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The structure–activity relationships of mansonone F, a potent anti-MRSA sesquiterpenoid quinone: SAR studies on the C6 and C9 analogs

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Abstract—For the systematic SAR study on mansonone F, a series of C6 and C9 analogs of mansonone F have been synthesized and their anti-MRSA activities were evaluated. Most of the analogs exhibited good or excellent anti-MRSA activities. In particular, the 6-*n*-butylmansonone F showed fourfold higher antibacterial activities compared to that of vancomycin.

Life-threatening infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most serious problems for the management of nosocomial infections. Particularly, *S. aureus* is known to be easily able to develop resistance to the commonly used antibiotics due to its high adaptability.[1] Though several new antibacterial agents such as quinupristin/dalfopristin,[2] linezolid,[3] vancomycin as well as teicoplanin[4] are currently available, the increase of resistant strains to those antibiotics is still a major clinical problem. This prompted many scientists to investigate a new class of anti-MRSA agents having a new mode of action.

Recently, we have reported isolation, synthesis, and preliminary SAR study of mansonone F, which is structurally unique and highly potent in anti-MRSA activity.[5] The structural feature of mansonone F may impose that the mode of antibiotic action would be different from that of the antibiotics currently used for anti-MRSA therapies. The new mode of action has been expected to provide a solution to overcome the resistance problem of the common antibacterial agents (see Fig. 1).

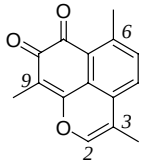

Figure 1. Structure of mansonone F (**1**).

Our preliminary SAR studies on mansonone F have revealed that (1) both the quinone moiety and the tricyclic system of mansonone F are essential for anti-MRSA activities, (2) the alkyl and the electron-withdrawing groups at C-3 do not significantly affect antibacterial activities, (3) the polar substituents at C-3 eliminate the antibacterial activities, and 4) the C2,3-olefin is slightly beneficial for the higher antibacterial activities.[5c]

We herein report the syntheses and anti-MRSA activities of the C6 and C9 mansonone F analogs for the systematic structure–activity relationships of mansonone F. In particular, a novel candidate for the promising anti-MRSA therapy is also reported.

All analogs were synthesized via a divergent synthetic route developed in our laboratory. The 5-alkyl-1-methoxynaphthalenes (**3a**–**3c**) were synthesized from the

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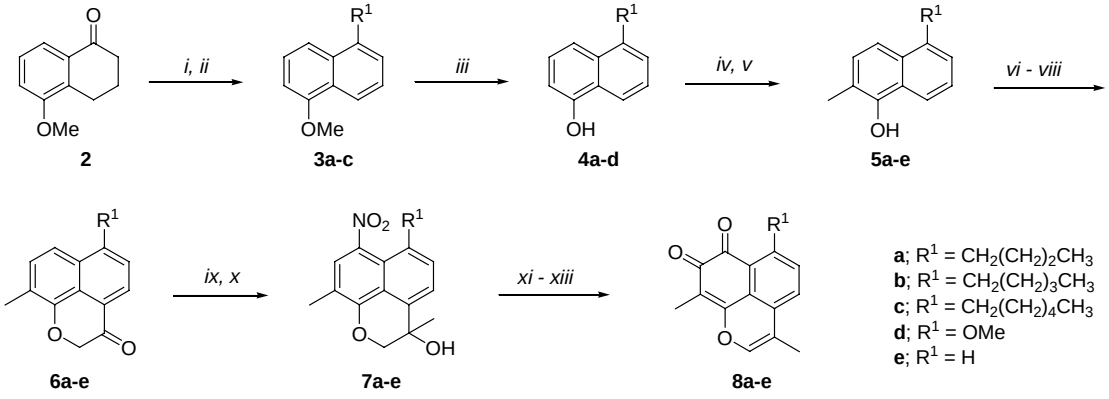
tetralone **2** by a sequence of organocerium reactions, dehydroaromatization and demethylation, to provide the naphthols **4a**–**4c**. The naphthol **4d** was prepared by monoetherification of 1,5-dihydroxynaphthalene. The *ortho* methyl groups of **4a**–**4d** were introduced by hydroxymethylation of the corresponding **4a**–**4d** followed by hydrogenolysis of the resulting alcohols to afford **5a**–**5d**. The 2-methylnaphthol **5e** is commercially available. O-Alkylation of **5a**–**5e** with bromoacetate followed by ester hydrolysis and ring closing Friedel–Crafts acylation gave the tricyclic ketones **6a**–**6e**, which were transformed into the alcohols **7a**–**7e** by two-step process of Grignard reaction and nitration. Finally, the quinones **8a**–**8e** were prepared by sequential catalytic hydrogenation of the nitro group, Teuber oxidation[6] of the resulting amines, and dehydration (Scheme 1).

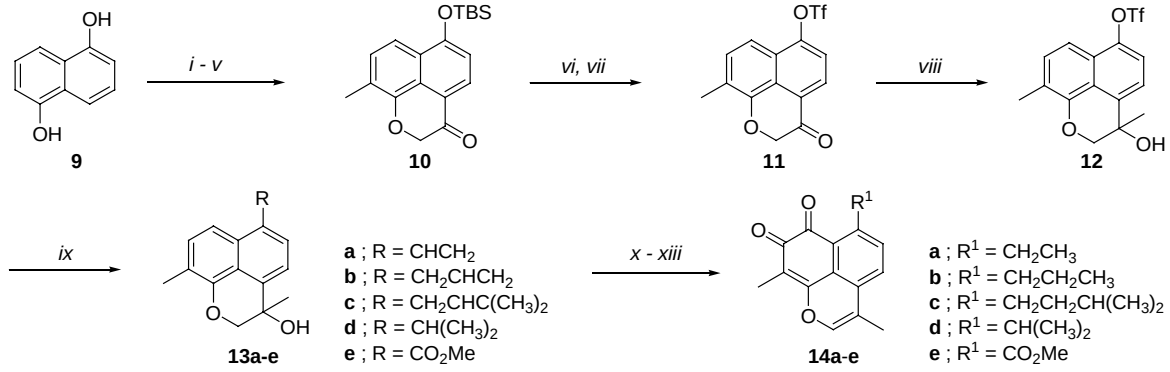
The C6-substituents of **14a**–**14e** were introduced by palladium-catalyzed coupling reaction of the *O*-triflate **12** with the corresponding tin reagents[7] (Scheme 2). The transformations of **13a**–**13e** into **14a**–**14e** were carried out by analogy with the procedure employed for **8a**–**8e**.

The syntheses of the C9 mansonone F analogs (**19a**–**19f**) are summarized in Scheme 3. The bromonaphthol **15**, prepared by bromination of 5-methylnaphthol,[5b] was transformed into the 9-bromo-2,3-dihydrooxaphenalene **16** via combination of the procedure employed for **6** in Scheme 1 and Grignard reaction. The 9-substituted dihydrooxaphenalenes **17b**–**17e**, prepared from **16** by palladium-catalyzed coupling reaction,[8] were converted to **19a**–**19f** by analogy with **8a**–**8e**. It is noticeable that the reduction condition (Pd/C, HCO_2NH_4 in MeOH) for **18a** also induced a debromination, which resulted in production of **19f** (Scheme 3).

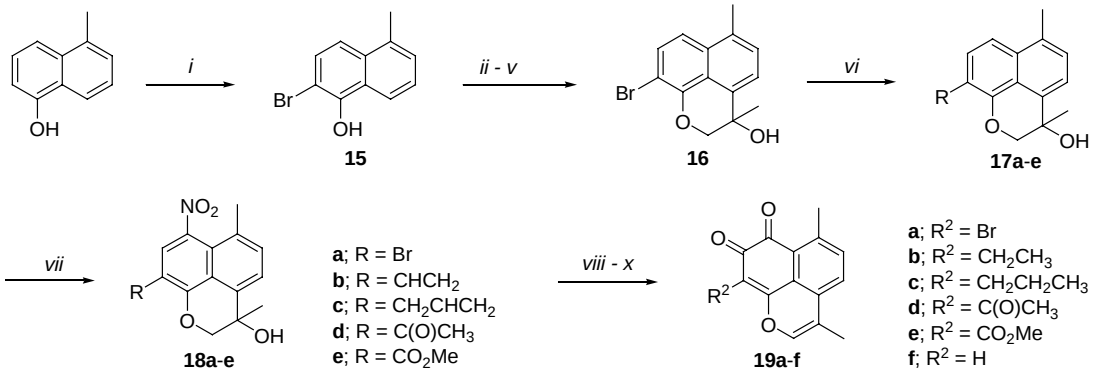
The synthesized mansonone F analogs were tested for anti-MRSA activities.[9,10] Most of the C6 mansonone analogs exhibited good antibacterial activities against the standard MRSAs as shown in Table 1. The analogs possessing alkyl substituent at C6 displayed almost equi-



Scheme 1. Reagents and conditions: (i) RMgX, $CeCl_3$, Et_2O, −78 °C; (ii) Pd/C, triglyme, reflux; (iii) BBr_3, CH_2Cl_2, −78 °C, 65–87% for three steps; (iv) $PhB(OH)_2$, $(CH_2O)_n$, $C_2H_5CO_2H$, C_6H_6, reflux; (v) Pd/C, H_2, c-HCl, MeOH/THF(1/3), rt, 68–82%; (vi) $BrCH_2CO_2Me$, NaH, THF, 40 °C, 89–95%; (vii) LiOH, THF/H_2O (3/1); (viii) $(COCl)_2$, C_6H_6; reflux; then $AlCl_3$, CH_2Cl_2, 0 °C, 74-87% for two steps; (ix) MeMgI, Et_2O, rt; (x) $Cu(NO_3)_2$–xH_2O, Ac_2O, 77–83% for two steps; (xi) Pd/C, H_2, MeOH, rt; (xii) Fremy's salts, 0.06 M NaH_2PO_4, acetone, rt, 64–81% for two steps; (xiii) H_2SO_4/EtOH (1/20), reflux, 34–72%. **a**; $R^1 = CH_2(CH_2)_2CH_3$, **b**; $R^1 = CH_2(CH_2)_3CH_3$, **c**; $R^1 = CH_2(CH_2)_4CH_3$, **d**; R^1 = OMe, **e**; R^1 = H.



Scheme 2. Reagents and conditions: (i) TBSCl, imidazole, DMF, rt, 65%; (ii) Et_2AlCl, $(CH_2O)_n$, CH_2Cl_2, 0 °C; (iii) Pd-C, H_2, MeOH, rt, 52% for two steps; (iv) $BrCH_2CO_2Me$, NaH, THF, 50 °C, 97%; (v) BBr_3, CH_2Cl_2, −5 °C, 50%; (vi) TBAF, THF, rt; (vii) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 70% for two steps; (viii) MeMgI, Et_2O, rt, 71%; (ix) Pd(0) catalyzed reaction[7], 80–91%; (x) $Cu(NO_3)_2$–xH_2O, Ac_2O, 43–78%; (xi) Pd/C, H_2, MeOH, rt; (xii) Fremy's salts, 0.06M NaH_2PO_4, acetone, rt, 56–81% for two steps; (xiii) H_2SO_4/EtOH(1/20), reflux, 37–52%. **a**; R = $CHCH_2$ **b**; R = CH_2CHCH_2, **c**; R = $CH_2CHC(CH_3)_2$, **d**; R = $CH(CH_3)_2$, **e** R = CO_2Me, **a**; $R^1 = CH_2CH_3$, **b**; $R^1 = CH_2CH_2CH_3$, **c**; $R^1 = CH_2CH_2CH(CH_3)_2$, **d**; $R^1 = CH(CH_3)_2$ **e**; $R^1 = CO_2Me$.



Scheme 3. Reagents and conditions: (i) NBS, *t*-$BuNH_2$, CH_2Cl_2, 0 °C, 40%; (ii) $BrCH_2CO_2Me$, NaH, THF, 40 °C, 94%; (iii) LiOH, THF/H_2O (3/1); (iv) $(COCl)_2$, C_6H_6; then $AlCl_3$, CH_2Cl_2, 83% for two steps; (v) MeMgI, THF, rt, 67%; (vi) Pd(0) catalyzed reaction[8], 60–81%; (vii) $Cu(NO_3)_2$–xH_2O, Ac_2O, 45–81%; (viii) Pd/C, H_2, MeOH, rt for **18b–18e** and Pd/C, HCO_2NH_4, MeOH, rt for **18a** and **18f**; (ix) Fremy's salts, 0.06 M NaH_2PO_4, acetone, rt, 41–83% for two steps; (x) H_2SO_4/EtOH (1/20), 32–48%. **a**; R = Br, **b**; R = $CHCH_2$, **c**; R = CH_2CHCH_2, **d**; R = $C(O)CH_3$, **e**; R = CO_2Me, **a**; R^2 = Br, **b**; R^2 = CH_2CH_3, **c**; R^2 = $CH_2CH_2CH_3$, **d**; R^2 = $C(O)CH_3$, **e**; R^2 = CO_2Me, **f**; R^2 = H.

Table 1. Antibacterial activities of the synthesized mansonone F analogs against MRSAs

Compound	R^1	R^2	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Vancomycin			2	2
1 (Mansonone F)	CH_3	CH_3	2	4
8e	H	CH_3	8	8
14a	CH_2CH_3	CH_3	8	16
14b	$CH_2CH_2CH_3$	CH_3	1	4
14d	$CH(CH_3)_2$	CH_3	4	16
8a	$CH_2(CH_2)_2CH_3$	CH_3	0.5	0.5
8b	$CH_2(CH_2)_3CH_3$	CH_3	4	8
14c	$CH_2CH_2CH(CH_3)_2$	CH_3	8	16
8c	$CH_2(CH_2)_4CH_3$	CH_3	8	16
8d	OCH_3	CH_3	8	8
14e	CO_2CH_3	CH_3	16	16
19f	CH_3	H	8	16
19a	CH_3	Br	8	16
19b	CH_3	CH_2CH_3	16	>32
19c	CH_3	$CH_2CH_2CH_3$	4	8
20	CH_3	CH_2Br	16	16
19d	CH_3	$COCH_3$	16	32
19e	CH_3	CO_2CH_3	16	32
21	H	H	>32	>32

The clinical isolates were obtained from Seoul National University Hospitals in Seoul, Korea.

potent anti-MRSA activities compared with mansonone F (**1**). In particular, the 6-*n*-butylmansonone F (**8a**) exhibited 0.5 μg/ml of MIC_{90}, which is fourfold potent than that of vancomycin and it turned out to be the most potent analog among the C6-analog series. Contrary to our expectations, neither the electron-donating group (**8d**) nor the electron-withdrawing one (**14e**) at C6 enhanced the anti-MRSA activities. However, the lipophilicity of the C6 substituents seems quite important, and the butyl substituent is likely to impose the optimal length of the C6 alkyl chain.

The C9 substituents were anticipated to provide significant effects on the anti-MRSA activities because they are adjacent to quinone moiety, which proved to be crucial for the anti-MRSA activity of the mansonone F in the preliminary studies.[5c] However, the C9 alkyl substituents of the analogs **19b**, **19c**, and **19f** have little effect on anti-MRSA activities. The analogs **19a**, **19d**, and **19e** possessing the electron-withdrawing substituents at C9 such as bromide, acetyl or methoxycarbonyl group were disappointingly less potent than the parent mansonone F (**1**). The 9-bromomethyl analog **20** exhibited only 16 μg/ml of MIC_{90} and the 6,9-demethylmansonone F (**21**) showed no anti-MRSA activities up to 32 μg/ml.

The antibacterial activity of the 6-butylmansonone F (**8a**) was further examined against additional MRSAs and other Gram-positive strains. As shown in Table 2, the 6-butylmansonone F (**8a**) exhibited more potent antibacterial activities than mansonone F and vancomycin.

A series of the C6 and C9 mansonone F analogs were synthesized and their antibacterial activities were evaluated for the investigation of the substituent effects on

Table 2. Antibacterial activities of **8a** against MRSA and Gram-positive strains

	Strains	MIC (μg/ml)		
		Mansonone F	**8a**	Vancomycin
1	*B. subtilis* ATCC 6633	2	0.5	0.5
2	*B. cereus* ATCC 27348	4	1	4
3	*S. aureus* ATCC 25923	1	0.25	8
4	*S. aureus* ATCC 6538P	4	0.25	1
5	*S. epidermidis* ATCC12228	0.5	0.25	8
6	*K. pneumoniae* ATCC10031	8	2	>32
7	*S. aureus* TMS 33	8	0.5	4
8	*M. luteus* ATCC 9341	1	0.25	8
9	*S. aureus* ATCC 29213	4	0.25	4
10	*M. luteus* ATCC 10240	1	0.25	4
11	*S. aureus* TMS 64	8	0.25	4
12	*S. aureus* TMS 417	4	0.25	1
13	*S. aureus* Smith	4	0.25	4

The clinical isolates were obtained from Seoul National University Hospitals in Seoul, Korea.

anti-MRSA activities. A variety of the formidable mansonone F analogs were synthesized by the palladium-catalyzed reaction of the C6-triflate and the C9-bromide. The quantitative structure–activity relationships of mansonone F were established via our intensive systematic studies on the antibacterial activities of C6 and C9 mansonone F analogs. The steric effect (lipophilicity) of the substituents turned out to be more important than the electronic effect. In particular, the 6-butylmansonone F (**8a**), which is fourfold potent than vancomycin, was identified as a new candidate for MRSA therapy. Currently, the optimization of **8a** is in progress and the successful result will be reported in due course.

Acknowledgment

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7. Pd(0) catalyzed reaction conditions: $Pd(PPh_3)_4$, $Bu_3SnCHCH_2$ (for **14a**), $Bu_3SnCH_2CHCH_2$ (for **14b**) or $Bu_3SnCH_2CHC(CH_3)_2$ (for **14c**), LiCl, DTBMP, DMF, 98 °C, 90–91%; $Pd(OAc)_2$, DPPF, $(CH_3)_2CHMgCl$, toluene, rt, 80% for **14d**; $Pd(OAc)_2$, DPPF, CO(g), MeOH, Et_3N, THF, 81% for **14e**.
8. Pd(0) catalyzed reaction conditions: $Pd(PPh_3)_4$, $Bu_3SnCHCH_2$, DTBMP, THF, reflux, 78% for **17b**; $Pd(PPh_3)_4$, $Bu_3SnCH_2CHCH_2$, DTBMP, THF, reflux, 81% for **17c**; $Pd(PPh_3)_4$, $Bu_3SnC(OCH_2CH_3)CH_2$, toluene, 80–100 °C, 60% for **17d**; $Pd(OAc)_2$, DPPF, CO(g), MeOH, Et_3N, DMF, 60 °C, 80% for **17e**.
9. Bacterial strains; Clinical isolates were obtained from hospitals in Seoul, Korea, between 1997 and 1999 and were stored at −70 °C until use Choi, K. H.; Hong, J. S.; Kim, S. K.; Lee, D. K.; Yoon, S. J.; Choi, E. C. *J. Antimicrob. Chemother.* **1997**, *39*, 509.
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