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Total synthesis of agastaquinone, a diterpenoid quinone isolated from *Agastache rugosa*

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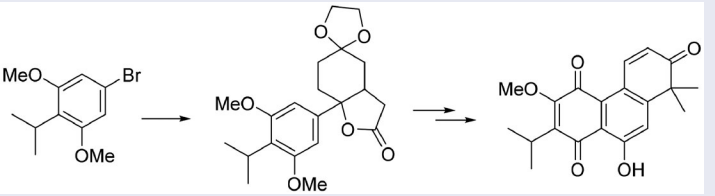
ABSTRACT

Agastaquinone is a tricyclic diterpenoid isolated from *Agastache rugose*. The first total synthesis of agastaquinone was accomplished based on intramolecular Friedel-Crafts acylation of aryl lactone followed by aromatization leading to the tricyclic phenol core structure as a key step.

GRAPHICAL ABSTRACT



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KEYWORDS
Friedel-Crafts acylation; diterpenoid; quinone; total synthesis

Introduction

Agastaquinone, a tricyclic diterpenoid isolated by our research group from the roots of *Agastache rugose*, showed nonspecific cytotoxic activities against several human cancer cell lines in vitro such as A549, SK-OV-3, SK-MEL-2, XF498, and HCT15.[1] It was reported to show a potent inhibitory effect against human immunodeficiency virus type 1 (HIV-1) protease activity with an IC_{50} value of 87 uM.[2] As we have been interested in further biological studies including in vivo activities, the total synthesis of agastaquinone should be accomplished, thereby enabling to provide a synthetic way that would prepare its analogues for the development of new therapeutics. Herein we report a concise total synthesis of agastaquinone. To the best of our knowledge this is the first report on the total synthesis of agastaquinone.

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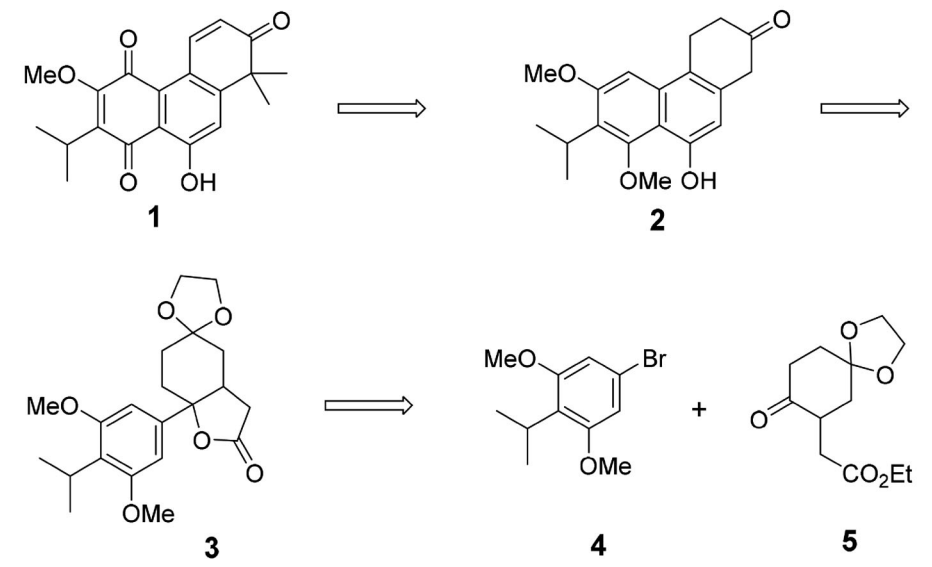
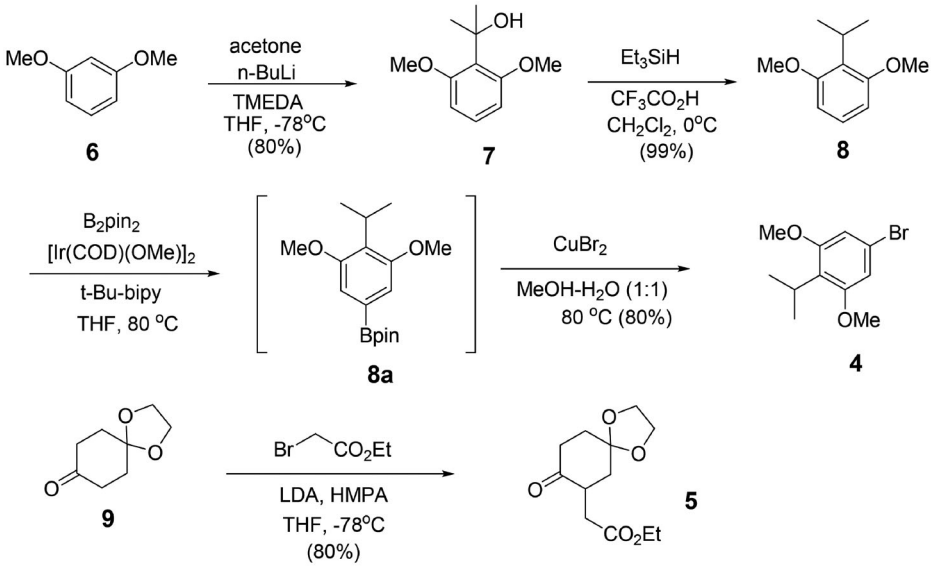


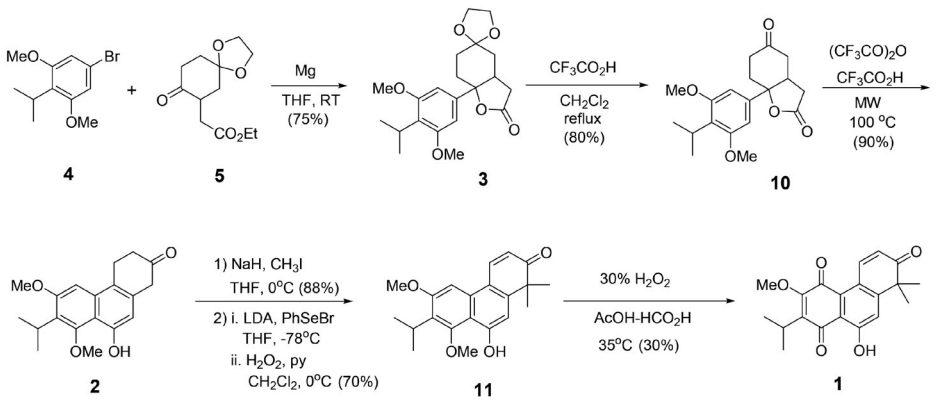
Scheme 1. Retrosynthetic analysis of agastaquinone (**1**)



Scheme 2. Preparation of aryl bromide **4** and ketone **5**

Results and discussion

Scheme 1 depicted the strategy we envisioned to achieve the synthesis of agastaquinone (**1**). Quinone **1** would be formed from compound **2** through sequential di-methylation, olefination, and oxidation procedures. Tricyclic phenol **2** could be constructed from compound **3** by intramolecular Friedel-Crafts acylation and subsequent aromatization. Lactone **3** would be generated by Grignard reaction of aryl bromide **4** with ketone **5**.



Scheme 3. Synthesis of agastaquinone (**1**)

To accomplish the synthetic route for agastaquinone (**1**), we required aryl bromide **4** and ketone **5**. We thus began our synthetic venture with preparation of the known aryl bromide **4** (Scheme 2).[3] Lithiation of 1,3-dimethoxybenzene (**6**) and followed by addition of acetone afforded tertiary alcohol **7**, which was reduced by treatment with Et_3SiH in the presence of trifluoroacetic acid to yield compound **8**.[4] To avoid bromination at the position located ortho to the two methoxy groups of compound **8**, a one-pot, two step-sequence to prepare aryl bromide was utilized.[3] A sterically controlled iridium-catalyzed borylation of compound **8** and subsequent bromination with copper (II) bromide provided aryl bromide **4**. On the other hand, ketone **5** was prepared by alkylation of 1,4-cyclohexanedione monoethyleneketal (**9**) with ethyl bromoacetate.[5]

With both aryl bromide **4** and ketone **5** in hand, our synthetic approach to agastaquinone (**1**) was outlined in Scheme 3. The reaction of Grignard reagent obtained from aryl bromide **4** with ketone **5** afforded lactone **3** in 73% yield.[6] After conversion of ketal **3** to the corresponding ketone **10** by acidic hydrolysis, microwave irradiation of ketone **10** in the presence of trifluoroacetic acid-trifluoroacetic anhydride (1:1) at 100 °C via Friedel-Crafts acylation and susequent aromatization furnished tricyclic phenol **2** in 90% yield.[6,7] Attempts to produce compound **2** directly from ketal lactone **3** via Friedel-Crafts acylation under acidic conditions (PPA, TFA, H_3PO_4, H_2SO_4, AcOH) failed.[8] Unfortunately, all attempts to effect the Friedel-Crafts acylation provided a complicated mixture of products. After conversion of ketal **3** to the corresponding ketone **10**, the Friedel-Crafts acylation for the formation of compound **2** could be successful. An acidic condition using trifluoroacetic acid-trifluoroacetic anhydride (1:1)[7] and heating by microwave irradiation enhanced the formation of tricyclic phenol **2** in terms of yield and short reaction times. Dimethylation of compound **2** and subsequent olefination gave α,β-unsaturated ketone **11**. Finally, Oxidation of compound **11** with 30% H_2O_2 in HCO_2H-AcOH (1:1)[9] afforded agastaquinone (**1**), which was in good agreement with the reported naturally occuring agastaquinone in all aspects including ^1H NMR, ^{13}C NMR, and HRMS spectra.[1]

Conclusions

In conclusion, we have completed the first total synthesis of agastaquinone in 6 steps and 10% overall yield from the known compounds **4** and **5**. We have described the

efficient synthetic approach to agastaquinone based on intramolecular Friedel-Crafts acylation of aryl lactone followed by aromatization leading to the tricyclic phenol core structure, which through sequential dimethylation, olefination and oxidation yielded a tricyclic diterpenoid quinone, agastaquinone.

Experimental

Preparation of compound 2

A solution of lactone **10** (0.12 g, 0.36 mmol) and trifluoroacetic acid (1 mL) in trifluoroacetic anhydride (1 mL) was placed in a microwave vessel (2–5 mL). The vessel was sealed and subjected to microwave irradiation for 2 h at 100 °C in a Biotage Initiator microwave synthesizer. After cooling, the mixture was diluted with water, extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (4:1 hexane-EtOAc) to afford 0.11 g (90%) of tricyclic phenol **2** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.01 (s, 1H), 6.53 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.65 (s, 2H), 3.59 (m, 1H), 3.29 (t, $J = 5.1$ Hz, 2H), 2.69 (t, $J = 5.1$ Hz, 2H), 1.41 (d, $J = 5.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 158.6, 153.8, 152.4, 132.8, 132.6, 127.6, 120.5, 110.2, 108.7, 99.4, 63.7, 55.0, 44.5, 38.7, 25.4, 24.4, 20.9; HRMS (ESI) m/z 313.1395 [(M-H)+, calculated for $C_{19}H_{21}O_4$ 313.1440]

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