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o-Quinone Methides via Oxone-Mediated Benzofuran Oxidative Dearomatization and Their Intramolecular Cycloaddition with Carbonyl Groups: An Expeditious Construction of the Central Tetracyclic Core of Integrastatins, Epicoccolide A, and Epicocconigrone A

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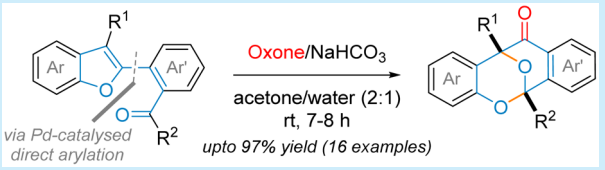
Supporting Information

ABSTRACT: The intramolecular cycloaddition of *o*-quinone methides (*o*-QMs) with a carbonyl group has been envisaged and executed successfully in the context of constructing the complex and rare [6,6,6,6]-tetracyclic core found in the integrastatins, epicoccolide A, and epicocconigrone A. These transient *o*-QMs were generated easily from the oxidative dearomatization of the corresponding C2-(aryl)benzofuran by employing Oxone in acetone−water at rt. The subsequent cycloaddition with the carbonyl (or conjugated olefin) present on the C2-aryl group was spontaneous.



In 2002, Singh and co-workers from Merck laboratories reported the isolation of integrastatins A and B from an unnamed fungal source (ATCC74478) and from an endophytic *Ascochtya* species (ATCC74477).[1] Both compounds have been identified as potent inhibitors for the strand-transfer reaction of the recombinant HIV-1 integrase enzyme. Integrastatins are characterized by an unprecedented [6,6,6,6]-tetracyclic skeleton having a central [3.3.1]-bicyclic ketal core where the perimeter is fused with two aromatic rings on both sides and pendant methyl groups are present on the bridge-head carbon atoms. To date, there are three approaches reported for assembling the central tetracyclic skeleton of integrastatins.[2−4] The Taylor (2003)[2] and Stoltz (2011)[4] groups have executed the synthesis of **1a** as a model target. We documented a one-step assembly of the central core by employing McMurry cross coupling of *o*-phthaladehyde with *o*-hydroxy-benzaldehyde/acetophenones.[3] Although a number of derivatives could be synthesized in moderate yields, this method is limited to *o*-phthaladehyde, and thus only one of the pendant bridge-head methyl groups could be placed. Interestingly, in 2013, the Laatsch[5] and Proksch groups[6] have independently reported the isolation of two closely related congeners of integrastatins, namely epicoccolide A and epicocconigrone A, respectively (Figure 1). The epicocconigrone A inhibited 15 tyrosine kinases with IC_{50} values ranging from 0.07 to 9.00 μM and histone deacetylase with IC_{50} = 9.8 μM, and epicoccolide A showed potential antimicrobial and antifungal activity.

The promising HIV-integrase inhibition of integrastatins, taken together with the diverse bioactivities by the newly added members of this rare family, has led us to revisit their synthesis. In this paper, we document a simple approach for the synthesis

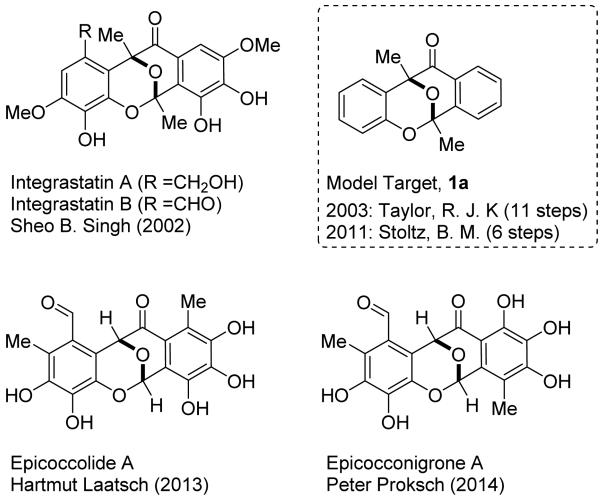


Figure 1. Structures of integrastatins and related natural products with a rare [6,6,6,6]-tetracyclic core and the model target compound synthesized by the Taylor and Stoltz groups.[2,4]

of the tetracyclic core of these natural products by employing a novel benzofuran oxidative dearomatization cascade.

A possible biosynthetic pathway to form a [3.3.1] ring system and epicoccolide B was proposed by Laatsch's group and parallels our disconnection of integrastatins.[6] They proposed a benzoin path comprising the dimerization of flavipin (*o*-phthalaldehyde derivative) for the biogenesis of epicoccolide A

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Org. Lett. XXXX, XXX, XXX−XXX

and epicocconigrone A. Interestingly, the epicoccolide B having a simple benzofuran core has been assumed from the initial benzoin product of the flavipin following a sequence of reduction, acetalization, and dehydration. We wondered whether this forward reaction cascade leading to 2-arylbenzofuran can be a backward retrosynthetic transform to disconnect the [3.3.1]-tetracyclic heterocyclic skeleton, in other words, the oxidation of a benzofuran to *o*-QM and its subsequent intramolecular cycloaddition with a suitably positioned carbonyl group leading to the key tetracyclic skeleton.[7−9] In this regard, a report from the Adam's group on generation of *o*-QM from benzofuran via dimethyldioxirane (DMDO)-mediated oxidative dearomatization, and its [4 + 2]−hetero-Diels−Alder reaction with olefins (Figure 2b), is inspirational.[10,11]

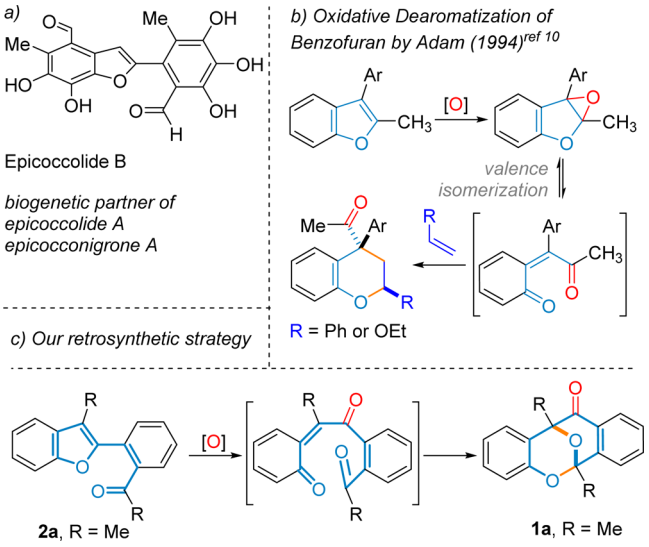
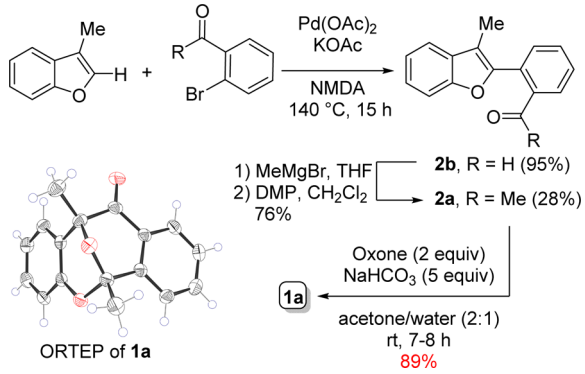


Figure 2. (a) Structure of epiococcolide B, a biogenetic partner isolated along with epicocconigrone A and epicoccolide A; (b) Adam's benzofuran oxidative dearomatization and [4 + 2]-cycloaddition; (c) proposed disconnection of central core of the [6,6,6,6]-tetracyclic system featuring a intramolecular [4 + 2]-cycloaddition of *o*-QM with a carbonyl group.

In the forward sense, the synthesis of compound **1a**, a model target representing the central ketal core of integrastatins and synthesized by the Taylor and Stoltz groups, has been planned. The benzofuran **2a** has been identified as the model substrate for the proposed oxidative skeletal reorganization. Interestingly, the only report available on the existence of **2a** has been documented by Taylor's group as a side product resulting from an unwarranted intramolecular rearrangement of a penultimate compound while synthesizing **1a**.[2] Otherwise, the synthesis of this selected model substrate **2a** has not been reported. This warranted the necessity to develop enabling chemistry. Our initial experiments in this regard have been focused on the preparation of **2a** by employing the Pd-catalyzed direct coupling that has been documented by Doucet's group employing simple aryl halides.[12] As shown in Scheme 1, the coupling of 3-methylbenzofuran with 2-bromoacetopheone under the prescribed conditions was sluggish, and the requisite **2a** was obtained in moderate yields. However, when 2-bromobenzaldehye was employed as a coupling partner, the corresponding product **2b** was obtained in excellent yields (95%). The Grignard reaction of **2b** with methylmagensium bromide, followed by the oxidation of the intermediate alcohol,

Scheme 1. Synthesis of Benzofuran 2a and Its Oxidative Dearomatization Cascade



provided **2a** in 76% overall yield (Scheme 1). Having the model substrate **2a** with excellent yield, the stage was set for the realization of the proposed hypothesis. The oxidation of benzofurans reported by Adam's group,[10] in general, employed the anhydrous DMDO at −78 °C. Considering recent developments on the use of Oxone−acetone as a practical alternative in DMDO-mediated oxidations, a careful screening of the various alterations employing Oxone have been examined.[13] To this end, it has been realized that when acetone alone is employed as the solvent along with water, the oxidation of the benzofuran **2a** can be successfully accomplished employing 2 equiv of Oxone at rt, and gratifyingly, the intended cyclization was found to be realized with the formation of the **1a** in very good yields (89%) (Scheme 1).[14]

With the reaction conditions for the synthesis of complex [3.3.1] tetracyclic heterocyclic skeleton present in integrastatins in hand, we then examined the substrate scope of this reaction. As shown in Table 1, various benzofuran substrates that have been accessed by using Pd chemistry (see the SI for complete details) have been found to undergo this oxidative transformation leading to the corresponding tetracyclic bridged bicyclic ketals in good to excellent yields without any interference from the nature of the substituents present on both aromatic rings.

In general, the *o*-QM intermediates are electrophilic in nature and prefer cycloaddition with electron-rich olefins and undergo conjugate additions with the nucleophiles.[15] The current successful cycloaddition with carbonyls is interesting. Next, in order to examine the involvement of *o*-QM, as Adam's group had suggested,[10] and also to examine the compatibility of conjugated olefins, the *α,β*-unsaturated compound **3a** has been prepared from the corresponding aldehyde **2b** and subjected to the current reaction conditions.[16] As indicated in Scheme 2, the tandem *o*-QM generation and subsequent [4 + 2]−cycloaddition reaction proceeded smoothly and provided the tetrahydronaphthalene framework **4a** resulting with the retention of the initial *E*-configuration of the olefin. The scope of this *o*-QM/[4 + 2]-cycloaddition was examined employing substrates **3b−f**, and the corresponding tetrahydronaphthalenes **4b−f** were obtained in moderate to good yields (Scheme 2). It is to be noted that the resulting tetrahydronaphthalene framework is abundant in many natural products such as podophyllotoxin, a famous anticancer natural drug lead.[17]

Coming to the course of the reaction, the product formation takes place via the formation of an *o*-QM followed by cycloaddition with a suitably disposed carbonyl or olefin

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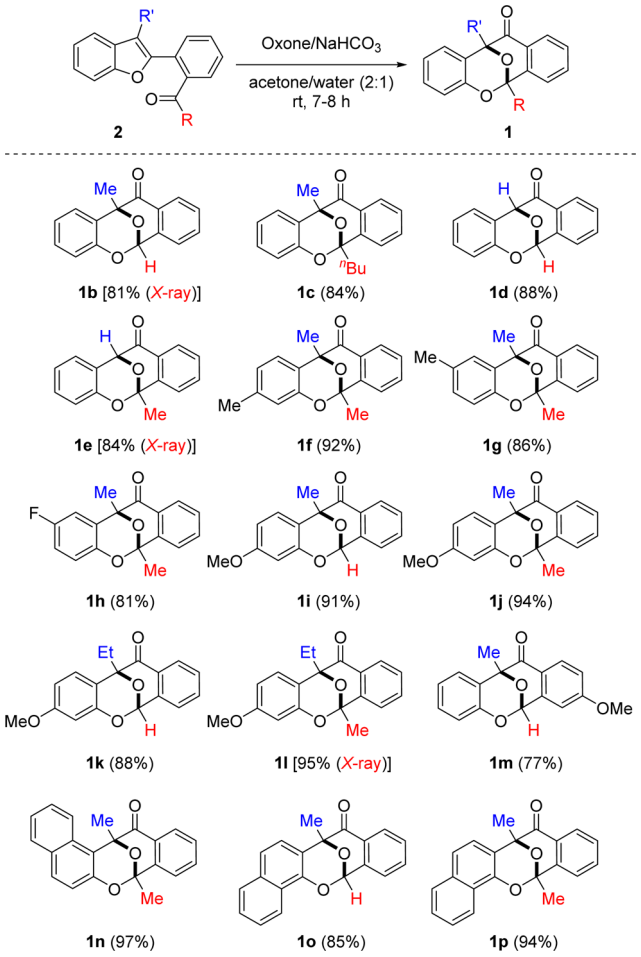
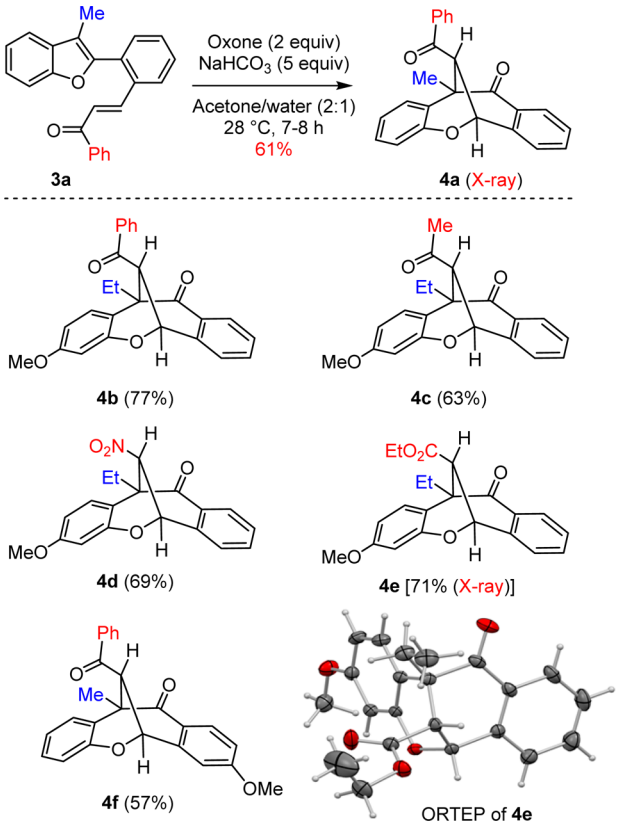
Table 1. Scope of the Oxone-Mediated Benzofuran Oxidative Dearomatization and *o*-QM Cycloaddition with Carbonyl Groups



functional group. The facile cycloaddition with conjugated olefins and the exclusive formation of products resulting in the retention of the initial olefin configuration is suggestive of a concerted process. To examine the possibility of any alternative stepwise processes, the reaction of **2a** was carried out employing $H_2{}^{18}O$ under similar conditions. A nominal ^{18}O labeling was noticed in the resulting product **1a**. This experiment clearly ruled out the an alternative path involving the possible participation of the external water as a nucleophile adding to the *o*-QM followed by intramolecular acetalization.[7b,18] Thus, these ^{18}O-labeling experiments and the reactions with olefin are indicative of the concerted nature of the current cycloaddition process and clearly suggested the involvement of an *o*-QM intermediate. Moreover, the compatibility of the aryl aldehyde group under these conditions is really interesting and revealed that the benzofuran oxidation is preferred over the oxidation of the aldehyde unit despite the fact that the reacting heterocyclic olefin is fully substituted.[19] In addition, the successful cyclization with both the substrates, especially in the presence of acetone as solvent, is remarkable, thus revealing complete dominance of the intramolecular cyclization over the intermolecular one with acetone.

In conclusion, a simple approach for the construction of the rare [6,6,6,6]-tetracyclic core present in the integrastatins, epicoccolide A, and epicocconigrone A has been developed featuring a novel benzofuran oxidative dearomatization cascade.

Scheme 2. Scope of the Conjugated Olefins as the Dienophiles in Oxone-Mediated Benzofuran Oxidative Dearomatization and *o*-QM Cycloaddition Cascade



This cascade process comprises the Oxone-mediated oxidation of the benzofuran ring leading to the transient *o*-QM and its subsequent intramolecular [4 + 2]-cycloaddition with aldehydes, ketones, and olefins. This cascade process is simple to execute by employing Oxone at rt in aqueous acetone and will have potential implications in the chemical synthesis of natural products containing chroman as well as tetrahydronaphthalene frameworks. Further studies aimed at the total syntheses of integrastatins A/B, epicoccolide A, and epicocconigrone A are currently in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03707.

Full experimental procedures, characterization data, and NMR/mass spectra of all new compounds (PDF)
Crystallographic data for compound **1a** (CIF)
Crystallographic data for compound **1b** (CIF)
Crystallographic data for compound **1e** (CIF)
Crystallographic data for compound **1l** (CIF)
Crystallographic data for compound **4a** (CIF)
Crystallographic data for compound **4e** (CIF)

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Notes

The authors declare no competing financial interest.

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