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Studies toward the Biomimetic Synthesis of Tropolone Natural Products via a Hetero Diels–Alder Reaction

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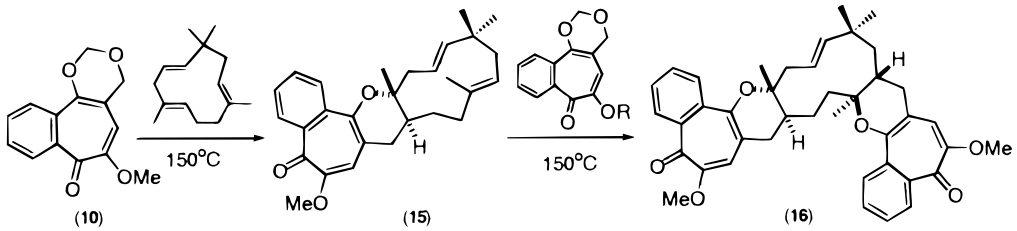
ABSTRACT



(10) (15) (16)

Analogues of the tropolone natural products pycnidione and epolone B were synthesized via a hetero Diels–Alder reaction of benzotropolone 10 with humulene. The quinone methide benzotropolone 13 was generated in situ by thermalisation of benzotropolone 10. Benzotropolone 10 was derived from phthalic acid via carbonyl ylide 8a followed by an intramolecular 1,3-dipolar cycloaddition and subsequent acid-catalyzed ring opening.

Pycnidione (**1**), epolone B (**2**), and eupenifeldin (**3**) are members of a family of tropolone fungal metabolites recently isolated (Figure 1).[1−3] Pycnidione has been extracted from *Phoma* sp. strain MF5726 isolated from soil collected on Korase Island, Federated States of Micronesia. Pycnidione was also isolated from a culture of fungus OS-F69284, along with epolone B. Eupenifeldin was extracted from cultures of *Eupenicillium brefeldanium* ATCC 74184 and differs from pycnidione only in the stereochemistry at the C9 ring junction. All three natural products have been shown to possess interesting biological activities. Pycnidione and epolone B induced erythropoietin gene expression and are thus of interest as a potential alternative treatment of patients with anemia due to chronic renal failure.[1] Pycnidione was further shown to inhibit stromelysin, an enzyme postulated to cause cartilage degradation, one of the proposed causes for arthritis.[4] Eupenifeldin was shown to have in vivo antitumor activity in the P388 leukemia model.[3]

All three metabolites show a high degree of structural similarity, each featuring identical tropolone rings attached to a sesquiterpene backbone. The 11-membered sesquiterpene ring shows great resemblance to humulene, differing only in the hydroxy functionality at C11. Biosynthetically, these fungal metabolites can be viewed as addition products of tropolones[5] to a sesquiterpene such as humulene, which may be hydroxylated prior or after addition (Scheme 1). We

(1) Cai, P.; Smith, D.; Cunningham, B.; Brown-Shimer, S.; Katz, B.; Pearce, C.; Venables, D.; Houck, D. *J. Nat. Prod.* **1998**, *61*, 791−795.
(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*, 2139−2144.
(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*, 1082−1088.
(4) MacNaul, K. L.; Chartrain, N.; Lark, M.; Tocci, M. J.; Hutchinson, N. I. *J. Biol. Chem.* **1990**, *28*, 17238−17245.
(5) For tropolone biosynthesis, see: (a) O'Sullivan, M. C.; Schwab, J. M. *Bioorg. Chem.* **1995**, *23*, 131−143. (b) Scott, A. I.; Guilford, H.; Lee, E. *J. Am. Chem. Soc.* **1971**, *93*, 3534−3536.

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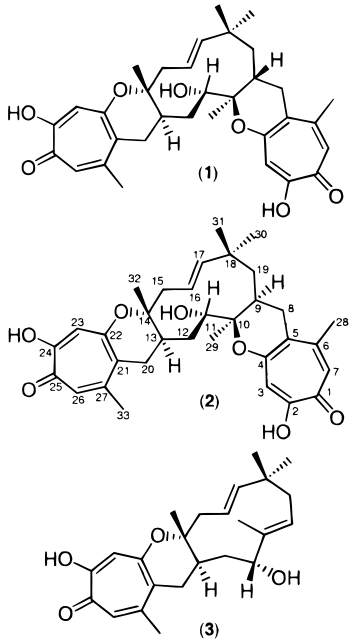
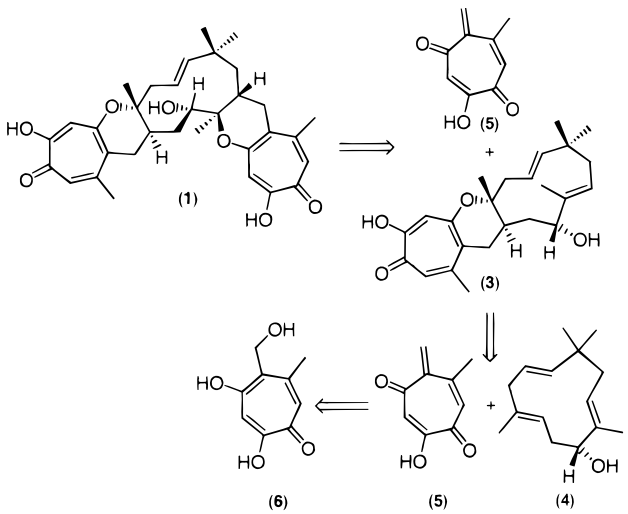


Figure 1. Structures of pycnidione (**1**), eupenifeldin (**2**), and epolone B (**3**).

Scheme 1. Retrosynthetic Approach to Pycnidione (**1**) and Epolone B (**3**)

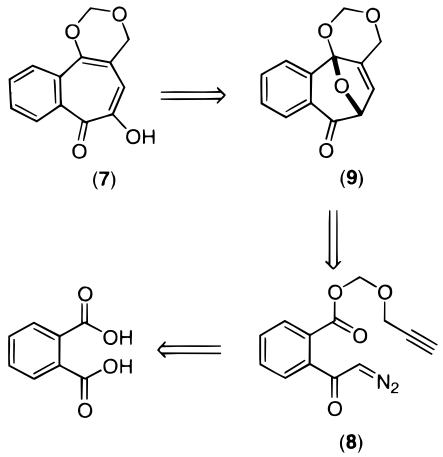


propose that these natural products can be formed via a hetero Diels−Alder reaction of quinone methide tropolone **5** with the 11-membered sesquiterpene **4**. The quinone methide species can be derived from dihydroxy species **6**, through the elimination of water.[6] Cai et al. have recently suggested that monotropolone epolone B (**3**) is a biosynthetic precursor to pycnidione.[1] Hence a further hetero Diels−Alder reaction of **3** with **5** would afford pycnidione. All three natural products were isolated in an enantiomerically pure form though it is not clear whether, biosynthetically, the addition of the tropolone occurs enzymatically or nonenzymatically.

Studies toward the synthesis of the quinone methide tropolone precursor **6** are currently in progress. To determine whether a hetero Diels−Alder reaction is a chemically feasible biomimetic strategy for the synthesis of these tropolone sesquiterpenes, benzotropolone **7**, a model of **6**, was developed. This benzotropolone was synthetically more accessible and the fused benzene ring provided a more manageable compound. The model, however, features opposite regiochemistry to that of the biomimetic precursor **6**. Instead of the hydroxylsesquiterpene **4**, humulene was used as a model of the 11-membered ring backbone.

Carbonyl ylides and their use in synthesis via 1,3-dipolar cycloadditions to acetylenic dipolarophiles have been well documented.[7] Recently this strategy has been applied to the synthesis of novel annulated benzotropolones.[8] The shown retrosynthesis seemed a viable strategy for the construction of benzotropolone **7** (Scheme 2).

Scheme 2. Retrosynthetic Approach to Benzotropolone **7**



Benzotropolone **7** was thus prepared starting from commercially available phthalic acid (Scheme 3). Formation of the monoester using (propargyloxy)methyl chloride[9] followed by conversion to a mixed anhydride and subsequent treatment with an excess of CH_2N_2 gave the α-diazoketone **8**. Exposure of this α-diazoketone to $Rh_2(OAc)_4$ in CH_2Cl_2 resulted in the formation of a reactive metal-carbenoid intermediate which underwent intramolecular carbonyl ylide (**8a**) formation and subsequent 1,3-dipolar cycloaddition to give tetra-

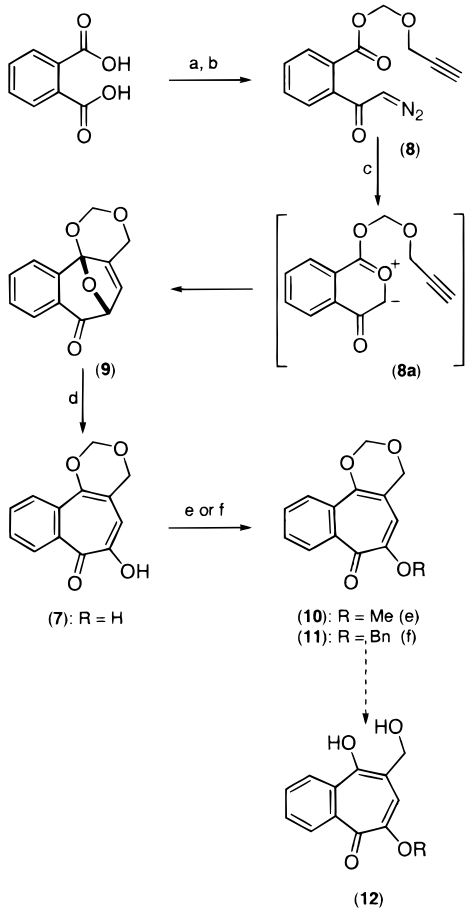
(6) For general *o*-quinone methide generation in aromatic systems, see: (a) Chambers, J. D.; Crawford, J.; Williams, H. W. R.; Dufresne, C.; Scheigetz, J.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1992**, *70*, 1717−1732. (b) Talley, J. J. *J. Org. Chem.* **1985**, *50*, 1695−1699. (c) Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. *J. Chem. Soc., Chem. Commun.* **1999**, 691−692.

(7) (a) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100−3109. (b) Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894−2900. (c) Toshikazu, I.; Jitsuhiro, K.; Tsubokura, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 240−244.

(8) (a) Friedrichsen, W.; Plüg, C. *Tetrahedron Lett.* **1992**, *33*, 7509−7510. (b) Friedrichsen, W.; Plüg, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1035−1040. (c) Friedrichsen, W.; Plüg, C.; Debaerdemaeker, T. *J. Prakt. Chem.* **1997**, *339*, 205−316.

(9) Hasan, A.; Srivastava, P. C. *J. Med. Chem.* **1992**, *35*, 1435−1439.

Scheme 3[a]



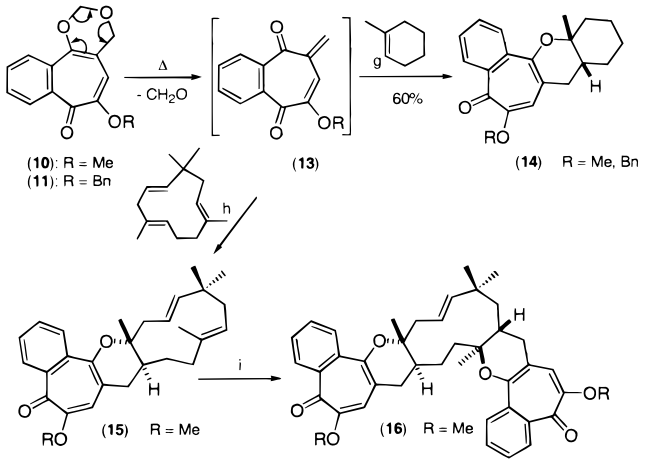
[a] Reagents and conditions: (a) $N(^iPr)_2Et$ (1 equiv), $ClCH_2OCH_2$-CCH, DMF, rt., 6 h, 65%; (b) isobutyl chloroformate (1 equiv), NEt_3 (1 equiv), THF, then CH_2N_2 (3 equiv)/Et_2O, −15 to −5 °C, 24 h, 51%; (c) $Rh_2(OAc)_4$ (3 mol %), CH_2Cl_2, rt, 5h, 74%; (d) 6 N HCl, 1,4-dioxane, rt., 3 h, 93%; (e) NaH, MeI, DMF, rt, 6 h, 73%; (f) NaH, BnBr, DMF, 50 °C, 68%.

cycle **9**. Acid-catalyzed ring opening of **9** yielded tricyclic tropolone **7**, with the methylene acetal still in place.[10] Protection of the free hydroxy functionality as either the methyl or benzyl ether using standard protocol afforded tropolones **10** and **11**. Subsequent removal of the acetal functionality to yield the diol **12** was met with considerable resistance, and results will be reported in due course.

Funk et al. have reported that 4*H*-1,3-dioxins can be thermally converted to α,*β*-unsaturated aldehydes via a retro Diels−Alder reaction with the extrusion of formaldehyde.[11]

It was thus found that a thermal retro-hetero Diels−Alder reaction of the protected benzotropolones **10** or **11**, with the extrusion of formaldehyde at 150 °C, generated the required tropolone quinone methide **13** in situ. This was trapped initially by 1-methylcyclohexene to give the inverse electron demand hetero Diels−Alder adduct **14** (Scheme 4).

Scheme 4[a]



[a] Reagents and conditions: (g) sealed tube, excess 1-methylcyclohexene, 150 °C, 24 h, 62%; (h) sealed tube, humulene (1.5 equiv), *p*-xylene, 150 °C, 24 h, 60%; (i) sealed tube, **10** (4 equiv), *p*-xylene, 150 °C, 24 h, 20%.

Thermolosis of benzotropolone **10** followed by a hetero Diels−Alder reaction in situ with 1.5 equiv of humulene in *p*-xylene at 150 °C afforded the least hindered monosubstituted epolone B analogue **15** with correct regiochemistry in good yield.[12] Addition of the second tropolone proved to be less facile, presumably due to steric factors. However, reaction with an additional 4 equiv of tropolone **10** in xylene gave pycnidione analogue **16** in 20% yield as a 1:1 mixture of diastereomers.[13]

In summary, an efficient synthesis of benzotropolone **10** was devised which, via thermolosis, could undergo a tandem retro-hetero Diels−Alder/hetero Diels−Alder reaction with humulene to give natural product analogues of epolone B (**3**) and pycnidione (**1**). Further results and experimental details will be published in due course.

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(10) Structures of **9**, **11**, and **15** were confirmed by single-crystal X-ray crystallography and details will be reported in due course.

(11) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1988**, *110*, 1290−1292.

(12) Compounds **15** and **16** were fully characterised by ^1H NMR, ^{13}C NMR, IR, MS, and HRMS.

(13) Diastereomers were separated by HPLC; details will be reported in due course.