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Exploring Chemical Diversity of Epoxyquinoid Natural Products: Synthesis and Biological Activity of (–)-Jesterone and Related Molecules

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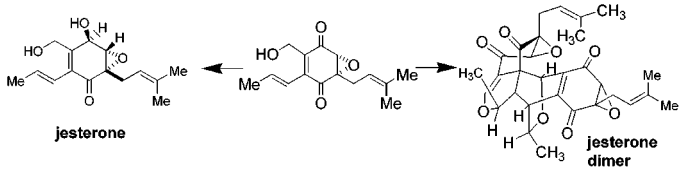
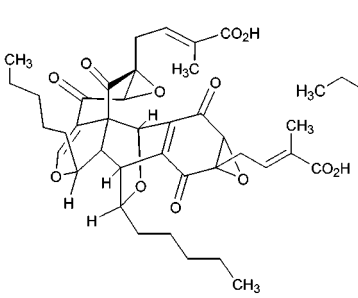
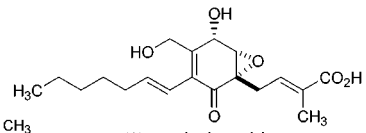
ABSTRACT

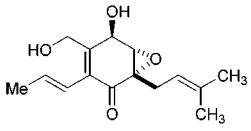


Enantioselective syntheses of the potent antifungal agent (–)-jesterone, its hydroxy epimer, and a dimeric quinone epoxide derivative are reported. The synthesis involves diastereoselective epoxidation of a chiral quinone monoketal derivative and regio- and stereoselective reduction of a quinone epoxide intermediate.

Endophytic fungi from the world's rainforests have provided numerous pharmacologically active compounds with a broad range of biological activities. Recently, a number of novel compounds have been isolated from *Pestalotiopsis* spp., a fungal genus that is well-known for the production of important secondary metabolites, including taxol.[1] For example, the quinone epoxide dimer torreyanic acid (**1**), isolated from the fungal species *P. microspora*, causes cell death by apoptosis in human cancer cells.[2] We recently


(1) torreyanic acid


(2) ambuic acid


(3) jesterone

reported[3] the total synthesis of (±)-torreyanic acid using a biomimetic dimerization of a quinone epoxide precursor related to the highly functionalized cyclohexenone ambuic acid (**2**), also produced by *P. microspora*.[4] The structurally related monomeric epoxyquinol jesterone (**3**) was recently isolated from *P. jesteri*.[5,6] Noteably, jesterone displays

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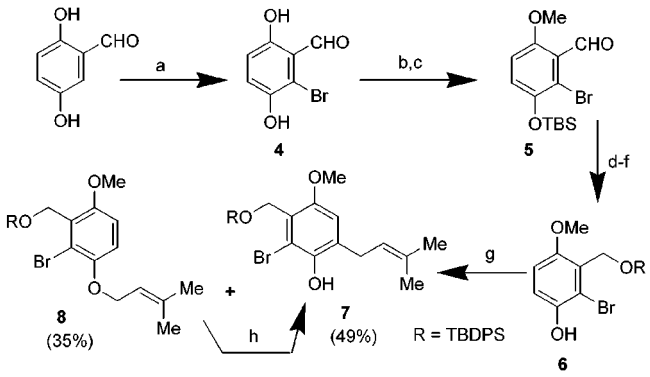
selective biological activity (minimum inhibitory concentration (MIC) values 6−25 μg/mL) against the oomycetous fungi, which are some of the most pathogenic of all disease-causing fungi. On the basis of examples of other anti-oomycete agents that have antitumor activity (e.g., taxol),[1] it was anticipated that jesterone, as an anti-oomycete agent, may also have cytotoxic activity. Taking a lead from the *biological diversity* of fungal metabolites, we have initiated a program to explore *chemical diversity* through the chemical synthesis of jesterone and related molecules. In this Letter, we report the synthesis, stereochemical assignment, and biological evaluation of (−)-jesterone and related epoxyquinoid compounds, including a novel "jesterone dimer" produced by a tandem oxidation-6π electrocyclization−dimerization cascade sequence.[3]

For the synthesis of jesterone and related epoxyquinoids, we first devised a synthesis of an *ortho*-prenyl phenol intermediate (Scheme 1), which would ultimately be converted to a quinone monoepoxide. Bromination of commercially available 2,5-dihydroxybenzaldehyde[7,8] afforded 2-bromo-3,5-dihydroxybenzaldehyde **4** (94%).[9] Regioselective silylation of the most nucleophilic phenol[10] of **4** followed by methylation of the 5-hydroxyl group provided methyl ether **5**. Reduction of **5** with $NaBH_4$ afforded an alcohol, which was silylated (TBDPSCl) and treated with TBAF (0 °C) to effect selective desilylation of the phenolic TBS ether. Using this procedure, the overall yield of phenol **6** for six steps was 53%, and multigram (5−10 g) amounts may be prepared with minimal purification. After considerable experimentation, we found that the prenyl side chain could optimally be installed using direct C-prenylation. After careful consideration of reaction conditions,[11] we adopted a two-step protocol involving prenylation of **6** (0.7 M in toluene) with NaH and prenyl bromide (−30 °C), which afforded the desired *ortho*-prenyl phenol **7** (49%) and prenyl ether **8** (35%). Rearrangement of **8** to produce further amounts of **7** was accomplished using Montmorillonite KSF in benzene[12] to afford **7** in an overall yield of 60%.

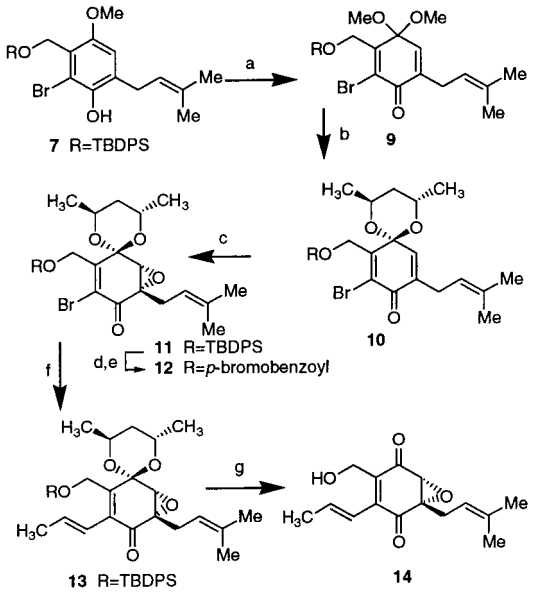
In analogy to our route to (±)-torreyanic acid,[3] advancement of **7** to jesterone and related structures required preparation and regio- and stereoselective epoxidation of a quinone monoketal intermediate (Scheme 2). Hypervalent iodine oxidation[13] of **7** ($PhI(OAc)_2$, room temperature, 30 min) afforded dimethoxyketal **9**. In line with established literature precedent for use of chiral acetals in diastereoselective epoxidations of quinone monoketals,[12b,14] **9** was transketalized with (2*S*,4*S*)-(+)-pentanediol to afford chiral acetal **10**. Epoxidation of **10** with Ph_3COOH (KHMDS, −35 °C) afforded monoepoxide **11** as a single diastereomer. Stereochemical assignment of **11** followed literature analogy and was based on examination of molecular models of the

Scheme 1[a]



[a] Reagents and conditions: (a) Br_2, $CHCl_3$, rt, 2.5 h, 94%; (b) TBSCl, imidazole, CH_2Cl_2, rt, 20 min, 94%; (c) MeI, NaH, THF, 65 °C, 6 h, 72%; (d) $NaBH_4$, EtOH, 0 °C, 0.5 h, 100%; (e) TBDPSCl, imidazole, DMF, rt, 2 h, 93%; (f) TBAF, THF, 0 °C, 10 min, 93%; (g) NaH, toluene, 50 °C, then prenyl bromide, −30 °C, 4 h; (h) Montmorillonite KSF, benzene, rt, 48 h, 31%.

Scheme 2[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$, MeOH, 20 min, rt, 83%; (b) (2*S*,4*S*)-(+)-pentanediol, PPTS, benzene, 80 °C, 20 min, 80%; (c) KHMDS, TrOOH, THF, −35 °C, 15 h, 80%; (d) TBAF/AcOH, THF, rt, 10 h, 91%; (e) 4-bromobenzoyl chloride, DMAP, pyridine, CH_2Cl_2, rt, 30 min, 78%; (f) (*E*)-tributyl-1-propenylstannane, $Pd(PPh_3)_4$, toluene, 110 °C, 6 h, 88%; (g) HF, CH_3CN, rt, 4.5 h, 82%.

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two possible conformers **10a** and **10b**, which indicate that the former should be preferred as a result of the presence of a severe steric interaction between the indicated axial methyl group in **10b** and the allylic silyl ether moiety (Figure 1a).

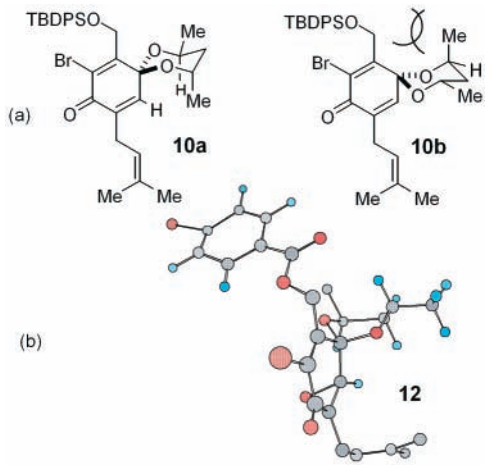
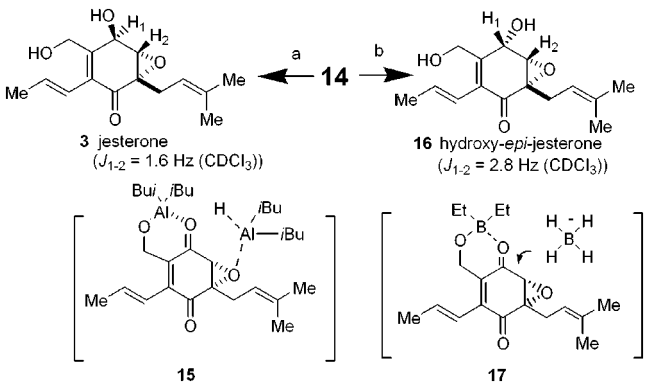


Figure 1. (a) Conformations of 1,3-dioxane **10**. (b) Chem 3D representation of the X-ray structure of **12**.

Selective formation of **11** thus may be explained by steric blocking of the β-face of the dienone by the axial methyl group in conformer **10a**. Unambiguous stereochemical assignment was achieved by conversion of **11** into *p*-bromobenzoate **12** and single X-ray crystal structure analysis (Figure 1b). Interestingly, in this structure the conformation of the chiral 1,3-dioxane is boatlike, presumably to avoid steric interactions between the emerged epoxide methine and the axial methyl group in a chair conformation. Stille coupling of **10** with (*E*)-tributyl-1-propenyl-stannane in the presence of $Pd(PPh_3)_4$ provided propenyl enone **13**, which was treated with HF in CH_3CN to afford the target quinone monoepoxide intermediate **14**.

Completion of the synthesis of jesterone required a hydroxyl-directed reduction to an *anti*-epoxy alcohol. A number of stereoselective reduction methods have been reported to prepare *anti*-epoxy alcohols from epoxy ketones, including $Zn(BH_4)_2$,[15] $NaBH_4/CeCl_3$,[16] and $NaBH_4/CaCl_2$.[17] Because of established precedent for chelation-controlled reduction of quinone monoepoxides using Dibal-H to afford *anti*-epoxy quinols[12b,18] we first evaluated reduction of **14** using metal chelation-based protocols. Gratifyingly, treatment of **14** using Kiyooka's conditions[19] (2 equiv of Dibal-H, THF, −78 °C) afforded (−)-jesterone **3** (84%). The structure of **3** was confirmed to be identical to natural (−)-jesterone by ^1H and ^{13}C NMR, IR, mass spectrum, $[\alpha]_D$ (−202.6° (c = 0.43, $CHCl_3$)) and TLC R_f values in three different solvent systems. The regio- and stereoselectivity of the reduction step may be explained by initial formation of aluminum chelate **15**, followed by chelation-controlled reduction to produce **3**. Alternatively, reduction of **14** using $NaBH_4$/$MeOBEt_2$[20] afforded hydroxy-*epi*-jesterone **16** and **3** in a 9:1 ratio (72%) (Scheme 3). In this case, the reduction selectivity

Scheme 3[a]



[a] Reagents and conditions: (a) 2 equiv Dibal-H, THF, −78 °C, 10 min, 84%; (b) $MeOBEt_2$, $NaBH_4$, THF/MeOH, −72 °C, 3 h, 72%.

may be explained by formation of boron chelate **17** and preferential activation of the complexed ketone toward reduction with borohydride.[21] The coupling constants observed for **3** and epimer **16** (J_{1-2} = 1.6 and 2.8 Hz, respectively) are also consistent with values reported for related epoxyquinol compounds.[6d, 22]

In an effort to further explore chemical diversity in the jesterone series, we prepared a novel "jesterone dimer" employing the tandem oxidation-6π-electrocyclization process previously used to produce torreyanic acid and related core structures (Scheme 4).[3] Dess−Martin oxidation of quinone epoxide **14** provided a crude product mixture consisting largely of 2*H*-pyran diastereomers **18** (^1H NMR). Further treatment with silica gel in CH_2Cl_2, followed by silica gel chromatography, led to the production of **19** (84%) as

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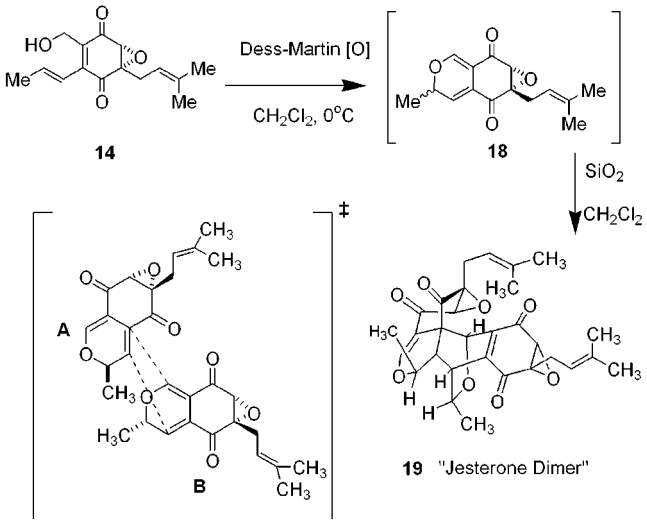
Scheme 4



the sole dimeric product. Selective formation of **19** may be explained by Diels−Alder dimerization of two diastereomeric 2*H*-pyran monomers **A** and **B**, in which case the methyl groups of the pyran are *anti* to one another and the dienophile (**A**) approaches the diene (**B**) *anti* to the epoxide moiety.[3] In effect, **19** is a torreyanic acid analogue, which may be more cell permeable as a result of the absence of the two carboxylate groups.

Evaluation of monomeric and dimeric epoxyquinoid compounds against various plant pathogens is shown in Table 1.[23] These results indicate that the biological activity of synthetic jesterone mimics the antifungal effect of natural jesterone. In addition, the synthetic compounds, including **14** and **16**, retain potent bioactivity against *P. cinnamomi* and *P. ultimum* and exhibit relatively low MIC values against these important pathogenic fungi. In preliminary studies, synthetic **3** and dimer **19** have also been tested in several cell lines derived from human cancers: a human breast cancer cell line (MDA MB231) and two human leukemia cell lines (HL60 and U937).[23] Noteably, the dimer **19** displays low μM activity against these cell lines and demonstrates the potential for bioactivity of novel epoxyquinoids (Table 2). Evaluation of this compound against other tumor cell lines and mechanism of action studies are warranted and are in progress.

Table 1. Minimum Inhibitory Concentration (μg/mL) of (−)-Jesterone and Other Related Compounds for a Representative Group of Plant Pathogenic Fungi

	jesterone				
test fungus	nat	synth	**14**	**16**	**19**
Pythium ultimum	25	25	50	50	>100
Phytophthora cinnamomi	6	6	6	6	12
Sclerotinia sclerotiorum	100	100	>100	100	>100
Rhizoctonia solani	25	50	50	50	50
Geotrichum candidum	>100	>100	>100	>100	>100
Pyricularia oryzae	25	25	50	nd	25

Table 2. Preliminary Evaluation of Jesterone **3** and Jesterone Dimer **18** against Human Tumor Cell Lines (IC_{50}, μM)

compound	HL60	MDA MB 231	U937
jesterone **3**	150	528	109
jesterone dimer **19**	19	2.8	1.5

In summary, the synthesis and stereochemical assignment of the potent antifungal compound (−)-jesterone has been accomplished. Synthesis of a hydroxy epimer, as well as a related quinone epoxide precursor and a novel "jesterone dimer" resulting from Diels−Alder dimerization of a 2*H*-pyran intermediate, underscores the possibility to prepare chemically diverse, bioactive compounds using a natural product lead. Continued studies of (−)-jesterone and related epoxyquinoid compounds are in progress and will be reported in due course.

Acknowledgment. We thank Ms. Susan Corona (Cytoclonal Pharmaceutics, Inc.) for assays. G.S. thanks HMV (San Diego, CA), the NSF, and the Montana Agricultural Experiment Station for partial support.

Supporting Information Available: Experimental procedures and characterization data for all new compounds, including X-ray structure of **12** (PDF). X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http:// pubs.acs.org.

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(23) See the Supporting Information for experimental methods.