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

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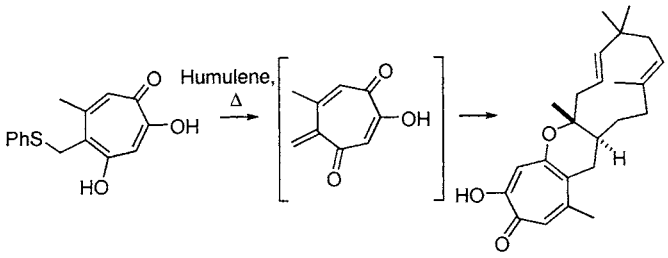
ABSTRACT



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).[1−5] 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.

We recently reported a model study toward a biomimetic approach to these tropolone natural products via a hetero Diels−Alder reaction.[6] 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,

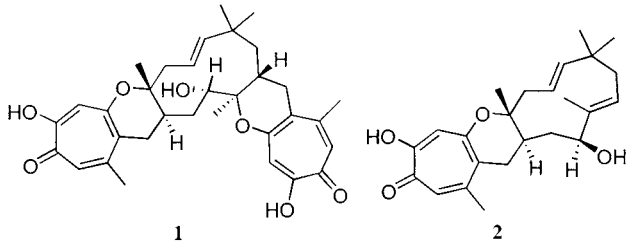


Figure 1. Structures of pycnidione (**1**) and epolone B (**2**).

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(1) Cai, P.; Smith, D.; Cunningham, B.; Brown-Shimer, S.; Katz, B.; Pearce, C.; Venables, D.; Houck, D. *J. Nat. Prod.* **1998**, *61*, 791.
(2) Harris, G. H.; Hoogsteen, K.; Silverman, K. C.; Raghoobar, S. L.; Bills, G. F.; Lingham, R. B.; Smith, J. L.; Dougherty, H. W.; Cascales, C.; Paláez, F. *Tetrahedron* **1993**, *49*, 2139.
(3) Mayerl, F.; Gao, Q.; Huang, S.; Klohr, S. E.; Matson, J. A.; Gustavson, D. R.; Pirnik, D. M.; Berry, R. L.; Fairchild, C.; Rose, W. C. *J. Antibiot.* **1993**, *46*, 1082.
(4) Itô, T. *Agric. Biol. Chem.* **1979**, *43*, 1237.
(5) Itô, T.; Arai, T.; Oshashi, Y.; Sasada, Y. *Agric. Biol. Chem.* **1981**, *45*, 1689.

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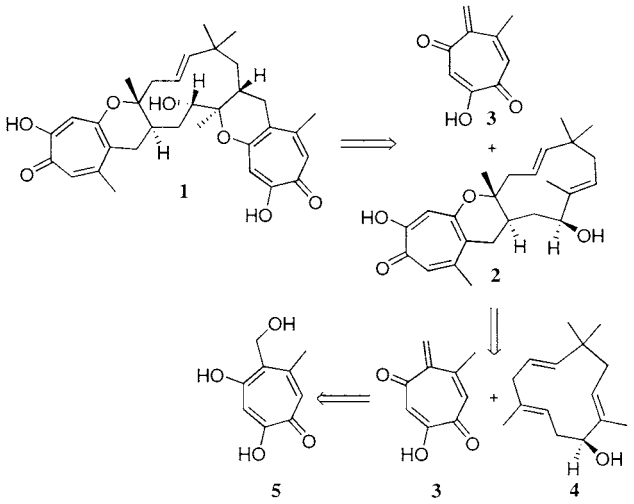
Scheme 1. Retrosynthetic Approach to Pycnidione (**1**) and Epolone B (**2**)



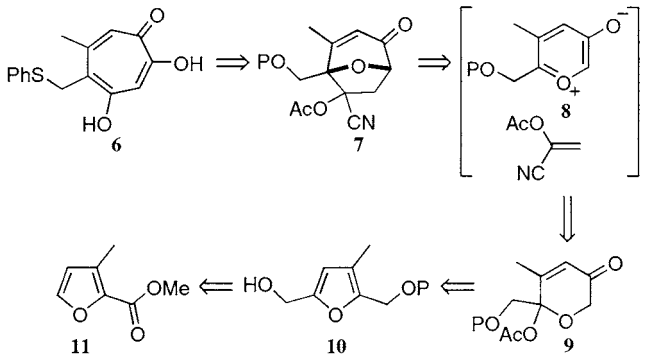
such a tropolone ortho-quinone methide is a completely novel reactive intermediate and has not been previously described. The tropolone ortho-quinone methide **3** could be derived from tropolone **5** by the elimination of water. Epolone B (**2**) has been described as a possible biosynthetic precursor of pycnidione (**1**), which is consistent with our proposal.[1] 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.[7] 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 1,3-dipolar cycloaddition of an 3-oxidopyrylium ylide **8** and a ketene equivalent as the key step (Scheme 2).[8] 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 $LiAlH_4$ afforded the corresponding alcohol, which was protected as the TBS-ether **12** using a standard

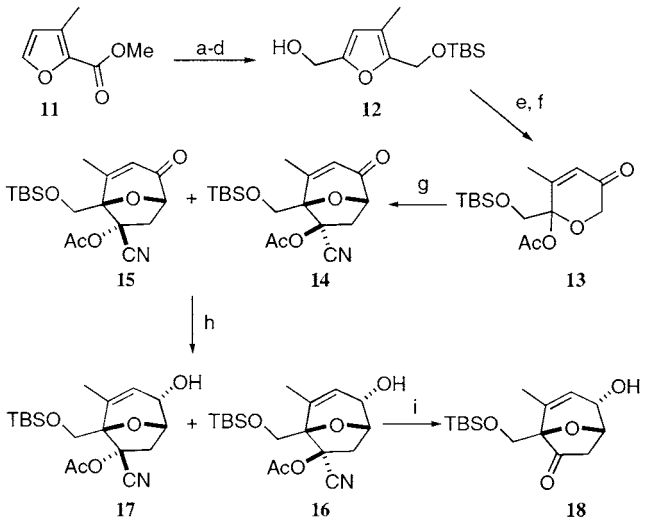
Scheme 2. Retrosynthetic Approach to Tropolone **6**



protocol. Formylation of furan **12** using ^{n}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_2O/DMAP conditions. Gratifyingly, it was found that heating the pyranulose acetate **13** in the presence of an excess of α-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

Scheme 3. Synthesis of Keto-alcohol **18**[a]



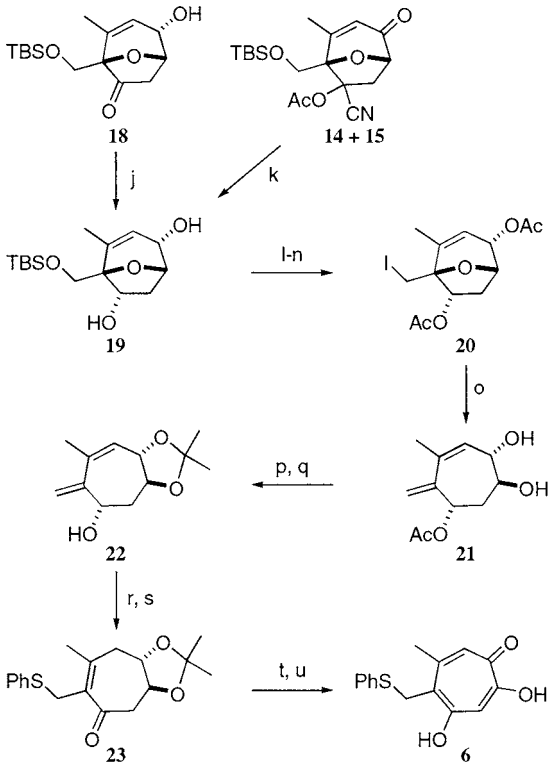
[a] Reagents and conditions: (a) $LiAlH_4$, Et_2O/THF, rt, 99%; (b)TBSCl, imidazole, DMF, rt, 90%; (c) *n*-BuLi, DMF, THF, from −78 °C to rt, 93%; (d) $NaBH_4$, EtOH/THF, rt, 1 h, 98%; (e) *m*-CPBA, DCM, −78 °C, 3 h, 97%; (f) Ac_2O, DMAP, pyridine, 0 °C, 90 min, 65%; (g) α-acetoxyacrylonitrile, toluene, 120 °C, 6 h, 54% overall; (h) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 10 min, 99%; (i) NaOMe, MeOH, rt, 30 min, 98%.

(6) Baldwin, J. E.; Mayweg, A. V. W.; Neumann. K.; Pritchard, G. J. *Org. Lett.* **1999**, *1*, 1933.

(7) Inoue, T.; Inoue, S.; Sato, K. *Chem. Lett*. **1989**, 653; **1990**, 55.

(8) For further examples of 1,3-dipolar cycloadditions with 3-oxidopyrylium species, see: Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359. Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3361. Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1261. Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1983**, 666. Sammes, P. G.; Street, L. J. *J. Chem. Res.* **1984**, 196. Bromidge, S. M.; Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1725. Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 281. Bromidge, S. M.; Archer, D. A.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 353. Marshall, K. A.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9135. Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. Magnus, P.; Diorazio, L.; Donohoe, T. J.; Giles, M.; Pye, P.; Tarrant, J.; Thom, S. *Tetrahedron* **1996**, *52*, 14147.

Scheme 4. Synthesis of Tropolone **6**[a]



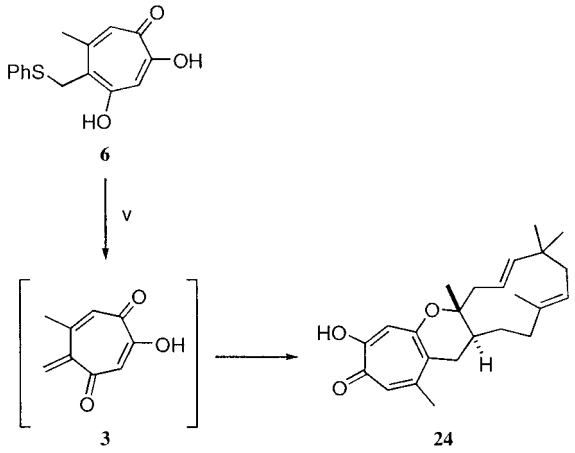
[a] Reagents and conditions: (j) $NaBH_4$, MeOH, rt, 20 min, 99%; (k) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, then $NaBH_4$ (2 equiv), 6 h, rt, 83%; (l) Ac_2O, DMAP, pyridine, 96%; (m) HF, MeCN, 96%; (n) (*i*) Tf_2O, NEt_3, DCM, −20 °C; (*ii*) TBAI, MeCN, 92% overall; (o) activated Zn, EtOH, 2 h, 78%; (p) 2-methoxypropene, PPTS, 0 °C, 2h, 88%; (q) K_2CO_3, MeOH, 98%; (r) $(ClCO)_2$, DMSO, DCM, −65 °C, then $N(^iPr)_2Et$, −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_3, −60 °C, 1.5 h, 64%.

20 (Scheme 4).[9] The iodide was derived from keto-alcohol **18**. Reduction of **18** with $NaBH_4$ 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 $NaBH_4$. Protection of the diol **19** as the bis-acetate, 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

(9) Ohmori, N. *J. Chem. Soc., Chem. Commun.* **2001**, 1552. Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1984**, *67*, 1328.

Scheme 5. Biomimetic Hetero Diels−Alder Reaction[a]



[a] 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[10] 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**).

Acknowledgment. The authors thank the EPSRC for a studentship to A.V.W.M.

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(10) For an account of the reactivity of the double bonds of humulene, see: Allen, F. H.; Brown, E. D.; Rogers, D.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1964**, 1116.