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Efficient Construction of the Oxatricyclo[6.3.1.$0^{0,0}$]dodecane Core of Komaroviquinone Using a Cyclization/Cycloaddition Cascade of a Rhodium Carbenoid Intermediate

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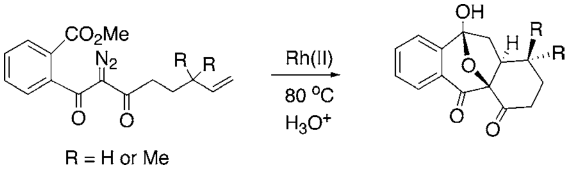
ABSTRACT



The rhodium(II)-catalyzed cyclization/cycloaddition cascade of a *o*-carbomethoxyaryl diazo dione is described as a potential route to the oxatricyclo[6.3.1.$0^{0,0}$]dodecane substructure of the icetexane diterpene komaroviquinone. The initially formed carbonyl ylide dipole prefers to cyclize to an epoxide at 25 °C but can be induced to undergo cycloaddition across the tethered π-bond at higher temperatures.

Dracocephalum komarovi Lipsky (Labiatae) is a perennial semishrub[1] that is called “buzbosh” in Uzbekistan, and local people use the aerial parts in a tea to treat various inflammatory diseases. Dried whole plants of *D. komarovi* were extracted and fractionated to give several icetexane diterpenes whose structures were elucidated by extensive analysis of their NMR data.[2] The major fraction isolated from the plant was assigned structure **1** and was named komaroviquinone. This compound showed strong in vitro trypanocidal activity against epimastigotes of *Trypanosoma cruzi*, the causative agent of Chagas’ disease in Central and South America.[3]

Several types of natural quinones have been reported to show trypanocidal activity, and their activities have been partly ascribed to the production of reactive oxygen species in the parasite.[4,5] In addition to compound **1**, a minor diterpene **2** was also isolated from the same plant, and since it possessed a novel spiro-octahydroindene skeleton, it was named komarovispirone (**2**).[6] Biogenetically, komarovispirone (**2**) may be derived from komaroviquinone (**1**) through a novel ring-contraction sequence as outlined in Scheme 1. The stereochemistry of **2** was tentatively assigned as indicated in Scheme 1.

On the basis of previous work in our laboratory using the intramolecular dipolar-cycloaddition reaction of carbonyl ylides for the synthesis of various natural products,[7−10] we

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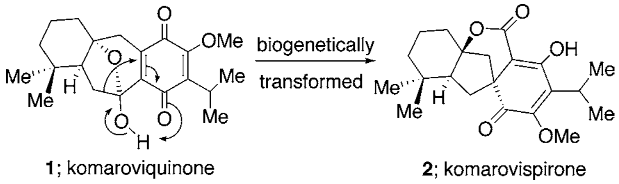
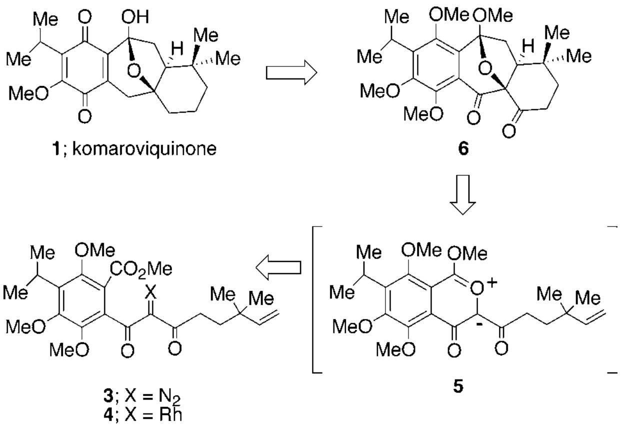
Scheme 1



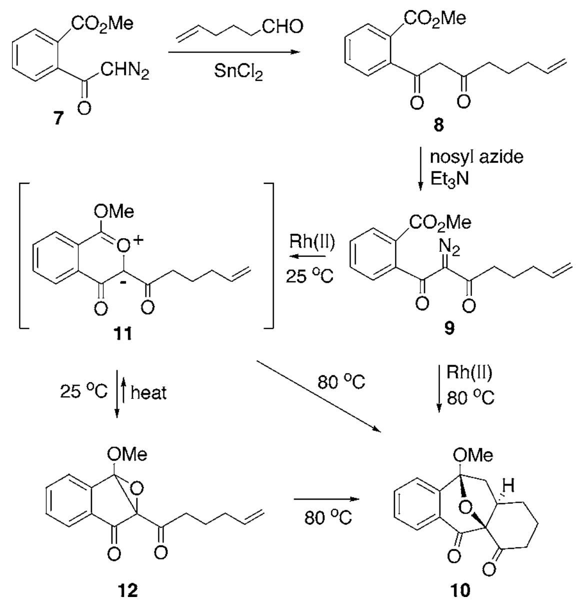
felt that the Rh(II)-catalyzed reaction of a diazo dione precursor (i.e., **3**) might allow for a facile entry to the icetexane core of komaroviquinone (**1**). The eventual formation of the oxatricyclo[6.3.1.0^{0,0}]dodecane skeleton of **1** was envisioned to come about from cyclization of the rhodium carbenoid intermediate **4** with the adjacent carbomethoxy group.[9] The ensuing dipole **5** was expected to undergo an intramolecular [3 + 2]-cycloaddition across the tethered π-bond. The resulting cycloadduct **6** would then be converted to komaroviquinone in several steps by sequential reduction of the keto groups, oxidation to the benzoquinone core, and acid hydrolysis of the ketal moiety (Scheme 2).

Scheme 2



To test the feasibility of the retrosynthetic strategy outlined in Scheme 2, our initial efforts were focused on some model substrates. According to our design, we hoped to employ a tandem cyclization/cycloadddition reaction of a rhodium carbenoid intermediate to rapidly generate the 9,10-benzo-12-oxatricyclo[6.3.1.0^{0,0}]dodecanedione skeleton from a relatively simple precursor (i.e., **9**). Our synthesis of the key diazo dione **9** commenced with *o*-carbomethoxy diazo ketone **7**, which is readily available in high yield from phthalic acid monomethyl ester. We anticipated that under suitable reaction conditions **7** would react with hex-5-enal to give diketone **8** following a protocol developed by Holmquist and Roskamp for β-keto esters.[11] These authors have found that aldehydes can be converted into β-keto esters by the addition of ethyl diazoacetate in the presence of tin(II) chloride. In our hands, a modest (but unoptimized) yield of **8** (ca. 40%) was obtained from the reaction of **7** with hex-5-enal. A subsequent Regitz diazo transfer reaction[12] using nosyl azide and Et_3N furnished diazo dione **9** in 98% yield. Treating a sample of **9** with $Rh_2(OAc)_4$ in benzene at 80 °C afforded cycloadduct **10** in 75% yield (Scheme 3).

Scheme 3



Interestingly, when the Rh(II)-catalyzed reaction was carried out at room temperature, the major product isolated corresponded to epoxyindanone **12** (71%) with only a small amount (<10%) of cycloadduct **10** being formed. Heating a sample of **12** at 100 °C in benzene gave **10** in 78% isolated yield. This reaction presumably occurs by thermal C−C bond cleavage of the epoxide ring to generate dipole **11**, which undergoes a subsequent intramolecular [3 + 2]-cycloaddition to give **10**.

Many studies support the intermediacy of carbonyl ylides in reactions involving the interaction of a metallo carbenoid with a carbonyl oxygen.[13] The great majority of literature reports on carbonyl ylides are dominated by 1,3-dipolar cycloaddition reactions rather than cyclization of the dipole to produce the oxirane ring system.[7−10] Huisgen was the first to report the formation of an epoxide from the reaction of dimethyl diazomalonate with benzaldehyde, but in only 7% yield when the reaction was carried out at 125 °C in the presence of 1 mol % of Cu(acac)$_2$.[14] More recently, the Doyle[15] and Davies[16] groups have reported stereospecific

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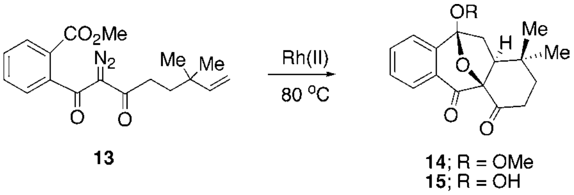
epoxide formation from rhodium acetate catalyzed reactions of aryl, heteroaryl, and vinyl diazoacetates with α,*β*-unsaturated aldehydes or ketones. Later, a similar epoxidation process was used to prepare spiro-indoloxiranes with cyclic diazoamides by the Mathusamy group.[17] When dimethyl diazomalonate was used as the carbenoid source, a competition between dioxolane and epoxide formation was noted. Doyle was able to direct the decomposition of the diazomalonate system to produce either epoxide or dioxolane by influencing the stability of the intermediate carbonyl ylide dipole.[18] When the electron-rich *p*-anisaldehyde was used as the trapping reagent, only epoxide formation was observed. Stabilization of the intermediate ylide was suggested to account for its diminished reactivity toward cycloaddition with a second molecule of the added aldehyde. The fact that we were able to isolate epoxide **12** in 71% yield from the cyclization of dipole **11** is perfectly consistent with the Doyle observations (Scheme 3). Thus, stabilization of the positive center of the dipole by interaction with the adjacent methoxy group diminishes the rate of the dipolar cycloaddition reaction and promotes cyclization of the ylide to the epoxide ring.

The Rh(II)-catalyzed reaction of the related dimethyl substituted diazo ester **13** was also studied since this system contained the appropriate substituent groups needed for the eventual synthesis of komaroviquinone (**1**). The rate of an intramolecular reaction is often increased when alkyl groups are placed on a chain between the two reacting centers.[19] This is known as the gem-dialkyl effect and is often exploited to promote difficult cyclization reactions.[20] Indeed, the reaction of diazo dione **13**, prepared in a manner similar to that outlined in Scheme 3, gave cycloadduct **14** in 92% yield. Most importantly, when **14** was treated with aqueous acid it was readily converted to **15** in essentially quantitative yield (Scheme 4). The conversion of **13** to **15** via this method suggests that a similar approach could be used in our planned synthesis of komaroviquinone (**1**).

Scheme 4



In summary, an efficient approach to the core skeleton of komaroviquinone was accomplished by an intramolecular [3 + 2]-cycloaddition reaction of a carbonyl ylide dipole obtained by the interaction of a metallo carbenoid with an adjacent carbomethoxy group. Application of this strategy to the synthesis of komaroviquinone is currently underway and will be reported at a later date.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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