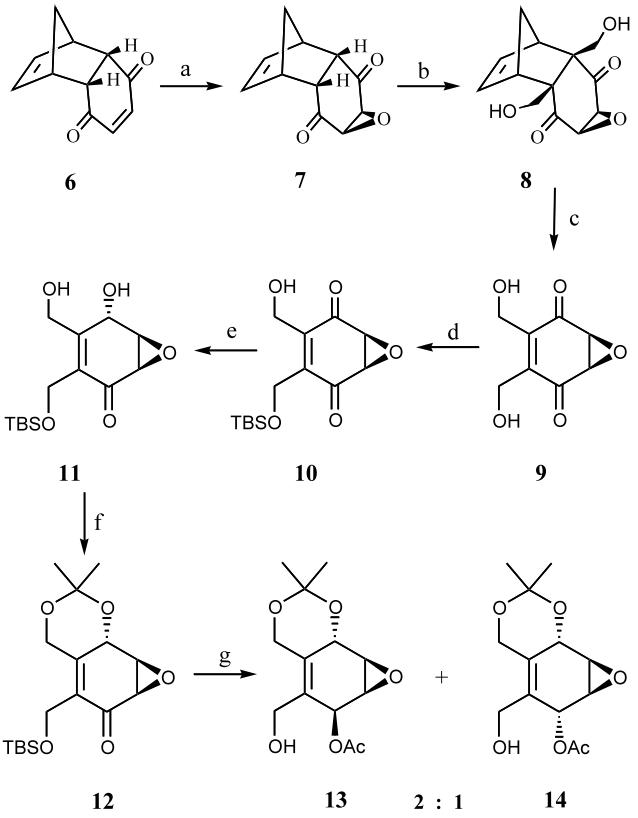
The origin of the 2*H*-pyran monomers **3a**,**b** can be traced to the precursor dienal **4** through a 6π electrocyclization and further to the more robust monocyclic diol epoxide **5** (Scheme 1). Isolation of **5** from the same fungus along with **1** and **2** provides strong support to the biosynthetic 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-κB. 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**.

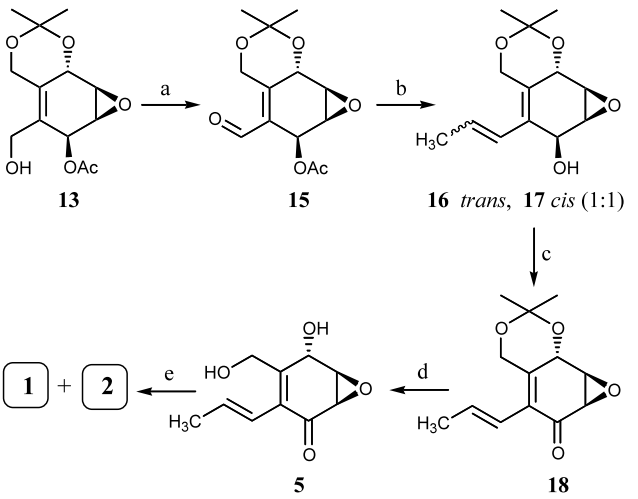
The monocyclic epoxyquinol natural product **5** was identified as the initial target and its synthesis emanated from the readily available Diels–Alder adduct **6**[5] of cyclopentadiene and *p*-benzoquinone. Base-mediated epoxidation to **7** and exhaustive hydroxymethylation in the presence of DBU 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 reduction[7] 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 MnO_2 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



6 **7** **8** **11** **10** **9** **12** **13** **14**

Scheme 2. *Reagents and conditions*: (a) 30% H_2O_2, 10% Na_2CO_3, 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. Ac_2O, pyridine, DMAP, DCM, 0°C, quant.; iii. HF–pyridine, THF, rt 87%.



13 **15** **16** *trans*, **17** *cis* (1:1) **5** **18**

Scheme 3. *Reagents and conditions*: (a) MnO_2, DCM, 0°C, 84%; (b) i. $Ph_3P(CH_2CH_3)I$, *n*BuLi, THF, 0°C, 50%; ii. K_2CO_3, MeOH, 0°C, quant.; (c) PDC, DCM, rt 81%; (d) Amberlyst 15, MeOH, rt 85%; (e) MnO_2, DCM, 0°C–rt **1** (40%), **2** (25%).

revealed by ^{1}H 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 ^{1}H NMR spectrum of the crude reaction mixture indicated the presence of **4** along with **3a**,**b** in a ratio of ~60:40. On allowing the reaction product to warm-up to ambient temperature (~28°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.

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6. All new compounds were fully characterized on the basis of spectral data (IR, ^{1}H and ^{13}C NMR, Mass).
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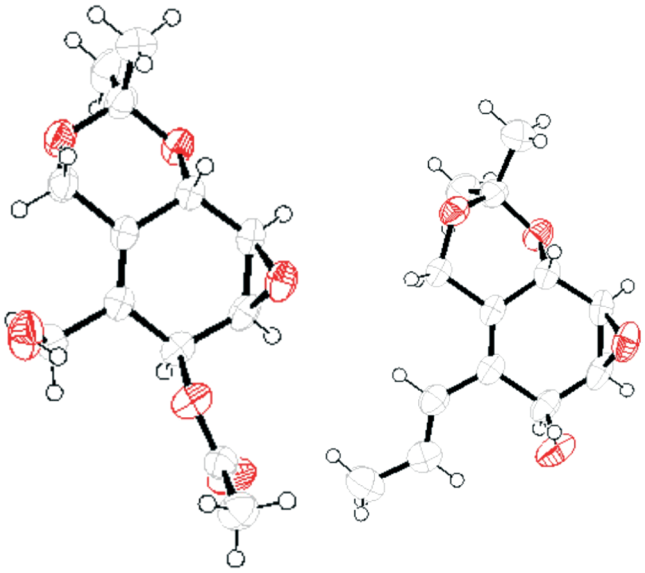
8. ***Crystal data***: X-ray data were collected at 293 K on a SMART CCD–BRUKER diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.7107$ Å). The structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. Compound **13**: $C_{13}H_{18}O_6$, 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) Å^3, $Z = 4$, $D_{calcd} = 1.365$ 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**: $C_{13}H_{18}O_4$, 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, $V = 629.45$ Å^3, $Z = 2$, $D_{calcd} = 1.257$ 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 others[4] 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.