



Expeditious cascade reactions: controlled syntheses of fenestradienes and cyclooctatrienes under palladium catalysis



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ABSTRACT

Palladium cyclization cascades represent an elegant way to access complex polycyclic scaffolds in a minimum amount of steps. Herein we provide a complete account on two new methodologies including these kind of cascades, each leading to two types of attractive compounds, cyclooctatrienes and [4.6.4.6]fenestradienes. The reader will first discover a strategy requiring three steps starting from alkenyl bromides, based on a first 4-*exo*-dig carbopalladation/Sonogashira coupling tandem reaction, and a subsequent P-2 Ni induced semi-hydrogenation. This leads to a first generation of cyclooctatrienes and [4.6.4.6]fenestradienes. Next, the second approach will be presented, in which the second generation of these compounds is accessed in a one-pot reaction including five steps, starting from the same alkenyl bromide compounds. These methods are appealing in terms of atom economy, the use of easy to handle conditions as well as the variability of its scope.

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1. Introduction

The usefulness of strategies based on palladium cyclization cascades leading to polycyclic frameworks in a regio- and stereo-selective manner has been demonstrated in the past.¹ Today, one of the challenges of modern synthetic method development is to form as many bonds as possible in the least number of steps, ideally in a single operation.² Significant recent studies in our laboratory are directed toward the development of synthetic methodologies to design highly strained scaffolds from simple starting materials using common reagents and mild reaction conditions. In this context, we report herein our investigations of cascade reactions involving a semi-hydrogenation of an alkyne moiety in first generation and in a second one a fascinating palladium catalyzed alkyne addition reaction. Both lead to two types of polycyclic structures, fenestradienes and cyclooctatrienes.

Eight-membered ring substructures are present in over 100 different natural products, many of which demonstrate exceptional and broad-ranging biological activity. For example, Ophiobolin A³

exhibits a broad spectrum of biological activity against nematodes, fungi, and bacteria,⁴ as well as showing potent antitumor activity.⁵ Aleurodiscal⁶ is an antifungal and antibiotic, while one of the most notable examples is the diterpene paclitaxel (taxol), that is, a major anticancer agent used in clinics today.⁷ Synthesis of eight-membered ring compounds has constantly been a challenging area due to high degree of ring strain, transannular interactions and unfavorable entropic and enthalpic factors. However, modern synthetic methods allow access toward a large variety of cyclooctanoids⁸ (Fig. 1).

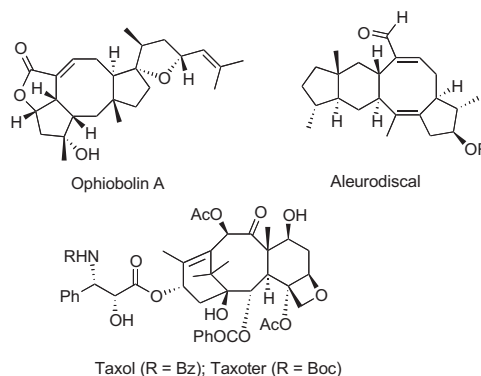


Fig. 1. Natural products containing an eight-membered ring.

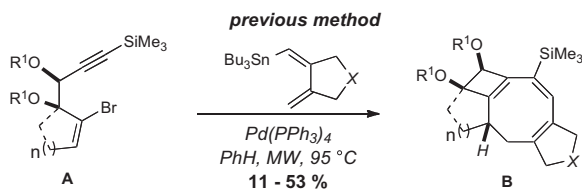
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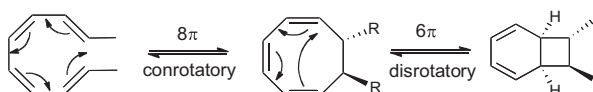
Sato et al. recently reported a Rh^I -catalyzed intermolecular cycloaddition of 4-allenals with alkynes to provide various monocyclic eight-membered rings in good to high yields in a stereoselective manner.⁹ Another example by Snyder et al. displays a rapid access to diverse members of the lauroxocane family, natural products containing an oxocene core. This oxygen-containing eight-membered ring compound is designed by a novel diastereoselective ring-expanding bromoetherification reaction of tetrahydrofurans triggered by a unique bromonium source (BDSB, $Et_2SBr \cdot SbBrCl_5$). Strategically positioned and designed nucleophilic traps, afford diverse functionalities on the eight-membered ring backbone.¹⁰ Despite diversity in strategy and in product structures, none of these approaches involve the direct formation of a 5-8-5 or 6-8-5 tricyclic skeleton.

We have previously reported a straightforward preparation of 5-8-5 or 6-8-5 condensed polycycles that employs an 8π electrocyclization reaction (Scheme 1).¹¹ Cyclooctatrienes **B** can be obtained in a one-step operation starting from simple alkenyl bromides **A**, using mild reaction conditions, and common palladium catalysts and solvents. The key step is a tandem reaction, namely a 4-*exo*-dig carbopalladation/Stille coupling. In some cases, the reaction suffered from low yields (<20%), but these were compensated for the complexity of the products formed in a one-step operation. To the best of our knowledge, this is the shortest reported route to functionalized polycyclic cyclooctanoid structures of this type and degree of complexity. Encouraged by these promising results, we investigated this methodology further in hope of developing a new versatile and efficient route to this type of cyclooctatriene derivatives in higher yields.



Scheme 1. Cyclooctatriene synthesis starting from alkenyl bromides **A**.

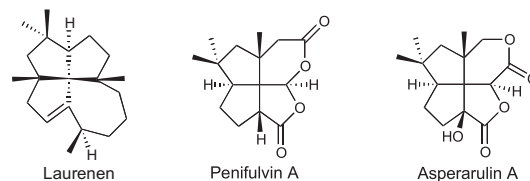
In general, few methodologies utilize the 8π electrocyclization reaction because of the formation of cyclohexadiene by a spontaneous 6π electrocyclization reaction, which leads to a 4-6 bicyclic skeleton (Scheme 2).¹² The equilibrium between the cyclooctatriene and the bicyclooctadiene depends on the reaction conditions used, and examples have been shown by several authors in total syntheses.¹³ For this reason, the 1,3,5-cyclooctatriene moiety is not a common substructure and is very rarely encountered in natural products.¹⁴ Therefore it appears to be of interest to develop new accesses to this type of structure, which can be the starting point of the synthesis of more complex natural or unnatural compounds.¹⁵



Scheme 2. Equilibrium between cyclooctatrienes and bicyclooctadienes.

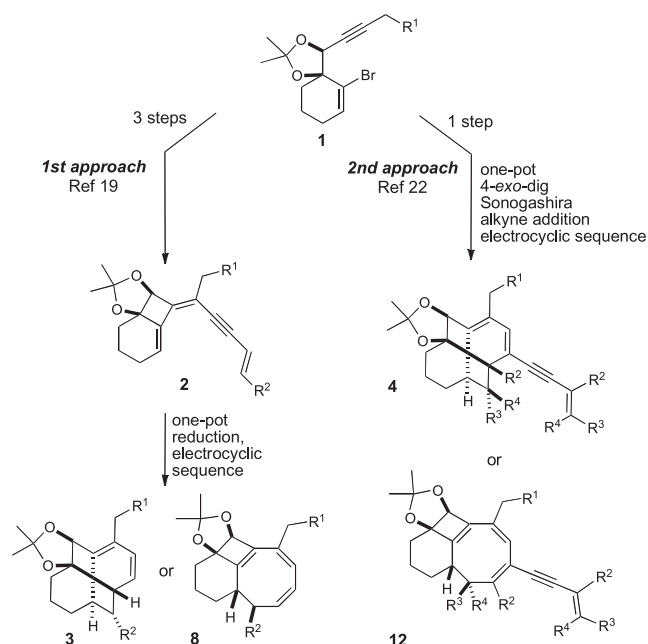
During our initial investigations on the uses of the 8π electrocyclization for the synthesis of stable 1,3,5-cyclooctatrienes, we were pleased to discover that a subsequent 6π electrocyclization reaction took place at room temperature after the 8π process providing in excellent yields a new class of fenestranes: the [4,6,4,6] fenestradienes and fenestrenes. The fenestrane family represents structurally fascinating compounds, which contain four condensed

cycles sharing the same central carbon atom (Scheme 3). Laurenen is the only all carbon fenestrane natural product known.¹⁶ This compound does not present any significant biological activity. However, natural products of the fenestrane family, which contain various heteroatoms, such as the penifulvines and asperarulines, have been reported.¹⁷ The fenestranes have attracted much synthetic interest over the past 40 years, because of the planar geometry of the central carbon atom.¹⁸ For some examples, the bond angles around this central carbon atom can be enlarged up to 130° instead the regular 109.5° .



Scheme 3. Some examples of natural product structurally related to the fenestrane family.

Our group has developed methodologies toward both cyclooctatrienes and new members of this family, the [4.6.4.6]fenestradienes (Scheme 4).¹⁹ Herein we present for the first time a complete account on two different approaches: the earlier P-2 Ni strategy, leading to the first generation of polycycles, and the alkylation strategy, leading to the second generation. In the first approach, fenestradienes **3** were obtained with excellent yields, from precursor trienyne **2** synthesized in three steps from alkenyl bromides **1**.²⁰ This sequence requires the use of stannanes for the 4-*exo*-dig carbopalladation/Stille coupling in the preparation of the precursors **2**, and then a sensitive nickel(0) catalyst and hydrogen gas. The stannanes could later be eliminated by the development of a new tandem reaction, 4-*exo*-dig carbopalladation/Sonogashira coupling.²¹ In the second approach, a new type of fenestradienes **4** was directly prepared from alkenyl bromides **1**, thus shortening the synthesis drastically and avoiding dangerous hydrogenation.²² We will describe the results for this one-pot synthesis of fenestradienes **4**, the limits of this method as well as the synthesis of a new series of 6-4-8, 7-4-8 or 4-8 fused systems.



Scheme 4. Different pathways toward [4.6.4.6]fenestradienes **3** and **4** or cyclooctatrienes **8** and **12**.

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