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Total synthesis of NADH:ubiquinone oxidoreductase (complex I) antagonist pterulone and its analogue

Sheng-Tung Huang,* Hsien-Shou Kuo and Chien-Tsu Chen

Department of Biochemistry, Taipei Medical University, Taipei, Taiwan, ROC

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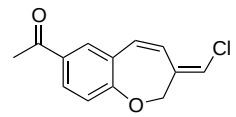
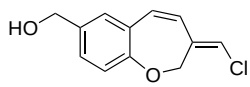
Abstract—Concise synthesis of NADH:ubiquinone oxidoreductase (complex I) antagonist pterulone (**1**) and its analogue (**2**) are reported. Natural products **1** and **2** were prepared in four and five steps, respectively, from 5-bromosalicylaldehyde.

NADH:ubiquinone oxidoreductase comprises the first phosphorylation site of mitochondria and is the energy-conserving enzyme complex that is commonly known as 'complex I'.[1] There are a wide variety of natural and synthetic inhibitors of complex I which have found multiple applications.[2] Complex I inhibitors have been used to elucidate the role of this enzyme in normal cell physiology.[3] Inhibitors of complex I have also been a preferred target for the development of commercial insecticides and acaricides for years.[4] Recently, it has been shown that inhibition of complex I causes concomitant reduction in the activity of orthine decarboxylase (ODC).[5] ODC is responsible for the biosynthesis of polyamine growth factors required for cellular proliferation.[6] Since the overexpression of ODC activity has been associated with tumor promotion, complex I inhibitors capable of interfering with ODC activity and subsequent polyamine levels makes them promising candidates as next generation antitumor agents.[7]

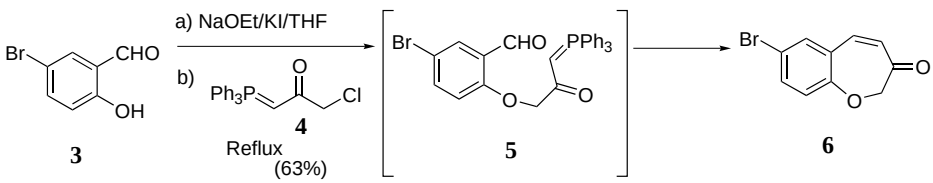
The fungal metabolites pterulone (**1**) and its analogue **2** were isolated from fermentations of a *Pterula* sp. 82168 species, and *Mycena galopus*, respectively.[8,9] The structures of both **1** and **2** were assigned based on their physical and spectral characteresitcs.[9,10] The architectural framework that is common to **1** and **2** is a monochlorinated 2,3-dihydro-1-benzoxepine ring skeleton. The differences between **1** and **2** are found in the substitution at the 7-position and in the geometric configuration of the vinyl chloride. Pterulone (**1**) bears an acetyl group at the 7-position and its vinyl chloride is in the *E*-configuration. On the other hand, compound **2** bears a hydroxymethyl group at the 7-position and its vinyl chloride is in the *Z*-configuration. Pterulone (**1**) exhibited significant antifungal activity, and it is a highly potent inhibitor of complex I with an IC_{50} value of 36 μM.[8] The pharmacological profile of **2** has not yet been reported. Since **2** is structurally related to **1**, it is believed that **2** will exhibit similar biological activity as pterulone (**1**).[9]



pterulone (1)



2



Scheme 1.

Keywords: NADH:ubiquinone oxidoreductase; pterulone; 1-benzoxepine.

* Corresponding author. Tel.: 886-2-2736-1661 ext 575; fax 886-2-2784-6579; e-mail: ws75624@tmu.edu.tw

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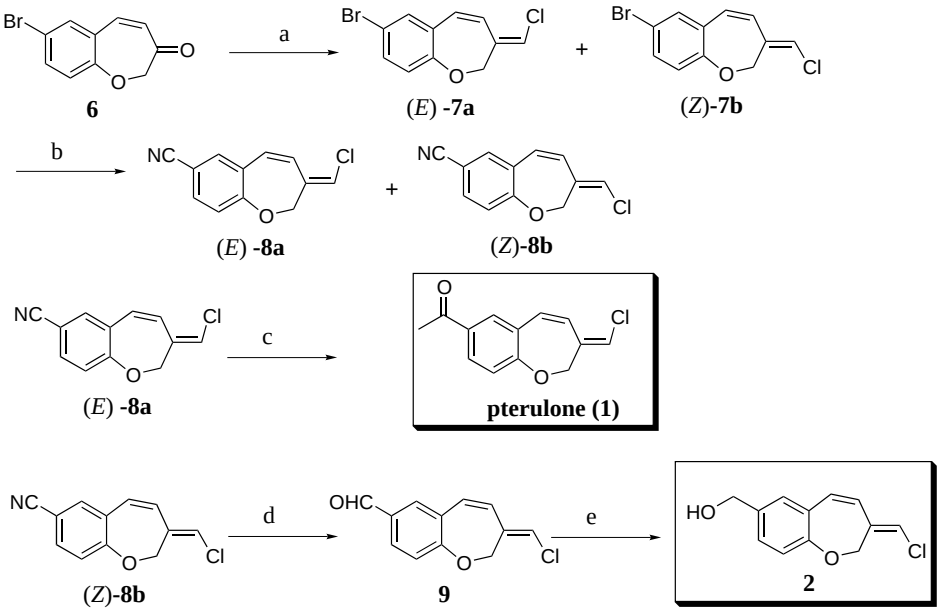
Synthesis of pterulone (**1**) and **2** is compelling due to their complex I antagonist activity, the synthetic challenges posed by their structure, and their status as potential new leads in drug discovery efforts. An extensive survey of the literature did not reveal any efficient methods for the preparation of the 2,3-dihydro-1-benzoxepine ring skeleton, the architectural framework resident in **1** and **2**. Disclosed herein is the first total synthesis of **1** and **2** requiring only four and five steps, respectively, from commercially available 5-bromosalicylaldehyde (**3**). Key to the synthesis is a tandem S_N2/Witting reaction sequence for construction of the 2,3-dihydro-1-benzoxepine ring skeleton. We believe this approach is very efficient for preparation of the 2,3-dihydro-1-benzoxepine ring skeleton and holds promise for providing future analogues of **1**, if desired.

The first step in the synthesis of **1** was the preparation of 7-bromobenzoxepine-3-one (**6**) via a tandem S_N2/Witting reaction (Scheme 1). Treatment of 5-bromosalicylaldehyde (**3**) with 1.2 equiv. of sodium ethoxide generated the corresponding sodium salt of 5-bromosalicylaldehyde; its subsequent *O*-alkylation with α-chloroketone (**4**)[11] produced **5**. Intramolecular ring formation via Witting olefination between the tethered triphenylacetophosphorane and the formyl group in **5** gave highly functionalized **6** in 63% overall yield based on **3**.

Next, the vinyl chloride moiety was installed (Scheme 2). Benzoxepin-3-one (**6**) was treated with chloromethylphosphonium ylide (generated in situ with *n*-BuLi) to give **7**, in 78% yield, as an inseparable mixture of two diastereomers in a ratio of 1:4, *E*:*Z* (calculated from the integrals in the ^{1}H NMR spectrum). Treatment of aryl bromides **7** with 10 equiv. of CuCN in refluxing DMF gave aryl nitrile **8** in 64% yield.[12] At this point, the diastereomeric mixture of aryl nitrile **8** could be separated by silica column chromatography (ethyl acetate:hexanes, 1:35), and the final assignment of the configuration for purified (*E*)-**8a** and (*Z*)-**8b** was determined by NOE and 2D-heteronuclear correlation experiments.

The final transformation to complete the synthesis is outlined in the latter half of Scheme 2. Treatment of aryl nitrile (*E*)-**8a** with methyl lithium in THF at −30°C produced pterulone (**1**) in 78% yield. Reduction of aryl nitrile (*Z*)-**8b** with DIBAL-H gave aryl aldehyde **9** in 81% yield, and further reduction of **9** with $NaBH_4$ in MeOH produced **2** in 88% yield. The spectral and physical characteristics (IR, ^{1}H, ^{13}C NMR, and melting points) of synthetic **1** and **2** were identical to the published data.[8,9]

The synthesis reported herein provided pterulone (**1**) in four steps and in 5% overall yield from **3**, and provided analog **2** in five steps and in 19% overall yield from **3**. The stereoselectivity on chloromethylenation of **6** via Witting olefination is not satisfactory, which diminishes the overall yield, especially in the case of *E*-olefin **1**; this outcome was anticipated since the Witting olefination produces *Z*-configuration olefin preferentially.[13] Since both *E*- and *Z*-isomers of **2** exit in the nature, a stereoselective preparation of both isomers are developing under way. The advantage of tandem reactions sequences is an efficient strategy for construction of structurally and stereochemically complex structures from relative simple starting materials. The one-pot, tandem S_N2/Witting reaction sequences of salicylaldehyde (**3**) and α-chloroketone phosphorane (**4**) producing highly functionalized benzoxepine-3-one (**6**) is unprecedented, and it is an efficient strategy to construct 1-benzoxepine ring skeleton. This concise synthetic strategy may be exploited for the preparation of analogues of both natural products.



Scheme 2. (a) *n*-BuLi, $ClCH_2PPh_3Cl$, THF, rt (78%); (b) 10 equiv. CuCN, DMF, reflux (64%); (c) MeLi, THF, −30°C (78%); (d) DIBAL-H, THF, rt (81%); (e) $NaBH_4$, MeOH (88%).

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