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Syntheses and anti-MRSA activities of the C3 analogs of mansonone F, a potent anti-bacterial sesquiterpenoid: insights into its structural requirements for anti-MRSA activity

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Abstract—Syntheses and excellent anti-MRSA activities of the mansonone F analogs are reported. In addition, the minimal structural requirements for its anti-MRSA activities as well as its structure–activity relationship including the C3 substituents effects on anti-MRSA activity are also described. In particular, this study revealed that both *ortho*-quinone and tricyclic systems of mansonone F are essential for anti-MRSA activities.

1. Introduction

During the last two decades, the increasing prevalence of antibiotic-resistant bacteria has had an enormous impact on infection control policies.[1] In particular, the resistance to multiple antibiotics of Gram-positive bacterial strains, methicillin-resistant *Staphylococcus aureus* (MRSA), is currently considered as serious clinical problem. Even though vancomycin and teicoplanin of glycopeptide antibiotics,[2] quinupristin/dalfopristin,[3] and linezolid[4] of new antibiotics are clinically used for the treatment of MRSA infections, the structural complexity or toxic side effects of these antibiotics as well as the recent occurrences of new resistant strains have prompted the increased efforts for novel antibiotics. Thus, the discovery of novel classes of anti-bacterial agents employing new mode of action is of great concern due to the rapid acquirement of multidrug resistance by Gram-positive pathogens.

Recently, one of the major efforts in our laboratory has been the search, design, and synthesis of novel and highly potent anti-MRSA agents. In this connection, we have recently reported isolation and excellent anti-MRSA activity of mansonone F (**1**), a new anti-bacterial sesquiterpenoid.[5] It has been shown to have excellent anti-bacterial activities against Gram-positive bacteria, MRSA (2 μg/mL of MIC_{90} in vitro), which is comparable to that of vancomycin. The unique structure of Mansonone F consists of oxaphenalene skeleton and *ortho*-naphthoquinone moiety (Fig. 1).

We herein report syntheses and anti-MRSA activities of the C3 mansonone F analogs. In addition, we describe its structure–activity relationship, which revealed the minimal structural requirements for anti-MRSA activity and C3 substituents effects.

The mechanism of anti-bacterial activity of mansonone F has not been completely elucidated yet. However, on the

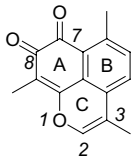

Figure 1. Structure of mansonone F (**1**).

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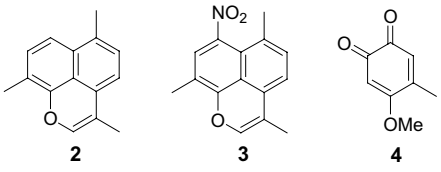
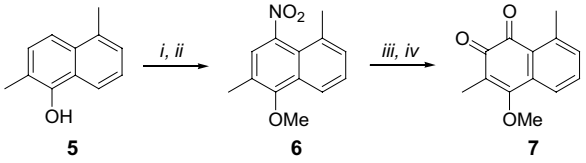
basis of structural features of mansonone F, its anti-MRSA activities can be understood by two possible mode of actions.[6] The first mechanism involves generation of superoxide, particularly cytotoxic superoxide radical, which was reported for anti-bacterial and anti-protozoal activities of several naphthoquinones and isoxazolyl naphthoquinones.[7] However, we have observed that no strains survived when we cultured the strain of *S. aureus* over the MIC of mansonone F in the presence of 4,5-dihydroxy-1,3-benzene-disulfonic acid (Tiron, SIGMA), a specific superoxide scavenger. This supported that the anti-bacterial activity of mansonone F is not mainly due to the production of cytotoxic superoxide radical. The possible alternative mechanism is an attack of certain nucleophile such as thiol, amine, or alcohol of the bacterial growth-related enzymes to the enedione carbonyl of mansonone F, thus rendering the corresponding enzyme inactive although base stacking or intercalation of the planar oxaphenalene system in bacterial DNA is also possible.[8] This is partly supported by recent report in several literatures of 1,2 or 1,4-addition of thiol and nitrogen nucleophile to quinone moiety.[9] Thus, these recent information gave us a starting point for the studies on structure–activity relationship of mansonone F that was initially focused on the identification of pharmacophoric parts of mansonone F and the role of C-ring system including C3 substituents effects on anti-bacterial effect.

2. Chemistry

Most of the structural analogs were synthesized starting from the intermediate **5** or **8** according to the divergent synthetic routes as shown in Schemes 1 and 2. The known analogs **2** and **3**, which are devoid of *ortho*-quinone moiety, were prepared from the tricyclic ketone **8**[5a] and the benzoquinone analog **4** as an A-ring equivalent of mansonone F is commercially available.



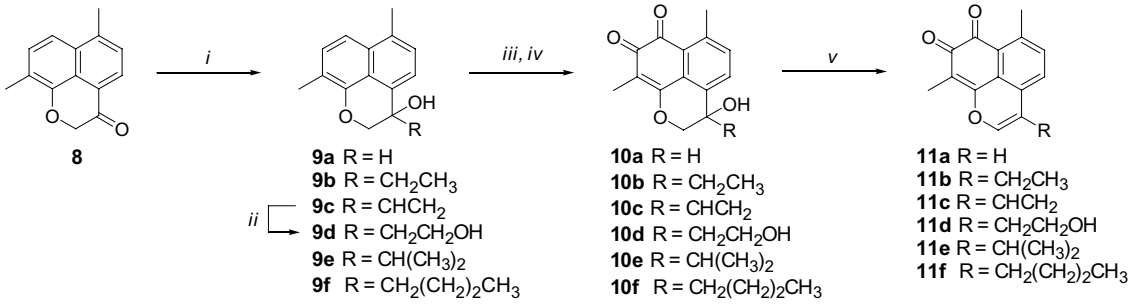


Scheme 1. Reagents and conditions: (i) MeI, NaH, THF, 97%; (ii) $Cu(NO_3)_2{\cdot}xH_2O$, Ac_2O, rt, 73%; (iii) 10% Pd/C, H_2, MeOH, rt; (iv) Fremy's salt, 0.06 M NaH_2PO_4, acetone, rt, 65% for two steps.

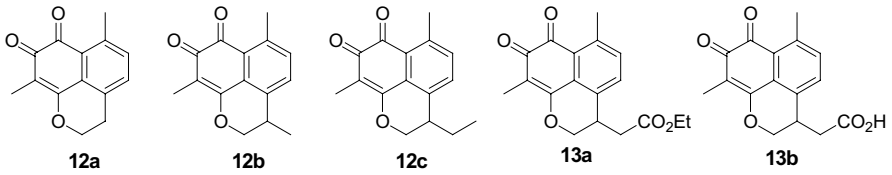
The analog **7**, which consists of A,B-ring skeleton of mansonone F, was prepared by four steps sequence as shown in Scheme 1. *O*-Methylation of 2,5-dimethyl-1-naphthol (**5**) with methyl iodide, nitration of the resulting methyl ether, followed by catalytic hydrogenation, and Teuber oxidation afforded the naphthoquinone **7**.

The tricyclic analogs **11a**–**f** were prepared according to the synthetic method[5a] developed for the synthesis of mansonone F with some proper modifications. Sodium borohydride reduction of the intermediate **8** or appropriate Grignard addition reactions provided the secondary alcohol **9a** or the tertiary alcohols **9b**, **9e**, and **9f**. The vinyl alcohol **9c** was obtained by reaction of **8** with organocerium reagent prepared from vinylmagnesium chloride and anhydrous cerium chloride. Reduction (10% Pd/C, H_2, MeOH) of nitro group of **9a**, **9b**, and **9d**–**f** followed by direct amine oxidation gave the tricyclic quinoids **10a**, **10b**, and **10d**–**f**. Chemoselective reduction of nitro group of the nitrated product of **9c** in the presence of terminal olefin could be achieved by a combination of sodium borohydride and element sulfur. Finally, dehydration of the tertiary alcohols was carried out by Burgess procedure or under acidic or basic conditions.

The analogs **12a**–**c** were obtained by hydrogenolysis of the corresponding alcohols prepared by carbonyl reduction or Grignard addition of **8**. The dicarbonyl moiety was introduced by analogy with **11a**–**f**. The analogs **13a** and **13b** were prepared by sequential Horner–Emmons reaction of ketone **8**, catalytic hydroge-



Scheme 2. Reagents and conditions: (i) DIBAL, CH_2Cl_2, −78 °C, 94% for **9a**; RMgBr, Et_2O, rt, 72–93% for **9b**, **9e**, and **9f**; $CH_2CHMgBr$, $CeCl_3$, THF, −78 °C to 0 °C, 78% for **9c**; (ii) $BH_3{\cdot}Me_2S$, THF, 0 °C then H_2O_2, NaOH, 43%; (iii) $Cu(NO_3)_2{\cdot}xH_2O$, Ac_2O, rt, 65–87%; (iv) 10% Pd/C, H_2, MeOH, rt then Fremy's salt, 0.06 M NaH_2PO_4, acetone, rt, 56–78% for **10a**, **10b**, and **10d**–**f**; sulfur, $NaBH_4$, THF, reflux then Fremy's salt, 0.06 M NaH_2PO_4, acetone, rt, 75% for **10c**; (v) Burgess reagent, benzene, reflux, 47% for **11a**; H_2SO_4/EtOH (1:20), reflux, 37–67% for **11b** and **11d**–**f**; MsCl, DMAP, Et_3N, CH_2Cl_2, −78 °C, 13% for **11c**.



nation of the resulting double bond and the same procedure employed for **11a**–**f**.

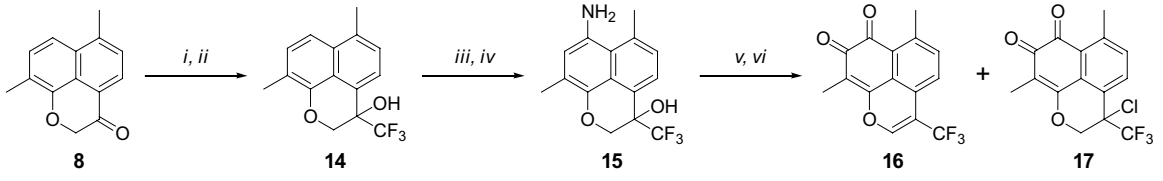
The transformations of the ketone **8** into the C3-trifluoromethyl analog **16** and the cyano analog **21** are summarized in Schemes 3 and 4, respectively. Introduction of a trifluoromethyl group to the carbonyl of **8** was executed by fluoride-induced trifluoromethylation, followed by the standard procedure employed for other analogs, to give the C3-trifluoromethylmansonone F (**16**). The initially attempted dehydration of the trifluoromethyl alcohol **15** was unsuccessful under the general conditions, such as H_2SO_4/EtOH, Burgess reagent, PTSA/benzene, or TFAA/Et_3N. However, treatment of the alcohol **15** with excess $POCl_3$/pyridine followed by direct amine oxidation gave a 1.2:1 mixture of the dehydrated quinone **16** and the chloroquinone **17**, which were separable by flash column chromatography. Thioketal **18** prepared from the ketone **8** by nitration and thioketalization was mono-cyanated by TMSCN in the presence of $SnCl_4$ to give the cyano intermediate **19**, which was further transformed into the cyano sulfide **20**. During this process, the desired C3-cyano analog **21** was produced from **20** by spontaneous elimination of sulfoxide generated by sulfide oxidation. Finally *m*-CPBA-induced *syn*-elimination of **20** afforded C3-cyanomansonone F (**21**).

3. Results and discussion

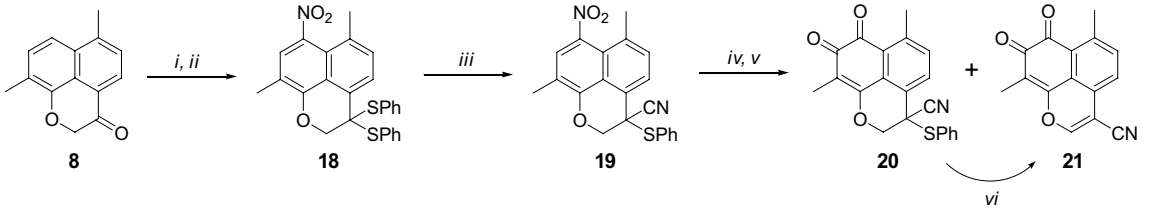
The in vitro anti-bacterial activities of the synthesized analogs along with the reference compounds were assayed against 140 MRSA strains according to the standard procedure, and the minimal inhibitory concentrations (MIC_{50}, MIC_{90}) are listed in Table 1.[10,11]

The analogs **2** and **3** of which C7-hydrogen or C7-nitro group replaces the dicarbonyl moiety of mansonone F exhibit no anti-bacterial activities against MRSA even at more than 100 μg/mL. The analogs **4** and **7**, which are devoid of C-ring or B,C-ring moiety of mansonone F did also not show anti-bacterial activities up to the highest concentration tested. These results revealed that the *ortho*-quinone moiety as well as the tricyclic skeleton is essential for anti-MRSA activity of mansonone F.

None of the analogs possessing bulky and/or lipophilic substituents at C3 (**11b**, **11e**, and **11f**) displayed higher potency than mansonone F, though 3-ethylmansonone F (**11b**) and 3-isopropylmansonone F (**11e**) were nearly equipotent. However, an introduction of vinyl substituent at C3 (**11c**) unexpectedly eliminated anti-bacterial activity. It was anticipated that change of electronic

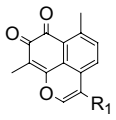
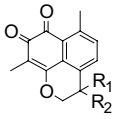


Scheme 3. Reagents and conditions: (i) $(CH_3)_3SiCF_3$, TBAF, THF, rt; (ii) TBAF, THF, rt, 93% for two steps; (iii) $Cu(NO_3)_2{\cdot}xH_2O$, Ac_2O, rt, 86%; (iv) 10% Pd/C, H_2, MeOH, rt, 87%; (v) $P(O)Cl_3$, pyridine, rt; (vi) Fremy's salt, 0.06 M NaH_2PO_4, acetone, rt, 21% for **16**, 18% for **17** for two steps.



Scheme 4. Reagents and conditions: (i) $Cu(NO_3)_2{\cdot}xH_2O$, Ac_2O, rt, 94%; (ii) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 87%; (iii) $(CH_3)SiCN$, $SnCl_4$, CH_2Cl_2, 0 °C, 93%; (iv) 10% Pd/C, H_2, MeOH, rt, 72% (v) Fremy's salt, 0.06 M NaH_2PO_4, acetone, rt, 81%; (vi) *m*-CPBA, CH_2Cl_2, rt, 86%.

Table 1. Anti-bacterial activities of the synthesized mansonone F analogs against MRSAs

Analogs		R_1	R_2	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Vancomycin				2	2
Mansonone F		CH_3		2	4
2				>32	>32
3				>32	>32
4				>32	>32
7				>32	>32
	**11a**	H		8	8
	11b	CH_2CH_3		4	4
	11c	$CHCH_2$		>32	>32
	11d	CH_2CH_2OH		>32	>32
	11e	$CH(CH_3)_2$		4	4
	11f	$CH_2(CH_2)_2CH_3$		8	8
	16	CF_3		16	>32
	21	CN		8	16
	**12a**	H	H	16	16
	12b	H	CH_3	8	16
	12c	H	CH_2CH_3	32	32
	13a	H	CH_2CO_2Et	16	32
	13b	H	CH_2CO_2H	>32	>32
	10g	OH	CH_3	16	>32
	10b	OH	CH_2CH_3	16	16
	17	Cl	CF_3	16	16

The synthesis of **10g** was reported in Ref. 5a.
The clinical isolates were obtained from Seoul National University Hospitals in Seoul Korea.

character of C3-substituent such as nitrile (**16**) or trifluoromethyl (**21**) would enhance anti-bacterial activity by inducing higher electrophilicity of quinone moiety through the fully conjugated system. However, contrary to our expectation, they reduced anti-bacterial activities of mansonone F. The analog **11d**, of which hydroxyethyl group was introduced, in expectation of improved physical properties of natural mansonone F, was disappointingly inactive.

The C2,3-olefin seems to be beneficial for anti-bacterial activity because reduction of C2,3-olefin of mansonone F drops the activities as shown in **12a–c** compared to those of mansonone F, **11a** and **11c**. In addition, the hydroxy substitution (**10g**) for C3-H of **12b** also reduced the anti-bacterial activity as shown in **11d**.

In conclusion, based on the studies on the anti-bacterial activities of the synthesized analogs, both *ortho*-quinone moiety and tricyclic system of mansonone F seem to be essential for their excellent anti-MRSA activities. Change of the C3-methyl or C2,3-olefin of mansonon F reduces the anti-bacterial activity regardless of electronic and steric characters of the new substituents although C3-alkyl substituents do not significantly affect the anti-bacterial activity. During the studies on the structure–activity relationship of mansonone F, the anti-bacterial activity-enhanced analogs have not been found. However, the information on structure–activity relationship of mansonone F as well as the structural requirements for its highly potent anti-MRSA activity envisions development of the novel and promising anti-MRSA agent. In addition, the unique procedures for trifluoromethyl and nitrile introductions at C3-carbonyl would be importantly utilized for wide range of medicinal chemistry. Currently, the work on the novel anti-MRSA agents based on the structure–activity relationship of mansonone F is in good progress and the highly advanced results will be reported in near future.

Acknowledgements

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11. MICs were determined by an agar dilution method with Mueller-Hinton agar (MHA, Difco Laboratories, Detroit, MI) following the National Committee for Clinical Laboratory Standards (NCCLS) procedure. The detailed procedure is described in Ref. 5b.