



Digest paper

Recent topics in total syntheses of natural dimeric naphthoquinone derivatives

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ARTICLE INFO

Article history:

Received 21 November 2017

Revised 9 December 2017

Accepted 11 December 2017

Available online 12 December 2017

Keywords:

Total synthesis

Natural product

1,4-Naphthoquinones

Dimerization

ABSTRACT

This digest overviews successful synthetic approaches to natural dimeric 1,4-naphthoquinones. Several natural dimeric 1,4-naphthoquinone derivatives have been isolated from natural sources including plants, bacteria, and fungi. They have diverse structures and attractive biological activities. However, it is difficult to construct the dimeric scaffolds efficiently and selectively, because 1,4-naphthoquinones and their derivatives are highly reactive. Efficient and attractive synthetic methodologies to construct unique dimeric 1,4-naphthoquinone skeletons are reviewed.

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Introduction

A wide variety of naturally occurring quinones have been isolated from natural sources including plants, bacteria, and fungi.¹ Quinones serve as vital links in electron transport chains in metabolic pathways and participate in multiple biological oxidative processes.^{1a,2} Reversible transfers of electrons and protons between quinones and hydroquinones are involved in these processes. Among quinones, 1,4-naphthoquinones are considered as privileged structures in medicinal chemistry, because they have attractive biological activities and chemical properties (Fig. 1).³ 1,4-Naphthoquinones serve as electrophiles and partici-

pate in 1,2-addition and 1,4-addition reactions with nucleophiles. On the other hand, 1,4-dihydroxynaphthalenes (1,4-naphthohydroquinones), the reduced forms of 1,4-naphthoquinones, act as nucleophiles. Thus, coupling between naphthoquinones and the corresponding 1,4-dihydroxynaphthalenes can occur to give dimeric products.^{1a,4} 2-Alkyl-1,4-naphthoquinones are also known to produce dimeric products via *o*-quinone methides.⁵ *o*-Quinone methides derived from 2-alkyl-1,4-naphthoquinones have both nucleophilic and electrophilic properties because they have a nucleophilic dienol/enol and an electrophilic α,β -unsaturated enone/ketone in the same molecule. Several natural dimeric 1,4-naphthoquinones have been isolated from plants, bacteria, and fungi.¹ They have diverse structures and attractive biological activities. However, 1,4-naphthoquinones chemically dimerize in various ways, depending on their structures and the particular set of

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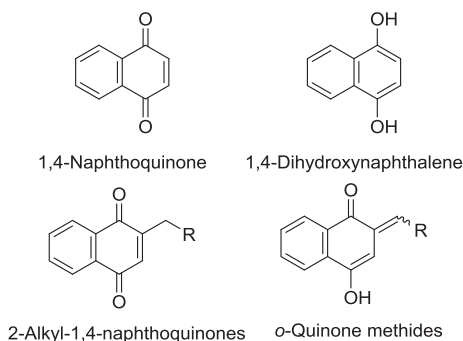


Fig. 1. Structures of 1,4-naphthoquinone derivatives.

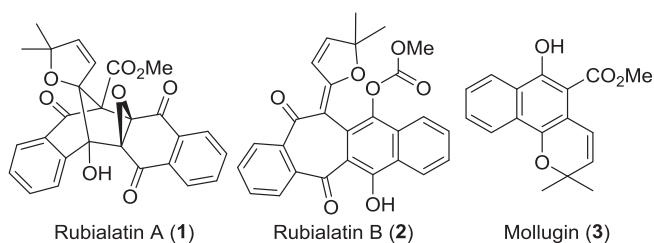


Fig. 2. Structures of rubialatins A (1) and B (2), and mollugin (3).

conditions.⁶ For this reason, the products of the dimerizations are difficult to predict or control, and only limited methods for efficient and selective syntheses of dimeric naphthoquinones have been reported. Thus, it is necessary to develop new synthetic methodologies to generate the dimeric skeletons of each of the individual natural dimeric naphthoquinones.

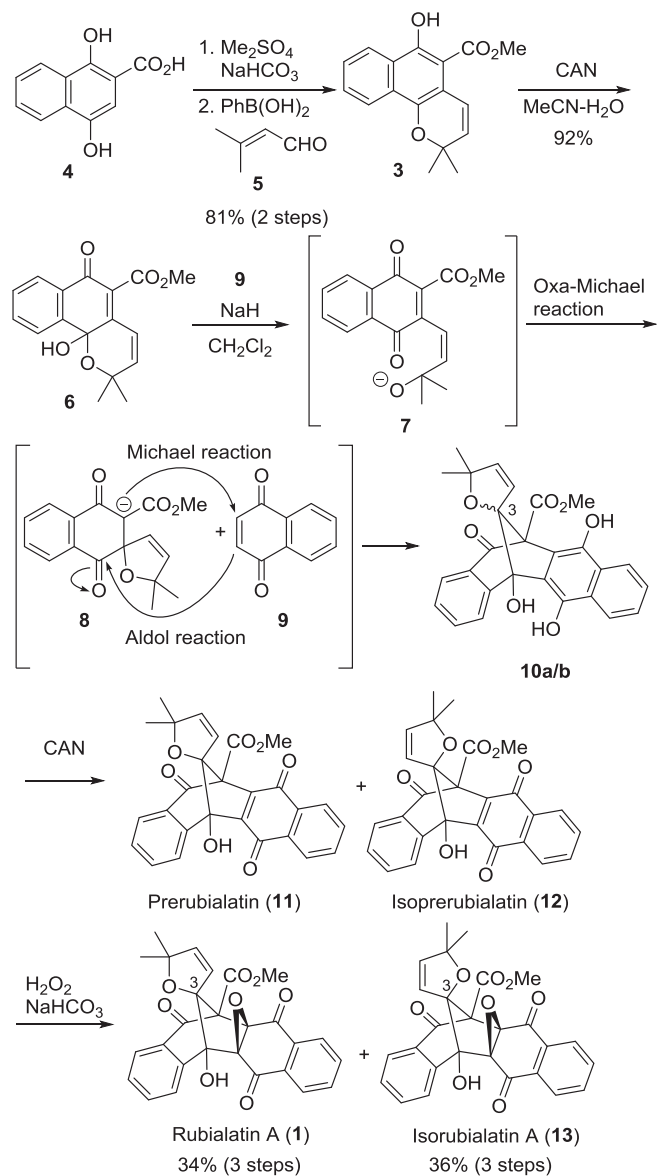
This digest details recent publications concerning the total syntheses of natural dimeric 1,4-naphthoquinones. Efficient and attractive synthetic methodologies to construct unique dimeric skeletons are reviewed.

Total syntheses of natural dimeric naphthoquinone derivatives

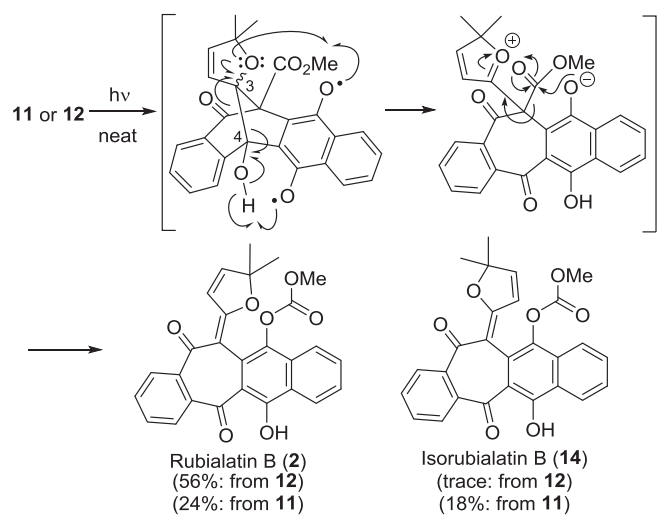
Synthesis of rubialatins A and B

Rubialatins A (1) and B (2) are naphthohydroquinone dimers isolated from the herbal plant *Rubia alata* (Fig. 2).⁷ Compound 1 has a 6/6/5/6/6 carbon skeleton coupled with a 2,5-dihydrofuran moiety, and compound 2 has a rearranged 6/7/6/6 tetracyclic system. Compound (+)-1 showed weak cytotoxicity against SGC-7901 cells and is believed to inhibit the NF- κ B activation induced by TNF- α . Compound 2 showed moderate cytotoxicity against A549, SGC-7901, and HeLa cells. In contrast to compound 1, compound 2 activated the NF- κ B pathway in the presence of TNF- α , which revealed the synergistic effect of 2 with TNF- α on NF- κ B activation. These compounds are considered to be biogenetically synthesized via coupling of mollugin (3)⁸ with 1,4-naphthoquinone and subsequent oxidative skeletal rearrangement. Mollugin (3) is a naphthohydroquinone found in the same plant as 1 and 2.

Tang and coworkers reported biomimetic syntheses of rubialatins A and B (Schemes 1 and 2).⁹ Mollugin (3) was first synthesized from commercially available 1,4-dihydroxy-2-naphthoic acid (4) and 3-methyl-2-butenal (5) using an electrocyclization reaction promoted by phenylboronic acid as a key step (Scheme 1).¹⁰ Oxidative dearomatization of 3 with cerium ammonium nitrate (CAN) proceeded smoothly to afford 6. A biomimetic tandem oxa-Michael/Michael/aldol reaction was achieved by treatment of 6 with NaH and 1,4-naphthoquinone (9) in dichloromethane¹¹ to



Scheme 1. Synthesis of rubialatin A (1).



Scheme 2. Synthesis of rubialatin B (2).

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