Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7205–7207

TETRAHEDRON LETTERS

# Reaction modes of oxidative dimerization of epoxycyclohexenols

Mitsuru Shoji,[a] Satoshi Kishida,[a] Yusuke Kodera,[a] Isamu Shiina,[b] Hideaki Kakeya,[c] Hiroyuki Osada[c] and Yujiro Hayashi[a,*]

[a]*Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*

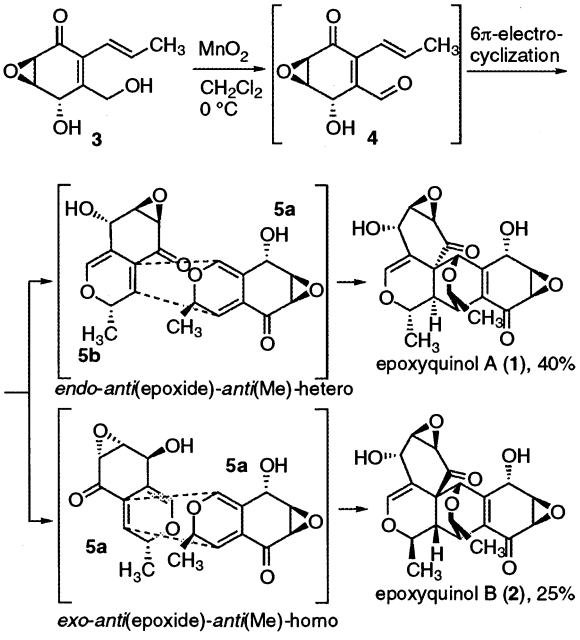
[b]*Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*

[c]*Antibiotics Laboratory, Discovery Research Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan*

Received 25 June 2003; revised 14 July 2003; accepted 18 July 2003

**Abstract**—Of the 16 possible modes of the oxidation-6π-electrocylization-Diels–Alder reaction cascade for an epoxyquinone, and eight for a 2-alkenyl-3-hydroxymethyl-2-cyclohexen-1-one, only the *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *endo*-*anti*(Me)-hetero are respectively observed, while both the *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *exo*-*anti*(epoxide)-*anti*(Me)-homo reaction modes occur with epoxy-4-hydroxycyclohexenones owing to a hydrogen-bonding interaction.


Recently we have reported the first asymmetric total synthesis of epoxyquinols A (**1**)[1] and B (**2**),[2] novel angiogenesis inhibitors with a highly-functionalized and complicated heptacyclic ring system containing 12 stereocenters, and determined their absolute stereochemistry.[3] Key steps of the synthesis are the $HfCl_4$-mediated Diels–Alder reaction of furan[4] with the acrylate of Corey's chiral auxiliary, and a biomimetic, oxidative Diels–Alder reaction of monomer **3**. We have also established a practical synthetic route to both enantiomers of epoxyquinols A and B using the chromatography-free preparation of an iodolactone and a lipase-mediated kinetic resolution as key steps.[5] Soon after our first synthesis, Porco et al. published an elegant synthesis of epoxyquinols A and B,[6] and just recently Mehta et al. have also reported the synthesis of racemic epoxyquinols A and B.[7] In our biomimetic oxidative dimerization (Scheme 1), oxidation of monomer **3** with $MnO_2$ afforded an aldehyde **4**, which was converted to 2*H*-pyran derivatives **5a**/**b** via 6π-electrocyclization. Hetero-dimerization of **5a** and **5b**, in which the reacting diene face in the Diels–Alder reaction is *anti* to the diene epoxide (*anti*(epoxide)) and *anti* to Me group (*anti*(Me)), afforded epoxyquinol A (**1**) via the orbitally-preferred *endo*-transition state (*endo*-*anti*(epoxide)-*anti*(Me)-hetero),[8] while homo dimerization of **5a**, also in which face of the diene *anti* to both the epoxide and Me group reacts, gave epoxyquinol B (**2**) via the *exo*-mode (*exo*-*anti*(epoxide)-*anti*(Me)-homo).[8] Although there are 16 possible reaction

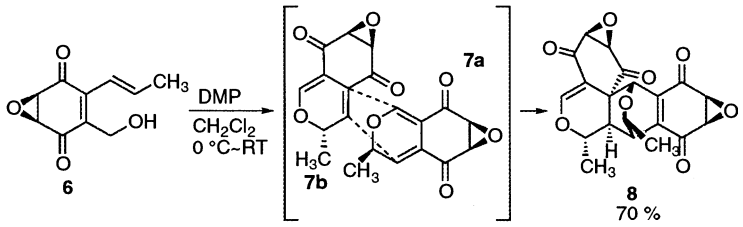



**Scheme 1.** Oxidative dimerization of the monomer **3**.

*Keywords*: Diels–Alder reaction; 6π-electrocylization; hydrogen-bonding; epoxyquinol.

* Corresponding author. Fax: +81-3-5261-4631; e-mail: hayashi@ci.kagu.tus.ac.jp

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01781-7

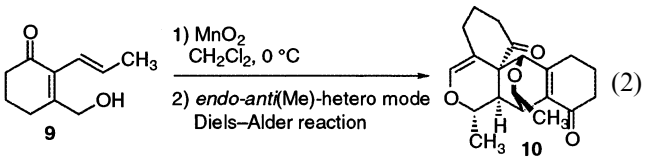



(1)

modes,[9] only the *endo-anti*(epoxide)-*anti*(Me)-hetero and *exo-anti*(epoxide)-*anti*(Me)-homo have been observed. In order to clarify the reaction course, we have investigated the oxidative dimerization with monomers possessing different substituents, with results disclosed in this paper.

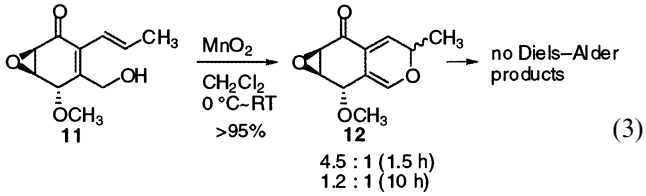
In the course of our total synthesis of epoxyquinols A and B, we examined carefully the oxidation of monomer **3** and observed the following interesting phenomenon: When monomer **3** was treated with the Dess–Martin periodinane (DMP),[10] both primary and secondary hydroxy groups were oxidized, affording cyclized 2*H*-pyran derivatives **7a**/**b**, which gave *endo-anti*(epoxide)-*anti*(Me)-hetero mode-dimerized product **8** (epoxyquinol A-type) in 21% yield without formation of the *exo-anti*(epoxide)-*anti*(Me)-homo product (epoxyquinol B-type). The yield of **8** was increased to 70% when isolated epoxyquinone **6**[11] was treated with DMP (Eq. (1)). Porco et al. also reported the same phenomenon in the syntheses of epoxyquinol A,[6] torreyanic acid[12] and jesterone dimer (unnatural product).[13] Epoxycyclohexenol **3** is oxidatively dimerized via both the *endo-anti*(epoxide)-*anti*(Me)-hetero and *exo-anti*(epoxide)-*anti*(Me)-homo modes, while only the *endo-anti*(epoxide)-*anti*(Me)-hetero dimer is formed in the dimerization of epoxyquinone **6**.

As **3** has both epoxy and secondary hydroxy groups on the cyclohexene ring, the oxidative dimerization of a monomer **9** without these functional groups has been examined (Eq. (2)). Oxidation of **9**[11] afforded the corresponding aldehyde quantitatively, and this was allowed to stand neat at room temperature, affording epoxyquinol A-type dimer **10** (*endo-anti*(Me)-hetero mode) in 70% yield after 10 h, while none of the epoxyquinol B-type dimer obtained. That is, of the eight possible reaction modes,[14] only the *endo-anti*(Me)-hetero occurred.




(2)

Of the monomers examined, only **3** having the secondary hydroxy group afforded both epoxyquinol A and B dimers, while the other monomers **6** and **9** gave only epoxyquinol A-type dimer. To investigate the effect of this secondary hydroxy group, it was converted to its methyl ether. Oxidation and 6π-electrocyclization of **11**[11] proceeded smoothly, affording a 4.5:1 diastereo-mixture of 2*H*-pyran derivative **12** (Eq. (3)). Although the diastereomer ratio of **12** had changed to 1.2:1 after 10 h, no Diels–Alder reaction occurred under various reaction conditions.




(3)

These results clearly indicate that the secondary hydroxy group is important not only for the formation of epoxyquinol B, but also to accelerate the Diels–Alder reaction. As illustrated in Figure 1, the secondary hydroxy group may be important in the dimerization because a hydrogen-bond is possible in the transition states leading to both epoxyquinols A and B.

In the *endo-anti*(epoxide)-*anti*(Me)-hetero Diels–Alder reaction a hydrogen-bond could activate the ketone function, while the two monomers may interact with each other by hydrogen-bonding in the *exo-anti*(epoxide)-*anti*(Me)-homo Diels–Alder reaction.[15] This latter assumption is reasonable because a hydrogen-bond between these two OHs has in fact been observed in the crystal structure of epoxyquinol B.[6] Moreover, if these hydrogen-bonds exist, the distribution of epoxyquinols A and B should be affected by solvent, which is found

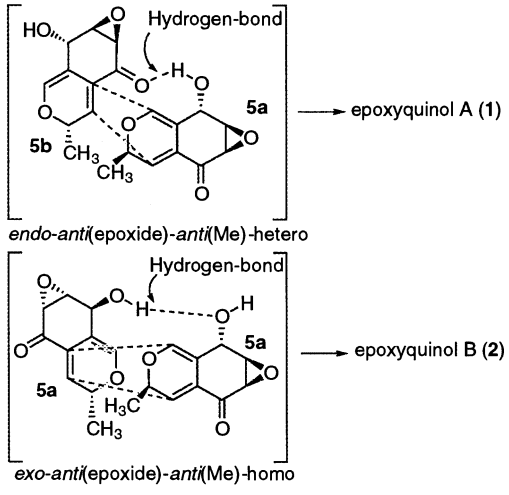



**Figure 1.** Hydrogen-bond in the transition states.

to be the case although its precise mechanism is not clear. As shown in Table 1, epoxyquinol A (**1**) was formed predominantly in neat conditions or in benzene solution, while epoxyquinol B (**2**) was the major product in toluene and $CH_2Cl_2$. Lewis acids such as $LiClO_4$[16] accelerate the reaction, affording epoxyquinol A predominantly. This is a piece of evidence that the orbitally-preferable mode is *endo*-*anti*(epoxide)-*anti*(Me)-hetero even in the 4-hydroxycyclohexenone case **3**.

**Table 1.** Solvent effect on the oxidative dimerization of **3**

| Entry | Solvent | Time (h) | Yield (%) | |
|---|---|---|---|---|
| | | | **1** | **2** |
| 1 | Neat | 4 | 40 | 25 |
| 2 | $LiClO_4/Et_2O$ | 2.5 | 46 | 25 |
| 3 | Benzene | 12 | 39 | 32 |
| 4 | Toluene | 12 | 25 | 45 |
| 5 | $CH_2Cl_2$ | 33 | 21 | 38 |
| 6 | $Et_2O$ | 46 | 25 | 21 |
| 7 | MeOH | 94 | 21 | 21 |
| 8 | $CH_3CN$ | 140 | 14 | 21 |

Of the sixteen or eight possible reaction modes for the oxidative dimerization, only the *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *endo*-*anti*(Me)-hetero modes were observed in the reactions of epoxyquinone **6** and cyclohexenone **9**, respectively, while both the *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *exo*-*anti*(epoxide)-*anti*(Me)-homo modes occurred in the reaction of epoxy-4-hydroxycyclohexenone **3**. The *anti*(epoxide)-*anti*(Me) mode is favorable because this face of the diene (*anti* to epoxide and *anti* to Me group) is sterically accessible.[17] The *endo*-mode is preferred according to the Frontier orbital theory (*endo*-rule).[18] Among *anti*(epoxide)-*anti*(Me) modes, the *endo*-homo and *exo*-hetero modes are disfavored,[6] because of the steric hindrance between the methyl groups of diene and dienophile. The *endo*-hetero mode is orbitally and sterically favorable since the methyl groups of diene and dienophile orient themselves away from one another to avoid steric hindrance.[6] The epoxy-4-hydroxycyclohexenone is a special case, in which both *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *exo*-*anti*(epoxide)-*anti*(Me)-homo modes occur because of the hydrogen-bonding interactions shown in Figure 1.

In summary, in the oxidative dimerization of 2-alkenyl-3-hydroxymethyl-2-cyclohexen-1-ones, the preferred reaction mode is the *endo*-*anti*(epoxide)-*anti*(Me)-hetero, affording the epoxyquinol A-type product, while both epoxyquinol A- and B-type products are formed via the *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *exo*-*anti*(epoxide)-*anti*(Me)-homo modes in substrates with a 4-hydroxygroup owing to intermolecular hydrogen-bonding.

Further studies, including the theoretical calculations, are under progress, and will be reported in due course.

## Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

## References

1. Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496.
2. Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829.
3. Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192.
4. Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4079.
5. Shoji, M.; Kishida, S.; Takeda, M.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2002**, *43*, 9155.
6. Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.; Gilmore, T. D.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 3267.
7. Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 3569.
8. In this paper the designation of '*endo*' and '*exo*' follows that in the paper by Porco et al.,[6] and is different from that in our previous reference.[3]
9. The 16 possible reaction modes are as follows: *endo*-*anti*(epoxide)-*anti*(Me)-hetero, *exo*-*anti*(epoxide)-*anti*-(Me)-homo, *endo*-*anti*(epoxide)-*anti*(Me)-homo, *exo*-*anti*(epoxide)-*anti*(Me)-hetero, *endo*-*anti*(epoxide)-*syn*-(Me)-hetero, *exo*-*anti*(epoxide)-*syn*(Me)-homo, *endo*-*anti*(epoxide)-*syn*(Me)-homo, *exo*-*anti*(epoxide)-*syn*(Me)-hetero, *endo*-*syn*(epoxide)-*anti*(Me)-hetero, *exo*-*syn*(epoxide)-*anti*(Me)-homo, *endo*-*syn*(epoxide)-*anti*(Me)-homo, *exo*-*syn*(epoxide)-*anti*(Me)-hetero, *endo*-*syn*(epoxide)-*syn*(Me)-hetero, *exo*-*syn*(epoxide)-*syn*(Me)-homo, *endo*-*syn*(epoxide)-*syn*(Me)-homo, *exo*-*syn*(epoxide)-*syn*(Me)-hetero.
10. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4115; (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277; (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
11. Syntheses of **6**, **9** and **11** will be published in a full account.
12. (a) Li, C.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484; (b) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095.
13. Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A., Jr. *Org. Lett.* **2001**, *3*, 1649.
14. Because of the lack of epoxide in **9**, the number of possible reaction modes is reduced from sixteen in **3** to eight.
15. References using inter-molecular hydrogen-bonding for the control of stereochemistry of Diels–Alder reaction, see: (a) Atherton, C. J. C.; Jones, S. *Tetrahedron Lett.* **2001**, *42*, 8239; (b) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 6743; (c) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625.
16. Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.
17. Gillard, J. R.; Newlands, M. J.; Bridson, J. N.; Burnell, D. J. *Can. J. Chem.* **1991**, *69*, 1337.
18. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: Chichester, UK, 1976.