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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 chemotheraphy. Indeed, several angiogenesis inhibitors from natural products, such as endostatin[2] 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]

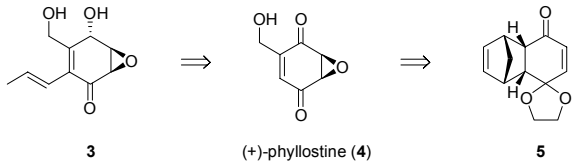
In 2002, Osada and co-workers reported the isolation and structual elucidation of two novel angiogenesis inhibitors, epoxyquinols A[6a] and B[6b] from fungal metabolites. These compounds have been known to inhibit the VEGF (vascular endothelial growth factor)-induced migration. Recent studies showed **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 epoxiquinols **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 CH_2Cl_2 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 CH_2Cl_2-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**

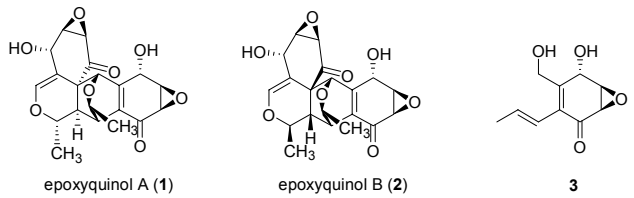
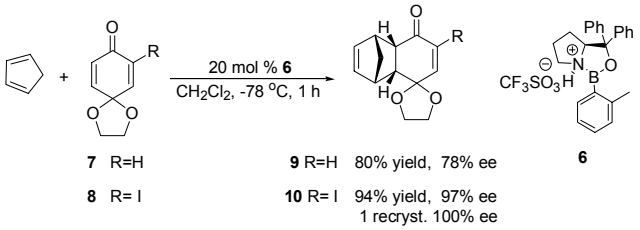


Figure 1. Structures of epoxyquinols A, B and their monomer **3**.



Scheme 2. Synthesis of *endo*-Diels-Alder adducts **9** and **10**

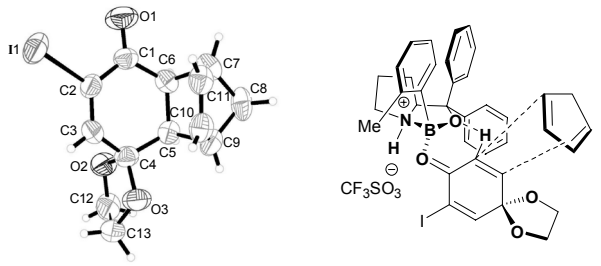
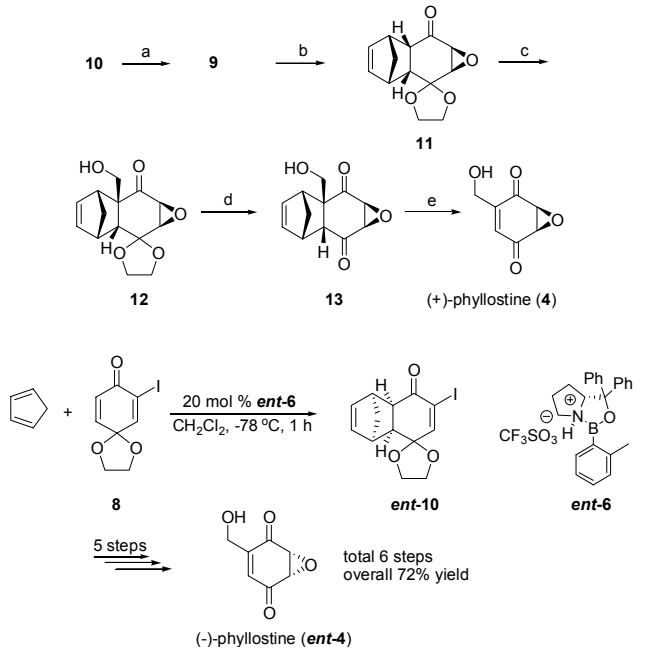
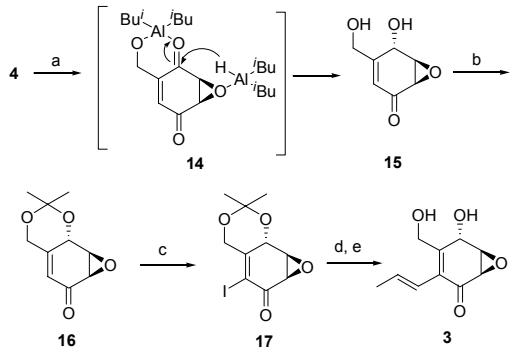


Figure 2. Crystal structure of **10** and pre-transition-state assembly for the Diels-Alder reaction of **8** in the presence of catalyst **6**.



Scheme 3. Reagents and conditions (a) *n*-Bu_3SnH, benzene, 80 °C (88%); (b) 30 wt % H_2O_2, DBU, CH_3CN, 0 °C (92%); (c) 37 wt % formaldehyde, DBU, THF, 0 °C to 25 °C (98%); (d) 1 N H_2SO_4, Acetone-THF(1:1), 60 °C (98%); (e) Ph_2O, 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, CH_2Cl_2, 25 °C (87%); (c) I_2, PhI $(OCOCF_3)_2$, pyridine, 2,6-di-*tert*-butyl-4-methylphenol, CH_2Cl_2, 25 °C (78%); (d) (*E*)-tributyl-1-propenyl-stannane, Pd_2dba_3, $PhCH_3$, 110 °C; (e) 1 N H_2SO_4, Acetone-THF (1:1), 25 °C (76% for two steps).

Regioselective and stereoselective reduction of **4** using Kiyooka's conditions[14] (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 aluminium 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 ^{13}C 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 μm particle size). ^1H and ^{13}C 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 × 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*,4a'*RS*,8a'*SR*)-1',4',4a',8a'-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 CH_3CN (13 mL) was added 30 wt % H_2O_2 (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 $NaHCO_3$ (aq). Organic materials were extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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-CH_2-CH_2-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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{14}O_4$: *m/z* 235.0965 ($[M + H]^+$), found: *m/z* 235.0970 ($[M + H]^+$); $[\alpha]_D^{22}$ = +28 (c 1.0, $CHCl_3$).

(1'*RS*,4'*SR*,4a'*RS*,8a'*SR*)-8a'-(Hydroxymethyl)-1',4',4a',8a'-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 $NaHCO_3$ (aq). Organic materials were extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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-CH_2-CH_2-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, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{17}H_{26}O_2Si$: *m/z* 307.1724 ($[M + H]^+$), found: *m/z* 307.1729 ($[M + H]^+$). HRMS (EI) exact mass calcd. for $C_{14}H_{16}O_5$: *m/z* 265.1071 ($[M + H]^+$), found: *m/z* 265.1076 ($[M + H]^+$); $[\alpha]_D^{22}$ = −66 (c 1.0, $CHCl_3$).

(1*RS*,4*SR*,4a*RS*,8a*SR*)-8a-(Hydroxymethyl)-1,4,4a,8a-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 H_2SO_4 (1.5 mL) at rt, and the mixture was stirred for 6 h at that same temperature. The reaction mixture was quenched with 10% Na_2CO_3 (aq). Organic materials were extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{12}H_{12}O_4$: *m/z* 221.0808 ($[M + H]^+$), found: *m/z* 221.0814 ($[M + H]^+$); $[\alpha]_D^{21}$ = −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:** $C_{13}H_{13}IO_3$, $M = 344.15$. Orthorhombic, space group $P2_12_12_1$, $\lambda = 0.71073$ Å, $a = 5.8347(11)$, $b = 14.046(3)$, $c = 15.419(3)$ Å, $\alpha = 90^o$, $\beta = 90^o$, $\gamma = 90^o$, $V = 1263.7(4)$ Å^3, $Z = 4$, $D_c = 1.809$ Mg/m^{-3}, $F(000) = 672$, $T = 296$ (2) K, $\mu = 2.528$ mm^{-1}, size: $0.28 \times 0.18 \times 0.10$ mm^3. θ range = $3.01 \sim 28.38^o$, Reflections collected: 20039, Independent reflections: 3105 [R(int) = 0.0314], Final R indices [$I > 2$sigma(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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