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Total synthesis of asterriquinone B1

Kun Liu,* Harold B. Wood and A. Brian Jones

Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

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Abstract

This communication describes the first total synthesis of asterriquinone B1, a representative member of a group of anti-tumor metabolites of *Aspergillus terreus*. The synthesis described herein is potentially applicable to other members of the asterriquinone family.

Asterriquinone B1 (**1**) is a member of a group of tryptophan-derived indolyl benzoquinones isolated from *Aspergillus terreus* by researchers in Japan.[1] The corresponding demethylasterriquinone B1 (**2**) was later on isolated independently from a strain of *Pseudomassaria* species by scientists at Merck in the United States.[2] Other members of the asterriquinone family are interrelated by the presence or absence of either 1,1-dimethylallyl and/or 3,3-dimethylallyl side chains in different positions of the indolyl moieties. The asterriquinones have been shown to exhibit in vivo anti-tumor activity against Ehrlich carcinoma, ascites hepatoma AH13 and mouse P388 leukemia.[3] We herein describe the first total synthesis of asterriquinone B1.

Our selection of asterriquinone B1 (**1**) as a goal structure for total synthesis arose from the combination of its interesting biological activity and its being the most challenging target of the asterriquinone family. The chemistry developed in the synthesis of asterriquinone B1 can be readily applied to the syntheses of other group members. Our synthetic strategy toward **1** is illustrated in Scheme 1. It has been well-established in grevillin synthesis that the hydroxyquinone structure can be derived from the rearrangement of pyrandione **3**.[4] Compound **3** would be obtained from the condensation of pyrandione intermediate **4** with aldehyde **5**.[5] This convergent approach would also allow rapid syntheses of a large number of asterriquinone analogs for biological study.

Starting from methyl indole-3-carboxaldehyde **6**, the reverse prenyl function was introduced at C-2 position of the indole in a one-pot fashion (Scheme 2).[6] Treatment of **6** with *tert*-butyl hypochlorite in THF in the presence of triethylamine (–78°C for 2 h) generated the corresponding chloroindolenine,[7] which suffered the subsequent nucleophilic attack at C-2 position by prenyl-9-BBN[8] (–78°C for 4 h and 23°C for 10 h) to afford compound **7** in 63% yield. Saponification of **7** gave the corresponding acid, which was converted to the acid chloride **8** using oxalyl chloride. Transformation of acid chloride **8** to

* Corresponding author.

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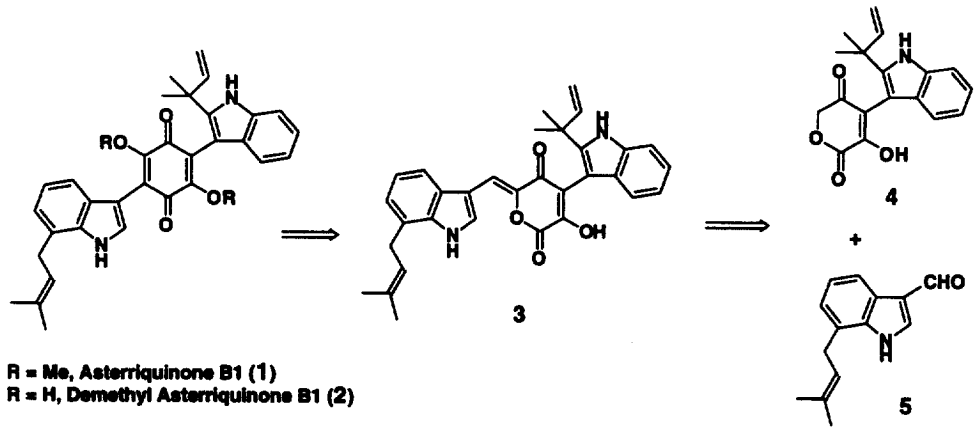
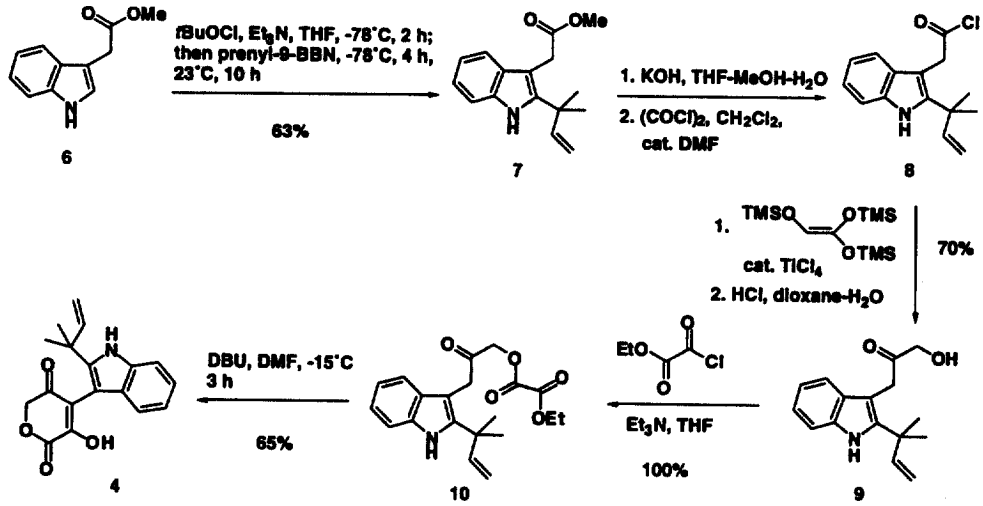


Scheme 1.

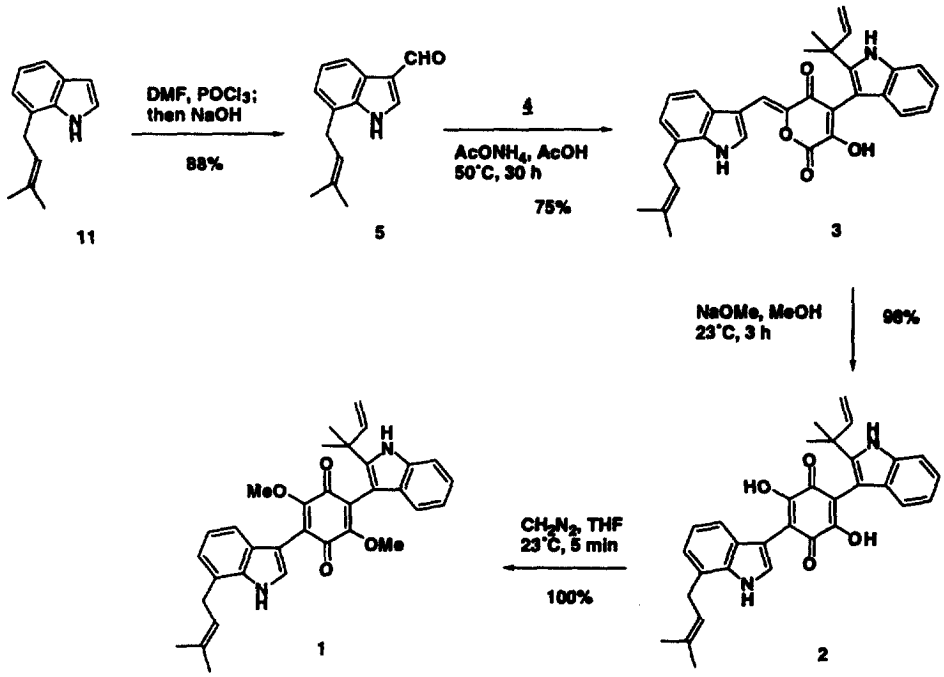
α-hydroxyl ketone **9** was achieved using the methodology developed by Wissner.[9] Reaction of **8** with tris(trimethylsilyloxy)ethylene in the presence of catalytic $TiCl_4$ (23°C for 1 h and 50°C for 40 min) followed by hydrolysis-decarboxylation of the intermediate afforded α-hydroxy ketone **9** in 70% yield. Acylation of **9** with ethyl oxalyl chloride gave oxalate **10** in quantitative yield, which was cyclized by using 2 equivalents of DBU in DMF (−15°C, 3 h) to generate the key pyrandione intermediate **4** in 65% yield.



Scheme 2.

The known 7-prenyl indole **11** was prepared from 2-iodoaniline in four steps following the literature procedure (Scheme 3).[10] Compound **11** underwent smooth Vilsmeier formylation to provide 3-formylindole **5** in 88% yield.[11] Condensation of **4** and **5** was initially carried out in acetic acid with concentrated HCl as catalyst,[5] which produced the desired product **3** in less than 10% yield. The major side reactions were the hydration of the 7-prenyl group and the cyclization of the 7-prenyl group to the nearby indole nitrogen to form the 6-membered ring. By running this condensation reaction in acetic acid in the presence of ammonium acetate (50°C, 30 h), the yield of **3** was improved to 75%. Sodium methoxide catalyzed rearrangement of **3** produced 98% of demethylasterriquinone B1 (**2**), which itself is a natural product.[2] The synthetic demethylasterriquione B1 (**2**) was indistinguishable by mp, TLC, ^{1}H NMR, ^{13}C NMR, IR, and MS from an authentic sample. Finally, reaction of **2** with diazomethane in

THF generated quantitatively asterriquinone B1 (**1**) (mp 209–210°C, lit.[1a] 208–209°C), identical in all respects with a sample derived from natural demethylasterriquinone B1.[12]



Scheme 3.

The synthesis described herein confirms the structural assignments of demethylasterriquinone B1 and asterriquinone B1. By condensing different aromatic aldehydes with pyrandione intermediates such as **4**, we can rapidly synthesize a large number of asterriquinone analogs for biological study. With minor modifications, the approach to **1** should be readily applicable to the syntheses of other members of the asterriquione family.

Acknowledgements

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12. ^{1}H NMR (400 MHz) data of **4** (acetone-d_6): δ 7.29 (d, J=8.0 Hz, 1H), 7.19 (d, J=8.0 Hz, 1H), 7.02 (t, J=8.0 Hz, 1H), 6.90 (t, J=8.0 Hz, 1H), 6.13 (dd, J=10.6, 17.5 Hz, 1H), 5.09 (m, overlapping signals, 3H), 5.00 (d, J=10.6 Hz, 1H); **2** (acetone-d_6): δ 7.62 (d, J=2.8 Hz, 1H), 7.43 (d, J=7.6 Hz, 1H), 7.32 (d, J=8.0 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.08–6.90 (m, overlapping signals, 4H), 6.15 (dd, J=10.5, 17.5 Hz, 1H), 5.48 (m, 1H), 5.09 (d, J=17.5 Hz, 1H), 5.00 (d, J=10.5 Hz, 1H), 3.64 (d, J=7.4 Hz, 2H), 1.77 (s, 3H), 1.75 (s, 3H), 1.49 (s, 6H); **1** ($CDCl_3$): δ 8.52 (s, broad, 1H), 8.12 (s, broad, 1H), 7.56 (d, J=2.7 Hz, 1H), 7.40 (d, J=7.6 Hz, 1H), 7.32 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.19–7.05 (m, overlapping signals, 4H), 6.09 (dd, J=10.5, 17.4 Hz, 1H), 5.43 (m, 1H), 5.16 (d, J=17.4 Hz, 1H), 5.12 (d, J=10.5 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.60 (d, J=7.6 Hz, 2H), 1.83 (s, 3H), 1.79 (d, J=1.2 Hz, 3H), 1.48 (s, 6H).