## Biomimetic Cycloaddition Approach to Tropolone Natural Products via a Tropolone Ortho-quinone Methide

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## ABSTRACT



A study toward a possible biomimetic hetero Diels–Alder reaction is reported between humulene and a novel tropolone ortho-quinone methide. A suitable tropolone ortho-quinone methide precursor has been prepared from 3-methyl-2-furoate. Heating the ortho-quinone methide precursor gave a tropolone ortho-quinone methide, which in the presence of humulene underwent a hetero Diels–Alder reaction to give a deoxy analogue of epolone B.

Pycnidione (1) and epolone B (2) are members of a small family of tropolone natural products isolated from a variety of fungi (Figure 1).<sup>1–5</sup> Both metabolites 1 and 2 have been shown to induce erythropoietin gene expression and are thus of interest as a potential alternative treatment for patients with anemia.

The tropolone natural products in this series show striking structural interrelationships, all featuring one or two identical tropolone units fused to a hydrocarbon backbone.

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We recently reported a model study toward a biomimetic approach to these tropolone natural products via a hetero Diels–Alder reaction.<sup>6</sup> We proposed that pycnidione (1) is biosynthesized via two consecutive hetero Diels–Alder reactions of a novel tropolone *o*-quinone methide 3 with the sesquiterpene backbone 4 (Scheme 1). To our knowledge,



Figure 1. Structures of pycnidione (1) and epolone B (2).

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such a tropolone ortho-quinone methide is a completely novel reactive intermediate and has not been previously described. The tropolone ortho-quinone methide **3** could be derived from tropolone **5** by the elimination of water. Epolone B (**2**) has been described as a possible biosynthetic precursor of pycnidione (**1**), which is consistent with our proposal.<sup>1</sup> Herein we report the synthesis of tropolone **6**, a precursor of the tropolone ortho-quinone methide **3**, as well as the synthesis of a deoxy analogue of epolone B (**2**).

Work by Sato has shown that ortho-(1-(alkylthio)alkyl)phenols are suitable precursors to benzo ortho-quinone methides.<sup>7</sup> Thus, it appeared to us that an alkylthio derivative of **5**, e.g., **6**, would be a suitable target to prepare in order to generate the tropolone ortho-quinone methide precursor.

The desired tropolone **6** was disconnected using a 1,3dipolar cycloaddition of an 3-oxidopyrylium ylide **8** and a ketene equivalent as the key step (Scheme 2).<sup>8</sup> The 3-oxidopyrylium ylide **8** is available from a corresponding pyranulose acetate **9**, which in turn is derived from furan **10** via an oxidative ring expansion.

The synthesis of **6** started with commercially available 3-methyl-2-furoate (**11**) (Scheme 3). Reduction of 3-methyl-2-furoate with LiAlH<sub>4</sub> afforded the corresponding alcohol, which was protected as the TBS-ether **12** using a standard



protocol. Formylation of furan 12 using "BuLi and DMF followed by reduction and then oxidative ring expansion with *m*-CPBA afforded the corresponding pyranulose, which was subsequently activated as the acetate 13 using Ac<sub>2</sub>O/DMAP conditions. Gratifyingly, it was found that heating the pyranulose acetate 13 in the presence of an excess of  $\alpha$ -acetoxyacrylonitrile in toluene in a sealed tube for 6 h at 120 °C afforded the desired cycloadducts 14 and 15 as a 2:5 mixture in moderate but acceptable yield. Surprisingly, the collapse of the cyanohydrin of cyloadducts 14 and 15 to a stable bis ketone could not be achieved. This transformation, however, proceeded without difficulty if the carbonyl of the cycloadducts was first reduced to give 16 and 17. Subsequent efforts focused on the cleavage of the ether bridge of 18.

It was found that the most suitable method of cleaving the ether bridge was via an iodo ether elimination of iodide



<sup>*a*</sup> Reagents and conditions: (a) LiAlH<sub>4</sub>, Et<sub>2</sub>O/THF, rt, 99%; (b)TBSCl, imidazole, DMF, rt, 90%; (c) *n*-BuLi, DMF, THF, from -78 °C to rt, 93%; (d) NaBH<sub>4</sub>, EtOH/THF, rt, 1 h, 98%; (e) *m*-CPBA, DCM, -78 °C, 3 h, 97%; (f) Ac<sub>2</sub>O, DMAP, pyridine, 0 °C, 90 min, 65%; (g) α-acetoxyacrylonitrile, toluene, 120 °C, 6 h, 54% overall; (h) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, rt, 10 min, 99%; (i) NaOMe, MeOH, rt, 30 min, 98%.

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<sup>*a*</sup> Reagents and conditions: (j) NaBH<sub>4</sub>, MeOH, rt, 20 min, 99%; (k) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, then NaBH<sub>4</sub> (2 equiv), 6 h, rt, 83%; (l) Ac<sub>2</sub>O, DMAP, pyridine, 96%; (m) HF, MeCN, 96%; (n) (*i*) Tf<sub>2</sub>O, NEt<sub>3</sub>, DCM, -20 °C; (*ii*) TBAI, MeCN, 92% overall; (o) activated Zn, EtOH, 2 h, 78%; (p) 2-methoxypropene, PPTS, 0 °C, 2h, 88%; (q) K<sub>2</sub>CO<sub>3</sub>, MeOH, 98%; (r) (CICO)<sub>2</sub>, DMSO, DCM, -65 °C, then N(<sup>i</sup>Pr)<sub>2</sub>Et, -20 °C, 94%; (s) NaSPh, EtOH, 0 °C, 1 h, then rt, 2 h, 92%; (t) 70% aqueous AcOH, 48 h; (u) 4 equiv of TFAA and DMSO, -60 °C, 1.5 h, then NEt<sub>3</sub>, -60 °C, 1.5 h, 64%.

**20** (Scheme 4).<sup>9</sup> The iodide was derived from keto-alcohol **18**. Reduction of **18** with NaBH<sub>4</sub> afforded diol **19**. Further experimentation showed that cycloadducts **14** and **15** could be directly converted into diol **19** using a one-pot procedure with 3 equiv of NaBH<sub>4</sub>. Protection of the diol **19** as the bisacetate, removal of the TBS group with aqueous HF in MeCN, and activation of the alcohol as the triflate followed by treatment with tetrabutylamonium iodide afforded iodide **20** in 84% yield over four steps.

Gratifyingly, iodide **20** efficiently underwent iodo-ether elimination with the simultaneous loss of one of the acetyl protecting groups when treated with activated zinc in refluxing ethanol, affording exo-ene **21** in good yield. Protection of the diol of **21** as the acetonide followed by the saponification of the acetate afforded alcohol **22**. The alcohol

Scheme 5. Biomimetic Hetero Diels-Alder Reaction<sup>a</sup>



<sup>*a*</sup> Reagents and conditions: (v) humulene, *p*-xylene, sealed tube, 150 °C, 24 h, 22%.

could now be oxidized with Swern reagent, and the resulting unstable exo-enone was immediately exposed to thiophenol sodium salt in EtOH to afford enone **23**. Removal of the acetonide using aqueous acetic acid afforded the corresponding diol, which was oxidized to the desired tropolone **6** using TFAA-activated DMSO.

With the tropolone **6** in hand, the hetero Diels-Alder reaction was attempted (Scheme 5). Humulene was used as a model of the sesquiterpene backbone **4**. It was found that tropolone **6** acted directly as a precursor of the tropolone ortho-quinone methide **3** without prior need for oxidation of the thiol to the sulfoxide. Thus, heating tropolone **6** in *p*-xylene in the presence of humulene at 150 °C for 24 h afforded deoxy epolone B **24** in an encouraging yield. The cycloadduct **24** features the regiochemistry and stereochemistry as would be expected from a concerted inverse electron-demanding hetero Diels-Alder reaction between the C5-C6 double bond<sup>10</sup> of humulene and a novel tropolone ortho-quinone methide **3**.

In conclusion, we have developed a synthesis of tropolone **6** via a 3-oxidopyrylium 1,3-dipolar cycloaddition reaction. Tropolone **6** acted as a precursor to the entirely novel biomimetic tropolone ortho-quinone methide **3**. This intermediate reacted selectively, and without the need of any protecting groups, with humulene to give a deoxy analogue of epolone B (**2**), thus offering experimental support to a possible hetero Diels—Alder biosynthesis of epolone B (**2**) and pynidione (**1**).

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