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Cite this: *Chem. Sci.*, 2021, **12**, 4747

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 30th December 2020
Accepted 19th February 2021

DOI: 10.1039/d0sc07089k

rsc.li/chemical-science

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

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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 Ca^{2+} 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[9c] 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

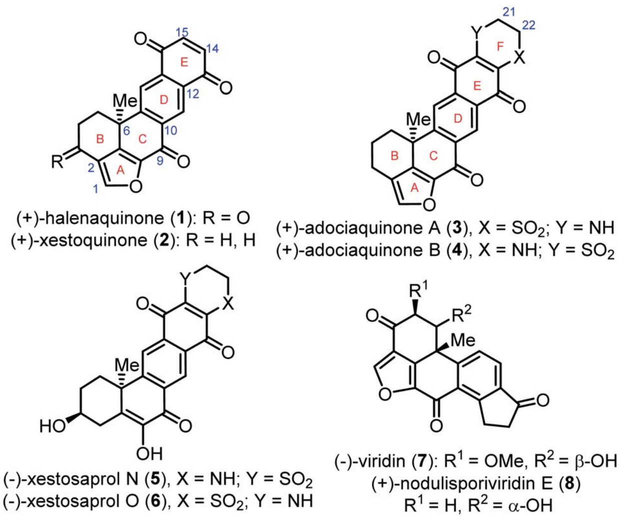

Fig. 1 Structure of halenaquinone-type natural products and viridin-type furanosteroids.

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† Electronic supplementary information (ESI) available. CCDC 2050867–2050869. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc07089k

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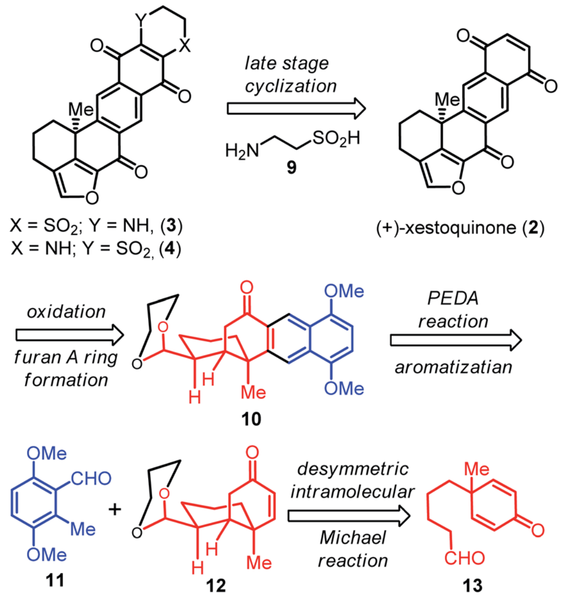


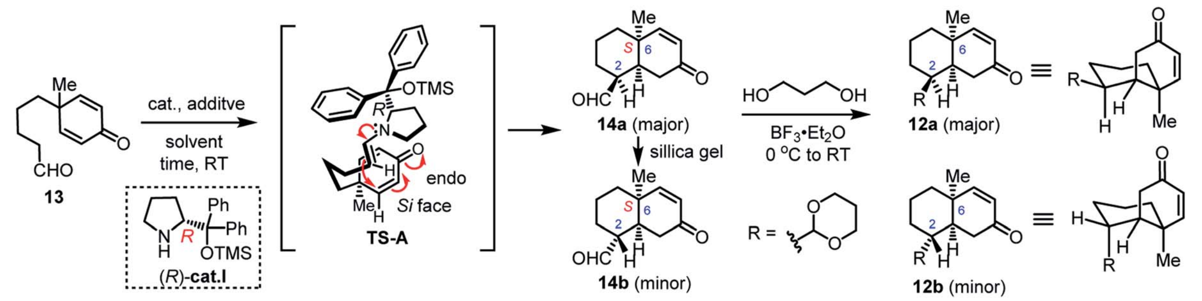
Scheme 1 Retrosynthetic analysis of (+)-xestoquinone and (+)-adociaquinones A and B.

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 hypotaurine (**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†).

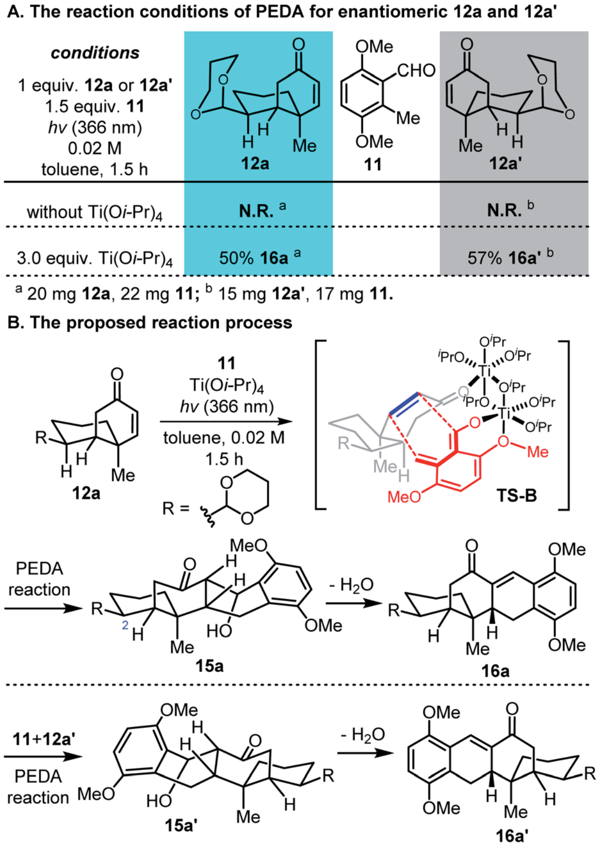
We initially investigated the desymmetric intramolecular Michael addition of **13** using (*S*)-Hayashi–Jørgensen catalysts,[17]

Table 1 Attempts of organocatalytic desymmetric intramolecular Michael addition[a]



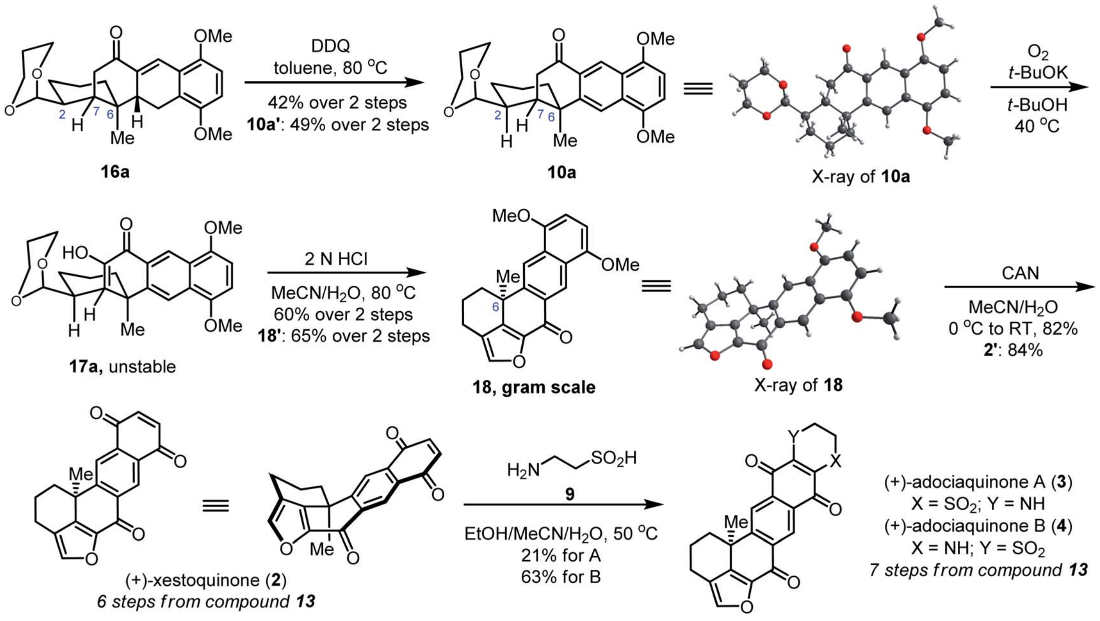
Entry	Cat. (equiv.)	Additive (equiv.)	Solvent	Time	Yield/d.r. at C2[b]	e.e.[c]
1	(*R*)-**cat.I** (0.5)	—	Toluene	10.0 h	52%/10.3 : 1	**14a**: 96%; **14b**: 75%
2	(*R*)-**cat.I** (1.0)	—	Toluene	4.0 h	60%/10.0 : 1	**14a**: 93%; **14b**: 75%
3	(*R*)-**cat.I** (1.0)	—	MeOH	4.0 h	47%/5.5 : 1	**14a**: 86%; **14b**: −3%
4	(*R*)-**cat.I** (1.0)	—	DCM	10.0 h	28%/24.0 : 1	**14a**: 91%; **14b**: 7%
5	(*R*)-**cat.I** (1.0)	—	Et$_2$O	10.0 h	22%/22.0 : 1	**14a**: 91%; **14b**: 65%
6	(*R*)-**cat.I** (1.0)	—	MeCN	10.0 h	12%/2.6 : 1	**14a**: 90%; **14b**: 62%
7	(*R*)-**cat.I** (1.0)	—	Toluene/MeOH (2 : 1)	4.0 h	47%/10.0 : 1	**14a**: 87%; **14b**: −38%
8[d]	(*R*)-**cat.I** (1.0)	AcOH (5.0)	Toluene	4.0 h	60%[e]/2.1 : 1	**14a**: 96%; **14b**: 95%
9[d]	(*R*)-**cat.I** (0.5)	AcOH (2.0)	Toluene	6.0 h	75%[e]/4.0 : 1	**14a**: 97%; **14b**: 91%
10[d]	(*R*)-**cat.I** (0.5)	AcOH (0.2)	Toluene	6.0 h	73%[e]/4.3 : 1	**14a**: 96%; **14b**: 92%
11[f]	(*R*)-**cat.I** (0.5)	AcOH (0.2)	Toluene	6.0 h	75%[e]/8.0 : 1[g]	**14a**: 95%; **14b**: 93%
12[h]	(*R*)-**cat.I** (0.2)	AcOH (0.2)	Toluene	9.0 h	80%[i]/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 ^{1}H NMR spectrum of **14** using CH$_2$Br$_2$ 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 ^{1}H NMR spectrum of **12** obtained from the one-pot 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,[11d,e] 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 sp^2 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 PEDA reaction.

Afterward, we selected the major cyclized *cis*-decalins **12a** and **12a′** (obtained by using (*S*)-**cat.I** 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 PEDA, 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 PEDA 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 ^{1}H and ^{13}C 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,[4j] 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 PEDA 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.

Acknowledgements

We thank the National Natural Science Foundation of China (21971068 and 21772044), the "National Young Top-Notch Talent Support Program", the Program of Shanghai Academic/Technology Research Leader (18XD1401500), the Program of Shanghai Science and Technology Committee (18JC1411303), the "Shuguang Program" supported by the Shanghai Education Development Foundation (grant numbers 19SG21), the Program for Changjiang Scholars and Innovative Research Team in University and "the Fundamental Research Funds for the Central Universities" for generous financial support.

Notes and references

1 For reviews of the natural products isolated from *Xestospongia* gens marine sponges and their bioactivities, see: (*a*) X. Zhou, T. Xu, X.-W. Yang, R. Huang, B. Yang, L. Tang and Y. Liu, *Chem. Biodiversity*, 2010, **7**, 2201–2227; (*b*) F. L. Liang, H. Liu, Y. Li, W. Ma, Y. Guo and W. He, *Yaoxue Xuebao*, 2014, **49**, 1218–1237.

2 For the first isolation and bioactivities of halenaquinone, see: D. M. Roll, P. J. Scheuer, G. K. Matsumoto and J. Clardy, *J. Am. Chem. Soc.*, 1983, **105**, 6177–6178.

3 For the synthesis of halenaquinone, see: (*a*) N. Harada, T. Sugioka, Y. Ando, H. Uda and T. Kuriki, *J. Am. Chem. Soc.*, 1988, **110**, 8483–8487; (*b*) A. Kojima, T. Takemoto, M. Sodeoka and M. Shibasaki, *J. Org. Chem.*, 1996, **61**, 4876–4877; (*c*) A. Kojima, T. Takemoto, M. Sodeoka and M. Shibasaki, *Synthesis*, 1998, 581–589; (*d*) H. S. Sutherland, F. E. S. Souza and R. G. A. Rodrigo, *J. Org. Chem.*, 2001, **66**, 3639–3641; (*e*) M. A. Kienzler, S. Suseno and D. Trauner, *J. Am. Chem. Soc.*, 2008, **130**, 8604–8605; (*f*) S. Goswami, K. Harada, M. F. El-Mansy, R. Lingampally and R. G. Carter, *Angew. Chem., Int. Ed.*, 2018, **57**, 9117–9121.

4 For the isolation and bioactivities of xestoquinone and adociaquinones A and B see: (*a*) H. Nakamura, J. i. Kobayashi, M. Kobayashi, Y. Ohizumi and Y. Hirata,

Chem. Lett., 1985, 713–716; (*b*) F. J. Schmitz and S. J. Bloor, *J. Org. Chem.*, 1988, **53**, 3922–3925; (*c*) M. Kobayashi, A. Muroyama, H. Nakamura, J. Kobayashi and Y. Ohizumi, *J. Pharmacol. Exp. Ther.*, 1991, **257**, 90–94; (*d*) K. A. Alvi, J. Rodriguez, M. C. Diaz, R. Moretti, R. S. Wilhelm, R. H. Lee, D. L. Slate and P. Crews, *J. Org. Chem.*, 1993, **58**, 4871–4880; (*e*) M. A. Bae, T. Tsuji, K. Kondo, T. Hirase, M. Ishibashi, H. Shigemori and J. Kobayashi, *Biosci., Biotechnol., Biochem.*, 1993, **57**, 330–331; (*f*) G. P. Concepcion, T. A. Foderaro, G. S. Eldredge, E. Lobkovsky, J. Clardy, L. R. Barrows and C. M. Ireland, *J. Med. Chem.*, 1995, **38**, 4503–4507; (*g*) M. Nakamura, T. Kakuda, Y. Oba, M. Ojika and H. Nakamura, *Bioorg. Med. Chem.*, 2003, **11**, 3077–3082; (*h*) S. Cao, C. Foster, M. Brisson, J. S. Lazo and D. G. Kingston, *Bioorg. Med. Chem.*, 2005, **13**, 999–1003; (*i*) M. Nakamura, T. Kakuda, J. Qi, M. Hirata, T. Shintani, Y. Yoshioka, T. Okamoto, Y. Oba, H. Nakamura and M. Ojika, *Biosci., Biotechnol., Biochem.*, 2005, **69**, 1749–1752; (*j*) D. Laurent, V. Jullian, A. Parenty, M. Knibiehler, D. Dorin, S. Schmitt, O. Lozach, N. Lebouvier, M. Frostin, F. Alby, S. Maurel, C. Doerig, L. Meijer and M. Sauvain, *Bioorg. Med. Chem.*, 2006, **14**, 4477–4482; (*k*) S. Cao, B. T. Murphy, C. Foster, J. S. Lazo and D. G. I. Kingston, *Bioorg. Med. Chem.*, 2009, **17**, 2276–2281; (*l*) L. Du, F. Mahdi, S. Datta, M. B. Jekabsons, Y. D. Zhou and D. G. Nagle, *J. Nat. Prod.*, 2012, **75**, 1553–1559.

5 For the synthesis of xestoquinone and adociaquinones A and B, see: (*a*) N. Harada, T. Sugioka, H. Uda and T. Kuriki, *J. Org. Chem.*, 1990, **55**, 3158–3163; (*b*) K. Kanematsu, S. Soejima and G. Wang, *Tetrahedron Lett.*, 1991, **32**, 4761–4764; (*c*) N. Harada, T. Sugioka, T. Soutome, N. Hiyoshi, H. Uda and T. Kuriki, *Tetrahedron: Asymmetry*, 1995, **6**, 375–376; (*d*) S. P. Maddaford, N. G. Andersen, W. A. Cristofoli and B. A. Keay, *J. Am. Chem. Soc.*, 1996, **118**, 10766–10773; (*e*) R. Carlini, K. Higgs, C. Older, S. Randhawa and R. Rodrigo, *J. Org. Chem.*, 1997, **62**, 2330–2331; (*f*) F. Miyazaki, K. Uotsu and M. Shibasaki, *Tetrahedron*, 1998, **54**, 13073–13078; (*g*) H. S. Sutherland, K. C. Higgs, N. J. Taylor and R. Rodrigo, *Tetrahedron*, 2001, **57**, 309–317.

6 For the isolation and bioactivities of xestosaprol N and O, see: (*a*) H.-S. Lee, Y.-J. Lee, C.-K. Kim, S.-K. Park, J. Soon Kang, J.-S. Lee and H. Jae Shin, *Heterocycles*, 2012, **85**, 895–901; (*b*) R. M. Centko, A. Steinø, F. I. Rosell, B. O. Patrick, N. de Voogd, A. G. Mauk and R. J. Andersen, *Org. Lett.*, 2014, **16**, 6480–6483.

7 For the synthesis of xestosaprol N and O, see: Y. Shi, Y. Ji, K. Xin and S. Gao, *Org. Lett.*, 2018, **20**, 732–735.

8 For the isolation and bioactivities of viridin and nodulisporiviridin E, see: (*a*) P. W. Brian and J. G. McGowan, *Nature*, 1945, **156**, 144–145; (*b*) J. S. Moffatt, *J. Chem. Soc. C*, 1966, 734–743; (*c*) J. F. Grove, P. McCloskey and J. S. Moffatt, *J. Chem. Soc. C*, 1966, 743–747; (*d*) Q. Zhao, G.-D. Chen, X.-L. Feng, Y. Yu, R.-R. He, X.-X. Li, Y. Huang, W.-X. Zhou, L.-D. Guo, Y.-Z. Zheng, X.-S. Yao and H. Gao, *J. Nat. Prod.*, 2015, **78**, 1221–1230.

9 For the synthesis of viridin and nodulisporiviridin E, see: (*a*) E. A. Anderson, E. J. Alexanian and E. J. Sorensen, *Angew. Chem., Int. Ed.*, 2004, **43**, 1998–2001; (*b*) M. Del Bel, A. R. Abela, J. D. Ng and C. A. Guerrero, *J. Am. Chem. Soc.*, 2017, **139**, 6819–6822; (*c*) Y. Ji, Z. Xin, H. He and S. Gao, *J. Am. Chem. Soc.*, 2019, **141**, 16208–16212; (*d*) Y. Ji, Z. Xin, Y. Shi, H. He and S. Gao, *Org. Chem. Front.*, 2020, **7**, 109–112.

10 For the reviews of desymmetrization, see: (*a*) G. Maertens, M.-A. Ménard and S. Canesi, *Synthesis*, 2014, **46**, 1573–1582; (*b*) X. P. Zeng, Z. Y. Cao, Y. H. Wang, F. Zhou and J. Zhou, *Chem. Rev.*, 2016, **116**, 7330–7396.

11 For the selected studies of organocatalytic desymmetric Michael addition, see: (*a*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212–4215; (*b*) Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui and M. Shoji, *J. Am. Chem. Soc.*, 2005, **127**, 16028–16029; (*c*) N. T. Vo, R. D. M. Pace, F. O'Har and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 404–405; (*d*) K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach and Y. Hayashi, *Helv. Chim. Acta*, 2011, **94**, 719–745; (*e*) H. Chen, X.-H. Li, J. Gong, H. Song, X.-Y. Liu and Y. Qin, *Tetrahedron*, 2016, **72**, 347–353.

12 For the first study of the PEDA reaction, see: N. C. Yang and C. Rivas, *J. Am. Chem. Soc.*, 1961, **83**, 2213.

13 For the studies of the PEDA reaction in the Gao group, see: (*a*) B. Yang, K. Lin, Y. Shi and S. Gao, *Nat. Commun.*, 2017, **8**, 622; (*b*) B. Yang and S. Gao, *Chem. Soc. Rev.*, 2018, **47**, 7926–7953; (*c*) D. Xue, M. Xu, C. Zheng, B. Yang, M. Hou, H. He and S. Gao, *Chin. J. Chem.*, 2019, **37**, 135–139; (*d*) D. Jiang, K. Xin, B. Yang, Y. Chen, Q. Zhang, H. He and S. Gao, *CCS Chem.*, 2020, **2**, 800–812; (*e*) X.-L. Lu, B. Yang, H. He and S. Gao, *Org. Chem. Front.*, 2021, DOI: 10.1039/d0qo01346c.

14 For the studies of the PEDA reaction in the Melchiorre group, see: (*a*) L. Dell'Amico, A. Vega-Peñaloza, S. Cuadros and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2016, **55**, 3313–3317; (*b*) L. Dell'Amico, V. M. Fernández-Alvarez, F. Maseras and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2017, **56**, 3304–3308; (*c*) S. Cuadros, L. Dell'Amico and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2017, **56**, 11875–11879; (*d*) H. B. Hepburn, G. Magagnano and P. Melchiorre, *Synthesis*, 2017, **49**, 76–86; (*e*) S. Cuadros and P. Melchiorre, *Eur. J. Org. Chem.*, 2018, **2018**, 2884–2891.

15 For the studies of the PEDA reaction in the Nicolaou group, see: (*a*) K. C. Nicolaou and D. Gray, *Angew. Chem., Int. Ed.*, 2001, **40**, 761–763; (*b*) K. C. Nicolaou, D. Gray and J. Tae, *Angew. Chem., Int. Ed.*, 2001, **40**, 3675–3678; (*c*) K. C. Nicolaou, D. Gray and J. Tae, *Angew. Chem., Int. Ed.*, 2001, **40**, 3679–3683; (*d*) K. C. Nicolaou and D. L. F. Gray, *J. Am. Chem. Soc.*, 2004, **126**, 607–612; (*e*) K. C. Nicolaou, D. L. F. Gray and J. Tae, *J. Am. Chem. Soc.*, 2004, **126**, 613–627.

16 For the selected studies of the PEDA reaction in other groups, see: (*a*) T. Durst, E. C. Kozma and J. L. Charlton, *J. Org. Chem.*, 1985, **50**, 4829–4833; (*b*) K. Hashimoto, M. Horikawa and H. Shirahama, *Tetrahedron Lett.*, 1990, **31**, 7047–7050; (*c*) A. G. Griesbeck and S. Stadtmüller, *Chem. Ber.*, 1993, **126**, 2149–2150; (*d*) T. J. Connolly and T. Durst, *Tetrahedron*, 1997, **53**, 15969–15982; (*e*) M. Sobczak and P. J. Wagner, *Tetrahedron Lett.*, 1998, **39**,

2523–2526; (*f*) B. Grosch, C. N. Orlebar, E. Herdtweck, W. Massa and T. Bach, *Angew. Chem., Int. Ed.*, 2003, **42**, 3693–3696; (*g*) O. A. Mukhina, N. N. Bhuvan Kumar, T. M. Arisco, R. A. Valiulin, G. A. Metzel and A. G. Kutateladze, *Angew. Chem., Int. Ed.*, 2011, **50**, 9423–9428; (*h*) N. N. B. Kumar, O. A. Mukhina and A. G. Kutateladze, *J. Am. Chem. Soc.*, 2013, **135**, 9608–9611; (*i*) O. A. Mukhina, D. M. Kuznetsov, T. M. Cowger and A. G. Kutateladze, *Angew. Chem., Int. Ed.*, 2015, **54**, 11516–11520; (*j*) O. A. Mukhina and A. G. Kutateladze, *J. Am. Chem. Soc.*, 2016, **138**, 2110–2113; (*k*) D. M. Kuznetsov, O. A. Mukhina and A. G. Kutateladze, *Angew. Chem., Int. Ed.*, 2016, **55**, 6988–6991; (*l*) A. Mavroskoufis, K. Rajes, P. Golz, A. Agrawal, V. Ruß, J. P. Götze and M. N. Hopkinson, *Angew. Chem., Int. Ed.*, 2020, **59**, 3190–3194.

17 For the reviews of Hayashi–Jørgensen catalysts, see: (*a*) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht and K. A. Jørgensen, *Acc. Chem. Res.*, 2012, **45**, 248–264; (*b*) G. J. Reyes-Rodríguez, N. M. Rezayee, A. Vidal-Albalat and K. A. Jørgensen, *Chem. Rev.*, 2019, **119**, 4221–4260.

18 Based on our previous studies (ref. 13*a* 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. 13*a*). 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.