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Total Synthesis of (+)-Komarovispirone

George Majetich* and Jianhua Yu

Department of Chemistry, University of Georgia, Athens, Georgia 30602

majetich@chem.uga.edu

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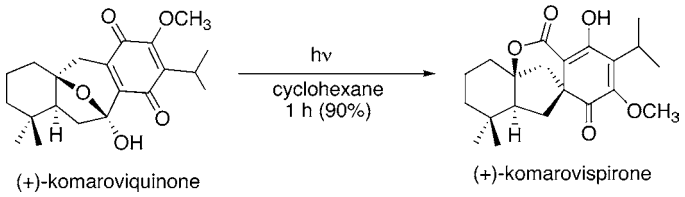
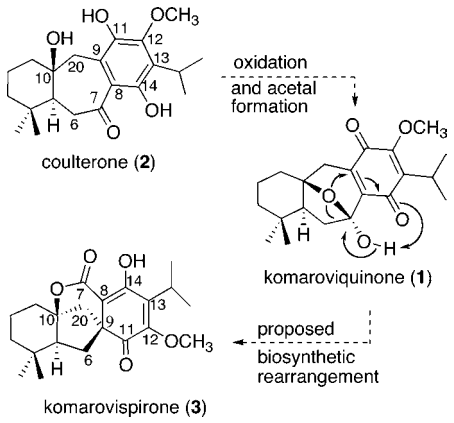
ABSTRACT



(+)-Komaroviquinone photolytically rearranges to (+)-komarovispirone. A rationalization of this isomerization is presented.

The local inhabitants of the west Tian Shan Mountains in Uzbekistan use the above the ground parts of the semi-shrub *Dracocephalum komarovi* Lipsky[1] known as "buzbosh" to cure inflammatory diseases and hypertony. In the course of a systematic study of the organic extracts of buzbosh, Honda and co-workers isolated the icetexane-based diterpenes komaroviquinone (**1**)[2a] and coulterone (**2**)[2b] as well as komarovispirone (**3**),[3] which has a novel spiro-octahydroindene skeleton (Scheme 1). While coulterone and komaroviquinone undoubtedly interconvert through an oxidative/reductive process, it has been proposed that komarovispirone may be biosynthetically derived from komaroviquinone through a novel ring-contraction sequence. Because of its useful biological activity,[4,5] komarovispirone has attracted the attention of others within the synthetic community.[6] Herein we report the conversion of (+)-komaroviquinone into (+)-komarovispirone.[7]

Scheme 1



Our synthesis of (±)-komaroviquinone[8] provided us sufficient insight to achieve an enantiospecific synthesis of (+)-komaroviquinone[9] and enabled us to investigate the proposed

(1) Vvednski, A. I. *Flora Uzbekistana*; Editio Academiae Scientiarum USSR: Tashkent, 1961; Vol. 5, p 313.

(2) (a) Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128−131. (b) For the isolation of coulterone from other plants, see: Frontana, B.; Cardenas, J.; Rodriguez-Hahn, L. *Phytochemistry* **1994**, *36*, 739−741.

(3) Uchiyama, N.; Ito, M.; Kiuchi, F.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *Tetrahedron Lett.* **2004**, *45*, 531−533.

(4) While coulterone, komaroviquinone, and komarovispirone demonstrate trypanocidal activity against epimastigotes of *T. cruzi*, the causative agent of Chagas' disease in Central and South America,[5] komaroviquinone is the most potent with a minimum lethal concentration (MLC) of 0.4 μM, which contrasts with a MLC of 23.0 μM for komarovispirone.

(5) Bastien, J. W. *The Kiss of Death, Chagas' Disease in the Americas*; University of Utah Press: Salt Lake City, UT, 1998.

(6) For other strategies to prepare the icetexane skeleton of **1**, see: (a) Padwa, A.; Boonsombat, J.; Rashatasakhon, P.; Willis, J. *Org. Lett.* **2005**, *7*, 3725−3727. (b) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883−2886. (c) Srikrishna, A.; Beeraiah, B. *Tetrahedron Lett.* **2007**, *48*, 2291−2294.

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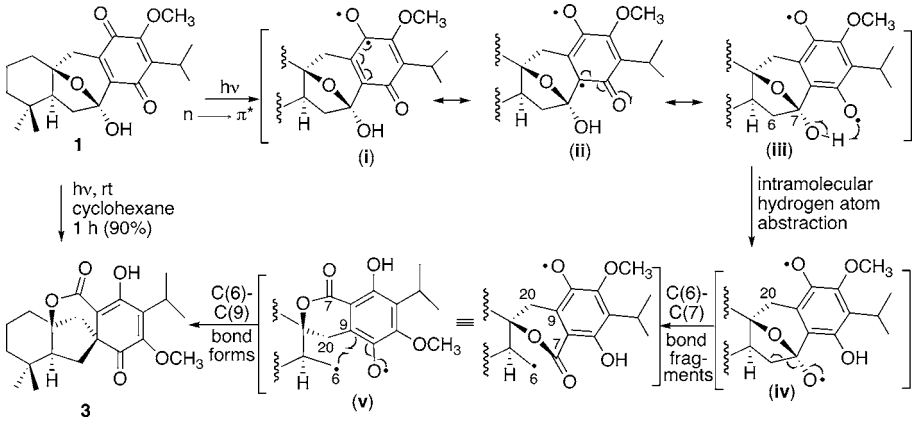
Scheme 2



biogenetic rearrangement of **1** to **3**. We doubted that this isomerization occurs under acidic or basic conditions and were not surprised when komaroviquinone did not rearrange to **3** using common mineral acids, trifluoroacetic acid, TEA, or DBU. We recognized that a photochemically promoted isomerization would convert komaroviquinone to komarovispirone through a fragmentation/coupling process. Indeed, irradiation for 1 h of a deoxygenated solution of komaroviquinone in cyclohexane with 254 nm light produced a 90% yield of (+)-komarovispirone (Scheme 2).[10,11] The spectral data and the optical rotation of our synthetic material matched the reported data for "natural" komarovispirone.[3]

Scheme 2 also presents our mechanistic rationalization for this light-induced isomerization. Excitation of the n → π^* transition of either of the carbonyls of benzoquinone **1** generates a diradical species (cf. resonance contributors **i**, **ii**, and **iii**),[12] which can undergo an intramolecular hydrogen atom abstraction to form diradical **iv**. Fragmentation of **iv** leads to intermediate **v**. Scrutiny of a Dreiding molecular model of **v** reveals that the C(6) free radical is positioned directly above the sp^2-hybridized C(9) carbon atom, thereby facilitating the creation of the C(6)−C(9) σ bond and the C(9) asymmetric center.

Since **1** cleanly photolyzes to only **3**, we were unable to isolate, or trap, any of the proposed intermediates to verify this mechanism. Nevertheless, literature precedents support this mechanism. For example, verbenone (**4**) is photochemically converted into chrysanthenone (**5**) (Scheme 3).[13] The redistribution of electrons in the excited state of **vi** leads to the cleavage of the C(4)−C(7) σ bond to produce tertiary diradical **vii**; coupling of the diradicals at C(2) produces **5**. Of more relevance is the work of Zimmerman and Chapman and their co-workers which showed that cyclic enones, such as **6**, rearrange via diradical species (i.e., **viii** and **ix**).[14] Note that a primary free radical (**ix**) is formed at C(1) by homolytic cleavage of the C(1)−C(10) σ bond which then adds to the styrenyl double bond at C(5) to generate a new more stable tertiary, benzylic free radical (cf. **x**). The coupling of the diradicals of **x** forms the C(2)−C(10) σ bond and ketone **7**.

(7) The spectroscopic data obtained for all new compounds were fully consistent with the assigned structures. Reaction conditions have not been optimized.

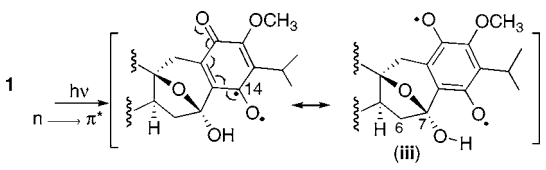
(8) (a) For the first synthesis of (±)-komaroviquinone (**1**), see: Sengupta, S.; Drew, M. G. B.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2005**, *70*, 7694−7700. (b) For our synthesis of (±)-komaroviquinone, see: Majetich, G.; Li, Y.; Zou, G. *Heterocycles* **2007**, *73*, 217−225.

(9) For a synthesis of (+)-komaroviquinone, see: Majetich, G.; Yu, J.; Li, Y. *Heterocycles* **2007**, *73*, 227−235.

(10) (+)-Komaroviquinone (6.0 mg, 0.0167 mmol) was dissolved in 1 mL of dry and deoxygenated cyclohexane. The resulting solution was placed in an ACE glass microscale photochemical reactor[11] and irradiated using a Pen-Ray, 5.5 W low pressure, cold cathode, mercury lamp. After 1 h at room temperature, TLC analysis indicated that all **1** had been consumed. The solvent was evaporated in vacuo, and the resulting crude residue was chromatographed on silica gel (elution with petroleum ether/ethyl acetate, 10:1) to give 5.4 mg (90%) of komarovispirone (**3**) which was homogeneous by TLC analysis (R_f **1** = 0.38, R_f **3** = 0.55, hexanes/EtOAc = 4:1).

(11) Penn, J. H.; Orr, R. D. *J. Chem. Educ.* **1989**, *66*, 86−88.

(12) Scheme 2 depicts only the excitation of the C(11) carbonyl of **1** prior to the generation of diradical species **iii**. If the C(14) carbonyl, a vinylogous ester, is the dominant chromophore, its excitation also results in the intermediacy of **iii**, as shown below.

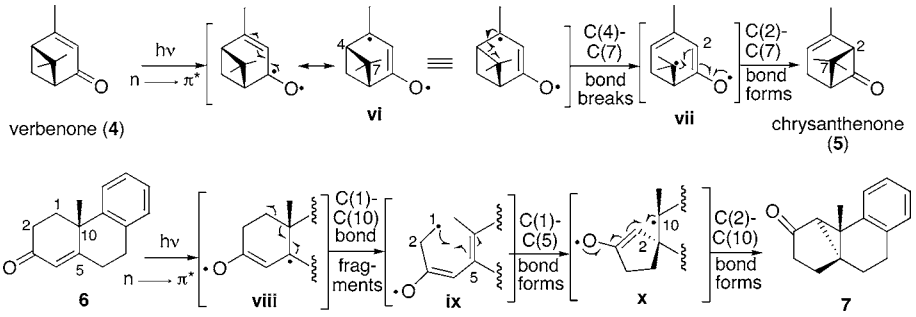


(13) Hurst, J. J.; Whitham, G. H. *J. Chem. Soc.* **1960**, 2864−2869.

(14) (a) Zimmerman, H. E.; Lewis, R. G.; McCullough, J. J.; Padwa, A.; Staley, S.; Semmelhack, M. *J. Am. Chem. Soc.* **1966**, *88*, 159−161. (b) Chapman, O. L.; Sieja, J. B.; Welstead, W. J., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 161−162.

(15) Komarovispirone was isolated as a minor component from a side fraction of a silica gel column in which komaroviquinone was isolated as the major component. It has been suggested that komarovispirone may be produced via the proposed photochemical pathway while still in aerial parts of the semi-shrub *Dracocephalum komarovi* Lipsky prior to isolation. Since the photoisomerization of komaroviquinone to komarovispirone is rapid, if it occurred within the semi-shrub, then komaroviquinone should not have been isolated and komarovispirone would have been the major component isolated.

Scheme 3



Storage of komaroviquinone in deuterochloroform in the dark for 7 days at room temperature confirmed that **1** was stable under these conditions; however, exposing this same solution to daylight at room temperature for 2 days produced **3** and trace quantities of an unknown. These observations, coupled with our photochemically promoted isomerization of komaroviquinone, suggest that komarovispirone is not a natural product but is an artifact of the isolation process.[15]

Acknowledgment. We thank the National Science Foundation (CHE-0506486) for support of this research.

Supporting Information Available: The ^{1}H and ^{13}C NMRs of synthetic (+)-komaroviquinone (**1**) and (+)-komarovispirone have been provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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