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Utilization of Tandem Oxyanionic Cyclization/Claisen Rearrangement Strategies for the Construction of Seven and Eight-Membered Carbocyclic Ring Systems

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Abstract

This article describes the development of microwave-assisted oxyanionic 5-exo-dig cyclization-Claisen rearrangement sequence as a convenient "one-pot" route to a variety of seven- and eight membered carbocyclic ring systems. This process was used as the key transformation for the construction of several natural products, including frondosins A, B, and C.

Keywords: Claisen Rearrangement; Sigmatropic Rearrangement; 5-*Exo-Dig* Cyclization; 6-*Exo-Dig* Cyclization; Oxyanionic Cyclization; Microwave-Assisted Synthesis

Introduction

Carbocyclic seven- and eight membered rings are found as common structural units in a variety of polycyclic natural products that have been isolated from several different sources, including pathogenic fungi, marine organisms, terrestrial plants and insects. Structurally, they represent sesquiterpenoids, diterpenoids, sesterterpenoid systems, dibenzocyclooctadiene lignans, and polyphenol lignans [1-3]. Due to their medicinal relevance, numerous research groups are actively engaged in developing strategies for their construction by synthetic means. However, unlike five and six-membered carbocycles which are readily accessible through various cyclization reactions, methods allowing the construction of seven-membered rings are generally limited to processes other than direct intramolecular reactions. Among the most important of these are various cycloaddition strategies, such as the [5+2] and [4+3] reactions (seven-membered rings) [4], including several [4+4] and [4+2+2] cycloadditions (eight-membered rings) [5] (Figure 1).

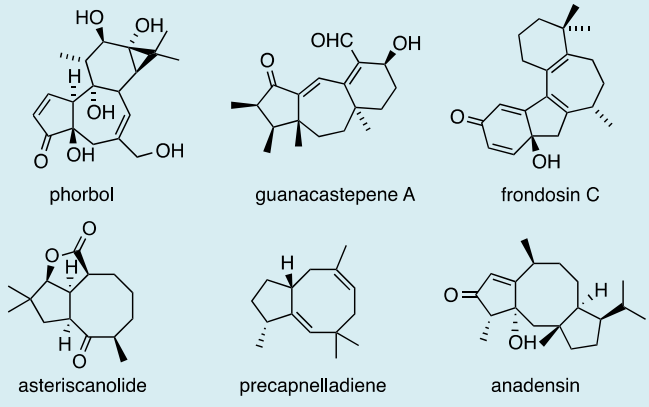


Figure 1: Representative natural products containing carbocyclic seven- and eight membered carbocyclic rings.

Sequential Oxyanionic Cyclization/Claisen Rearrangement Strategy

We have recently demonstrated that a variety of cycloheptanoid and cyclooctanoid ring systems may be conveniently accessed through a previously reported Marvell, et al. [6] but largely ignored tandem sequence that involves base-catalyzed intramolecular cyclization of appropriately substituted acetylenic alcohols, followed by in situ [3.3]-sigmatropic rearrangement (Claisen rearrangement) of the intermediate 2-alkylidenetetrahydrofurans (Figure 2) [7].

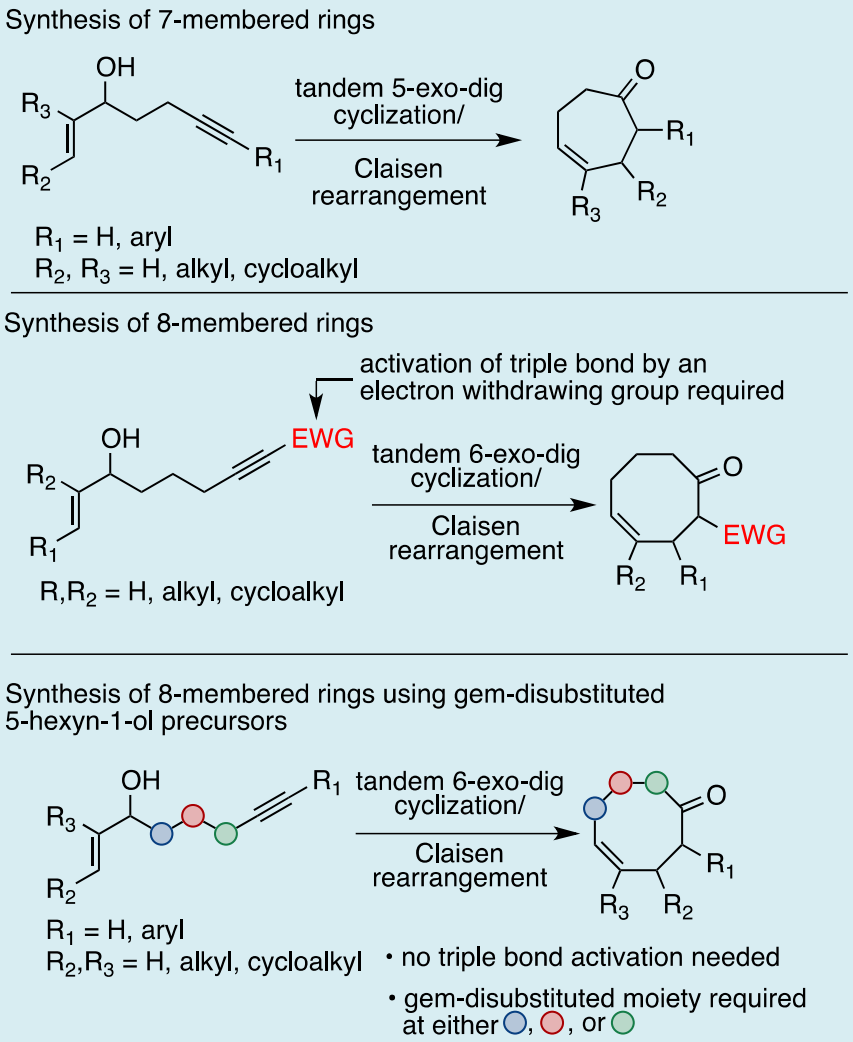


Figure 2: Strategies for the construction of seven- and eight-membered ring systems via tandem oxyanionic cyclization/ Claisen rearrangement sequence.

The requisite allyl vinyl ether precursor in these reactions (Figure 3) is produced as a transient species through a 5- or 6-*exo dig* process, which involves the intramolecular addition of an alkoxide moiety to a proximal triple bond (Figure 3). Upon heating, this intermediate undergoes in situ [3,3] sigmatropic rearrangement, affording a cyclohept-4-enone or cyclooct-5-enone derivative. In a typical case, this tandem cyclization-Claisen rearrangement process is effected simply by treatment of an appropriately substituted acetylenic alcohol, dissolved in phenetole or DME with approximately 10 mol-% of LiHMDS (or MeLi), and heating the mixture to 150-210 °C for approximately an hour (most conveniently under microwave irradiation). Table 1 highlights some of the cycloheptanoid compounds that are accessible through this methodology.

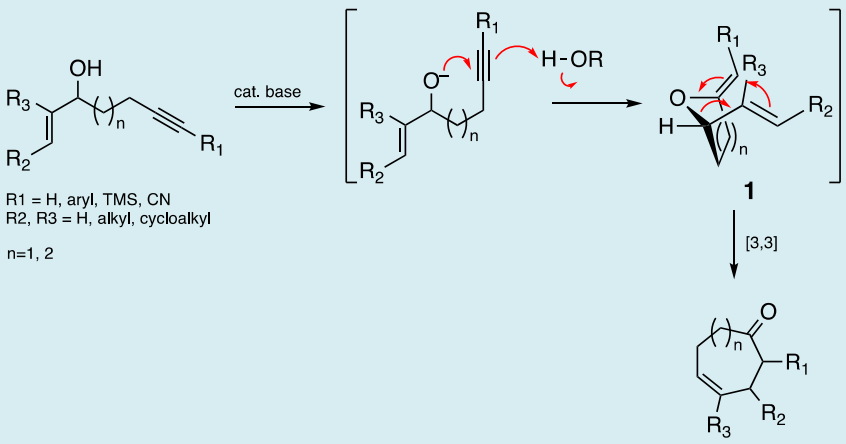


Figure 3: General strategy for the synthesis of polycyclic carbocyclic seven- and eight-membered ring systems via tandem cyclization/Claisen rearrangement.

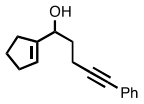
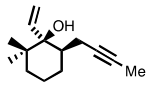
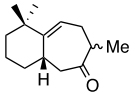
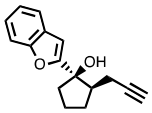
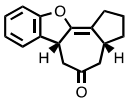
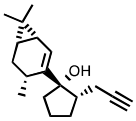
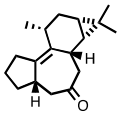
Entry	4-Alkyn-1-ol	Conditions[a]	Product	Yield (%)
1		210 °C 45 min[b]		77
2		200 °C 15 min[c]		77
3		200 °C 30 min[c]		63
4		185 °C 60 min[d]		76

Table 1: Synthesis of seven-membered carbocyclic structures by sequential 5-*exo* cyclization/Claisen rearrangement strategy. [a]Reactions were performed using a CEM microwave (unless otherwise noted) oven in the presence of 10-15 mol-% MeLi. [b]phenetole was used as the solvent. [c] DMF was used as the solvent. [d] Reaction was done using conventional heating (oil bath).

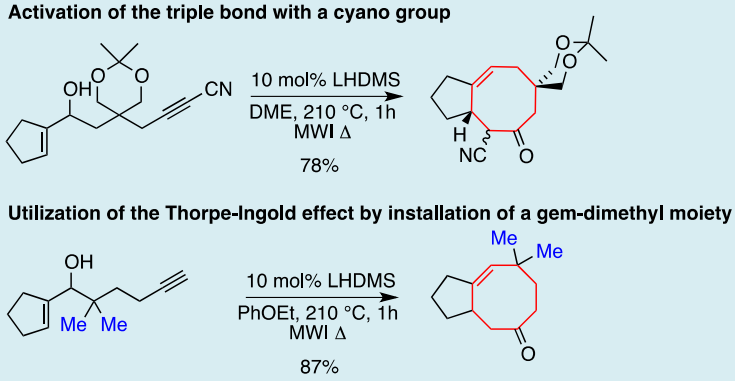


Figure 4: Strategies for the synthesis of cyclooctanoid derivatives.

Our initial attempts to apply of these strategies for the synthesis of eight-membered ring systems were met with failure, stemming largely from the inability of 5-alkyn-1-ol precursors to undergo 6-exo isomerizations. These issues were ultimately resolved by two different strategies: a) "activating" the triple bond with an electron withdrawing group prior to cyclization [8] and 2) taking advantage of the Thorpe-Ingold effect [9]. Examples of these strategies are highlighted in Figure 4.

Application to Natural Product Synthesis: The Frondosins

Frondosins A–E comprise five related novel sesquiterpene hydroquinone derivatives recently isolated from the Micronesian marine sponge *Dysidea frondosa* [10]. All members of the frondosin family (A–E) are antagonists of interleukin-8 (IL-8) and inhibitors of protein kinase C (PKC) in the low micromolar range [11]. In addition to being involved in cellular inflammatory events, IL-8 is now known to also play an important role in tumor progression and metastasis in several human cancers, including lung cancers [12]. It is has also been reported that IL-8, along with growth-regulated oncogene alpha, is involved in chemoattraction, neovascularization and stimulation of HIV-1 replication both in T-lymphocytes and macrophages [13]. Importantly, it has been demonstrated that compounds which inhibit the actions of IL-8 also inhibit HIV-1 replication [14].

As an example, the bicyclic 6-7 core of frondosin B was readily constructed in a "one-pot" procedure from the optically active secondary alcohol **2** (prepared from the corresponding ketone via CBS reduction) as depicted in Figure 5 [15]. The resulting ketone was subsequently methylated under kinetic conditions, affording compound **3** in excellent yield (the stereochemistry of the dimethoxy precursor to **3** was unequivocally established by X-ray crystallography) [16]. The key step in the remainder of the sequence was the Lewis acid induced cyclization of hydroquinone **4** which provided the entire tetracyclic scaffold of frondosin B. Subsequent isomerization of the trisubstituted double bond on the seven-membered ring was achieved in refluxing benzene in the presence of catalytic TsOH, completing the total synthesis of (–)-frondosin B [15]. The formal total synthesis (±) frondosin A was also achieved from the common intermediate **3** (racemic analogue) [16] in a few additional steps [17].

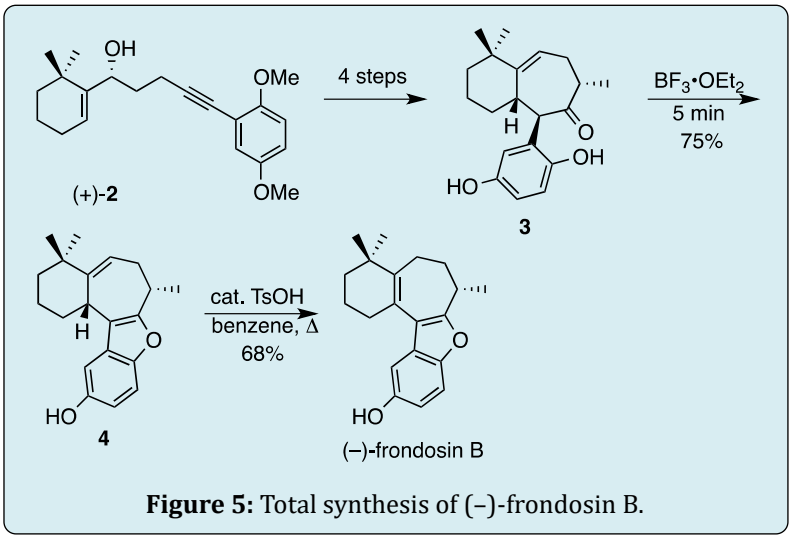


Figure 5: Total synthesis of (–)-frondosin B.

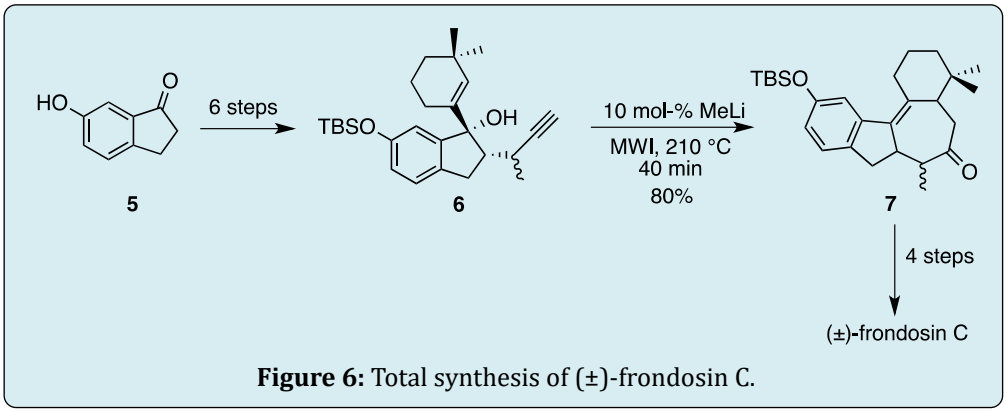


Figure 6: Total synthesis of (±)-frondosin C.

Similarly, frondosin C was synthesized according to the strategy depicted in Figure 5 [18]. Thus, the key tertiary alcohol **6** was readily synthesized from commercially available indanone **5** in six steps. Standard cyclization/Claisen rearrangement strategy involving catalytic base and microwave irradiation (MWI) at 210 °C afforded the tetracyclic intermediate **7**, which was converted to racemic frondosin C in four additional steps (Figure 5).

Conclusion

In summary, sequential oxyanionic 5- and 6-*exo-dig* cyclization/Claisen rearrangement has been developed, allowing the straightforward synthesis of a number of interesting cycloheptanoid and cylooctanoid ring systems. The methodology is ideally suited for natural product synthesis and has been so far applied to the preparation of three meroterpenoid natural products frondosin A, B and C. In addition, an asymmetric variant of the process has been developed which may be readily employed to access optically active cycloheptenone and potentially cyclooctenone ring systems [15].

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