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One-pot preparation of 1*H*-naphtho[2,3-*c*]pyran-5,10-diones and its application to concise total synthesis of (±)-eleutherin and (±)-isoeleutherin

Kazuhiro Kobayashi,* Masaharu Uchida, Tomokazu Uneda, Miyuki Tanmatsu, Osamu Morikawa, and Hisatoshi Konishi

Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680-8552, Japan

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Abstract

1*H*-Naphtho[2,3-*c*]pyran-5,10-dione derivatives, including a natural product (pentalongin), were generally synthesized in one-pot using a tandem conjugate addition–cyclization sequence between 2-(1-hydroxyalkyl)-1,4-naphthoquinones and enamines (or imines). The utility of this method was demonstrated in the synthesis of pyranonaphthoquinone antibiotics, (±)-eleutherin and (±)-isoeleutherin.

Keywords: quinones; pyrans; enamines; imines

The compounds based on the 1*H*-naphtho[2,3-*c*]pyran-5,10-dione skeleton have aroused considerable interest amongst synthetic chemists, because some members of this family have been found in nature and shown to possess a variety of biological properties [1–8]. Therefore, a number of interesting methods have been reported to prepare this class of compounds [8–23]. Most of them, however, involve multi-step conversions, although Aldersley et al. [15] have prepared one of these derivatives in one-pot from phenacylpyridinium ylide and 2-(phenoxymethyl)-1,4-naphthoquinone. We now wish to report a novel one-pot procedure for the general preparation of 1*H*-naphtho[2,3-*c*]pyran-5,10-diones. The method relies on the reaction of 2-(1-hydroxyalkyl)-1,4-naphthoquinones with enamines or imines [24,25] and can allow very rapid access to biologically active natural products, such as pentalongin (**5a**) [13,14,26], eleutherin (**6b**) [9–12,27,28], and isoeleutherin (**7**) [9–12,27,28].

We began our study by investigating reactions of 2-(1-hydroxyalkyl)-1,4-naphthoquinones **1** with enamines **2**, in expectation of the formation of 1*H*-naphtho[2,3-*c*]pyran-5,10-diones **3** through addition of **2** to **1** in the 1,4-addition manner followed by the intramolecular cyclization of the resulting zwitter ion intermediates. As expected, the reactions in toluene at

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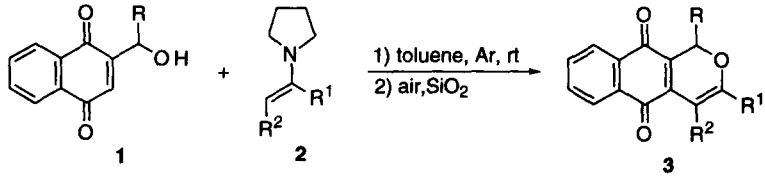


Scheme 1.

Table 1.
Preparation of 1*H*-naphtho[2,3-c]pyran-5,10-dione **3** from 2-(1-hydroxyalkyl)-1,4-naphthoquinones **1** and pyrrolidine enamines **2** according to Scheme 1

Entry	Quinone **1**	Enamine **2**	Naphthopyrandione **3** (Yield/%)[a]
1	**1a** (R=H)[b]	**2a** [R^1-R^2=$(CH_2)_3$][d]	**3a** (81)
2	**1a**	**2b** [R^1-R^2=$(CH_2)_4$][d]	**3b** (83)
3	**1a**	**2c** (R^1=Et, R^2=Me)[e]	**3c** (81)
4	**1b** (R=Me)[c]	**2a**	**3d** (73)
5	**1b**	**2b**	**3e** (62)

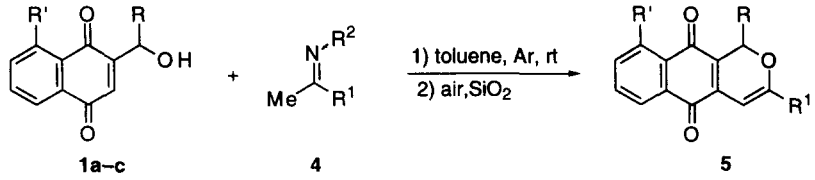
[a]Isolated yield. [b]Ref. 31. [c]Ref. 32. [d]Commercially available. [e]Ref. 33. A mixture of stereoisomers.

room temperature under argon, followed by usual aqueous workup and subsequent purification by preparative TLC on SiO_2, gave **3** (Scheme 1; Table 1).[1]

Subsequently, envisaging that imines would tautomerize to their enamine forms in the reaction mixtures and should react with the hydroxyquinones to give the desired naphthopyrandiones, we examined the reactions of **1** with imines **4**. It was found that the sequence proceeded slowly and gave somewhat complicated mixtures compared to that using enamines, from which 1*H*-naphtho[2,3-*c*]pyran-5,10-diones **5** were isolated in moderate yields (Scheme 2; Table 2).[1] The use of imines may offer an advantage, because these imines are generally easy to prepare compared to the corresponding enamines.

We next turned our attention to application of the present method to the synthesis of useful natural products and planned the conversion of the naphthopyrandione **5e** into (±)-eleutherin (**6b**). The conversion was accomplished by the reduction using triethylsilane in TFA, and is summarized in Scheme 3 and Table 3. First, as the model reaction, compound **5d** was treated with triethylsilane in TFA at room temperature to afford *cis*-1,3-dimethyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (**6a**) (demethoxyeleutherin) exclusively in excellent yield (entry 1). Compound **5e** was then subjected to the reduction under the same conditions. Unfortunately, however, this reaction is less reliable, affording a ca. 1:5 mixture of the desired **6b** along with its diastereoisomer, (±)-isoeleutherin (**7**), in moderate combined yield (entry 2), while these products were easily separated from each other. Although this result was disappointing, we reached the conclusion that **6b** had isomerized to **7** under the reaction

1) All new compounds were characterized by ^1H and/or ^{13}C NMR, IR, and mass spectra, and gave satisfactory elemental analyses.



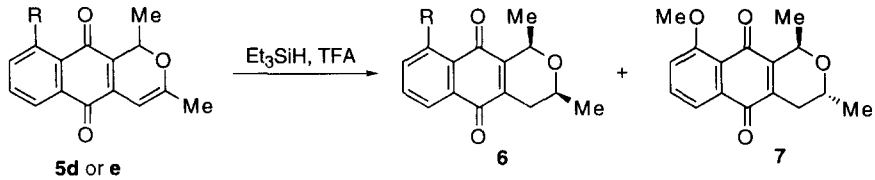
1a–c 4 5

Scheme 2.

Table 2
Preparation of 1*H*-naphtho[2,3-c]pyran-5,10-dione **5** from 2-(1-hydroxyalkyl)-1,4-naphthoquinones **1** and imines **4** according to Scheme 2

Entry	Quinone **1**	Imine **4**	Naphthopyrandione **5** (Yield/%)[a]
1	**1a** (R=R'=H)	**4a** (R^1=H, R^2=*c*-Hex)[c,d]	**5a**[f] (44)
2	**1a**	**4b** (R^1=Me, R^2=*i*-Pr)[e]	**5b** (60)
3	**1a**	**4c** (R^1=Ph, R^2=*c*-Hex)[e,d]	**5c**[g] (39)
4	**1b** (R=Me, R'=H)	**4b**	**5d** (53)
5	**1c** (R=Me, R'=OMe)[b]	**4b**	**5e** (55)

[a]Isolated yields. [b]Prepared quantitatively from 1-(1-hydroxy-4,8-dimethoxynaphthalen-2-yl)ethanone [12] by the $NaBH_4$ reduction, followd by the CAN oxidation. [c]Ref. 34. [d]A mixture of stereoisomers. [e]Ref. 35. [f]Pentalongin, mp 160–162 °C (lit. [26] 161–162 °C). [g]Mp 187–190 °C (lit. [15] 188–191 °C).



5d or **e** 6 7

Scheme 3.

Table 3
Preparation of demethoxyeleutherin (**6a**), (±)-eleutherin (**6b**), and (±)-isoeleutherin (**7**) according to Scheme 3

Entry	Naphthopyrandion **5**	Reaction temp	Product(s) (Yield/%)[a]
1	**5d** (R=H)	r. t.	**6a** (98)[b]
2	**5e** (R=OMe)	r. t.	**6b** (8),[c,d] **7** (42)[d,e]
3	**5e**	–20 °C	**6b** (66)

[a]Isolated yields. [b]Mp 143–144 °C (lit. [12] 143.5–145 °C). [c]Mp 157–158 °C (lit. [27] 155–156 °C). [d]Separable by preparative TLC on SiO_2. [e]Mp 153–155 °C (lit. [27] 154–155 °C).

conditions [29,30] and reasoned that carrying out the reaction at lower temperature should suppress the isomerization and allow us to obtain the desired **6b** exclusively in satisfactory yield. As expected, the reaction at –20 °C proceeded more cleanly than that at room temperature to give **6b** as the sole diastereoisomer in fair yield (entry 3). IR and ^{1}H NMR data as well as the melting points for these products are consistent with literature values [9–12,27,28].

In conclusion, we have developed a novel one-pot procedure for the general preparation of 1*H*-naphtho[2,3-*c*]pyran-5,10-diones. The procedure is particularly useful because of its efficiency, the ready availability of the starting materials and the ease of operation, and its applicability to the synthesis of important natural products. We are continuing to investigate the possibilities of applying the present method to the synthesis of related heterocycle-fused quinone derivatives as well as other useful natural products having this naphthopyrandione skeleton.

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