A unified strategy toward total syntheses of lindenane sesquiterpenoid \([4 + 2]\) dimers

Biao Du\(^1\), Zhengsong Huang\(^1\), Xiao Wang\(^1\), Ting Chen\(^1\), Guo Shen\(^1\), Shaomin Fu\(^1\) & Bo Liu\(^{1,2}\)

The dimeric lindenane sesquiterpenoids are mainly isolated from the plants of Chloranthaceae family. Structurally, they have a crowded molecular scaffold decorated with more than 11 stereogenic centers. Here we report divergent syntheses of eight dimeric lindenane sesquiterpenoids, shizukaols A, C, D, I, chlorajaponilide C, multistalide B, sarcandrolide J and sarglabolide I. In particular, we present a unified dimerization strategy utilizing a base-mediated thermal \([4 + 2]\) cycloaddition between a common furyl diene, generated in situ, and various types of dienophiles. Accordingly, all the three types of lindenane \([4 + 2]\) dimers with versatile biological activities are accessible, which would stimulate future probing of their pharmaceutical potential.
The dimeric lindenane sesquiterpenoids are a group of biologically active complex natural products mainly isolated from the plants of Chloranthaceae family. Structurally, these $[4+2]$ dimers possess congested frameworks of at least eight rings decorated by more than 11 stereogenic centers. Three types (types 1–3, Fig. 1a) can be categorized according to various substitution patterns on the ring B. Owing to their structural diversity and biological activities, numerous efforts have been made toward syntheses of the corresponding dimers or monomers. Following our long-standing interest in the syntheses of terpenoids, we reported the first syntheses of lindenane sesquiterpenoid $[4+2]$ dimers, sarcandrolide J and shizukaol D (type 2) in the guidance of our modified biosynthetic hypothesis (Fig. 1b). Recently, the Peng group reported their

---

**Fig. 1** Three types of natural lindenane $[4+2]$ dimers and related biosynthetic hypothesis. a The dimeric lindenane sesquiterpenoids can be categorized into three types, among which type 3 dimers are superior in numbers. b The skeleton of the dimeric lindenane sesquiterpenoids can be constructed through a $[4+2]$ cycloaddition between the common diene and different types of dienophiles.
achievement of total syntheses of shizukaols A and E, types 1 and 2 \([4+2]\) dimers, respectively, through the other modified biomimetic Diels–Alder reaction\(^7\).

However, no synthesis of type 3 \([4+2]\) dimers has yet been reported, despite their predominant numbers accounting for more than four-fifths across the whole lindenane family. Notably, direct functionalization of the \(\text{gem}\)-disubstituted alkene on ring B failed to convert type 1 dimers into types 2 or type 3, because the inherent stereochemical control from the robust 3/5/6/5 backbone favors the undesired \(\text{exo}/\text{endo}\) isomerization was observed, transforming bolivianine to \(\text{isobolivianine}\) via the acid-promoted \(\text{exo}/\text{endo}\) cyclic alkene isomerization. Thus, a unified synthetic strategy is in demand to provide all the three types of lindenane \([4+2]\) dimers and their synthetic analogs, by following the plausible \([4+2]\) biosynthetic pathways with a common furyl diene and various dienophiles.

Since the corresponding furyl diene is instable and not isolable, an acid-mediated diene-formation is pivotal to trigger the subsequent cycloaddition in our previous synthesis of type 2 \([4+2]\) dimers (Fig. 2a)\(^6\). However, the \(\text{gem}\)-disubstituted alkene substructure on ring B of type 2 \([4+2]\) dimers may be vulnerable under acidic conditions, as the acid-promoted \(\text{exo}/\text{endo}\) cyclic alkene isomerization was observed, transforming bolivianine to isobolivianine (Fig. 2b)\(^{23-25}\).

We conceive and realize a unified base-promoted strategy enabling divergent and biomimetic syntheses of all types of lindenane \([4+2]\) dimers (Fig. 2c). Among this strategy, a type 3 lindenane dimer, sarglabolide I, could serve as a common synthetic precursor toward other type 3 dimers through versatile acetylations. Of note, the common diene precursor used in this strategy is more synthetically viable than that previously used in acid-promoted cycloaddition (12 steps vs. 17 steps).

### Results

#### Synthesis of the diene precursor.

We initiated synthesis of the common diene precursor from a known Michael adduct \(\text{verbenone}\) (Fig. 3a)\(^{23-25}\). Oxidation to a 1,2-diketone and subsequent ring-opening of the cyclobutane in the presence of boron trifluoride afforded enone \(\text{20}\). Then, a formal oxidative \([3+2]\) cycloaddition in the presence of cerium ammonium nitrate (CAN), followed by treatment with Amberlyst-15, was employed between compound \(\text{20}\) and silyl enol ether \(\text{21a}\) to afford adduct \(\text{22}\)\(^{20,27}\). Other single oxidants such as 2,3-Dichloro-5,6-dicyano-\(\text{p}\)-benzoquinone (DDQ) and Cerium(IV) sulfate only got the complex mixture. Intriguingly, acetonitrile/benzene \((4:1)\) co-solvents serve as the optimal solvent system for the oxidative coupling step, whereas the individual solvent only delivered inferior results, probably due to compromised equilibrium between solubility of CAN and the solvent polarity. Moreover, application of \(\text{21b}\) and \(\text{21c}\) instead of \(\text{21a}\) in this reaction resulted in lower yields. Mechanistically, CAN may serve as the single electron oxidant to convert \(\text{21a}\) into the radical cation I, which could undergo a radical Michael addition to compound \(\text{20}\)\(^{26}\). The forming intermediate II would be further oxidized to the cationic intermediate III, which would be quenched by water to produce a mixture of aldehyde \(\text{IVA}\) and semi-acetal \(\text{1VB}\). Subsequently, Amberlyst-15 promoted dehydration and facilitated aromatization to give furan \(\text{22}\) (Fig. 3b).

A chemo-selective allylic oxidation of \(\text{22}\) yielded an enal smoothly using selenium dioxide, while the furyl methylene and methyl remained untouched. The hydrazone formation followed by the Rh-catalyzed intramolecular cyclopropanation generated compound \(\text{23}\) with proper stereochemistry. In contrast, our original Pd-catalyzed cyclopropanation was proved unsuccessful\(^{24}\). Treating \(\text{23}\) with \(\text{SeO}_2\) yielded \(\text{24}\) and...
an unidentified intermediate presumably as allylic selenide.\textsuperscript{29–31} Accordingly, sodium periodate was introduced into the reaction mixture, exclusively producing 24 in 83% yield\textsuperscript{32–34}, while no furan benzylic oxidation product was detected. Finally, acid-promoted acetylation of the tertiary alcohol, diastereoselective reduction of the ketone, and the MOM protection resulted in diene precursor 25. Mesylation and tosylation of the corresponding tertiary alcohol of 24 failed due to low reactivity.

Synthesis of the dienophile. We validated our proposed unified synthetic strategy by first aiming at total syntheses of type 3 [4 + 2] dimers. Thus, sarglabolide I (11) was chosen as the first target molecule and we began to synthesize the corresponding cerium reagent of 21a from verbenone\textsuperscript{6,23} (Fig. 4a), accessible from verbenone\textsuperscript{6,23} (Fig. 4b). The mechanism for formation of 31 was presumed to be a nucleophilic addition at the enone, serving as a thermodynamic intermediate. The desired adduct 31 could be purified by column chromatography and was transformed to sarglabolide I (11).

Fig. 3 Synthesis of the diene precursor 25. a Compound 25 can be synthesized from compound 19 in 11 steps. b The mechanism for formation of 22 was proposed. DCM = dichloromethane, DMF = N,N-dimethylformamide, Ac = acetyl, DIPEA = N,N-diisopropylethylamine, MOMCl = methoxymethyl chloride

Total syntheses of type 3 [4 + 2] lindenane dimers. With both 25 and 36 in hand, we next executed the diene formation/cycloaddition cascade. As shown in Fig. 5, diene precursor 25 was pre-mixed with dienophile 36 and pyridine in a sealed tube upon
Fig. 4 Synthesis of the dienophile 36 for type 3 [4 + 2] natural dimers. a Compound 36 can be synthesized from 26 in 8 steps. b Direct dihydroxylation of 26 fails to afford the desired diol 27. c Both Prévost trans-dihydroxylation and sequential halogen hydroxylation-basic hydrolysis fail to afford 27. PPTS = pyridinium p-toluenesulfonate.

Fig. 5 Total syntheses of type 3 [4 + 2] lindenane dimers. TPP = 5,10,15,20-tetraphenylporphyrin, DMAP = N,N-4-dimethylaminopyridine, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, MNBA = 2-methyl-6-nitrobenzoic anhydride.
the heat. The extrusion of acetate generated diene 37 in situ, which underwent an intermolecular [4 + 2] cycloaddition with 36 to form cycloadduct 39 as the major diastereomer. An optimal 71% yield of 39 was obtained at 200 °C, whereas a Cope rearrangement byproduct (38) was also observed, which is stable under this thermal condition. After simultaneous dehydration of MOM ether and acetone and reduction of the ethyl ester, compound 40 was obtained in 75% yield over two steps. A one-pot protocol afforded sarcandrolide I (11) in 87% yield through sequential photolytic oxidation of the furan and esterification of the resultant acid. Selective esterifications of 11 using acetic anhydride and tiglic acid afforded multistalide B (12) and shizukaol C (13), respectively. Shizukaol C exhibits potent inhibitory activities against various plant pathogenic fungi. In addition, acylation of sarcandrolide I (11) offered compound 43 utilizing acid 41, and the final silyl deprotection afforded shizukaol I (15). Moreover, the second O-acylation of 43 gave compound 44, which went through silyl deprotection to afford chlorajaponilide C (16). Notably, this natural product shows very potent inhibition of Plasmodium falciparum growth in vitro and in vivo.

**Total syntheses of [4 + 2] lindenene dimers of types 1 and 2.** We further applied the unified strategy in synthesis of type 1 and type 2 dimers (Fig. 6a). In the presence of pyridine, mixing compound 25 and previously reported dienophile 45, generated compound 46 as the major diastereomer (> 20:1 dr) under thermal conditions. In accordance with reported protocols, 46 can be transformed into sarcandridole J (6) and shizukaol D (7), two [4 + 2] lindenene dimers of type 2. Similarly, compound 48 was synthesized in a moderate yield (43%) by heating the mixture of 25 and chloranthalactone A (47), synthesized from verbenone as well, under thermal conditions. After deprotection of the MOM ether and oxidative elaboration of the furan ring, shizukaol A (4), a [4 + 2] lindenene dimer of type 1, was synthesized. In comparison with the 16% yield of 48 acquired from the acid-mediated dimerization between 47 and previously known 49 (Fig. 6b), this base-mediated dimerization protocol showcases its satisfactory synthetic efficacy and panoramic tolerance of versatile dienophiles.

**Discussion**

In summary, we developed an effective and unified strategy enabling feasible access to all the three types of lindenene sesquiterpenoid [4 + 2] dimers exemplified by syntheses of eight natural products. This natural family consists of more than one hundred dimeric compounds possessing versatile biological activities. Our divergent strategy would undoubtedly lay solid foundation for creation of the analog library and thus facilitate biological evaluations of these lindenene dimers.

**Methods**

**General.** All reactions were performed under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. DCM, DIPA, DIPEA, HMDS, MeCN, DMF, Et3N, and toluene were distilled from calcium hydride under argon; MeOH was distilled from dry maganese turnings and used without further purification. Flash chromatography was performed using silica gel (200–300 mesh). Thin layer chromatography (TLC) was used for monitoring reactions and visualized by a UV lamp (254 nm and 365 nm), I2, and developing the plates with p-anisaldehyde or phosphomolybdic acid.1H and 13C NMR were recorded on Bruker DRX-400 MHz NMR spectrometer or Bruker 800 MHz NMR spectrometer with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference (CDCl3: 1H NMR = 7.26, 13C NMR = 77.16; CD2OD: 1H NMR = 7.16, 13C NMR = 128.06; CD3COCD3: 1H NMR = 2.05, 13C NMR = 29.84; CD3OD: 1H NMR = 3.31 and 4.87, 13C NMR = 49.00; Pyridine-d5: 1H NMR = 8.74, 7.58 and 7.22). Abbreviations in 1H NMR data are illustrated as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dtd = doublet of triplet, td = triplet of doublet.

**Experimental data.** For detailed experimental procedures, see Supplementary Methods. For NMR spectra of the synthesized compounds in this article, see...
Supplementary Figs. 26–94. For the comparison of NMR spectra of the natural products and synthetic products, see Supplementary Tables 1–12.

Data availability
The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information files. Furthermore, all other data are available from the authors upon reasonable request.

Received: 7 March 2019 Accepted: 3 April 2019
Published online: 23 April 2019

References
1. Cao, C.-M., Peng, Y., Shi, Q.-W. & Xiao, P.-G. Chemical constituents and bioactivities of plants of Chloranthaceae. Chem. Biodivers. 5, 219–238 (2008).
2. Xu, Y.-J. Phytochemical and biological studies of chloranthus medicinal plants. Chem. Biodivers. 10, 1754–1773 (2013).
3. Wang, A.-R. et al. Secondary metabolites of plants from the genus Chloranthus: Chemistry and biological activities. Chem. Biodivers. 12, 1201–1235 (2015).
4. Liu, Y.-S. & Peng, X.-S. A concise construction of the chloranohlide heptacyclic core. Org. Lett. 13, 2940–2943 (2011).
5. Yang, L. et al. Synthetic studies toward lindenane-type sesquiterpenoid dimers. Synlett 25, 2471–2474 (2014).
6. Yuan, C., Du, B., Deng, H., Man, Y. & Liu, B. Total synthesis of sarcandralactone J and shizukaol D: Lindenane sesquiterpene 

ARTICLE
**Additional information**

**Supplementary Information** accompanies this paper at [https://doi.org/10.1038/s41467-019-09858-8](https://doi.org/10.1038/s41467-019-09858-8).

**Competing interests:** The authors declare no competing interests.

**Reprints and permission** information is available online at [http://npg.nature.com/reprintsandpermissions/](http://npg.nature.com/reprintsandpermissions/)

**Journal peer review information:** *Nature Communications* thanks Xiao-Shui Peng and the other anonymous reviewer for their contribution to the peer review of this work. Peer reviewer reports are available.

**Publisher’s note:** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

---

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit [http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/).

© The Author(s) 2019