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Asymmetric total synthesis of (+)-xestoquinone and (+)-adociaquinones A and B†

Xiao-Long Lu,[‡] Yuanyou Qiu,[‡] Baochao Yang,^a Haibing He[Ⓛ]^b and Shuanhu Gao[Ⓛ]^{*ab}

The asymmetric total synthesis of (+)-xestoquinone and (+)-adociaquinones A and B was achieved in 6–7 steps using an easily accessible *meso*-cyclohexadienone derivative. The [6,6]-bicyclic decalin B–C ring and the all-carbon quaternary stereocenter at C-6 were prepared *via* a desymmetric intramolecular Michael reaction with up to 97% ee. The naphthalene diol D–E ring was constructed through a sequence of Ti(Oi-Pr)₄-promoted photoenolization/Diels–Alder, dehydration, and aromatization reactions. This asymmetric strategy provides a scalable route to prepare target molecules and their derivatives for further biological studies.

Various halenaquinone-type natural products with promising biological activity have been isolated from marine sponges of the genus *Xestospongia*¹ from the Pacific Ocean. (+)-Halenaquinone (1),^{2,3} (+)-xestoquinone (2), and (+)-adociaquinones A (3) and B (4)^{4,5} bearing a naphtha[1,8-*bc*]furan core (Fig. 1) are the most typical representatives of this family. Naturally occurring (–)-xestosaprol N (5) and O (6)^{6,7} have the same structure as 3 and 4 except for a furan ring, while a naphtha[1,8-*bc*]furan core can also be found in fungus-isolated furanosteroids (–)-viridin (7) and (+)-nodulisporiviridin E (8)^{8,9} (Fig. 1). Halenaquinone (1) was first isolated from the tropical marine sponge *Xestospongia exigua*² and it shows antibiotic activity against *Staphylococcus aureus* and *Bacillus subtilis*. Xestoquinone (2) and adociaquinones A (3) and B (4) were firstly isolated, respectively, from the Okinawan marine sponge *Xestospongia* sp.^{4a} and the Truk Lagoon sponge *Adocia* sp.,^{4b} and they show cardiotonic,^{4a,c} cytotoxic,^{4b,i} antifungal,⁴ⁱ antimalarial,^{4j} and antitumor^{4l} activities. These compounds inhibit the activity of pp60v-src protein tyrosine kinase,^{4d} topoisomerases I^{4e} and II,^{4f} myosin Ca²⁺ ATPase,^{4c,g} and phosphatases Cdc25B, MKP-1, and MKP-3.^{4h,k}

Owing to their diverse bioactivities, the synthesis of this family of natural compounds has been extensively studied, with published pathways making use of Diels–Alder,^{3a,d,e,5a–c,e,g} furan

ring transfer,^{5b} Heck,^{3b,c,5f,7,9b,d} palladium-catalyzed polyene cyclization,^{5d} Pd-catalyzed oxidative cyclization,^{3f} and hydrogen atom transfer (HAT) radical cyclization^{9e} reactions. In this study, we report the asymmetric total synthesis of (+)-xestoquinone (2), (–)-xestoquinone (2'), and (+)-adociaquinones A (3) and B (4) (Fig. 1).

The construction of the fused tetracyclic B–C–D–E skeleton and the all carbon quaternary stereocenter at C-6 is a major challenge towards the total synthesis of xestoquinone (2) and adociaquinones A (3) and B (4). Based on our retrosynthetic analysis (Scheme 1), the all-carbon quaternary carbon center at C-6 of *cis*-decalin 12 could first be prepared stereoselectively from the achiral aldehyde 13 *via* an organocatalytic

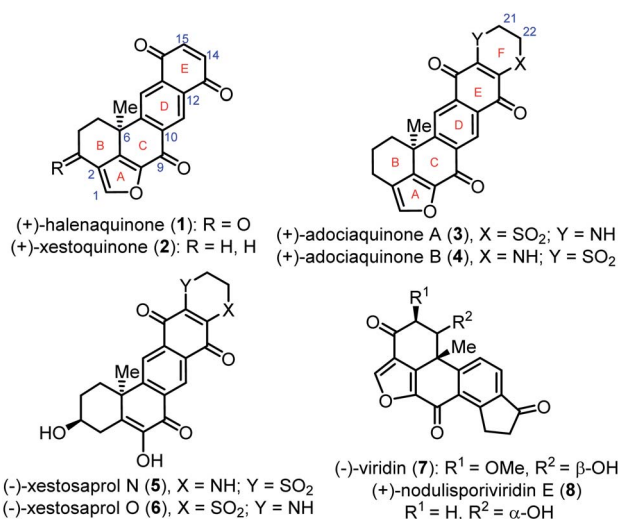


Fig. 1 Structure of halenaquinone-type natural products and viridin-type furanosteroids.

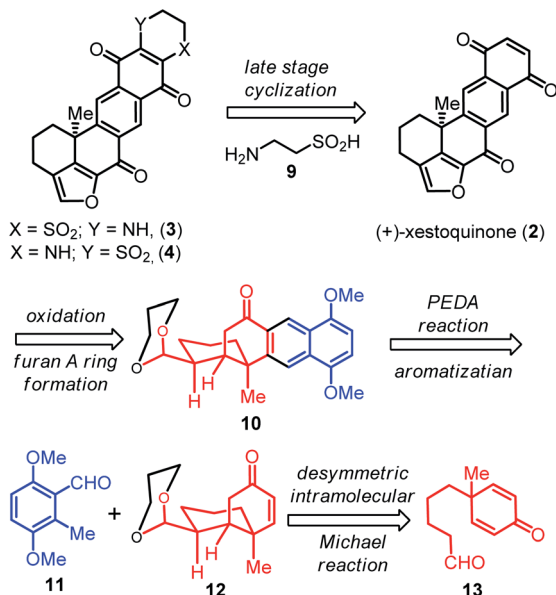
^aShanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, 3663N Zhongshan Road, Shanghai 200062, China. E-mail: hbhe@chem.ecnu.edu.cn; shgao@chem.ecnu.edu.cn

^bShanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, 3663N Zhongshan Road, Shanghai 200062, China

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‡ These authors contributed equally to this work.





Scheme 1 Retrosynthetic analysis of (+)-xestoquinone and (+)-adociaquinones A and B.

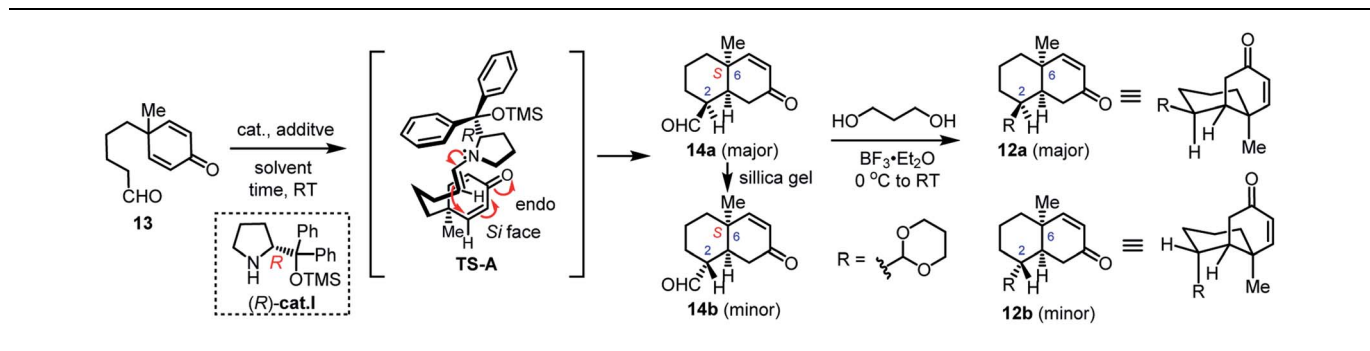
desymmetric intramolecular Michael reaction.^{10,11} The tetracyclic framework **10** could then be formed *via* a Ti(Oi-Pr)₄-promoted photoenolization/Diels-Alder (PEDA) reaction^{12–16} of

11 and enone **12**. Acid-mediated cyclization of **10** followed by oxidation state adjustment could be subsequently applied to form the furan ring A of xestoquinone (**2**). Finally, based on the biosynthetic pathway of (+)-xestoquinone (**2**)^{4b,5c} and our previous studies,⁷ the heterocyclic ring F of adociaquinones A (**3**) and B (**4**) could be prepared from **2** *via* a late-stage cyclization with hypotaourine (**9**).

The catalytic enantioselective desymmetrization of *meso* compounds has been used as a powerful strategy to generate enantioenriched molecules bearing all-carbon quaternary stereocenters.^{10,11} For instance, two types of asymmetric intramolecular Michael reactions were developed using a cysteine-derived chiral amine as an organocatalyst by Hayashi and co-workers,^{11a,b} while a desymmetrizing secondary amine-catalyzed asymmetric intramolecular Michael addition was later reported by Gaunt and co-workers to produce enantioenriched decalin structures.^{11c} Prompted by these pioneering studies and following the suggested retrosynthetic pathway (Scheme 1), we first screened conditions for organocatalytic desymmetric intramolecular Michael addition of *meso*-cyclohexadienone **13** (Table 1) in order to form the desired quaternary stereocenter at C-6. Compound **13** was easily prepared on a gram scale *via* a four-step process (see details in the ESI†).

We initially investigated the desymmetric intramolecular Michael addition of **13** using (*S*)-Hayashi-Jørgensen catalysts,¹⁷

Table 1 Attempts of organocatalytic desymmetric intramolecular Michael addition^a



Entry	Cat. (equiv.)	Additive (equiv.)	Solvent	Time	Yield/d.r. at C2 ^b	e.e. ^c
1	(<i>R</i>)-cat.I (0.5)	—	Toluene	10.0 h	52%/10.3 : 1	14a : 96%; 14b : 75%
2	(<i>R</i>)-cat.I (1.0)	—	Toluene	4.0 h	60%/10.0 : 1	14a : 93%; 14b : 75%
3	(<i>R</i>)-cat.I (1.0)	—	MeOH	4.0 h	47%/5.5 : 1	14a : 86%; 14b : –3%
4	(<i>R</i>)-cat.I (1.0)	—	DCM	10.0 h	28%/24.0 : 1	14a : 91%; 14b : 7%
5	(<i>R</i>)-cat.I (1.0)	—	Et ₂ O	10.0 h	22%/22.0 : 1	14a : 91%; 14b : 65%
6	(<i>R</i>)-cat.I (1.0)	—	MeCN	10.0 h	12%/2.6 : 1	14a : 90%; 14b : 62%
7	(<i>R</i>)-cat.I (1.0)	—	Toluene/MeOH (2 : 1)	4.0 h	47%/10.0 : 1	14a : 87%; 14b : –38%
8 ^d	(<i>R</i>)-cat.I (1.0)	AcOH (5.0)	Toluene	4.0 h	60%/2.1 : 1	14a : 96%; 14b : 95%
9 ^d	(<i>R</i>)-cat.I (0.5)	AcOH (2.0)	Toluene	6.0 h	75%/4.0 : 1	14a : 97%; 14b : 91%
10 ^d	(<i>R</i>)-cat.I (0.5)	AcOH (0.2)	Toluene	6.0 h	73%/4.3 : 1	14a : 96%; 14b : 92%
11 ^f	(<i>R</i>)-cat.I (0.5)	AcOH (0.2)	Toluene	6.0 h	75%/8.0 : 1 ^g	14a : 95%; 14b : 93%
12 ^h	(<i>R</i>)-cat.I (0.2)	AcOH (0.2)	Toluene	9.0 h	80%/6.0 : 1 ^j	14a : 97%; 14b : 91%

^a All reactions were performed using **13** (5.8 mg, 0.03 mmol, 1.0 equiv., and 0.1 M) and a catalyst at room temperature in analytical-grade solvents, unless otherwise noted. ^b The yields and diastereoisomeric ratios (d.r.) were determined from the crude ¹H NMR spectrum of **14** using CH₂Br₂ as an internal standard, unless otherwise noted. ^c The enantiomeric excess (e.e.) values were determined by chiral high-performance liquid chromatography (Chiralpak IG-H). ^d Compound **13**: 9.6 mg, 0.05 mmol, and 0.1 M. ^e Isolated combined yield of **14a** + **14b**. ^f Compound **13**: 192 mg, 1.0 mmol, and 0.1 M. ^g The d.r. values decreased to 1 : 1 after purification by silica gel column chromatography. ^h Compound **13**: 1.31 g, 6.82 mmol, and 0.1 M. ⁱ Isolated combined yield of **12a** + **12b**. ^j The d.r. values were determined from the crude ¹H NMR spectrum of **12** obtained from the one-pot process.

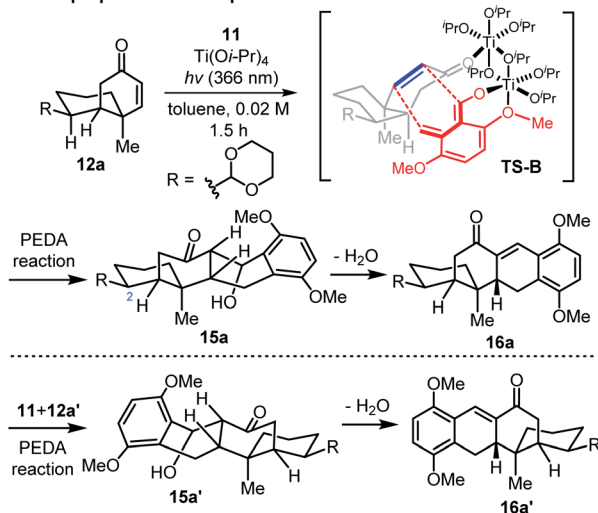


A. The reaction conditions of PEDA for enantiomeric **12a** and **12a'**

conditions	12a	12a'
1 equiv. 12a or 12a' 1.5 equiv. 11 $h\nu$ (366 nm) 0.02 M toluene, 1.5 h		
without Ti(O <i>i</i> -Pr) ₄	N.R. ^a	N.R. ^b
3.0 equiv. Ti(O <i>i</i> -Pr) ₄	50% 16a ^a	57% 16a' ^b

^a 20 mg **12a**, 22 mg **11**; ^b 15 mg **12a'**, 17 mg **11**.

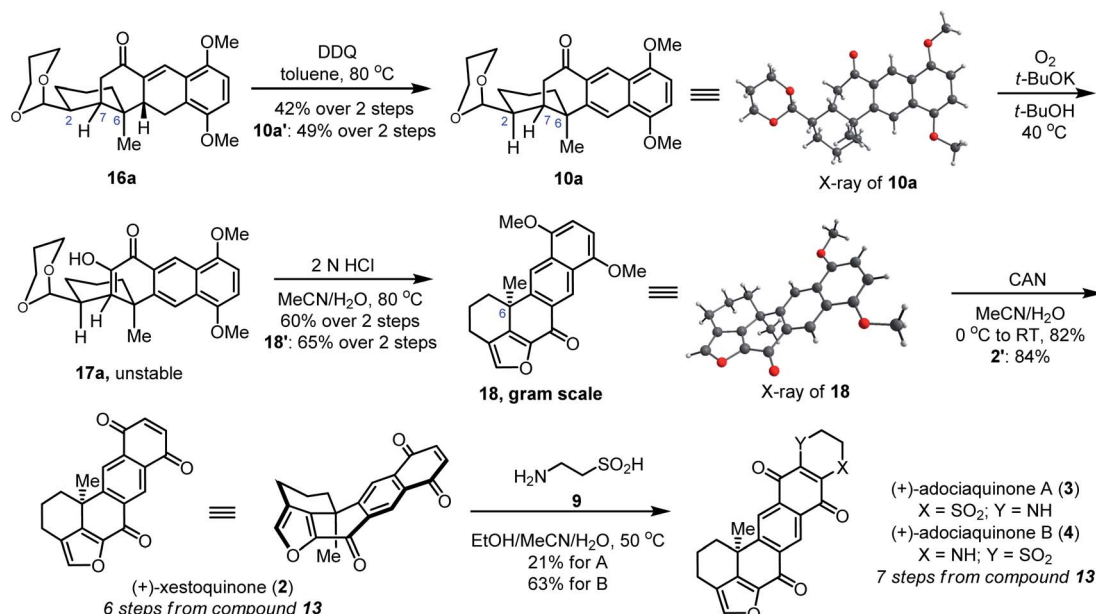
B. The proposed reaction process



Scheme 2 PEDA reaction of **11** and enone **12**.

and found that the absolute configuration of the obtained *cis*-decalin was opposite to the required stereochemistry of the natural products (see Table S1 in the ESI[†]). In order to achieve

the desired absolute configuration of the angular methyl group at C-6, (*R*)-**cat.I** was used for further screening. In the presence of this catalyst, the intramolecular Michael addition afforded **14a** (96% e.e.) and **14b** (75% e.e.) in a ratio of 10.3 : 1 and 52% combined yield (entry 1, Table 1). We assumed that the enantioselectivity of the reaction was controlled by the more sterically hindered aromatic group of (*R*)-**cat.I**, which protected the upper enamine face and allowed an *endo*-like attack by the *si*-face of cyclohexadienone, as shown in the transition state **TS-A** (Table 1). In order to increase the yield of this reaction and improve the enantioselectivity of **14b**, we further screened solvents and additives. Increasing the catalyst loading from 0.5 to 1.0 equivalents and screening various reaction solvents did not improve the enantiomeric excess of **14b** (entries 2–7, Table 1). Therefore, based on previous studies,^{11,de} we added 5.0 equivalents of acetic acid (AcOH) to a solution of compound **13** and (*R*)-**cat.I** in toluene, which improved the enantiomeric excess of **14b** to 95% with a 60% combined yield (entry 8, Table 1). And, the stability of (*R*)-**cat.I** has also been verified in the presence of AcOH (see Table S2 in the ESI[†]). Further adjustment of the (*R*)-**cat.I** and AcOH amount and ratio (entries 9–12, Table 1) indicated that 0.2 equivalents each of (*R*)-**cat.I** and AcOH were the best conditions to achieve high enantioselectivity for both **14a** and **14b**, and it also increased the reaction yield (entry 12, Table 1). The enantioselectivity was not affected when the optimized reaction was performed on a gram scale: **14a** (97% e.e.) and **14b** (91% e.e.) were obtained in 80% isolated yield (entry 12, Table 1). We also found that the gram-scale experiments needed a longer reaction time which led a slight decrease of the diastereoselectivity. The purification of the cyclized products by silica gel flash column chromatography indicated that the major product **14a** was epimerized and slowly converted to the minor product **14b** (entry 11, Table 1). Both **14a**



Scheme 3 Total synthesis of (+)-xestoquinone and (+)-adociaquinones A and B.



and **14b** are useful in the syntheses because the stereogenic center at C-2 will be converted to sp² hybridized carbon in the following transformations. Therefore, the aldehyde group of analogues **14a** and **14b** was directly protected with 1,3-propanediol to give the respective enones **12a** and **12b** for use in the subsequent PEDAs reaction.

Afterward, we selected the major cyclized *cis*-decalins **12a** and **12a'** (obtained by using (*S*)-**cat.1** in desymmetric intramolecular Michael addition, see Table S1 in the ESI†) as the dienophiles to prepare the tetracyclic naphthalene framework **10** through a sequence of Ti(Oi-Pr)₄-promoted PEDAs, dehydration, and aromatization reactions (Scheme 2). When using 3,6-dimethoxy-2-methylbenzaldehyde (**11**) as the precursor of diene, no reaction occurred between **12a/12a'** and **11** under UV irradiation at 366 nm in the absence of Ti(Oi-Pr)₄ (Scheme 2A). In contrast, the 1,2-dihydronaphthalene compounds **16a** and **16a'** were successfully synthesized when 3.0 equivalents of Ti(Oi-Pr)₄ were used. Based on our previous studies,^{13a,e} the desired hydroanthracenol **15a** was probably generated through the chelated intermediate **TS-B** and the cycloaddition occurred through an *endo* direction (Scheme 2B).¹⁸ The newly formed β-hydroxyl ketone groups in **15a** and **15a'** could then be dehydrated with excess Ti(Oi-Pr)₄ to form enones **16a** and **16a'**. These results confirmed the pivotal role of Ti(Oi-Pr)₄ in this PEDAs reaction: it stabilized the photoenolized hydroxy-*o*-quinodimethanes and controlled the diastereoselectivity of the reaction.

Subsequent aromatization of compounds **16a** and **16a'** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) at 80 °C afforded compounds **10a** and **10a'** bearing a fused tetracyclic B-C-D-E skeleton. The stereochemistry and absolute configuration of **10a** were confirmed by X-ray diffraction analysis of single crystals (Scheme 3). The synthesis of (+)-xestoquinone (**2**) and (+)-adociaquinones A (**3**) and B (**4**) was completed by forming the furan A ring. Compound **10** was oxidized using bubbling oxygen gas in the presence of *t*-BuOK to give the unstable diosphenol **17a**, which was used without purification in the next step. The subsequent acid-promoted deprotection of the acetal group led to the formation of an aldehyde group, which reacted *in situ* with enol to furnish the pentacyclic compound **18** bearing the furan A ring. The stereochemistry and absolute configuration of **18** were confirmed by X-ray diffraction analysis of single crystals (Scheme 3). Further oxidation of **18** with ceric ammonium nitrate afforded (+)-xestoquinone (**2**) in 82% yield. Following the same reaction process, (–)-xestoquinone (**2'**) was also synthesized from **10a'** in order to determine in the future whether xestoquinone enantiomers differ in biological activity. Further heating of a solution of (+)-xestoquinone (**2**) with hypotaurine (**9**) at 50 °C afforded a mixture of (+)-adociaquinones A (**3**) (21% yield) and B (**4**) (63% yield). We also tried to optimize the selectivity of this condensation by tuning the reaction temperature and pH of reaction mixtures (see Table S3 in the ESI†). The ¹H and ¹³C NMR spectra, high-resolution mass spectrum, and optical rotation of synthetic (+)-xestoquinone (**2**), (+)-adociaquinones A (**3**) and B (**4**) were consistent with those data reported by Nakamura,^{4a,g} Laurent,^{4f} Schmitz,^{4b} Harada^{5a,c} and Keay.^{5d}

Conclusions

In summary, we developed a concise approach for the asymmetric total synthesis of (+)-xestoquinone (**2**) in 6 steps and of (+)-adociaquinones A (**3**) and B (**4**) in 7 steps from a known compound **13**. Organocatalytic desymmetric intramolecular Michael addition was used to construct the *cis*-decalin skeleton bearing the all-carbon quaternary carbon center at the C-6 position. The B-C-D-E tetracyclic framework was then prepared through a Ti(Oi-Pr)₄-mediated PEDAs reaction, and further modifications led to the desired naphtha[1,8-*bc*]furan core. The application of this strategy to the synthesis of structurally related natural products is currently under investigation.

Conflicts of interest

There are no conflicts to declare.

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- 18 Based on our previous studies (ref. 13a and e), we concluded that Ti(Oi-Pr)₄ plays a key role in the PEDA reaction, which chelated with the photo-generated Z-dienol and *ortho* methoxy group of **11**, forming a relatively stable complex. This complex may exist as a dimeric titanium complex, given the observed relationships between the Ti dosage and reaction yield (ref. 13a). The *ortho* methoxy may serve as a key neighbouring group that helps to stabilize the short-lived photoenolized hydroxy-*o*-quinodimethane diene, which then interacts with dienophile **12a** to give a chelated intermediate **TS-B**. Then the activated enone reacts with the diene component from the *endo* direction. After dissociation, cycloaddition product **15a** was generated stereospecifically.

