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A short and efficient asymmetric synthesis of komaroviquinone

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ABSTRACT

An asymmetric total synthesis of komaroviquinone (**1**), which is a natural product isolated from *Dracocephalum komarovi* and shows novel potent trypanocidal activity, was achieved in five steps from the known starting materials. The synthetic route is shorter and more efficient than the reported methods and also useful for the scale-up synthesis.

Trypanosoma cruzi (*T. cruizi*) is a parasitic protozoan transmitted by bloodsucking triatomine insects and the infection by *T. cruizi* is known as Chagas' disease, which is a main health problem in endemic countries across Central and South America.[1] The disease is potentially life-threatening and acute and/or chronic one is associated with severe complications. However, there are no efficacious vaccines, and anti-chagastic drugs in use such as nifurtimox and benznidazole have undesirable side effects.[2] In addition, the emergence of parasitic drug resistance is also problematic. Thus, the development of new anti-chagastic agents is an urgent requirement and of particular interest.

Recently, novel chemotherapeutic targets for Chagas' disease have been identified with reports that both synthetic compounds[3] and natural products[4] showed attractive trypanocidal activity. Various natural products such as flavonoids and terpenoids have been identified as trypanocidal agents. Among them, komaroviquinone (**1**),[5] isolated from *Dracocephalum komarovi*, exhibited a remarkably high trypanocidal activity specifically against trypomastigotes of *T. cruzi*, known as an infective form in mammalian host. The IC_{50} value in vitro of komaroviquinone (**1**) was reported to be 9 nM against trypomastigotes of *T. cruzi*.[6] The mechanistic study on trypanocidal activity of komaroviquinone (**1**) has been carried out, and its activity is experimentally estimated to be due to reactive oxygen species generated by the reduction of drugs.[6] The key enzyme involved in the generation of reactive oxygen species is known as *T. cruzi* old yellow enzyme (TcOYE),[7] which is expressed in all stages of the parasite life cycle. The old yellow enzymes have been identified in yeasts, plants, and bacteria but not in animals. These results clearly indicate that komaroviquinone (**1**) is a good candidate to develop new anti-chagastic drugs. To date, two groups have reported the total synthesis of komaroviquinone (**1**),[8] however, one[8a] of them is not feasible for the asymmetric synthesis, and the other[8c] is relatively lengthy and not suitable for further investigations. Therefore, to develop new anti-chagastic agents, it is required to establish a well-designed and efficient asymmetric synthetic route to komaroviquinone (**1**), which is amenable to analogs and comprehensive SAR studies. Herein, we report the short and efficient asymmetric synthesis of komaroviquinone (**1**) from the easily accessible starting materials.

The preliminary retro-synthetic analysis is shown in Scheme 1. Based on the retro-synthetic analysis, the construction of the key intermediate **2** having trans 10-hydroxy-1,1-dimethyloctahydrodibenzo [*a*,*d*] cycloheptene-7-one core structure is crucial. Komaroviquinone (**1**) was synthesized from the intermediate **2** by reported procedure.[8a] Under the oxidative conditions of the aromatic part of the intermediate **2**, the seven membered hemiketal was simultaneously formed. The intermediate **2** should be obtained via intra-molecular nucleophilic addition to the lactone moiety of **3**. Lactone **3** would be synthesized from **4** through hydrolysis and cyclization under acidic conditions. Negishi coupling reaction between vinyl iodide **5** and benzyl bromide **6** would afford the ester **4**. Both vinyl iodide **5**[10] and benzyl bromide **6**[8b,9] are known compounds and can be synthesized in three and six steps from commercially available compound, respectively.

Negishi coupling reaction[11] of benzyl bromide **6** with vinyl iodide **5**, which was prepared in 98% ee from 4,4-dimethyl-2-cyclohexen-1-one, was initially carried out, and the reaction smoothly proceeded at room temperature in the presence of 2.5 mol % of $Pd(PPh_3)_2Cl_2$ to give **4** in 82% yield (Scheme 2). Hydrolysis of the ester moiety of **4**, and the following cyclization reaction afforded lactone **3** in 93% yield in a highly diastereoselective manner. The relative configuration of **3** was confirmed by NOESY. Iodination of **3** was carried out using NIS in the presence of catalytic amount of acid. After treatment of **7** with isopropylmagnesium chloride at −40 °C, the subsequent intra-molecular nucleophilic cyclization proceeded smoothly at the same temperature to afford compound **2** in 96% yield.[12] Compound **2** exists in equilibrium with hemiketal **8** in solution[8a] as revealed by the ^1H and ^{13}C NMR spectra (see Supplementary data and Ref. 8a). The direct oxidation of this mixture of **2** and **8** with Ag(II)O in diluted HNO_3 gave komaroviquinone (**1**) as

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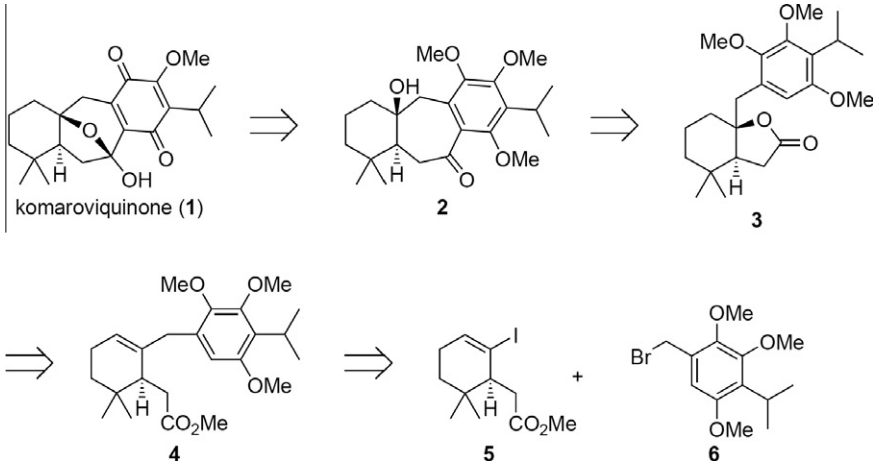
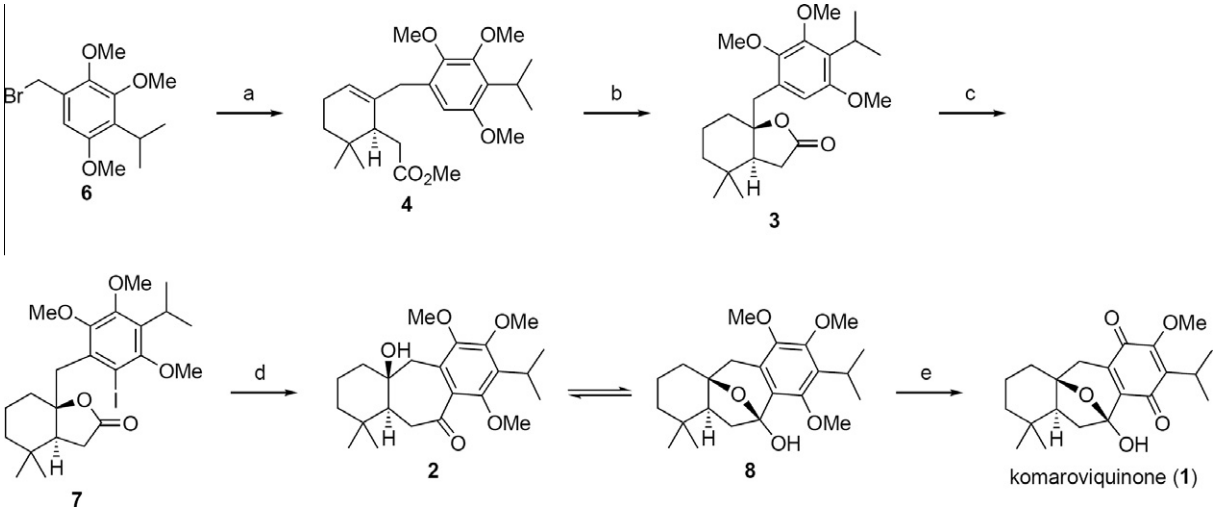


Scheme 1. Synthetic plan.



Scheme 2. Synthetic route to komaroviquinone. Reagents and conditions: (a) (1) Zn, THF, 0 °C then rt; (2) **5** (98% ee), $PdCl_2(PPh_3)_2$ (2.5 mol %), DMF/THF, rt, 82%; (b) 3 N HCl, $AcOH/H_2O$, 70 °C, 93%; (c) NIS, TsOH, 1,2-dichloroethane, 45 °C, 92%; (d) ^iPrMgCl, Et_2O, −40 °C, 96%; (e) AgO, HNO_3, 1,4-dioxane/H_2O, 10 °C, 65%.

the isolable product.[8a] All spectral data of synthetic komaroviquinone (**1**) were consistent with those reported in the literature, and the absolute configuration was confirmed to be identical with the natural material by optical rotation.[5a]

In summary, we succeeded in developing a short and efficient asymmetric synthetic route to komaroviquinone (**1**). Under the optimized conditions, the known precursor (**2**) was obtained in 67% overall yield via four steps from known compounds **5** and **6**. Further studies to develop new anti-chagastic agents are now ongoing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.110.

References and notes

1. (a) Dias, J. C. *Mem. Inst. Oswaldo Cruz* **2009**, *104*, 41–45; (b) de Souza, W. *Microbes Infect.* **2007**, *9*, 544.
2. Castro, J. A.; deMecca, M. M.; Bartel, L. C. *Human Exp. Toxicol.* **2006**, *25*, 471.
3. (a) Sanchez-Sancho, F.; Campillo, N. E.; Paez, J. A. *Curr. Med. Chem.* **2010**, *17*, 423; (b) Rivera, G.; Bocanegra-Garcia, V.; Ordaz-Pichardo, C.; Nogueda-Torres, B.; Monge, A. *Curr. Med. Chem.* **2009**, *16*, 3286; (c) Duschak, V. G.; Couto, A. S. *Recent Patent Anti-Infective Drug Discov.* **2007**, *2*, 19.
4. Uchiyama, N. *J. Health Sci.* **2009**, *55*, 31.
5. (a) Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128; (b) Uchiyama, N.; Ito, M.; Kiuchi, F.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *Tetrahedron Lett.* **2004**, *45*, 531.
6. Uchiyama, N.; Kabututu, Z.; Kubata, B. K.; Kiuchi, F.; Ito, M.; Nakajima-Shimada, J.; Aoki, T.; Ohkubo, K.; Fukuzumi, S.; Martin, S. K.; Honda, G.; Urade, Y. *Antimicrob. Agents Chemother.* **2005**, *49*, 5123.
7. Kubata, B. K.; Kabututu, Z.; Nozaki, T.; Munday, C. J.; Fukuzumi, S.; Ohkubo, K.; Lazarus, M.; Maruyama, T.; Martin, S. K.; Duszenko, M.; Urade, Y. *J. Exp. Med.* **2002**, *196*, 1241.
8. (a) Sengupta, S.; Drew, M. G. B.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2005**, *70*, 7694; (b) Majetich, G.; Li, Y.; Zou, G. *Heterocycles* **2007**, *73*, 217; (c) Majetich, G.; Yu, J.; Li, Y. *Heterocycles* **2007**, *73*, 227.
9. Majetich, G.; Grove, J. L. *Org. Lett.* **2009**, *11*, 2904.
10. Jan, N. W.; Liu, H. J. *Org. Lett.* **2006**, *8*, 151.
11. Negishi, E.; Tan, Z.; Liou, S. Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197.
12. Werner, T.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 4302.