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Enantioselective total synthesis of antiangeogenic pentaketide dimers, epoxyquinols A and B, through an asymmetric aldol approach to their common monomeric precursor

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Abstract—A new enantioselective total synthesis of epoxyquinols A and B possessing unique pentaketide dimeric structures and potent antiangeogenic activity was achieved by oxidative dimerization of a monomeric pentaketide precursor obtained by the Evans asymmetric aldol reaction and a series of operationally simple transformations.

Angiogenesis, the formation of new blood capillaries from preexisting ones, is strictly controlled in the healthy human body by various endogenous angiogenic and angiostatic factors, and plays essential roles in many physiological processes such as wound heeling, embryogenesis, and the formation of the corpus luteum.[1] It also occurs in many pathological conditions like cancer, diabetic retinopathy, rheumatoid arthritis, and other chronic inflammatory diseases, among which the relationship between cancer and angiogenesis have, in particular, attracted a great deal of interest to physiologists.[2] At present, angiogenesis is considered to be an absolute requirement for tumor growth and metastasis, and, therefore, its inhibitors are drawing increasing attention as new drugs in cancer therapy.[1–3] In 2002, Osada and co-workers reported the identification of two novel angiogenesis inhibitors, epoxyquinols A and B (**1** and **2**, respectively), from a fermentation broth of an uncharacterized fungus of soil origin (Scheme 1).[4,5] The complicated unique structures of **1** and **2** coupled with their potent antiangiogenic activity immediately prompted synthetic chemists to their total synthesis, and several successful total syntheses[6–10] as well as some related synthetic studies[11–13] have been reported to date. All the syntheses reported so far were based on the proposal by Osada co-workers[4,5] that epoxyquinols A and B are both biosynthesized from monomeric pentaketide precursor **4**, which actually exists in the same fermentation broth as **1** and **2**,[14] via oxidation to **3** followed by 6π-electrocyclic ring closure into two diastereomeric 2*H*-pyrans (**a** and **b**), and their intermolecular Diels–Alder dimerization in the combinations shown in Scheme 1. Indeed, Hayashi and co-workers accomplished the first total synthesis of **1** and **2** by employing, as the final step, MnO_2-oxidation of **4**, which in turn were prepared by using a $HfCl_4$-mediated asymmetric Diels–Alder reaction and a series of efficient transformations.[6,15] Their synthesis was immediately followed by Porco's elegant synthesis using an asymmetric nucleophilic epoxidation[7] and Mehta's practical synthesis through an enzymatic desymmetrization,[10] both of which were, again, achieved by oxidative dimerization of **4**. Herein, we describe a new approach to the dimerization precursor (**4**) through the Evans asymmetric aldol reaction, and its conversion into epoxyquinols A and B.

Our synthesis began with the Evans asymmetric aldol reaction[16] between a known *N*-acyl-2-oxazolidinone derivative (**5**)[17] and senecialdehyde to give stereoselectively *syn*-aldol **6** in 87% isolated yield (Scheme 2). Reductive removal of the chiral auxiliary of **6** with lithium borohydride afforded diol **7a**, the hydroxyl groups of which were then protected by reaction with TBSCl

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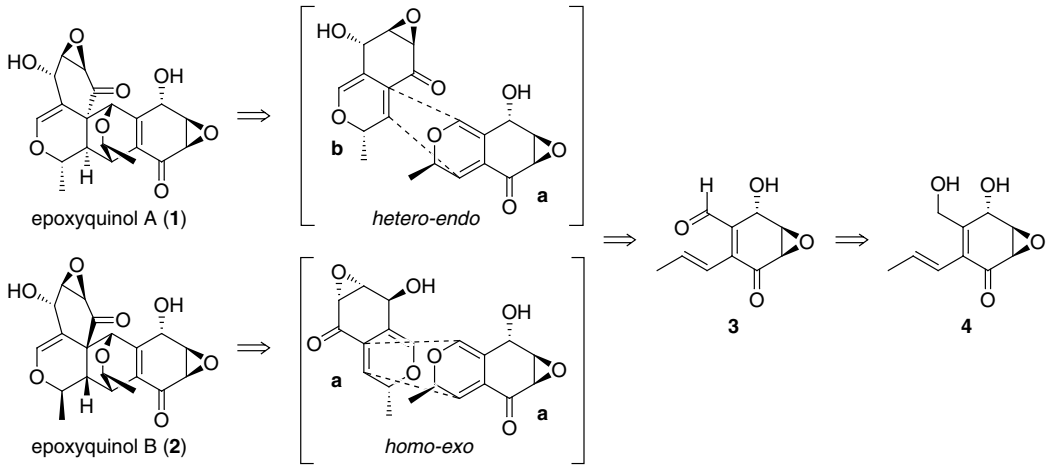
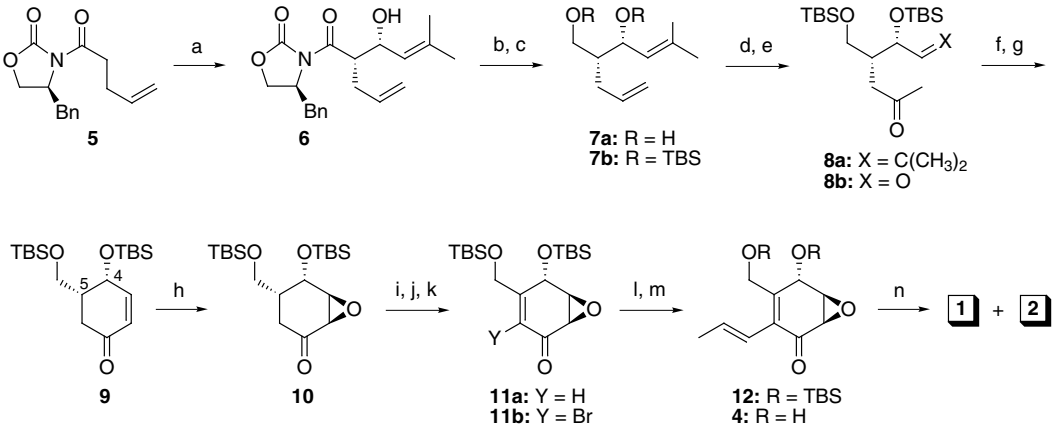


Scheme 1. Structures of epoxyquinols A and B, and their proposed biosynthetic pathway.



Scheme 2. Reagents and conditions: (a) $(n\text{-Bu})_2$BOTf, $(i\text{-Pr})_2$NEt, $Me_2C{=}CHCHO$, CH_2Cl_2, −78 °C (87%); (b) $LiBH_4$, THF–MeOH, 0 °C to rt; (c) TBSCl, imidazole, DMF, 0 °C to rt; (d) $PdCl_2$, $Cu(OAc)_2{\cdot}H_2O$, O_2, rt (93%, three steps); (e) O_3, MeOH–CH_2Cl_2, −78 °C, Me_2S (86%); (f) 6 M NaOH aq, ether, rt (70%); (g) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt (93%); (h) TBHP, DBU, toluene, 0 °C to rt (quant); (i) LDA, PhSeCl, THF, −78 °C; (j) 30% H_2O_2, CH_2Cl_2, rt (63%, two steps); (k) Br_2, Et_3N, CH_2Cl_2, rt (93%); (l) (*E*)-MeCH=CHSn(*n*-Bu)$_3$, $Pd_2(dba)_3$, Ph_3As, toluene, reflux (96%); (m) HF·Py, THF, 0 °C to rt (88%); (n) TEMPO, CuCl, O_2, DMF,rt; neat, rt (46% for **1** and 20% for **2**).

to provide **7b** almost quantitatively. Preferential Wacker oxidation of the terminal double bond of **7b** proceeded smoothly to give ketone **8a** in 93% overall yield from **6**. The remaining trisubstituted double bond of **8a** was oxidatively cleaved with ozone to deliver, in 86% yield, keto aldehyde **8b**, which was then subjected to various basic or acidic intramolecular aldol condensation conditions to obtain six-membered enone derivative **9**. Among several reaction conditions employed (PPTS/toluene, AcOH/pyrrolidine/MeOH, K_2CO_3/*t*-BuOH, $(n\text{-Bu})_4$NOH/THF/H_2O, KOH/18-crown-6/toluene, etc.), the best result was obtained by a two-step sequence consisting of conversion of **8b** into the corresponding cyclic aldol intermediate (NaOH, H_2O–ether two-phase system,[18] 70% yield) and subsequent exposure of the aldol intermediate to dehydration conditions (MsCl/Et_3N/CH_2Cl_2) to give the desired product **9** in 93% yield. The stereochemical homogeneity of the cyclohexenone derivative (**9**) possessing two *cis*-oriented substituents was confirmed by its ^{1}H NMR spectrum, in which the coupling constant between 4-H and 5-H was 3.5 Hz in good accordance with data for analogous *cis*-disubstituted cyclohexenones[19] and no signal due to the corresponding *trans*-diastereomer[20] with more thermodynamic stability was observed. Stereoselective epoxidation of **9** was performed by treating the enone with *t*-BuOOH and DBU in toluene to afford quantitatively **10** as a single stereoisomer. Two-step conversion of **10** into **11a** was performed by α-selenylation and oxidative elimination in a moderate yield of 63%. Introduction of an iodine atom to the double bond of **11a** was troublesome as in the case of an analogous conversion in the first total synthesis of **1** and **2** by Hayashi and co-workers.[6] Although various iodination conditions including those investigated by Hayashi and co-workers (I_2/DMAP, I_2/$TMSN_3$, and I_2/PhI(OCOCF$_3$)/Py) were attempted to convert **11a** into **11b** (Y = I),[6] we failed to obtain any satisfactory outcome. Quite gratifyingly, however, the corresponding bromination proceeded smoothly by using a conventional method (Br_2/Et_3N/CH_2Cl_2) to give **11b** in 93% yield. The Stille coupling of the bromide (**11b**) with (*E*)-tributyl(1-propenyl)stannane was

accomplished in 96% yield by adding a solution of $Pd_2(dba)_3$ and Ph_3As in toluene to a refluxing mixture of **11b** and the tin reagent in toluene over a period of 1 h according to Porco's procedure.[7,21] Deprotection of the TBS-protecting groups of the resulting coupling product (**12**) with HF·Py in THF proceeded without event to give the oxidative dimerization precursor **4** [$\alpha]_D^{24}$ +260 (*c* 0.785, $CHCl_3$)] in 88% yield. The ^1H NMR spectrum of **4** was exactly the same as that of an authentic sample.[6] The final conversion of the diol (**4**) into epoxyquinols A and B (**1** and **2**, respectively), was conducted by chemoselective oxidation of the primary hydroxyl group of **4** (TEMPO/CuCl/O_2/DMF)[22] followed by leaving the resulting neat reaction product at room temperature for 10 h to furnish **1** [46%, [$\alpha]_D^{24}$ +61 (*c* 0.075, MeOH), mp 184–185 °C; lit.[4] [$\alpha]_D^{21}$ +61.0 (*c* 0.146, MeOH), mp 186 °C] and **2** [20%, [$\alpha]_D^{24}$ +150 (*c* 0.22, MeOH), mp 208–210 °C; lit.[5] [$\alpha]_D^{21}$ +153.0 (*c* 0.315, MeOH); lit.[7] mp 210–212 °C].[23] The ^1H and ^{13}C NMR spectra of our synthetic epoxyquinols A and B were identical with those of the natural material.

In summary, a new enantioselective total synthesis of epoxyquinols A [(+)-**1**] and B [(+)-**2**] was accomplished by oxidative dimerization of the monomeric pentaketide precursor (**4**), which in turn was prepared from known oxazolidinone **5** in 22% overall yield by an operationally simple 13-step sequence including the Evans asymmetric aldol reaction as the source of chirality.

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20. See, for example: Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984–3988.
21. When a solution of **11b** in toluene and a solution of the tin reagent in toluene were successively added to a solution of $Pd_2(dba)_3$ and Ph_3As in toluene at room temperature and the resulting mixture was heated at reflux, the reaction was very sluggish, resulting in only 21% yield of **12**.
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23. Besides **1** and **2**, the oxidative dimerization generated trace amounts of two other minor products. The ^1H NMR spectrum of one of the minor products, obtained in ca. 5% yield, was identical with that of another diastereomer of **1** produced by microwave irradiation of **1**,[7] which was also reported to be produced in 1% yield by dimerization of **3** in toluene at room temperature. For the formation of this minor diastereomer (epoxyquinol C) in toluene, see: Shoji, M.; Imai, H.; Hayashi, Y; Shiina, I.; Kakeya, H.; Osada, H. *Abstracts*. The 46th Symposium on the Chemistry of Natural Products, Hiroshima, Japan, October 6–8, 2004; pp 305–310. The other product, formed in this oxidative dimerization in less than 5% yield, could not be fully purified, and its scarcity precluded us from determining the structure, although its ^1H NMR spectrum suggested that the product might be another diastereomer of **1**.