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A Novel, Facile Approach to Frondosin B and 5-*epi*-Liphagal *via* a New [4 + 3]-Cycloaddition

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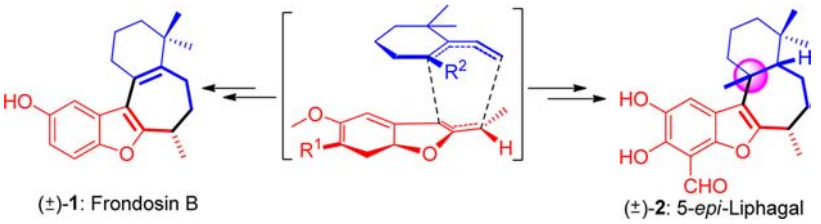
ABSTRACT



A new [4 + 3]-cycloaddition between benzofuran allylic alcohols and dienes, promoted by camphorsulfonic acid, has been identified. A novel strategy which used this cycloaddition as a key step has been developed for the synthesis of 6,7,5-tricyclic skeleta, and syntheses toward frondosin B (1) and 5-*epi*-liphagal (2) have been achieved *via* short routes in good yields.

One of the most fundamental goals of synthetic chemists is to develop efficient and elegant chemical processes that allow the rapid creation of diverse and complex multicyclic skeleta.[1] Among the most effective methods for creating such skeleta are cycloadditions such as [2 + 2]-, [3 + 2]-, [4 + 2]-, and [4 + 3]-additions.[2] In recent years, investigations into [4 + 3]-cycloaddition have yielded a convenient and conceptually straightforward method for preparing seven-membered rings. The potential of this type of cycloaddition as a synthetic method could approach that of the [4 + 2]-cycloaddition (Diels–Alder) reaction in terms of selectivity and efficiency. In recent years, numerous applications of [4 + 3]-cycloadditions catalyzed by Lewis acids and transition-metal complexes have been developed and applied in total synthesis.[3]

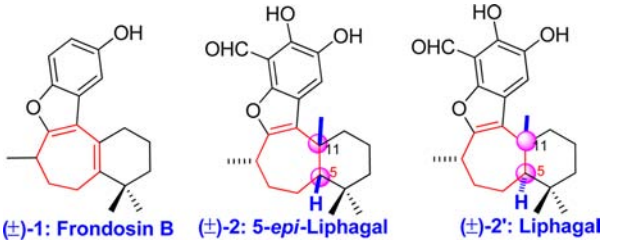


Figure 1. Frondosin B, liphagal, and 5-*epi*-liphagal.

Marine sponges are a rich source of natural products with very unusual molecular patterns and a wide variety of biological activities.[4] Liphagal and frondosin B (Figure 1) are marine sponge derived meroterpenoids that have special 5,7,6-tricyclic skeleta. Because of its activity,[5] frondosin B (**1**) has been used as an interleukin-8 (IL-8) receptor

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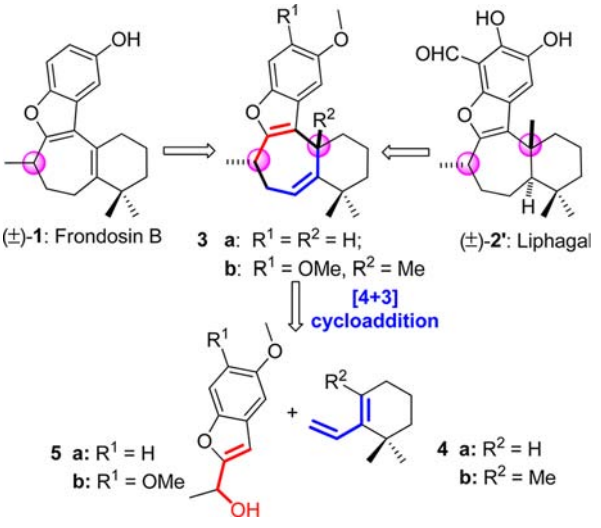
antagonist. Liphagal (**2′**) was isolated in 2006 by Andersen and co-workers from the Caribbean sponge *Aka coralliphagum* and was demonstrated to have inhibitory activity against PI3K,[6] with an IC50 of 100 nM.

The excellent biological activities of these compounds have inspired several research groups to develop complete syntheses of these compounds.[7] The first enantioselective total synthesis of frondosin B (**1**) was completed by Danishefsky and co-workers in 2001 using a classical Friedel–Crafts reaction.[8] Subsequently, Trauner and Hughes employed two palladium-catalyzed reactions to produce the key core.[9] In 2006, Andersen and co-workers reported the first biosynthesis of liphagal (**2′**).[10] Shortly thereafter, a biomimetic ring expansion was reported by Adlington and co-workers in the asymmetric synthesis of these targets.[11] Tandem pinacol rearrangement/benzyldeprotection/hemiketalization/dehydration was also used in the total synthesis of liphagal.[12] However, the most efficient synthesis of this type of target was achieved by MacMillan and co-workers in a synthesis of frondosin B that involved only three linear steps *via* Friedel–Crafts alkylation.[13]

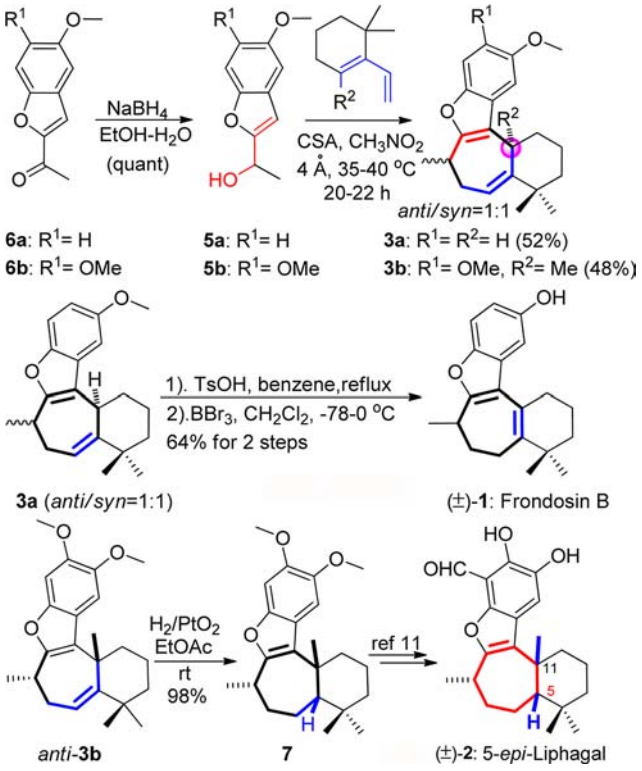
Scheme 1. Retrosynthesis of Frondosin B and Liphagal



Although challenging, it is important that we continue to develop efficient strategies for the synthesis of 6,7,5-tricyclic molecules that can be widely used. During our investigation into such cycloadditions,[14] an intermolecular [4 + 3]-cycloaddition[15] was found that serves as an efficient strategy for the construction of the 6,7,5-tricyclic skeleta. The application of this type of cycloaddition to the synthesis of such natural products was therefore investigated, and efficient syntheses of frondosin B and liphagal were developed and are described herein.

As shown in the retrosynthetic analysis in Scheme 1, liphagal and frondosin B were divided into two components: diene **4** and allylic alcohol **5** which would be united *via* a [4 + 3] strategy. The precursors **3a** and **3b** would be required for **1** and **2**, respectively, and these would be the corresponding products of the [4 + 3]-cycloaddition of **4** and **5** and be capable of being converted into the targets by normal transformations.

Scheme 2. Synthesis of (±)-Frondosin B and (±)-5-*epi*-Liphagal



The synthesis began from easily prepared allylic alcohol **5** and diene **4**.[16] [4 + 3]-Cycloaddition requires

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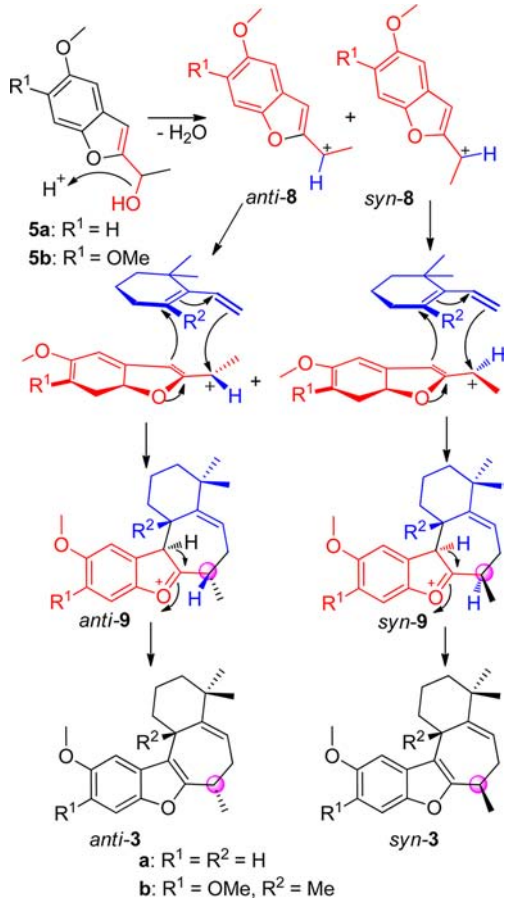
(16) Commercially available 2,2-dimethylcyclohexanone and β-cyclocitral were converted to the dienes **4a** and **4b** following standard procedures. The requisite benzofuranones **6a** and **6b** were easily prepared according to Danishefsky's procedure, (ref 8) and $NaBH_4$ reduction quantitatively generated benzofuranol **5a** and **5b**.

Scheme 3. [4 + 3]-Cycloaddition Process



cation-generating conditions, and a number of such conditions (TFA, TFAA/lutidine, $SnCl_4$, $TiCl_4$, BBr_3 at −78 °C and $PdCl_2$, $ZnCl_2$ at rt) were screened. Unfortunately, all of these conditions failed to produce the seven-membered ring and mostly yielded diene homopolymers. Stronger protic acids were therefore investigated. CSA (camphorsulfonic acid) promoted the desired transformation, giving intermediate **3** in moderate yield. The polarity of the solvent has an obvious influence on the stability of carbocations and, therefore, could also affect the cycloaddition. In this study, no reaction was observed in solvents with weak polarity, such as toluene, and only trace amounts of the cycloaddition products were found in dichloromethane. Nitromethane, a polar solvent, was found to be the best reaction medium. Furthermore, this transformation was sensitive to temperature. The reaction was very slow at 0 °C, and high temperatures accelerated the self-polymerization of dienes. After a thorough investigation, the following conditions were determined to be the most efficient: allylic alcohol and diene were reacted in the presence of CSA in nitromethane at 35−40 °C for 20−22 h. Under these conditions, **4a** reacted with **5a** to yield **3a** as a pair of diastereoisomers in a 1:1 ratio with a 52% yield, and the reaction of **4b** and **5b** yielded **3b** as a pair of diastereoisomers in a 1:1 ratio with a 48% yield (Scheme 2).

During this process, the allylic alcohol is first protonated and then dehydrated to form an allylic carbocation in which the p−π conjugation produces two configurations of the carbocation, *syn*-**8** and *anti*-**8** (Scheme 3). These carbocations are then captured by the diene, with the two configurations yielding a pair of diastereoisomers, *anti*-**9** and *syn*-**9**. The subsequent elimination generates intermediates *anti*-**3** and *syn*-**3**.

After we obtained the mixture of *anti*-**3a** and *syn*-**3a**, these products were then treated with *p*-TsOH in benzene under reflux, and the double bond migrated smoothly. The product was then deprotected with BBr_3 to generate the desired frondosin B (**1**). *Anti*-**3b** was hydrogenated by PtO_2 catalysis in EtOAc. Unfortunately, the reduction resulted in the 6,7-*cis*-ring junction product **7** in 98% yield.[17] Varying the catalyst and the conditions did not result in any improvement, and many attempts to invert the configuration of 5-H also failed.[18]

Thus, a synthesis of (±)-frondosin B has been achieved in four steps starting with 2-acetylbenzofuran **6a**, in a 33% yield. A formal synthesis of (±)-5-*epi*-liphagal has also been accomplished.

In conclusion, a novel approach to 6,7,5-tricyclic skeleta has been put in place based on an acid-catalyzed intermolecular [4 + 3]-cycloaddition. This strategy has been successfully applied in syntheses of frondosin B (**1**) and 5-*epi*-liphagal (**2**). Further investigations into the application of this strategy in the asymmetric total synthesis of more challenging natural products will be reported in due course.

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Supporting Information Available. Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Further NOE experiments showed that the H-atom at position 5 has an orientation opposite that in the natural product.

(18) (a) The Pd/C-catalyzed hydrogenation resulted in a complex product mixture, which turned out to be a mixture of double-bond reduction and furan reduction products. (b) TFA and Et_3SiH promoted the reduction, resulting in a complex that was difficult to purify. (c) Incubation in a sealed tube in *n*-octane at 180 °C for 24 h failed to invert the configuration.

The authors declare no competing financial interest.