The Direct and Metal-Catalyzed Photochemical Dimerization of the Phthalide (Z)-Ligustilide Leading to Both [2+2] and [4+2] Cycloadducts: Application to Total Syntheses of Tokinolides A-C and Riligustilide

Bingbing Sheng,[†] Yen Vo,[‡] Ping Lan,[†] Michael G. Gardiner, [‡] Martin G. Banwell*,[†,‡] and Pinghua Sun*,[†]

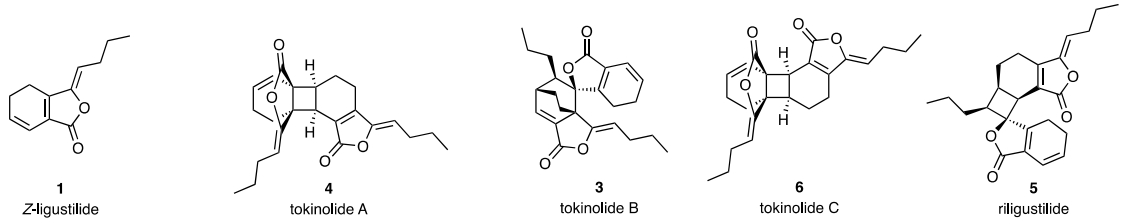
[†] Institute for Advanced and Applied Chemical Synthesis, Jinan University,

Zhuhai, 519070, China

[‡]Research School of Chemistry, Institute of Advanced Studies

The Australian National University, Canberra, ACT 2601, Australia

Supporting Information Placeholder



ABSTRACT: Synthetically-derived (*Z*)-ligustilide (**1**) has been subjected to photochemically-promoted dimerization processes under a range of conditions. By such means varying distributions of the dimeric natural products tokinolides A-C (**4**, **3** and **6**, respectively) and riligustilide (**5**) as well certain related (isomeric) compounds have been obtained. The structures of three of them have been confirmed by single-crystal X-ray analysis. The biosynthetic implications of the outcomes of this study are discussed.

The phthalide (*Z*)-lugustilide (**1**) (Figure 1) is a prominent constituent in a range of plants, perhaps most notably *Angelica sinensis* (Danggui) which is exploited extensively in traditional Chinese medicine (TCM).[1]

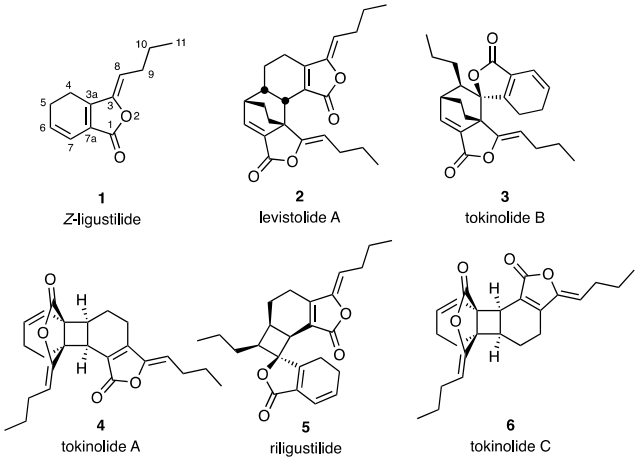


Figure 1: The structure of (*Z*)-lugustilide (**1**) and its dimeric co-metabolites **2**-**6**.

Compound **1** is often accompanied by one or more of a range of its possible [2+2]- and/or [4+2]-dimers[2] including, for example, levistolide A (**2**, a.k.a. diligustilide), tokinolide B (**3**), tokinolide A (**4**), riligustilide (**5**) and tokinolide C (**6**).[3] Normally these dimers are isolated in racemic form and so suggesting they are derived, *in vivo*, from monomer **1** by non-enzymatic processes. Natural products such as **1**-**5** are also encountered in the traditional medicines based upon several genera of the plant family Apiaceae (Umbelliferae) and used in Native American cultures.[3b,4] Many of the phthalide-based components of such medicines have been subject to biological evaluations and so revealing they can exert a plethora of significant activities. So, for example, the parent compound **1** displays, *inter alia*, anti-oxidant, anti-spasmodic, anti-asthmatic, anti-viral, analgesic, anti-microbial, insecticidal, phytotoxic and vasodilatory effects as well having neurologically beneficial impacts.[1, 3-5]

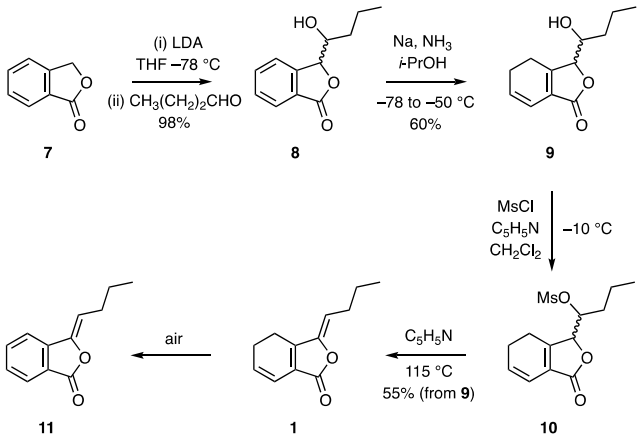
Dimers **2**-**5** and their various congeners exert a similarly broad range of activities and have also been shown to act as antioxidants and reduce blood viscosity. They also display progestogenic and cytotoxic effects.[1,3-6] Two naturally occurring trimeric forms of **1** have also been reported[7]

recently and these, too, were obtained in racemic form. Preliminary biological evaluation of them revealed that they possess dose-dependent anti-inflammatory properties but do not exert any notable cytotoxic or antimicrobial effects.[7]

Given the significant therapeutic potential of compounds such as **2**-**5** and their likely biogenesis, both the thermally and photochemically-promoted dimerization reactions of (*Z*)-lugustilide (**1**) have been studied, albeit in a cursory fashion. So, for example, heating a solution of compound **1** in benzene at 80 °C provided a mixture of the Diels-Alder dimers **2** and **3** in 2% and 3% yields, respectively.[8] The former adduct can be obtained in 22% yield by heating the neat monomer **1** in a sealed tube at 160 °C.[9] Furthermore, it was shown[8] that on heating adduct **3** at 200 °C this is converted into isomer **2**, a process that presumably involves a cycloreversion/re-addition process operating under thermodynamic control. In attempts to promote such Diels-Alder reactions, substrate **1** was treated with a range of Lewis acids but only linear dimers resulting from intermolecular Michael addition reactions were observed.[10] There has been just one study of the photolysis of compound **1** and this involved irradiating an acetone solution of it with a low-pressure mercury lamp under nitrogen at near ambient temperatures.[11] Under such (presumably triplet sensitized) conditions a mixture of four products was obtained, one of which was shown to be riligustilide **5** (7%) and the other three being described as "novel" (but see below) and symmetrical [2+2] photodimers that were obtained in 18.5%, 11% and 7.5% yields. The structure of one of these was established by single-crystal X-ray analysis.[11]

The advent of new techniques for effecting photocycloaddition reactions of olefins[12] prompted us to consider applying certain of these to substrate **1** in an effort to establish how they might influence the distribution of product dimers and higher order oligomers. In order to do so we required access to compound **1** and obtained this from the parent phthalide (**7**) using the route reported by Stermitz (Scheme 1).[13] Thus, the enolate derived from compound **7** was trapped with butanal and the mixture of aldol-type products **8** (98%) so-formed was subjected to a dissolving metal reduction using sodium in liquid ammonia/isopropanol and thereby affording the dihydro-aromatic **9** (60%). Mesylation of the hydroxyl group within this last compound was achieved under standard conditions and heating the resulting ester **10** in refluxing pyridine afforded the target monomer **1** in 55% yield (from **9**). All the spectral data recorded on the latter material matched those reported previously for the natural product,[11] a compound that we found was readily oxidized (when exposed to air as a solution in a range of solvents) to its fully aromatic, previously reported[14] and naturally occurring counterpart **11**.

Scheme 1: The synthesis of (*Z*)-lugustilide (**1**) from phthalide (**7**)



In commencing our studies of the photochemical behaviors of (*Z*)-lugustilide (**1**) (Table 1) we first exposed a ca. 0.13 M toluene solution of this compound in a sealed quartz cuvette to Australian summertime sunlight for 10 h (Entry 1, Table 1) but only observed extensive decomposition.

Table 1: Outcomes of the photochemical reactions of compound **1** under a range of different conditions

Entry	light source	solvent[a] catalyst	temp.[e] time	products (%)
1	sunlight	toluene none	amb.[f] 10 h	decomposition
2	halogen	acetone none	amb.[e] 72 h	**12** (<5%) **13** (<5%)
3	halogen	toluene[b] rose bengal	–78 °C 72 h	complex mixture
4	halogen	toluene[b] none	–78 °C 72 h	**3**, **4** ,**5** and **6** (2% each) **14** (7%), **15** (2%) **16** and **17** (<1% each)
5	halogen	toluene[b] $Ir(ppy)_3$	–78 °C 48 h	**3** and **5** (5% each) **14** (55%), **15** (5%) **3** and **5** (9% each)
6	halogen	toluene[b] F-$Ir(ppy)_3$[c]	–78 °C 36 h	**14** (58%), **15** (9%) **18** or **19** (15%)
7	halogen	CH_2Cl_2[b] aromatic ketone[d]	5 °C 48 h	**3** and **5** (6% each) **14** (63%), **15** (6%) **18** or **19** (11%)
8	330 nm LED	MeCN[b] $Ir(ppy)_3$ *i*-PrNEt$_2$ $LiBF_4$	amb.[e] 36 h	**3** and **5** (8% each) **14** (70%), **15** (8%) **18** or **19** (5%)
9	390 nm ("blue") LED	MeCN[b] $Ru(bpy)Cl_2$ *i*-PrNEt$_2$ $LiBF_4$	amb.[e] 4 h	**3** (5%) **14** (46%) **21**/**22** (4%)

(a) in every instance a 0.13 M solution of substrate **1** was used and this was normally contained in a Pyrex® vessel with either a ca. 0.4 or 2 mm thick wall; (b) this reaction was conducted under nitrogen; (c) F-$Ir(ppy)_3$ = $Ir[dF(F)ppy]_2$ (dtbbpy)PF_6 where ppy = 2-phenylpyridinyl; (d) acetophenone, benzophenone or 2-acetylnaphthalene; (e) temp = temperature; (f) amb. = ambient

When a 0.13 M acetone solution of the substrate was irradiated with a 500 W halogen lamp in a vessel open to the air for 72 h (Entry 2) a complex mixture of products was again formed but now small amounts (<5%) of the mono-epoxides **12** and **13** (Figure 2) could be isolated from the product mixture by flash chromatography. The former product, viz. **12**, has been obtained previously[14,15] from natural extracts that may also contain substrate **1** while the isomeric system **13** does not appear to have been reported before. In an effort to suppress decomposition pathways, a deoxygenated toluene solution of substrate **1** containing rose bengal was cooled to –78 °C then irradiated with the halogen lamp (Entry 3) but, once again, only complex mixtures of products were observed.

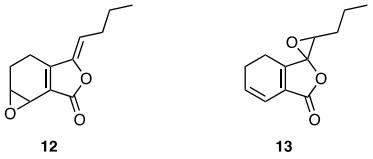


Figure 2: The mono-epoxides **12** and **13** obtained by photolysis of an acetone solution of substrate **1** in the presence of air.

In contrast, under the same conditions but now without sensitizer (Entry 4), a mixture of eight photoproducts was obtained and these could be isolated as discrete compounds using a combination of flash chromatographic and reverse-phase HPLC techniques. Five of these were identified, through comparison with published spectroscopic data, as the natural products tokinolide B (**3**)[8,16] (2%), tokinolide A (**4**)[6d] (2%), riligustilide **5** (2%),[6a,7,17] tokinolide C (**6**)[6d] (2%), and *exo*-*Z*,*Z*-3.3′,8.8′-diligustilide (**14**)[11,18-20] (7%) (Figures 1 and 3).

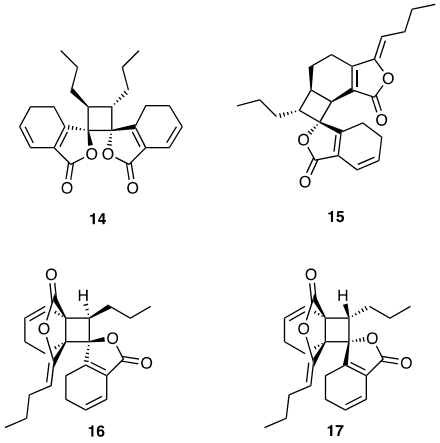


Figure 3: The structures of the four cyclobutane-containing photoproducts **14-17**

The structures of compounds **5** and **14** were confirmed by single-crystal X-ray analysis (See Supporting Information – SI – for details). Of the remaining three compounds, one proved to be, as established by single-crystal X-ray analysis, the *exo*-isomer of riligustilide, namely compound **15** (2%). The other two, which were the chromatographically most mobile ones, must be (based on the nature of the olefinic proton resonances observed in the derived ^{1}H NMR spectra) dimers linked through the $\Delta^{3,8}$- and $\Delta^{3a,7a}$-bonds of two separate (*Z*)-lugustilide (**1**) subunits. Since the two possible head-to-head forms of such dimers have been found to occur naturally (as tokiaerialide[21] and neodiligustilde[22]) and for which the ^{13}C NMR data do not match, we conclude these photoproducts are the corresponding head-to-tail adducts **16** and **17** (each obtained in <1% yield).

A significantly cleaner dimerization process was observed when 5 mole % $Ir(ppy)_3$[12d] was added to the reaction mixture and irradiation sustained for just 48 h (Entry 5). Dimer **14** was now produced in 55% yield with the remaining three, viz. **3**, **5** and **15**, each being obtained in 5% yield. Using an iridium catalyst incorporating fluorinated ligands, viz. $Ir[dF(F)ppy]_2(dtbbpy)PF_6$,[23] led (Entry 6) to slightly better outcomes in terms of the yields of these same products but now a new and chromatographically less mobile one was also obtained in 15% yield. This must be (based on the nature of the olefinic proton resonances observed in the derived ^{1}H NMR spectrum) a dimer linked through the $\Delta^{3,8}$- and $\Delta^{6,7}$-bonds of two separate (*Z*)-lugustilide (**1**) subunits and a head-to-tail analogue of compounds **5** and **15** and thus represented by either structure **18** or **19** (Figure 4). Unfortunately, the unstable nature of this crystalline product prevented the acquisition of spectroscopic data that would allow a distinction to be made between these two possibilities.

The same combination of products was obtained (Entry 7) in similar proportions on irradiating a dichloromethane solution of compound **1** at 5 °C for 48 h in the presence of acetophenone, benzophenone or 2-acetylnaphthalene[24] as sensitizer. However, the most effective protocol (Entry 8) involved irradiating an acetonitrile solution of substrate **1**, containing $Ir(ppy)_3$, Hünig's base and lithium tetrafluoroborate maintained at ambient temperatures, with a 330 nm LED source (see Experimental Section for details) for 36 h. Under such conditions the same range of products was obtained but now in essentially quantitative combined yield. When the same light source was employed at ambient temperatures in the presence of copper(II) triflate, $(Ph_3P)_3AuCl$, rhodium acetate dimer or acetophenone then very slow reactions occurred and so only delivering small amounts of a mixture of dimers **3**, **5**, **6**, **14** and **15**.

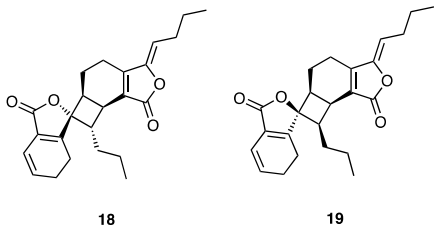


Figure 4: The structures of dimers **18** and **19**

In an effort to establish a capacity to change product distributions by manipulating the reaction conditions, an

acetonitrile solution of compound **1** was irradiated, in the presence of $Ru(bpy)Cl_2$, Hünig's base and lithium tetrafluoroborate,[25] with a 390 nm ("blue") LED at –78 °C for 4 h (Entry 9). This gave, in addition to the previously observed products **3** (5%) and **14** (46%), a small amount (5%) of two inseparable centro-symmetric dimers wherein, as judged by ^{1}H NMR spectroscopic analysis, the $\Delta^{3,8}$-bond of two separate monomer units had been joined in the formation of these cyclobutane-containing adducts. There are four possible products of such a dimerization process, namely two head-to-head and two head-to-tail adducts[2] and given that dimeric pairs of the same type have very similar chromatographic properties (see **5**/**15** and **16**/**17**) and that the corresponding head-to-head dimer **14** had a distinctly different mobility, we tentatively propose that this inseparable and ca. 1:1 mixture is comprised of compounds **20** and **21** (Figure 5). Interestingly, structure **20** has been assigned[11] to a photo-dimer derived from (*Z*)-lugustilide (**1**) while the isomeric one **22** has been assigned to a natural product isolated from *Angelica sinensis*.[19] However, comparisons of the ^{13}C NMR spectral data sets reported for these compounds reveal that they should both, in fact, be represented by structure **14**.[20]

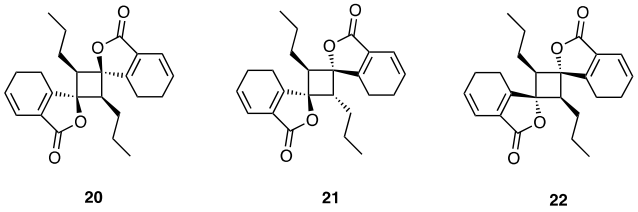


Figure 5: Structures of the centro-symmetric dimers **20**, **21** and **22**

In attempts to prepare the recently isolated trimeric forms of (*Z*)-lugustilide,[7] 1:1 mixtures of the last compound (viz. **1**) and the naturally occurring dimers **4**, **5** or **6** were each subjected to photolysis under a range of different conditions but in no instance could any such adducts (trimers) be isolated from these reaction mixtures. It is also interesting to note that photolysis of the (*Z*)-lugustilide precursor **9** under various of the conditions detailed above did not produce any reaction. We have not investigated Lewis-acid catalyzed[12e] variants of such processes or those that could afford the dimers themselves.

The foregoing results clearly demonstrate that a diverse array of dimeric adducts of (*Z*)-lugustilide (**1**) can be obtained under under a range of photolytic conditions and that the precise distribution of products is influenced, to a significant degree, by the mode of irradiation. The biosynthetic implications of our studies remain to fully understood but raise questions, for example, about whether or not naturally-occurring photosensitizers are involved in the production of cyclobutane-containing natural products **4**-**6**. The persistent formation, albeit at modest levels, of the thermodynamically less-favored Diels-Alder adduct tokinolide B (**3**) in these photochemically-promoted reactions is also intriguing and clearly indicates that mechanistic studies of all of these processes are warranted. We are currently pursuing such matters as well as investigating the dimerization of monomer **1** under various (other) open-shell conditions.[26]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free-of-charge on the ACS Publications website at DOI: 10.1021/acs.orglett.XXXXXX.

Plots and cifs arising from the single crystal X-ray analyses of compounds **5**, **14** and **15**; Experimental procedures for the formation of compounds **3-6**, **9**, **11-17**, **18** (or **19**) and the mixture of compounds **20** and **21** as well as ^{1}H and ^{13}C NMR spectra of the same and of compound **1**.

Accession Codes

CCDC files 1918547, 1918548 and 1918549 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: Martin.Banwell@anu.edu.au

*E-mail: tsunph@jnu.edu.cn

ORCID Martin G. Banwell: 0000-0002-0582-475X

ORCID Pin Lan: 0000-0002-9285-3259

ORCID Pinghua Sun: 0000-0001-8693-6731

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

We thank the Australian Research Council, the ANU Institute of Advanced Studies, the National Natural Science Fund (Grant 81872759) of China, and the Pearl River Scholar Program of Guangdong Province for financial support. The Sichuan Wei Keqi Biological Technology Co. Ltd. is gratefully acknowledged for providing us with copies of the ^{1}H and ^{13}C NMR spectra of angelicide and Dr Hideki Onagi (ANU) is warmly thanked for assistance with HPLC separations.

REFERENCES

1. (a) Yi, L.; Liang, Y.; Wu, H.; Yuan, S. The Analysis of Radix Angelicae Sinensis (Danggui). *J. Chromat. A.* **2009**, *1216*, 1991-2001; (b) Chao, W.-W.; Lin, B.-F. Bioactivities of Major Constituents Isolated from Angelica Sinensis (Danggui). *Chin. Med.* **2011**, *6*, 29-35.

2. In principle each of the C3-C8, C3a-C7a and C6-C7 bonds within compound **1**, and which we label A, B and C respectively, could participate in a [2+2] cycloaddition reaction. There are six possible modes for engaging these bonds in such dimerization processes, namely through AA, BB, CC, AB, AC or BC pairings. Since each dimerization process could involve a head-to-head or head-to-tail pairing and each of these could proceed in either an *exo*- or *endo*-manner then 6 x 2 x 2 or 24 possible regio- or diastereo-isomerically-related cyclobutane-containing dimers could be obtained. Similarly, each of bonds A, B or C within substrate **1** could (in principle) add, as the dieneophile in a [4+2] cycloaddition reaction, to the *s*-cissoid diene unit within a second molecule of the same compound. Since each of these addition processes could also proceed in a head-to-head or head-to-tail fashion and either an *exo*- or *endo*-manner then 3 x 2 x 2 or 12 possible regio- or diastereo-isomerically-related [4+2] dimers could be obtained.

3. (a) Li, W.; Wu, Y.; Liu, X.; Yan, C.; Liu, D.; Pan, Y.; Yang, G.; Yin, F.; Weng, Z.; Zhao, D.; Chen, Z.; Cai, B. Antioxidant Properties of *cis*-*Z*,*Z*′-3a.7a′,7a.3a′-Dihydroxyligustilide on Human Umbilical Vein Endothelial Cells in Vitro. *Molecules*, **2013**, *18*, 520-534; (b) León, A.; Del-Ángel, M.; Ávila, J. L.; Delgado, G. Phthalides: Distribution in Nature, Chemical Reactivity, Synthesis, and Biological Activity. *Prog. Chem. Nat. Prod.*, **2017**, *104*, 128-246.

4. Beck, J. J.; Chou, S.-C. The Structural Diversity of Phthalides from the Apiaceae. *J. Nat. Prod*. **2007**, *70*, 891-900.

5. See Su, Z.Y.; Khor, T. O.; Shu, L.; Lee, J. H.; Saw, C. L.-L.; Wu, T.-Y.; Huang, Y.; Suh, N.; Yang, C. S.; Conney, A. H.; Wu, Q.; Kong, A.-N. T. Epigenetic Reactivation of Nrf2 in Murine Prostate Cancer TRAMP C1 Cells by Natural Phytochemicals *Z*-Ligustilide and Radix Angelica Sinensis via Promoter CpG Demethylation. *Chem. Res. Toxicol*. **2013**, *26*, 477-485 and references cited therein.

6. See, for example, (a) Deng, S.; Chen, S.-N.; Lu, J.; Wang, Z. J.; Nikolic, D.; Van Breemen, R. B.; Santarsiero, B. D.; Mesecar, A.; Fong, H. H. S.; Farnsworth, N. R.; Pauli, G. F. GABAergic Phthalide Dimers from Angelica Sinensis (Oliv.) Diels. *Phytochem. Anal*. **2006**, *17*, 398-405; (b) Lim, L. S.; Shen, P.; Gong, Y. H.; Yong, E. L. Dimeric Progestins from Rhizomes of Ligusticum Chuanxiong. *Phytochem*. **2006**, *67*, 728-734; (c) Wei, W.; Wu, X.-W.; Yang, X.-W. Novel Phthalide Derivatives from the Rhizomes of Ligusticum Chuanxiong and their Inhibitory Effect Against Lipopolysacchardide-Induced Nitric Oxide Production in RAW 264.7 Macrophage Cells. *RSC Adv*. **2016**, *6*, 61037-61046; (d) Gong, W.; Zhou, Y.; Li, X.; Gao, X.; Tian, J.; Qin, X.; Du, G. Neuroprotective and Cytotoxic Phthalides from *Angelicae Sinensis* Radix. *Molecules*, **2016**, *21*, 549-559; (e) King, J.; Han, L.; Su, H.; Hu, Y.; Huang, X.; Lou, Y. Riligustilide Attenuated Renal Injury by the Blockade of Renin. *Cell Physiol. Biochem*. **2018**, *50*, 654-667.

7. Zou, J.; Chen, G.-D.; Zhao, H.; Huang, Y.; Luo, X.; Xu, W.; He, R.-R.; Hu, D.; Yao, X.-S.; Gao, H. Riligustilides A and B: Two Pairs of Phthalide Trimers from Angelica Sinensis with a Complex Polycyclic Skeleton and their Activities. *Org. Lett*. **2018**, *20*, 884-887.

8. Ogawa, Y.; Mori, Y.; Maruno, M.; Wakamatsu, T. Diels-Alder Reaction of Ligustilide Giving Levistolide A and Tokinolide B. *Heterocycles*, **1997**, *45*, 1869-1872.

9. Rios, M. Y.; Delgado, G.; Toscano, R. A. Chemical Reactivity of Phthalides. Relay Synthesis of Diligustilide, *Rel*-(3′*R*)-3′,8′-Dihydrodiligustilide and Wallichilide. *Tetrahedron*, **1998**, *54*, 3355-3366.

10. Rios, M. Y.; Delgado, G. Lewis Acid Catalyzed Transformations of *Z*-Ligustilide. *J. Mex. Chem. Soc*. **1999**, *43*, 127-132.

11. Quiroz-García, B.; Figueroa, R.; Cogordan, J. A.; Delgado, G. Photocyclodimers from *Z*-Ligustilide. Experimental Results and FMO Analysis. *Tetrahedron Lett*. **2005**, *46*, 3003-3006.

12. See, for example, (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev*. **2013**, *113*, 5322-5363; (b) Hoyt, J. M.; Schmidt, V. A.; Tondreau, A. M.; Chirik, P. J. Iron-catalyzed Intermolecular [2+2] Cycloadditions of Unactivated Alkenes. *Science*, **2015**, *349*, 960-963; (c) Yoon, T. P. Photochemical Stereocontrol Using Tandem Photoredox–Chiral Lewis Acid Catalysis. *Acc. Chem. Res*. **2016**, *49*, 2307-2315; (d) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent Advances in the Synthesis of Cyclobutanes by Olefin 2+2] Photocycloadditions Reactions. *J. Am. Chem. Soc*. **2016**, *116*, 9748-9815 ; (e) Poplata, S.; Bauer, A.; Storch, G.; Bach, T. Intramolecular [2+2] Photocycloaddition of Cyclic Enones: Selectivity Control by Lewis Acids and Mechanistic Implications. *Chem. Eur. J*. **2019**, *25*, 8135-8148.

13. Beck, J. J.; Stermitz, F. R. Addition of Methyl Thioglycolate and Benzylamine to (*Z*)-Ligustilide, A Bioactive Unsaturated Lactone Constituent of Several Herbal Medicines. An Improved Synthesis of (*Z*)-Ligustilide. *J. Nat. Prod*. **1995**, *58*, 1047-1055.

14. Wisetsai, A.; Lekphromn, R.; Schevenels, F. T. A Novel Cyclohexenone from Trachyspermum Roxburghianum. *Nat. Prod. Res*. **2018**, *32*, 2499-2504.

15. Kaouadji, M.; De Pachtere, F.; Pouget, C.; Chulia, A. J. Three Additional Phthalide Derivatives, An Epoxymonomer and Two Dimers, From Ligusticum Wallichii Rhizomes. *J. Nat. Prod*. **1986**, *49*, 872-877.

16. Naito, T.; Katsuhara, T.; Niitsi, K.; Ikeya, Y.; Okada, M.; Mitsuhashi, H. Phthalide Dimers from Ligusticum Chuangxiong Hort. *Heterocycles*, **1991**, *32*, 2433-2442.

17. The natural product angelicide (Chen, Y.; Zhang, H. Analysis of the Chemical Ingredients of Angelica Sinensis – Analysis of Nonvolatile Constituents of Roots. *Gaodeng Xuexiao Huaxue Xuebao*, **1984**, *5*, 515-520) is, in fact, identical, by NMR and single-crystal X-ray spectroscopic analysis, to riligustilide.

18. Lin, L.-Z.; He, X.-G.; Lian, L.-Z.; King, W.; Elliot, J. Liquid Chromatographic-Electrospray Mass Spectrometric Study of the Phthalides of Angelica Sinensis and Chemical Changes of *Z*-Ligustilide. *J. Chromat. A*, **1998**, *810*, 71-79.

19. Lu, X.; Zhang, J.; Zhang, X.; Liang, H.; Zhao, Y. Study on Biligustilides from Angelica Sinensis. *Zhongguo Zhongyao Zazhi (China J. Chin. Materia Medica)*, **2008**, *33*, 2196-2201.
20. Compound **14** has been isolated in earlier photochemical studies (ref. 11) but it structure assigned incorrectly. It also appears to have been isolated from natural sources (refs. 18 and 19) but its structure assigned either without full stereochemical detail or incorrectly.
21. Uto, T.; Tung, N. H.; Taniyama, R.; Miyanowaki, T.; Morinaga, O.; Shoyama, Y. Anti-inflammatory Activity of Constituents Isolated from the Aerial Part of Angelica Acutiloba Kitagawa. *Phytotherapy Res*. **2015**, *29*, 1956-1963.
22. Chen, Q. C.; Lee, J.; Jin, W.; Youn, U.; Kim, H.; Lee, I. S.; Zhang, X.; Song, K.; Seong, Y.; Bae, K. Cytotoxic Constituents from Angelicae Sinensis Radix. *Arch. Pharm. Res*. **2007**, *30*, 565-569.
23. Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. Metallaphotoredox-catalyzed sp^3-sp^3 Cross-coupling of Carboxylic Acids with Alkyl Halides. *Nature*, **2016**, *536*, 322-325.
24. Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. Total Synthesis and Revised Structure of Biyouyanagin A. *Angew. Chem. Int. Ed*. **2007**, *46*, 4708-4711.
25. Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions. *J. Am. Chem. Soc*. **2008**, *130*, 12886-12887.
26. See, for example, (a) Donoghue, P. J.; Wiest, O. Structure and Reactivity of Radical Ions: New Twists on Old Concepts. *Chem. Eur. J*. **2006**, *12*, 7018-7026; (b) Okada, Y.; Yamaguchi, Y.; Ozaki, A.; Chiba, K. Aromatic "Redox Tag"-Assisted Diels-Alder Reactions by Electrocatalysis. *Chem. Sci.* **2016**, *7*, 6387-6393 and references cited therein.