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Platinum-Catalyzed α,β-Unsaturated Carbene Formation in the Formal Syntheses of Frondosin B and Liphagal

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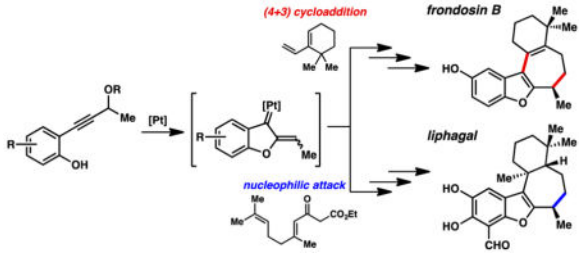
Abstract

Formal syntheses of tetracyclic terpenoids frondosin B and liphagal are described. Both synthetic routes rely on the use of platinum-catalyzed α,β-unsaturated carbene formation for the key C–C bond forming transformations. The successful route toward frondosin B utilizes a formal (4 + 3) cycloaddition, while the liphagal synthesis features the vinylogous addition of an enol nucleophile as a key step. Both synthetic routes are discussed, revealing insights into structural requirements in the catalytic α,β-unsaturated carbene reaction manifold.

Graphical Abstract



Frondosin B and liphagal are tetracyclic terpenoids that share a common carbon skeleton, and both possess promising and distinct bioactivity.[1] Frondosin B was reported to be an antagonist toward interleukin-8 receptors, which are involved in inflammatory disorders such as rheumatoid arthritis.[1a,2] Liphagal has been found to have human phosphatidylinositol-3-kinase (PI3K) α-selective inhibitory activity;[1b,3] compounds that modulate the PI3K signaling pathway may have therapeutic potential in the treatment of autoimmune disorders, cancer, and cardiovascular disease. Their interesting architectures

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03682.

Experimental procedures, compound characterization data and spectra (PDF)

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coupled with their potential to serve as leads in the search for therapeutics have inspired numerous groups to undertake total syntheses of both frondosin B[4] and liphagal.[1b,5]

We and others have been investigating the formation and application of transient α,β-unsaturated Pt carbenes generated via Pt catalysis.[6] These intermediates are capable of reacting in a variety of ways, including cycloadditions,[6a–d] 1,2-migrations,[6e–g] and interception by nucleophiles.[6h–j] As such they can construct a diverse spectrum of products, portending considerable utility in synthesis. It was therefore somewhat surprising that methods associated with the generation of α,β-unsaturated Pt carbenes had in fact not been used en route to a natural product at the outset of this work. Nonetheless, we anticipated that both frondosin B and liphagal could be prepared using this chemistry, ideally utilizing Pt catalysis to rapidly construct the B and C rings of these molecules (Figure 1). Specifically, we planned to employ a general strategy joining a carbene originating from precursor phenol **3** with diene **5**. The resulting tetracyclic products, when appropriately decorated, could then be transformed to frondosin B via alkene isomerization (**6** → **1**, R′ = H), while alkene reduction would complete the synthesis of liphagal (**6** → **2**, R′ = Me).

This strategy raised some pertinent questions. Mainly, how would the respective dienes react with the carbene intermediate? Dienes featuring enhanced nucleophilicity (largely silyl enol ethers) have been demonstrated to undergo net (4 + 3) cycloadditions.[6b,c,7] On the other hand, we had observed intramolecular ene-type reactivity with electron-rich alkene nucleophiles.[6h,8] We anticipated that we could potentially advance several possible adducts to the tetracyclic motif, but the uncertainty of which product(s) would form would undoubtedly impact our strategy. Other more subtle questions (e.g., steric characteristics of specific diene, electronic nature of phenol precursor) may also need to be examined.

We began our effort targeting the structurally simpler frondosin B, preparing the two components of the key cycloaddition reaction (Scheme 1). The phenol component (**3a**) was synthesized by a four-step sequence beginning with *p*-methoxyphenol (**7**). The phenol moiety was first converted to a methoxymethyl acetal. Ortho-iodination[9] followed by hydrolysis afforded iodophenol **9**. Sonogashira coupling[10] with benzyl ether **10**[11] produced the target alkyne for carbene generation (**3a**). A known two-step sequence converted 2,2-dimethylcyclohexanone (**11**) to the requisite diene.[12]

With phenol **3a** and diene **5a** in hand, we investigated the key carbene reaction (Scheme 2). To our delight, treating the two components with catalytic $[(C_2H_4)_2PtCl_2]_2$ (Zeise's dimer) in 1,4-dioxane at 100 °C led to observable formation of tetracycle **6aa**. From this result it was clear that electron-neutral diene **5a** was a competent cycloaddition partner and that the (4 + 3) process[6b,c] was the predominant pathway. Interestingly, a notable amount of structural isomer **12** was also produced; this compound presumably arises from a differential bond migration onto the Pt-carbene species after an initial (4 + 2) process.[13] Both of these compounds were formed as apparently single diastereomers, indicating these carbene-based cycloadditions can be highly stereoselective. The addition of ligand appeared to somewhat diminish the formation of the alternate product (**12**), and also improved the yield to a measurable degree. We evaluated different ligand systems and found that inclusion of Feringa's phosphor-amidite[14] provided the best results, with a 74% isolated yield of

chromatographically inseparable tetracycles **6aa** and **12**, in a 2.5:1 ratio.[15] These compounds could be separated after the acid-mediated isomerization[4i] to conjugated benzofurans **13** and **14**.[16] The syntheses of tetracycle **6aa**, and subsequently tetracycle **13**, represent a formal total synthesis of frondosin B; demethylation affords the natural product.[4a,b,g,i,k]

Having established the capacity of the (4 + 3) reaction to efficiently generate this tetracyclic skeleton in the formal synthesis of frondosin B, we turned our attention to the more highly substituted liphagal (Scheme 3). Here, we chose sesamol (**15**) as a starting point for the phenol component because its use would ultimately lead to late stage intermediates that should be viable precursors to the natural product. To this end, silyl protection of **15** followed by TFA-catalyzed iodination[17] gave aryl iodide **17**. Sonogashira coupling[10] with alkyne **10** followed by removal of the TBS group provided phenol **3b**. A known procedure allowed us to prepare diene **5b** in one step from β-cyclocitral (**19**).[18] Unfortunately, our attempts to perform the cycloaddition between phenol **3b** and diene **5b** failed to give detectable amounts of the desired product (**6bb**). The reason for this reaction failure was not immediately clear; both the diene and phenol components had been changed from the frondosin B cycloaddition.

To diagnose the origin of the failure of this cycloaddition, we systematically paired each of the components from the successful process with those of the unsuccessful one (Figure 2). Reacting the methyl-containing diene (**5b**) with less electron-rich phenol **3a** failed to give the predicted cycloadduct, instead forming compound **20**, the electrophilic substitution product via diene attack on the carbene. Evidently, in this case the presence of the methyl group was responsible for the inability to complete the cyclization event, but the exact role that it may play depends on the mechanistic nature of the cycloaddition itself. In the case that the cycloaddition prefers a concerted pathway, the methyl group would disfavor the reactive *s-cis* conformation of the diene necessary for the cycloaddition (Scheme 4). The inability of the diene to achieve this conformation would then force the reaction to follow an asynchronous pathway, a mechanism that may be favored regardless.[19] An allylic cation generated by nucleophilic attack of diene **5b** on carbene **4a** could be unable to undergo cyclization because of the steric congestion of the reacting centers. This cation would then simply undergo loss of a proton to generate diene **20**.

Curiously, pairing the simpler (and previously successful) diene **5a** with sesamol-derived phenol **3b** also failed to give a cycloaddition product, this time leading only to decomposition. This seems to indicate that the electron-rich nature of this phenol was also detrimental toward affording the desired reactivity. We hypothesized that electron density from the benzene ring could be delocalized into the Pt carbene, attenuating its electrophilicity (Figure 3).[20] The cycloaddition route to liphagal therefore appeared to suffer from problems arising from both components, but this realization did not necessarily imply that phenol **3b** would be unsuccessful in all manifolds of α,β-unsaturated Pt carbene chemistry.

Depending on to what extent delocalization reduces the electrophilicity of putative carbene intermediate **4b**, we thought it may still react with *stronger nucleophiles*. In fact, we recently reported that enols derived from β-dicarbonyl compounds are competent nucleophiles in this

chemistry.[6j] With the correct substitution pattern, a β-dicarbonyl compound may lead to nucleophilic addition products that could intercept the Andersen biomimetic approach[1b] downstream. Along those lines, our revised route to liphagal is illustrated in Figure 4. An acid catalyzed cyclization of an unconjugated diene similar to known cases[1b,5a,b] would give the tetracyclic core of the natural product. This intermediate (**23**) could be produced from ketoester **24** via decarboxylation and reduction. We would prepare ketoester **24** from alkyne **3b** and dicarbonyl compound **25** using our previously reported method.

Toward this end, we prepared the pronucleophile component (**25**) via the Roskamp reaction[21] from geranial (**26**, Scheme 5). We were pleased to find that this β-ketoester approach was significantly more effective than the previous attempts using a diene. We were able to produce alkylation adduct **24** in 76% yield using the more reactive enol nucleophile,[22] whereas, before, reactions with phenol partner **3b** had given only decomposition as discussed above. From this stage, a decarboxylation/reduction/acetylation sequence afforded acetate **28**. Mild allylic reduction[23] yielded a polyene that, after treatment with chlorosulfonic acid, gave tetracycle **22** in modest yield, with this species constituting a formal synthesis of liphagal.[5f]

In summary, we were pleased that our efforts not only culminated in the total syntheses of frondosin B and liphagal but also provided important insights into unsaturated Pt-carbene catalysis. The (4+3) cycloaddition chemistry was easily applicable to the synthesis of frondosin B, and our finding that phosphoramidite ligands improve the carbene-based cycloaddition suggests future opportunities in catalytic reaction design. The analogous cycloaddition was unsuccessful in the liphagal context, but gratifyingly the enol interception strategy we developed provided a fruitful solution. We anticipate that the studies herein may prove beneficial to the inclusion of these methods in future synthetic strategies toward complex molecules. Further studies of α,β-unsaturated Pt carbenes are ongoing, and their results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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7. Xue/Li and Winne also reported comparable (4 + 3) cycloaddition approaches in their syntheses of frondosin B and 5-*epi*-liphagal, utilizing a presumed benzofuranyl cationic species as their three-atom component. See refs 4i and 4j.
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15. (a) The intermediacy of a furanyl cation via benzofuran formation followed by ether ionization was ruled out as a mechanistic pathway. The benzofuranyl Bn ether from intramolecular hydroalkoxylation of **3a** was unreactive under the catalytic conditions. (b) Although the phosphoramidite ligand is chiral, enantioinduction in the cycloaddition was modest (<15% ee).
16. Benzofuran **13** was isolated as a 2.5:1 mixture of conjugated olefin isomers. These isomers can be purified after demethylation. See refs 4a, g, j.
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20. An alternative possibility is that the electron-rich arene is acting as a competing nucleophile, leading to complex oligomerization of phenol **3b**.
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22. In our experience, carbene interception will occur at lower temperature ranges (23–50 °C) for more reactive nucleophiles (e.g., enol ethers), while less reactive nucleophiles (e.g., electron-neutral dienes) tend to require more elevated temperatures (80–100 °C) for efficient reaction times.

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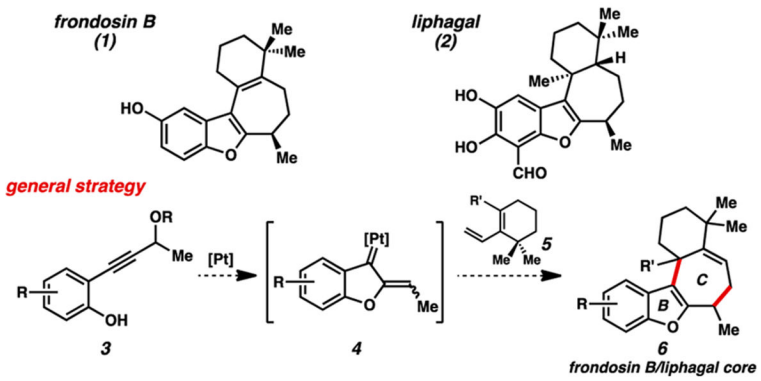


Figure 1.
Generalized Pt-carbene approach to frondosin B/liphagal molecular core.

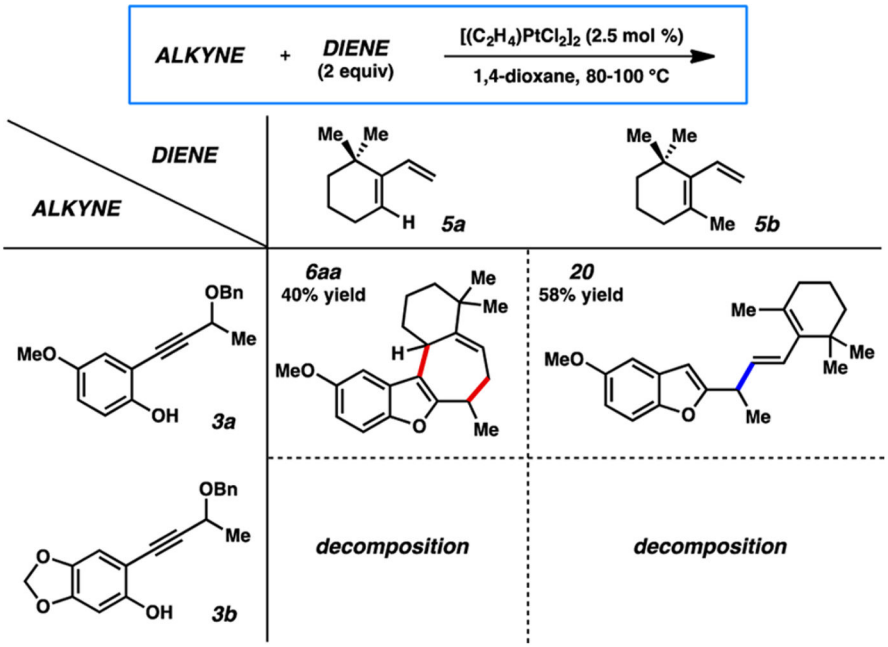


Figure 2.
Alkyne/diene reaction combinations in Pt carbene catalysis.

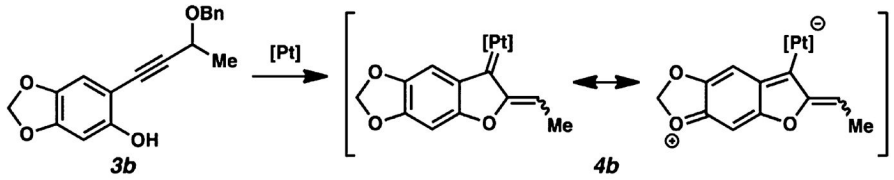


Figure 3.
Electronic rationale for poor reactivity of phenol **3b**.

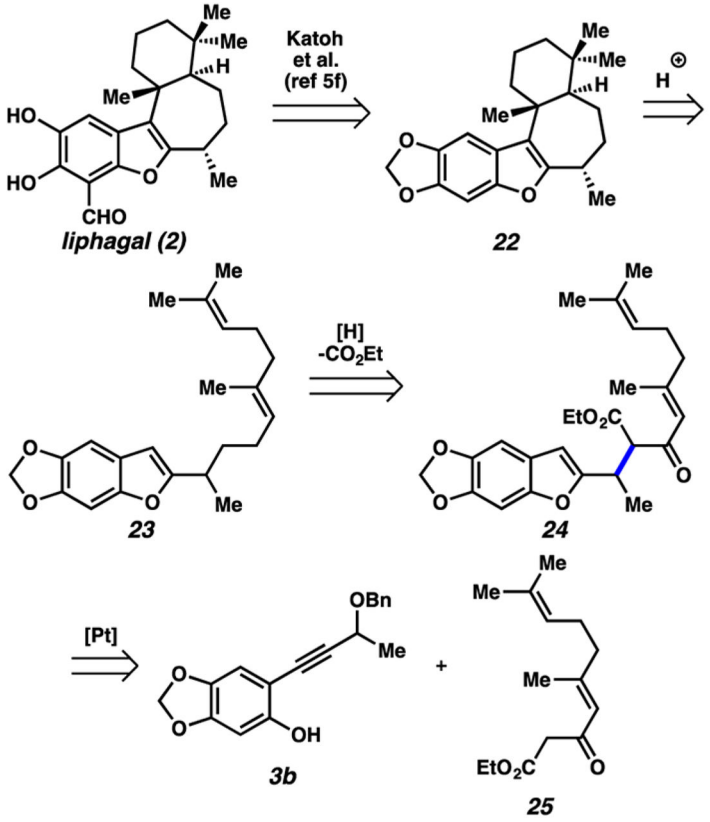
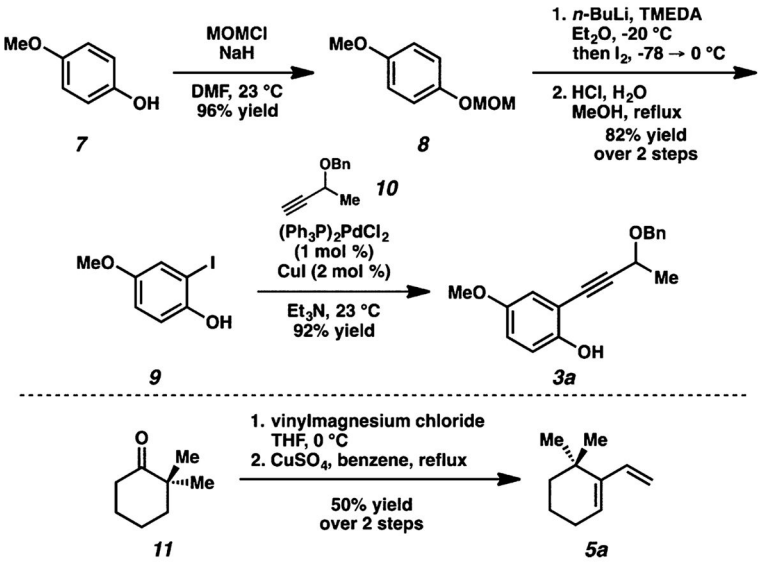
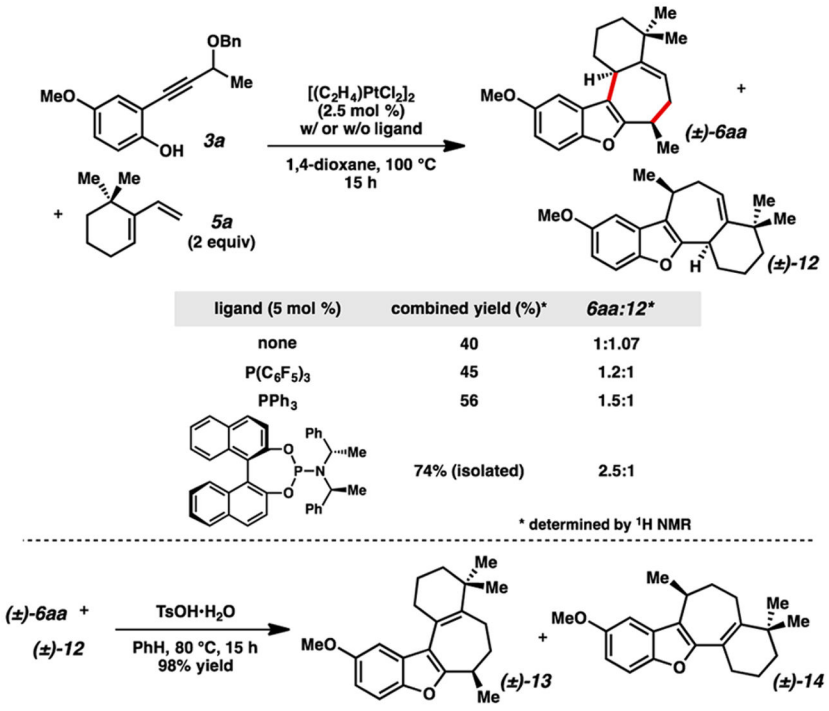


Figure 4.
Revised synthetic approach toward liphagal.



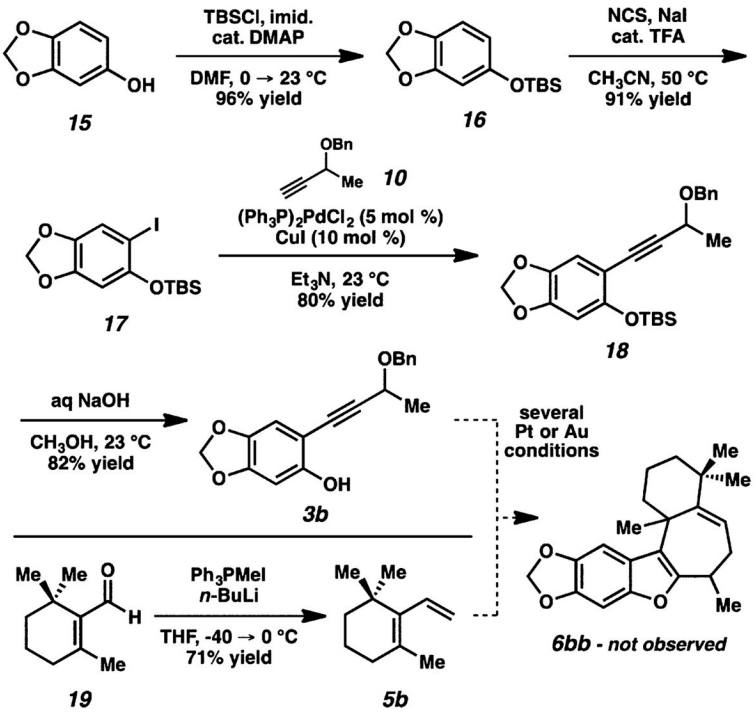
Scheme 1.

Frondosin B: Syntheses of Reactants Alkyne 3a and Diene 5a

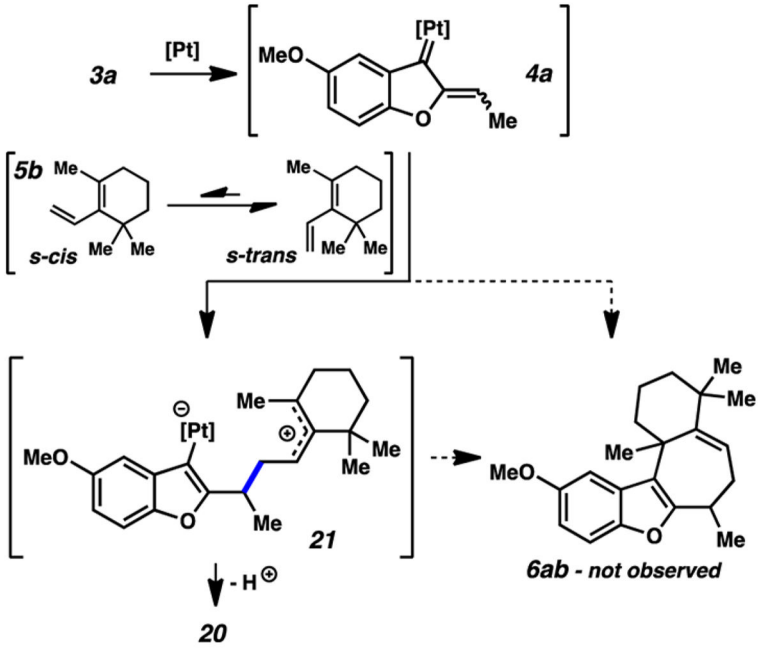


Scheme 2.

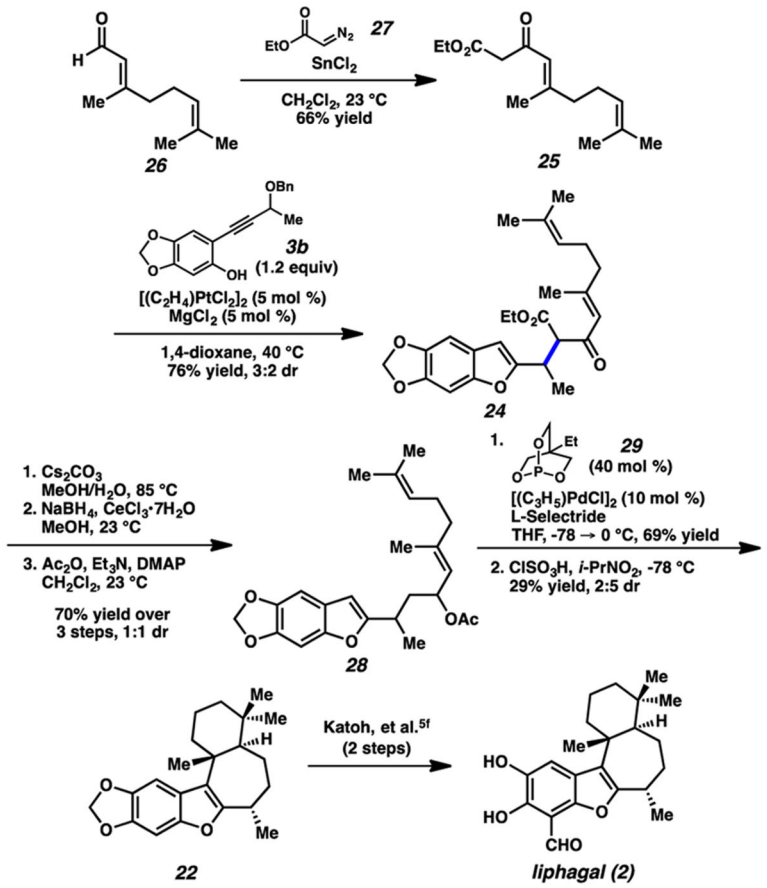
Pt-Catalyzed (4 + 3) Cycloaddition toward Frondosin B



Scheme 3.
Cycloaddition Approach to Liphagal



Scheme 4.
Failed Cycloaddition–Electrophilic Substitution on Diene 5b



Scheme 5.

Completed Formal Total Synthesis of Liphagal Using Pt-Carbene Formation in Combination with Stabilized Nucleophile