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Synthesis of Polyprenylated Acylphloroglucinols Using Bridgehead Lithiation: The Total Synthesis of Racemic Clusianone and a Formal Synthesis of Racemic Garsubellin A

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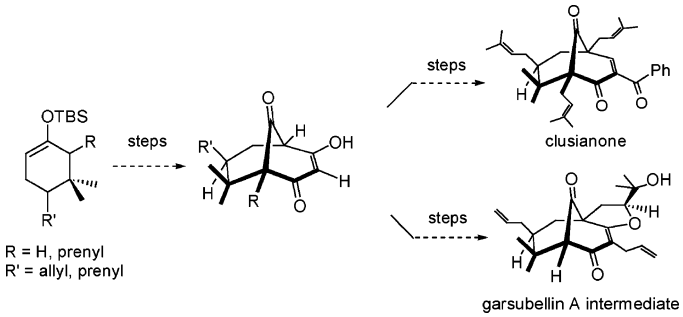

The synthesis of polyprenylated phloroglucinol natural products, including clusianone, nemorosone, and garsubellin A, was pursued by a strategy involving construction of a core bicyclo[3.3.1]nonanetrione structure and subsequent elaboration via organolithium intermediates. Appropriate bridged core structures were obtained through the cyclization of a suitably substituted cyclohexanone enol ether or enol silane with malonyl dichloride. Additional substituents were then introduced by means of regioselective lithiation reactions, including the generation of bridgehead enolates, thus enabling the total synthesis of clusianone and also of an advanced intermediate toward nemorosone. In the case of garsubellin A, an additional THF-like ring was elaborated by a biomimetic 5-*exo-tet* cyclization of an enol ether (or enol) with a side-chain epoxide. This enabled a formal synthesis of racemic garsubellin A by accessing one of the late intermediates in the Danishefsky synthesis.

Introduction

Plants and trees of the family Clusiaceae (Guttiferae) are a rich source of polyprenylated acylphloroglucinols (PPAPs). These are characterized by a bicyclo[3.3.1]nonanetrione core structure bearing additional acyl and prenyl substituents, e.g., garsubellin A (**1**), hyperforin (**2**), clusianone (**3**), and nemorosone (**4**) (Figure 1).[1]

The various PPAPs have been divided into three classes, depending on the relative position of the acyl substituent on the core bicyclic structure, Figure 2.[2] Type A structures, including garsubellin, hyperforin, and nemorosone, have the acyl residue at the C-1 bridgehead position, whereas type B systems like clusianone have a C-3 acyl group. The more scarce type C structures bear an acyl group at the bridgehead carbon C-5. Additional elaboration of these structures, involving cyclization of the olefinic (most frequently prenyl) side chains and the enolic β-diketone, is commonplace, as exemplified by the furanoid ring present in garsubellin A.

Perhaps the most well-known member of the PPAP family, hyperforin (**2**), is thought to be the major bioactive constituent from *Hypericum perforatum* (St. John's wort, SJW), which has well-known antidepressant properties.[3] The use of SJW extracts for the treatment of mild to moderate depression is widespread

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(1) For a recent and comprehensive review of the area, see: (a) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963−3986. See also: (b) Verotta, L. *Phytochem. Rev.* **2002**, *1*, 389−407.

(2) Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cardenas, J. *Phytochemistry* **2001**, *57*, 279.

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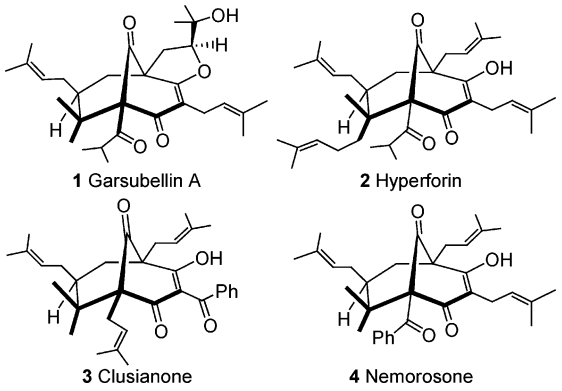


FIGURE 1. Structure of some PPAPs.

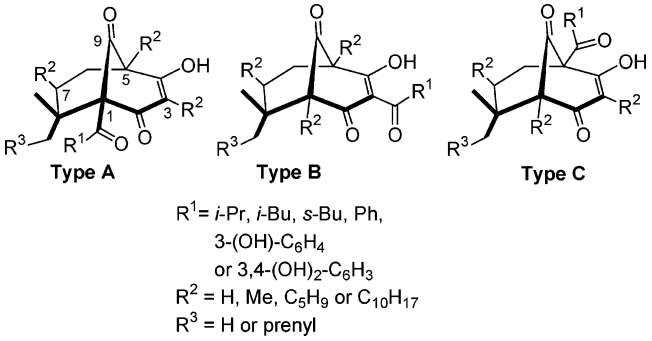
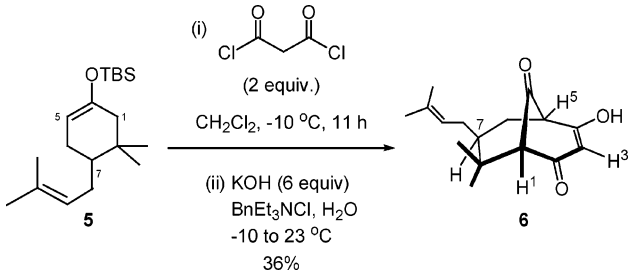


FIGURE 2. Three types of PPAPs.

in Europe but remains controversial in terms of efficacy, especially with regard to undesirable prescription drug interactions.[4] More recently isolated in 1997 from *Garcinia subelliptica*, garsubellin A (**1**) has since attracted significant synthetic attention, in part due to its ability to induce choline acetyltransferase, a key enzyme involved in acetylcholine biosynthesis.[5] Clusianone (**3**) has been known since 1976, and recent screening has ascribed potent anti-HIV and cancer chemopreventive properties to **3** and related compounds such as the regioisomeric PPAP nemorosone (**4**).[6,8a] Although the structure of **3** was originally determined by X-ray crystallography,[7] more recently there was some confusion of this compound with a C-7 epimer.[8]

The broad range of biological activities exhibited by this family of compounds, together with the challenging structure of PPAPs, has stimulated much synthetic activity, and several groups have described progress toward specific members of the PPAP family.[1a] Only very recently, however, has **1** succumbed to total synthesis by the groups of Shibasaki[9] and Danishefsky.[10]

SCHEME 1. Stoltz's Synthesis of the [3.3.1]Trione Core of 1



Our interest in this field first arose from the observation that most PPAPs possess two substituted bridgehead positions flanked by activating ketone functions. Having recently shown that bridgehead lithiation−substitution processes in related [3.3.1] systems were possible,[11] we identified an opportunity to apply this approach to the synthesis of PPAP natural products and their analogues. The idea of accessing various types of PPAPs by the late-stage affixing of appropriate substituents onto a common [3.3.1] trione core system is an attractive one. In particular, this strategy holds the promise of a very flexible access to various types of natural PPAPs from a common core structure, through appropriate functionalization of the C-1, C-3, and C-5 positions. In addition, this would allow us to access diverse unnatural analogue structures in order to probe the largely unexplored SAR in these systems. This strategy, however, required a rapid access to a suitable "core" trione system. A solution to this problem was first proposed by Spessard and Stoltz during their elegant approach to garsubellin A (Scheme 1).[12] In a modification of a procedure originally described by Effenburger and co-workers,[13] they were able to convert the substituted enol silane **5** directly into the bridged trione **6** by reaction with malonyl dichloride, with complete diastereoselectivity at C-7.

The yield of bridged triketone product was modest, but the ketone corresponding to the starting enol silane could also be recovered. Unfortunately, enol derivatives having additional α- and α′-substituents, destined to emerge as the C-1 and C-5 bridgehead groups, were even less satisfactory participants in the cyclization. This deficiency provided an obvious spur for our bridgehead substitution approach.

Despite the relatively low efficiency of the key Effenburger cyclization, the brevity of this approach encouraged us to adopt it for accessing a core structure, which could then be further substituted by sequential regioselective lithiations. We envisaged that target PPAPs **7** would be available by controlled substitution at C-1, C-3, and C-5 of a vinylogous ester (*O*-alkylated 1,3-diketone) such as **8** or its regioisomer. Compounds like **8** would be prepared by Effenburger-type cyclization of appropriate cyclohexanone-derived enol ethers or enol silanes **9**, themselves available by fairly routine and concise sequences starting from a suitable cyclohexan-1,3-dione derivative **10** (Scheme 2).

We reasoned that regioselectivity for metalation at one bridgehead position should be possible as a result of the different

(3) (a) Structure: Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, 2791−2794. (b) Biosynthesis: Adam, P.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Med. Chem*. **2002**, *45*, 4786−4793.

(4) Madabushi, R.; Frank, B.; Drewelow, B.; Hartmut, D.; Butterweck, V. *Eur. J. Clin. Pharm.* **2006**, *62*, 225−233.

(5) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull*. **1997**, *45*, 947−949.

(6) (a) Ito, C.; Itoigawa, M.; Miyamoto, Y.; Onoda, S.; Sundar, Rao, K.; Mukainaka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod*. **2003**, *66*, 206−209. (b) US Patent US 2005/0090693 A1.

(7) McCandlish, L. E.; Hanson, J. C.; Stout, G. H. *Acta Crystallogr., Sect B* **1976**, *32*, 1793−1801.

(8) (a) Piccinelli, A. L.; Cuesta-Rubio, O.; Chica, M. B.; Mahmood, N.; Pagano, B.; Pavone, M.; Barone, V.; Rastrelli, L. *Tetrahedron* **2005**, *61*, 8206−8211. (b) Delle Monache, F.; Delle, Monache, G.; Gacs-Baits, E. *Phytochemistry* **1991**, *30*, 2003−2005.

(9) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2005**, *127*, 14200−14201.

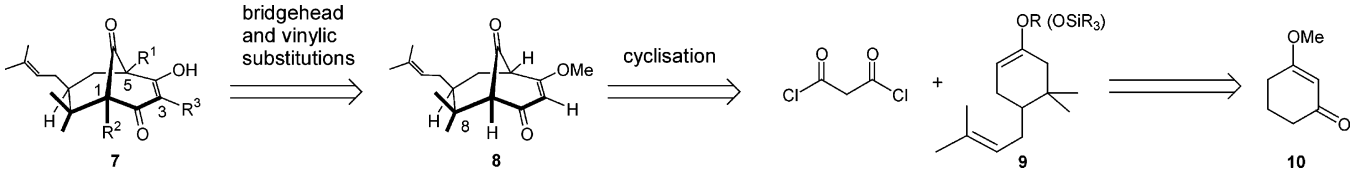
(10) Siegal, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2006**, *128*, 1048−1049.

(11) Giblin, G. M. P.; Kirk, D. T.; Mitchell, L.; Simpkins, N. S. *Org. Lett*. **2003**, *5*, 1673−1675.

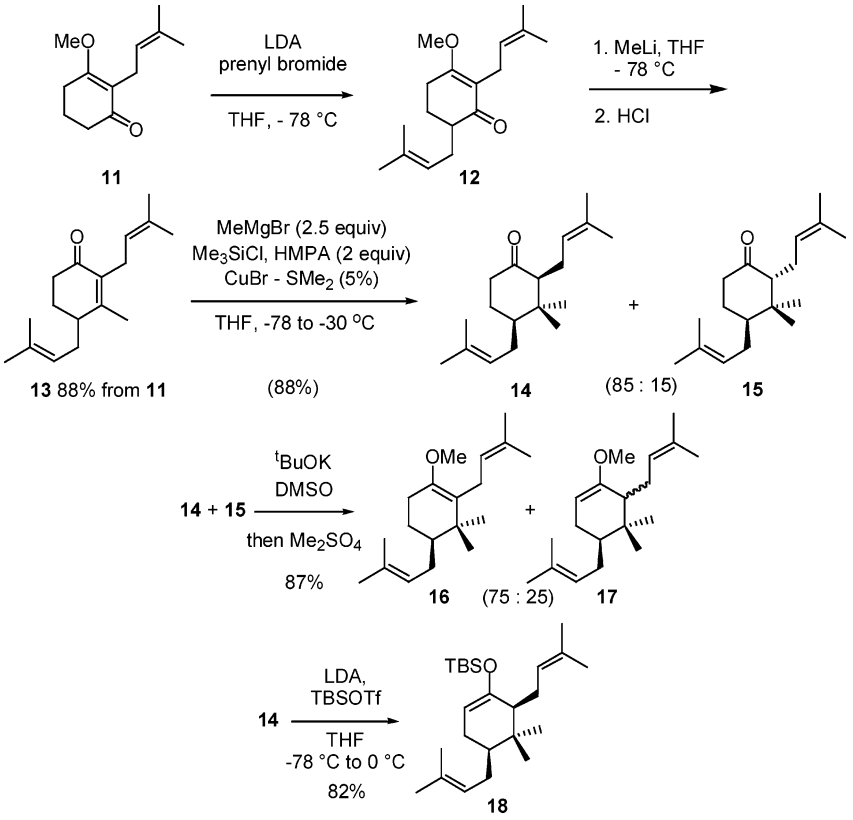
(12) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943−1946.

(13) Schönwälder, K-H.; Kollatt, P.; Stezowski, J. J.; Effenburger, F. *Chem. Ber.* **1984**, *117*, 3280−3296.

SCHEME 2. A General Strategy To Access Various PPAPs



SCHEME 3. Synthesis of Enol Derivatives for Effenberger Cyclization



steric environments for positions C-1 and C-5 resulting from the *gem*-dimethyl substituents at C-8. The position of diketone alkylation in structures like **6** *might* also be expected to affect the regioselectivity of bridgehead metalation, and there was some precedent from the Stoltz work that single regioisomeric vinylogous ester structures could be prepared (vide infra).

The introduction of substituents at the vinylic position (C-3) by direct metalation also appeared to be viable according to literature precedents.[14] Careful planning in the order of introduction of bridgehead vs C-3 prenyl groups would be required in cases where regioselective side chain oxidation−cyclization is required (e.g., garsubellin A). For our initial targets, we also wanted to avoid oxidation of the exo-orientated C-7 prenyl substituent, and it was unclear if we could rely on steric effects or directing effects (e.g., from the enolized diketone system) in this regard. A tactic involving the use of a C-7 allyl group as a less reactive "bystander" group capable of ultimately being converted into a prenyl group looked attractive.

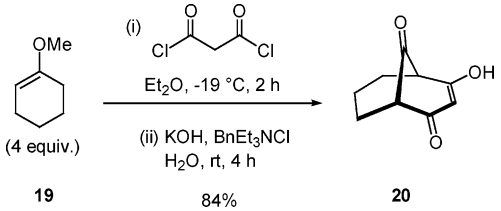
In our previous communication, we described a concise synthesis of clusianone (**3**) using the approach outlined above.[15] In this full report, we present the full details of this synthesis, along with our synthetic efforts toward nemorosone (**4**), and we present a formal synthesis of garsubellin A (**1**) by a new access to an advanced intermediate previously prepared by the Danishefsky group.[10]

Results and Discussion

1. Synthesis of Clusianone. As installation of a substituent at the hindered C-1 position of **8** was considered an extreme test of our strategy (vide infra), we first decided to focus on substitution reactions at C-3 and C-5 of the core trione derivative. The synthesis started with known vinylogous ester **11**,[16] bearing a prenyl group at the position which would become C-1 in the cyclized product (Scheme 3).

Prenylation of **11** using LDA and prenyl bromide gave **12**, which was then reacted with MeLi and hydrolyzed under mildly

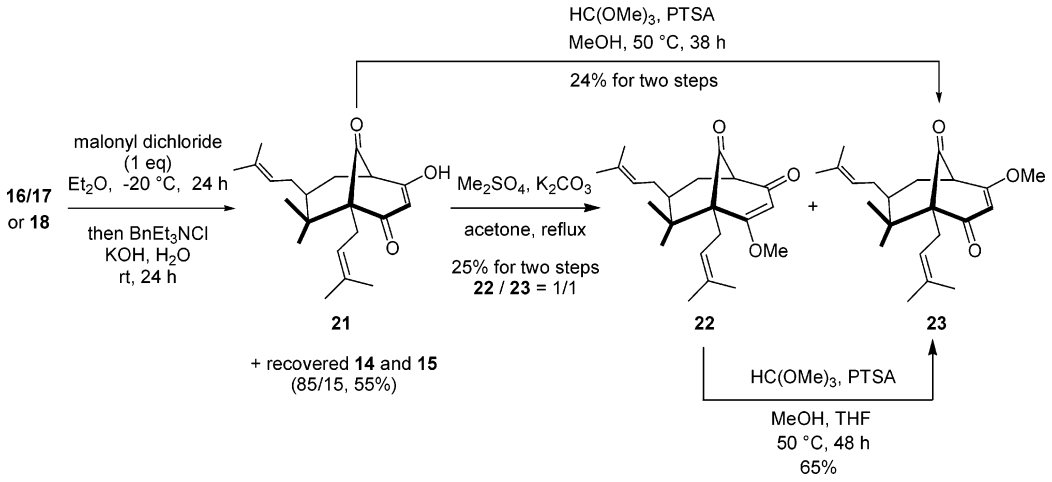
SCHEME 4. Effenberger Cyclization



(14) (a) Miyata, O.; Schmidt, R. R. *Tetrahedron Lett.* **1982**, *23*, 1793−1796. (b) For a more recent example, see: Zapf, C. W.; Harrison, B. A.; Drahl, C.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6533−6537.

(15) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283−5285.

SCHEME 5. Synthesis of Bridged Trione and Trione−Ether Derivatives



acidic conditions to give enone **13**. Conjugate addition of a methyl group to this tetrasubstituted system proved more difficult than anticipated. The use of stoichiometric higher order cuprate reagents (Me_2CuLi), alone or in the presence of Lewis acids (TMSCl, BF_3-OEt_2), failed to deliver useful quantities of ketones **14**/**15**. In contrast, copper-catalyzed Grignard addition in the presence of HMPA and TMSCl provided the ketone product as a mixture of diastereoisomers in a satisfying 88% yield. The cis derivative **14** was the major component, as determined by NOE experiments. This was of no consequence, however, as the mixture of diastereoisomers was easily converted into a regioisomeric mixture of enol ethers **16** and **17** in a combined 87% yield under thermodynamic conditions.[17]

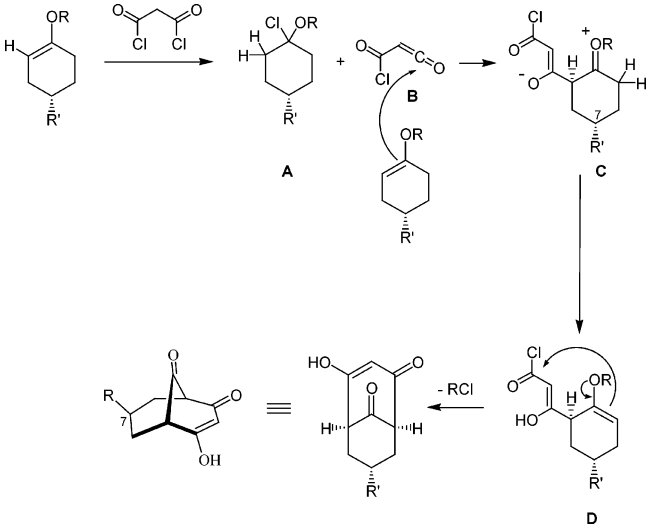
Alternatively, enol silane **18** was obtained as a single isomer starting from the *cis*-diprenylated ketone **14** under kinetic conditions in 82% yield.

Having obtained a few appropriate enol ether and enol silane substrates, we started to explore the Effenburger-type cyclization. Originally, the Effenberger group reported quite efficient cyclizations, but these were based on the use of the enol component in excess. For example, reaction of *4* equiv of methyl enol ether **19** with 1 equiv of malonyl dichloride, at −19 °C, using Et_2O as solvent, allowed the isolation of the cyclized product **20** in 84% yield (Scheme 4).

However, the use of more elaborate enol ethers, such as **16**−**18**, in excess was not attractive in our case, and we preferred to start our study with the modified conditions described by Stoltz, which employed malonyl dichloride in excess.

Under these conditions, reaction of enol ether mixture **16**/**17** with malonyl dichloride (2 equiv) in Et_2O at −20 °C for 24 h, followed by a basic workup, furnished the desired trione **21** as a single diastereomer (ca. 30% crude material), which could be separated by base extraction from recovered ketones **14**/**15** (55% recovered, Scheme 5). In this case, both regioisomeric enol methyl ethers appear to participate in the process. Essentially the same results were achieved by using the TBS enol ether **18**. A rapid screening of conditions indicated that either CH_2Cl_2 or Et_2O could be used as the solvent (although in general Et_2O gave cleaner results) and that the number of equivalents of malonyl dichloride could be reduced to 1 equiv without reducing conversion or product yield.

SCHEME 6. Proposed Mechanism for the Reaction of an Enol Ether with Malonyl Dichloride



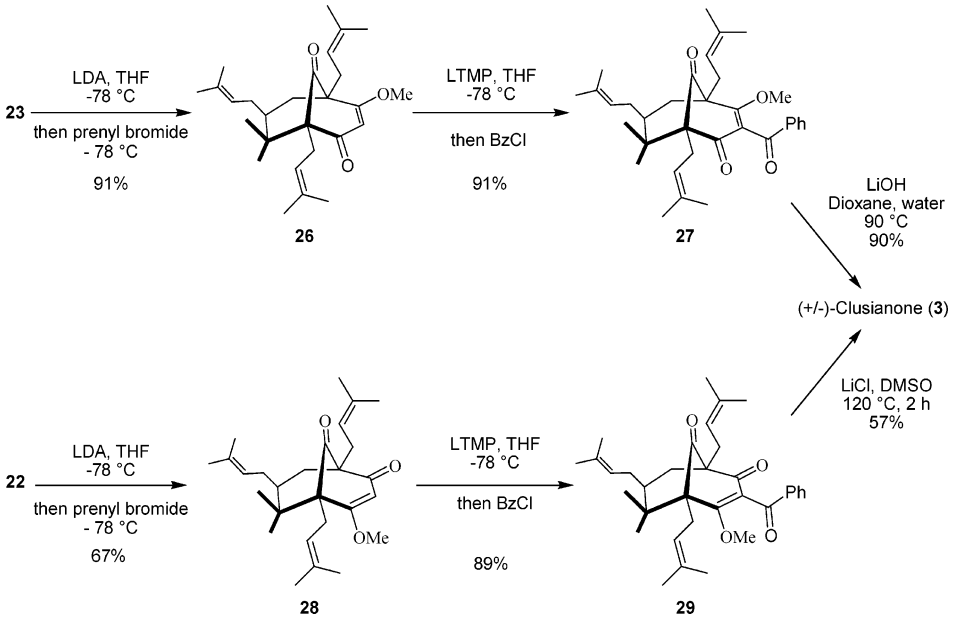
Having viable quantities of triketone **21**, we next explored its conversion into the corresponding vinylogous ester as a means to protect the 1,3-diketone function during the planned lithiation chemistry. *O*-Methylation under basic conditions provided an equimolar mixture of the regioisomeric vinylogous esters **22** and **23**, which could easily be separated by column chromatography. In contrast, under acidic conditions (PTSA), used by Stoltz to prepare a similar enol ether, completely regioselective methylation occurred providing **23** as the sole product in 24% overall yield from **16** and **17** (or alternatively from **18**). The contrasting results were shown to be due to the greater thermodynamic stability of regioisomer **23**, as demonstrated by converting **22** completely into **23** (no **22** remained at the end of the reaction) under the same acidic conditions (Scheme 5).

Although this short sequence of reactions gave us rapid access to our desired core [3.3.1] trione structure, the consistently low conversions obtained in the key cyclization were frustrating, and we decided to investigate alternative conditions for this reaction. The mechanism for this transformation, as originally proposed by Effenburger et al., involved the initial conversion of malonyl dichloride into ketene **B**, the intervention of one

(16) Majetich, G.; Hull, K.; Casares, A. M.; Khetani, V. *J. Org. Chem.* **1991**, *56*, 3958−3973.

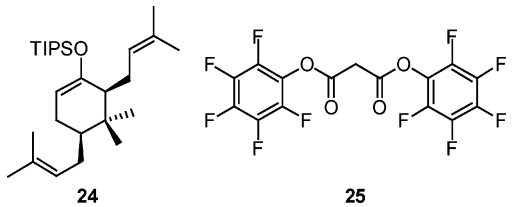
(17) Heiszwolf, G.J.; Kloosterziel, H. *J. Chem. Soc., Chem. Commun.* **1966**, 51.

SCHEME 7. Completion of the Synthesis of Clusianone



molecule of enol ether serving to mop up HCl and forming chloroether **A** (Scheme 6). Electrophilic ketene **B** then reacts with the remaining enol ether diastereoselectively through an axial approach, delivering the malonyl unit on the opposite face to the substituent on position that emerges as C-7. Proton exchange on oxonium species **C** generates a transposed enol ether **D**, which finally undergoes a Dieckmann type reaction leading to the observed cyclized product.

This mechanism might account for the good yields obtained by the original authors when using the enol ether component in excess. Since we required use of the valuable enol ether (or enol silane) as the limiting component in our chemistry we sought to form the putative ketene by the more conventional action of a base. Following this idea, we tried to generate the ketene in situ by adding a bulky amine to the reaction mixture. However, in the presence of Huenig's base ($^{i}Pr_2NEt$) or proton sponge (1,8-bis(dimethylamino)naphthalene), no cyclized product was obtained. The mechanism proposed above also requires the regeneration of an enol ether from the oxonium species **B**, and such a process has been shown to be particularly favored in the case of triisopropylsilyl enol ether derivatives.[18] In our case, however, the use of TIPS enol ether **24**[19] led to no cyclization at all, and **24** was recovered unaffected after the workup.



24 **25**

The use of an alternative electrophile, the so-called "magic malonate" **25**,[20] similarly led to no annulation under otherwise similar conditions. Spessard and Stoltz had described one cyclization using bis(cyclopentadienyl)hafnium dichloride as a Lewis acid mediator, but we were unable to improve the yields of bicyclic adducts using this approach.[21] After expending some considerable effort, we found ourselves unable to improve on the modest cyclization yields reported above and decided to proceed with the more advanced aspects of the synthesis.

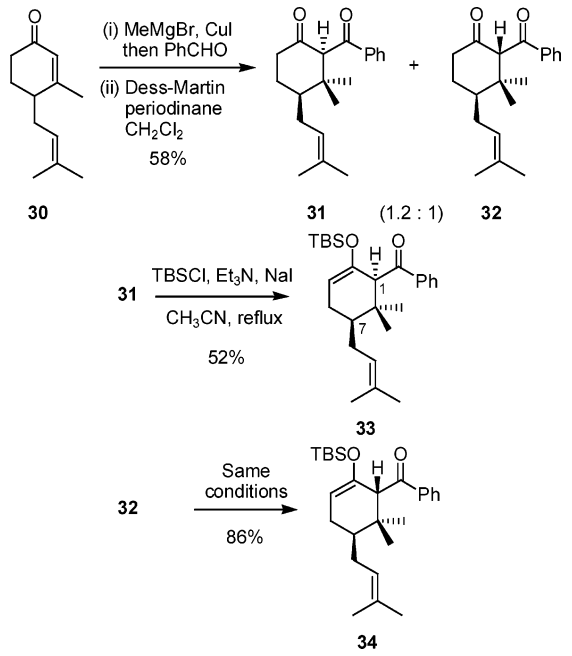
Although the key cyclization reaction was (predictably) low yielding, this short sequence provided viable quantities of the cyclized products, and the recovered ketones **14**/**15** could easily be recycled through conversion to **16**/**17** to provide more of the cyclized product. We then established that *either* regioisomeric ether **22** or **23** could be converted into the natural product clusianone, as shown in Scheme 7.

The total synthesis was first accomplished starting from isomer **23**, which, on treatment with excess LDA, followed by alkylation with prenyl bromide, gave **26** in an excellent 91% yield. For this transformation, the use of 2 equiv of base proved optimal, although no evidence could be found for dianion formation (e.g., by quenching with deuterium sources). When applied to isomer **22**, the same conditions gave the desired product **28**, although in a lower 67% yield. It therefore appears that the orientation of the vinylogous ester is of little significance in this particular metalation−substitution process, which is perhaps controlled mainly by the ketone in the one-carbon bridge.

Acylation at C-3 was accomplished by the action of LTMP followed by quenching the intermediate vinyllithium with benzoyl chloride. The process was equally efficient for both regioisomers **26** and **28**, providing the fully substituted derivatives **27** and **29**, respectively. Finally, hydrolysis of the vinylogous ester **27**, under conditions akin to those described previously,[12] gave (±)-clusianone in 90% yield. Hydrolysis of regioisomer **29** proved much more difficult, and under the same conditions (LiOH, dioxane, 90 °C), no deprotection occurred

(18) Magnus, P.; Mugrage, B. *J. Am. Chem. Soc.* **1990**, *112*, 462−464.
(19) Derivative **18** was prepared in the same way as for TBS enol ether **14**; see the Supporting Information for details.
(20) Kappe, T. *Monatsch. Chem.* **1967**, *98*, 883−895.
(21) During the preparation of this manuscript, another synthesis of clusianone appeared, using a similar approach, where improved yields of bridged adduct were obtained from the Effenberger cyclization by use of BF_3·OEt_2 as Lewis acid mediator; see: Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287−289.

SCHEME 8. Synthesis of Enol Silanes 33 and 34

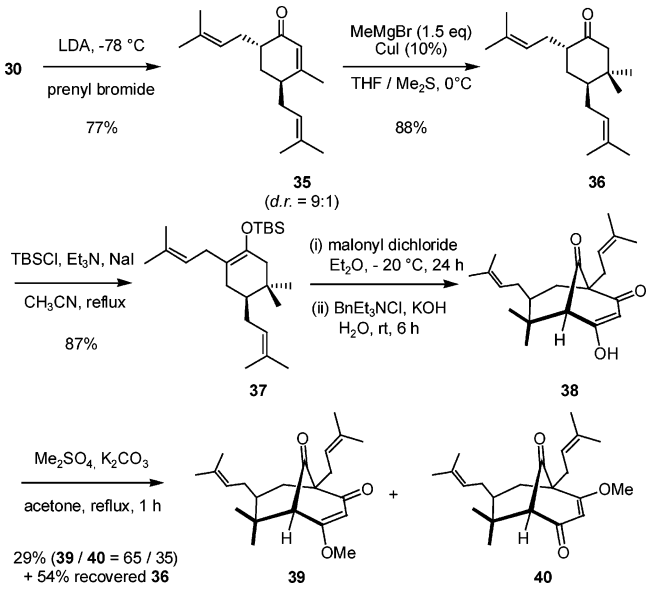


even after prolonged reaction times or at a higher temperature. In contrast, when submitted to Krapcho-type conditions (LiCl, DMSO, 120 °C),[22] **29** was readily deprotected to give **3** in 57% yield. Clusianone was thus obtained as a mixture of enol tautomers, with spectroscopic data identical to those reported for the natural product.[8a] Further evidence for the identity of our synthetic sample was obtained by comparison of the spectral data of intermediate **27** with those of a previously reported methylated derivative of clusianone.[23] Despite the low yields for the key cyclization, the synthesis of **3** was concisely achieved in only nine synthetic steps with a 12% overall yield.

2. Progress toward a Synthesis of Nemorosone. Encouraged by the brevity and overall efficiency of our route to clusianone, we then decided to further probe our strategy by applying it to the synthesis of the close isomer of clusianone, nemorosone (**4**). Adoption of *exactly* the same strategy as before—namely pre-installation of the eventual C-1 bridgehead substituent in the enol silane—would require an electronically very different cyclization partner for the Effenburger procedure. In this case, the benzoyl substituent required in the bridged product necessitates the use of an enol ether from a 1,3-diketone. Hoping that this dramatic change might influence the yields of the reaction favorably, we proceeded to prepare a suitably substituted enol silane bearing a benzoyl group at position C-1 (nemorosone numbering) (Scheme 8).

Conjugate methyl addition to the known enone **30**,[12] followed by quenching of the intermediate enolate with benzaldehyde, afforded a mixture of aldol products which, following Dess–Martin periodinane oxidation, gave the easily separated isomeric *β*-diketones **31** and **32**. To our initial surprise, reaction of each diketone **31** and **32** with TBSCl under thermodynamic conditions led to the formation of a nonconjugated enol silane derivatives **33** and **34**, respectively. This is presumably a result of the steric interaction between the benzoyl substituent and

SCHEME 9. Preparation of Bicyclo[3.3.1]nonane Derivatives 39 and 40



the neighboring *gem*-dimethyl groups in the diketones **31** and **32**. This would be expected to result in noncoplanar carbonyl functions, thereby reducing the acidity of the methine proton at the normally "doubly activated" position (labeled C-1), which is also in a very hindered position.

Upon attempted reaction with malonyl dichloride under our previously determined conditions, these derivatives failed to give any cyclized product. Following this fruitless diversion, we decided to return to the use of enol silane precursors in which one bridgehead prenyl group was "pre-installed", with the intention of introducing the bridgehead benzoyl substituent at C-1 late on. Following this strategy, we next prepared the bis-prenylated cyclohexanone **36** (Scheme 9).

The revised sequence started with the prenylation of enone **30**, followed by copper catalyzed methyl conjugate addition to give **36** (9:1 trans/cis),[24] which was then straightforwardly converted into enol silane **37**. As observed before, the cyclization produced a moderate yield of the trione **38**, together with some recovered ketone **36**. Crude trione **38** was directly protected as a mixture of regioisomers **39** and **40**, with an overall 29% yield starting from enol silane **37**, the regio and stereochemistry of the major isomer **39** being confirmed by X-ray crystallography (see the Supporting Information).

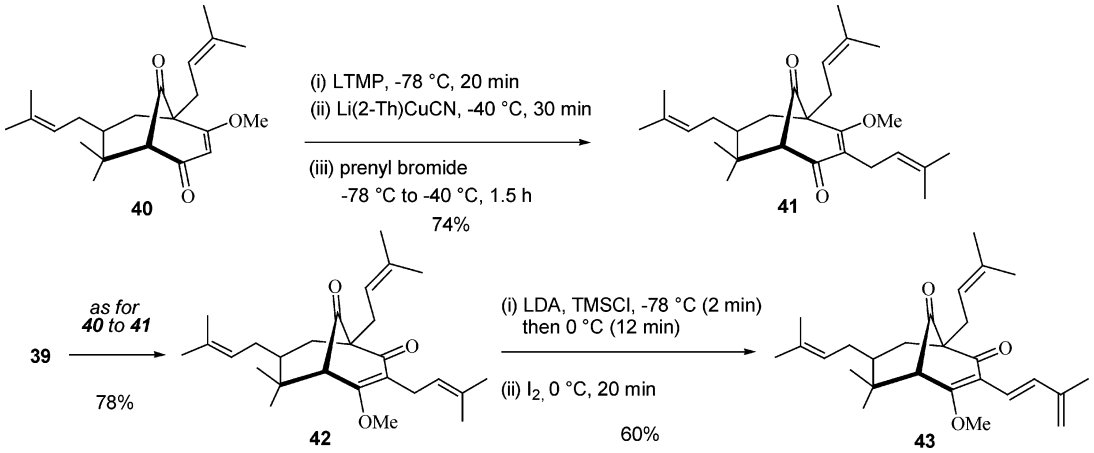
With both regioisomers in hand, the next task was the installation of the required prenyl substituent at the C-3 vinylic position. This proved much more sluggish than the acylation carried out previously in the case of clusianone synthesis. After deprotonation of **39** or **40** using LTMP, no substantial reaction with an excess of prenyl or allyl bromide occurred at −78 °C, only starting material being recovered. While changing the base to LDA or warming the reaction mixture to 0 °C did not improve the outcome, we were pleased to find that the use of a mixed higher order cuprate nicely solved this issue. Thus, after deprotonation with LTMP, the resulting vinyllithium species was transmetalated at −40 °C using freshly prepared Lipschutz's

(22) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

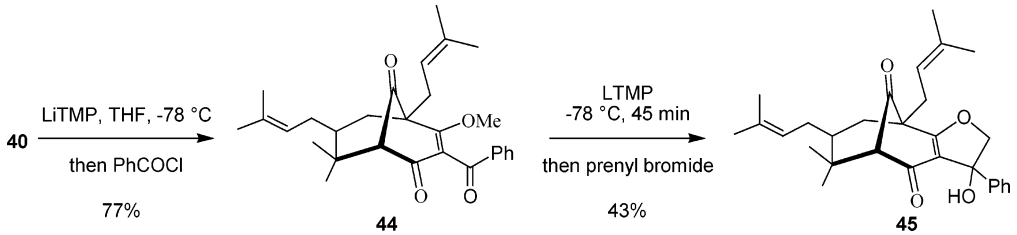
(23) De Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427–6430.

(24) The trans stereochemistry of derivative **35**, and thus of **36**, was tentatively assigned as a result of the favored axial approach of prenyl bromide toward the transient enolate species derived from **30**.

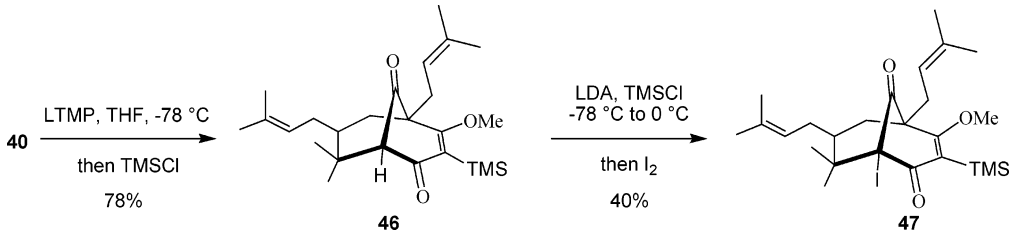
SCHEME 10. Copper-Mediated Vinylic Alkylation and Attempted Bridgehead Substitution



SCHEME 11. Formation of Ether 45



SCHEME 12. Synthesis of Iodo Derivative 47



higher order cyanocuprate.[25] The resulting mixed cyanocuprate then reacted smoothly with prenyl bromide, and thus, derivatives **41** and **42** were obtained in good yields (Scheme 10). Having obtained these two polyprenylated derivatives, all that was needed to achieve the synthesis of **4** was to introduce a benzoyl group at bridgehead position C-1 and to hydrolyze the vinylogous ester.

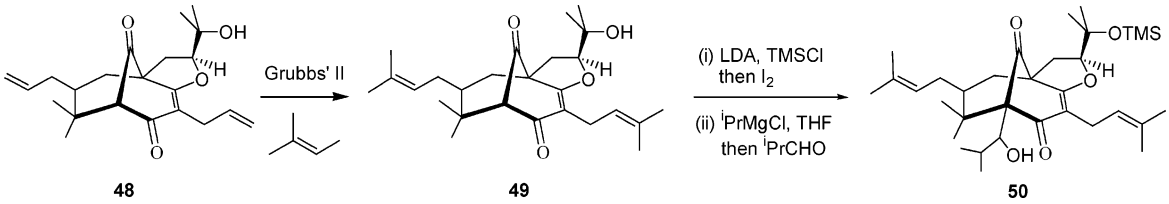
Disappointingly, our initial misgivings concerning the viability of bridgehead substitution proximal to the *gem*-dimethyl groups were now shown to have good foundation, and all our attempts to substitute at C-1 of **41** or **42** using LDA or LTMP in conjunction with various electrophiles failed. This result was frustrating, taking into account the contemporaneous report of Siegel and Danishefsky of bridgehead iodination at this position on a similar (but more complex) substrate, albeit in low yield, during a synthesis of garsubellin A (vide infra). Their sequence used initial iodination using LDA and TMSCl, followed by an iodine−magnesium exchange and electrophilic quenching (vide infra). The metalation conditions appeared substantially different to our standard procedures, and required use of excess LDA with TMSCl as the in situ quench, initially for 2 min at −78 °C and then 12 min at ice bath temperature, prior to iodine quenching. When applied to our substrate **42**, these conditions failed and bridgehead substitution did not occur. Instead, the C-3 prenyl residue underwent a formal dehydrogenation to give conjugated diene **43** in 60% yield (Scheme 10). A similar observation was made using regioisomeric dione **41** as the starting material, but the transformation was much lower-yielding and the product difficult to separate from other by-products.

We decided to explore substitution at the troublesome C-1 position in more detail and prepared derivative **44** from **40** using LTMP and benzoyl chloride, where the seemingly sensitive prenyl residue at C-3 was replaced by a benzoyl moiety. In this case, bridgehead prenylation would have provided us with an alternative route to clusianone. Quite surprisingly, upon treatment with LTMP at low temperature, no sign of bridgehead substitution was observed, but instead ether **45**, arising via deprotonation of the methyl ether, was isolated in 43% yield (Scheme 11).

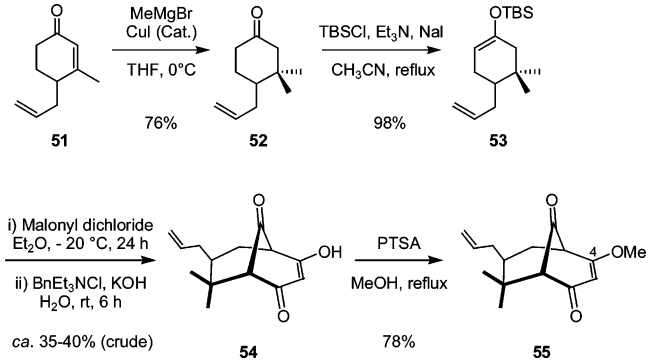
Eventually, we found that using the C-3 trimethylsilyl derivative **46** in conjunction with Danishefsky's conditions allowed isolation of bridgehead iodide **47** in 40% yield (Scheme 12).[10] This result is significant in providing an additional example of metalation at the sterically congested C-1 position (vide infra), but the modest yields in this step and the earlier cyclization make the approach unattractive.

(25) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945−948.

SCHEME 13. Danishefsky's Final Steps toward Garsubellin A



SCHEME 14. Synthesis of Bicyclo[3.3.1]nonane Derivative 55



It appears that bridgehead substitution at C-1 is much less facile than that at C-5 and that metalation at other positions on this type of substrate can often compete successfully. Although the preparation of iodide **47** provides some encouragement that a synthesis of nemorosone might be possible by this route, we instead turned our attention to the synthesis of the more elaborate PPAP derivative, garsubellin A.

3. Formal Synthesis of Garsubellin A. It was during the course of our studies that the aforementioned Siegel and Danishefsky synthesis of garsubellin A appeared, which featured a bridgehead metalation for the installation of the C-1 ^{i}PrCO acyl group. During the final steps of their sequence, they were able to convert the allyl groups in intermediate **48** into the required prenyl groups of **49**, using Grubbs' second-generation metathesis catalyst. This was followed by the bridgehead iodination, iodine−magnesium exchange, and electrophilic quenching with isobutyraldehyde to give **50**. Subsequent oxidation and deprotection of the tertiary alcohol then led to garsubellin A (Scheme 13).

We thought that the use of the Effenburger cyclization would give us rapid access to the advanced tricyclic intermediate **48** and thus could provide an alternative route to garsubellin A. The synthesis would also provide further examples of selective bridgehead substitution, as well as providing new chemistry for the additional THF-type of ring present in this natural product.

We commenced our synthesis with the known enone **51**,[26] which was converted into ketone **52** by the copper-catalyzed Michael addition of MeMgBr (Scheme 14). Cyclohexanone **52** was easily converted into the corresponding enol silane **53** (the structure shown was the major component in a ca. 5:1 regioisomeric mixture), which was then subjected to our modified Effenburger cyclization protocol. This process furnished the desired bicyclic system **54** in a modest but usable 35−40% yield, and the crude product was immediately converted to the more stable ether **55** with complete regioselectivity for the formation of enol at C-4 by heating to reflux in acidic MeOH.

The incorporation of an allyl substituent at C-7 rather than a prenyl appendage, in this series of compounds was dictated by our anticipation of bridgehead prenylation at C-5 of **55**, followed by side chain epoxidation. The higher reactivity of a trisubstituted alkene over a terminal one in reactions with peracids andrelated oxidants was expected to secure the desired regioselectivity in this latter step. The synthesis proceeded, as shown in Scheme 15, culminating in the synthesis of the Danishefsky intermediate **48**.

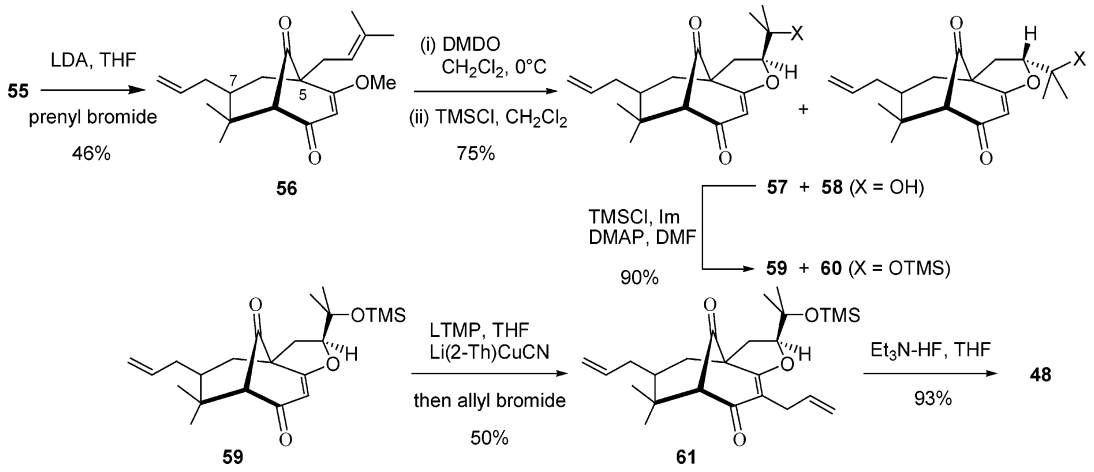
Bridgehead prenylation of **55** proved more problematic than in our clusianone work, and gave the desired compound **56** in only 46% yield. Since up to 91% yield had been obtained in the analogous prenylation of the methyl ether **23**, we were initially tempted to assign the difficulties to the presence in **55** of *two* free bridgehead positions and a free C-3 position. However, bearing in mind the extreme difficulties experienced in C-1 substitution in other systems, and the sluggish prenylation seen at C-3 in the absence of copper, we considered competing substitution at these positions unlikely. Indeed, we were unable to isolate products from reaction at either the C-1 bridgehead position or the C-3 vinylic position. Both regio- and stereochemistry of derivative **56** were secured by X-ray crystallography (see the Supporting Information).

Stereocontrol in the oxidation of the bridgehead prenyl group, required for the formation of the THF ring of **1**, has not been fully addressed. For example, Shibasaki's dihydroxylation approach was totally non-diastereoselective. We chose to focus on a (probably) biomimetic side-chain epoxidation−epoxide opening strategy but found a similar lack of diastereoselectivity. Epoxidation of **56** using *m*-CPBA did not give clean conversions, and the use of DMDO gave a rather unstable mixture of diastereomeric epoxides. Eventually, we found that combining DMDO epoxidation with a novel THF-forming cyclization mediated by TMSCl enabled the efficient formation of isomers **57** and **58** as a 1:1 mixture. Trimethylsilyl chloride was found to be much more effective than the corresponding iodide for this cyclization, which we assume proceeds via silicon-mediated activation of the epoxide. Surprisingly, however, we have not been able to directly isolate the silicon-protected alcohol derivatives from this reaction, but these compounds (**59** and **60**) could be prepared by silylation under standard conditions. At this stage, the stereochemical assignment of these two isomers was tentative, based on comparison of our NMR data with that in the literature, the assignment being demonstrated as correct by subsequent transformations.

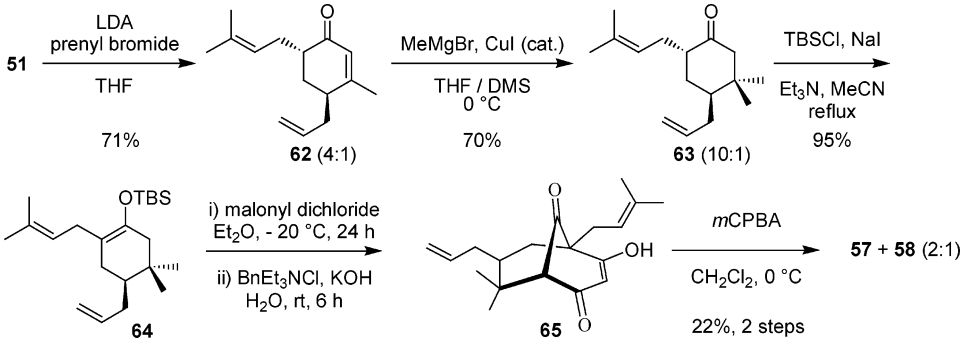
The correct side chain isomer **59** was then subjected to C-3 lithiation and allylation with recourse to the mixed higher order cuprate as described previously. Using this protocol we were able to access the Danishefsky intermediate in protected form (**61**), and subsequent treatment with Et_3N−HF then

(26) Johnson, W. S.; McCarry, B. E.; Markezich, R. L.; Boots, S. G. *J. Am. Chem. Soc.* **1980**, *102*, 352−359.

SCHEME 15. Alternative Access to Intermediate 48



SCHEME 16. Modified Approach to THF Installation



provided **48** identical in all respects with that reported previously (Scheme 15).

The route described is quite a step-efficient approach to intermediate **48**; however, the poor yields in some of the key steps and the lack of stereoselectivity in the side-chain oxidation detract significantly. In an attempt to address these issues, we briefly examined a variant of the above route in which the C-5 prenyl group was installed *prior* to the Effenburger cyclization (Scheme 16).

Enol silane **64** was prepared in a similar way to the bis-prenylated analogue **37**. Prenylation of enone **51** afforded **62** and was followed by copper-catalyzed Grignard addition to give ketone **63** (as a mixture of trans and cis isomers), which was then efficiently converted into the more substituted enol silane **64** in 95% yield. Then, cyclization using malonyl dichloride provided ∼30% of crude **65** (together with 58% ofrecovered ketone **63**). The synthesis of **65** provided an opportunity to re-assess side chain oxidation using a compound with an unprotected 1,3-diketone, and rather than purifying the cyclized product at this stage (which resulted in mass losses), we found it more efficient to react it directly with *m*-CPBA. Pleasingly, this epoxidation proved effective and led directly to the previously synthesized alcohols but now with a diastereomeric ratio favoring the desired isomer **57**.

This revised approach has the advantage of avoiding the modest yielding bridgehead prenylation step as well as the formation of a vinylogous ester (cf. **55**), and the selectivity in the epoxidation is also improved. Balanced against this is the drop in yield for the Effenburger cyclization. Nevertheless, the overall process is quite step-efficient, allowing the rapid formation of relatively elaborate tricyclic structures (**57**/**58**) from a simple, readily available enol silane precursor.

Conclusion

The present study serves to further delineate the potential for an Effenburger-type of cyclization in the synthesis of PPAP natural products and their analogues while highlighting the shortcomings of the currently available protocols. By teaming this powerful transformation with regioselective lithiation processes, we have been able to achieve the synthesis of clusianone (**3**) in nine steps, and Danishefsky's intermediate **48** for garsubellin A (**1**) has been obtained in a 10-step sequence for our shortest route, although with modest yields. We have also shown that the THF ring of garsubellin A can be obtained through a biomimetic epoxidation−cyclization sequence, with modest selectivity. Our strategy holds the promise of flexibility in the installation of different substituents at C-1, C-3, and C-5, which is an important feature for probing the intriguing biological activities of these systems. A limitation is the difficulty in introducing substituents at the sterically congested C-1 bridgehead position, which at the moment prevents easy access to nemorosone. Work within our group is ongoing to supersede the existing method with a more efficient variant. In addition, we are accessing nonracemic PPAPs by employing kinetic resolution in the bridgehead lithiation by use of chiral base reagents, and we are currently probing the SAR for this series of PPAPs by screening our final products and intermediates for their biological activities.

Experimental Section

(±)-(4*S*,6*S*)-1-*tert*-Butyldimethylsilyloxy-5,5-dimethyl-4,6-bis-(prenyl)cyclohex-1-ene (18). A solution of ^{n}BuLi (1.42 mL, 1.6 M in hexanes, 2.27 mmol, 1.2 equiv) was added dropwise to a solution of $^{i}Pr_2NH$ (345 μL, 2.46 mmol, 1.3 equiv) in THF (3 mL) at 0 °C. After 15 min, the LDA solution was cooled to −78 °C, and a solution of ketone **14** (495 mg, 1.89 mmol) in THF (3 mL) was transferred via cannula. The resulting mixture was stirred 30 min at −78 °C, and then TBSOTf (651 μL, 2.84 mmol, 1.5 equiv) was added. The resulting mixture was allowed to warm slowly to 0 °C and then quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted using petroleum ether. The combined organic phases were dried over $MgSO_4$ and concentrated to a colorless oil, which was purified by column chromatography (eluent petroleum ether/Et_2O/Et_3N 98/1/1) to give pure **18** (582 mg, 82%): R_f = 0.75 (petroleum ether/Et_2O 95/5); colorless oil; FTIR ($CHCl_3$) 2950, 1664, 1385 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.25 (m, 1H), 5.09 (m, 1H), 4.75 (m, 1H), 2.24−2.14 (m, 3H), 2.04 (dtd, *J* = 17.0, 5.0, 2.5, 1H), 1.91 (m, 1H), 1.79−1.61 (m, 2H), 1.69 (s, 3H), 1.65 (s, 3H), 1.60 (s, 6H), 1.23 (m, 1H), 0.98 (s, 3H), 0.90 (s, 9H), 0.73 (s, 3H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.3, 131.6, 128.5, 127.5, 124.4, 102.0, 51.1, 44.9, 36.8, 28.2, 27.1, 26.9, 26.0, 25.9, 25.8, 25.7, 18.3, 17.9, 17.8, 16.2, −4.2, −4.3; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{45}OSi$ 377.3234, found 377.3229 $[M + H]^+$.

(±)-(4*S*,6*S*)-(1-Triisopropylsilyloxy-5,5-dimethyl-4,6-bis(prenyl)cyclohex-1-ene (24). A solution of ^{n}BuLi (937 μL, 1.6 M in hexanes, 1.5 mmol, 1.5 equiv) was added dropwise to a solution of $^{i}Pr_2NH$ (210 μL, 1.5 mmol, 1.5 equiv) in THF (5 mL) at 0 °C. After 15 min, the LDA solution was cooled to −78 °C, and a solution of ketone **14** (266 mg, 1.01 mmol) in THF (3 mL) was transferred via cannula. The resulting mixture was stirred for 15 min at −78 °C, and then TIPSOTf (463 μL, 1.70 mmol, 1.7 equiv) was added. The resulting mixture was allowed to warm to 0 °C and then quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous phase was extracted using petroleum ether. The combined organic phases were dried over $MgSO_4$ and concentrated to a colorless oil, which was purified by column chromatography (eluent petroleum ether/Et_3N 99/1) to give pure **24** (360 mg, 85%): R_f = 0.54 (petroleum ether); colorless oil; FTIR ($CHCl_3$) 2866, 1665, 1461, 1384, 1366, 883 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.30 (br t, *J* = 6.5, 1H), 5.10 (br t, *J* = 7.0, 1H), 4.69 (m, 1H), 2.38 (t, *J* = 6.0, 2H), 2.18 (br d, *J* = 14.0, 1H), 2.03 (dtd, *J* = 17.0, 5.5, 2.0, 1H), 1.98 (m, 1H), 1.74 (m, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.64 (m, 1H), 1.61 (s, 3H), 1.60 (s, 3H), 1.24 (m, 1H), 1.18 (m, 3H), 1.09 (m, 18H), 0.99 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 152.3, 131.5, 128.3, 127.8, 124.5, 100.3, 51.1, 44.9, 36.8, 28.3, 27.1, 27.0, 26.0, 25.9, 25.7, 18.2, 18.1, 17.9, 17.8, 16.1, 13.1; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{50}OSi$ 419.3709, found 419.3690 $[M + H]^+$.

(±)-(1*S*,5*R*,7*S*)-2-Methoxy-8,8-dimethyl-1,7-bis(prenyl)bicyclo[3.3.1]non-2-ene-4,9-dione (22) and (±)-(1*S*,5*R*,7*S*)-4-Methoxy-8,8-dimethyl-1,7-bis(prenyl)bicyclo[3.3.1]non-3-ene-2,9-dione (23). To a solution of enol ethers **16** and **17** (470 mg, 1.70 mmol) in Et_2O (1.5 mL) at −20 °C (dry ice/CCl_4 bath) was added dropwise malonyl dichloride (165 μL, 1.70 mmol, 1 equiv). The reaction mixture was stirred at −20 °C for 24 h, and then benzyltriethylammonium chloride (19 mg, 85 μmol, 0.05 equiv) was added, followed by a solution of KOH (381 mg, 6.8 mmol, 4 equiv) in H_2O (1.5 mL). The reaction mixture was allowed to reach rt and stirred for 5 h. After dilution with water (25 mL) and petroleum ether (25 mL), the pH was adjusted to ∼10 using 2 N NaOH. The phases were separated, and the aqueous phase was extracted using petroleum ether (2 × 25 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was evaporated. The residue obtained was purified by column chromatography (eluent petroleum ether/AcOEt 95/5) to provide ketones **14** and **15** as an 85/15 mixture (260 mg, 58%). The aqueous layer was cooled to 0 °C, carefully acidified to pH ∼1 using 2 M HCl, and then extracted using DCM (4 × 25 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo to provide crude **21** as an orange foam (190 mg): ^{1}H NMR (400 MHz, $CDCl_3$) 5.96 (s, 1H), 4.98 (m, 1H), 4.71 (m, 1H), 3.23 (m, 1H), 2.53 (m, 2H), 2.10 (m, 2H), 1.77−1.52 (m, 4H), 1.65 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.55 (s, 3H), 1.10 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 208.2, 192.5, 184.7, 133.8, 133.3, 122.5, 119.8, 109.3, 68.1, 56.2, 45.8, 41.1, 32.9, 28.2, 25.9, 25.8, 23.8, 23.2, 18.1, 17.9, 16.0; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{31}O_3$ 331.2268, found 331.2252, $[M + H]^+$. Crude **21** obtained above was dissolved in acetone (15 mL), K_2CO_3 (320 mg, 4 equiv) and Me_2SO_4 (73 μL, 1.2 equiv) were added, and the resulting suspension was heated under reflux for 2 h under N_2. The mixture was cooled to rt, the solid was removed by filtration, and the solvent was removed in vacuo. The residue was purified by column chromatography (eluent petroleum ether/CH_2Cl_2/AcOEt 70/28/2, then 50/40/10) to give pure **23** (73 mg) and then pure **22** (71 mg) in 25% combined yield over two steps. **22**: R_f = 0.27 (petroleum ether/AcOEt 4/1); white amorphous solid; FTIR ($CHCl_3$) 2930, 1730, 1650, 1590, 1347 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.82 (s, 1H), 4.96 (m, 1H), 4.73 (m, 1H), 3.72 (s, 3H), 3.22 (dd, *J* = 4.5, 2.5, 1H), 2.58 (br dd, *J* = 14.0, 5.0, 1H), 2.51 (dd, *J* = 14.0, 8.0, 1H), 2.13 (ddd, *J* = 13.5, 4.0, 3.0, 1H), 2.08 (m, 1H), 1.75−1.56 (m, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H), 1.08 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 207.4, 195.2, 177.6, 133.5, 133.3, 122.5, 119.7, 107.7, 64.4, 61.7, 56.3, 45.2, 41.3, 34.2, 28.6, 25.9, 25.8, 23.9, 23.8, 18.0, 17.9, 16.1; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{32}O_3Na$ 367.2244, found 367.2245. **23**: R_f = 0.31 (petroleum ether/AcOEt 4/1); colorless oil; FTIR ($CHCl_3$) 2930, 1728, 1644, 1612, 1377 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.73 (s, 1H), 4.95 (m, 1H), 4.66 (m, 1H), 3.75 (s, 3H), 3.18 (br s, 1H), 2.59 (dd, *J* = 14.0, 6.5, 1H), 2.41 (dd, *J* = 14.0, 5.8, 1H), 2.12 (m, 1H), 2.02 (m, 1H), 1.75−1.65 (m, 3H), 1.67 (2 s, 6H), 1.58 (s, 3H), 1.55 (s, 3H), 1.08 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 208.3, 196.7, 174.4, 133.5, 133.1, 122.6, 120.1, 106.6, 70.8, 56.7, 53.2, 46.3, 41.0, 32.7, 27.9, 25.9, 25.8, 24.1, 22.6, 18.1, 17.9, 16.0; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{33}O_3$ 345.2435, found 345.2422 $[M + H]^+$.

Isomerization of 22 To Give 23. Ester **22** (150 mg, 435 μmol) was dissolved in MeOH (5 mL), trimethyl orthoformate (1 mL) and PTSA (10 mg) were added, and the resulting solution was heated at 50 °C for 48 h under N_2. The mixture was cooled to room temperature, Et_3N (2 drops) was added, and the mixture was concentrated in vacuo. The residue was purified by column chromatography (eluent petroleum ether/AcOEt 9/1 then 4/1) to give pure **23** (97 mg, 65%).

(±)-(1*S*,5*R*,7*S*)-2-Methoxy-8,8-dimethyl-1,5,7-tris(prenyl)-bicyclo[3.3.1]non-2-ene-4,9-dione (28). At −78 °C, prenyl bromide (176 μL, 1.53 mmol, 5 equiv) was added to a solution of **22** (105 mg, 305 μmol) in THF (12 mL), followed by a solution of LDA (1.53 mL, 0.5 M, 2.5 equiv, prepared by adding a solution of ^{n}BuLi (625 μL, 1 mmol, 1.6 M in hexanes) to a 0 °C solution of $^{i}Pr_2NH$ (140 μL, 1 mmol) in THF (1.23 mL). The resulting solution was stirred for 15 min at −78 °C and then quenched with saturated aqueous NH_4Cl and allowed to reach rt. The layers were separated, and the aqueous phase was extracted using Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated to an oil, which was purified by column chromatography (eluent petroleum ether/AcOEt 95/5 to 9/1) to give pure **28** (85 mg, 67%): R_f = 0.21 (petroleum ether/AcOEt 9/1); colorless oil; FTIR ($CHCl_3$) 2982, 1725, 1644, 1596, 1376, 1271 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 5.81 (s, 1H), 4.98 (m, 2H), 4.72 (m, 1H), 3.69 (s, 3H), 2.60 (br d, *J* = 14.0, 1H), 2.50 (dd, *J* = 14.0, 8.0, 1H), 2.43 (m, 2H), 2.06 (dm, *J* = 13.5, 1H), 1.88 (dd, *J* = 13.5, 4.5, 1H), 1.70 (m, 1H), 1.66 (s, 12H), 1.66 (m, 1H), 1.64 (s, 3H), 1.53 (s, 3H), 1.32 (t, *J* = 13.5, 1H), 1.04 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 208.1, 196.8, 176.3, 133.3, 133.1, 133.0, 122.7, 120.2, 120.1, 107.9, 64.2, 63.9, 56.0, 45.0, 41.7, 41.0, 29.7, 28.7, 26.0,

25.9, 25.8, 24.2, 23.9, 18.0, 17.9, 17.8, 16.0; HRMS (ESI) *m/z* calcd for $C_{27}H_{41}O_3$ 413.3061, found 413.3044 $[M + H]^+$.

(±)-(1*S*,5*R*,7*S*)-3-Benzoyl-2-methoxy-8,8-dimethyl-1,5,7-tris(prenyl)bicyclo[3.3.1]non-2-ene-4,9-dione (29). A LTMP solution (0.5 M, 824 μL, 412 μmol, 2 equiv), prepared from ^{n}BuLi (312 μL, 1.6 M in hexanes, 0.5 mmol) and 2,2,6,6-tetramethylpiperidine (85 μL, 0.5 mmol) in THF (600 μL) at 0 °C, was added to a −78 °C solution of **28** (85 mg, 206 μmol) in THF (4 mL). The solution was stirred for 35 min, and then benzoyl chloride (71.5 μL, 618 μmol, 3 equiv) was added and the resulting solution stirred for 30 min at −78 °C. The mixture was quenched using saturated aqueous NH_4Cl and allowed to reach rt. The layers were separated, and the aqueous phase was extracted using Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated to an oil, which was purified by column chromatography (eluent petroleum ether/AcOEt 95/5 to 9/1) to give **29** (95 mg, 89%): R_f = 0.44 (petroleum ether/AcOEt 9/1); white solid; mp = 91−95 °C; FTIR ($CHCl_3$) 2914, 1726, 1675, 1645, 1587, 1376, 1318 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.81 (d, *J* = 7.5, 2H), 7.54 (t, *J* = 7.5, 1H), 7.42 (t, *J* = 7.5, 2H), 5.04 (m, 2H), 4.92 (m, 1H), 3.59 (s, 3H), 2.70 (br d, *J* = 13.5, 1H), 2.57 (dd, *J* = 13.5, 8.8, 1H), 2.42 (d, *J* = 7.2, 2H), 2.14 (br d, *J* = 12.5, 1H), 1.99 (m, 2H), 1.72 (m, 1H), 1.67 (s, 9H), 1.63 (s, 3H), 1.55 (s, 6H), 1.38 (t, *J* = 14.0, 1H), 1.16 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 207.6, 196.3, 195.5, 173.4, 137.9, 134.1, 133.5, 133.4, 133.3, 129.2, 128.7, 123.3, 122.5, 120.5, 119.9, 65.7, 64.1, 60.5, 46.1, 41.8, 41.4, 29.5, 28.7, 26.0, 25.9, 25.8, 25.1, 24.1, 18.1, 18.0, 17.9, 16.3; HRMS (ESI) *m/z* calcd for $C_{34}H_{45}O_4$ 517.3323, found 517.3314 $[M + H]^+$.

(±)-Clusianone from Derivative 29. To a solution of **29** (18 mg, 9.3 μmol) in DMSO (1 mL) was added LiCl (3 mg, 70 μmol, 8 equiv), and the resulting solution was stirred at 120 °C for 2 h. The mixture was cooled at rt, diluted with H_2O (3 mL), and extracted using Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (eluent petroleum ether/AcOEt 4/1) afforded (±)-clusianone as white solid (10 mg, 57%). Data were identical to those previously reported, and a detailed comparison of our NMR data with those previously reported can be found in the Supporting Information associated with our earlier communication.[15]

4-Allyl-3,3-dimethylcyclohexanone (52). Methylmagnesium bromide (17.1 mL, 3 M in Et_2O, 1.3 equiv) was slowly cannulated into a solution of enone **51** (5.93 g, 0.039 mol) and copper iodide (0.376 g, 1.95 mmol, 0.05 equiv) in THF/DMS (100/10 mL) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 15 min and then poured into a mixture of saturated aqueous NH_4Cl/NH_4OH (1/1, 50 mL) and Et_2O (80 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a dark yellow oil. Purification by column chromatography (petroleum ether/EtOAc 97/3 to 95/5) gave the title compound **52** as a pale yellow oil (4.88 g, 74%): R_f = 0.81 (petroleum ether/EtOAc 4/1); FTIR ($CHCl_3$) 3678, 3599, 2926, 1713, 1605, 1075, 1006, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.85−5.76 (m, 1H), 5.08−5.03 (m, 2H), 2.46−2.40 (m, 1H), 2.37−2.23 (m, 3H), 2.11 (dd, *J* = 13.5, 2.2, 1H), 2.09−2.04 (m, 1H), 1.79−1.71 (m, 1H), 1.61 (tt, *J* = 11.0, 3.1, 1H), 1.54−1.44 (m, 1H), 1.07 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 212.0, 137.8, 116.2, 55.8, 44.9, 40.7, 38.5, 34.0, 29.8, 27.4, 20.8; HRMS (ESI) *m/z* calcd for $C_{11}H_{19}O$ 167.1436, found 167.1430 $[M + H]^+$.

1-*tert*-Butyldimethylsilyloxy-4-allyl-5,5-dimethylcyclohex-1-ene (53). Sodium iodide (4.3 g, 0.028 mol, 2 equiv), *tert*-butyldimethylsilyl chloride (4.3 g, 0.028 mol, 2 equiv), and freshly distilled triethylamine (8.0 mL, 0.057 mol, 4.0 equiv) were added to a solution of cyclohexanone **52** (2.37 g, 0.014 mol) in CH_3CN (30 mL). The reaction mixture was heated under reflux for 4.5 h and then cooled to rt and concentrated to give a brown solid. After trituration of the solid with petroleum ether and concentration in vacuo, a pale yellow oil was obtained which was purified by column chromatography (1% Et_3N in petroleum ether) to give **53** as a 5:1 inseparable mixture of regioisomers (colorless oil, 4.13 g, 98%): FTIR ($CHCl_3$) 2927, 2856, 1713, 1639, 1471, 1369, 1189, 1006, 939, 819, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 5.81−5.70 (m, 1H), 5.02−4.94 (m, 3H), 4.79−4.76 (m, 1H), 2.34−2.26 (m, 1H), 2.15−2.07 (m, 1H), 1.93−1.86 (m, 1H), 1.75−1.65 (m, 3H), 1.32−1.25 (m, 1H), 0.96 (s, 3H), 0.91 (s, 9H), 0.85 (s, 3H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 149.2, 138.6, 115.2, 102.5, 44.5, 41.9, 34.0, 33.0, 28.8, 26.7, 24.0, 23.8, 22.0, −2.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{33}OSi$ 281.2301, found 281.2306 $[M + H]^+$.

(±)-(1*S*,5*R*,7*S*)-7-Allyl-4-methoxy-8,8-dimethylbicyclo[3.3.1]non-3-ene-2,9-dione (55) via 54. Malonyl dichloride (0.70 mL, 14.2 mmol, 2 equiv) was added to a solution of the enol ether **53** (2.00 g, 7.11 mmol) in Et_2O (4 mL) at −20 °C (dry ice/CCl_4 bath). The reaction mixture was stirred at −20 °C for 24 h, and then a solution of $BnEt_3NCl$ (81 mg, 0.35 mmol, 0.05 equiv) and KOH (3.19 g, 57.9 mmol, 8 equiv) in H_2O (6 mL) was added dropwise. The reaction mixture was allowed to reach rt over 6 h. After dilution with H_2O (25 mL) and petroleum ether (25 mL), the pH was adjusted to ∼12 using 1 M KOH. The phases were separated, and the aqueous phase was extracted using petroleum ether (2 × 25 mL). The combined organic phases were dried over $MgSO_4$ and then concentrated in vacuo. Purification by column chromatography gave ketone **52** as a clear yellow oil (567 mg, 48%). The aqueous layer was then acidified to pH ∼1 using 2 M HCl and extracted using CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give **54** as a light yellow foam (705 mg), used without purification in the next step: FTIR ($CHCl_3$) 3205, 2873, 1738, 1613, 1586, 1538, 1137, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 5.87 (s, 1H), 5.71−5.61 (m, 1H), 5.05−4.80 (m, 2H), 3.16−3.14 (m, 1H), 2.83−2.81 (m, 1H), 2.35−2.28 (m, 1H), 2.20−2.13 (m, 1H), 1.88−1.78 (m, 1H), 1.76−1.60 (m, 2H), 1.15 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 206.2, 190.2, 186.3, 136.4, 117.0, 107.7, 68.9, 57.3, 42.0, 38.1, 33.8, 32.4, 27.1, 20.5; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}O_3$ 235.1329, found 235.1329 $[M + H]^+$. The crude bicyclic product **54** (1.20 g) was dissolved in CH_3OH (20 mL), *p*-TsOH (97 mg, 10 mol %) was added, and the solution then heated under reflux for 10 h. The mixture was allowed to cool and concentrated in vacuo. Purification by column chromatography (petroleum ether/EtOAc 8/2) afforded **55** (996 mg, 29% from enol ether **53**) as a yellow solid: mp 129−131 °C; R_f = 0.24 (petroleum ether/AcOEt 4/1); FTIR ($CHCl_3$) 3678, 2928, 1736, 1650, 1603, 1373, 1348, 1223, 1185, 1001, 919, 858 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 5.69 (s, 1H), 5.70−5.61 (m, 1H), 5.03−4.99 (m, 2H), 3.77 (s, 3H), 3.20−3.16 (m, 1H), 2.79−2.78 (m, 1H), 2.34−2.30 (m, 1H), 0.88 (s, 3H), 1.12 (s, 3H), 1.78−1.62 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 205.9, 193.9, 175.8, 136.6, 116.8, 105.3, 73.9, 56.9, 53.1, 42.6, 38.5, 33.5, 31.9, 26.8, 20.5; HRMS (ESI) *m/z* calcd for $C_{15}H_{21}O_3$ 249.1491, found 249.1485 $[M + H]^+$.

(±)-(1*S*,5*R*,7*S*)-7-Allyl-4-methoxy-8,8-dimethyl-5-prenylbicyclo[3.3.1]non-3-ene-2,9-dione (56). A solution of LDA·LiCl was prepared by treatment of a suspension of DIPA·HCl (472 mg, 3.42 mmol, 5 equiv) in THF (5 mL) at −78 °C with ^{n}BuLi (1.6 M solution in hexanes; 4.3 mL, 6.85 mmol). The solution was allowed to warm to rt and after 10 min recooled to −78 °C. This LDA·LiCl solution was added dropwise via syringe to a solution of bicycle **55** (170 mg, 0.68 mmol) in THF (1 mL) at −78 °C, resulting in a deep yellow solution. The solution was stirred at −78 °C for 35 min and then quenched with prenyl bromide (0.79 mL, 10 equiv) and stirred for a further 2.5 h at −78 °C. The reaction mixture was quenched after this period with H_2O (5 mL) followed by extraction with EtOAc (3 × 5 mL). The organic layers were combined and washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (petroleum ether/AcOEt 4/1) gave the title compound **56** as a yellow solid (115 mg, 0.36 mmol, 53%): mp 90−92 °C; R_f = 0.53 (petroleum ether/AcOEt 4/1); FTIR ($CHCl_3$) 2932, 2857, 1731, 1650, 1592, 1454, 1395, 1371, 1112, 1057, 983, 980, 916, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.73 (s, 1H), 5.70−5.61

(m, 1H), 5.04−4.94 (m, 3H), 3.75 (s, 3H), 2.85−2.84 (m, 1H), 2.47 (dd, J = 14.4, 7.7, 1H), 2.37 (dd, J = 14.4, 7.7, 1H), 2.32−2.24 (m, 1H), 1.96 (dd, J = 13.9, 4.4, 1H), 1.81−1.73 (m, 1H), 1.73−1.67 (m, 1H), 1.64 (s, 3H), 1.63 (s, 3H), 1.38 (t, J = 12.5, 1H), 1.10 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 206.0, 193.6, 177.7, 136.8, 133.8, 119.2, 116.6, 106.1, 74.6, 57.0, 56.8, 42.7, 39.7, 39.1, 33.6, 29.6, 26.5, 25.9, 20.6, 17.9; HRMS (ESI) m/z calcd for $C_{20}H_{29}O_3$ 317.2117, found 317.2111 $[M + H]^+$.

(±)-(1*S*,3*S*,8*S*,10*S*)-10-Allyl-3-(1-hydroxy-1-methylethyl)-9,9-dimethyl-4-oxatricyclo[6.3.1.0^{1,5}]dodec-5-ene-7,12-dione (57) and (±)-(1*S*,3*R*,8*S*,10*S*)-10-Allyl-3-(1-hydroxy-1-methylethyl)-9,9-dimethyl-4-oxatricyclo[6.3.1.0^{1,5}]dodec-5-ene-7,12-dione (58). A solution of dimethyldioxirane (9.5 mL, ∼0.05 M in acetone, 1.5 equiv) was added to substrate **56** (100 mg, 0.31 mmol) in CH_2Cl_2 (4 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 2.5 h. $MgSO_4$ was then added to the solution which was filtered and then concentrated in vacuo. The crude yellow solid was redissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C, and then trimethylsilyl chloride (0.08 mL, 0.61 mmol, 2 equiv) was added and the reaction further stirred for 2.5 h. The reaction was quenched with $NaHCO_3$ (8 mL), and the organic layer was separated and washed with saturated NaCl (8 mL), extracted with CH_2Cl_2 (2 × 10 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (petroleum ether/AcOEt 85/15) gave first **58** as a clear, colorless oil (37 mg, 38%) and second **57** also as a clear, colorless oil (37 mg, 38%). Data for **58**: R_f = 0.63 (petroleum ether/AcOEt 1/1); FTIR ($CHCl_3$) 3600, 2922, 2856, 1731, 1649, 1625, 1373, 1199, 1120, 1045, 1008, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.80 (s, 1H), 5.72−5.63 (m, 1H), 5.04−4.99 (m, 2H), 4.34 (dd, J = 10.4, 4.8, 1H), 2.98 (dd, J = 13.4, 10.4, 1H), 2.85−2.82 (s, 1H), 2.51 (dd, J = 14.1, 4.6, 1H), 2.34−2.29 (m, 1H), 1.89−1.67 (m, 3H), 1.46 (dd, J = 14.1, 12.5, 1H), 1.42 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 203.8, 194.2, 179.0, 136.6, 116.8, 105.6, 91.9, 72.8, 70.9, 59.5, 41.9, 40.1, 40.0, 33.3, 27.4, 27.3, 26.6, 25.6, 20.3; HRMS (ESI) m/z calcd for $C_{19}H_{27}O_4$ 319.1909, found 319.1904 $[M + H]^+$. Data for **57**: R_f = 0.49 (petroleum ether/AcOEt 1/1); FTIR ($CHCl_3$) 3589, 2922, 1734, 1708, 1650, 1627, 1518, 1362, 1176, 920, 849 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.77 (s, 1H), 5.72−5.63 (m, 1H), 5.70−5.00 (m, 2H), 4.58 (dd, J = 11.0, 5.5), 2.83 (s, 1H), 2.63 (dd, J = 13.0, 11.0), 2.39−2.33 (m, 1H), 2.13 (dd, J = 13.7, 4.6, 1H), 1.91 (br s, 1H), 1.89−1.82 (m, 1H), 1.78−1.68 (m, 2H), 1.52 (t, J = 13.7, 1H), 1.35 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 0.9 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 203.9, 194.3, 178.8, 136.5, 117.1, 104.4, 90.9, 73.1, 70.8, 59.8, 42.5, 39.2, 37.5, 33.4, 29.3, 26.6, 26.6, 24.1, 20.5; HRMS (ESI) m/z calcd for $C_{19}H_{27}O_4$ 319.1909, found 319.1897 $[M + H]^+$.

(±)-(1*S*,3*S*,8*S*,10*S*)-10-Allyl-9,9-dimethyl-3-(1-methyl-1-trimethylsilanyloxyethyl)-4-oxatricyclo[6.3.1.0^{1,5}]dodec-5-ene-7,12-dione (59) and (±)-(1*S*,3*R*,8*S*,10*S*)-10-Allyl-9,9-dimethyl-3-(1-methyl-1-trimethylsilanyloxyethyl)-4-oxatricyclo[6.3.1.0^{1,5}]dodec-5-ene-7,12-dione (60). Imidazole (160 mg, 2.35 mmol, 5 equiv), DMAP (6 mg, 10 mol %), and trimethylsilyl chloride (0.30 mL, 2.35 mmol, 5 equiv) were added to the tricyclic compounds **57** and **58** (150 mg, 1:2 diastereoisomeric mixture, 470 μmol) in DMF (5 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C after which time the reaction was complete by TLC. Purification by column chromatography (10% EtOAc in petroleum ether) afforded first the title compound **59** as a cream-colored oil (113 mg, 62%) and then the title compound **60** as as a clear oil (52 mg, 28%). Data for **59**: R_f = 0.33 (petroleum ether/EtOAc 95/5); FTIR ($CHCl_3$) 2920, 1731, 1642, 1620, 1048, 859 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.75 (s, 1H), 5.73−5.63 (m, 1H), 5.07−5.01 (m, 2H), 4.47 (dd, J = 10.3, 5.7, 1H), 2.83 (s, 1H), 2.66 (dd, J = 13.0, 10.4, 1H), 2.39−2.33 (m, 1H), 2.10 (dd, J 13.8, 4.6, 1H), 1.92−1.84 (m, 1H), 1.76−1.68 (m, 2H), 1.51 (dd, J = 13.6, 12.5, 1H), 1.31 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H), 0.90 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.1, 194.4, 179.4, 136.6, 116.9, 104.0, 91.5, 73.6, 73.2, 59.7, 42.3, 39.3, 38.0, 33.5, 29.1, 26.6, 26.6, 25.7, 20.5, 2.3; HRMS (IC) m/z calcd for $C_{22}H_{35}O_4Si$ 391.2305, found 391.2312 $[M + H]^+$. Data for **60**: R_f = 0.30 (petroleum ether/EtOAc 95/5); FTIR ($CHCl_3$) 2922, 1732, 1643, 1635, 1373, 1199, 1046, 1008, 844 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.79 (s, 1H), 5.75−5.64 (m, 1H), 5.07−4.97 (m, 2H), 4.18 (dd, J = 10.2, 5.6, 1H), 2.94 (dd, J = 13.2, 10.2, 1H), 2.82 (s, 1H), 2.31 (dd, J = 13.8, 4.8, 1H), 2.36−2.29 (m, 1H), 1.91−1.71 (m, 3H), 1.48 (dd, J = 13.7, 12.2, 1H), 1.40 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H), 0.88 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.0, 194.3, 179.3, 136.8, 116.8, 105.0, 93.2, 73.5, 72.8, 59.7, 41.9, 40.7, 40.3, 33.4, 27.2, 27.0, 26.7, 26.4, 20.4, 2.3; HRMS (CI) m/z calcd for $C_{22}H_{35}O_4Si$ 391.2305, found 391.2299 $[M + H]^+$.

(±)-(1*S*,3*S*,8*S*,10*S*)-6,10-Diallyl-9,9-dimethyl-3-(1-methyl-1-trimethylsilanyloxyethyl)-4-oxatricyclo[6.3.1.0^{1,5}]dodec-5-ene-7,-12-dione (61). A solution of LTMP was prepared by adding ^{n}BuLi (0.208 mL, 1.6 M in hexanes, 0.33 mol, 2 equiv) to a solution of tetramethylpiperidine (0.056 mL, 0.33 mmol, 2 equiv) in THF (0.6 mL) at −78 °C. The solution was stirred at 0 °C for 15 min then recooled to −78 °C. The LTMP solution was then added to the tricyclic compound **59** (65 mg, 0.167 mmol) in THF (0.6 mL) at −78 °C and stirred at that temperature for 20 min. After this period, freshly prepared Li(2-Th)CuCN solution (1.3 mL, 0.25 M, 2 equiv) was added to the reaction mixture, which was then stirred at −40 °C for 30 min. The reaction mixture was recooled to −78 °C, and allyl bromide (0.07 mL, 0.83 mmol, 5 equiv) was added dropwise. The solution was allowed to warm from −78 to 0 °C over 4 h. The reaction mixture was quenched by pouring it into a mixture of saturated aqueous NH_4Cl/NH_4OH (1:1, 3 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to a viscous oil which was purified by column chromatography (petroleum ether/EtOAc 9/1) to give the title compound **61** as an opaque colorless oil (36 mg, 0.084 mmol, 50%): R_f = 0.55 (petroleum ether/EtOAc 95/5); FTIR ($CHCl_3$) 2925, 1732, 1623, 1371, 1176, 1050, 844 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.81 (s, 1H), 5.66 (s, 1H), 5.06−5.00 (m, 3H), 4.96−4.92 (m, 1H), 4.20 (dd, J = 10.3, 5.8, 1H), 3.12−3.01 (m, 2H), 2.87 (s, 1H), 2.65 (dd, J = 13.0, 10.3, 1H), 2.37−2.29 (m, 1H), 2.10 (dd, J = 13.7, 4.5, 1H), 1.82−1.68 (m, 3H), 1.48 (dd, J = 13.7, 12.1, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H), 0.89 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.0, 193.0, 175.0, 136.7, 135.4, 116.9, 114.9, 114.1, 90.9, 73.9, 73.2, 59.7, 42.3, 39.4, 38.1, 33.5, 29.6, 27.2, 26.7, 26.4, 25.7, 20.5, 2.3; HRMS (ESI) m/z calcd for $C_{25}H_{39}O_4Si$ 431.2617, found 431.2624 $[M + H]^+$.

(±)-(1*S*,3*S*,8*S*,10*S*)-6,10-Diallyl-3-(1-hydroxy-1-methylethyl)-9,9-dimethyl-4-oxatricyclo[6.3.1.0^{1,5}]dodec-5-ene-7,12-dione (48). Triethylamine trihydrofluoride (0.68 mL, 4.18 mmol, 20 equiv) was added to diallyl **61** (9 mg, 0.21 mmol) in THF (1.5 mL) at rt and the resulting solution stirred for 2 h. Concentration in vacuo followed by column chromatography (petroleum ether/EtOAc 4/1 to 7/3) afforded the title compound as a clear, colorless oil (7 mg, 93%): R_f = 0.84 (petroleum ether); FTIR ($CHCl_3$) 2934, 1735, 1629, 1365, 992, 887 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.84−5.63 (m, 2H), 5.09−4.95 (m, 4H), 4.57 (dd, J = 10.8, 5.7, 1H), 3.15 (ddt, J = 14.8, 5.7, 1.7, 1H), 3.05 (dd, J = 14.8, 7.0, 1H), 2.90 (s, 1H), 2.67 (dd, J = 12.7, 10.8, 1H), 2.38−2.33 (m, 1H), 2.03 (dd, J = 13.7, 4.4, 1H), 1.79−1.68 (m, 3H), 1.48 (dd, J 13.7, 12.2, 1H), 1.35 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 203.7, 192.9, 174.5, 136.6, 135.6, 117.0, 114.8, 114.3, 90.3, 73.2, 70.9, 59.9, 42.4, 39.5, 37.7, 33.4, 29.6, 27.1, 26.8, 26.7, 23.9, 20.5; HRMS (ESI) m/z calcd for $C_{22}H_{31}O_4$ 359.2222, found 359.2216 $[M + H]^+$.

(±)-(4*S*,6*S*)-4-Allyl-3-methyl-6-prenylcyclohex-2-enone (62). A solution of LDA was prepared by adding ^{n}BuLi (28.7 mL, 2.5 M in hexanes, 0.046 mol, 1.1 equiv) to a solution of ^{i}Pr$_2$NH (6.42 mL, 0.046 mol, 1.1 equiv) in THF (150 mL) at −78 °C. The solution was stirred at 0 °C for 15 min and then recooled to

−78 °C. A solution of enone **51** (6.22 g, 0.041 mol) in THF (25 mL) was then slowly cannulated into the freshly prepared LDA solution. The resulting solution was stirred at −78 °C for 15 min, 0 °C for 30 min, and then recooled to −78 °C. Prenyl bromide (6.16 mL, 0.053 mol, 1.3 equiv) was added dropwise, and the solution was allowed to warm to rt over 3 h. The reaction mixture was quenched with saturated NH_4Cl, the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over $MgSO_4$ and then concentrated in vacuo to a dark yellow oil. Purification by column chromatography (petroleum/AcOEt 9/1) gave **62** as a mixture of diastereoisomers (4:1, pale yellow oil, 6.4 g, 71%): R_f = 0.59 (petroleum ether/EtOAc 4/1); FTIR ($CHCl_3$) 2860, 1666, 1378, 1107, 1052, 996, 922, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 5.90−5.66 (m, 2H), 5.14−5.03 (m, 3H), 2.55−2.45 (m, 1H), 2.43−2.39 (m, 2H), 2.25−2.16 (m, 2H), 2.10−1.96 (m, 2H), 1.95 (s, 3H), 1.79−1.71 (m, 1H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 201.0, 200.9, 163.9, 162.8, 136.3, 135.1, 133.3, 133.2, 128.1, 126.6, 121.9, 121.7, 117.5, 117.1, 46.6, 41.6, 39.8, 38.9, 36.8, 35.6, 33.4, 31.2, 28.0, 27.5, 25.8, 25.8, 22.9, 21.9, 18.1, 18.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}O$ 219.1749, found 219.1748 $[M + H]^+$.

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Supporting Information Available: Full experimental data for compounds **31**−**47** and **62**−**65**. X-ray crystallographic data (ORTEP and CIF) for compounds and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds except **65**. This material is available free of charge via the Internet at http://pubs.acs.org.

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