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Biomimetic Total Syntheses of Linderaspirone A and Bi-linderone and Revisions of Their Biosynthetic Pathways

Haibo Tan,[†] Chao Zheng,[†] Zheng Liu, and David Zhigang Wang*

Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen, China 518055

dzw@szpku.edu.cn

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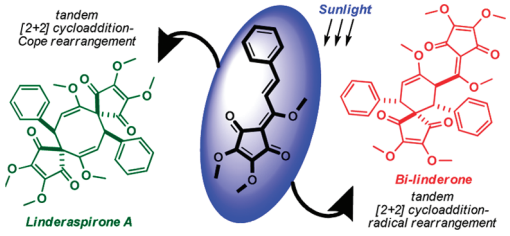
ABSTRACT



Simple exposure to sunlight is sufficient for triggering photochemical [2 + 2] cycloaddition−Cope or radical rearrangement cascades in the naturally occurring methyl linderone, leading to efficient biomimetic total syntheses of linderaspirone A and bi-linderone, two recently discovered bioactive spirocyclopentenedione natural products.

The medical utilities of *Lindera* plant species have long been widely appreciated in traditional Chinese and Japanese herbal medicine formulations. The chemical constituents of these plants have thus been extensively investigated, leading to the discovery of an impressive range of structurally highly diverse natural products that include sesquiterpenoids, flavonoids, alkaloids, lignans, butanolides, and various cyclopentenedione derivatives.[1] These compounds demonstrate useful bioactivities in antioxidation; display anti-inflammatory and antiviral properties, cytotoxicity, and protection against postischemic myocardial dysfunction; and retard the progression of diabetic nephropathy in db/db mice.[2] It is therefore a remarkable event that very recently Liu and his co-workers have been able to isolate and characterize linderaspirone A (**1**) and bi-linderone (**2**) (Figure 1), two novel structural skeletons from the root of *Lindera aggregata* that both feature unprecedented spirocyclopentenedione units attached to a highly congested

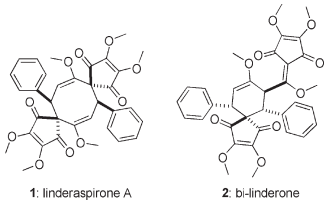


Figure 1. Structures of linderaspirone A and bi-linderone.

[†] These two authors contributed equally to the work.

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(2) (a) Gu, L. H.; Wu, T.; Zhang, Z. J.; Chou, G. X.; Wang, Z. T. *Acta Pharm. Sin.* **2006**, *41*, 956–962. (b) Li, S. Y.; Chen, C.; Zhang, H. Q.; Guo, H. Y.; Wang, H.; Wang, L.; Zhang, X.; Hua, S. N.; Yu, J.; Xiao, P. G.; Li, R. S.; Tan, X. H. *Antiviral Res.* **2005**, *67*, 18–23. (c) Ohno, T.; Takemura, G.; Murata, I.; Kagawa, T.; Akao, S.; Minatoguchi, S.; Fujiwara, T.; Fujiwara, H. *Life Sci.* **2005**, *77*, 1391–1403.

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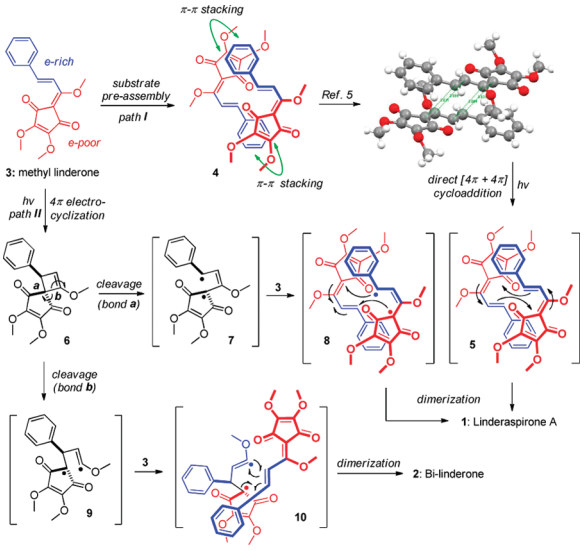
eight- or six-membered ring framework.[3] Naturally occurring **1** and **2** are both racemic. Preliminary biological tests have already shown significant activities of **1** and **2** against glucosamine-induced insulin resistance in HepG2 cells at 1 μg/mL.[3]

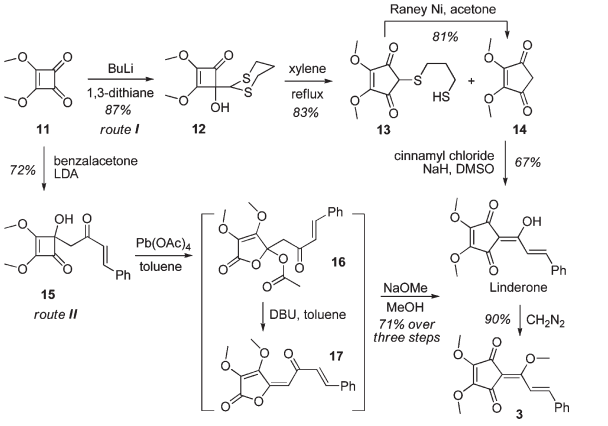
Scheme 1. Original Biosynthetic Hypothesis to **1** and **2**



An inspection on the stereochemical architectures of **1** and **2** quickly reveals their dimeric nature from a much simplified monomeric precursor, i.e., methyl linderone (structured as **3**, Scheme 1), which itself is a known natural product with established bioactivities.[4] Thus biosynthetically it appears to be reasonable, as already sketched by Liu and co-workers, that the formations of **1** and **2** might have been initiated from **3** through formal [4 + 4] cycloaddition[3b] and radical-induced rearrangement pathways,[3a] respectively. A substantially refined version of their biosynthetic proposal is illustrated in Scheme 1.

The development of these biosynthetic hypotheses takes advantage of the ability of the diene moiety in **3** participating in a photochemical 4π-electrocyclization as well as the tendency of **3** in engaging itself in intermolecular $\pi-\pi$ stacking (*vide infra*) owing to its highly polarized electron density distribution pattern (electron-rich and -poor regions shown in blue and red, respectively within structure **3**). When **3** organizes itself through a dimeric "head-to-tail" $\pi-\pi$ stacking model as revealed previously by X-ray study (shown in structure **4**, path **I**, Scheme 1) by Yamin et al.,[5] upon irradiation, the conformational packing force may be sufficient to bring about the entropy-disadvantaged [4π + 4π] cycloaddition[6] in a *pseudo*-intramolecular fashion in transition state **5** thus leading directly to the dimerization product **1**. Meanwhile, **3** could readily convert into cyclobutene **6** through photochemical 4π-electrocyclization (see path **II**, Scheme 1). As hypothesized,[3] subsequent cyclobutene ring opening by breaking bond ***a*** or ***b*** would yield diradical intermediates **7** or **9**, respectively. **7** could further recombine with another molecule of **3** in transition state **8** to effect radical-initiated cycloaddition again giving rise to **1**. In a similar fashion, diradical **9** could yield **2** through a possible transition-state assembly **10**.

Scheme 2. Two Practical Routes for the Rapid Synthesis of **3**



With this mechanistic scenario in mind, we set out to pursue first the critical monomer **3**. The total and formal syntheses of **3** and linderone-related compounds have been the topics of several published works.[7] These investigations were fueled by very promising bioactivities they displayed. In particular, antifungal and human chymase inhibition functions were uncovered by Aoyama, Konoike,[7a] Li, and Clark[8] and their corresponding co-workers through detailed structure−activity profiling. As these compounds are only available in small amounts from natural sources, clearly more efficient, practical, and scalable routes to **3** would greatly support in-depth pharmacological studies on this class of interesting cylcyclopentendione natural derivatives. We therefore feel a need to develop an improved synthesis of **3** not only serving the purposes mentioned above but also providing a higher efficiency toward the total syntheses of our targets **1** and **2** herein, whose further biological investigations had been again hampered by their extremely limited natural availability.[3]

(4) (a) Leong, Y. W.; Harrson, L. J.; Bennett, G. J.; Kadir, A. A.; Connolly, J. D. *Phytochemistry* **1998**, *47*, 891–894. (b) Kiang, K.; Lee, H. H.; Sim, K. Y. *J. Chem. Soc.* **1962**, 4338–4345.

(5) The X-ray structure of **3** and its intermolecular packing mode had been reported; see: Syah, Y. M.; Suastri, N. S.; Latip, J.; Yamin, B. M. *Acta. Crystallogr., Sect. E* 2005, *61*, o1530−o1531 and its supporting CIF file.

(6) For recent references on photochemical [4π + 4π] cycloadditions: (a) Kulyk, S.; Dougherty, W. G., Jr.; Kassel, W. S.; Fleming, S. A.; Sieburth, S. McN. *Org. Lett.* **2010**, *12*, 3296–3299. (b) Chen, P. L.; Carroll, P. J.; Sieburth, S. McN. *Org. Lett.* **2010**, *12*, 4510–4512.

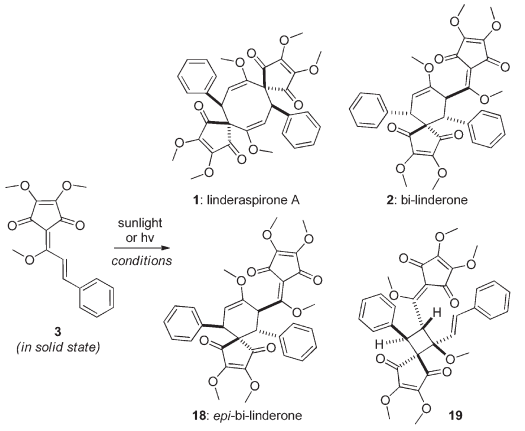
(7) (a) Aoyama, Y.; Konoike, T.; Kanda, A.; Naya, N.; Nakajima, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1695–1697. (b) Lee, H. H.; Tan, C. H. *J. Chem. Soc. C* **1967**, 1583–1585. (c) Bennett, G. J.; Lee, H. H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 633–638. (d) Bose, G.; Langer, P. *Synlett* **2005**, *6*, 1021–1023.

(8) (a) Li, X. C.; Ferreira, D.; Jacob, M. R.; Zhang, Q. F.; Kahn, S. I.; Elsohly, H. N.; Nagle, D. G.; Smillie, T. J.; Kahn, I. A.; Walker, L. A.; Clark, A, M. *J. Am. Chem. Soc.* **2004**, *126*, 6872–6873. (b) Babu, K. S.; Li, X. C.; Jacob, M. R.; Zhang, Q. F.; Kahn, S. I.; Ferreira, D.; Clark, A. M. *J. Med. Chem.* **2006**, *49*, 7877–7886.

Our synthetic strategies for **3** leveraged on key discoveries made earlier on ring expansion and opening reactivities of cyclobutenones and related squaric acid derivatives by Eguchi,[9a] Ohno,[9b] and Moore[9c] and their co-workers. The two short routes we developed both started with commercially available dimethyl squarate **11**[10] and took advantage of some simple operations capable of delivering consistently good-to-high isolated yields.

As summarized in Scheme 2, in route **I**, carbonyl alkylation on **11** with a 1,3-dithiane/BuLi protocol gave **12** which subsequently thermally rearranged to cyclopentendiones **13** and **14** under xylene refluxing conditions with a ratio of **13**:**14** = 4:1. **13** could be quickly converted into **14** by Raney Ni-

Scheme 3. Photochemical Dimerizations of **3**



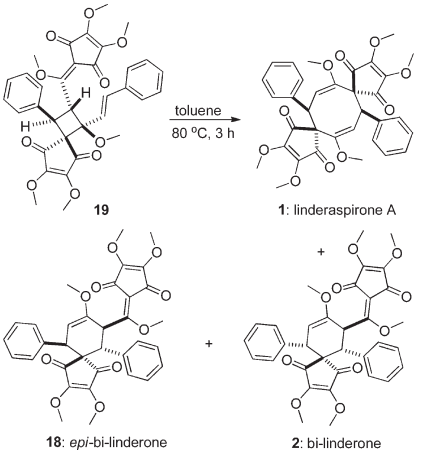
irridiation conditions	time [h]	temperature [°C]	light source [nm]	total yield [by ^{1}H NMR]	products [%] (**1**:**2**:**18**:**19**)
1	24	50	365	77%	35:18:24:0
2	24	40	365	82%	41:24:9:8
3	8	r.t.	sunlight	73%	9:3:3:58
4	48	r.t.	254	53%	5:3:3:42

mediated cleavage of its thiol chain. Upon treatment with NaH and cinnamyl chloride in DMSO, **14** underwent smooth acylation to yield linderone. It is noteworthy that the choice of DMSO, which is a potential acid chloride activator under this particular condition, proved to be critical for the success of this key coupling transformation, as other common solvents, such as DMF, THF, and toluene, completely failed.

In route **II**, **11** was alkylated with benzalacetone/LDA to give **15** in 72% yield, which then under the action of Pb(OAc)$_4$ rearranged to a mixture of **16** and **17** with a ratio of **16**:**17** = 4:1. This mixture was next directly subjected to the action of DBU promoting elimination of AcOH from **16** to form **17**. Upon exposure to NaOMe/MeOH conditions, **17** was transformed into linderone in a total isolated yield of 71% over this three-step sequence. It is significant that the conversions from **15** to linderone required neither chromatography purification nor air-sensitive manipulation, ensuring easy scalability of the process. Lastly, linderone was rapidly methylated with CH_2N_2 to give **3** in high yield. The overall yield in route **II** is 45%.

With methyl linderone **3** in hand, various photochemical conditions were investigated to determine the feasibility of effecting its dimerizations into **1** and/or **2**. Surprisingly, although solution-phase photolysis of **3** in such solvents as MeOH, toluene, benzene, MeCN, THF, and acetone did result in the formations of **1** and **2**, the yields were always disappointedly low (less than 20%). To our delight, direct photolysis of **3** in its solid state thin-film form resulted in much higher yields of dimerization products (Scheme 3). When **3** was irradiated primarily with light (365 nm wavelength) at 50 °C for 24 h, the total yields of dimerized products were 77%, with linderaspirone A and bi-linderone being produced in 35% and 18% yields, respectively. Their ^{1}H, ^{13}C NMR and HRMS characterization data fully match those reported by Liu and his co-workers. The third product, which we identified to be an epimer of bi-linderone (**18**), accounted for the

Scheme 4. Rearrangement of Cyclobutane **19**



remaining 24% yield. The fact that the photodimerizations were markedly more effective in the solid state and that **3** possesses a highly polarized π-electronic system collectively shows the importance of the substrate packing force within solid **3** in controlling reactivity and selectivity.[5]

When the above experiment was repeated at a lower temperature (40 °C), a fourth product, a cyclobutane-fused dimer structured as **19**, emerged in 8% yield, and the total yield was 82% (with a product distribution of 41:24:9:8). **19** became predominant (42% yield out of 53% total) when irradiated with a shorter wavelength light (254 nm) at room temperature for two days. Noteworthy is the observation that **1**, **2**, **18**, or **19** was not produced in all experiments attempted so far to thermally activate **3** (with or without Lewis acid reagents) toward dimerizations. Remarkably, it was subsequently found that sunlight was sufficient to bring about the photochemical dimerizations of **3** at room temperature, giving rise to a 73% total yield in just 8 h! The product distribution is now **1**:**2**:**18**:**19** = 9:3:3:58, again with **19** as the leading dimeric structure. Noting that **3** had been previously isolated from the

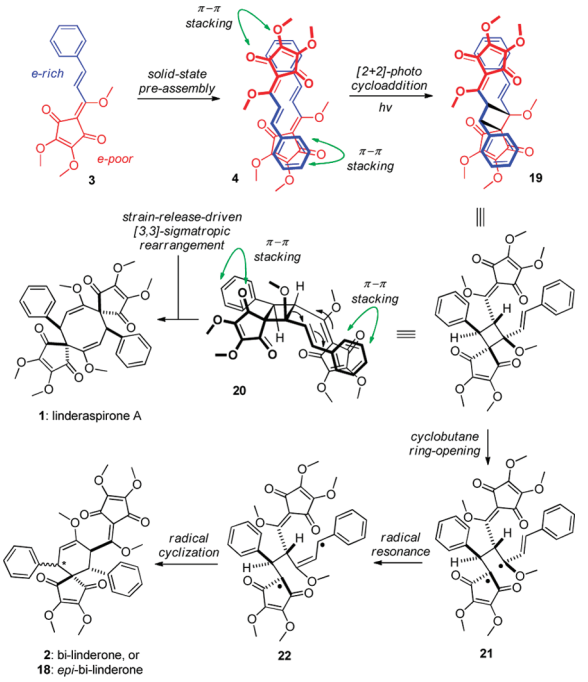
(9) (a) Yamamoto, Y.; Ohno, M.; Eguchi, S. *J. Am. Chem. Soc.* **1995**, *117*, 9653–9661. (b) Ohno, M.; Noda, M.; Yamamoto, Y.; Eguchi, S. *J. Org. Chem.* **1999**, *64*, 707–712. (c) Lee, K. H.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 735–738.

(10) For instructive synthetic utilities of squarates, see: Paquette, L. A.; Sturino, C. F.; Doussot, P. *J. Am. Chem. Soc.* **1996**, *118*, 9456–9457.

same plant source and that simple sunlight exposure represents an exceptionally mild reaction condition, this dimerization process may carry a highly biomimetic nature and may in fact mimic the actual biosynthesis pathways for these compounds. It is not yet clear whether **18** and **19** found here are also natural products that have eluded isolation and identification so far from *Lindera* plants species. This hopefully would invite further investigations in this area.[11]

The strong tendency of **3** for dimerization into the sterically highly congested and relatively unstable (*vide infra*) structure **19** caught our attention. With a hypothesis in mind that **19** might well represent an intermediate leading to **1** and **2**, we next studied its reactivity (Scheme 4). Indeed, by heating **19** in toluene at 80 °C we were able to convert it completely into **1**, **2**, and **18**. Under these conditions, an

Scheme 5. Revised Biosynthetic Pathways to **1** and **2**



original mixture with a compound distribution ratio of **1**:**2**:**18**:**19** = 30:26:5:39 was readily transformed into a thermodynamically equilibrated system of **1**, **2**, and **18** in the ratio of 64:29:7. A similar process could also be promoted by silica gel, albeit with lower efficiency. Thus, exposure of a mixture of **1**:**2**:**18**:**19** of an initial ratio of 35:14:7:44 with silica gel in the presence of acetone/hexane (1:4 volume ratio) at room temperature for 24 h resulted in the ending compound distribution reaching 50:20:10:20.

Overall these experimental findings posed a serious challenge to the original biosynthetic hypothesis outlined in Scheme 1. Central to the problem is that the formation of cyclobutane-fused skeleton **19** and its thermal liability for transforming into **1**, **2**, and **18** are both not accommodated by either pathway **I** or **II** therein. Although the possibility of direct photoexcitation of preorganized **3** leading to cycloadduct **1** cannot be conclusively ruled out, it appears to be more reasonable and economical to map these key stereochemical events in a unified mechanistic framework (Scheme 5). It is likely that, in the $\pi-\pi$ stacking-organized solid-state substrate preassembly **4** (shown here in a slightly different conformation as compared to that in Scheme 1 and matches exactly with the X-ray packing mode), photolysis first promoted a direct [2 + 2] cycloaddition to give **19**.[12] With ring strain release from the highly congested cyclobutane core as a critical driving force, **19** may then either participate in a [3,3]-Cope rearrangement (illustrated in transition state assembly **20**)[13] to yield linderaspirone A or, alternatively, engage in a cyclobutane ring opening at the weak bond of vicinal quanternary carbons to generate diradical species **21**.[14] **21** may then resonance to biradical **22** of more electronic stabilization and less steric crowding. Finally, radical recombinations within **22** close the cyclohexene rings to yield bi-linderone and *epi*-bi-linderone respectively, depending on the transient configuration at the benzylic radical carbon center right before the ring closure event.

In summary, we have achieved the first total syntheses of both linderaspirone A and bi-linderone, two recently discovered and biologically meaningful natural products from the traditionally acclaimed *Lindera* species medical plants. Our strategies take advantage of photochemical dimerization of methyl linderone under very mild conditions and help shed light on these natural products' biomimetic synthetic nature. The work also yields a refined and unified mechanistic framework that suggests interesting reaction cascades involved in the biosynthesis pathways. Given the efficiency and simplicity of the synthetic routes defined herein, it is anticipated that this study will pave the way for rapid construction of some structurally focused libraries of linderone-derived compounds and for mapping their more detailed structure–activity relationships. Efforts along this line are now underway in our laboratories and will be communicated in due course.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) This finding may also stimulate further investigation on the intriguing possibility of the formations of **1** and **2** during isolation process *via* accidental and prolonged sunlight exposure.

(12) For substrate packing-assisted photochemical [2 + 2] cycloadditions, see: Kole, G. K.; Tan, G. K.; Vittal, J. J. *Org. Lett.* **2010**, *12*, 128–131 and references cited therein.

(13) For an example of Cope rearrangement on a cyclobutane ring, see: Wender, P. A.; Correia, C. R. D. *J. Am. Chem. Soc.* **1987**, *109*, 2523–2525.

(14) An alternative possibility is that the bond cleaves heterolytically to give a cation stabilized by the OMe group and a cyclopentenedione enolate.