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Facile construction of the oxaphenalene skeleton by *peri* ring closure. Formal synthesis of mansonone F

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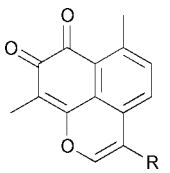
A concise and divergent total synthesis of mansonone F has been accomplished *via* an efficient construction of the oxaphenalene skeleton by facile *peri* ring closure of the naphthol ether, and an effective preparation of the cyclization precursor starting from readily available 5-methoxy-1-tetralone by employing a palladium-induced aromatization of the naphthalinol.

Mansonone F (**1**) and biflorin, which are members of the naturally occurring *ortho*-naphthoquinone family, contain the unusual oxaphenalene skeleton.[1] Biflorin, the first oxaphenalene natural product, was found to have antibiotic properties.[2] More interestingly, mansonone F, a tricyclic sesquiterpenoid, has been reported as a phytoalexin[3–5] which is accumulated in the heartwood of the genus *Ulmus* in response to infections. Recently, mansonone F has also been isolated from the root bark of *Ulmus davidiana*, which has been traditionally used as a medicinal plant for treatment of infections in Korea. In addition, the highly potent anti-MRSA activity of mansonone F, comparable to that of vancomycin, has been studied in our laboratory.[6] However, the paucity of natural mansonone F, as well as its inherent structural constraint, has limited the optimization of its biological properties by structural modification and its therapeutic application. These reasons prompted us to develop a practical and divergent synthetic route to mansonone F, although an elegant synthesis of mansonone F employing intramolecular Diels–Alder addition of benzynes to furans has already been reported.[7] We report herein a concise and divergent synthesis of mansonone F starting from readily available 5-methoxy-1-tetralone.

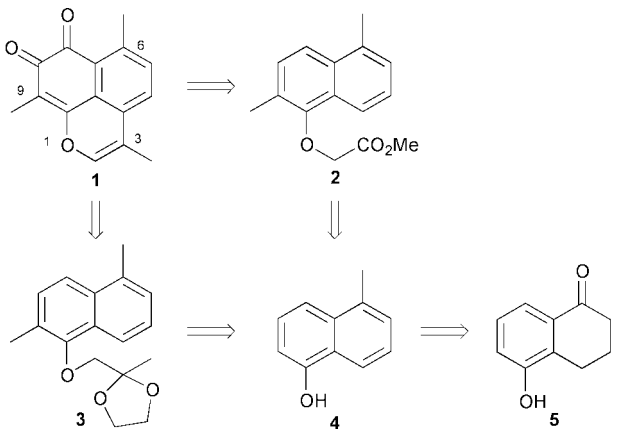


1 Mansonone F R=CH_3

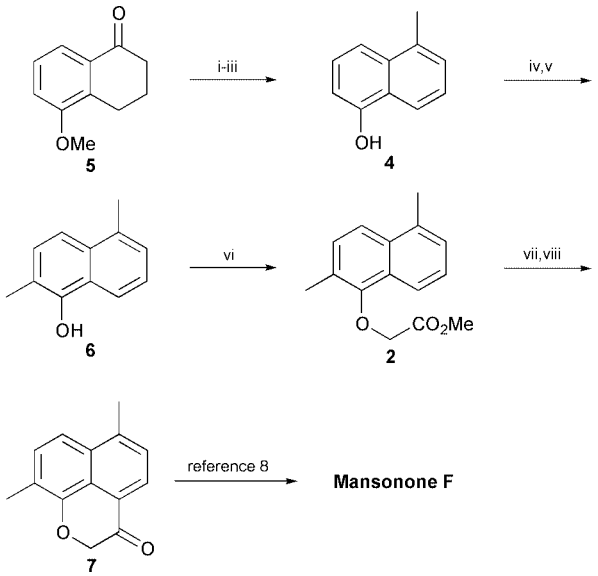
Biflorin R=$CH_2CH_2CHC(CH_3)_2$

Our synthetic strategy (Scheme 1) envisions a highly efficient construction of the tricyclic oxaphenalene skeleton *via peri* ring closure[8] by an intramolecular Friedel–Crafts acylation of the dimethylnaphthol ether **2** or **3**. The cyclization precursors **2** and **3** are readily accessible from the commercially available methoxytetralone **5** by sequential introduction of the alkyl substituents and an effective aromatization of the tetralinol intermediate.

Our synthesis (Scheme 2) commenced with preparation of the methylnaphthol **4**. The first methyl substituent, corresponding to the C6-methyl of mansonone F, was conveniently introduced by methyl Grignard addition to the carbonyl of the tetralone **5**. Aromatization[9] of the resulting carbinol by palladium-induced concurrent dehydration and dehydrogenation and then demethylation of the resulting methoxynaphthalene by boron tribromide provided the methylnaphthol **4**. The methylnaphthol **4** was transformed in a straightforward manner into the cyclization precursor **2** by a three step sequence. The second methyl substituent corresponding to the C9-methyl of mansonone F was effectively introduced by benzeneboronic acid-assisted hydroxymethylation[10] followed by hydrogenolysis of the resulting benzyl alcohol. *O*-alkylation of the naphthol **6** with bromoacetate afforded the dimethylnaphthol ether **2** as a cyclization precursor. The key tricyclic oxaphenalene skeleton of mansonone F was efficiently constructed by a facile *peri* ring closure[8] of the dimethylnaphthol ether **2**. Conversion of the ester **2** to an acid halide and then intramolecular Friedel–Crafts



Scheme 1 Synthetic strategy.



Scheme 2 First synthetic route to mansonone F. *Reagents and conditions*: i, MeMgI, Et_2O, reflux, 1 h; ii, 10% Pd/C, triglyme, reflux, 2 days; iii, BBr_3, CH_2Cl_2, −78 °C, then warm to room temp. (94% in 3 steps); iv, $PhB(OH)_2$, $(CHO)_n$, propionic acid, PhH, reflux, 1 h, then H_2O_2, THF; v, 10% Pd/C, H_2, MeOH, 5 h (63% in 2 steps); vi, $BrCH_2CO_2Me$, K_2CO_3, acetone, reflux (82%); vii, $LiOH·H_2O$, THF–H_2O, 10 min; viii, $(COCl)_2$, PhH, reflux, 1 h, then $AlCl_3$, CH_2Cl_2 (74% in 2 steps).

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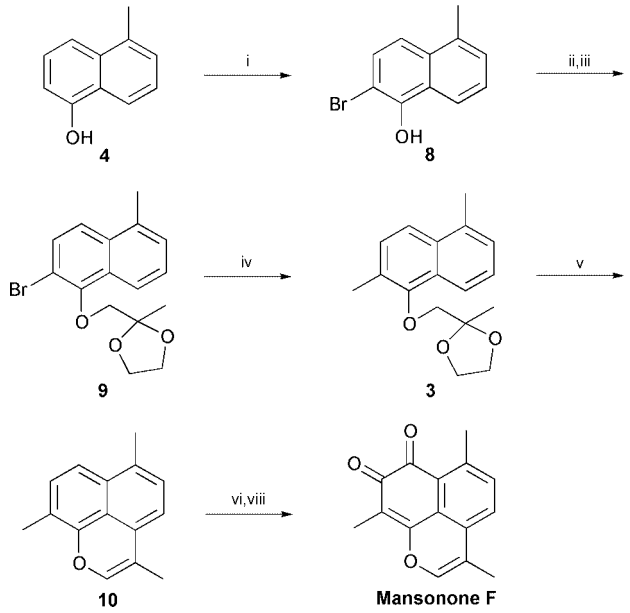

Scheme 3 Alternative synthetic route to mansonone F. *Reagents and conditions*: i, NBS, CH_2Cl_2, 0 °C (60–70%); ii, $BrCH_2COMe$, K_2CO_3, acetone, reflux (96%); iii, $(CH_2OH)_2$, PTSA, PhH, reflux (89%); iv, Bu^nLi, MeI, THF, −78 °C, then warm to room temp. (95%); v, PPA, 100 °C (87%); vi, $Cu(NO_3)_2{\cdot}xH_2O$, Ac_2O (83%); vii, 10% Pd/C, $NaBH_4$, MeOH, then Fremy's salt, 0.06 M NaH_2PO_4, acetone (41%).

acylation of the acid halide afforded the advanced intermediate **7**, which was transformed into mansonone F by a known procedure.[7]

Our alternative synthetic route for the transformation of methylnaphthol **4** into mansonone F is summarized in Scheme 3. The tether for *peri* ring closure was introduced to the bromonaphthol **8** by sequential *O*-alkylation with bromoacetone and carbonyl protection. Addition of the methyl substituent corresponding to the C9-methyl of mansonone F was achieved by halogen–metal exchange followed by methylation. Finally, construction of the oxaphenalene skeleton was executed by facile *peri* ring closure induced by polyphosphoric acid, to give the key intermediate **10**. In order to complete the synthesis, the ortho-quinone moiety of mansonone F was elaborated by application of the reported procedure.[7] The synthetic mansonone F was identical in all aspects to the naturally occuring compound.[1,10]

In summary, the total synthesis of mansonone F has been accomplished *via* a 10 step sequence, starting from the readily available 5-methoxy-1-tetralone (**5**). The key part of this synthesis involves the efficient preparation of 1,6-dimethyl-5-alkoxynaphthalene as a divergent cyclization precursor and its facile conversion to form the oxaphenalene skeleton by *peri* ring closure. This concise and practical synthetic procedure, providing a variety of substituents at the C3, C6 and C9 positions, offers a useful synthetic route to this important prospective anti-MRSA drug.

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