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Letter

Efficient Synthesis of 1-Thiomansonones with Anti-MRSA Activity

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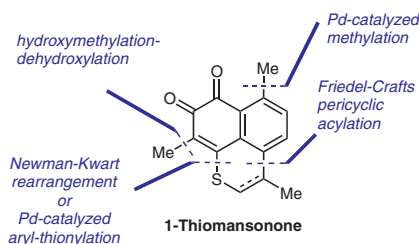
1-Thiomansonone

Anti-MRSA Activity

Compound	MIC$_{50}$ (µg/ml)
Mansonone I	8
1-Thiomansonone I	16
1-Sulfonmansonone I	>32
Mansonone F	2
1-Thiomansonone F	8

Abstract In this study, we developed an efficient and general synthetic strategy for thiaphenalene, a sulfur-containing polyaromatic heterocycle, and applied for the synthesis of 1-thio derivatives of mansonone I and F, natural 1-oxaphenalenic orthoquinones. The pivotal steps for the construction of thiophenalene skeleton include formation of arylsulfide by Newman–Kwart rearrangement of thiocarbamate or palladium-catalyzed cross-coupling, and pericyclic ring closure. Three bioisosterically modified orthoquinones were synthesized and were evaluated for anti-MRSA activity.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most important pathogenic bacteria.[1,2] Rapid acquisition of multidrug resistance to various antibiotics and severe nosocomial infections caused by MRSA have become major problems in the clinic.[2] Despite recent introduction of several new classes of antibiotics, including linezolid, quinupristin/dalfopristin, and new glycopeptide antibiotics, drug resistance, potency, and toxicity remain unsolved problems.[1] Therefore, discovery of novel anti-MRSA agents persists as a focus of medicinal chemistry efforts.[3–5]

One of the continuing research interests in our laboratory is the synthesis and evaluation of structurally novel small molecules with potent anti-MRSA activity, which could overcome multidrug resistance. We previously reported the isolation and synthesis of mansonone F, found in root bark of *Ulmus davidiana*, a Korean medicinal plant (Figure 1).[6,7] Mansonone F is a phytoalexin[8] and structurally belongs to naturally occurring sesquiterpenoid orthoquinones, with many congeners reported from different plants.[9–11] Mansonones have a unique oxaphenalene skele-

ton and, due to orthoquinone moiety and high degree of conjugation, exhibit distinct colors in solution, e.g., deep purple color of CHCl$_3$ solution of mansonone F. Most importantly, mansonones show potent anti-MRSA activity comparable with vancomycin, a drug of choice for treating MRSA infections.[12]
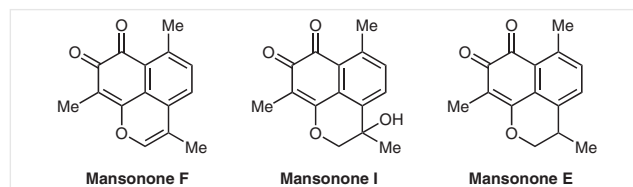

Figure 1 Structures of natural mansonone congeners

Systematic structure–activity relationship study of mansonone F indicated that any change of the tricyclic oxaphenalene skeleton and the orthoquinone moiety markedly reduced anti-MRSA activity, implying that these features are essential pharmacophores for antibacterial activity. Maintaining the tricyclic orthoquinone core structure, subsequent SAR study showed that 1) loss of C1–C2 double bond slightly reduced the activity, and 2) any polar groups or electron-withdrawing ones at C3 also reduced or eliminated the potency, while saturated alkyl chains have little effect on activities. Most of the C6, C9 analogues were less potent than mansonone F regardless of substituents, while the steric effect was proven to be more important than the electronic effect. Unexpectedly, the 6-butylmansonone presented exceptionally powerful anti-MRSA and antibacterial effect for the Gram-positive pathogens.[13,14]

To discover new and more potent anti-MRSA compounds we extended the SAR analysis to 1-thiomansonone derivatives. We hypothesized that as orthoquinone moiety and oxaphenalene core are crucial for antimicrobial activity and as the structure is fully conjugated, substitution of

oxygen in oxaphenalene with other atoms such as sulfur would alter electronic characteristics, and therefore biological activity of the compounds. Sulfur is one of the classic oxygen bioisosteres, and bioisosteric displacement is frequently used in medicinal chemistry.[15–17] However, introduction of the sulfhydryl group on the benzene ring, directly or by functional group interconversion, has proven synthetically challenging. In this communication, we report efficient syntheses of 1-thio derivatives (**1**, **2**, and **3**) of mansonone and evaluation of their anti-MRSA activities (Figure 2).

Synthetic strategy and retrosynthetic plan for the synthesis of 1-thio mansonones are briefly outlined in Figure 3 and Scheme 1.
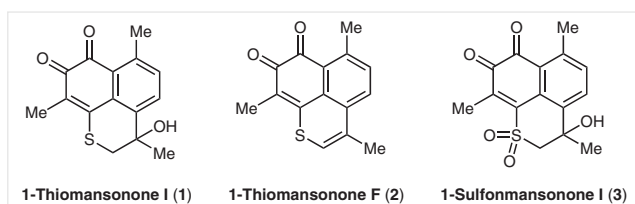

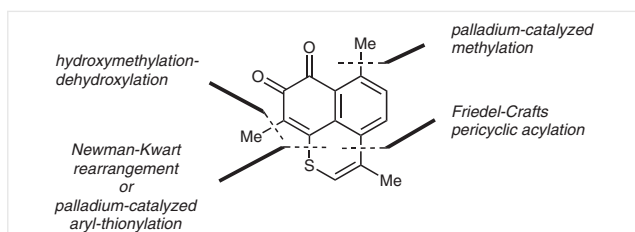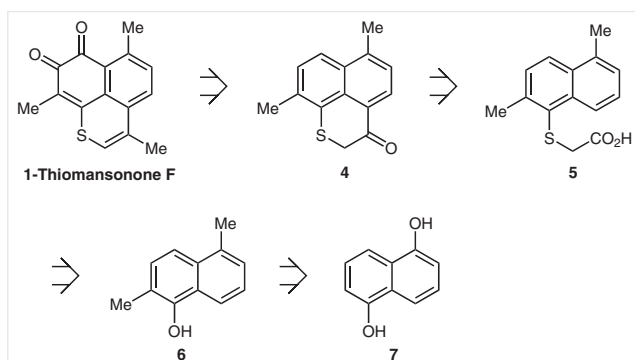**Figure 2** Structures of 1-thio and 1-sulfonmansonone I and F


Figure 3 Synthetic strategy

Scheme 1 Retrosynthesis

1-Thiomansonone can be synthesized from tricyclic ketone **4**, whereas the tricyclic thiophenalene skeleton can be constructed by Friedel–Crafts *peri* ring closure of acid **5**. The key reaction of this synthesis is the creation of the aryl-sulfide bond. Formation of the carbon–sulfur bond could be achieved by Newman–Kwart rearrangement[18] of an aryl thiocarbamate or by palladium-catalyzed cross-coupling of aryl *O*-triflate, starting from naphthol **6** and an appropriate thiol.[19] 6- and 9-Methyl groups could be introduced by palladium-catalyzed methylation and sequential *ortho*-hydroxymethylation–benzylic dihydroxylation from 1,5-dihydroxynaphthalene (**7**), respectively. 2,5-Dimethyl-naphth-1-ol (**6**) was prepared by modifying our previously established procedure (Scheme 2).
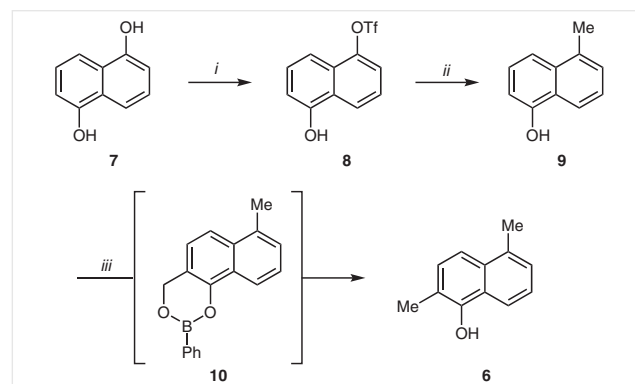
Scheme 2 Synthesis of naphthol **6**. *Reagents and conditions*: *i*. PhN(Tf)$_2$, DMAP, Et$_3$N, rt, 45% *ii*. MeB(OH)$_2$, Pd(dppf)Cl$_2$, K$_2$CO$_3$, THF/H$_2$O (10:1), reflux, 78% *iii*. a. PhB(OH)$_2$, (CH$_2$O)$_n$, CH$_3$CH$_2$CO$_2$H, benzene, reflux b. H$_2$, 10% Pd/C, EtOH/THF, *c*-HCl, rt, 84% for 2 steps.

Commercially available 1,5-dihydroxynaphthalene (**7**) was treated with *N*-phenylbis(trifluoromethanesulfon-imide) (PhNTf$_2$), DMAP, and Et$_3$N in CH$_2$Cl$_2$ to give mono-trifluoromethanesulfonylated naphthol (**8**),[20] which was subjected to Suzuki reaction using [1,1′-bis(diphenylphos-phino)ferrocene] dichloropalladium(II) [Pd(dppf)Cl$_2$] as a catalyst and methylboronic acid as a methyl donor under THF reflux to obtain 5-methyl-1-naphthol (**9**) in 78% yield.[21] *ortho*-Hydroxymethylation of naphthol **7** in the presence of phenylboronic acid, paraformaldehyde, and propionic acid in benzene yielded boronic ester **10**,[22] which was readily converted into 2,5-dimethylnaphthol in excellent yield by hydrogenolysis without any purification steps. The reaction was performed using crude boronic ester under the following conditions: H$_2$ (balloon), 10% Pd/C, EtOH/THF, and catalytic amount of *c*-HCl at room temperature.

Methods for introducing an alkylthio group at an aryl ring include substitution of aryl halides or diazonium salts with sulfur nucleophiles, intramolecular rearrangement of arylthiocarbamates, known as Newman–Kwart rearrangement, and transition-metal-catalyzed coupling of aryl-halides or aryltriflates with alkyl or aryl mercaptanes developed by the Buchwald group. Our first attempt to synthesize compound **5** used thermal Newman–Kwart rearrangement, as shown in Scheme 3.
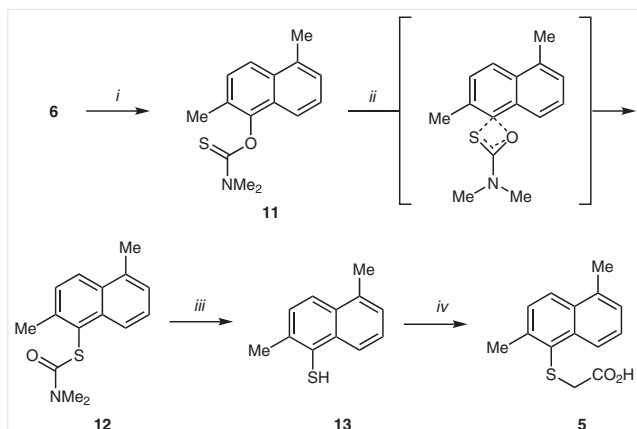
Scheme 3 Newman–Kwart rearrangement approach for thioether synthesis. *Reagents and conditions*: i. *N,N*-dimethylthiocarbamoyl chloride, pyridine, rt, 75% *ii*. *N,N*-dimethylacetamide, reflux, 71% *iii*. 4 N KOH, MeOH, reflux, 85% *iv*. iodoacetic acid, NaH, DMF, rt, 76%.

N,N-Dimethylthiocarbamoyl group was introduced to naphthol **6**, followed by thermal Newman–Kwart re-arrangement under *N,N*-dimethylacetamide reflux to obtain the desired carbamothioate **12** in good yield.[23] Carbamoyl moiety in **12** was readily removed with KOH treatment to yield naphthyl thiol **13**, which was alkylated with iodoacetic acid to generate **5**. Additionally, we de-signed an alternate synthesis route, a transition-metal-catalyzed thioalkylation between aryl halides or triflate and a thiol donor (Scheme 4).
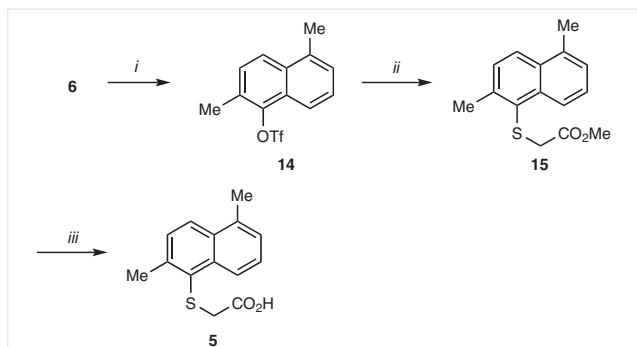
Scheme 4 Palladium-catalyzed cross-coupling approach to thioether synthesis. *Reagents and conditions*: i. PhN(Tf)$_2$, DMAP, Et$_3$N, rt, 95% *ii*. HSCH$_2$CO$_2$CH$_3$, Pd$_2$(dba)$_3$, dppf, NaO*t*-Bu, toluene, reflux, 43% *iii*. LiOH·H$_2$O, THF/H$_2$O (3:1), rt, 92%

Naphthyl-*O*-triflate **14**[20] was prepared by treating naphthol **6** with PhN(Tf)$_2$ and used for the cross-coupling. Methyl 2-mercaptoacetate was successfully introduced to the naphthyl ring using tris(dibenzylideneacetone)-dipalla-dium catalyst and 1,1′-bis(diphenylphosphino)-ferrocene ligand, sodium *tert*-butoxide as base, in toluene, to afford methyl 2-(1,6-dimethylnaphthalen-5-ylthio)acetate (**15**) in 43% yield.[24] The ester was hydrolyzed to give acid **5**.

Tricyclic ketone **4** was synthesized using an intra-molecular pericyclic Friedel–Crafts reaction. Generation of acid chloride from acid **14** using oxalyl chloride, followed by aluminum chloride treatment resulted in the desired ketone **4** in 90% yield in two steps. Methyl substituent at C3 was introduced by Grignard reaction (MeMgI, Et$_2$O). Sequential nitration at C7 by copper nitrate and reduction to aniline followed by oxidation with Fremy's salt, delivered 1-thiomansonone I (**1**).[25] Thiomansonone I (**1**) was de-hydrated to 1-thiomansonone F (**2**) according to a previously described procedure for the synthesis of mansonone F from mansonone I, as shown in Scheme 5. Sulfone derivative **3** of mansonone I was synthesized by sulfide oxidation of **1** with mCPBA.
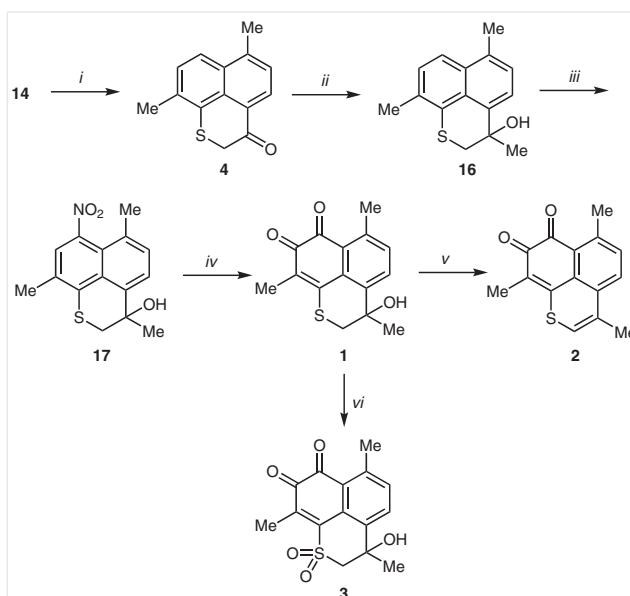
Scheme 5 Synthesis of thiomansonones. *Reagents and conditions*: i. (COCl)$_2$, benzene, reflux; AlCl$_3$, CH$_2$Cl$_2$, 0 °C, 90% *ii*. CH$_3$MgI, Et$_2$O, rt, 81% *iii*. Cu(NO$_3$)$_2$·xH$_2$O, Ac$_2$O, rt, 83% *iv*. H$_2$, Pd/C, MeOH; Fremy's salt, 0.06 M NaH$_2$PO$_4$, acetone, 47% for two steps *v*. c-H$_2$SO$_4$/EtOH (1:20), reflux, 35% *vi*. mCPBA, CH$_2$Cl$_2$, 0 °C, 67%.

As depicted in Table 1, antimicrobial activities of the synthesized analogues were determined in vitro against MRSA strains. Vancomycin, mansonone I, and mansonone F were used as control compounds.

As previously reported, mansonone F (MIC$_{50}$ = 2 µg/mL) shows anti-MRSA activity comparable to vancomycin (MIC$_{50}$ = 1 µg/mL), whereas mansonone I is slightly less potent (MIC$_{50}$ = 8 µg/mL). Thiomansonone I (**1**) displayed slightly lower activity (MIC$_{50}$ = 16 µg/mL) compared to mansonone I, whereas 1-sulfonmansonone I (**3**) showed no notable anti-MRSA activity (MIC$_{50}$ > 32 µg/mL) in the con-centration range tested. Dehydrated analogue, 1-thiomano-none F (**2**) showed mild anti-MRSA activity, but did not enhance the antibacterial activity compared with manso-none F. In designing this experiment, we expected that,

Table 1 Anti-MRSA Activity

Entry	Compound	MIC$_{50}$ (µg/mL)	MIC$_{90}$ (µg/mL)
1	vancomycin	1	2
2	mansonone I	8	16
3	1-thiomansonone I (**1**)	16	16
4	1-sulfonmansonone I (**3**)	>32	>32
5	mansonone F	2	2
6	1-thiomansonone F (**2**)	8	16

based on the differences in electronegativity and reactivity, substitution of 1-oxygen with sulfur or sulfone moiety would make a significant influence on compound anti-MRSA activity. However, 1-thio and 1-sulfonmansonones displayed reduced anti-MRSA activity.

In conclusion, we designed new 1-thio- and 1-sulfonmansonones I and F based on previous SAR studies and carried out total synthesis of three sulfur-substituted analogues of mansonone F. The two methyl substituents were introduced using Stille reaction and sequential hydroxymethylation–hydrogenolysis, respectively. The carbon–sulfur bond was formed through Newman–Kwart rearrangement or palladium-catalyzed thioalkylation, whereas intramolecular Friedel–Crafts cyclization completed the tricyclic ring system. In summary, three sulfur-containing mansonone analogues were successfully synthesized and evaluated for anti-MRSA activity. The compounds did not show enhanced activity; however, our results provide valuable information for future mechanistic and SAR studies.

Funding Information

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591894.

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(23) **Procedure for Newman–Kwart Rearrangement**: *S*-(2,5-Dimethylnaphthalen-1-yl)dimethylcarbamothioate (**12**)
A solution of *O*-(2,5-dimethylnaphthalen-1-yl)dimethylcarbamothioate (**11**, 300 mg, 1.15 mmol) in *N,N*-diethylaniline (10 mL) was equipped with sure-sealed round-bottom flask. And the solution was stirred for 12 h at 240 °C. After cooling, the solution was quenched with 10% HCl and diluted with EtOAc. The organic layer was washed with H$_2$O and brine and dried with MgSO$_4$. The filtered solution was concentrated, and the residue was purified with SiO$_2$ column chromatography (EtOAc/hexane = 1:10) to obtain the desired product as a yellowish oil (214 mg, 71%). ^{1}H NMR (600 MHz, CDCl$_3$): δ =8.30 (d, *J* = 9.0 Hz, 1 H), 8.01 (d, *J* = 9.0 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 7.26 (d, *J* = 7.2 Hz, 1 H), 3.27 (s, 3 H), 3.01 (s, 3 H), 2.68 (s, 3 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (150 MHz, CDCl$_3$): δ = 165.9, 142.6, 136.1, 134.6, 131.8, 128.4, 126.7, 126.3, 126.1, 124.9, 124.0, 22.5, 19.6 ppm. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for C$_{15}$H$_{18}$NOS: 260.1104; found: 260.1103.

(24) **Synthesis of Ethyl 2-[(2,5-dimethylnaphthalen-1-yl)thio]ace-tate (15)**

To a solution of 2,5-dimethylnaphthalen-1-yl trifluoromethane-sulfonate (**14**, 283 mg, 0.930 mmol) in degassed toluene was added $Pd_2(dba)_3$ (85 mg, 0.093 mmol), 1,1′-bis(diphenylphos-phino)ferrocene (57 mg, 0.102 mmol), NaO*t*-Bu (156 mg, 1.39 mmol), and then ethyl thioglycolate (97 μL, 1.39 mmol) was added. And the reaction mixture was refluxed for 1 day. And then the reaction solvent was evaporated. The residue was puri-fied with SiO_2 column chromatography with EtOAc/hexane (20:1) to obtain the desired product as a colorless oil (104 mg, 43%). [1] H NMR (600 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 7.46 (t, *J* = 7.2 Hz, 1 H), 7.43 (d, *J* = 9.0 Hz, 1 H), 7.30 (d, *J* = 7.2 Hz, 1 H), 3.97 (q, *J* = 7.2 Hz, 2 H) 3.44 (s, 2 H), 2.78 (s, 3 H), 2.69 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.9, 141.9, 135.4, 134.8, 132.0, 129.1, 128.4, 126.7, 126.2, 125.7, 124.4, 61.2, 37.5, 22.3, 19.6, 13.9 ppm. HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for $C_{15}H_{17}O_2S$: 261.0944; found: 261.0942.

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