

Efficient Asymmetric Synthesis of Chiral Monomer of Epoxyquinols and (-)-Phyllostine

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Angiogenesis, the formation and growth of new blood capillaries from preexisting vessels, is a vital function for tumor growth and metastasis.¹ Therefore, the inhibition of angiogenesis is believed to be an important approach for developing new drugs in cancer chemotherapy. Indeed, several angiogenesis inhibitors from natural products, such as endostatin² and TNP-470,³ are undergoing clinical trials.⁴ In addition to the application in oncology, anti-angiogenic drugs are in demand for various diseases that are associated with pathological angiogenesis, including rheumatoid arthritis and diabetic retinopathy.⁵

In 2002, Osada and co-workers reported the isolation and structural elucidation of two novel angiogenesis inhibitors, epoxyquinols A^{6a} and B^{6b} from fungal metabolites. These compounds have been known to inhibit the VEGF (vascular endothelial growth factor)-induced migration. Recent studies showed **2** is a novel multiple kinase inhibitor, suggesting that **2** would be a good lead compound for the development of potent antiangiogenic and antitumor drugs.⁷

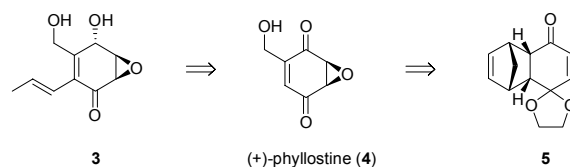
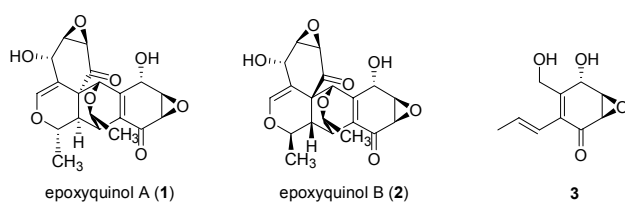
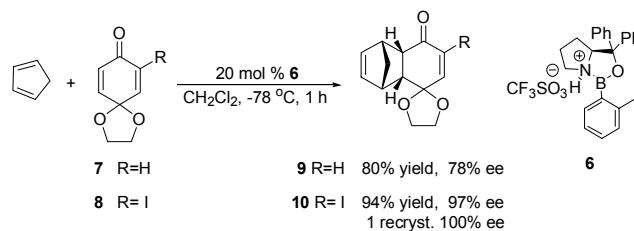
Since Hayashi and co-workers first proved that epoxyquinols **1** and **2** are synthesized from monomeric pentaketide precursor **3** by oxidative dimerization,^{8a} the efficient enantioselective synthesis of **3** is an essential strategy to obtain large amount of epoxyquinols A and B. Hayashi group reported two different approaches to **3** by using diastereoselective Diels-Alder reaction^{8a} and enzymatic resolution.^{8b} Porco, Mehta and Kuwahara groups achieved the enantioselective synthesis of **3** through an asymmetric epoxidation,^{8c} an enzymatic desymmetrization^{8d} and Evans asymmetric aldol reaction,^{8e} respectively. However, there has been no report for the synthetic routes to **3** using catalytic enantioselective manner. Herein, we describe an efficient approach to the monomer **3** via (+)-phyllostine **4** through catalytic asymmetric Diels-Alder reaction and the short synthesis of natural product (-)-phyllostine.

Since it was envisaged that stereoselective reduction of **4** would provide chiral alcohol of **3**, our synthesis began with the enantioselective synthesis of (+)-phyllostine, an enantiomer of

natural metabolite (-)-phyllostine (Scheme 1). (-)-Phyllostine was isolated from the culture filtrate of *Phyllosticta sp.*, a pathogenic fungus of red clover, and is known as a phytotoxic compound.⁹

We considered that chiral Diels-Alder adduct **5** could be a good starting material for the synthesis of **4**. Initially, the enantioselective Diels-Alder reactions of cyclopentadiene with 1,4-quinone monoketal **7**, which is easily prepared from *p*-methoxyphenol,¹⁰ were attempted. The reaction was carried out at -78 °C by stirring 1,4-quinone monoketal **7** and cyclopentadiene in the presence of (*S*)-cationic chiral oxazaborolidium catalysts **6**¹¹ (20 mol %) in CH₂Cl₂ under nitrogen atmosphere. However, the *endo*-cycloadduct **9** was generated in 80% yield with 78% ee.¹² On the other hand, when the dienophile was changed to 2-iodo-1,4-quinone monoketal **8**, the chiral *endo*-Diels-Alder adduct **10** was afforded in 94% yield with excellent 97% ee.^{11d,f} The reason for this is that the iodine substituent blocks catalyst coordination to carbonyl lone pair which is *syn* to it and also deactivates the C=C subunit to which it is attached (Fig. 2).^{11c} Enantiomerically pure **10** was obtained simply by one recrystallization from CH₂Cl₂-hexanes and the absolute structure of **10** was confirmed by X-ray crystallographic studies (Fig. 2).¹³ The absolute stereochemical course of enantioselective Diels-Alder reaction can be explained in terms of a favored reaction channel *via* the pre-transition-state assembly, shown in Fig. 2.^{11b,d}

With the enantiomerically pure **10** in hand, the synthesis of

**Scheme 1.** Retrosynthetic analysis of chiral monomer **3****Figure 1.** Structures of epoxyquinols A, B and their monomer **3**.**Scheme 2.** Synthesis of *endo*-Diels-Alder adducts **9** and **10**

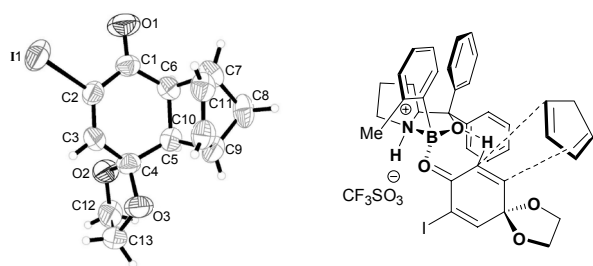
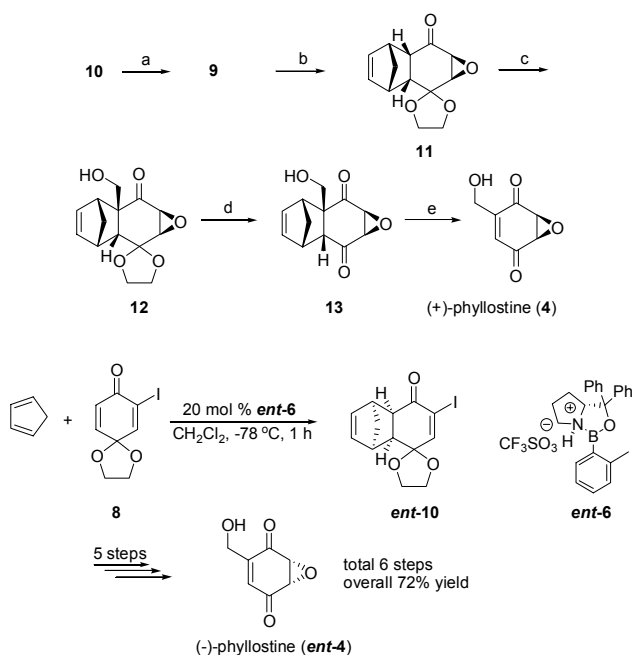
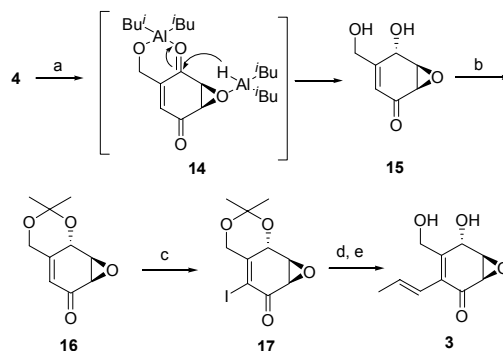


Figure 2. Crystal structure of **10** and pre-transition-state assembly for the Diels-Alder reaction of **8** in the presence of catalyst **6**.



Scheme 3. Reagents and conditions (a) *n*-Bu₃SnH, benzene, 80 °C (88%); (b) 30 wt % H₂O₂, DBU, CH₃CN, 0 °C (92%); (c) 37 wt % formaldehyde, DBU, THF, 0 °C to 25 °C (98%); (d) 1 N H₂SO₄, Acetone-THF (1:1), 60 °C (98%); (e) Ph₂O, 230 °C (98%).

(+)-phyllostine was achieved over five steps. Reaction of **10** with tributyltin hydride provided **9** in 88% yield. Base-mediated epoxidation of enone **9** was attempted in various conditions. It was found that the epoxidation with hydrogenperoxide and DBU at 0 °C occurred from convex direction to provide only the *exo*-epoxide **11** in 92% yield. Stereoselective hydroxymethylation afforded the alcohol **12** in 98% yield. Deprotection of ketal **12** under acidic condition followed by retro-Diels-Alder reaction of **13** gave (+)-phyllostine in 96% two steps yield. Spectral data for synthetic one were in accord with those of the natural isolate, (-)-phyllostine except the sign of optical rotation. Comparison of optical rotation $\{[\alpha]_D^{22} = +117$ ($c = 1.00$, EtOH) $\}$ determined the absolute stereochemistry to be as shown in (+)-**4**. Since (*R*)-cationic oxazaborolidium catalyst **ent-6** is readily available, natural (-)-phyllostine was synthesized by using the same route with an overall yield of 72% in only six steps and its optical rotation $\{[\alpha]_D^{22} = -116$ ($c = 1.00$, EtOH) $\}$ corresponds well with the values of $[\alpha]_D^{28} = -120$ ($c = 0.28$, EtOH) and $[\alpha]_D^{24} = -108$ ($c = 1.61$, EtOH) found in the literature.^{9e,f}



Scheme 4. Reagents and conditions (a) DIBAL-H, THF, -78 °C (70%); (b) 2,2-dimethoxypropane, PPTS, CH₂Cl₂, 25 °C (87%); (c) I₂, PhI(OAcF₃)₂, pyridine, 2,6-di-*tert*-butyl-4-methylphenol, CH₂Cl₂, 25 °C (78%); (d) (*E*)-tributyl-1-propenyl-stannane, Pd₂dba₃, PhCH₃, 110 °C; (e) 1 N H₂SO₄, Acetone-THF (1:1), 25 °C (76% for two steps).

Regioselective and stereoselective reduction of **4** using Kiyooka's conditions¹⁴ (2 eq. DIBAL-H, THF, -78 °C) was directed by the primary hydroxyl group and epoxide oxygen to furnish **15** in 70% yield through the intermediacy of the aluminum complex **14**. The diol in **15** was protected as the acetonide **16** in 87% yield. The α -iodination of **16** afforded iodoenone **17** in 78% yield.^{8b} Finally, Stille cross-coupling^{8c} with (*E*)-1-propenyl stannane followed by deprotection of the acetonide under acidic conditions gave chiral monomer **3** of epoxyquinols A and B in 76% two steps yield. The identity of our synthetic material was fully established through the comparison of the ¹H and ¹³C NMR spectra. The specific rotation of **3** $\{[\alpha]_D^{21} = +282$ ($c = 0.10$, MeOH) $\}$ is in perfect agreement with the literature value of $[\alpha]_D^{25} = +285$ ($c = 0.41$, MeOH).^{8b}

In summary, we have accomplished an efficient enantioselective synthesis of chiral monomer **3** of epoxyquinols A and B *via* (+)-phyllostine in 26% overall yield by an 11-step sequence through a catalytic asymmetric Diels-Alder reaction. Also, this approach has resulted in the short synthesis of natural product (-)-phyllostine with an overall yield of 72% in only six steps.

Experimental

Unless stated otherwise, reactions were carried out under a dry argon atmosphere in vacuum-flame dried glassware. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254. Flash chromatography was performed using E. Merck silica gel (40 ~ 60 μ m particle size). ¹H and ¹³C NMR spectra were recorded on a Varian at 300 and 75 MHz. Infrared spectra were recorded on a Bruker Vertex 70. HRMS were recorded on JEOL JMS-SX102A mass spectrometer with EI or FAB resource. Analytical high performance liquid chromatography (HPLC) was performed on FUTECS NS 4000 at 256 nm using the indicated chiral column (4.6 mm \times 25 cm). Optical rotations were determined on a Perkin-Elmer Polarimeter Model 343 plus at 589 nm. Commercial grade reagents and solvents were used without further purification.

(1'*RS*,4'*SR*,4*a*'*RS*,8*a*'*SR*)-1',4',4*a*',8*a*'-Tetrahydrospiro- $\{1,3$ dioxolane-2,5'(8'*H*)-[1',4']methanonaphtho[2,3-*b*]oxiren $\}$ -7'-

one (11). To a solution of **9** (0.2875 g, 1.32 mmol) in CH₃CN (13 mL) was added 30 wt % H₂O₂ (1.35 mL, 13.2 mmol) and DBU (0.986 mL, 6.6 mmol) at 0 °C, and the mixture was stirred for 1 h at that same temperature. The reaction mixture was quenched with saturated NaHCO₃ (aq). Organic materials were extracted with CH₂Cl₂ (3 × 20 mL), and the combined organic phases were washed with brine and dried over Na₂SO₄. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (ethyl acetate : hexane, 1 : 3) to afford 0.2839 g (92%) of **11**: TLC : *R_f* = 0.38 (ethyl acetate : hexane, 1 : 3); mp 123 ~ 125 °C; IR (NaCl) : 2983, 2901, 2361, 2341, 1709, 1148, 1075, 1018, 866, 746, 613; ¹H NMR (300 MHz, CDCl₃) δ 6.15 (dd, *J* = 3.0, 5.4 Hz, 1 H, =CH), 6.03 (dd, *J* = 3.0, 5.7 Hz, 1 H, =CH), 4.26-3.76 (m, 4 H, O-CH₂-CH₂-O), 3.33-3.27 (m, 2 H, CH-CH), 3.18 (dd, *J* = 3.6, 11.4 Hz, 1 H, CH), 3.11 (bs, 1 H, CH), 3.04 (dd, *J* = 3.0, 11.4 Hz, 1 H, CH), 2.95 (bs, 1 H, CH), 1.42 (dt, *J* = 4.8, 8.4 Hz, 1 H, CHH), 1.24 (d, *J* = 8.4 Hz, 1 H, CHH); ¹³C NMR (75 MHz, CDCl₃) δ 206.3, 135.6, 133.7, 107.9, 65.5, 64.7, 58.1, 55.3, 49.5, 48.5, 47.0, 43.2, 42.5; HRMS (EI) exact mass calcd. for C₁₃H₁₄O₄: *m/z* 235.0965 ([M + H]⁺), found: *m/z* 235.0970 ([M + H]⁺); [α]_D²⁵ = +28 (c 1.0, CHCl₃).

(1*RS*,4*SR*,4*aRS*,8*aSR*)-8*a'*-(Hydroxymethyl)-1',4',4*a*',8*a'*-tetrahydrospiro-{1,3 dioxolane-2,5'(8*H*)-[1',4']methanonaphtho[2,3-*b*]oxiren}-8'-one (12). To a solution of **11** (0.4156 g, 1.77 mmol) in THF (17 mL) was added DBU (0.292 mL, 1.95 mmol) and 37 wt % formaldehyde (1.32 mL, 17.7 mmol) at 0 °C, and the mixture was stirred for 1 h at that same temperature. The reaction mixture was quenched with saturated NaHCO₃ (aq). Organic materials were extracted with CH₂Cl₂ (3 × 25 mL), and the combined organic phases were washed with brine and dried over Na₂SO₄. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (ethyl acetate : hexane, 1 : 1) to afford 0.4595 g (98%) of **12**: TLC : *R_f* = 0.31 (ethyl acetate : hexane, 1 : 1); IR (NaCl): 3500, 3461, 2979, 2887, 2360, 1701, 1158, 1000, 877, 746, 606; ¹H NMR (300 MHz, CDCl₃) δ 6.14 (dd, *J* = 2.7, 5.4 Hz, 1 H, =CH), 6.05 (dd, *J* = 3.0, 5.1 Hz, 1 H, =CH), 4.29 (dd, *J* = 7.2, 11.4 Hz, 1 H, OCH), 4.24-3.85 (m, 4 H, O-CH₂-CH₂-O), 3.66 (dd, *J* = 5.4, 11.4 Hz, 1 H, OCH), 3.34 (m, 2 H, CH-CH), 3.14 (bs, 1 H, CH), 2.91 (bs, 1 HCH), 2.51 (d, *J* = 3.6 Hz, 1 H, CH), 1.92 (t, *J* = 6.3 Hz, 1 H, OH), 1.39 (m, 2 H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 206.7, 137.8, 134.4, 107.5, 69.4, 66.0, 64.8, 61.3, 58.8, 55.6, 52.4, 46.1, 45.0, 43.9; HRMS (EI) exact mass calcd. for C₁₇H₂₆O₂Si: *m/z* 307.1724 ([M + H]⁺), found: *m/z* 307.1729 ([M + H]⁺). HRMS (EI) exact mass calcd. for C₁₄H₁₆O₅: *m/z* 265.1071 ([M + H]⁺), found: *m/z* 265.1076 ([M + H]⁺); [α]_D²⁵ = -66 (c 1.0, CHCl₃).

(1*RS*,4*SR*,4*aRS*,8*aSR*)-8*a'*-(Hydroxymethyl)-1,4,4*a*,8*a'*-tetrahydro[1,4]methanonaphtho[2,3-*b*]oxiren}-5,8-dione (13). To a solution of **12** (0.0858 g, 0.32 mmol) in Acetone-THF (1 : 1, 3 mL) was added 1 N H₂SO₄ (1.5 mL) at rt, and the mixture was stirred for 6 h at that same temperature. The reaction mixture was quenched with 10% Na₂CO₃ (aq). Organic materials were extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic phases were washed with brine and dried over Na₂SO₄. The organic phase was concentrated in vacuo, and the residue was purified by silica gel column chromatography (ethyl acetate :

hexane, 1 : 1) to afford 0.07 g (98%) of **12**: TLC : *R_f* = 0.36 (ethyl acetate : hexane, 1 : 1); mp 146 ~ 148 °C; IR (NaCl): 2983, 2925, 2360, 2338, 1707, 1290, 1039, 991, 846, 719, 628; ¹H NMR (300 MHz, CDCl₃) δ 6.07 (m, 2 H, CH=CH), 4.36 (d, *J* = 11.4 Hz, 1 H, OCH), 3.82 (d, *J* = 11.4 Hz, 1 H, OCH), 3.58 (m, 2 H, CH, CH), 3.33 (bs, 2 H, CH-CH), 2.84 (d, *J* = 3.6 Hz, 1 H, CH), 1.91 (bs, 1 H, OH), 1.54-1.42 (m, 2 H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 204.7, 203.7, 138.2, 138.1, 68.5, 61.1, 58.9, 57.9, 53.4, 46.1, 44.2, 43.1; HRMS (EI) exact mass calcd. for C₁₂H₁₂O₄: *m/z* 221.0808 ([M + H]⁺), found: *m/z* 221.0814 ([M + H]⁺); [α]_D²¹ = -97 (c 1.0, THF).

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12. Triflic acid activated catalyst **6** provided the Diels-Alder adduct **9** with better enantioselectivity compared to triflimide or aluminium bromide activated catalyst.
13. Crystal data for **10**: C₁₃H₁₃O₃, *M* = 344.15. Orthorhombic, space group *P*2₁2₁2₁, $\lambda = 0.71073$ Å, *a* = 5.8347(11), *b* = 14.046(3), *c* = 15.419(3) Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, *V* = 1263.7(4) Å³, *Z* = 4, *D_c* = 1.809 Mg/m⁻³, *F*(000) = 672, *T* = 296 (2) K, $\mu = 2.528$ mm⁻¹, size: 0.28 × 0.18 × 0.10 mm³. θ range = 3.01 ~ 28.38°, Reflections collected: 20039, Independent reflections: 3105 [*R*(int) = 0.0314], Final *R* indices [*I* > 2σ(*I*)]: *R*₁ = 0.0271, *wR*₂ = 0.0651, *R* indices (all data): *R*₁ = 0.0341, *wR*₂ = 0.0694, Refinement method: Full-matrix least-squares on *F*². Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-763142). That data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/perl/catreq.cgi> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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