



Pergamon

Total synthesis of the novel angiogenesis inhibitors epoxyquinols A and B

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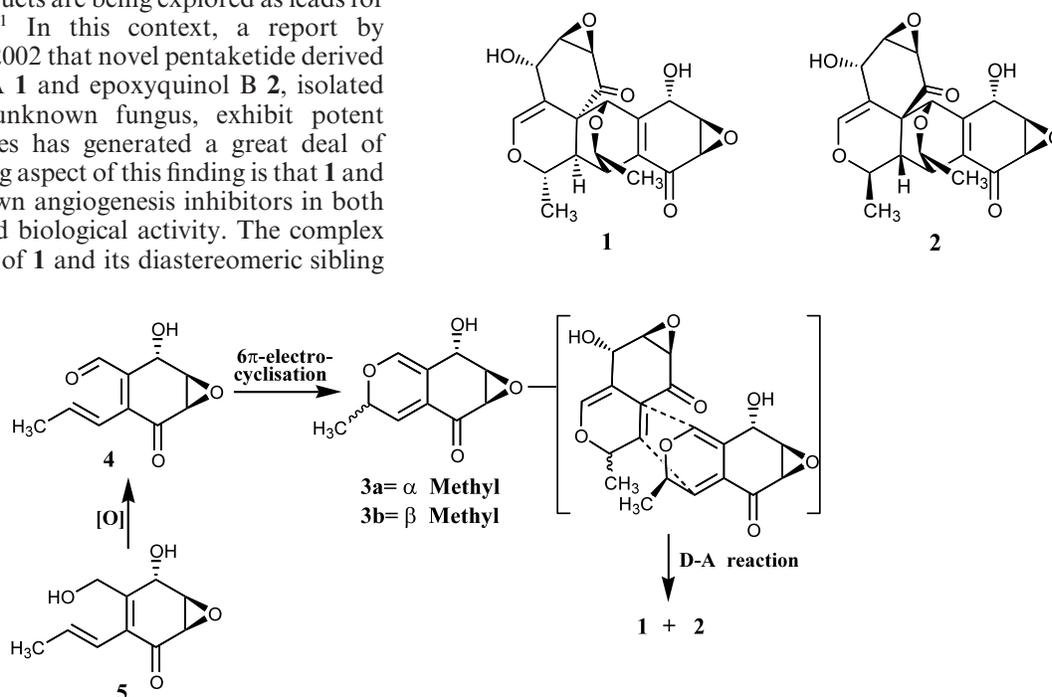
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Abstract—The synthesis of the recently discovered angiogenesis inhibitors epoxyquinols A and B, having novel polyketide derived dimeric structures, has been accomplished from the readily available Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone through a short, simple and flexible strategy that is diversity oriented and can be adapted to an asymmetric variant. © 2003 Elsevier Science Ltd. All rights reserved.

Angiogenesis or formation of new blood vessels is a complex, multi-step, biological event and abnormalities associated with this fundamental process have been implicated in cancer, rheumatoid arthritis and many other chronic inflammatory disorders. Thus, inhibition of angiogenesis has emerged as a promising approach for many diseases particularly cancer and many compounds including natural products are being explored as leads for clinical development.¹ In this context, a report by Japanese scientists in 2002 that novel pentaketide derived dimers epoxyquinol A **1** and epoxyquinol B **2**, isolated from a soil based unknown fungus, exhibit potent anti-angiogenic profiles has generated a great deal of interest.² An interesting aspect of this finding is that **1** and **2** differ from the known angiogenesis inhibitors in both structural features and biological activity. The complex heptacyclic structures of **1** and its diastereomeric sibling

2 were elucidated on the basis of extensive high-field NMR studies and X-ray crystal structure determination of epoxyquinol A **1**.^{2a} It was hypothesized that biosynthetically **1** and **2** could arise through an *endo*-selective Diels–Alder reaction between the diastereomeric 2*H*-pyran monomers **3a** and **3b** through hetero and homo dimerization, respectively (Scheme 1).^{2a}



Scheme 1. Biogenetic hypothesis for the natural products.

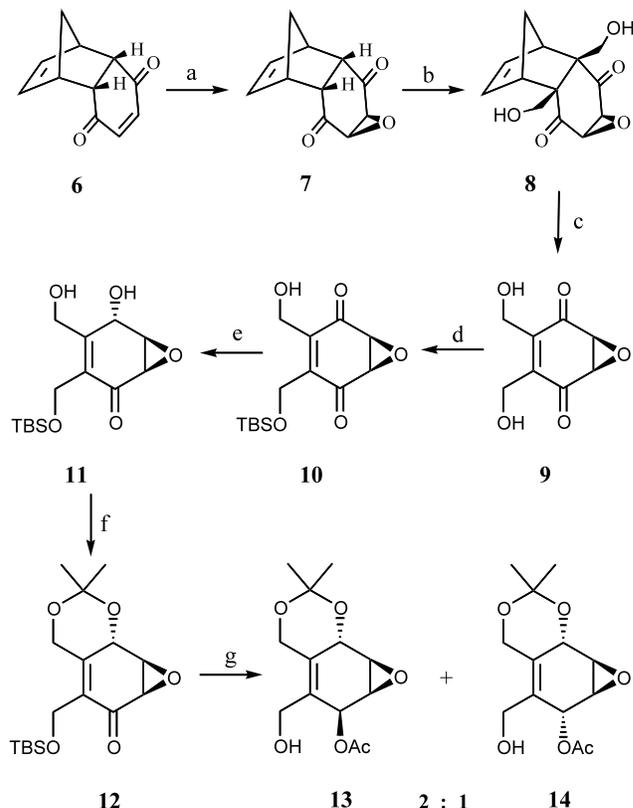
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The origin of the 2*H*-pyran monomers **3a,b** can be traced to the precursor dienal **4** through a 6 π electrocyclicization and further to the more robust monocyclic diol epoxide **5** (Scheme 1). Isolation of **5** from the same fungus along with **1** and **2** provides strong support to the biosynthetic proposal.^{2a} Interestingly, **5** bears a close structural resemblance to a family of epoxyquinol and epoxyquinone antibiotics that have aroused considerable biological and synthetic interest.³

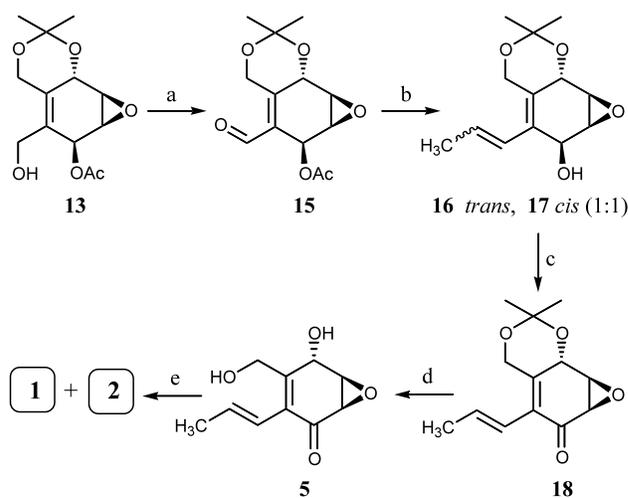
The unusual structure and anti-angiogenic activity profile of epoxyquinols A **1** and B **2** and the quest for new analogues of these natural products has drawn the immediate attention of the synthetic community.⁴ In the past few months, enantioselective syntheses of epoxyquinols A and B by the Hayashi^{4a,b} and Porco^{4c} groups have appeared and quite understandably their endeavors have followed the proposed biosynthetic pathway. In addition, Porco et al.^{4c} have also reported the preparation of new diastereomers related to **1** and **2** through thermally induced equilibration and studied their inhibitory activity towards the transcription factor NF- κ B. We too were enticed by the structures of epoxyquinols A and B as they surfaced^{2a} in the literature and wish to report here our accomplishment of the total synthesis of natural products **1** and **2** in racemic form. Our approach is also patterned along the biosynthetic pathway^{2,3d,4} shown in Scheme 1 but follows a different synthetic strategy to access the key monomeric precursors **4** and **5**.

The monocyclic epoxyquinol natural product **5** was identified as the initial target and its synthesis emanated from the readily available Diels–Alder adduct **6**⁵ of cyclopentadiene and *p*-benzoquinone. Base-mediated epoxidation to **7** and exhaustive hydroxymethylation in the presence of DBU delivered **8** and established two key C–C bonds in a single operation and in quantitative yield.⁶ Next, the epoxyquinone moiety with two strategically functionalized side arms in place was to be extracted from **8**. The retro-Diels–Alder reaction of **8** proceeded smoothly in nearly quantitative yield and led to the symmetrical epoxyquinone **9** in which the two hydroxymethyl arms now needed to be differentiated (Scheme 2). One of the hydroxyl groups in **9** was selectively protected as its bulky TBS-ether **10** to facilitate regio- and stereoselective DIBAL-H reduction⁷ to furnish the diol **11** (Scheme 2).⁶ The diol moiety in **11** was protected as the acetonide **12**. DIBAL-H reduction of **12** then led to a 2:1 mixture of epimeric alcohols which were directly acetylated and further deprotection of the TBS-group led to **13** and **14** (Scheme 2). The stereochemistry of the major hydroxy epimer **13** was secured through an X-ray crystal structure determination.⁸

The allylic primary hydroxy group in **13** was oxidized with MnO₂ and the resulting aldehyde **15** was subjected to Wittig olefination to furnish a 1:1 mixture of *E:Z*-isomers which on base hydrolysis furnished **16** and **17** (Scheme 3).^{6,9} The stereochemistry of **16**, although



Scheme 2. Reagents and conditions: (a) 30% H₂O₂, 10% Na₂CO₃, acetone, 0°C, 95%; (b) DBU (2.1 equiv.), 40% formalin (excess), 0°C, quant.; (c) diphenyl ether, 240°C, 5 min, 97%; (d) TBSCl, imidazole, DMAP, DCM, 0°C, 72%; (e) DIBAL-H (2 equiv.), THF, -78°C, 82%; (f) 2,2-dimethoxypropane, PPTS, acetone, rt 97%; (g) i. DIBAL-H, THF, -50°C, 86%; ii. Ac₂O, pyridine, DMAP, DCM, 0°C, quant.; iii. HF–pyridine, THF, rt 87%.



Scheme 3. Reagents and conditions: (a) MnO₂, DCM, 0°C, 84%; (b) i. Ph₃P(CH₂CH₃)I, *n*BuLi, THF, 0°C, 50%; ii. K₂CO₃, MeOH, 0°C, quant.; (c) PDC, DCM, rt 81%; (d) Amberlyst 15, MeOH, rt 85%; (e) MnO₂, DCM, 0°C–rt 1 (40%), **2** (25%).

revealed by ^1H NMR spectral analysis, was unambiguously secured through an X-ray crystal structure determination.⁸ The *E*-isomer **16**, required for elaboration to the natural products **5**, **1** and **2**, was subjected to PDC oxidation to deliver the dienone **18** which was found to be identical with the advanced intermediate of Hayashi et al.^{4a} in their synthesis of epoxyquinol A. Indeed, deprotection of the acetonide group in **18** yielded **5**, which was found to be identical with the natural product.^{4a,9} In a sequence similar to that described for **13**, the α -epimer **14** was also transformed to epoxyquinol **5**, thereby making both the diastereomers obtained from **12** serviceable, and neutralizing the lack of stereoselectivity in the DIBAL-H reduction of **12** and so enhancing the efficacy of our approach. Finally, MnO_2 oxidation of the exocyclic allylic hydroxy group in **5** was complete within minutes at 0°C and the ^1H NMR spectrum of the crude reaction mixture indicated the presence of **4** along with **3a,b** in a ratio of $\sim 60:40$. On allowing the reaction product to warm-up to ambient temperature ($\sim 28^\circ\text{C}$) and leaving aside for a few hours to complete the reaction,¹⁰ epoxyquinols A and B could be isolated along with an as yet uncharacterized but related dimeric product by column chromatography as envisaged in the biosynthetic proposal in Scheme 1.^{2a,4c} Our synthetic **1** and **2** were found to be spectroscopically identical^{2,4c} with the natural products (Scheme 3).

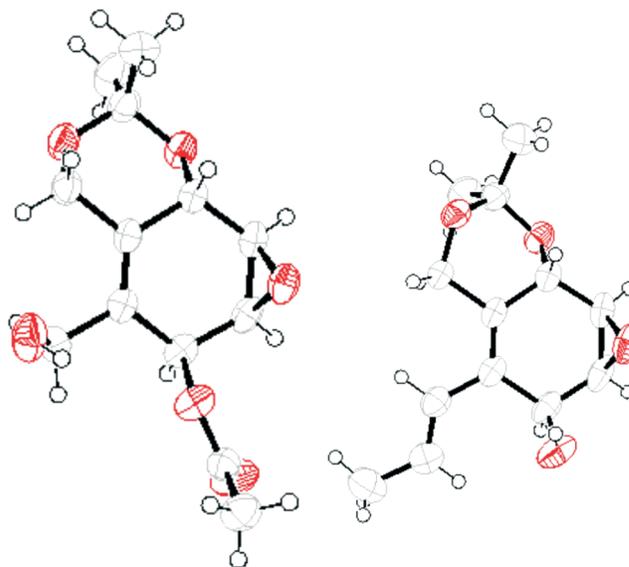
In summary, we have devised a simple and effective approach to the novel natural products, epoxyquinols A and B from the readily available Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone. Our approach can be readily adapted towards the generation of structural diversity and an asymmetric version is currently under development.

Acknowledgements

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- All new compounds were fully characterized on the basis of spectral data (IR, ^1H and ^{13}C NMR, Mass).
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- Crystal data:** X-ray data were collected at 293 K on a SMART CCD-BRUKER diffractometer with graphite monochromated $\text{MoK}\alpha$ radiation ($\lambda=0.7107$ Å). The structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. Compound **13**: $\text{C}_{13}\text{H}_{18}\text{O}_6$, MW = 270.27, colorless crystal, crystal system: triclinic, space group: *P*-1, cell parameters: $a=8.4101(8)$, $b=14.604(1)$, $c=10.737(1)$ Å, $V=1315.24$ (6) Å³, $Z=4$, $D_{\text{calcd}}=1.365$ g cm^{-3} , $F(000)=576.0$, $\mu=0.11$ mm^{-1} . Total number of l.s. parameters = 487, $R_1=0.0407$ for 4148 $F_o > 4\sigma(F_o)$ and 0.0521 for all 5232 data. $wR_2=0.1129$, GOF = 1.024, Restrained GOF = 1.024 for all data. Crystallographic data (without structure factors) have been deposited with the Cambridge Crystallographic Data Center and the depository number is CCDC 199401. Compound **16**: $\text{C}_{13}\text{H}_{18}\text{O}_4$, MW = 238.27, colorless crystal, Crystal system: triclinic, space group: *P*-1, cell parameters: $a=7.333(2)$, $b=8.465(2)$, $c=10.775(3)$ Å, $V=629.45$ Å³, $Z=2$, $D_{\text{calcd}}=1.257$ g cm^{-3} , $F(000)=256.0$, $\mu=0.09$ mm^{-1} . Total number of l.s. parameters = 226, $R_1=0.0437$ for

ORTEP of **13**ORTEP of **16**

2093 $F_o > 4\sigma(F_o)$ and 0.0517 for all 2476 data. $wR_2 = 0.1129$, GOF = 1.042. Restrained GOF = 1.042 for all data. Crystallographic data (without structure factors) have been deposited with the Cambridge Crystallographic Data Center and the depository number is CCDC 199400. ORTEP diagrams of **13** and **16** are shown above.

9. We have elaborated the *Z*-isomer **17** to a new *Z*-epoxyquinol corresponding to **5** and its chemistry is being investigated.
10. We and others⁴ have found that transformation of **4** to furnish **1** and **2** via **3a,b** is quite sensitive to time, temperature and solvent regimes and efforts are underway to optimize the conditions for this process.