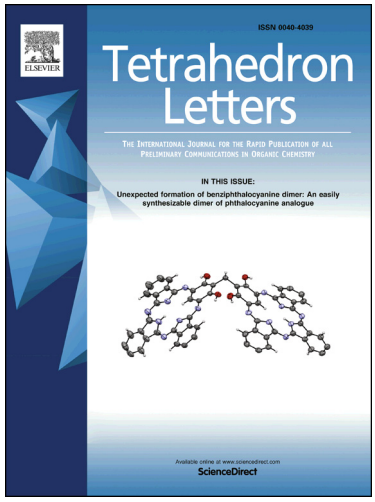

Concise synthesis of the bioactive natural polyhydroxynaphthoate parvinaphthol B *via* Hauser-Kraus annulation

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Concise synthesis of the bioactive natural polyhydroxynaphthoate parvinaphthol B *via* Hauser-Kraus annulation

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ABSTRACT

Herein, we describe the first total synthesis of parvinaphthol B, a polyhydroxynaphthoate derived from the root of *Pentas parvifolia* which exhibits cytotoxic effects against the TNBC cell line. The key feature of the synthesis involves a Hauser-Kraus annulation to provide the polyhydroxynaphthoate skeleton. The synthesis requires only six linear steps and afforded the product in 26.5% overall yield, thus representing a simple method for the further preparation of analogs and biological studies.

Natural polyphenolic compounds have been considered as important secondary metabolites because of their diverse and strong biological activities. Many compounds in this class can be used for the prevention and/or treatment of obesity,[1a] diabetes,[1b] cardiovascular disease,[1c] neurodegenerative diseases,[1d] and various cancers.[1e] In this connection, natural polyphenolic compounds have attracted considerable research attention as they represent not only potential candidates for therapeutic use, but also lead compounds for the identification of novel bioactive compounds.[2]

Parvinaphthol B (**1**) is a polyhydroxynaphthoate derivative isolated from the roots of *Pentas parvifolia*, which was recently reported by Erdélyi and co-workers.[3] Their study also revealed that this compound exhibits cytotoxic effects (LD_{50} = 96.5 μM) against the triple-negative human breast cancer (TNBC) cell line (MDA-MB-231), an aggressive breast cancer subtype, for which there are no targeted therapy options.[4] The 1,4,6-trihydroxy-4-methoxy-naphthalene moiety, the core structure of **1**, can be also regarded as an *O*-methyl analog of naphthoquinone. Naphthoquinones are well-known sub-structures in many bioactive natural and synthetic compounds.[5] Considering that its structure is embedded with the privileged polyphenol as well as naphthoquinone structures, parvinaphthol B can be expected to exhibit diverse therapeutically useful activities besides anticancer activity. The promising anti-TNBC activity and interesting structural features of **1** prompted us to establish a concise synthetic route that can be utilized for further medicinal chemistry research.

Our retrosynthetic analysis for **1** is outlined in Figure 1, which includes efficient construction of the polyhydroxynaphthoate skeleton. Parvinaphthol B (**1**) was anticipated to be obtained from dihydroxynaphthoate **2**, which comprises all the hydroxyl groups of the purposed naphthoate compound, by *O*-methylation and subsequent deprotection of the catechol group in the final step. The key naphthoquinone skeleton of **2** was expected to be synthesized from isobenzofuranone **3** by [4+2]-anionic annulations such as the Hauser-Kraus reaction.[6] The isobenzofuranone **3**, a 1,4-dipole synthon for the Hauser-Kraus annulation, was planned to be prepared from commercially available piperonylic acid **4** by amidation, *ortho*-formylation, and subsequent cyano-isobenzofuranone formation.

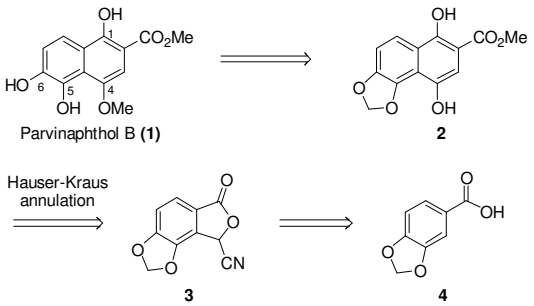

Figure 1. Structure of parvinaphthol B (**1**) and its retrosynthetic analysis

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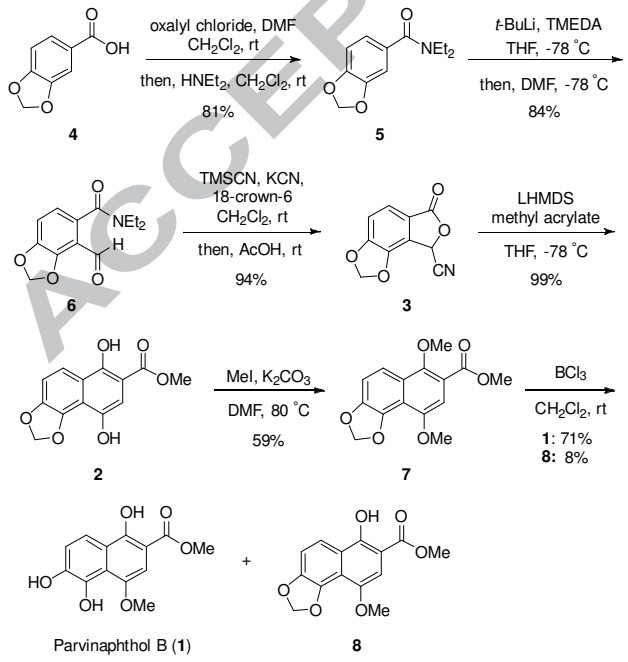
As shown in Scheme 1, the synthesis commenced with the preparation of known amide **5** from piperonylic acid **4** by amidation.[7] Aldehyde **6** was obtained in high yield *via* tetramethylethylenediamine (TMEDA)-promoted direct *ortho*-lithiation of amide **5** using *tert*-BuLi, followed by reaction with DMF.[8] On the other hand, regioisomeric mixtures were obtained when the bromination of **4** and **5** was performed to introduce the *ortho*-formyl moiety *via* halogen-lithium exchange and reaction with DMF. Cyano-isobenzofuranone **3** was readily prepared from *ortho*-formyl benzamide **6** according to a literature procedure.[9] Hauser-Kraus annulation of isobenzofuranone **3** with methyl acrylate using LHMDS afforded dihydroxynaphthoate **2** in almost quantitative yield.

Generally, phenols in the *ortho*-position to carbonyl groups are considered less reactive in *O*-alkylation reactions compared with those in other positions.[10] However, *O*-methylation of 1,4-dihydroxynaphthoate **2** did not proceed selectively at the 4-hydroxyl group and gave a mixture of 1,4-di-methoxynaphthoates, although equimolar amounts of the methyl electrophile and base were used. We supposed that the acidity of the phenol at the 4-position may be reduced by intramolecular hydrogen bonding with the oxygen at the 5-position, which causes a loss of regioselectivity. For this reason, to introduce a methyl moiety at the 4-hydroxyl group, we synthesized dimethoxynaphthoate **7** from **2** using excess CH_3I and K_2CO_3. Addition of boron trichloride (BCl_3) to a solution of **7** in CH_2Cl_2 at -78 °C afforded only 1-hydroxynaphthoate **8** even after stirring for 24 h.

Next, we investigated the reaction temperature and time required to simultaneously cleave the methylene acetal at the catechol group[11] and the methyl ether at the 1-position[12] of dimethoxynaphthoate **7** without demethylation at the 4-position. A mixture of parvinaphthol B (**1**) and dioxolane **8** was obtained at temperatures higher than -40 °C. The optimal yield (71%) of parvinaphthol B (**1**) was obtained when **7** was stirred at room temperature for 30 min with 8 equivalents of BCl_3. The spectral data for the synthesized parvinaphthol B (**1**) were identical to the reported data. When the reaction time exceeded 1 h, the yield was reduced due to complete demethylation. This undesired demethylation of the 4-methoxy group could be due to possible activation by the neighboring phenol at the 5-position of **1**.[13]



Scheme 1. Synthetic procedure of parvinaphthol B

In conclusion, a concise and efficient protocol (six linear steps and 26.5% overall yield) has been developed toward the first total synthesis of parvinaphthol B (**1**), a bioactive polyhydroxynaphthoate derived from the root of *P. parvifolia*. The key feature of our synthesis involves a Hauser-Kraus annulation, which afforded the polyhydroxynaphthoate skeleton. Because of its efficiency, our synthetic route can potentially be extended to structurally related naphthoates bearing phenolic groups. Further synthesis of analogs and biological studies are currently underway in our laboratory.

Acknowledgments

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Supplementary Material

Supplementary data (experimental section and copies of spectra for all of compounds) associated with this article can be found, in the online version, at http://

Graphical Abstract

Concise synthesis of the bioactive natural polyhydroxynaphthoate parvinaphthol B *via* Hauser-Kraus annulation reaction

Sungwan Ahn and Young Taek Han*

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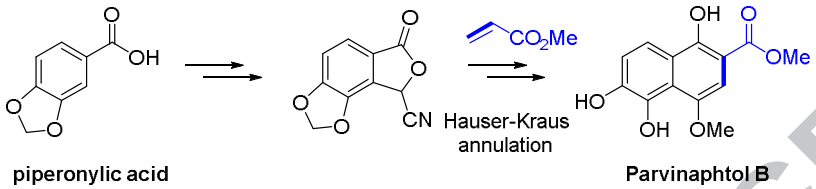

piperonylic acid

Parvinaphtol B

Highlights

- The first synthesis of the parvinaphthol B was presented.
- The efficient synthetic route toward polyhydroxynaphthoate skeleton was described.
- The selective ether-bond cleavage was also investigated.