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The First Syntheses of (±)-SDEF 678 Metabolite and (±)-Speciosins A–C

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The epoxyquinone natural products SDEF 678 metabolite, speciosin A, speciosin B and speciosin C have been prepared for the first time via a short synthetic route based around the palladium-catalysed coupling of a halogen-substituted 1,4-benzoquinone monoketal, a Diels–Alder/retro-Diels–Alder sequence and a diastereoselective epoxidation process.

Epoxyquinone natural products are widely distributed in nature and are of continuing interest due to their many and varied biological properties.[1] The highly functionalised and challenging structures present in the epoxyquinone family have stimulated the synthetic chemistry community for many years now,[1] and our own group have made contributions in this area [bromoxone, aranorosin, *epi*-epoxydon, harveynone (**1**), tricholomenyn A, LL-C10037α, alisamycin, manumycins, preussomerins, etc.].[2] The majority of the epoxyquinone natural products, including (–)-harveynone (**1**),[3] contain disubstituted epoxides. We were therefore excited when Ghisalberti and co-workers described the isolation of the plant growth promoting, anti-fungal metabolite **2** from an ectotrophic Australian fungus, SDEF 678;[4] compound **2** is isomeric with harveynone but contains a trisubstituted rather than a disubstituted epoxide (Figure 1). Then in 2009, Jiang et al. described the isolation of eleven new natural products from the Chinese fungus *Hexagonia speciosa* which they named speciosins, six of which (**3**–**8**) were epoxyquinones also containing a trisubstituted epoxide.[5] As can be seen, speciosin C (**3**) is simply the reduced form of the SDEF 678 metabolite (**2**), whereas speciosin A is closely related but contains a 2-(but-1-en-3-ynyl) side-chain rather than the methylated version found in compounds **1**–**3**. The additional oxidation observed in speciosins B (**5**) and D–F (**6**–**8**) is also noteworthy.

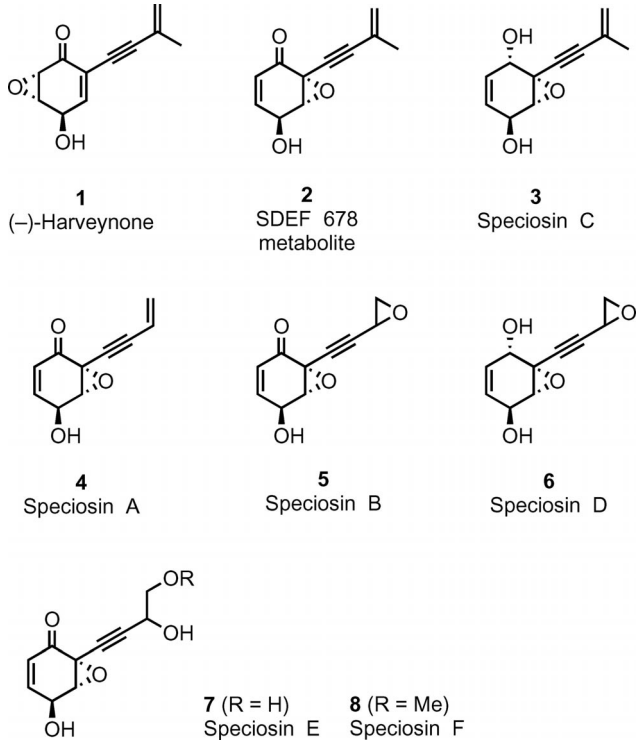

Figure 1. Representative epoxyquinone natural products.

Given the structural novelty of compounds **2**–**8**, we embarked on their synthesis. Having completed the first total synthesis of harveynone,[2e] we commenced this study by considering a retrosynthetic analysis (RSA) for the isomeric compound, SDEF metabolite (**2**). We also chose a route which would be easily adaptable to prepare the speciosins (Scheme 1). The key elements of this RSA are (i) the use of a Diels–Alder/retro-Diels–Alder sequence (as pioneered by the groups of Ichihara, Takano and Ogasawara)[6] to protect the less-substituted quinone alkene and to direct epoxidation and reduction, and (ii) the palladium-catalysed coupling of a halogen-substituted 1,4-benzoquinone monoketal (as pioneered in our harveynone synthesis[2e]).

The initial synthetic studies are summarised in Scheme 2.[7] The requisite starting material, 3-iodo-4,4-dimethoxycyclohexa-2,5-dienone (**13**), was prepared from either 2-bromo-1,4-dimethoxybenzene by electrochemical oxidation followed by lithiation/iodination and subsequent regioselective ketal hydrolysis as we originally described,[2d,8] or via the direct double oxidation of 3-iodophenol using hypervalent iodine reagents with methanol as

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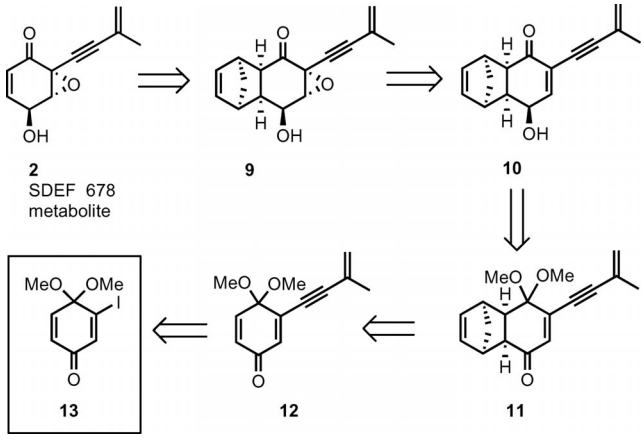
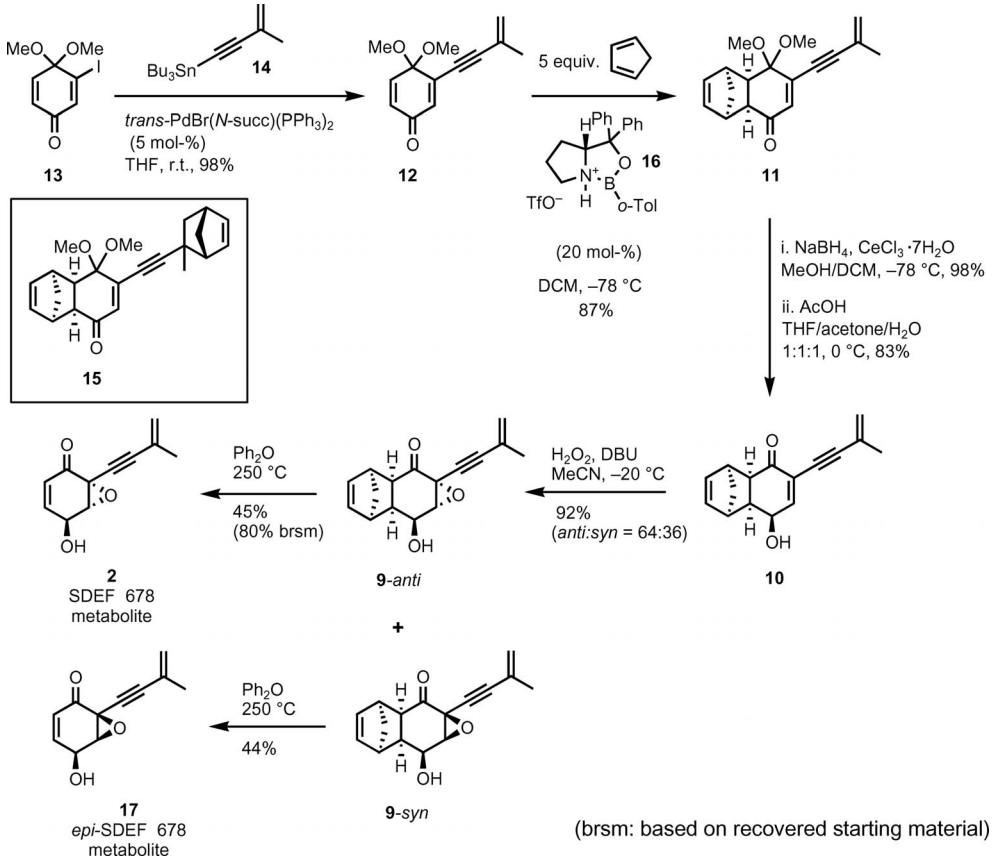


Scheme 1.

solvent.[9] The conversion of iodide **13** into enyne **12** was achieved in essentially quantitative yield using alkynylstannane **14** under Stille coupling conditions with catalytic *trans*-bromosuccinimidylbis(triphenylphosphane)palladium-(II);[10] Sonogashira coupling was not investigated due to the volatility of 3-methyl-but-3-en-1-yne. At this stage we decided to protect the disubstituted quinone double bond using the Diels–Alder reaction with cyclopentadiene. With a range of standard conditions and a number of Lewis acids, the reaction proceeded in poor yield, or double addition occurred giving adduct **15**. However, success was achieved using Corey's chiral oxazaborolidine/triflic acid adduct **16**[11] giving solely the *endo* adduct **11**, as expected, in 87% yield, although the product was essentially racemic.[12]

In principle, we could have explored the epoxidation at this stage but given the sterically encumbered nature of acetal **11** it was converted into enone **10** by stereoselective reduction followed by acetal removal; it should be noted that the use of strongly acidic deprotection conditions, prolonged reaction times or increased temperature resulted in the formation of an acid-catalysed rearrangement product.[13] Nucleophilic epoxidation of enone **10** was achieved using hydrogen peroxide in acetonitrile/DBU[14] giving a mixture of diastereomers from which the major epoxide **9**-*anti* could be isolated by column chromatography [the *anti*-relationship was subsequently confirmed by the conversion of **9**-*anti* into SDEF 678 metabolite (**2**)].[4] Finally, the retro-Diels–Alder reaction was explored. We were delighted to find that heating compound **9**-*anti* to 250 °C (external temperature) in diphenyl ether gave the SDEF metabolite **2** in 45% isolated yield [80% based on recovered starting material (brsm)]. A comparison of spectroscopic data confirmed the authenticity of the synthetic material [e.g. δ_C ($CDCl_3$) 53.3 (C-1), 63.4 (C-5), 66.2 (C-6); ref.[4] δ_C ($CDCl_3$) 53.3 (C-1), 63.3 (C-5), 66.2 (C-6)]. In a similar manner, thermolysis of **9**-*syn* gave the novel isomer **17** of SDEF metabolite **2**.



Scheme 2.

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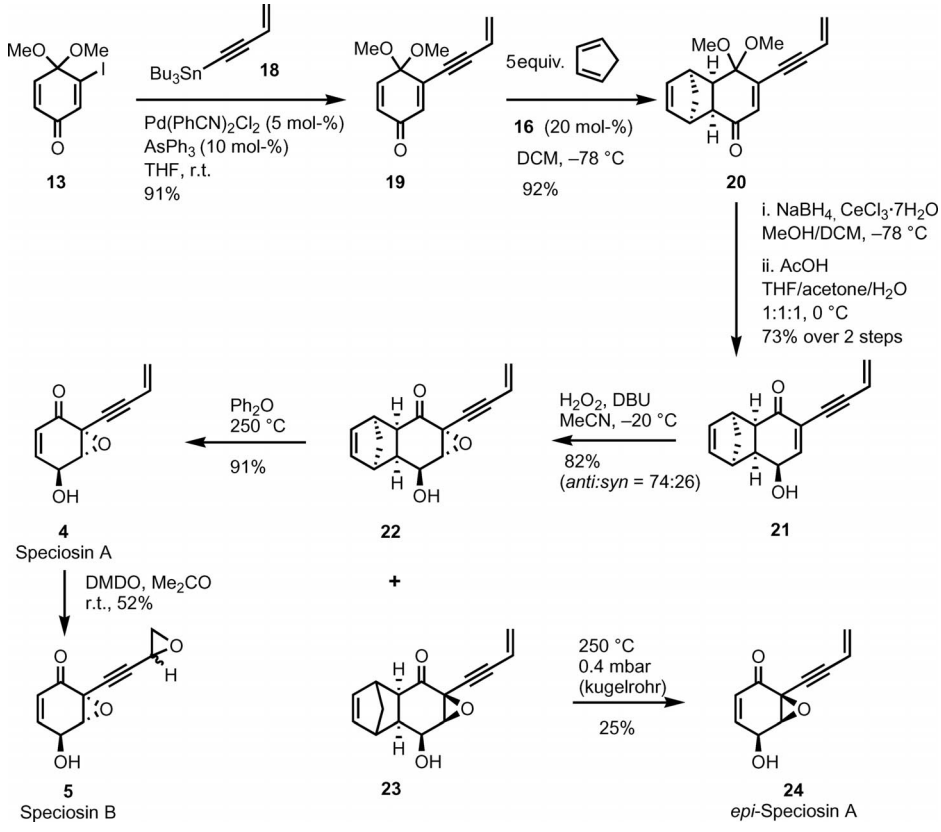
With the synthesis of SDEF 678 metabolite **2** complete, we next looked to utilise the methodology to prepare the speciosins (Scheme 3). First, the novel stannane **18** was required and this was easily prepared from monovinylacetylene[15] by a deprotonation-stannylation sequence. Stille coupling with 3-iodo-4,4-dimethoxycyclohexa-2,5-dienone (**13**) was then investigated and bis(benzonitrile)palladium dichloride/triphenylarsane[16] was found to be the most effective catalyst giving ene-yne **19** in 91% yield. Next, using the Diels–Alder protocol employed earlier, adduct **20** was obtained in 92% yield (again, as a racemic mixture). Diastereoselective Luche reduction and acetal hydrolysis, carried out without purification of the intermediate alcohol, then generated enone **21** in 73% overall yield (the corresponding hydroxy acetal was also isolated in 14% yield). As before, epoxidation was carried out using hydrogen peroxide/DBU to provide the desired *anti*-epoxide **22** in 61% isolated yield, along with the corresponding *syn*-isomer **23** (21%).

We were now in a position to investigate the retro-Diels–Alder processes (Scheme 3). First, we explored the use of high temperature kugelröhr distillation using *syn*-epoxide **23**; although the isolated yield was disappointing, we were able to obtain the novel *epi*-speciosin A (**24**) (25%). In order to prepare speciosin A (**4**) we therefore went back to the diphenyl ether procedure and found that much higher yields could be obtained by using a dilute solution of the starting material (0.03 M) in diphenyl ether, and by ensuring that the internal reaction temperature was above 200 °C. Using these modified thermolysis conditions, *anti*-epoxide **22** was converted into speciosin A (**4**) in a gratifying 91% isolated yield. This synthetic material was fully characterised and the NMR spectroscopic data were essentially identical to those reported for natural speciosin A (a comparison table is given in the Supporting Information).[5,17]

Treatment of speciosin A (**4**) with DMDO in acetone gave speciosin B (**5**) in a modest, but unoptimised, 52% yield as an inseparable 1:1 mixture of epoxide diastereomers. Again, the synthetic compound was fully characterised and the NMR spectroscopic data were consistent with those published [e.g. δ_H ($CDCl_3$) 3.46 (dd, *J* 3.9, 2.7, H-3); ref.[5] δ_H ($CDCl_3$) 3.45 (dd, *J* 4.0, 2.6, H-3); see Supporting Information for full comparison; speciosin B (**5**) was isolated as a single diastereomer but the epoxide configuration was not reported].[5]

Finally, we investigated the reduction of SDEF 678 metabolite (**2**) in order to prepare speciosin C (**3**) (Scheme 4). The use of $NaBH_4/CeCl_3$ gave reduction in quantitative yield but *epi*-speciosin C (**25**) was obtained as the major isomer (**3**/**25** = 1:8). However, as anticipated,[18] Super-Hydride® reduced the ketone from the opposite face to the epoxide with complete stereoselectivity giving speciosin C (**3**) in 92% yield. Again, the high field ^1H and ^{13}C NMR spectroscopic data matched those in the literature[5] (see Supporting Information for more details).



Scheme 3.

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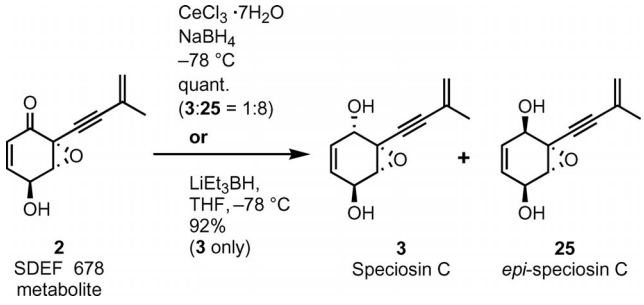

Scheme 4.

In summary, a concise synthetic sequence has been developed which has been applied to prepare the epoxyquinone natural products SDEF 678 metabolite (**2**), speciosin A (**4**), *epi*-speciosin A (**23**), speciosin B (**5**), speciosin C (**3**) and *epi*-speciosin C (**25**) all for the first time. Ongoing research is concentrating on the development of an enantioselective route to the speciosin family.

Supporting Information (see also the footnote on the first page of this article): Full experimental and characterisation data for all novel compounds, as well as NMR spectra for the natural products **2**–**5**.

Acknowledgments

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