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Total Synthesis of the Novel Antifungal Agent (±)-Jesterone

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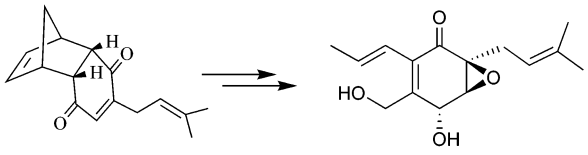
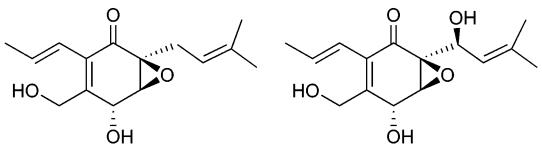
ABSTRACT



Jesterone

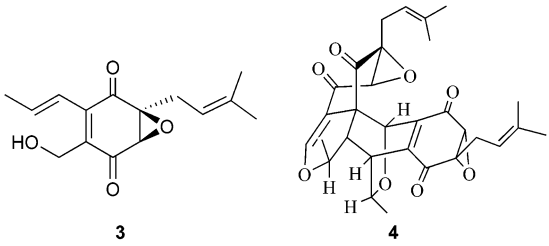
A total synthesis of the novel, biologically active epoxyquinone natural product (±)-jesterone has been accomplished from the readily accessible Diels–Alder adduct of cyclopentadiene and prenylated-*p*-benzoquinone. The approach delineated here is notable for its conceptual simplicity and efficient orchestration of a series of chemo-, regio-, and stereoselective operations.

In 2001, Li and Strobel[1a] reported the isolation and structure determination of novel epoxyquinone natural products jesterone **1** and its hydroxy derivative **2** from a new endophytic fungus *Pestalotiopsis jesteri* from the Southern Highland Province of Papua New Guinea.[1b] Besides its highly functionalized architecture and mixed polyketide−isoprenoid biogenesis, **1** has attracted attention on account of the selective biological activity (minimum inhibitory concentration values 6−25 μg/mL) it displays against the oomycetous fungi, which are some of the most pathogenic of all disease-



1 **2**

causing fungi.[1a] More recently, jesterone **1** was found to exhibit activity against human breast and human leukemia cell lines.[2] The first total synthesis of (−)-jesterone **1** was achieved by the group of Porco,[2] who also described a "jesterone dimer" **4** derived from the related quinone **3** via an intermolecular Diels−Alder reaction. Interestingly, the dimer **4** not only exhibits substantially enhanced anti-cancer activity against human cancer cell lines but also blocks activation of the transcription factor NF-κB by inhibiting the



3 **4**

inhibitor of the κB kinase.[3] These promising observations have further stimulated interest in the synthesis of jesterone **1** and related compounds. As part of our continuing efforts in the area,[4] we report here a total synthesis of racemic **1**, following a strategy that is simple, flexible, and amenable to diversity generation.

The starting material in our synthetic route to (±)-jesterone **1** was the prenylated *p*-benzoquinone **7**, which in turn is

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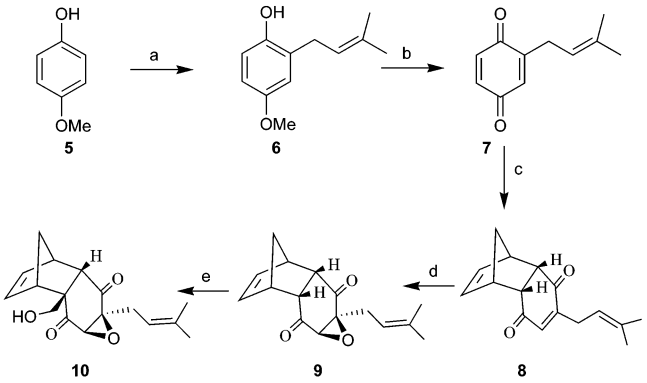
easily available from *p*-methoxyphenol **5** via 4-methoxy-2-prenylphenol **6** (Scheme 1).[5]

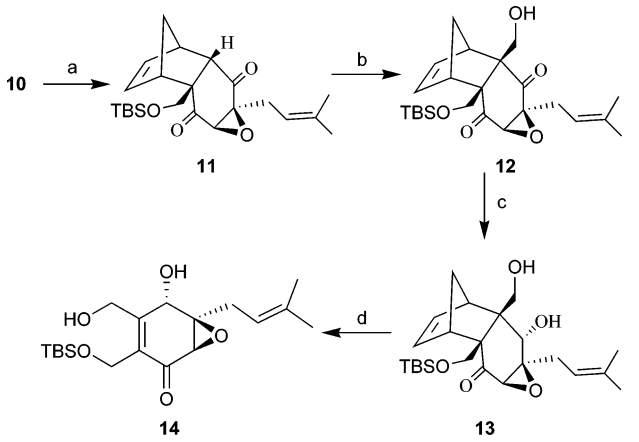
Scheme 1 [a]



[a] Reagents and conditions: (a) prenyl bromide, Na, ether, reflux, 87%; (b) CAN, CH_3CN-H_2O (1:1), 0 °C, 45 min, 85%; (c) cyclopentadiene, methanol, 0 °C, 2 h, 98%; (d) 10% Na_2CO_3, 30% H_2O_2, acetone, 0 °C, 40 min, 92%; (e) DBU, 35% formalin, THF, 0 °C, 2 h, 92%.

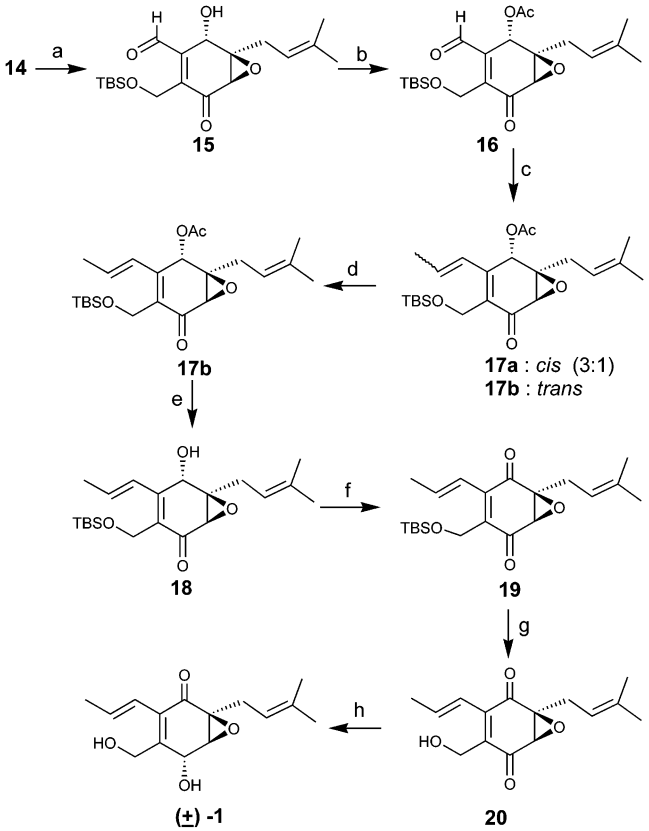
Diels−Alder reaction between **7** and cyclopentadiene was regioselective and furnished the endo-adduct **8**[6] in almost quantitative yield. Hydrogen peroxide-mediated epoxidation of **8** in the presence of base was both regio- and stereoselective to furnish a single epoxide **9** in excellent yield

Scheme 2 [a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 0 °C, 90%; (b) DBU, 35% formalin, THF, 0 °C, 36 h, 80%; (c) $NaBH_4$, methanol, −5 °C, 1 h, 84%; (d) diphenyl ether, 220 °C, 6 min, 98%.

Scheme 3 [a]



[a] Reagents and conditions: (a) TEMPO [TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl], O_2, CuCl, DMF, rt, 3 h, 90%; (b) Ac_2O, pyridine, DMAP, DCM, 0 °C, 3 h, 98%; (c) $C_2H_5PPh_3Br$, ^{t}BuOK, THF, 0 °C, 65%; (d) *hν*, Pyrex, 450 W (Hannovia), I_2, $CDCl_3$, 1.5 h, 95%; (e) LiOH, methanol, 0 °C, 2 h, 65%; (f) TPAP, NMMO, MS 4 Å, DCM, rt, 4 h, 92%; (g) HF, pyridine, THF, 0 °C, 7 h, 90%; (h) DIBAL-H (2 equiv), THF, −78 °C, 10 min, 84%.

(6) All new compounds were fully characterized on the basis of spectral data (IR, ^{1}H, ^{13}C NMR, and HRMS). Selected spectral data: **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 2H), 4.92 (t, 1H, J = 7.5 Hz), 3.50−3.41 (m, 2H), 3.35 (s, 1H), 3.27 (br s, 2H), 2.65 (dd, 1H, J = 6.9, 15.6 Hz), 2.54 (dd, 1H, J = 8.1, 15.9 Hz), 1.68 (s, 3H), 1.59 (s, 3H), 1.48 (d, 1H, J = 8.7 Hz), 1.29 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 205.2, 137.0, 136.6, 115.2, 66.9, 62.0, 50.5, 50.1, 46.7, 43.3, 43.1, 25.8, 25.7, 18.0; HRMS (ES) *m*/*z* calcd for $C_{16}H_{18}NaO_3$ $[M + Na]^+$ 281.1154, found 281.1134. **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (s, 2H), 4.82 (t, 1H, J = 7.2 Hz), 4.08−3.82 (m, 4H), 3.40 (dd, 1H, J = 3.0, 9.6 Hz), 3.29 (s, 1H), 3.05 (s, 1H), 2.98 (s, 1H), 2.66 (dd, 1H, J = 7.5, 15.3 Hz), 2.40 (dd, 1H, J = 6.6, 15.3 Hz), 1.61 (s, 3H), 1.52 (br s, 4H), 1.23 (d, 1H, J = 9.3 Hz), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 206.3, 138.5, 138.2, 136.6, 115.4, 68.1, 67.6, 66.5, 62.8, 62.7, 61.8, 50.6, 50.1, 42.7, 26.1, 25.7, 25.6, 18.1, 17.9, −5.7, −5.8; HRMS (ES) *m*/*z* calcd for $C_{24}H_{36}NaO_5Si$ $[M + Na]^+$ 455.2230, found 455.2205. **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (t, 1H, J = 7.2 Hz), 4.68 (d, 1H, J = 5.7 Hz), 4.56 (dd, 1H, J = 4.8, 14.4 Hz), 4.47−4.37 (m, 3H), 3.55 (br s, 1H), 3.48 (br s, 1H), 3.34 (s, 1H), 2.91 (dd, 1H, J = 7.8, 15.6 Hz), 2.43 (dd, 1H, J = 7.2, 15.3 Hz), 1.73 (s, 3H), 1.65 (s, 3H), 0.85 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 154.2, 136.7, 131.7, 116.5, 67.8, 65.1, 62.3, 58.2, 56.1, 28.9, 25.8, 25.7, 18.1, 18.0, −5.4, −5.5; HRMS (ES) *m*/*z* calcd for $C_{19}H_{32}NaO_5Si$ $[M + Na]^+$ 391.1917, found 391.1935. **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1H), 5.21 (br s, 1H), 5.14 (s, 1H), 4.82 (d, 1H, J = 14.4 Hz), 4.65 (d, 1H, J = 14.7 Hz), 3.46 (s, 1H), 2.98 (br s, 1H), 2.48 (br s, 1H), 1.77 (s, 3H), 1.69 (s, 3H), 0.88 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 194.5, 143.1, 141.9, 136.3, 115.6, 64.2, 62.8, 57.7, 56.3, 28.3, 25.2, 25.0, 17.4, −6.1, −6.2; HRMS (ES) *m*/*z* calcd for $C_{19}H_{30}NaO_5Si$ $[M + Na]^+$ 389.1760, found 389.1746. **17b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, 1H, J = 1.2, 15.6 Hz), 6.41−6.29 (m, 1H), 6.32 (s, 1H), 5.07 (t, 1H, J = 8.1 Hz), 4.52 (d, 1H, J = 12 Hz), 4.41 (d, 1H, J = 12 Hz), 3.38 (s, 1H), 2.57−2.43 (m, 2H), 2.05 (s, 3H), 1.88 (dd, 3H, J = 1.5, 6.6 Hz), 1.72 (s, 3H), 1.59 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 169.9, 145.6, 136.6, 135.6, 131.8, 127.5, 115.8, 66.1, 61.7, 57.1, 55.8, 29.0, 25.8, 20.9, 19.6, 18.2, 18.0, −5.2, −5.3; HRMS (ES) *m*/*z* calcd for $C_{23}H_{36}NaO_5Si$ $[M + Na]^+$ 443.2230, found 443.2246. **1**:^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, 1H, J = 15.9 Hz), 5.92−5.81 (m, 1H), 5.06 (t, 1H, J = 7.2 Hz), 4.93 (s, 1H), 4.75 (d, 1H, J = 14.4 Hz), 4.48 (d, 1H, J = 14.4 Hz), 3.67 (d, 1H, J = 1.8 Hz), 3.20 (d, 1H, J = 3.9 Hz), 2.78 (dd, 1H, J = 8.1, 15.6 Hz), 2.55 (dd, 1H, J = 6.6, 15.6 Hz), 2.18 (br s, 1H), 1.84 (dd, 3H, J = 1.5, 6.6 Hz), 1.71 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 145.5, 136.0, 134.9, 131.5, 122.2, 116.5, 65.3, 63.1, 60.1, 59.5, 26.6, 25.8, 19.2, 18.0; HRMS (ES) *m*/*z* calcd for $C_{15}H_{20}NaO_4$ $[M + Na]^+$ 287.1259, found 287.1255.

(Scheme 1). Mono-hydroxymethylation of **9** with aq HCHO in the presence of DBU was efficient as well as regioselective, furnishing a 9:1 mixture in which the desired isomer **10** predominated.[6] Protection of the primary hydroxyl group as TBS derivative **11** and repetition of the hydroxymethylation protocol exclusively furnished **12** with chemodifferentiated sidearms on the epoxyquinone moiety. The free hydroxyl group, the epoxy oxygen functionality, and the exo-propensity of the norbornyl scaffold were now fully exploited for the regio- and stereoselective reduction of **12** to furnish **13** (Scheme 2).[6] Retro-Diels−Alder reaction of **13** was smooth and led to the chemodifferentiated monocyclic precursor **14** of jesterone **1** (Scheme 2).[6]

Chemoselective TEMPO oxidation[7] of the primary hydroxyl group in **14** led to the hydroxyaldehyde **15**; its secondary hydroxyl group was now protected as the acetate **16** (Scheme 3).[6] Wittig ethylidenation of **16** was nonstereoselective and **17** was obtained as a cis:trans (3:1) mixture in which only the minor trans-isomer was serviceable. Efforts to improve the cis:trans stereoselectivity in the Wittig olefination, through variation of reaction regimes, were not very productive. Recourse was therefore taken to photochemical cis:trans equilibration of the dienone chromophore present in **17** and this indeed proved rewarding. Irradiation of the mixture **17a** and **17b** with a 450-W Hannovia Hg lamp resulted in complete isomerization to the desired trans-isomer **17b** (Scheme 3).[6]

With the key stereochemical issue resolved, functional group readjustments were now attended to, en route to target **1**. Acetate deprotection of **17b** to obtain **18** and further TPAP oxidation[8] led to the epoxyquinone **19** (Scheme 3).[6] TBS deprotection of **19** furnished **20** and set the stage for the hydroxyl and epoxy-directed regio- and stereoselective reduction.[2] Indeed, DIBAL-H reduction of **20** furnished exclusively jesterone **1** whose ^{1}H and ^{13}C NMR data were identical with those reported for the natural product.[1a]

In short, we have achieved a synthesis of jesterone **1** from easily available prenylated benzoquinone **7** through a series of simple, efficient, and highly chemo-, regio-, and stereoselective steps. This approach should enable access to many analogues of this biologically active natural product and efforts in this direction as well as toward a chiral version of the synthesis are in progress.

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Supporting Information Available: Spectral data (^{1}H, ^{13}C NMR, and HRMS) of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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