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Total Synthesis of Anti-MRSA Active Diorcinols and Analogues

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Dedicated to Professor Dr. Christian Griesinger on the occasion of his 60th birthday

Abstract: Diorcinols and related prenylated diaryl ethers were reported to exhibit activity against methicillin-resistant clinical isolates of *Staphylococcus aureus* (MRSA). Within these lines, we report the first total synthesis of diorcinol D, I, J, the proposed structure of verticilatin and recently isolated antibacterial diaryl ether by using an efficient and highly divergent synthetic strategy. These total syntheses furnish the diaryl ethers in only five to seven steps employing a Pd-catalyzed diaryl ether coupling as the key step. The total synthesis led to the structural revision of the natural product verticilatin, which has been isolated from a plant pathogenic fungus. Furthermore, these structures were tested in order to determine their antibacterial activities against different MRSA strains as well as further Gram-positive and -negative bacteria.

Introduction

In the recent decade, multiple diaryl ethers with antibacterial and antifungal properties have been isolated from various fungal sources which are usually derived from prenylation of diorcinol **1** (Figure 1). Most but not all of these compounds were named diorcinols.[1a–g]

The simplest diorcinols exhibit prenylation of the aromatic rings. Other diorcinol derivatives might be derived from these prenylated compounds and seem to be generated by oxidation of the prenyl side chain followed by hydrolysis, ring closure or rearrangement.[1c,2] Also examples of dibenzofuranes which might be generated by dehydrogenation have been isolated.[1c,e] We were interested in the synthesis of the compounds **2a**–**c**[1a–c] and **3a**[1d] due to their reported excellent antibacterial activities against MRSA.

The key synthetic steps are exemplified in the synthesis of **3a** (Scheme 1). Building block **6a** should be generated by prenylation of monomethyl orcinol **5** which is then supposed to be coupled in a diaryl ether coupling. The resulting diaryl ether **7a** may then be deprotected to generate the natural compound **2a**, or converted to **3a** in a biomimetic approach by oxidation and rearrangement.

The synthesis started with the monodemethylation of commercially available dimethyl orcinol **8**, which has to be carried out under basic conditions to selectively cleave only one methyl group.[3] The monodemethylation by NaHMDS at 185 °C under microwave irradiation in a sealed vessel gave monomethyl orcinol **5** in an excellent yield of 95% (Scheme 2).[4] Because these conditions generate an overpressure of ≈10 bar when using a half filled vessel, scaling of this reaction was achieved by running multiple batches, which were combined before workup with no effect on yield (≈5 g scale). For even larger scales the original procedure which employs NaSEt in DMF to give the product in 80–88% yield might be preferable.[3b] For the synthesis of the prenylated monomethyl orcinols **6b**,**c** a divergent approach was used. Tsuji–Trost allylation[5] of monomethyl orcinol **5** with *tert*-butyl (2-methylbut-3-en-2-yl) carbonate[6] then gave allyl ether **9** in 94% yield, which underwent a Claisen rearrangement[7] at 185 °C to give a ≈2:1 mixture of the prenylated monomethyl orcinols **6b**[8] and **6c** which can easily be separated by column chromatography.

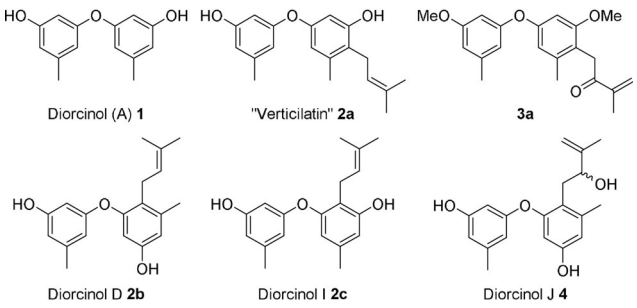
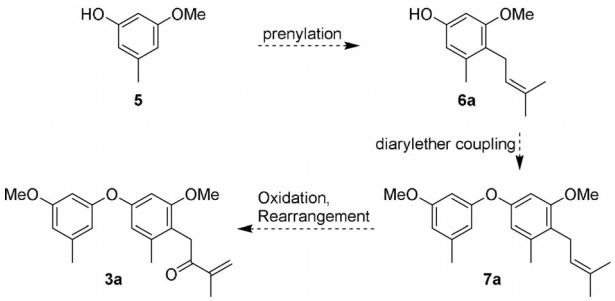


Figure 1. Structures of selected diorcinols and related compounds.

To synthesize the final isomer **6a** by a cross-coupling approach, bromide **10** was required. Because the literature-known procedure for this compound was a lengthy four step synthesis starting from orcinol yielding the desired compound **10** in 56% yield,[9] a direct bromination of monomethyl orcinol was investigated. The best results were achieved by a slightly modified procedure of Park et al.[10] using LiBr as bromine source and $(n\mathrm{Bu_4N})_2S_2O_8$ as oxidant to give 4-bromo-3-



Scheme 1. Key steps in the synthesis of diorcinols.

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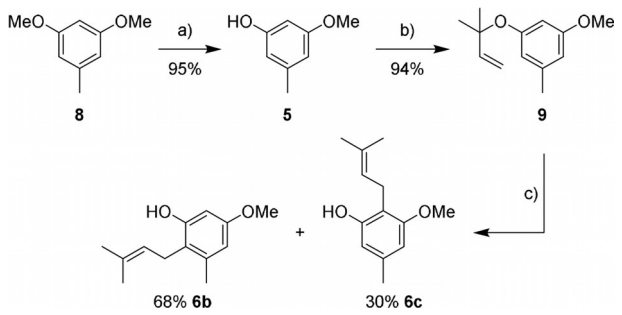
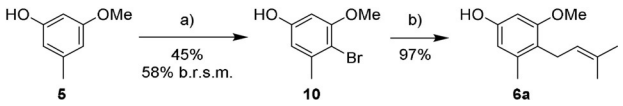


Scheme 2. Synthesis of prenylated monomethyl orcinols **6b**,**c**: a) NaHMDS (2.52 equiv) in THF, 1,3-dimethyl-2-imidazolidinone, 185 °C, 12 h; b) *tert*-butyl (2-methylbut-3-en-2-yl) carbonate (3.50 equiv), $Pd(PPh_3)_4$ (1.00 mol%), 4 Å molecular sieves, THF, 4 °C, 16 h; c) DMF, 185 °C, microwave irradiation, 1 h.

methoxy-5-methylphenol **10** as major product in 45% yield (Scheme 3). The isomer 2-bromo-5-methoxy-3-methylphenol (not shown) was isolated as major side product in 23% yield (see supporting information). Attempts to achieve full conversion by increasing the equivalents of LiBr and $(nBu_4N)_2S_2O_8$ or higher temperatures resulted in polybrominated products.

To achieve prenylation a Negishi coupling approach was employed.[11] Although, the original report recommends the use of Cphos over Xphos to prevent the formation of reverse prenylated products, Xphos was used as ligand to selectively give the prenylated monomethylorcinol **6a** in an excellent yield of 97%. Isomeric products have not been observed (Table 1).

The diaryl ether coupling using several Cu- and Pd-based procedures failed to yield the desired product as they either led to decomposition or no conversion at all.[12] Reaction conditions which were originally reported to dimerize aryl bromides into aryl ethers gave the desired diaryl ether **7a** in low yield (entry 5).[13] GC-MS revealed the presence of the monomethyl orcinol **5**. Since this product can only be formed in the presence of water as OH source, the reaction was attempted

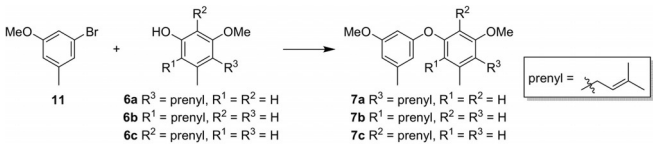


Scheme 3. Synthesis of prenylated monomethyl orcinol **6a**: a) LiBr (2.00 equiv), $(nBu_4N)_2S_2O_8$ (2.00 equiv), MeCN, 0 °C→r.t., 16 h; b) prenylzinc bromide (2.33 equiv) in THF, Xphos Pd G3 (2.00 mol%), XPhos (2.00 mol%), THF, r.t., 16 h. XPhos: 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

without water. This resulted in barely any conversion of the starting bromide, revealing that a certain amount of water was required for the aryl ether coupling to occur. Employing $K_3PO_4{\cdot}H_2O$ as base finally gave the product **7a** in a yield of 88%.[14] The regioisomers have been also synthesized using the same conditions as before giving equally satisfying results when applied to the prenylated monomethylorcinols **6b** and **6c** to yield **7b** (84%) and **7c** (80%).

The dimethylated diaryl ethers **7a–c** were successfully deprotected in excellent yields by in situ generated NaSEt to yield "verticilatin" **2a** (95%), diorcinol D **2b** (quant.) and diorcinol I **2c** (91%). BBr_3, TMSI and NaHMDS were also tested as deprotecting agents, but all led to decomposition of the starting material (Scheme 4).[15]

Table 1. Optimisation of the diaryl ether coupling. 1.2 equiv of bromide **11** were used.



Entry	Substrate	Precatalyst (mol%)	Ligand (mol%)	Base (equiv.)	Solvent	T [°C]	t [h]	Product (yield)[a]
1[f]	**6a**	CuI (10)	–	Cs_2CO_3 (2.0)	NMP	195 $\mu\approx$	2	– (decomposition)
2[f]	**6a**	CuI (1.0) + $Fe(acac)_3$ (2.0)	–	K_2CO_3 (2.0)	DMF	135	16	– (no conversion)
3[f]	**6a**	$Cu(PPh_3)_3Br$ (20)	–	Cs_2CO_3 (3.0)	NMP	100	24	– (no conversion)
4[f]	**6a**	$Pd(OAc)_2$ (2.0)	*t*BuXphos (3.0)	K_3PO_4 (2.0)	toluene	100	16	– (no conversion)
5	**6a**	$Pd_2(dba)_3$ (4.0)	*t*BuXphos (16)	K_3PO_4 (3.0)	dioxane/water 1:1	100	20	**7a** (16%)
6	**6a**	$Pd_2(dba)_3$ (4.0)	*t*BuXphos (16)	K_3PO_4 (3.0)	dioxane	100	20	**7a** (traces)
7	**6a**	$Pd_2(dba)_3$ (4.0)	*t*BuXphos (16)	$K_3PO_4{\cdot}H_2O$ (3.0)	dioxane	100	20	**7a** (88%)
8	**6a**	$Pd_2(dba)_3$ (2.0)	*t*BuXphos (8.0)	$K_3PO_4{\cdot}H_2O$ (3.0)	dioxane	100	20	**7a** (67%)
9	**6b**	$Pd_2(dba)_3$ (4.0)	*t*BuXphos (16)	$K_3PO_4{\cdot}H_2O$ (3.0)	dioxane	100	20	**7b** (84%)
10	**6c**	$Pd_2(dba)_3$ (4.0)	*t*BuXphos (16)	$K_3PO_4{\cdot}H_2O$ (3.0)	dioxane	100	20	**7c** (80%)

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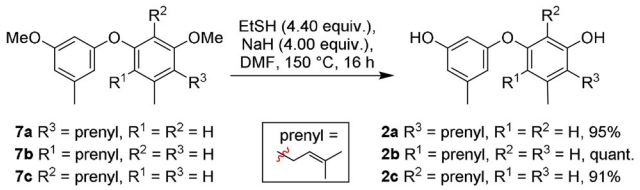


Scheme 4. Deprotection of methylated diorcinols **7a–c**.

The NMR data of synthesized diorcinol D[1b] **2b** and I[1c] **2c** in [D_6]DMSO both matched the reported data for these compounds. In contrast, the data for diaryl ether **2a** were not in agreement with the NMR spectra for "verticilatin",[1a] which were measured in MeOD. However, the NMR data of diorcinol D **2b** in MeOD matched the reported data for "verticilatin" which implies that these two compounds actually have the same structure. This also means that compound **2a** has not been isolated from natural sources so far.

The chemical structures of diorcinol D **2b** and diorcinol I **2c** were unambiguously confirmed by single crystal X-ray crystallography (Figure 2), which confirm the correct assignment of our NMR data. We also attempted to synthesize compound **3a**, because of reported biological activity against MRSA. The compound **3a** and its analogues **3b**,**c** were synthesized from **7a–c**.

Epoxidation of the prenyl unit followed by rearrangement of the epoxide led to the allyl alcohols **12a–c** in sufficient yield ranging from 51–56% (Scheme 5).[17] Subsequent Dess–Martin oxidation gave the compounds **3a–c** in good yields ranging from 89–92%.[18] Yet again, the data of the presumed natural product, diaryl ether **3a**, did not match the reported data.

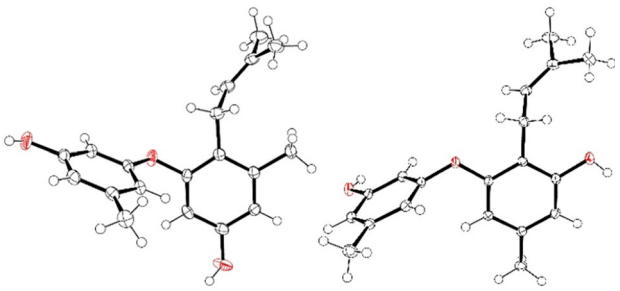
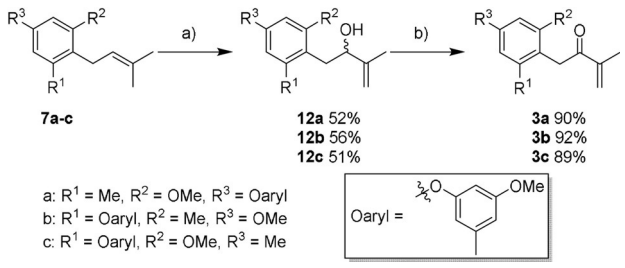
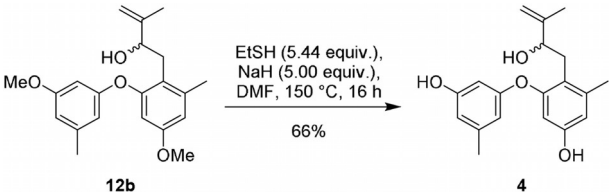


Figure 2. Single-crystal X-ray crystal structures of diorcinol D **2b** (left) and diorcinol I **2c** (right).[16]



Scheme 5. Endgame in the synthesis of **3a–c**: a) *m*CPBA (1.50 equiv), DCM, r.t., 1 h then camphorsulfonic acid (1.15 equiv), nBu$_4$NBr (5.00 mol%), water, r.t., 2 h; b) Dess–Martin periodinane (1.50 equiv), r.t., 2 h.

However, this time it was not possible to identify the actual structure of the reported antibiological compound as the synthetic isomers **3b** and **3c** also did not match the reported data. Thus, further research is required to determine the actual structure of the reported antibiological compound. In addition, demethylation of **12b** gave *rac*-diorcinol J **4** with matching NMR data (Scheme 6).



Scheme 6. Deprotection of methylated diorcinol J **4**.

The antibacterial properties of diorcinols **2a–c**, *rac*-**4** and the compounds **3a–c** against Gram-positive bacteria (*Staphylococcus aureus* ATCC25923, MRSA GK2235, MRSA USA300 and *Enteroccocus faecalis* ATCC29212) as well as Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC27853 and *Escherichia coli* ATCC25922), were evaluated by disc diffusion[19] and minimal inhibitory concentration (MIC) broth dilution assays.[20] However, diorcinols **2a–c** were able to reduce the biofilm of the Gram-negative bacterium *Stenotrophomonas maltophilia* K279a up to 54% (supporting information).[21]

In contrast to earlier reports,[1d] compounds **3a–c** showed no antibacterial effects in our assays employing both methicillin-sensitive (MSSA) and -resistant (MRSA) *isolates*. *rac*-**4** also only showed minuscule inhibition of *E. faecalis* and *S. aureus* in the disc diffusion assays.

While the diorcinols **2a–c** did not show growth inhibition of the Gram-negative bacteria, they exhibited antibacterial properties against the Gram-positive bacterial strains *E. faecalis* and *S. aureus* at concentrations of 4–8 mg L^{-1}, regardless of methicillin resistance (Table 2). Out of all compounds, the so far non-natural diaryl ether **2a** performed the best in terms of antibiotic activity.

Table 2. MIC in mg L^{-1} of compounds **2a–c**, *rac*-**4** and **3a–c** against Gram-positive MSSA and MRSA clinical isolates. Tetracycline and vancomycin were used as references.

Compound	*MSSA* ATCC25923	MRSA GK2235	MRSA USA300	*E. faecalis* ATCC29212
tetracycline	1	64	1	16
vancomycin	2	2	1	4
2a	4	4	4	4
diorcinol D **2b**	8	8	4	8
diorcinol I **2c**	8	8	8	8
diorcinol J **4**	>64	>64	>64	>64
3a	–	–	–	–
3b	–	–	–	–
3c	–	–	–	–

In summary, the first syntheses of the natural products diorcinol D **2b**, I **2c** and J **4** are reported in only five linear steps with satisfying overall yields (51% (**2b**), 20% (**2c**), 16% (**4**)). Furthermore, structure **2a**, which originally was assigned to verticilatin, and **3a**, which was assigned to an antibiotic compound by Li et al., have been synthesized in overall yields of 35% (**2c**) and 17% (**3a**). The synthesis revealed that verticilatin, which was originally assigned to structure **2a**, is actually diorcinol D **2b**. In addition, the actual structure of the antibiotic compound **3a** reported by Li et al. could not be confirmed by our total synthetic approach. The analogues **3b** and **3c**, which have been synthesized in six linear steps and overall yields of 26% (**3a**) and 10% (**3c**), also did not match with the reported data for the natural product. Of all the synthesized compounds, only diorcinol D **2b**, I **2c** and their synthetic isomer **2a** showed significant inhibition of both methicillin sensitive (MSSA) and resistant (MRSA) strains of *S. aureus* as well as *E. faecalis*. Overall, this short synthetic approach towards the diorcinols has been shown to be useful, not only for biological, but also structural evaluation of this compound class.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: biofilm · MRSA · natural products · structure elucidation · total synthesis

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[16] Deposition Number(s) 2003759 (diorcinol D **2b**), and 2003758 (diorcinol I **2c**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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