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Synthesis of chloroquinocin, a pyranonaphthoquinone antibiotic against Gram-positive bacteria

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Abstract—Chloroquinocin **1** is an antimicrobial agent against Gram-positive bacteria, including MRSA (methicillin-resistant *Staphylococcus aureus*). A successful synthesis of **1** was attained through a unique chlorination of the corresponding naphthoquinone derivative **12** as a key step.
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Chloroquinocin **1**, isolated from the culture broth of *Streptomyces* sp. LL-A9227,[1] shows a moderate inhibitory activity against Gram-positive bacteria, including MRSA[2] (MIC = 16 μg/ml), which is one of the most critical drug-resistant pathogens causing global infectious diseases over the past decades.[3] Although studies on antibiotics against Gram-positive bacterial pathogens[4] have been continued to overcome serious medical concerns, the development of ultimate chemotherapeutic agents effective against resistant-mechanisms remains unreported up to now. From among the extensive efforts to acquire highly potent agents, the inhibitory potential of **1** against Gram-positive bacteria would make it an interesting and significant lead for this purpose. In addition to a chlorine substituent, **1** has a novel pyranonaphthoquinone framework: a *p*-quinone moiety is settled at the edge of the molecule. Our recent synthesis of this class of natural products[5] promoted us to include a synthesis of **1**, which would necessitate chlorine-introduction and a careful construction of the chloro-enol residue. We disclose herein our synthetic investigation of **1**.

We planned to take advantage of naphthalene derivative **5**, which is used as a synthetic intermediate of pyranonaphthoquinone derivative **2**,[5] to elaborate the critical chlorination step in the synthetic pathway (Scheme 1). The pyran ring of chloroquinocin **1** might be constructed by using the Pd-induced cyclization reaction of chlorinated naphthoquinone **3**. The chlorine atom at the quinone part of **3** might be induced by a chlorination reaction of a quinone, which was produced by the oxidation of naphthalene **4**. The precursor for **4** might be obtained from aldehyde **5**.

The synthetic route of **4** is outlined in Scheme 2. Aldehyde **5** was synthesized from the known aldehyde **6**.[5] The addition of trimethylsilylacetylene to aldehyde **5** gave benzyl alcohol **7**. Deoxygenation, followed by silyl-deprotection and isomerization through **8** and **9**, afforded alkyne **10**. Naphthalene **4** was produced by using the bromine–lithium exchange of alkyne **10**, followed by rapid quenching with propionaldehyde.

Naphthoquinone **12** was obtained through the oxidation of **4** to a quinone and TIPS-protection (Scheme 3). After treatment with NCS/MeOH,[6] the resulting acetal **13** was exposed to the basic conditions to afford the chlorinated naphthoquinone **3**.

This chlorination steps[7] might commence with the nucleophilic reaction, owing to the electron-donating

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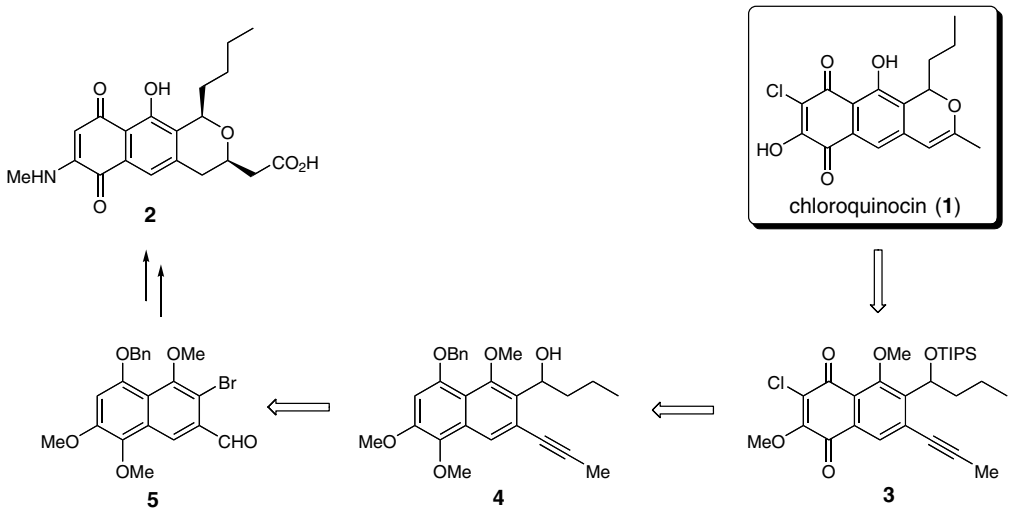
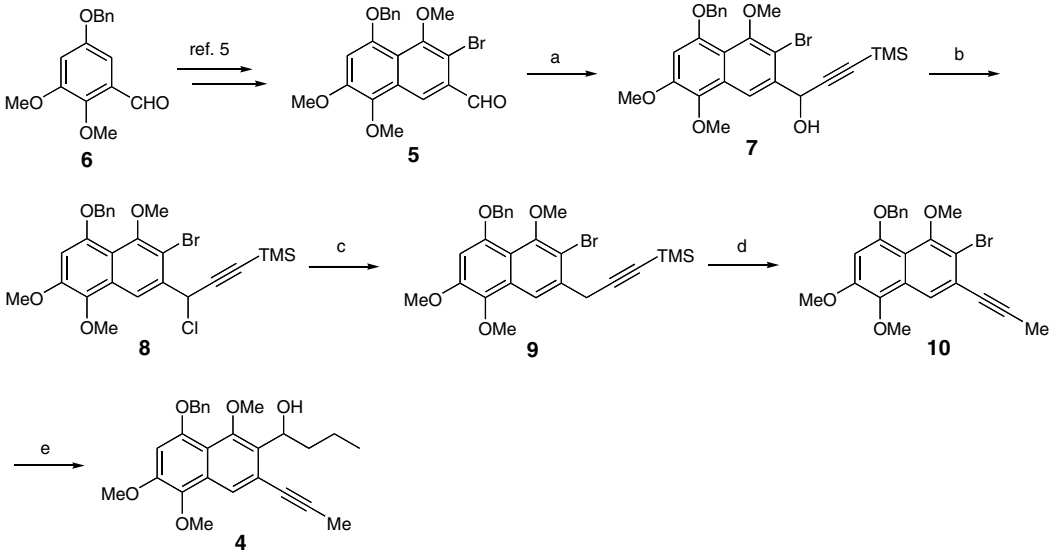
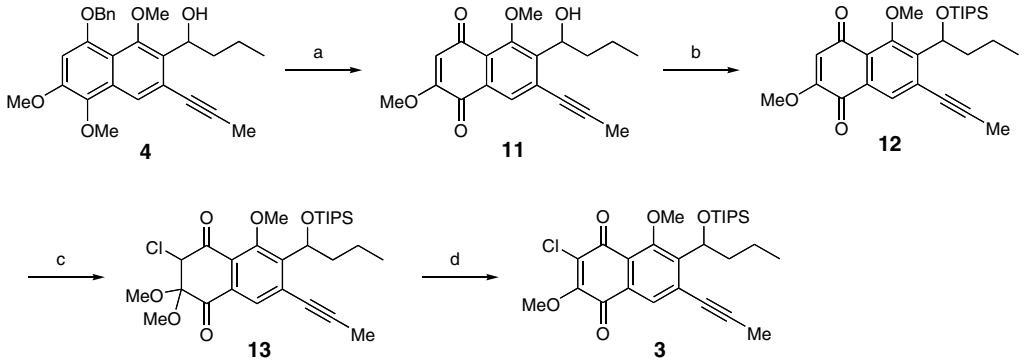


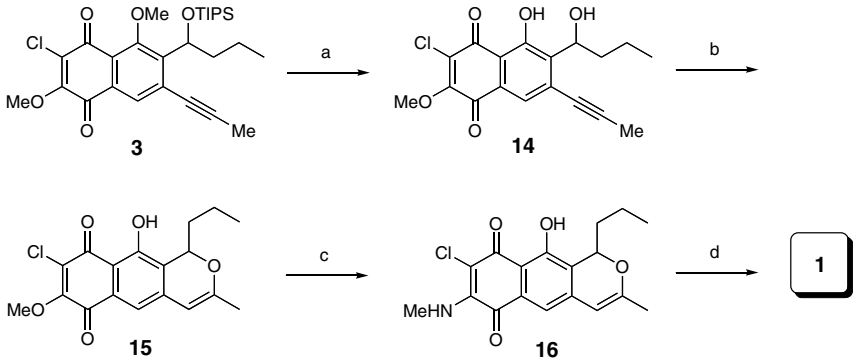
Scheme 1. Structure and retrosynthetic analysis of chloroquinocin **1**.



Scheme 2. Reagents and conditions: (a) trimethylsilylacetylene, *n*-BuLi, THF, −78 °C to rt, 96%; (b) MsCl, Et_3N, CH_2Cl_2, rt, 82%; (c) $LiEt_3BH$, THF, rt, 92%; (d) TBAF, THF, rt, 77%; (e) propionaldehyde, *n*-BuLi, THF, −78 °C, 78%.



Scheme 3. Reagents and conditions: (a) DDQ, 1,4-dioxane, H_2O, rt, 71%; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 88%; (c) NCS, MeOH, rt; (d) DBU, CH_2Cl_2, 0 °C, 67% in two steps.



Scheme 4. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 °C, 26%; (b) $PdCl_2(MeCN)_2$, CH_2Cl_2, 92%; (c) $MeNH_2$, THF, rt, 64%; (d) HCl, MeOH, 55 °C, 75%.

effect of the methoxy substituent of the quinone part, followed by the attack of the solvent MeOH to the oxonium ion, leading to **13**. Fortunately, this peculiar compound was a potential precursor of the desired chlorinated naphthoquinone **3**. Upon reacted with DBU, the elimination of one methoxy group smoothly proceeded to give the desired **3**.

The final conversion of the chlorinated naphthoquinone **3** into chloroquinocin **1** was shown in Scheme 4. After simultaneous deprotection of the methoxy and siloxy functions of **3**, quinone **14** was reacted with $PdCl_2(MeCN)_2/CH_2Cl_2$ to construct the pyran ring. To deprotect the methoxy group at the C-2 position, pyranonaphthoquinone **15** was exposed to $MeNH_2$ and the following acidic conditions to afford chloroquinocin **1**.[8] The spectroscopic data of synthetic **1** was superimposable to that of the reported data.[1]

In summary, the first synthesis of chloroquinocin **1** was accomplished from the same intermediate **5** as that of pyranonaphthoquinone derivative **2**. The synthetic approach to this unique pyranonaphthoquinone and the distinctive chlorination mechanism will open up the possibility to synthesize new leads for new chemotherapeutic agents.

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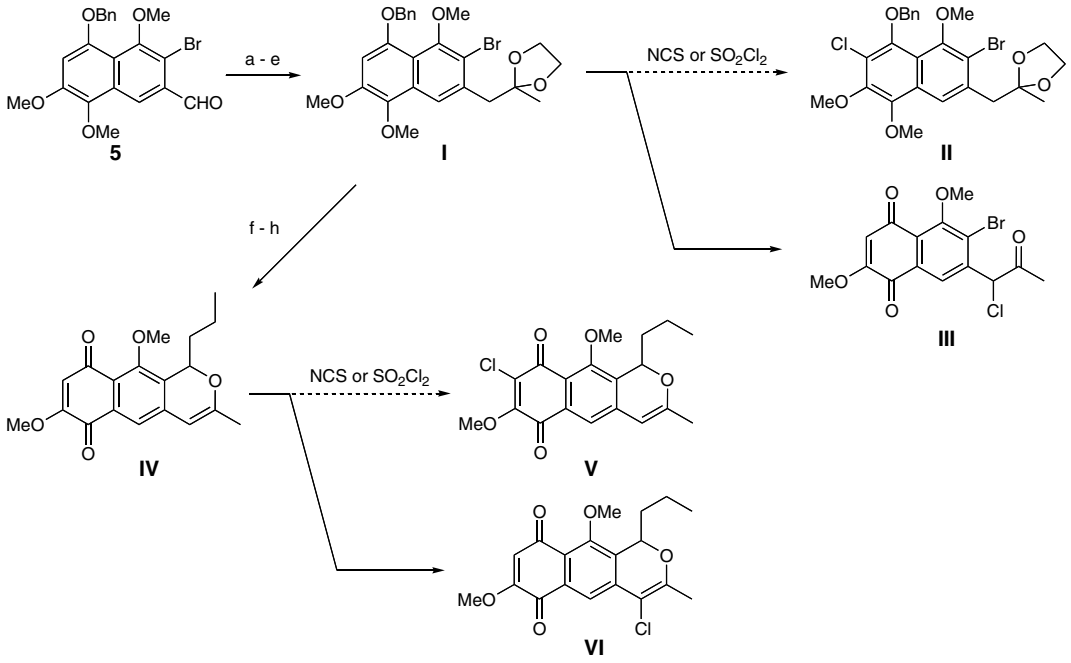
7. In the synthesis of **1**, this chlorination reaction was the crucial step for the construction of a chlorinated naphthoquinone. We have attempted the following approaches, in addition to the process (**13**–**3**). When naphthalene derivative **I**, synthesized from intermediate **5**, was used as a precursor of chlorination, the desired chlorinated naphthalene **II** was not obtained, but a complicated mixture including the oxidized product **III** (Scheme 5). Moreover, in the case of pyranonaphthoquinone **IV**, a chlorine atom was induced the benzylic position to give the undesired compound **VI**. Therefore, it was concluded that the naphthoquinone as a precursor and NCS/MeOH conditions were essential factors to build the chlorinated naphthoquinone framework.
8. ^1H NMR spectral data of chloroquinocin: δ_H (400 MHz, DMSO-d_6) 0.90 (t, 3H, $J = 7.2$ Hz), 1.42–1.47 (complex, 2H), 1.91 (complex, 2H), 5.53 (dd, 1H, $J = 2.9$, 9.2 Hz), 5.85 (s, 1H), 7.22 (s, 1H), and 12.67 (s, 1H).



Scheme 5. Reagents and conditions: (a) Me_3SI, DMSO, NaH, THF, 0 °C, 93%; (b) $ZnBr_2$, PhH, reflux; (c) MeMgBr, THF, −20 °C to 0 °C; (d) IBX, DMSO, THF, rt, 63% in three steps; (e) ethylene glycol, *p*-TsOH·H_2O, PhH, reflux, 77%; (f) propionaldehyde, *n*-BuLi, THF, −78 °C; (g) *p*-TsOH·H_2O, PhH, rt; (h) DDQ, 1,4-dioxane, H_2O, rt, 31% in three steps.