Tetrahedron Letters 57 (2016) 4001–4008

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest paper

Overview of the synthesis of carbazoloquinone natural products

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ARTICLE INFO

Article history:
Received 11 July 2016
Revised 27 July 2016
Accepted 28 July 2016
Available online 30 July 2016

Keywords:
Carbazoloquinone
Carbazole
Quinone
Natural products
Total synthesis

ABSTRACT

Carbazoloquinone alkaloids are the focus of intensive research due to their clinical potential as anti-malaria, anti-cancer, and neuronal protection agents. The synthetic strategies employed to generate the carbazoloquinone framework are often developed in the setting of natural product total synthesis. In this *Digest* we discuss recent synthetic strategies used to access three families of naturally occurring carbazoloquinone molecules: the murrayaquinones, the calothrixins, and the bismurrayaquinones. While concise and highly efficient strategies to some of these compounds have been reported, challenges and opportunities remain for the development of new approaches to carbazoloquinone natural products.

Contents

Introduction

The carbazoloquinone unit is a prominent structural feature in natural products isolated from the Rutaceae (citrus) family of plants, with the *Murraya* genus of flowering shrubs supplying the greatest number. Primarily used as flavoring agents during food preparation, *Murraya* plants have also been used in traditional medicine to treat such varied ailments as acute pain, high-temperature, skin discoloration, and even animal bites.[1] Consequently, carbazoloquinones have been extensively explored in medicinal chemistry settings and there are now more than 850 carbazoloquinone structures known. In contrast to their structural variety, synthetic methods used to access the carbazoloquinone motif are far fewer in number. Knölker published a comprehensive review covering the literature up to 2012.[2] In this *Digest*, we will provide an overview of the recent synthetic strategies and methods employed for the synthesis of carbazoloquinone-containing natural products, with a particular emphasis on the murrayaquinones, calothrixins, and bismurrayaquinone.

Organization of the digest

(1) Strategies to the murrayaquinone-type carbazole-quinones.
(2) Strategies to the calothrixin-type carbazoloquinones.
(3) Strategies to dimeric/heterodimeric carbazoloquinones.

Strategies to the murrayaquinone-type carbazoloquinones

The murrayaquinones and related molecules (**1**–**11**) shown in Figure 1 are the archetypical carbazole-1,4-quinone natural products and have served as target structures for development of synthetic methodologies. With the exception of clausenaquinone A (**4**), which possesses a methoxy group on the quinone core, these compounds are all derivatives of murrayaquinone A (**1**) possessing

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http://dx.doi.org/10.1016/j.tetlet.2016.07.092
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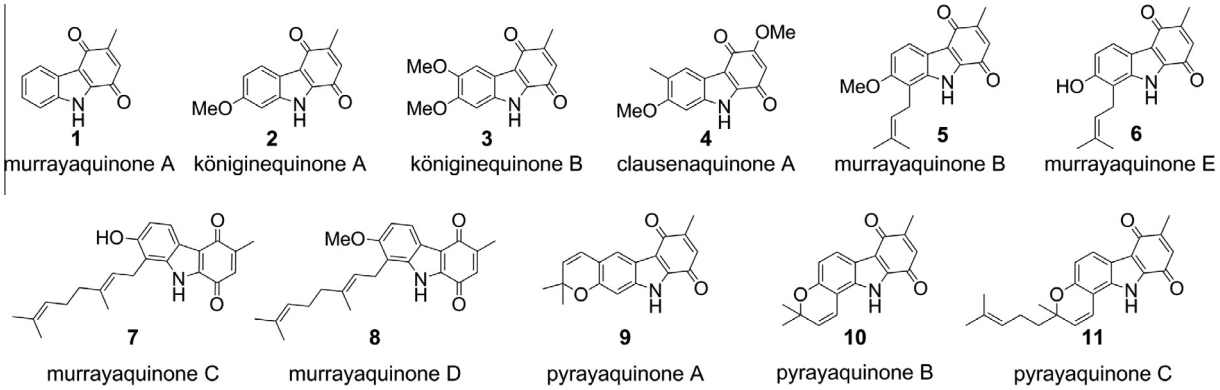
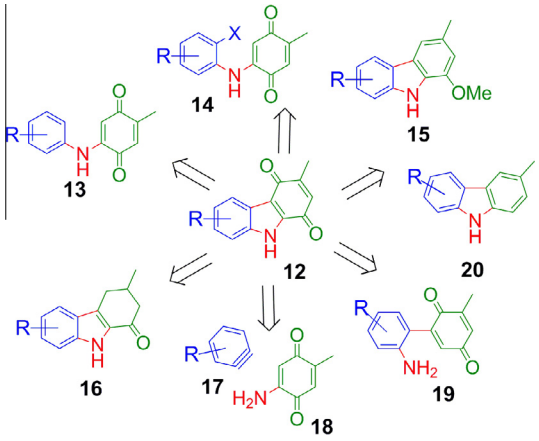
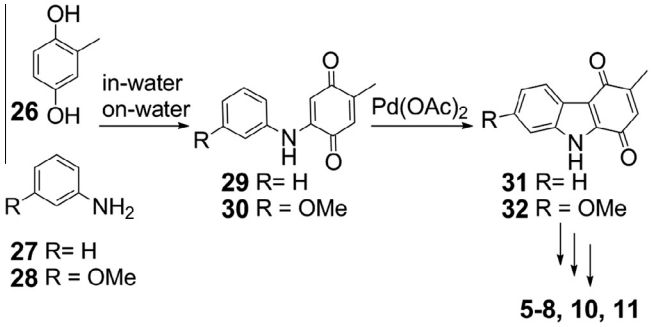


Figure 1. Murrayaquinone-type carbazoloquinones.



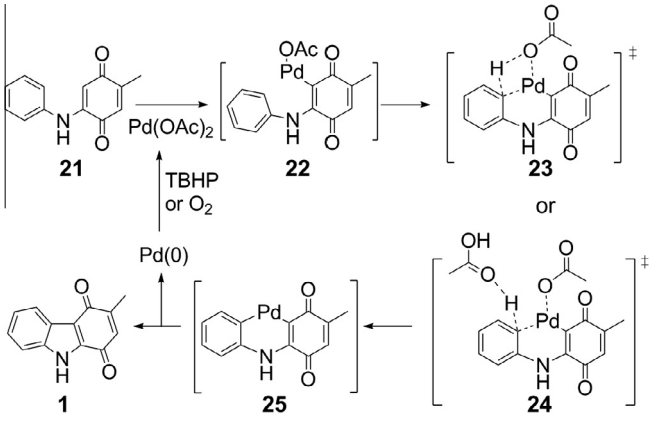
Scheme 1. Common synthetic disconnections of the murrayaquinone-type carbazoloquinones.



Scheme 3. In-water, on-water domino process for carbazoloquinone synthesis.

additional oxidation or alkylation on the aromatic ring. Some generalized synthetic routes to murrayaquinone-type natural products are displayed in Scheme 1.

The most common strategy for the synthesis of carbazoloquinones remains the palladium-mediated intramolecular cyclization of the corresponding anilinoquinone **13** (Scheme 1).[3] Mechanistic investigations by Glorius[4] and Knölker[5] have demonstrated that this proceeds by metalation of the enamine (Scheme 2), followed by aromatic palladation to give **25** (either by σ-bond metathesis **23** or concerted deprotonation-metalation **24**). Reductive elimination gives the carbazoloquinone **1** directly. Although Åkermark and co-workers have reported catalytic variants that use either *tert*-butyl hydroperoxide (TBHP) or oxygen as the external oxidant,[6,7] and Knölker and co-workers reported the use of Cu $(OAc)_2$ to facilitate catalyst turn-over,[8] the stoichiometric version is often higher yielding. The ubiquity of this approach has meant that synthetic innovations are largely limited to the generation of the cyclization precursor **13**.[2]



Scheme 2. Palladium-mediated intramolecular cyclization.

The conjugate addition of anilines onto the quinone core requires acid catalysis, and acetic acid is generally employed. When performed in an open reaction vessel, the intermediate dihydroquinone undergoes spontaneous oxidation to the desired anilinoquinone. McErlean and co-workers overcame the need for exogenous acid by employing an in-water, on-water domino cascade to deliver the anilinoquinone directly (Scheme 3).[9,10] Application of the stoichiometric palladium-mediated cyclization completed the synthesis of murrayaquinone A (**1**) and königinequinone A (**2**). An on-water catalyzed aromatic Claisen rearrangement then enabled the synthesis of murrayaquinones B–E (**5**–**8**) as well as pyrayaquinones B (**10**) and C (**11**).[10]

Given that quinones are generally employed as Michael acceptors, it is unsurprising that a related strategy generates the organopalladium species on the aromatic ring of anilinoquinone **14** (see Scheme 1). Kumar and co-workers recently used a catalytic version of this strategy in their total synthesis of murrayaquinone A (**1**) (Scheme 4).[11] Critical to the success of the cyclization was the combined use of PCy_3 and JohnPhos ligands.

Another common synthetic strategy to the murrayaquinone-type natural products involves oxidation of the corresponding carbazole **15** (see Scheme 1). In order to ensure oxidation of the desired ring in a chemoselective manner, pre-functionalization is required. Pleasingly, this approach can result in a biomimetic