Natural Product Research

Formerly Natural Product Letters

ISSN: 1478-6419 (Print) 1478-6427 (Online) Journal homepage: http://www.tandfonline.com/loi/gnpl20

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To cite this article: Hong-Shuang Wang, Hui-Jing Li, Long-Fei Wang, Zhi-Lun Shen & Yan-Chao Wu (2018): Regioselective synthesis of gentisyl alcohol-type marine natural products, Natural Product Research, DOI: 10.1080/14786419.2018.1478831

To link to this article: https://doi.org/10.1080/14786419.2018.1478831

NATURAL PRODUCT RESEARCH, 2018
https://doi.org/10.1080/14786419.2018.1478831

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Regioselective synthesis of gentisyl alcohol-type marine natural products

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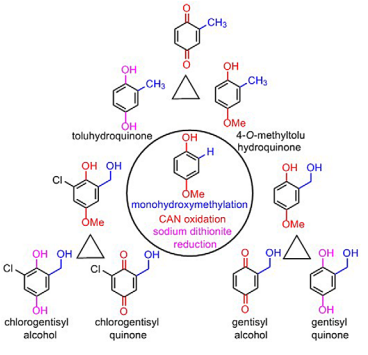
ABSTRACT

Gentisyl alcohol-type natural products, possessing various important biological properties, have been synthesized from 4-methoxyphenol by using a selective phenol monohydroxymethylation/monochlorination, a CAN oxidation and a sodium dithionite reduction as the key steps. The natural product synthesis is efficient, atom- and step-economical, and requires no protecting groups.



ARTICLE HISTORY
Received 21 March 2018
Accepted 16 May 2018

KEYWORDS
Natural products; synthesis; gentisyl alcohol; chlorogentisyl alcohol; hydroxymethylation; chlorination

1. Introduction

Gentisyl alcohol-type marine natural products (**1–6**, Figure 1) (Kim et al. 2005; Kwong et al. 2006; Yun et al. 2011; Leutou et al. 2012) possess a wide range of important biological activities such as angiogenesis (Kim et al. 2006), sphingomyelinase-inhibiting (Uchida et al. 2001), radical-scavenging (Alfaro et al. 2003), and antitumor (Zhang et al. 2007) properties. For example, chlorogentisyl alcohol (**1**) is in fact the first recorded compound from marine fungi that shows strong bioactivity against both macro- and microfoulers and has non- or

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Supplemental data for this article can be accessed at https://doi.org/10.1080/14786419.2018.1478831.

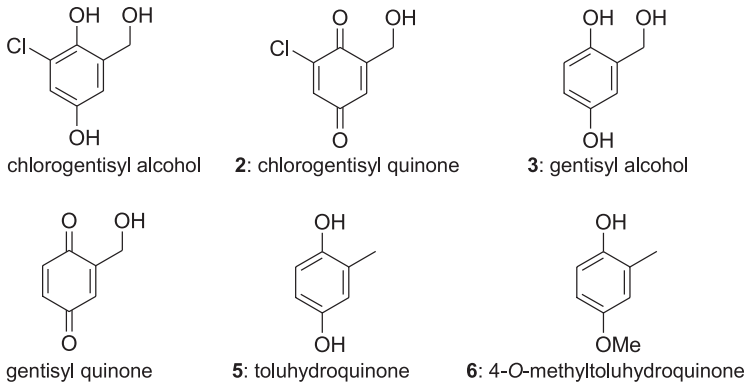


Figure 1. Representatives of gentisyl alcohol-type natural products.

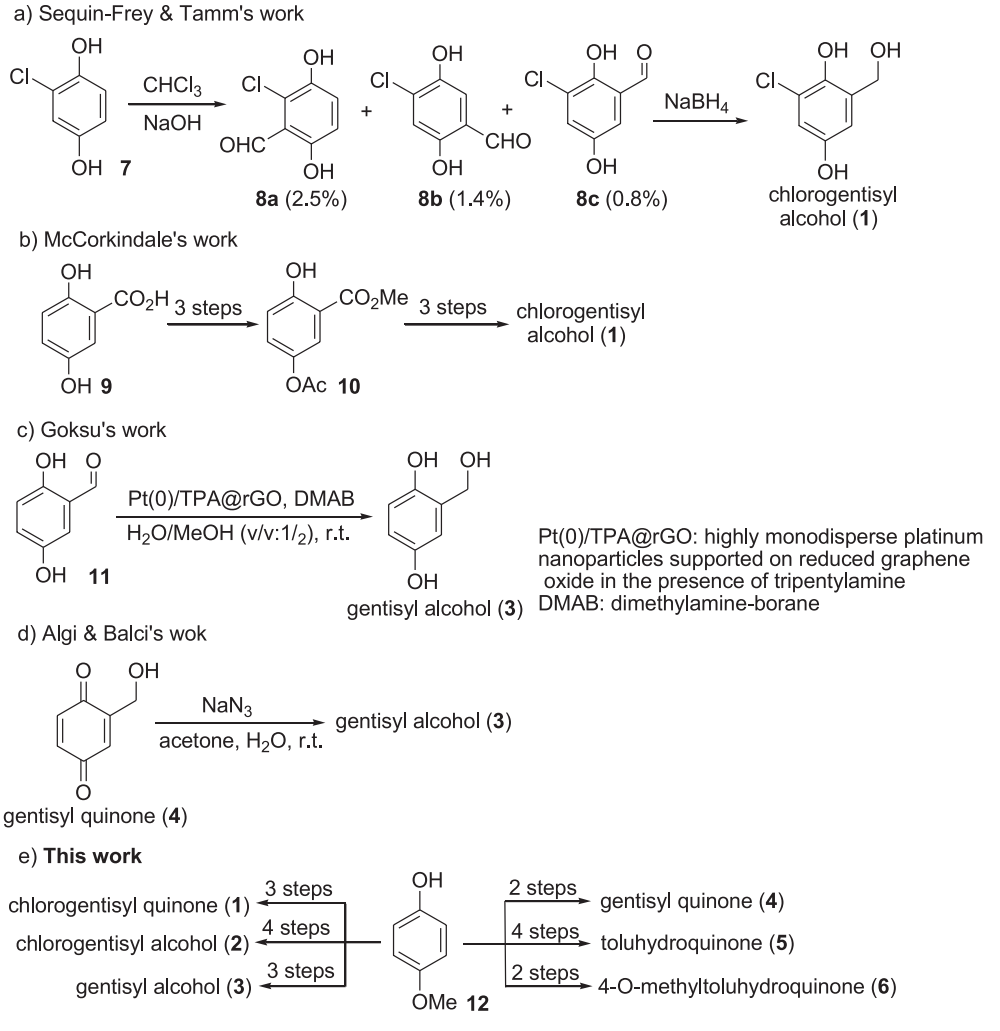
low-toxicity (Kwong et al. 2006), which indicates that it could be a potent antifoulant. However, most of these gentisyl alcohol-type natural products are difficult to obtain in large quantities on account of the limited quantities components, and thereby prevented their pharmacological research or development into commercial products.

The efficient synthesis of chlorogentisyl alcohol (**1**) and chlorogentisyl quinone (**2**) from commercially available and inexpensive starting materials is still a challenge. Séquin-Frey and Tamm reported the first synthesis of **1** via the Reimer-Tiemann reaction of 2-chlorobenzene-1,4-diol (**7**) and subsequent reaction with $NaBH_4$ (Scheme 1(a)). However, the regioselectivity was too poor and the yield of the intermediate **9c** was extremely low (0.8%, Scheme 1(a)) (Séquin-Frey and Tamm 1971). Afterwards, McCorkindale and coworkers developed a regioselective synthesis of **1** from 2,5-dihydroxybenzoic acid (**9**) in 6 steps via the key ester intermediate **11** (Scheme 1(b)) (McCorkindale et al. 1972). The synthesis of gentisyl alcohol (**3**) via reduction of gentisyl aldehyde (**11**) (Goksu et al. 2016) or gentisyl quinone (**4**) (Algi and Balci 2006) has been reported (Scheme 1(c) and 1(d)). However, **11** is expensive and **4** is not commercially available to date. Obviously, development of an efficient strategy to reduce the reaction steps is required. Moreover, strategies to divergently access this type of natural products from a single building block are still absent. Herein we report a practical synthesis of gentisyl alcohol-type natural products from inexpensive 4-methoxyphenol (**12**, 17.9 €/500 g, Aldrich) within 2–4 steps (Scheme 1(e)).

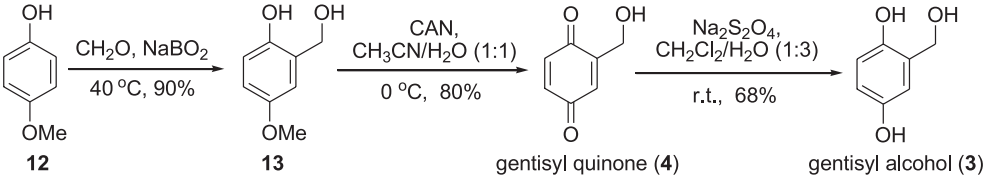
2. Results and discussion

Scheme 2 shows the synthesis of gentisyl alcohol (**3**) and gentisyl quinone (**4**) from 4-methoxyphenol (**12**). Treatment of **12** with aqueous formaldehyde and sodium metaborate ($NaBO_2$) afforded 4-*O*-methylgentisyl alcohol (**13**) in 90% yield (Li et al. 2014). Oxidation of **13** with ammonium cerium nitrate (CAN) provided **4** in 80% yield. Reduction of **4** with sodium dithionite ($Na_2S_2O_4$) gave **3** in 68% yield.

Scheme 3 illustrates our initial synthetic studies on chlorogentisyl alcohol (**1**). Vilsmeier-Haack reaction of 1,4-dimethoxybenzene (**14**) afforded benzaldehyde **15** in 66% yield. Unfortunately, chlorination of **15** with various chlorinating reagents such as sulfuryl chloride (SO_2Cl_2), *N*-chlorosuccinimide (NCS), and trichloroisocyanuric acid (TCAA) did not afford the desired *meta*-chlorobenzaldehyde **16**. Instead, *ortho*-chlorobenzaldehyde **17** was obtained

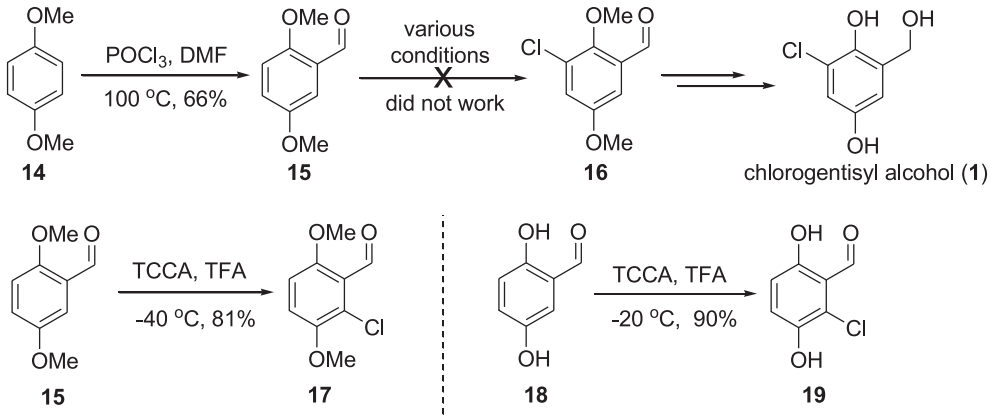


Scheme 1. Synthesis of gentisyl alcohol-type natural products.

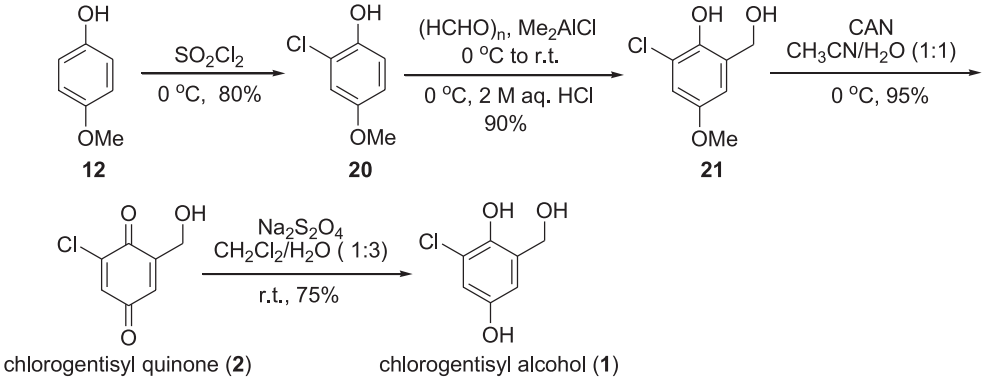


Scheme 2. Synthesis of gentisyl alcohol (**3**) and gentisyl quinone (**4**).

under these conditions. For example, treatment of **15** with TCAA and TFA in 1,2-dichloroethane (DCE) at –40 °C afforded exclusively **17** in 81% yield. Similarly, chlorination of benzaldehyde **18** provided *ortho*-chlorobenzaldehyde **19** in 90% yield, as the sole regioisomer under the similar condition (see Supporting Material for the discussion on the positional selectivity).



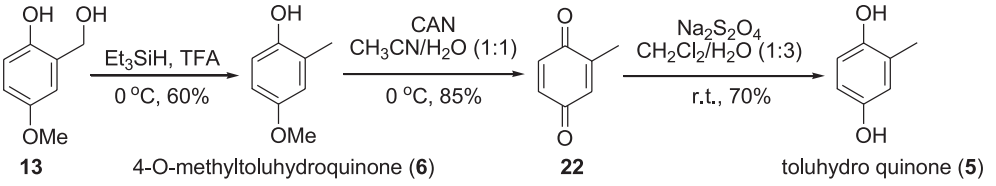
Scheme 3. Synthetic studies on chlorogentisyl alcohol (**1**).



Scheme 4. Synthesis of chlorogentisyl alcohol (**1**) and chlorogentisyl quinone (**2**).

The efficient synthesis of chlorogentisyl alcohol (**1**) and chlorogentisyl quinone (**2**) has been accomplished as shown Scheme 4. Treatment of **7** with SO_2Cl_2 and Et_2O at 0 °C gave exclusively *ortho*-chlorophenol **20** in 80% yield (Saper and Snider 2014), demonstrating a high mono-selectivity with respect to this phenol chlorination. With **20** in hand, we envisaged then to achieve the facile $NaBO_2$-promoted phenol hydroxymethylation mentioned in Scheme 2. Unfortunately, treatment of phenol **20** with aqueous formaldehyde in the presence of $NaBO_2$ did not work at room temperature, while degradation was observed when the reaction was performed at a higher temperature. Fortuitously, when the reaction was performed in the presence of lithium carbonate in water, the desired hydroxymethylated product **21** was isolated (see Supporting Material). Other promoters were further investigated to increase the yield of **21**. It was found that treatment of **20** with paraformaldehyde in the presence of Me_2AlCl in CH_2Cl_2 followed by acidic workup afforded **21** in 90% yield (see Supporting Material) (Tamiya et al. 2007). Oxidation of **21** with CAN provided **2** in 95% yield, and reduction of **2** with $Na_2S_2O_4$ generated **1** in 75% yield.

Synthesis of toluhydroquinone (**5**) and 4-*O*-methyltoluhydroquinone (**6**) is shown in Scheme 5. Reduction of 4-*O*-methylgentisyl alcohol (**13**) with triethylsilane (Et_3SiH) in the



Scheme 5. Synthesis of toluhydroquinone (**5**) and 4-O-methyltoluhydroquinone (**6**).

presence of trifluoroacetic acid afforded 4-*O*-methyltoluhydroquinone (**6**) in 60% yield. Oxidation of **6** with CAN afforded toluquinone (**22**) (Hwang et al. 2015) in 85% yield, which, in turn, underwent reduction with $Na_2S_2O_4$ to give toluhydroquinone (**5**) in 70% yield.

3. Conclusions

In conclusion, concise and divergent synthesis of seven gentisyl alcohol-type marine natural products has been accomplished from 4-methoxyphenol by a highly selective phenol mono-hydroxymethylation/monochlorination, CAN oxidation and sodium dithionite reduction as the key steps, which could be used for the preparation of sufficient quantities of these natural products for biological and medical studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the National Natural Science Foundation of China [grant number 21672046], [grant number 21372054]; the Fundamental Research Funds for the Central Universities [grant number HIT.NSRIF.201701].

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