Total Syntheses of Aurachins A and B

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Abstract: Aurachins A and B are alkaloids with 3-hydroxyquinoline *N*-oxide cores. We established an efficient method for the synthesis of 3-hydroxyquinoline *N*-oxides that is amenable to the total syntheses of aurachins A and B. Alkylation of 1-(2-nitrophenyl)butan-2-one (**13**) with farnesyl bromide took place selectively at the benzylic position, and subsequent treatment of the alkylated product with sodium *tert*-butoxide in dimethyl sulfoxide gave aurachin B. Alkylation of **13** with an epoxy iodide derived from farnesol afforded aurachin A.

Aurachins A–D (Figure 1, **1**–**4**) are quinoline alkaloids initially isolated from myxobacterium *Stigmatella aurantiaca* Sg a15 in 1987.[1] Since then, related quinoline alkaloids have also been isolated from myxobacteria[2] and actinobacteria.[3] Aurachins have a farnesyl side chain on the quinoline core, making them structurally similar to ubiquinone. Indeed, aurachins act as inhibitors of the respiratory chain by mimicking the electron-carrying ubiquinone/ubiquinol in the system.[1,4] Inhibition of photosynthesis by aurachins has also been reported.[5]

A proposed biosynthetic pathway of aurachins starting from anthranilic acid is as follows:[2a,6] (a) a type II polyketide synthase (PKS) converts anthranilic acid into 4-hydroxy-2-methylquinoline, to which the farnesyl residue is subsequently attached at the 3-position of the quinoline core, giving aurachin D (**4**) and (b) gradual oxidation via aurachin C (**3**) induced 1,2-migration of the farnesyl group to generate aurachins B (**2**) and A (**1**). Several synthetic studies on the 4-hydroxyquinoline series of aurachins, including aurachins C (**3**), D (**4**), and L (**7**), have been reported.[7] While these results have made it possible to provide analogues of aurachins, syntheses of the 3-hydroxyquinoline *N*-oxide series of aurachins, including aurachins A (**1**) and B (**2**), remain unexplored. Herein we disclose the total syntheses of aurachins A and B.

A unique feature of aurachins A and B is the quinoline *N*-oxide moiety. Although quinoline *N*-oxides are generally prepared via oxidation of the corresponding quinolines,[8] quinoline *N*-oxides have also been prepared directly from nitrobenzene derivatives.[9-10] One of the reactions involves an intramolecular addition of carbanions, stabilized by electron withdrawing groups, to the nitro group (Scheme 1).[11] While a variety of electron-withdrawing groups including a cyano group and an ester moiety were employed for this purpose, ketones were scarcely explored as the substrate for the quinoline *N*-oxides synthesis.[12-13] As illustrated in Scheme 1, addition of the anion generated from ketone **8** to the nitro group is likely to form 3-hydroxyquinoline *N*-oxide **9**, a common structural feature of aurachins A and B. Accordingly, we initiated our synthesis to first prepare the requisite ketone and then tried to convert it to a quinoline *N*-oxide.

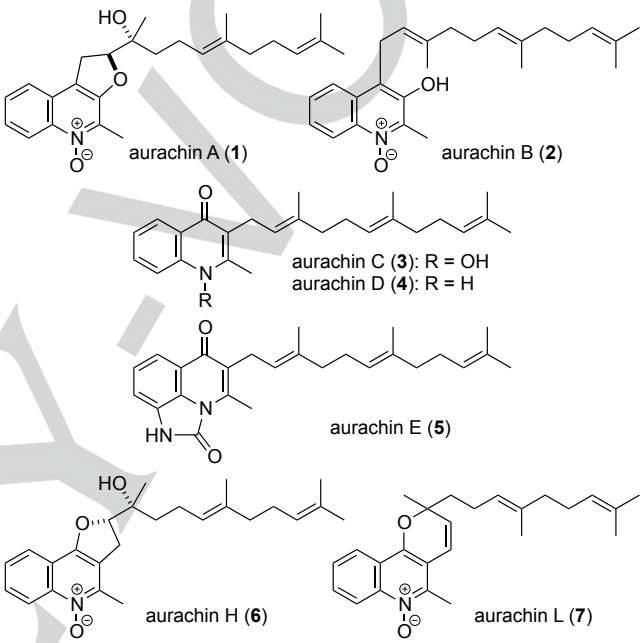
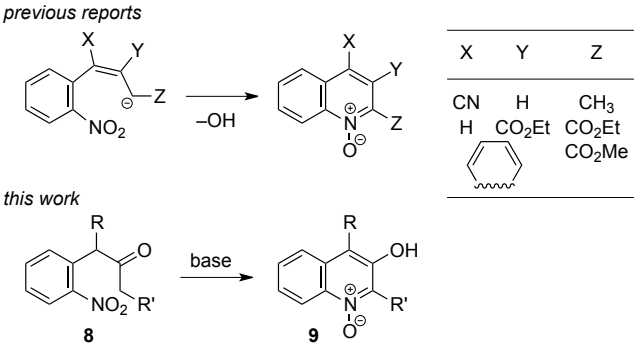


Figure 1. Structures of Aurachins.



Scheme 1. Quinoline *N*-Oxide Synthesis.

Treatment of 2-fluoronitrobenzene (**10**) with β-ketoester **11** in the presence of potassium carbonate afforded **12**, which was subjected to Krapcho dealkoxycarbonylation to furnish ketone **13** (Scheme 2).[14] Alkylation of the resulting ketone with 1-iodobutane occurred selectively at the benzylic position to give alkylated product **14**.[15-16] To our delight, formation of the quinoline *N*-oxide was realized by treatment of **14** with sodium *tert*-butoxide in DMSO, providing **15** in 84% yield.

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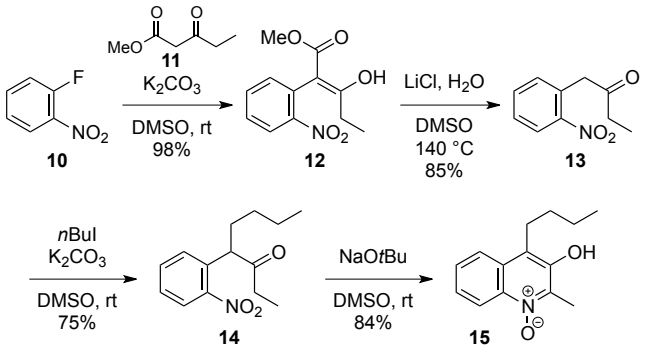
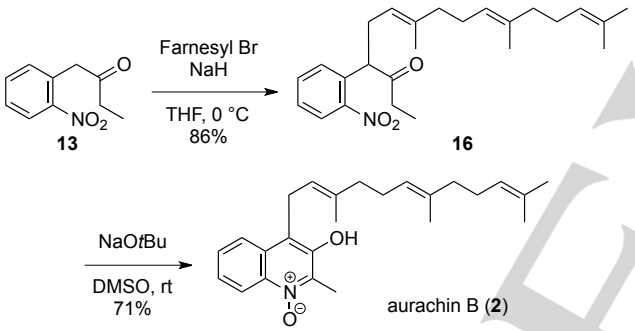


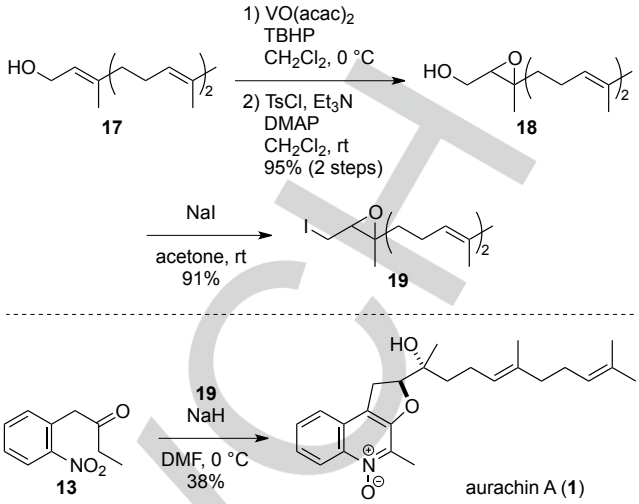
Scheme 2. 3-Hydroxyquinoline *N*-Oxide Synthesis.

Having successfully synthesized 3-hydroxyquinoline *N*-oxide **15** in good yield, we applied the protocol to the synthesis of aurachin B (**2**, Scheme 3). Ketone **13** was alkylated with commercially available farnesyl bromide to give **16** in 86% yield. Subsequent formation of the quinoline *N*-oxide proceeded uneventfully by treatment with sodium *tert*-butoxide in DMSO to afford aurachin B (**2**) in 71% yield.



Scheme 3. Synthesis of Aurachin B.

We next tried to synthesize aurachin A (**1**), which has an additional dihydrofuran ring fused to the quinoline core. The dihydrofuran ring would biogenetically be constructed via oxidation of the side chain in aurachin B (**2**). However, an attempted oxidation of aurachin B (**2**) with *m*CPBA resulted in non-selective epoxidation of the olefin moieties in the side chain. Vanadium-mediated epoxidation[17] did not provide the desired product either. We thus tried to install the epoxide moiety prior to alkylation. The requisite epoxy iodide **19** was prepared from farnesol (**17**) in 3 steps, which includes vanadium-mediated epoxidation (Scheme 4).[17-18] Gratifyingly, treatment of ketone **13** with iodide **19** in the presence of sodium hydride in DMF at 0 °C induced the alkylation and the cyclization sequentially to give aurachin A (**1**) in 39% yield.[19]



Scheme 4. Synthesis of Aurachin A.

In conclusion, we have developed a novel 3-hydroxyquinoline *N*-oxide synthesis, which led to the total syntheses of aurachins A and B. Quinoline *N*-oxides can be converted to quinolines via reduction of the *N*-oxide moiety[20] or rearrangement by activation with acyl halides.[21] Our method is likely to provide a variety of quinolines for research engaged in drug discovery and material sciences.

Acknowledgements

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Keywords: alkaloids • cyclization • nitro compounds • quinolines • *N*-oxides

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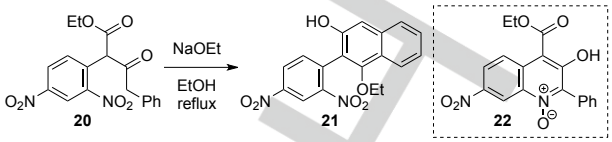
[13] Although Zaki and Iskander reported that a reaction of **20** with sodium ethoxide in refluxing ethanol provided naphthalene **21**, Loudon and Tennant pointed out that the product might be quinoline **22**, which is supported by the chemical behavior of the product and the IR spectrum. a) A. Zaki, Y. Iskander, *J. Chem. Soc.* **1943**, 68-70; b) J. D. Loudon, G. Tennant, *Quart. Rev.* **1964**, *18*, 389-413.



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[15] The selective alkylation at the benzylic position was realized by the electron-withdrawing nature of the 2-nitrophenyl group. The acidity of the benzylic position in **13** is higher than that of the other α-position of the carbonyl group. After alkylation, however, the benzylic position in **14** is not very acidic because conjugation of the 2-nitrophenyl group to the enolate is disrupted by the steric repulsion between the *n*-butyl group (or the enolate moiety) and the nitro group. The kinetic acidities of **13** and **14** were confirmed by reactions with *i*Pr_2NH in CD_3OD.

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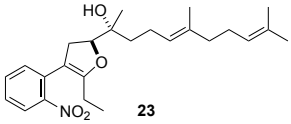
[19] In this transformation, dihydrofuran **23** was also isolated as a product, and it could not be converted into aurachin A under the same conditions.



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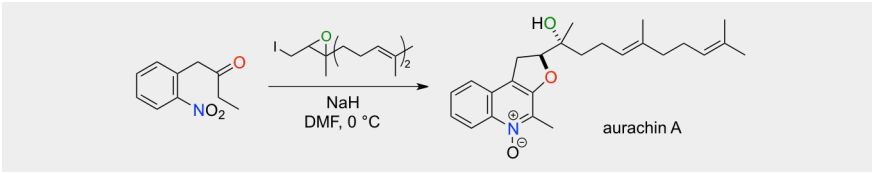

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Total Syntheses of Aurachins A and B

Total syntheses of aurachins A and B have been achieved. Reactions of 1-(2-nitrophenyl)butan-2-one with an epoxy iodide, which was derived from farnesol, in the presence of sodium hydride induced selective alkylation at the benzylic position followed by sequential cyclization to produce aurachin A.