Total Synthesis of (+)-Epoxyquinols A and B**

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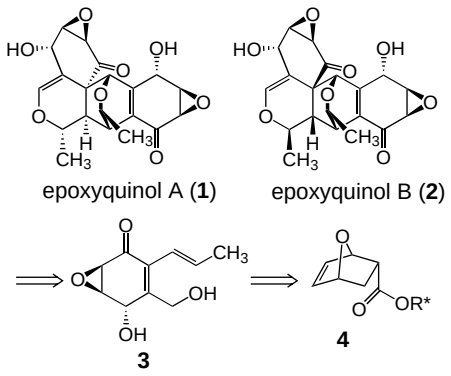
Angiogenesis inhibitors are promising drugs for the treatment of angiogenesis-related diseases such as cancer.[1] We have recently reported the isolation and structural determination of unique pentaketide dimers, epoxyquinols A (**1**)[2] and B (**2**; Scheme 1),[3] which show anti-angiogenic activity, but have different structural properties from the known



Scheme 1. Retrosynthesis of epoxyquinols A(**1**) and B (**2**).

angiogenesis inhibitors. To facilitate elucidation of the mechanism of action of epoxyquinols A and B, the development of a method for their total synthesis and derivatization is highly desirable. Though structurally epoxyquinols A and B have a highly functionalized and complicated heptacyclic ring system containing 12 stereocenters, biosynthetically it is proposed they are formed by an unusual oxidative dimerization of the much simpler epoxycyclohexenone **3** (Scheme 1).[2,3] Herein we report the first total synthesis of the naturally occurring enantiomers of (+)-epoxyquinols A and B using the postulated biomimetic oxidative dimerization, along with determination of their absolute stereochemistry.

The monomer **3** of epoxyquinols A and B was the initial target. The synthesis starts from the Diels–Alder reaction between furan and a chiral dienophile,[4] which is planned in such a way to establish the correct stereochemistry and introduce all the carbon atoms except those in the side chain. Though there are a number of methods for the diastereoselective Diels–Alder reaction of a chiral acrylate ester with furan,[5] few of these are synthetically useful with high *endo/exo* selectivities and diastereoselectivities. The low selectivities can be attributed to rapid *endo/exo* isomerization and/or to a retro-Diels–Alder reaction, which occurs at around −20 °C.[5c] Recently we have found that $HfCl_4$ is a highly efficient Lewis acid in the Diels–Alder reaction of furan, and enables the reaction to proceed at low temperature.[6] Thus, the $HfCl_4$-mediated Diels–Alder reaction of furan was applied to the chiral acrylate ester derived from Corey's chiral auxiliary ((−)-(1*R*,2*R*)-2-(naphthalene-2-sulfonyl)cyclohexanol),[7] in the expectation of high selectivity. In fact, in the presence of $HfCl_4$, the chiral acrylate ester **5** reacted with furan in toluene at low temperature (−45 °C) over 48 h to give the cycloadducts **4** in good yield with moderate *endo/exo* selectivities and high diastereoselectivities (Scheme 2).

The next stage was the preparation of *endo*-epoxide **7**. As an *exo*-epoxide was obtained by the direct epoxidation reaction of **4**,[8] a novel method was developed for the selective formation of the *endo*-epoxide via the iodolactone **6**. Though the usual two-step procedure (hydrolysis and iodolactonization) afforded iodolactone **6** in good yield, the chiral auxiliary was recovered in only 40% yield along with 55% of 1-(naphthalene-2-sulfonyl)cyclohexene. On the other hand, direct treatment of the *endo* isomer with I_2 in aqueous CH_3CN afforded iodolactone **6** in 81% yield with recovery of the chiral auxiliary in 94% yield. After recrystallization, optically pure lactone **6** was obtained, and its absolute stereochemistry was determined by comparing its optical rotation with that in the literature.[9] Though the direct transformation of iodolactone **6** to epoxy methyl ester **7** in MeOH under a variety of basic conditions was unsuccessful, a two-step conversion (hydrolysis and esterification) worked well: Treatment of **6** with KOH in DMF at 60 °C for 10 h, followed by esterification with MeI under sonication conditions for 1 h, furnished **7** in one pot, in high yield (94%).

Exposure of **7** to lithium diisopropylamide (LDA) at −90 °C for 30 min led to β-elimination, affording hydroxy ester **8**. An excess of LDA should be avoided owing to Michael addition of diisopropylamine to **8**, which provides a β-amino ester as a side product. Hydroxyl-directed epoxidation of homoallylic alcohol **8** using a catalytic amount of $[VO(acac)_2]$ (acac = acetylacetonate) and excess *tert*-butyl hydroperoxide (TBHP) under reflux in CH_2Cl_2[10] proceeded to give diepoxide **9** as a single isomer in high yield. Although reduction of ester **9** with diisobutylaluminum hydride (DIBAL) proceeded smoothly, the yield of the diol **10** was quite low owing to its water solubility. Thus, a nonaqueous workup was examined: Reduction with $NaBH_4$ in MeOH at room temperature for 15 min, removal of solvent, and flash column chromatography afforded the diol **10**. The primary alcohol of the diol **10** was selectively protected with *tert*-butyldimethylsilyl chloride (TBSCl), affording **11** in 81% yield over two steps. Though the oxidation of **11** with SO_3·pyridine[11] afforded an epoxyquinone,[12] the over-oxidation product of **12**, the use of the Dess–Martin periodinane[13] gave the desired β,γ-epoxyketone without formation of this by-product. Isomerization

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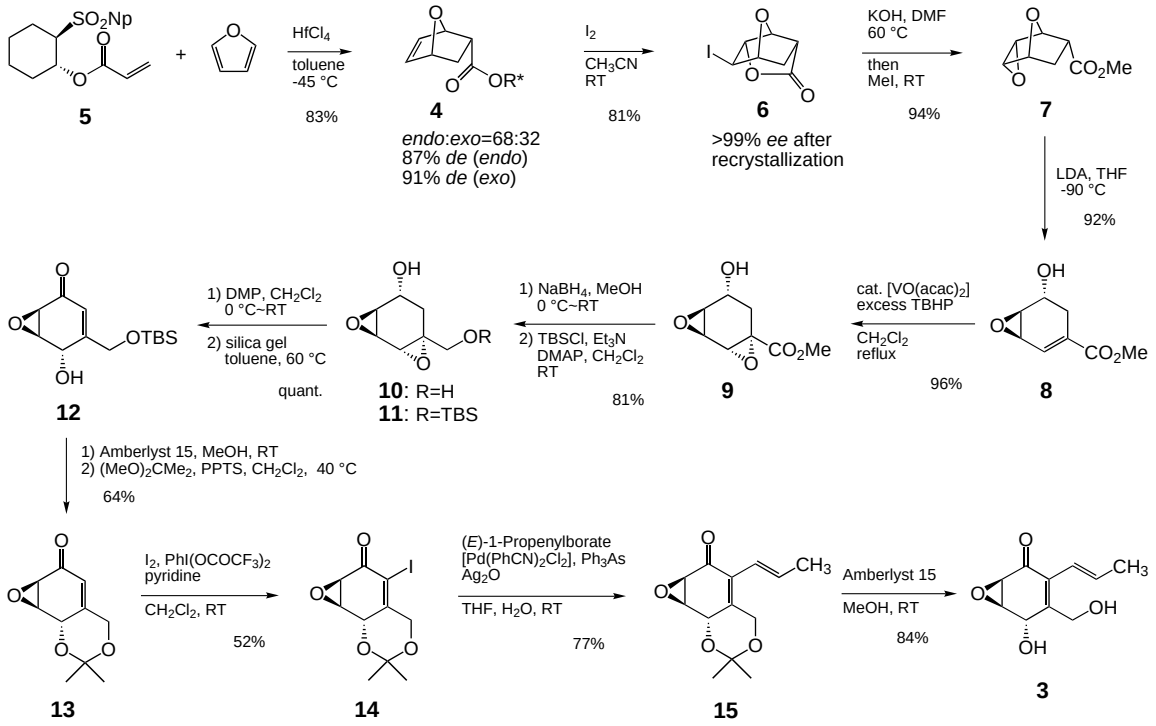
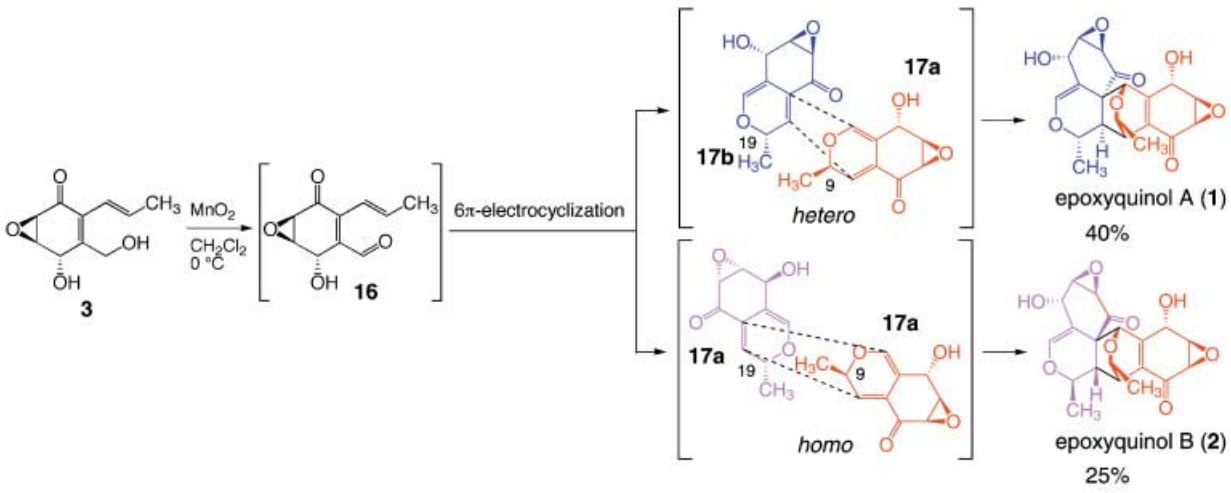


Scheme 2. Synthesis of the monomeric precursor **3** of epoxyquinols A (**1**) and B (**2**). DMAP = 4-dimethylaminopyridine; PPTS = pyridinium toluenesulfonate; for other abbreviations see text.

occurred on treatment of β,γ-epoxyketone with silica gel at 60 °C in toluene for 4 h,[14] affording α,β-unsaturated ketone **12** quantitatively over two steps.

The α-iodonation of cyclohexenone **12** was problematic, and the choice of diol protecting group and iodination reagent was found to be important for the success of this reaction: None of the desired product was obtained on treatment of hydroxy ketone **12** with I_2/DMAP[15] or I_2/trimethylsilylazide ($TMSN_3$)[16] and only a low yield was observed in the reaction using I_2/PhI$(OCOCF_3)_2$/pyridine.[17] On the other hand, the reaction of I_2/PhI$(OCOCF_3)_2$/pyridine with the corresponding acetonide **13** (prepared in 64% yield from **12** over two steps: 1) deprotection of the *tert*-butyldimethylsilyl group with Amberlyst in MeOH, and 2) protection of the resulting 1,3-diol with 2,2-dimethoxypropane) gave the iodinated cyclohexenone **14** in moderate yield. As **14** is labile, it was immediately subjected to the Suzuki coupling reaction with *trans*-1-propenylborate[18] under Johnson's conditions,[19] affording dienone **15** in 77% yield. Cleavage of the acetonide group under acidic conditions provided monomer **3** in 84% yield.

Next the biomimetic oxidative dimerization was examined. After several experiments, it was found that the monomer **3** could be directly oxidized without protection of the secondary hydroxy group. That is, the oxidation proceeded on treatment of epoxycyclohexenol **3** with excess MnO_2[20] in CH_2Cl_2 for



Scheme 3. Biomimetic dimerization approach towards epoxyquinols A (**1**) and B (**2**).

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40 min at 0 °C (Scheme 3), affording hydroxyaldehyde **16** and 2*H*-pyran derivatives **17a** and **17b** which would be formed by 6π-electrocyclization reaction of the former. The dimerization reaction proceeded when the crude oxidized mixture was allowed to stand at room temperature without solvent. After 4 h, epoxyquinols A (**1**) and B (**2**) were isolated in 40 and 25 % yields, respectively. Epoxyquinol A (**1**) is a heterodimer of **17a** and **17b**, which would be generated by an *exo* intermolecular Diels–Alder reaction with the *anti* stereochemistry at the C_9 and C_{19} methyl positions to reduce the steric hindrance at these positions.[2] On the other hand, epoxyquinol B (**2**) is a homodimer of **17a**, which would be generated by an *endo* intermolecular Diels–Alder reaction, also with the sterically favored *anti* stereochemistry at the C_9 and C_{19} methyl positions.[3] In their recent elegant total synthesis of torreyanic acid[21] and jesterone dimer (unnatural product),[22] Porco, Jr. et al. have demonstrated the oxidative dimerization of epoxyquinones, in which only heterodimers were formed. As shown by the dimerization of **3**, not only epoxyquinones, but also epoxycyclohexenones can be oxidatively dimerized to form highly functionalized heptacyclic ring systems, in which both hetero- and homodimerizations occur.

Synthetic epoxyquinols A (**1**) and B (**2**) exhibited identical properties to those of the natural substances (^{1}H NMR, ^{13}C NMR, IR). Comparison of the optical rotation (synthetic epoxyquinol A; $[\alpha]_D^{22} = +60$ ($c = 0.17$, MeOH), natural epoxyquinol A;[2] $[\alpha]_D^{21} = +61.0$ ($c = 0.146$, MeOH), synthetic epoxyquinol B; $[\alpha]_D^{21} = +150$ ($c = 0.060$, MeOH), natural epoxyquinol B;[3] $[\alpha]_D^{21} = +153.0$ ($c = 0.315$, MeOH)) determined the absolute stereochemistry to be as shown in **1** and **2**.

In summary, the first total synthesis of epoxyquinols A (**1**) and B (**2**) has been achieved, and their absolute stereochemistry has been determined. The combination of $HfCl_4$ and the chiral acrylate ester of Corey's auxiliary enables the highly diastereoselective Diels–Alder reaction of furan, which established the correct stereochemistry. All 12 chiral centers of epoxyquinols A and B are controlled by the highly diastereoselective reactions in the route from the initial Diels–Alder product. A diastereoselective synthesis of *endo*-epoxide **7** via iodolactone **6**, and a biomimetic oxidative 6π-electrocyclization, followed by Diels–Alder reaction of the nonprotected diol monomer **3** are other noteworthy features of the synthesis.

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[1] a) J. Folkman, *J. Natl. Cancer Inst.* **1990**, *82*, 4; b) W. Risau, *Nature*, **1997**, *386*, 671; c) M. Klagsbrum, M. A. Moses, *Chem. Biol.* **1999**, *6*, R217; d) G. Gasparini, *Drugs* **1998**, *58*, 17.

[2] H. Kakeya, R. Onose, H. Koshino, A. Yoshida, K. Kobayashi, S.-I. Kageyama, H. Osada, *J. Am. Chem. Soc.* **2002**, *124*, 3496.

[3] H. Kakeya, R. Onose, A. Yoshida, H. Koshino, H. Osada, *J. Antibiot.* submitted.

[4] Recent review of asymmetric Diels–Alder reactions: Y. Hayashi, Catalytic Asymmetric Diels–Alder Reactions in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jorgensen), Wiley-VCH, Weinheim, **2001**, pp. 5–56; Review of Diels–Alder reaction of furan; C. O. Kappe, S. S. Murphree, A. Padwa, *Tetrahedron* **1997**, *53*, 14179; Review of optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives; P. Vogel, D. Fattori, F. Gasparini, C. L. Drian, *Synlett* **1990**, 173.

[5] Catalytic asymmetric reaction by the use of a chiral Lewis acid; a) E. J. Corey, T. P. Loh, *Tetrahedron Lett.* **1993**, *34*, 3979; b) I. Yamamoto, K. Narasaka, *Chem. Lett.* **1995**, 1129; c) D. A. Evans, D. M. Barnes, *Tetrahedron Lett.* **1997**, *38*, 57. Diastereoselective reaction by the use of chiral dienophile; d) H. Takayama, A. Iyobe, T. Koizumi, *J. Chem. Soc. Chem. Commun.* **1986**, 771; e) J. M. Fraile, J. I. Garcia, D. Gracia, J. A. Mayoral, E. Pires, *J. Org. Chem.* **1996**, *61*, 9479; f) J. Adrio, J. C. Carretero, J. L. G. Ruano, L. M. M. Cabrejas, *Tetrahedron: Asymmetry* **1997**, *8*, 1623; g) O. Arjona, F. Iradier, R. Medel, J. Plumet, *Tetrahedron: Asymmetry* **1999**, *10*, 2237; h) M. J. Burke, M. M. Allan, M. Parvez, B. A. Keay, *Tetrahedron: Asymmetry* **2000**, *11*, 2733, and references therein.

[6] Y. Hayashi, M. Nakamura, S. Nakao, T. Inoue, M. Shoji, unpublished results.

[7] G. Sarakinos, E. J. Corey, *Org. Lett.* **1999**, *1*, 1741.

[8] a) M. M. Campbell, A. D. Kaye, M. Sainsbury, R. Yavarzadeh, *Tetrahedron Lett.* **1984**, *25*, 1629; b) M. M. Campbell, A. D. Kaye, M. Sainsbury, R. Yavarzadeh, *Tetrahedron* **1984**, *40*, 2461; c) D. Rajapaksa, B. A. Keay, R. Rodrigo, *Can. J. Chem.* **1984**, *62*, 826.

[9] Literature data; $[\alpha]_D^{25} = -113$ ($c = 1.04$, $CHCl_3$). S. Ogawa, M. Yoshikawa, T. Taki, *J. Chem. Soc. Chem. Commun.* **1992**, 406. Synthetic **6**; $[\alpha]_D^{23} = -114$ ($c = 0.906$, $CHCl_3$).

[10] a) K. B. Sharpless, R. C. Michaelson, *J. Am. Chem. Soc.* **1973**, *95*, 6136; b) R.-M. Meier, C. Tamm, *Helv. Chim. Acta* **1991**, *74*, 807.

[11] J. R. Parikh, W. van E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505.

[12] 2-(*tert*-Butyldimethylsilyloxymethyl)-5,6-epoxy-2-cyclohexene-1,4-dione was obtained as a major by-product.

[13] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4115; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277; c) R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899.

[14] P. Yadagiri, S. Lumin, P. Mosset, J. Capdevila, J. R. Falck, *Tetrahedron Lett.* **1986**, *27*, 6039.

[15] M. T. Barros, C. D. Maycock, M. R. Ventura, *Chem. Eur. J.* **2000**, *6*, 3991.

[16] C.-K. Sha, S.-J. Huang, *Tetrahedron Lett.* **1995**, *36*, 6927.

[17] R. Benhida, P. Blanchard, J.-L. Fourrey, *Tetrahedron Lett.* **1998**, *39*, 6849.

[18] a) A. S.-Y. Lee, W.-C. Dai, *Tetrahedron* **1997**, *53*, 859; b) D. S. Matteson, P. K. Jesthi, *J. Organometal. Chem.* **1976**, *110*, 25.

[19] F. S. Ruel, M. P. Braun, C. R. Johnson, *Org. Synth.* **1997**, *75*, 69.

[20] T. Aoyama, N. Sonoda, M. Yamauchi, K. Toriyama, M. Anzai, A. Ando, T. Shioiri, *Synlett* **1998**, 35.

[21] C. Li, E. Lobkovsky, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2000**, *122*, 10484.

[22] Y. Hu, C. Li, B. A. Kulkarni, G. Strobel, E. Lobkovsky, R. M. Torcznski, J. A. Porco, Jr., *Org. Lett.* **2001**, *3*, 1649.

  0044-8249/02/4117-3194 $ 20.00+.50/0