

# Total Synthesis of the Novel Antifungal Agent ( $\pm$ )-Jesterone

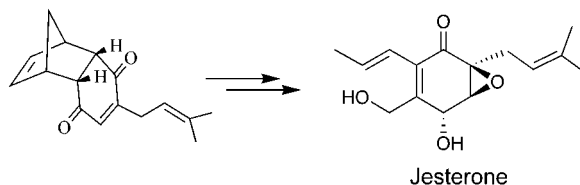
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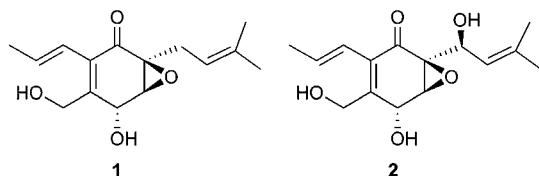
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## ABSTRACT



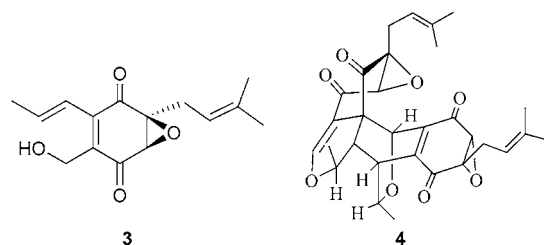
A total synthesis of the novel, biologically active epoxyquinone natural product ( $\pm$ )-jesterone has been accomplished from the readily accessible Diels–Alder adduct of cyclopentadiene and prenylated-*p*-benzoquinone. The approach delineated here is notable for its conceptual simplicity and efficient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

In 2001, Li and Strobel<sup>1a</sup> 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.<sup>1b</sup> 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  $\mu\text{g/mL}$ ) it displays against the oomycetous fungi, which are some of the most pathogenic of all disease-



causing fungi.<sup>1a</sup> More recently, jesterone **1** was found to exhibit activity against human breast and human leukemia cell lines.<sup>2</sup> The first total synthesis of (–)-jesterone **1** was achieved by the group of Porco,<sup>2</sup> 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- $\kappa\text{B}$  by inhibiting the



inhibitor of the  $\kappa\text{B}$  kinase.<sup>3</sup> 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,<sup>4</sup> 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 ( $\pm$ )-jesterone **1** was the prenylated *p*-benzoquinone **7**, which in turn is

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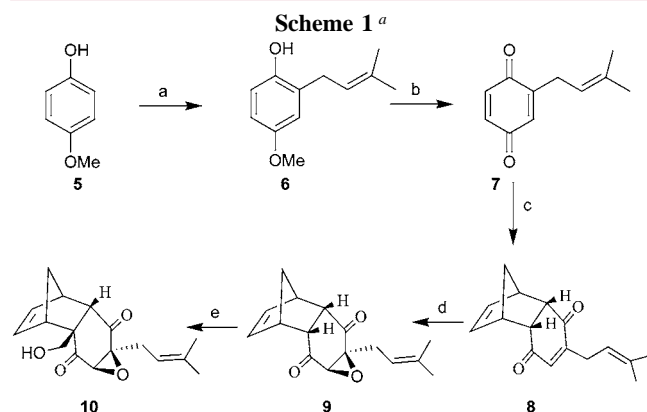
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easily available from *p*-methoxyphenol **5** via 4-methoxy-2-prenylphenol **6** (Scheme 1).<sup>5</sup>

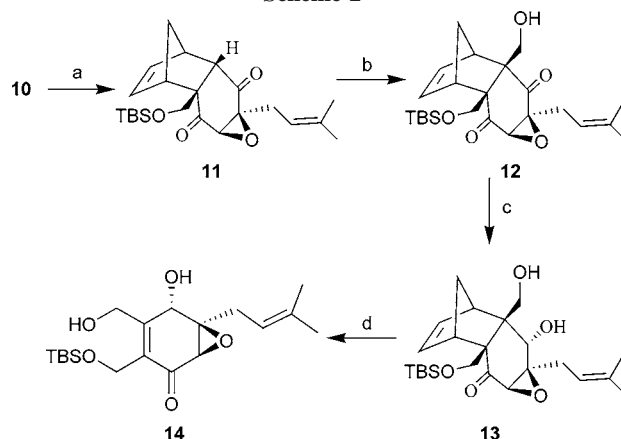


<sup>a</sup> Reagents and conditions: (a) prenyl bromide, Na, ether, reflux, 87%; (b) CAN, CH<sub>3</sub>CN–H<sub>2</sub>O (1:1), 0 °C, 45 min, 85%; (c) cyclopentadiene, methanol, 0 °C, 2 h, 98%; (d) 10% Na<sub>2</sub>CO<sub>3</sub>, 30% H<sub>2</sub>O<sub>2</sub>, acetone, 0 °C, 40 min, 92%; (e) DBU, 35% formalin, THF, 0 °C, 2 h, 92%.

Diels–Alder reaction between **7** and cyclopentadiene was regioselective and furnished the endo-adduct **8**<sup>6</sup> in almost quantitative yield. Hydrogen peroxide-mediated epoxidation

(6) All new compounds were fully characterized on the basis of spectral data (IR, <sup>1</sup>H, <sup>13</sup>C NMR, and HRMS). Selected spectral data: **9**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>16</sub>H<sub>18</sub>NaO<sub>3</sub> [*M* + Na]<sup>+</sup> 281.1154, found 281.1134. **12**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>24</sub>H<sub>36</sub>NaO<sub>5</sub>Si [*M* + Na]<sup>+</sup> 455.2230, found 455.2205. **14**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>19</sub>H<sub>32</sub>NaO<sub>5</sub>Si [*M* + Na]<sup>+</sup> 391.1917, found 391.1935. **15**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>19</sub>H<sub>30</sub>NaO<sub>5</sub>Si [*M* + Na]<sup>+</sup> 389.1760, found 389.1746. **17b**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>23</sub>H<sub>36</sub>NaO<sub>5</sub>Si [*M* + Na]<sup>+</sup> 443.2230, found 443.2246. **1**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>15</sub>H<sub>20</sub>NaO<sub>4</sub> [*M* + Na]<sup>+</sup> 287.1259, found 287.1255.

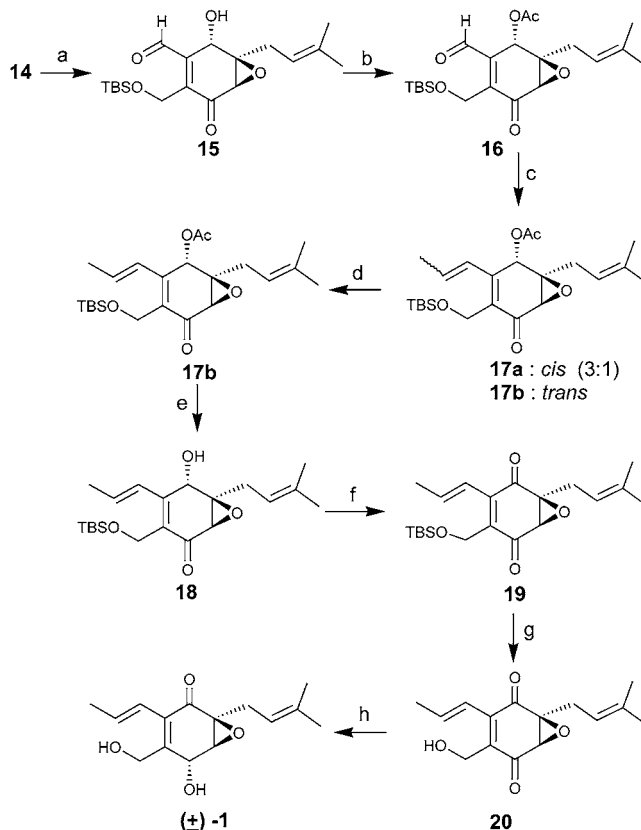
**Scheme 2<sup>a</sup>**



<sup>a</sup> Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 0 °C, 90%; (b) DBU, 35% formalin, THF, 0 °C, 36 h, 80%; (c) NaBH<sub>4</sub>, methanol, –5 °C, 1 h, 84%; (d) diphenyl ether, 220 °C, 6 min, 98%.

of **8** in the presence of base was both regio- and stereo-selective to furnish a single epoxide **9** in excellent yield

**Scheme 3<sup>a</sup>**



<sup>a</sup> Reagents and conditions: (a) TEMPO [TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl], O<sub>2</sub>, CuCl, DMF, rt, 3 h, 90%; (b) Ac<sub>2</sub>O, pyridine, DMAP, DCM, 0 °C, 3 h, 98%; (c) C<sub>2</sub>H<sub>5</sub>PPh<sub>3</sub>Br, BuOK, THF, 0 °C, 65%; (d) *hν*, Pyrex, 450 W (Hannovia), I<sub>2</sub>, CDCl<sub>3</sub>, 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%.

(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.<sup>6</sup> 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 exopropensity of the norbornyl scaffold were now fully exploited for the regio- and stereoselective reduction of **12** to furnish **13** (Scheme 2).<sup>6</sup> Retro-Diels–Alder reaction of **13** was smooth and led to the chemodifferentiated monocyclic precursor **14** of jesterone **1** (Scheme 2).<sup>6</sup>

Chemoselective TEMPO oxidation<sup>7</sup> 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).<sup>6</sup> 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).<sup>6</sup>

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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<sup>8</sup> led to the epoxyquinone **19** (Scheme 3).<sup>6</sup> TBS deprotection of **19** furnished **20** and set the stage for the hydroxyl and epoxy-directed regio- and stereoselective reduction.<sup>2</sup> Indeed, DIBAL-H reduction of **20** furnished exclusively jesterone **1** whose <sup>1</sup>H and <sup>13</sup>C NMR data were identical with those reported for the natural product.<sup>1a</sup>

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.

**Acknowledgment.** This work was supported by the Chemical Biology Unit of JNCASR, Bangalore. We thank S. Ramesh and K. Islam for useful discussions and A. Medda and P. Maity for the preparation of starting materials.

**Supporting Information Available:** Spectral data (<sup>1</sup>H, <sup>13</sup>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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