anion. Both the mono (**16**) and di-trimethylsilyl (**17**) enol ethers of **14** were synthesized according to literature procedures.[18] Unfortunately, reactions with C_3O_2

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[15]Butkus, E. *Synlett* **2001**, *12*, 1827; Gambacorta, A.; Botta, M.; Turchetta, S. *Tetrahedron* **1988**, *44*, 4837.

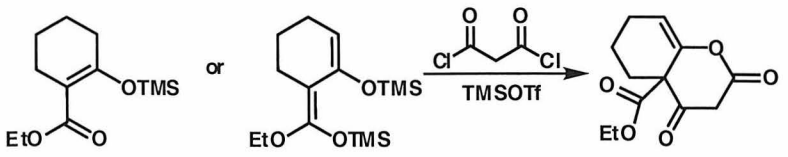
[16]For the generation of β-keto ester dianions, see: Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

[17]Carbon suboxide was generated in a simple three-step procedure. See: Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron* **1995**, *51*, 6651.

[18]Langer, P.; Schneider, T.; *Synlett* **2000**, 4, 497.

again yielded none of the desired cyclization product,[19] even upon treatment with Lewis acids. Bis(trimethylsilyl) enol ethers, however, have been reported to undergo C-acylation reactions with acid chlorides.[12] Thus, both mono- and bis- TMS enol ethers (**16** and **17**) were investigated for their reactivity with malonyl dichloride.

Scheme 3. Initial Cyclization Results with Malonyl Dichloride



16 *17* *18*

Gratifyingly, of the multiple products isolated from these reactions, a cyclization product (**18**) was finally obtained and characterized[20] as having the connectivity shown in Scheme 3. Although it was not the cyclization product we desired, this result was encouraging in that this method was successful in forming a sterically challenging quaternary carbon center. A brief examination of base-catalyzed rearrangements[21] of the lactone moiety was unsuccessful, however, so the decision was made to look at a simpler model system.

In 1984, Effenberger and coworkers reported the synthesis of bicycle **9** from 1-methoxy-1-cyclohexene (**19**)[22] and malonyl dichloride[23] a reaction that proceeds smoothly at -20 °C in just four hours (Scheme 4). In our hands, a similar result was obtained using the corresponding TBS enol ether (**20**),[24] which was promising since silyl enol ethers are more versatile than their methyl counterparts. Although the resultant

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[19]For precedent in the cyclization of silyl enol ethers with carbon suboxide, see: Bonsignore, L.; Cabiddu, S.; Loy, G.; Secci, D. *Heterocycles* **1989**, *29*, 913.

[20]This compound was characterized by proton and carbon NMR, IR, and GCMS.

[21]For precedent of base-catalyzed O-C isomerization of enol esters, see: Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.

[22]Shishido, K.; Hiroya, K.; Ueno, Y.; Fukumoto, K.; Kametani, T.; Honda, T. *J. Chem. Soc. Perk. Trans. 1* **1986**, *5*, 829.

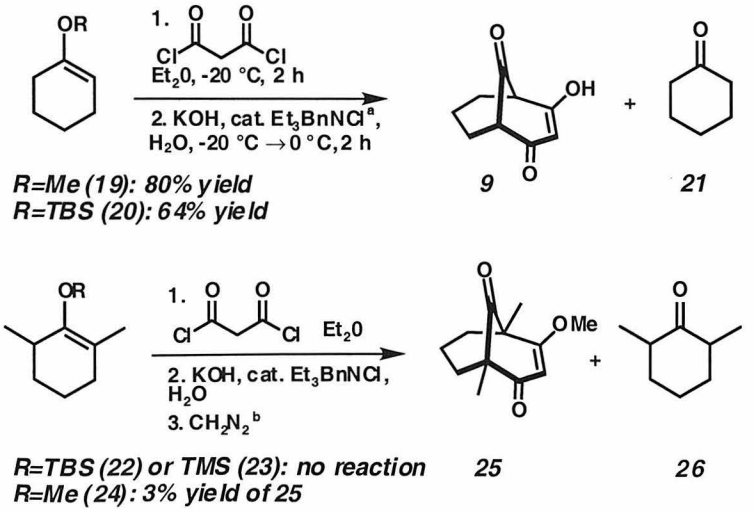
[23]Schönwälder, K.-H.; Kollat, P.; Stezwski, J. J.; Effenberger, F. *Chem. Ber.* **1984**, 117, 3280. This result was reported in the context of a study on aromaticity in metacyclophane systems of varying ring size. Such a cyclization reaction to produce bicyclic systems (e.g. **9**) has not appeared in the subsequent literature and remains a singular example.

[24]Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777-4786.

bicycle contained the desired connectivity, the reaction conditions required that a four-fold excess of enol ether be employed, which was to be the more labor-intensive subunit in our synthesis. Owing to the potential utility of this cyclization in the context of the phloroglucin [3.3.1] bicyclic natural products, we chose to investigate the efficiency and diastereoselectivity of such cyclizations in a more complex arena.

Using 2,6-dimethylcyclohexanone (**26**) as a model system, the TBS (**22**),[18] TMS (**23**),[25] and methyl (**24**)[26] enol ethers were easily accessed. As it was soon discovered, substitution at the α-position greatly diminished the reactivity of the system. For example, treatment of TBS enol ether **22** with malonyl dichloride produced none of the desired cyclized product **25**, even with prolonged reaction times and elevated temperatures. The TMS enol ether **23** was unreactive as well. Gratifyingly, methyl enol ether **24** did yield desired the bicycle **25**, albeit in very low yield. At this point, the reaction using substrate **24** was targeted for optimization, since the analogous step in our approach to garsubellin A would require an even more highly substituted enol ether.

Scheme 4. Enol Ether Cyclizations with Malonyl Dichloride



[a]phase transfer catalyst
[b]Diazomethane was added after work-up due to difficulties in purifying the corresponding vinylogous acid.

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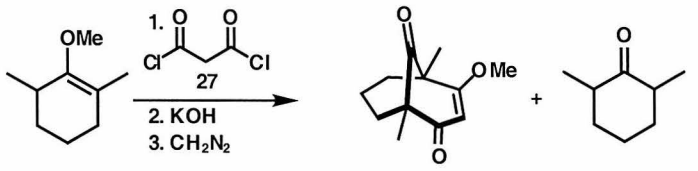
[25]Baranovsky, A.V.; Jansen, B. J. M.; Meulemans, T. M.; de Groot, A. *Tetrahedron* **1998**, *54*, 5623.
[26]Heiszwolf, G. J.; Kloosterziel, H. *Chem. Commun.* **1966**, *2*, 51.

One major goal was to obtain a comparable yield of cyclized product **25** with enol ether **24** as the limiting reagent instead of in four-fold excess as prescribed in the initial paper. After considerable optimization (Figure 4), bicycle **25** was obtained in 25% yield (50% yield based on recovered ketone **26**) by using a 1:1 ratio of **24**:malonyl dichloride (**27**) and stoichiometric bis(cyclopentadienyl)hafnium dichloride (entry 20).

Figure 4. Cyclization Optimizations



24 *25* *26*

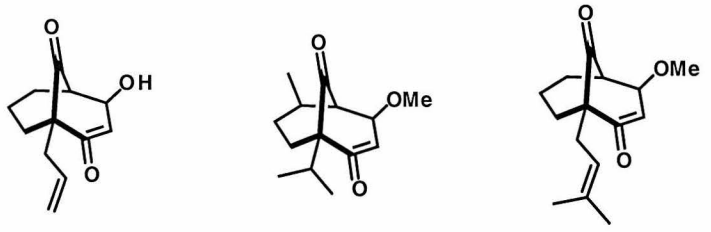
entry	ratio (*24*:*27*)	additive	time (h)	yield (% 25)
1[a]	2:1	---	48	3.3
2[b]	2:1	---	48	2.5
3[c]	2:1	---	48	4.8
4[d]	1:1	---	24	15.0
5[b]	1:10	---	24	6.5
6[b]	2:1	Et_3N	48	---
7[b]	2:1	$(iPr)_2NEt$	48	---
8[b]	1:2	imidazole	24	7.7
9[c]	2:1	KCl	48	10.3
10[b]	2:1	CuCl or $CuCl_2$	48	---
11[b]	2:1	AgTFA	48	---
12[b]	2:1	$SnCl_4$	24	16.0
13[b]	1:2	$TiCl_4$	24	19.6
14[b]	1:2	$FeCl_3$	24	---
15[b]	1:2	$Ti(O\text{-}iPr)_2Cl_2$	24	---
16[b]	1:2	Cp_2TiCl_2	24	8.5
17[b]	1:2	Cp_2ZrCl_2	24	5.8
18[b]	1:2	$Sc(OTf)_3$	24	---
19[b]	1:2	$Y(OTf)_3$	24	---
20[b]	1:1	Cp_2HfCl_2	72	25.0[e]

[a] Reaction run in Et_2O
[b] Reaction run in CH_2Cl_2
[c] Reaction run in CH_3CN
[d] neat
[e] 50% yield based on recovered ketone 26; 75% total mass recoverd

Although bicycle **25** is obtained in modest yield, the direct cyclization to produce the two bridgehead quaternary carbons present in the phloroglucinols compares well with lengthier procedures to form similarly substituted systems. These results establish the feasibility of a single-step strategy toward the synthesis of the bicyclic phloroglucin natural products.

A variety of monosubstituted enol ethers were also synthesized (Figure 5). As was the case with disubstituted enol ethers, the sterics of the enol ether piece resulted in a significantly lower yields relative to the unsubstituted substrates.

Figure 5. Representative Monosubstituted [3.3.1] Bicycles[a]



28: 28% yield *29*: 18% yield *30*: > 5% yield

[a]Prepared from the corresponding TBS enol ethers, which were derived from the readily available ketones

One feature that remained to be determined about this cyclization was its diastereoselectivity. We were particularly interested in the resulting relative stereochemical relationship between substitution at C(8) and the malonyl subunit, which exist in an *anti* relationship in the natural product. Therefore, silyl enol ether **35** was targeted as a reasonable model system for cyclization to the [3.3.1] bicyclic ring system (Scheme 5). The synthesis of silyl enol ether **35** commenced with readily available vinylogous ester **31**,[27] which was enolized by LDA and alkylated with prenyl bromide to give **32**.[28] Treatment of crude **32** with methyl lithium followed by elimination of the resulting 3°

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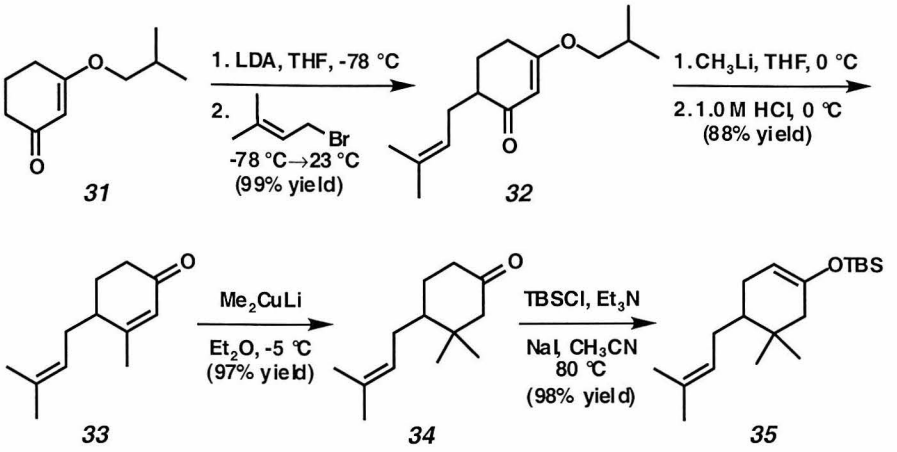
[27]Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072.
[28]Stork, G.; Danheiser, R.L. *J. Org. Chem.* **1973**, *38*, 1775.

alcohol under acidic conditions furnished enone **33**.[29] 1,4-Cuprate addition with Me_2CuLi and subsequent silyl enol ether formation provided **35** in 84% overall yield.[30]

Scheme 5. Synthesis of Silyl Enol Ether 33



With multigram quantities of **35** available, we began to investigate the critical cyclization step (Scheme 6). Following substantial experimentation, it was found that treatment of silyl enol ether **35** with 2 equiv of malonyl dichloride in CH_2Cl_2 at -10 °C, followed by addition of aqueous KOH under phase transfer catalysis produced a 36% yield of desired bicycle **36**.[31] Although yields were modest, mass recovery was excellent and unreacted enol ether could be recovered as ketone **34** providing an overall yield of 95%. Conversion of the recovered ketone to the silyl enol ether, followed by resubjection to the same cyclization conditions gave a 55% combined yield of trione **36** over two cycles. Gratifyingly, the cyclization of **35** to **36** proceeded with complete diastereoselectivity to produce the desired *anti* isomer with respect to the malonyl subunit and the remote prenyl substitution at C(8). The relative stereochemistry in **36** was unambiguously confirmed by single crystal X-ray diffraction (Figure 5).[32]

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[29]Johnson, W.S.; McCarry, B.E.; Markezich, R.L.; Boots, S.G. *J. Am. Chem. Soc.* **1980**, *102*, 352.
[30]Laval, G.; Audran, G.; Galano, J.-M.; Monti, H. *J. Org. Chem.* **2000**, *65*, 3551.
[31]Obtained as a 1:1 mixture of equilibrating enol isomers.
[32]Crystallographic data have been deposited at the Cambridge Crystallographic Data Center under deposition number 173065.

Scheme 6. Diastereoselectivity in the Synthesis of a Bicyclo[3.3.1]-nonane-1,3,5-trione System

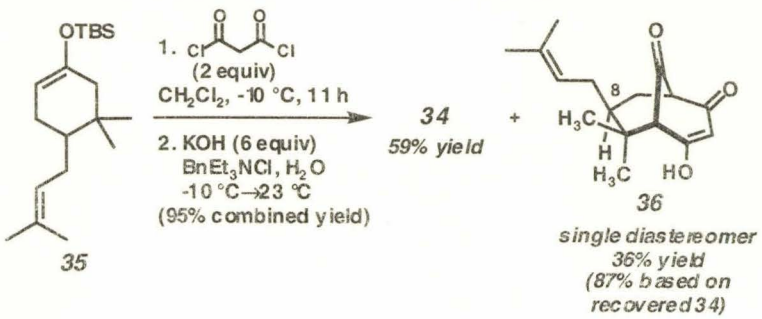
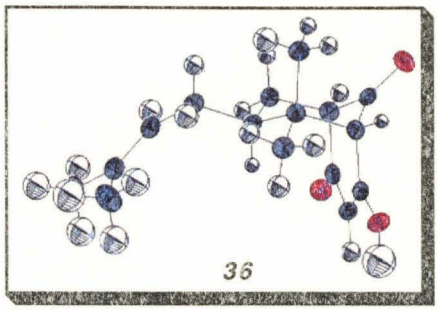


Figure 5. Crystal Structure of Bicycle 36



IV. Model Studies for the Completion of Garsubellin A

With a rapid synthesis of bicycle **36** in hand, studies were undertaken to explore the feasibility of installing the C(2) prenyl group (Scheme 7). While a variety of traditional methods proved unsatisfactory (e.g. direct C-alkylation, diazo chemistry, Pd-mediated couplings, etc.), a more stepwise route emerged as the most effective method. Condensation of bicycle **36** with allyl alcohol[33,34] followed by a thermal Claisen rearrangement and treatment with diazomethane produced the allylated bicycle **38**.[35,36] Completion of the prenyl installation was accomplished by an olefin cross metathesis using Grubbs ruthenium catalyst **39**.[37] Finally, saponification of vinylogous ester **40**

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[33]Tamura, Y.; Kita, Y.; Shimagaki, M.; Terashima, M. *Chem. Pharm. Bull.* **1971**, *19*, 571-575.

[34]Allyl ether **37** was obtained as a single enol isomer represented by the structure shown in Scheme 7 (by nOe analysis).

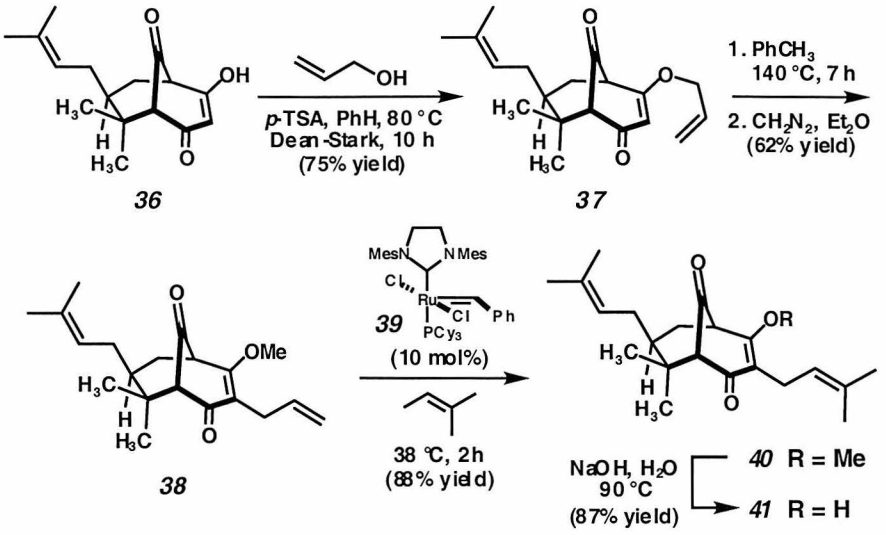
[35] Obtained as a 1:1 mixture of separable enol ether isomers.

[36] Isolated in addition to 30% yield of recovered enol ether **37**.

[37]Chatterjee, A.K.; Sanders, D.P.; Grubbs, R.H. *Org. Lett.* **2002**, *4*, 1939.

proceeded in good yield to furnish the semi-functionalized garsubellin A core system **41**. Overall, this highly efficient sequence of reactions produced the bis-prenylated bicyclic core of garsubellin A in just 10 steps.

Scheme 7. Installation of the C(2) Prenyl Group



V. Studies Toward the Synthesis of the Protected Diol Side Chain [C(17)-C(21)] of Garsubellin A

In an effort to investigate the cyclization with more functionalized cyclohexanone pieces, studies were also undertaken to explore the synthesis and installation of the C(17)-C(21) portion of the garsubellin A diol side chain (Scheme 8). The synthesis commenced with commercially available prenyl alcohol, which was converted to acetate **42** and dihydroxylated with catalytic OsO_4 and NMO as a stoichiometric oxidant. The resulting diol **43** was protected as acetonide **44**, which was followed by methanolysis of the acetate group to generate alcohol **45**. This alcohol was converted to both to triflate **46** (quantitative conversion) and iodide **47**[38] (22% yield). Unfortunately, neither piece was reactive under standard LDA alkylation conditions, perhaps due to the steric bulk of the acetonide protecting group.

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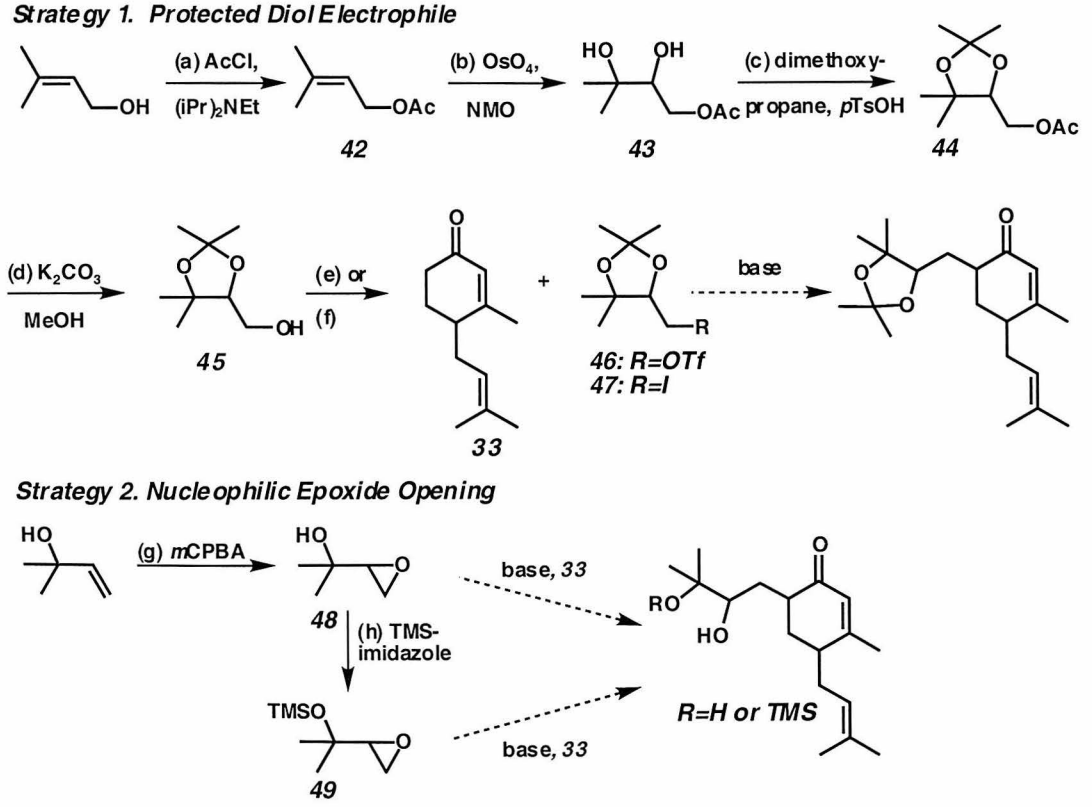
[38]Durmont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814-823.

A second strategy involved the formation of an anion at the α-position of enone **33** and using that anion to open an epoxide at the less hindered carbon, which would furnish the desired diol (Scheme 8). Epoxides **48** and **49**[39] were synthesized, but were unreactive to anion opening. These two routes merit further exploration, however, as only a few sets of conditions were tested with each substrate. Alternatively, perhaps it would be desirable to introduce this diol functionality earlier in the synthesis, an idea that may be explored in the future.

Scheme 8. Two strategies to Install the C17-C21 Side Chain[a]



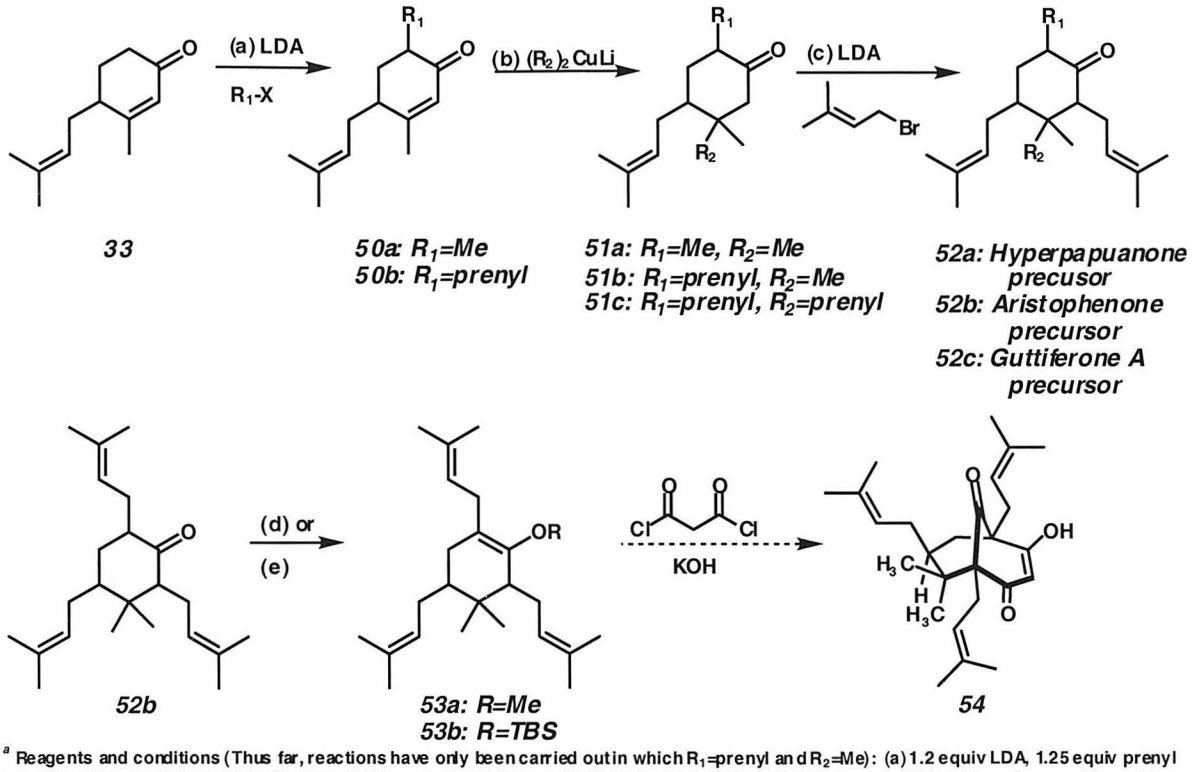
[a] Reagents and conditions: (a) 1.2 equiv acetyl chloride, 2.0 equiv Hünig's base, CH_2Cl_2, -78 °C, 1 h, 86% yield; (b) 0.05 equiv OsO_4, 1.2 equiv NMO, 1:1 H_2O: *t*-BuOH, 0 °C, 2 h, 55% yield; (c) 24.0 equiv dimethoxypropane, 0.1 equiv *p*TsOH, acetone, 23 °C, 3 h, 98% yield; (d) 1.0 equiv K_2CO_3, MeOH, 23 °C, 2 h, 99% yield; (e) 1.2 equiv pyridine, 1.2 equiv triflic anhydride, CH_2Cl_2, -5 °C, 3 h, quant.; (f) 2.4 equiv $P(OPh)_3MeI$, THF, 23 °C, 36 h, 22% yield; (g) 1.6 equiv mCPBA, CH_2Cl_2, -0 °C, 5 h, 75% yield; (h) TMS-imidazole, THF, 50 °C, 5 h, 25% yield.

VI. Synthesis of More Functionalized Cyclohexanones

[39]Overman, L.E.; Rucker, P.V. *Heterocycles*, **2000**, *52*, 1297.

The synthetic scheme developed to access TBS enol ether **35** (Scheme 5, *vide supra*) can easily be modified to provide a vast array of these natural products. For example, it is easy to imaging accessing the natural products hyperpapuanone (**5**), aristophenone A (**6**), guttiferone A (**7**) from a common intermediate (Scheme 9). Compound **53a** and **53b** have already been synthesized, although thus far, all cyclization attempts have been unsuccessful in producing the triprenylated bicycle **54**.

Scheme 9. Synthesis of More Functionalized Cyclohexanone Cyclization Substrates[a]



[a] Reagents and conditions (Thus far, reactions have only been carried out in which R_1=prenyl and R_2=Me): (a) 1.2 equiv LDA, 1.25 equiv prenyl bromide, THF, -78 °C to 23 °C, 80% yield; (b) 2.0 equiv CuI, 4.0 equiv MeLi, Et_2O, -5 °C, 90% yield; (c) 1.3 equiv LDA, 1.25 equiv prenyl bromide, THF, -78 °C to 23 °C, 80% yield; (d) 1.1 equiv KO*t*Bu, 1.1 equiv Me_2SO_4, DMSO, 23 °C, 38% yield; (e) 1.25 equiv Et_3N, 1.25 equiv TBSCl, 1.25 equiv NaI, CH_3CN, 80 °C, 68% yield.

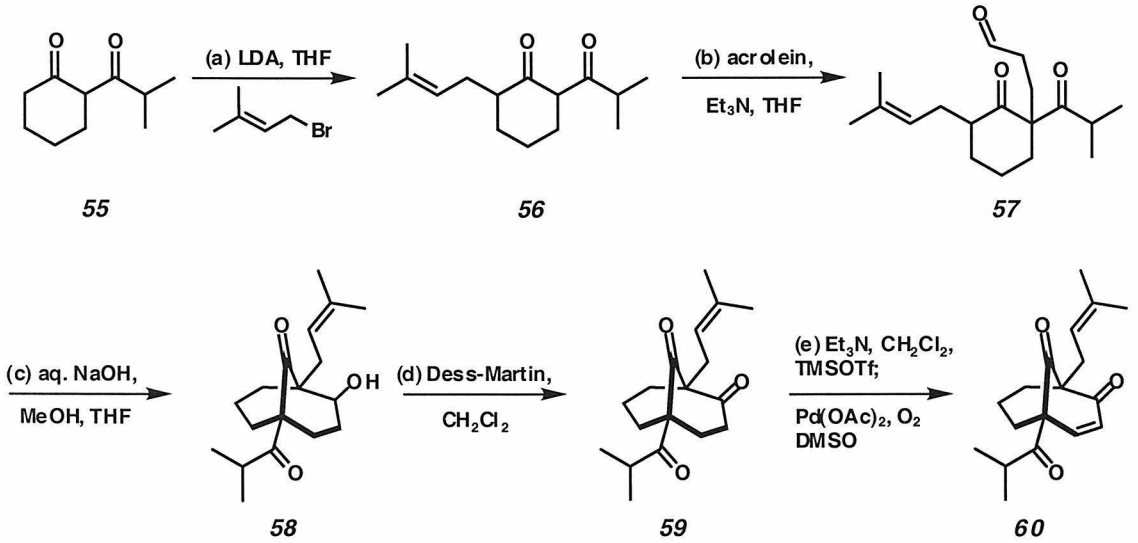
VII. Stepwise Approaches

Due to the difficulties in optimizing the malonyl dichloride cyclization on more complex substrates, we thought it might be worthwhile to investigate a stepwise approach (Scheme 10). Starting with readily available diketone **55** as a model system,[40]

[40]Kaga, H.; Miura, M.; Orito, K. *Synth.* **1989**, 864.

dianion alkylation with LDA and prenyl bromide produced prenylated diketone **56**.[10b] Michael addition to acrolein in the presence of triethylamine yielded aldehyde **57**, which smoothly underwent intramolecular aldol cyclization to hydroxy-bicycle **58**.[41,42] After oxidation to triketone **59**, formation of enone **60** was accomplished under Saegusa-Ito conditions.[43,44] Unfortunately, enone **60** was resistant to a variety of functionalizations, including nucleophilic epoxidations, hetereoatom conjugate additions, Pd-mediated functionalizations, and functional group manipulation (e.g. protecting ketones as acetals; reduction of ketones to alcohols before epoxidation). Other groups who have arrived at a similar enone intermediate have also found it to be difficult to further derivitize.[45]

Scheme 10. A Stepwise Route to a Functionalized Bicyclic Model System



[a] Reagents and conditions (unoptimized): (a) 2.5 equiv LDA, 1.05 equiv prenyl bromide, THF, -78 °C to 23 °C, 83% yield; (b) 1.5 equiv Et_3N, 1.5 equiv acrolein, THF, 50 °C to 60 °C, 70% yield (84% yield based on recovered SM); (c) 4.0 equiv 0.5 M aq. NaOH, 6:1 MeOH:THF, 0 °C to 23 °C, 85% yield; (d) 1.5 equiv Dess-Martin reagent (15% CH_2Cl_2 soln.), CH_2Cl_2, 0 °C to 23 °C, 84% yield; (e) 2.0 equiv Et_3N, 1.5 equiv TMSOTf, CH_2Cl_2, -78 °C to 0 °C; 0.1 equiv $Pd(OAc)_2$, O_2 balloon, DMSO, 23 °C, 74% yield (2 steps).

Due to the difficulties in functionalizing model enone **60**, we turned our attention

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[41] Paquette, L.A.; Montgomery, F.J.; Wang, T.-Z. *J. Org. Chem.* **1995**, *60*, 7863.

[42] This transformation (xx to xx) could also be accomplished in a lower-yielding one-step reaction. See: Filippini, M.-H.; Faure, R.; Rodriguez, J. *J. Org. Chem.* **1995**, *60*, 6872.

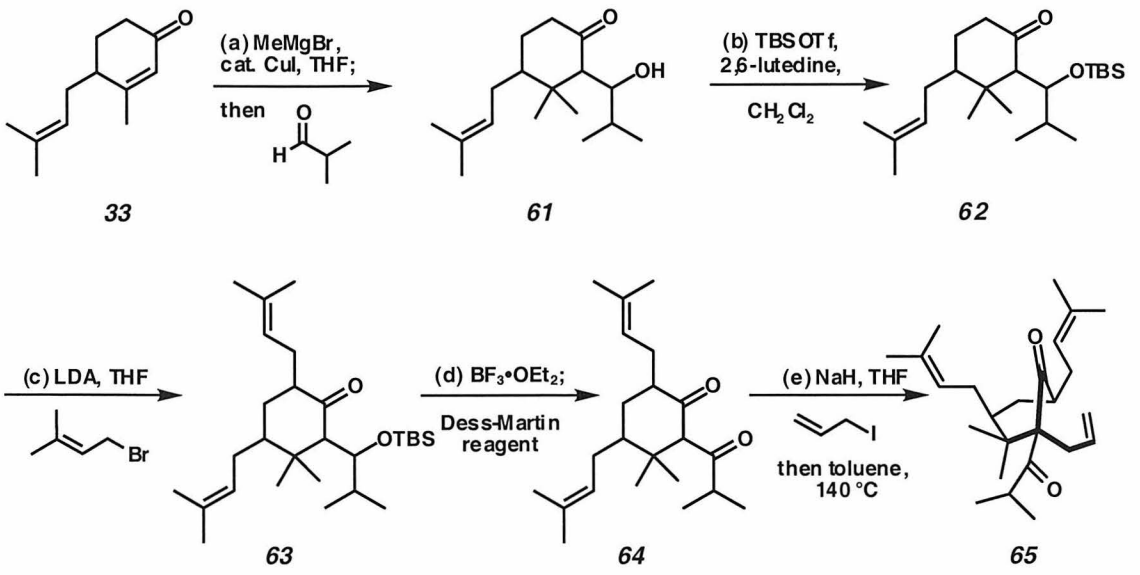
[43] TMS enol ether formation: Jin, S.; Choi, J.-R.; Oh, J.; Lee, D.; Cha, J.K. *J. Am. Chem. Soc.* **1995**, *117*, 10914; Saegusa-Ito conditions: Girlanda-Junges, C.; Keyling-Bilger, F.; Schmitt, G.; Luu, B. *Tetrahedron* **1998**, *54*, 7735.

[44] The use of IBX resulted in ~20% yield of desired enone. See: Nicolaou, K.C.; Zhong, Y.-L.; Baran, P.S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.

[45] Inouye, Y.; Kojima, T.; Owada, J.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4369; Kraus, G.A., Dneprovskaia, E. Nguyen, T.H.; Jeon, I. Unpublished results.

to the synthesis and cyclization of the fully functionalized Garsubellin A cyclohexanone piece, with the hope that a stepwise route might be more straightforward on such a system (Scheme 11). Beginning with previously synthesized enone **33**, 1,4-cuprate addition followed by trapping of the resulting enolate with isobutyraldehyde produced hydroxy-ketone **61** as a mixture of diastereomers (2:1 dr). Protection of the alcohol as a TBS ether, followed by prenylation in the presence of LDA produced ketone **63**.

Scheme 11. Synthesis of the Fully Functionalized Cyclohexanone Subunit



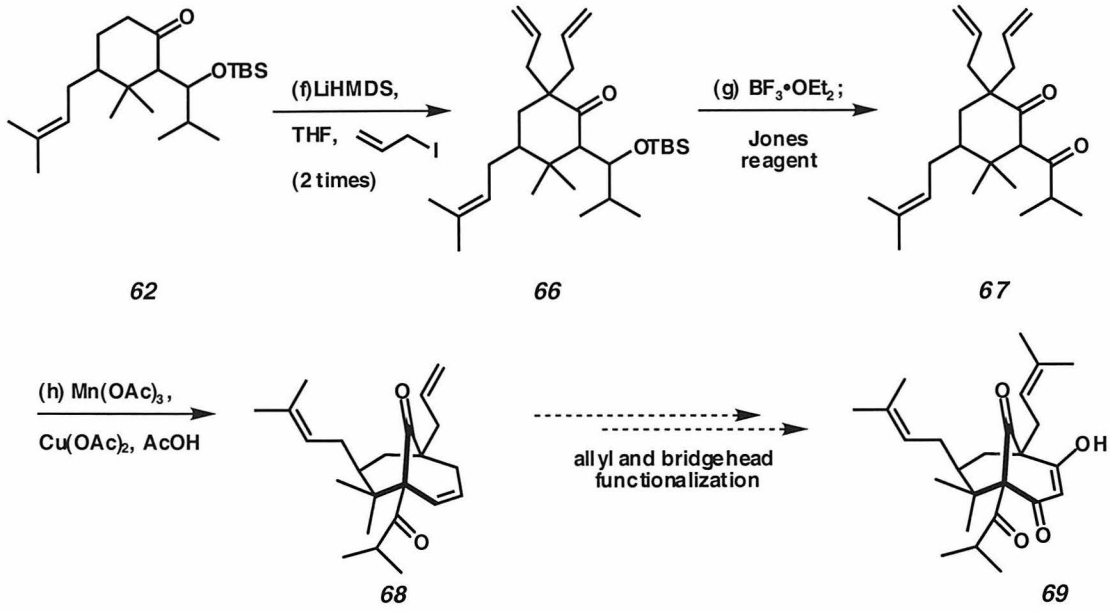
[a] Reagents and conditions (unoptimized): (a) 1.2 equiv MeMgBr, 0.1 equiv CuI, 4.0 equiv isobutyraldehyde, THF, -78 °C to 23 °C, 60% yield; (b) 2.0 equiv 2,6-lutedine, 1.5 equiv TBSOTf, CH_2Cl_2, -40 °C, 60% yield; (c) 1.5 equiv LDA, 1.2 equiv prenyl bromide, THF, -78 °C to 23 °C; (d) 7.0 equiv BF_3•OEt_2, CH_2Cl_2, 0 °C; 1.5 equiv Dess-Martin reagent (15% CH_2Cl_2 soln.), CH_2Cl_2, 0 °C to 23 °C, 57% yield (three steps); (e) 3.0 equiv NaH, 6.0 equiv allyl iodide, THF, 23 °C; toluene (degassed), 140 °C.

Deprotection using BF_3• OEt_2 and oxidation with Dess-Martin periodinane yielded the desired cyclohexanone subunit **64**. Under the conditions previously developed for the model system shown in Scheme 10, similar Michael additions were attempted with diketone **64** using acrolein and a variety of bases.[46] Disappointingly, no Michael product was observed under any of these conditions. Exchanging the isopropyl ketone group for a methyl ester failed to improve the reactivity of this system. Although the position α to

[46]conditions included Et_3N inTHF, K_2CO_3 in acetone, K_2CO_3 in methanol, DBU in THF, and NaH in THF (all run at 23 °C to 50 °C).

both ketones is usually quite activated, it seems that the geminal dimethyl groups play a significant role in preventing any sort of addition from occuring. Ultimately, an allyl functionality was able to be installed at that position first by allyl vinyl ether formation with NaH and allyl iodide, then thermal Claisen rearrangement to yield **65**. Attempts to further derivatize this allyl functionality, however, have been unsuccessful (selective hydroboration, Wacker oxidation, olefin metathesis with vinyl boronates,[47] and dihydroxylation).

Scheme 12. Cyclization of the Fully Functionalized Cyclohexanone Subunit



[a] Reagents and conditions (unoptimized): (f) 2.0 equiv LiHMDS, 2.0 equiv allyl iodide, THF, -78 °C to 23 °C, (2 times) 60% yield; (g) 7.0 equiv $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C; 20.0 equiv Jones reagent (1.25 M soln.), acetone, 0 °C; (h) 2.0 equiv $Mn(OAc)_3$, 1.0 equiv $Cu(OAc)_2$, degassed AcOH, 80 °C.

This allyl group could also be installed at the other bridgehead position using a modification of the route above (Scheme 12). TBS ether **62** was alkylated twice with LiHMDS and allyl iodide, deprotected, and oxidized to give diketone **67**. Using Snider's manganese(III) acetate cyclization protocol, bicycle **68** could be achieved in modest yield.[48] Bicycle **68** represents the most advanced intermediate along this synthetic route

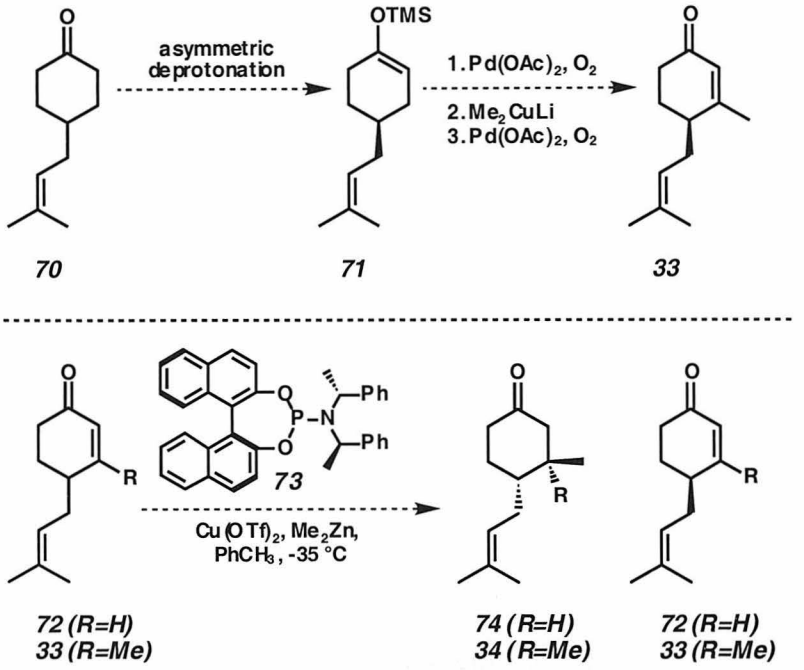
[47]Morrill, C.M.; Grubbs, R.H. Unpublished results.
[48]Cole, B.M.; Han, L.; Snider, B. *J. Org. Chem.* **1996**, *61*, 7832.

and current efforts involve functionalization of the 3-carbon alkene[49] unit as well as modification of the allyl group to access the fully functionalized bicyclic core of garsubellin A (**69**).[50]

VIII. Potential Enantioselective Routes to Garsubellin A

Since it has been previously shown that the remote prenyl stereocenter at C(8) is able to influence the stereochemical outcome of the cyclization, preparation of enantio-enriched garsubellin A will rely on the generation of this stereocenter asymmetrically.

Scheme 14. Possible Enantioselective Syntheses of Enone 33



While this has not been achieved yet, there are several different ways an enantioselective synthesis might be accomplished. One reasonable option involves an asymmetric deprotonation of ketone **70** and a successive Saegusa-Ito oxidation/cuprate addition/ oxidation sequence to access enantiopure enone **33**.[51] Another approach to **33** could utilize Feringa's asymmetric 1,4-addition of alkyl zinc reagents in a catalytic kinetic

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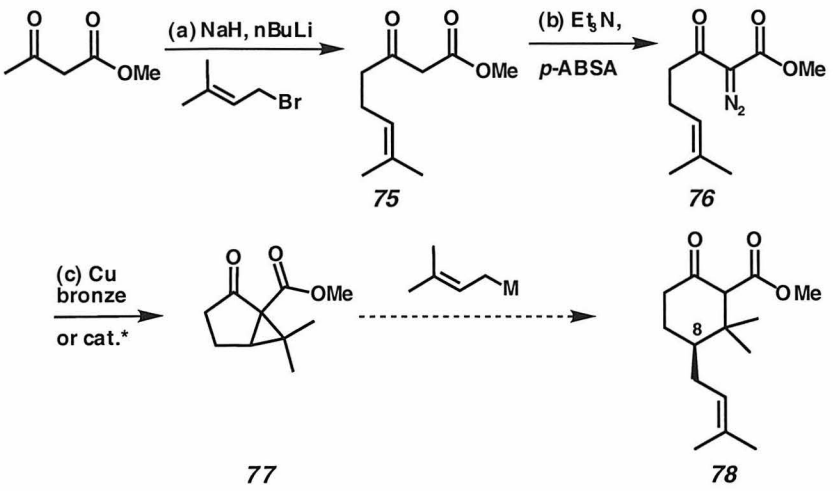
[49]The position of the double bond in the bridging 3-carbon unit has not been confirmed.

[50]We are also investigating directly accessing bicycle **69** by applying our cyclization methodology to enol ethers derived from diketone **64**

[51]Smith, A.B., III; Kanoh, N.; Ishiyama, H.; Hartz, R.A. *J. Am. Chem. Soc.* **2000**, *122*, 11254.

resolution manifold.[52] Treatment of either enone **72** or **33** wih Me_2Zn, $Cu(OTf)_2$, and chiral phosphorimidate **73** will result in a kinetic resolution producing **74** or **34** respectively as the major product with the resolution of **72** or **33** in the process .

Scheme 14. Proposed Enantioselective Installation of the C(8) Prenyl Group[a]



[a] Reagents and conditions: (a) 1.1 equiv NaH, 1.05 equiv nBuLi, 1.1 equiv prenyl bromide, THF, 0 °C, 2 h, 62% yield; (b) 1.0 equiv *p*ABSA, 3.0 equiv Et_3N, CH_3CN, 23 °C, 7 h, 98% yield; (c) 2.0 equiv Cu bronze, toluene, 110 °C, 30 h, 94% yield.

Another options that would involve altering our synthetic route but might be worth pursuing is outlined in Scheme 14. Enantiopure cyclopropane **77** could be synthesized from diazo compound **76** using a chiral cyclopropanation catalyst.[53] Upon opening of the cyclopropane with an anionic prenyl source (*e.g.* a cuprate reagent or a zinc reagent), a single enantiomer of β-keto ester **78** would result. Cyclopropane **77** already has been made in racemic form by modification of existing literature procedures.[54] Generation of the dianion of methyl acetoacetate with NaH and n-butyllithium, followed by treatment with prenyl bromide furnishes **75** in good yield. Conversion to its diazo

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[52]de Vries, A.H.M.; Meetsma, A.; Feringa, B.L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374.

[53]For examples of catalytic asymmetric cyclopropanation, see: Park, S.-W.; Son, J.-H.; Kim, S.-G.; Ahn, K. H. *Tetrahedron: Asymmetry* **1999**, *10*, 1903; Cho, D.-J.; Jeon, S.-J.; Kim, H.-S.; Cho, C.-S.; Shim, S.-C.; Kim, T.-J. *Tetrahedron: Asymmetry* **1999**, *10*, 3833.

[54]Roberts, R. A.; Volker, S.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 2076.

derivative **76** using triethylamine and *p*ABSA[55] as a diazo transfer reaction proceeds virtually quantitatively. Finally, refluxing diazo compound **76** in toluene in the presence of copper bronze affords cyclopropane **77** in 94% yield. Although preliminary studies with prenyl nucleophiles failed to yield any of the desired β-keto-ester **78**, this route represents an interesting and novel way to access enantiopure compounds of this type.

IX. Conclusion

We have developed a highly diastereoselective direct cyclization reaction that delivers the bicyclo[3.3.1]nonane-1,3,5-trione core of the phloroglucinol natural products in a single step. Successful elaboration of bicycle **36** establishes a viable endgame strategy for the introduction of the final prenyl group at C(2). We have also demonstrated the feasibility of this strategy toward the preparation of the bis-quaternary carbon array found at the bridgehead positions of the phloroglucinol natural products (see Figure 2). This cyclization methodology that we have developed compares well with lengthier, more stepwise routes. Current efforts are focused on further optimizing this cyclization, exploring an enantioselective synthesis, and expanding the substrate scope to include fully elaborated systems relevant to the synthesis of garsubellin A and related compounds.

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[55] *p*-ABSA=*p*-acetamidobenzenesulfonylazide; for the preparation of *p*-ABSA and its use as a diazo transfer reaction, see: *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Doyle, M. P.; McKervey, M. A.; and Ye, T.; Wiley-Interscience, New York, 1998.; *Org. Syn.* Vol. IX, p. 422-423.

X. Experimental

Material and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen or an argon atmosphere, using freshly distilled solvents. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV or anisaldehyde staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) and are referenced to the chloroform-d peak (7.27 ppm and 77.00 ppm, respectively) relative to Me_4Si. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Irvine Mass Spectral Facility.

Cyclohexenone 32: To a –78 °C solution of LDA (31.21 mmol, 1.05 equiv) in dry THF (125 mL) was added a solution of 3-isobutoxy-2-cyclohexenone (**31**, 5.0 g, 29.73 mmol, 1.0 equiv) in dry THF (20 mL). The reaction mixture was warmed to 0 °C for 1 h, cooled to -78 °C and treated with prenyl bromide (3.60 mL, 30.32 mmol, 1.02 equiv) in a dropwise fashion to afford an orange solution. After stirring for 4 h at 23 °C, the reaction was quenched with saturated ammonium chloride solution (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to provide **32** as a brown oil (6.95 g, 99% yield) that was used without further purification. R_F =0.5 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1657, 1609 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 5.31 (s, 1H), 5.10 (app.t, J = 6.6 Hz, 1H), 3.57 (d, J = 6.6 Hz, 2H), 2.55 (m, 1H), 2.41 (d, J = 5.0 Hz, 1H), 2.38 (d, J = 5.0 Hz, 1H), 1.97-2.15 (m, 4H), 1.70 (s, 3H), 1.64-1.76 (m, 1H), 1.61 (s, 3H), 0.96 (d, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 177.0, 160.9, 133.2, 121.9, 102.3, 74.7, 45.6, 28.2, 28.1, 27.8, 25.9, 19.1, 17.9; HRMS (EI) *m/z* calcd for 236.1775, found 236.1176.

Enone 33: To a –5 °C solution of **32** (6.89 g, 29.18 mmol, 1.0 equiv) in dry THF (100 mL) was added methyl lithium (34 mL, 1.3 M in Et_2O, 43.77 mmol, 1.50 equiv). After stirring for 30 min at 23 °C, no starting material remained, as judged by TLC. The reaction mixture was cooled to 0 °C and treated slowly with 1.0 M HCl (73 mL, 73.0 mmol, 2.5 equiv). After stirring for another 30 min at 23 °C, the layers were separated and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organic layers were dried and concentrated to a yellow oil, which was purified by silica gel chromatography (10% ethyl acetate in hexanes eluent) to afford enone **33** as a yellow oil (4.67 g, 88% yield). R_F= 0.44 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1716, 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.10 (m, 1H), 2.36-2.48 (m, 1H), 2.08-2.32 (m, 4H), 1.94-2.06 (m, 1H), 1.97 (s, 3H), 1.80-1.91 (m, 1H), 1.71 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, CDCl 3) δ 199.3, 165.5, 133.8, 126.8, 121.7, 40.0, 34.1, 29.8, 26.5, 25.9, 23.1, 17.9; HRMS (EI) *m/z* calcd for 178.1436, found 178.1432.

Dimethylcyclohexanone 34: To a -5 °C slurry of copper (I) iodide (9.83 g, 50.56 mmol, 2.0 equiv) in Et_2O (250 mL) was added dropwise methyl lithium (72.2 mL, 1.4 M solution in Et_2O, 101.12 mmol, 4.0 equiv). The resulting light tan solution stirred for 60 min at -5 °C before a solution of enone **33** (4.5 g, 25.28 mmol, 1.0 equiv) in Et_2O (100 mL) was added over 10 min via addition funnel. The bright yellow reaction mixture was stirred for an additional 10 min at -5 °C until all starting material appeared to be consumed by TLC. After quenching with saturated aqueous NH_4Cl/NH_4OH solution

(250 mL), the layers were separated and the aqueous layer was extracted with Et_2O (2 x 250 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to a yellow oil, which was purified by passing through a silica gel plug (10% ethyl acetate in hexanes eluent) to afford ketone **34** (4.76 g, 97% yield) as a pale yellow oil. R_F=0.56 (30% ethyl acetate in hexanes); FTIR (thin film) 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (app.t, J = 7.1 Hz, 1H), 2.20-2.40 (m, 4H), 1.97-2.17 (m, 2H), 1.79-1.65 (m, 1H), 1.72 (s, 3H), 1.62 (s, 3H), 1.56-1.39 (m, 2H), 1.06 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 132.5, 123.4, 56.0, 46.1, 41.0, 38.7, 29.9, 27.9, 27.7, 25.9, 20.8, 17.9; HRMS (EI) *m/z* calcd for 194.1665, found 194.1671.

Silyl enol ethers 35a and 35b: A round bottomed flask (200 mL) was charged with ketone **27** (4.75 g, 24.48 mmol, 1.0 equiv) in dry acetonitrile (50 mL). Freshly distilled triethylamine (4.30 mL, 30.61 mmol, 1.25 equiv) was added, followed by tert-butyldimethylsilyl chloride (4.61 g, 30.61 mmol, 1.25 equiv) and sodium iodide (4.59 g, 30.61 mmol, 1.25 equiv). The reaction flask was topped with a condenser and heated to 80 °C for 1 h, then cooled to room temperature and concentrated to a brown solid. After trituration of the solid with pentane (100 mL) and concentration, a pale yellow oil was obtained. Purification by silica gel chromatography (1% ethyl acetate and 1% triethylamine in hexanes eluent) yielded **35a** and **35b** (7.40 g, 98% yield) as a mixture of two silyl enol ether isomers in a 6:1 ratio (**a**:**b**), as determined by ^1H NMR. Major isomer (**35a**): R_F=0.71 (10% ethyl acetate in hexanes); FTIR 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (m, 1H), 4.77 (s, 1H), 2.06-2.18 (m, 2H), 1.64-1.92 (m, 4H), 1.70 (s, 3H), 1.60 (s, 3H), 1.22 (m, 1H), 0.96 (s, 3H), 0.92 (s, 9H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 131.6, 124.2, 102.6, 44.5, 42.9, 33.1, 28.9, 27.8, 26.8, 25.9, 25.8, 22.3, 18.1, 17.9, –4.2; HRMS (EI) *m/z* calcd for 308.2536, found 308.2535. The minor isomer (**35b**) was identified by a ^1H NMR vinyl stretch at 4.63 ppm (d, J=1.6 Hz, 1H).

Bicycle 36: To a solution of silyl enol ethers **35a** and **35b** (1.0 g, 3.24 mmol, 1.0 equiv) in dry methylene chloride (0.80 mL) at -10 °C (dry ice/ethylene glycol cold bath) was added dropwise a solution of malonyl dichloride (0.63 mL, 6.49 mmol, 2.0 equiv) in 0.80 mL methylene chloride. The reaction mixture was stirred at -10 °C for 11 h, then treated with a solution of potassium hydroxide (1.46 g, 25.95 mmol, 8.0 equiv) and benzyltriethylammonium chloride (0.037 g, 0.16 mmol, 0.05 equiv) in H_2O (1.60 mL). The reaction mixture was stirred at -10 °C for an additional 1 h, and then was allowed to warm to 23 °C over 10 h. After dilution with water (50 mL) and methylene chloride (50 mL), the phases were separated and the aqueous phase was extracted with methylene chloride (3 x 50 mL). These organic extracts were combined and dried over $MgSO_4$. Concentration and purification by silica gel chromatography (0% to 5% ethyl acetate in hexanes eluent) provided recovered ketone **34** (0.370 g, 1.91 mmol, 59% yield). The aqueous layer was acidified to pH 1 with 1 M HCl and extracted with methylene chloride (5 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to provide bicycle **36** as an orange-yellow solid (0.306 g, 36% yield, 87% yield based on recovered ketone, 95% yield of total mass recovery), which was used without further purification. Crystals suitable for X-ray analysis were obtained by crystallization from methylene chloride at 23 °C: mp 166-168 °C; R_F= 0.46 (20% methanol in methylene chloride eluent); FTIR (thin film) 1740, 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (broad s, 1H), 5.87 (s, 1H), 5.01 (m, 1H), 3.18 (s, 1H), 2.82 (s, 1H), 2.13 (m, 2H), 1.60 1.80 (m, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.15 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 189.9, 185.8, 133.4, 107.7, 68.9, 57.5, 42.2, 39.2, 32.7, 27.8, 27.2, 25.9, 20.6, 20.6, 18.0; HRMS (EI) *m/z* calcd for 262.1565, found 262.1569.

Allyl ether 37: To a solution of bicycle **36** (0.200 g, 0.762 mmol, 1.0 equiv) in benzene (5 mL) was added allyl alcohol (0.259 mL, 3.81 mmol, 5.0 equiv) and p-toluenesulfonic acid (3 mg, 0.015 mmol, 0.02 equiv). The reaction flask was fitted with a Dean-Stark

apparatus and a condenser, and the reaction mixture was heated to reflux for 10 h (oil bath temperature: 90-95 °C). Upon cooling, the reaction mixture was concentrated and purified by silica gel chromatography (25% ethyl acetate in hexanes to 100% ethyl acetate eluent) to afford **37** (172 mg, 75% yield) as a pale yellow oil. R_F=0.40 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1737, 1656, 1601 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H), 5.67 (s, 1H), 5.42-5.32 (m, 2H), 5.00 (m, 1H), 4.49 (d, *J* = 1.1 Hz, 1H), 4.47 (d, *J* = 1.1 Hz, 1H), 3.18 (s, 1H), 2.78 (d, *J* = 1.7 Hz, 1H), 2.08-2.18 (m, 2H), 1.64-1.80 (m, 3H), 1.69 (s, 3H), 1.57 (s, 3H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 193.9, 174.3, 133.2, 130.5, 122.2, 119.2, 106.2, 74.0, 70.1, 53.4, 42.8, 39.6, 32.1, 27.5, 26.9, 25.9, 20.6, 17.9; HRMS (EI) *m/z* calcd for 302.1882, found 302.1882.

Methyl ether 38: Allyl ether **37** (36 mg, 0.119 mmol) in dry toluene (1.3 mL) was placed in a sealed tube and heated to 140-145 °C (oil bath temperature) for 7 h. The reaction mixture was concentrated, then dissolved in THF (1 mL) and treated with diazomethane (10 mL of a 0.2 M solution in Et_2O) at 0 °C. After 1 h, the reaction mixture was warmed to 23 °C and then concentrated to give a clear oil, which was purified by preparative TLC (methylene chloride eluent) to yield **38** as separable isomers (**38a** and **38b**) in a 1:1 ratio (23.2 mg, 62% yield) along with recovered ether **37** (10.5 mg, 30% yield). Bicycle **38a** (faster eluting isomer): R_F=0.44 (30% ethyl acetate in hexanes eluent), FTIR (thin film) 1735, 1657, 1602 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (m, 1H), 4.97 (m, 3H), 3.83 (s, 3H), 3.23 (s, 1H), 3.20 (m, 1H), 3.14 (s, 1H), 3.12 (s, 1H), 1.90-2.50 (m, 3H), 1.56-1.70 (m, 2H), 1.66 (s, 3H), 1.55 (s, 3H), 1.13 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 195.0, 169.7, 135.4, 133.4, 124.0, 121.9, 114.8, 61.03, 60.5, 56.9, 42.1, 38.4, 33.5, 27.9, 27.1, 26.1, 25.9, 20.9, 17.9. Bicycle **38b** (slower eluting isomer): R_F= 0.43 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1734, 1648, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1H), 4.99 (m, 3H), 3.85 (s, 3H), 3.57 (broad s, 1H),

3.10 (d, J = 1.7 Hz, 1H), 3.08 (d, J = 1.1 Hz, 1H), 2.83 (d, J = 1.7 Hz, 1H), 2.13 (m, 2H), 1.60-1.80 (m, 3H), 1.70 (s, 3H), 1.58 (s, 3H), 1.10 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 192.4, 169.2, 135.4, 133.5, 122.1, 121.3, 114.6, 73.6, 55.8, 48.7, 43.1, 39.0, 31.6, 27.4, 26.9, 26.8, 25.9, 20.6, 18.0; HRMS (EI) *m/z* calcd for 316.2037, found 316.2038.

Prenyl bicycle 40: To a solution of allyl bicycle **38a** and **38b** (6.5 mg, 0.020 mmol, 1 equiv) in 2-methyl-2-butene (5 mL) was added ruthenium catalyst **39** (1.7 mg, 0.002 mmol, 0.1 equiv). The reaction flask was fitted with a dry ice-acetone condenser and the mixture was heated to reflux for 2 h. The reaction mixture was cooled, filtered through a small silica gel plug (ethyl acetate eluent), and concentrated to give a brown oil. Purification by preparative TLC (methylene chloride eluent) provided **40** (6.1 mg, 88% yield) as an off-white solid. R_F= 0.47 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1737, 1655, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92-5.02 (m, 2H), 3.81 (s, 3H), 3.21 (s, 1H), 3.19 (d, J = 3.8 Hz, 1H), 3.08 (s, 1H), 3.06 (s, 1H), 2.13 (m, 3H), 1.60-1.80 (m, 2H), 1.71 (s, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.55 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 195.2, 168.8, 133.3, 132.0, 126.0, 122.0, 121.6, 61.2, 60.4, 56.8, 42.0, 38.3, 33.6, 29.8, 27.9, 26.1, 25.9, 25.8, 22.1, 20.9, 17.9; HRMS (EI) *m/z* calcd for 344.2349, found 344.2351.

Trione 41: Bicycle **40** (3 mg, 0.009 mmol) was dissolved in 10% aqueous NaOH (1 mL, plus 100 μL of THF for solubility) and heated to 90 °C for 8 h in a sealed vial. Upon cooling, the solution was acidified with 1 M HCl, then concentrated under reduced pressure. Trituration with THF gave a yellow solid that was further purified by preparative TLC (50% ethyl acetate in hexanes eluent) to afford trione **41** (2.5 mg, 87% yield) as a pale yellow solid. R F = 0.43 (50% ethyl acetate in hexanes eluent); FTIR (thin film) 1728, 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (m, 1H), 4.99 (m, 1H), 3.24-

3.12 (m, 3H), 2.81 (d, J = 1.6 Hz, 1H), 2.46-1.90 (m, 3H), 1.84-1.52 (m, 2H), 1.80 (s, 3H), 1.68 (s, 3H), 1.57 (s, 6H), 1.13 (s, 3H), 0.94 (s, 3H).

Dimethyl Methyl Bicycle 25: To a solution of 2,6-dimethyl-1-methoxy-1-cyclohexene (**24**, 0.300 g, 2.14 mmol, 1.0 equiv) in methylene chloride (0.50 mL) was added a solution of malonyl dichloride (0.208 mL, 2.14 mmol, 1.0 equiv) in methylene chloride (0.50 mL) at -78 °C. Bis(cyclopentadienyl)hafnium dichloride (0.812 g, 2.14 mmol, 1.0 equiv) was added in one portion. The reaction mixture was warmed to 0 °C for 1 hour, then to 23 °C for 72 h. After cooling to 0 °C, a solution of KOH (1.20 g, 21.4 mmol, 10.0 equiv) and benzyltriethylammonium chloride (0.025 g, 0.011 mmol, 0.05 equiv) in H_2O (1 mL) and methylene chloride (1 mL) was added dropwise. The resulting dark red reaction mixture was allowed to warm to 23 °C over 3 h. It was then acidified with 1 M HCl (to ~pH 1) and filtered through a pad of celite, washing thoroughly with H_2O and methylene chloride. The filtrate was poured into a separatory funnel, extracted with methylene chloride (5 x 50 mL), and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was dissolved in THF (5 mL) and treated with diazomethane (30 mL of a 0.2 M solution in Et_2O) at 0 °C. Warming to 23 °C after 1 h and removal of solvent afforded a brown residue that was further purified by silica gel chromatography (5% to 30% ethyl acetate in hexanes eluent) to furnish bicycle **25** (0.111 g, 25% yield, 47% yield based on recovery of 0.125 g ketone **26**). R_F= 0.27 (30% ethyl acetate in hexanes eluent); FTIR (thin film) 1728, 1656, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1H), 3.77 (s, 3H), 1.94-2.04 (m, 2H), 1.50-1.80 (m, 4H), 1.29 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) • 209.8, 197.1, 176.4, 105.3, 60.3, 56.9, 53.0, 40.8, 38.6, 25.8, 19.4, 16.6, 16.2; HRMS (EI) *m/z* calcd for 208.1097, found 208.1099.

Appendix A.

Appendix

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