Gram-Scale Enantioselective Synthesis of (+)-Lucidumone

Guanghao Huang, Cyrille Kouklovsky, Aurélien de la Torre

Gram-Scale Enantioselective Synthesis of (+)-Lucidumone

Guanghao Huang, Cyrille Kouklovsky and Aurélien de la Torre*

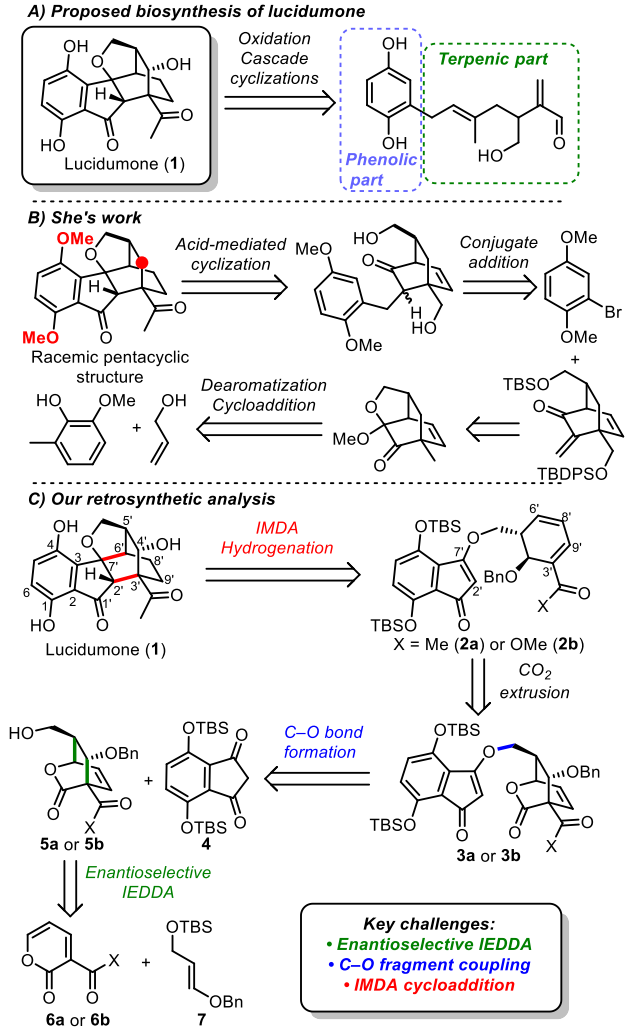
Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), Université Paris-Saclay, CNRS, 15 rue Georges Clémenceau, 91405 Orsay Cedex, France

ABSTRACT: The first enantioselective total synthesis of (+)-lucidumone is described through a 13-steps synthetic pathway (longest linear sequence). The key steps involve the formation of a bridged bicyclic lactone by an enantioselective inverse electron demand Diels-Alder cycloaddition, C–O bond formation to assemble two fragments and a one-pot retro-[4+2] / [4+2] cycloaddition cascade. The synthesis is scalable, and more than one gram of natural product was synthesized in one batch.

Meroterpenoids are an important class of natural products, displaying a partially terpenic skeleton, along with a part from different biogenetic origin, often polyketide. Due to their interesting structure and often powerful biological activities, meroterpenoids have attracted the interest of synthetic chemists for decades.[1,2] Lucidumone (**1**) is a meroterpenoid isolated in 2019 from the fruiting bodies of *Ganoderma lucidum*, a mushroom commonly used in traditional medicine in China and Japan.[3,4] This natural product presents an unprecedented 6/5/6/6/5 caged pentacyclic structure, with a hydroquinone, one secondary alcohol and two ketone motifs (Scheme 1A). Its structural complexity can be highlighted by the 6 contiguous stereogenic centers on the bicyclo[2.2.2]octane subunit. Moreover, preliminary studies indicate that lucidumone selectively inhibits COX-2 by directly binding with Tyr385 and Ser530 residues, providing it with an interesting therapeutic potential for the treatment of inflammation.[5] Interestingly, although lucidumone is produced as an enantiomeric mixture by *Ganoderma lucidum*, only one enantiomer displayed the selective COX-2 inhibitory activity. Nevertheless, this natural product was isolated in sub-mg scale (extraction yield of $1.5 \cdot 10^{-8}$, 0.4 mg of (+)-**1** isolated), hampering in-depth biological activity study.

The biosynthesis of lucidumone is believed to originate from a precursor bearing two isoprenic units and a hydroquinone motif (Scheme 1A), through a series of oxidations and cyclizations.[3] Recently, the team of She reported a synthetic study allowing the construction of a tetracyclic structure similar to lucidumone, without the secondary alcohol and where the hydroquinone was methylated (Scheme 1B).[6] This approach allowed a racemic synthesis of the skeleton in 18 steps, involving a Cu-mediated C–H oxidation, an intramolecular conjugate addition and an acid-mediated cyclization. However, the total synthesis of lucidumone was never achieved to date. Attracted by the structural complexity as well as the therapeutic potential of this natural product, we decided to engage in its total synthesis. In this manuscript, we describe an enantioselective gram-scale synthesis of (+)-lucidumone.

Scheme 1. Biosynthesis and retrosynthetic analysis of lucidumone

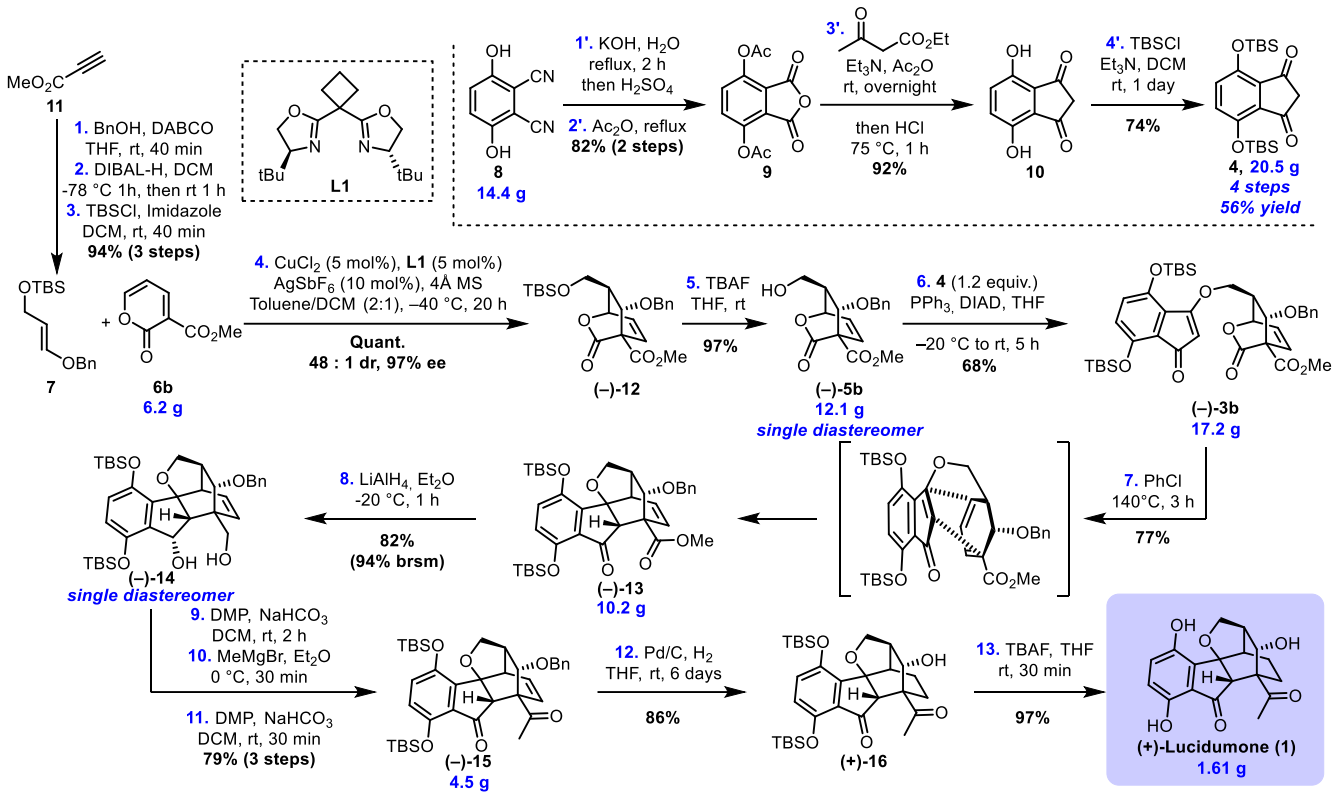


Our retrosynthetic analysis allowed us to identify $C^{2'}$–$C^{3'}$ and $C^{6'}$–$C^{7'}$ as key disconnections, which could be achieved through an intramolecular Diels-Alder (IMDA) cycloaddition, providing that $C^{8'}$–$C^{9'}$ is a double bond which can be reduced in a late stage (Scheme 1C).[7,8,9] This key disconnection could greatly simplify the structure into synthon **2**, bearing an indenone and a cyclohexadiene moieties for the key cycloaddition. Given the high instability of the cyclohexadiene, we would mask this function as a bicyclic lactone **3**, which could regenerate the desired cyclohexadiene by CO_2 extrusion. Fragment **3** would be obtained by C–O bond formation from two fragments of similar size **4** and **5**. To allow an enantioselective synthesis, fragment **5** should be obtained enantioselectively, for which we envisaged an inverse electron demand Diels-Alder (IEDDA) reaction involving a 2-pyrone **6** and an enol ether **7**.[10,11] The introduction of the methyl ketone moiety can be envisaged either in the early steps of the synthesis or in the endgame. This approach presents 3 key steps / challenges. (i) It is unclear whether the electron-demand in the late-stage IMDA reaction will be favorable or not, given the presence of an electron donating group at $C^{7'}$ (supposed to meet the electron-deficient site of the diene $C^{6'}$) and an electron-withdrawing group at $C^{2'}$ (supposed to meet the electron-enriched site $C^{3'}$). (ii) The C–O bond coupling between fragments **4** and **5** will also be an important challenge, as the formation of β-keto enol ethers typically requires the use of excess hydroxy partner, making it unsuitable for fragment coupling.[12] (iii) The challenge of enantioselective IEDDA reaction involving 2-pyrones and acyclic enol ethers for the synthesis of bridged bicyclic lactones was recently tackled by our group through the development of a new synthetic methodology.[13,14]

We then set out to achieve the synthesis of lucidumone. The synthesis of indandione fragment **4** was achieved starting from 3,6-dihydroxyphthalonitrile **8**. Hydrolysis of the dinitrile followed by dehydration and acetylation led to anhydride **9**, which was converted to indandione **10** in the presence of ethyl 3-oxobutanoate under basic conditions (Scheme 2). The phenolic moieties were protected as TBS ethers, affording **4** in 4 steps and 56% yield. Remarkably, this synthesis was easily scalable, as almost 20.5 g of fragment **4** was obtained starting from 14.4 g of starting material **8**.

Regarding the cyclohexadiene fragment, our first idea was to achieve the cycloaddition with a 2-pyrone derivative already bearing the methylketone functionality in C^3. However, all our attempts to prepare the 2-pyrone derivative **6a** proved unsuccessful (see Scheme S1-1, S1-2 and S1-3 in the supporting information). Therefore, we applied the IEDDA reaction developed by our group[13] with pyrone **6b**[15] and benzyl enol ether **7**. The synthesis of **(–)-12** could be efficiently performed in multigram scale. It should be noted that on such a scale, the minor diastereomer could be observed (dr = 48 : 1), although easily separated by column chromatography after the next step. Deprotection of the primary alcohol afforded **(–)-5b** in excellent yield, with 12 g easily obtained in one batch.

Scheme 2. Total synthesis of Lucidumone[a]



[a] DIAD = diisopropyl azodicarboxylate, DMP = Dess-Martin periodinane, TBAF = tetra-*n*-butylammonium fluoride

The C–O bond formation to couple **4** and (–)-**5b** proved to be particularly difficult. A selection of attempts using model substrates are represented in Table 1. All our attempts to use a primary alcohol as a nucleophile in the presence of bromo indenone **17** failed to give **22a** (entries 1-4). Converting the primary alcohol into a halide **19** to achieve O-alkylation of indandione **4** only led to small amounts of C-alkylation product and no **22b** was observed. (entry 5). Using tosylate **20** instead of halide **19** in order to favour O versus C alkylation resulted in decomposition of the indandione (entry 6). A combination of indandione **4** with primary alcohol **18** in the presence of Brønsted or Lewis acid was equally unfruitful (entries 7-8). Finally, Mitsunobu conditions smoothly led to O-alkylation, affording (±)-**23** in moderate yield (entry 9). After optimization using substrate **5b** (table S2), the fragments were efficiently coupled, affording (–)-**3** in acceptable yield on decagram scale.

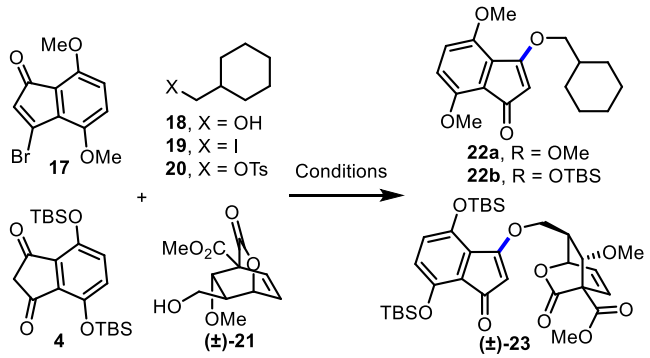


Table 1. Study of the C–O bond formation

Entry	Conditions	Result
1	**17**, **18**, CuI, 1,10-Phen, Cs_2CO_3, toluene, 100 °C	No reaction
2	**17**, **18**, CuCl, EtOAc, NaH, toluene, 120 °C	Decomposition
3	**17**, **18**, nBuLi, THF, 0 to 65 °C	Decomposition
4	**17**, **18**, K_2CO_3, DMF, 80 °C	Decomposition
5	**4**, **19**, K_2CO_3, DMF, 70 °C	C-alkylation
6	**4**, **20**, K_2CO_3, DMF, 0 °C	Decomposition
7	**4**, **18**, TsOH, toluene, reflux	No reaction
8	**4**, **18**, $TiCl_4$, toluene, rt to 60 °C	Decomposition
9	**4**, (±)-**21**, PPh_3, DEAD, THF, –20 °C to rt	(±)-**23** (51%)

From intermediate **(–)-3**, the key CO_2 extrusion *via* a retro-[4+2]-cycloaddition and subsequent [4+2] cycloaddition could be achieved in one-pot, by refluxing in chlorobenzene. In the endgame of the synthesis, we only needed to introduce the methyl ketone moiety, reduce the olefin and cleave the protecting groups. Despite all of our attempts, the formation of the methyl ketone could not be achieved without affecting the benzylic ketone. Thioesterification in prevision of a Fukuyama coupling[16] or amide formation (with the idea of performing chemoselective Tf_2O-mediated amide activation)[17] were unsuccessful. Nevertheless, we could introduce the methyl ketone by a sequence involving reduction of both the ester and the benzylic ketone using $LiAlH_4$, Dess-Martin oxidation, Grignard addition and reoxidation. This sequence, although requiring 4 steps, is high yielding (65% over 4 steps) and can be performed in only two days as the reaction time for each step is short (30 min to 2h). Moreover, the synthesis can be performed on multigram scale, and 4.5 g of intermediate **(–)-15** can be easily obtained. From **(–)-15** having all the carbon skeleton of lucidumone, reduction of the $C^{8'}$–$C^{9'}$ olefin and cleavage of the benzyl protecting group could be achieved in one-pot under hydrogenation conditions. It should be noted that although reduction of the alkene was completed in 2h, longer reaction times were required for the benzyl deprotection. Finally, deprotection of the phenol moieties allowed to complete the total synthesis of (+)-lucidumone **1**, with high optical purity. Remarkably, the synthesis was highly scalable, as 1.61 g of natural product was obtained in one batch.

To conclude, the first enantioselective total synthesis of lucidumone was achieved in 13 steps as the longest linear sequence and 25.8% overall yield from commercially available **11** (15.8% in 12 steps from **8**). The synthesis was enabled by an enantioselective IEDDA reaction developed by our group, a key C–O bond formation for fragment assembly and a one-pot retro-[4+2] / [4+2] cycloaddition cascade. The sequence could be performed on gram-scale, and over 1.6 g of natural product was synthesized in one batch, providing enough material for in-depth biological evaluation.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures, detailed optimizations and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* aurelien.de-la-torre@universite-paris-saclay.fr

Author Contributions

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

Funding Sources

China Scholarship Council (CSC) grant for Guanghao Huang. Université Paris Saclay and CNRS research credits for Cyrille Kouklovsky and Aurélien de la Torre.

ACKNOWLEDGMENT

G. H. thanks the China Scholarship Council for his PhD fellowship. All authors thank Université Paris-Saclay and CNRS for funding.

REFERENCES

(1) For reviews, see: (a) Toshiaki, S.; Ōmura, S. Total Synthesis of α-Pyrone Meroterpenoids, Novel Bioactive Microbial Metabolites. *Chem. Rev.* **2005**, *105*, 4559–4580. (b) Gomm, A.; Nelson, A. A radical approach to diverse meroterpenoids. *Nat. Chem.* **2020**, *12*, 109–111. (c) Murray, L. A. M.; McKinnie, S. M. K.; Moore, B. S.; George, J. H. Meroterpenoid natural products from *Streptomyces* bacteria – the evolution of chemoenzymatic syntheses. *Nat. Prod. Rep.* **2020**, *37*, 1334–1366. (d) George, J. H. Biomimetic Dearomatization Strategies in the Total Synthesis of Meroterpenoid Natural Products. *Acc. Chem. Res.* **2021**, *54*, 1843–1855.

(2) For recent examples, see: (a) Beck, J. C.; Lacker, C. R.; Chapman, L. M.; Reisman, S. E. A modular approach to prepare enantioenriched cyclobutanes: synthesis of (+)-rumphellaone A. *Chem. Sci.* **2019**, *10*, 2315–2319. (b) Brandstätter, M.; Freis, M.; Huwyler, N.; Carreira, E. M. Total Synthesis of (–)-Merchlorin A. *Angew. Chem. Int. Ed.* **2019**, *58*, 2490–2494. (c) Landry, M. L.; McKenna, G. M.; Burns, N. Z. Enantioselective Synthesis of Azamerone. *J. Am. Chem. Soc.* **2019**, *141*, 2867–2871. (d) Li, J.; Li, F.; King-Smith, E.; Renata, H. Merging chemoenzymatic and radical-based retrosynthetic logic for rapid and modular synthesis of oxidized meroterpenoids. *Nat. Chem.* **2020**, *12*, 173–179. (e) Zhang, Y.-A.; Milkovits, A.; Agarawal, V.; Taylor, C. A.; Snyder, S. A. Total Synthesis of the Meroterpenoid Manginoid A as Fueled by a Challenging Pinacol Coupling and Bicycle-forming Etherification. *Angew. Chem. Int. Ed.* **2021**, *60*, 11127–11132. (f) Baars, J.; Grimm, I.; Blunk, D.; Neudörfl, J.-M.; Schmalz, H.-G. Enantioselective Total Synthesis and Structural Revision of Dysiherbol A. *Angew. Chem. Int. Ed.* **2021**, *60*, 14915–14920. (g) Mashiko, T.; Shingai, Y.; Sakai, J.; Kamo, S.; Adachi, S.; Matsuzawa, A.; Sugita, K. Total Synthesis of Cochlearol B via Intramolecular [2+2] Photocycloaddition. *Angew. Chem. Int. Ed.* **2021**, *60*, 24484–24487. (h) Franov, L. J.; Hart, J. D.; Pullella, G. A.; Sumby, C. J.; George, J. H. Bioinspired Total Synthesis of Erectones A and B, and the Revised Structure of Hyperelodione D. *Angew. Chem. Int. Ed.* **2022**, *61*, e202200420. (i) Yang, F.; Porco, J. A. Unified, Asymmetric Total Synthesis of the Asnovolins and Related Spiromeroterpenoids: A Fragment Coupling Approach. *J. Am. Chem. Soc.* **2022**, *144*, 12970–12978.

(3) Yan, Y.-M.; Zhang, H.-X.; Liu, H.; Wang, Y.; Wu, J.-B.; Li, Y.-P.; Cheng, Y.-X. (+/–)-Lucidumone, a COX-2 Inhibitory Caged Fungal Meroterpenoid from *Ganoderma lucidum*. *Org. Lett.* **2019**, *21*, 8523–8527.

(4) Wachtel-Galor, S.; Yuen, J.; Buswell, J. A.; Benzie, I. F. F. *Ganoderma lucidum* (Lingzhi or Reishi): A Medicinal Mushroom. In *Herbal Medicine: Biomolecular and Clinical Aspects*, 2nd edition; Benzie, I. F. F., Wachtel-Taylor, S., Eds.; CRC Press/Taylor & Francis: Boca Raton, 2011; chapter 9.

(5) (a) Flower, R. J. The development of COX2 inhibitors. *Nat. Rev. Drug Discov.* **2003**, *2*, 179–191. (b) Dieppe, P. A.; Ebrahim, S.; Martin, R. M.; Jüni, P. Lessons from the withdrawal of rofecoxib. *BMJ* **2004**, *329*, 867–868.

(6) Ma, S.; Li, Z.; Yu, P.; Shi, H.; Yang, H.; Yi, J.; Zhang, Z.; Duan, X.; Xie, X.; She, X. Construction of the Skeleton of Lucidumone. *Org. Lett.* **2022**, *24*, 5541–5545.

(7) For general reviews on Diels-Alder reactions and their applications, see: (a) Funel, J.-A.; Abele, S. Industrial Applications of the Diels–Alder Reaction. *Angew. Chem. Int. Ed.* **2013**, *52*, 3822–3863. (b) Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H. The Asymmetric Hetero-Diels–Alder Reaction in the Syntheses of Biologically Relevant Compounds. *Angew. Chem. Int. Ed.* **2014**, *53*, 11146–11157. (c) Houk, K. N.; Liu, F.; Yang, Z.; Seeman, J. I. Evolution of the Diels–Alder Reaction Mechanism since the 1930s: Woodward, Houk with Woodward, and the Influence of Computational Chemistry on Understanding Cycloadditions. *Angew. Chem. Int. Ed.* **2021**, *60*, 12660–12681. (d) Briou, B.; Améduri, B.; Boutevin, B. Trends in the Diels-Alder reaction in polymer chemistry. *Chem. Soc. Rev.* **2021**, *50*, 11055–11097.

(8) For general reviews on IMDA reactions and their application in total synthesis, see: (a) Juhl, M.; Tanner, D. Recent applications of intramolecular Diels–Alder reactions to natural product synthesis. *Chem. Soc. Rev.* **2009**, *38*, 2983–2992. (b) Heravi, M. M.; Vavsari, V. F. Recent applications of intramolecular Diels–Alder reaction in total synthesis of natural products. *RSC Adv.* **2015**, *5*, 50890–50912. (c) Yang, B.; Gao, S. Recent advances in the application of Diels–Alder reactions involving o-quinodimethanes, aza-o-quinone methides and o-quinone methides in natural product total synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7926–7953. (d) Min, L.; Hu, Y.-J.; Fan, J.-H.; Zhang, W.; Li, C.-C. Synthetic applications of type II intramolecular cycloadditions. *Chem. Soc. Rev.* **2020**, *49*, 7015–7043. (e) Liu, J.; Xi, S.; Tang, Y. Biomimetic Diels–Alder Reactions in Natural Product Synthesis: A Personal Retrospect. *Synlett* **2022**, *33*, 836–850. (f) Sara, A. A.; Um-e-Farwa, U.-e.-F.; Saeed, A.; Kalesse, M. Recent Applications of the Diels–Alder Reaction in the Synthesis of Natural Products (2017–2020). *Synthesis* **2022**, *54*, 975–998.

(9) For selected examples of total synthesis involving IMDA as the key step, see: (a) Leung, J. C.; Bedermann, A. A.; Njardarson, J. T.; Spiegel, D. A.; Murphy, G. K.; Hama, N.; Twenter, B. M.; Dong, P.; Shirahata, T.; McDonald, I. M.; Inoue, M.; Taniguchi, N.; McMahon, T. C.; Schneider, C. M.; Tao, N.; Stoltz, B. M.; Wood, J. L. Total Synthesis of (±)-Phomoidride D. *Angew. Chem. Int. Ed.* **2018**, *57*, 1991–1994. (b) Yu, X.; Xiao, L.; Wang, Z.; Luo, T. Scalable Total Synthesis of (–)-Vinigrol. *J. Am. Chem. Soc.* **2019**, *141*, 3440–3443. (c) Nie, W.; Gong, J.; Chen, Z.; Liu, J.; Tian, D.; Song, H.; Liu, X.-Y.; Qin, Y. Enantioselective Total Synthesis of (–)-Arcutinine. *J. Am. Chem. Soc.* **2019**, *141*, 9712–9718. (d) Quintela-Varela, H.; Jamieson, C. S.; Shao, Q.; Houk, K. N.; Trauner, D. Bioinspired Synthesis of (–)-PF-1018. *Angew. Chem. Int. Ed.* **2020**, *59*, 5263–5267. (e) Haider, M.; Sennari, G.; Eggert, A.; Sarpong, R. Total Synthesis of the Cephalotaxus Norditerpenoids (±)-Cephanolides A–D. *J. Am. Chem. Soc.* **2021**, *143*, 2710–2715. (f) Yuan, P.; Gerlinger, C. K. G.; Herberger, J.; Gaich, T. Ten-Step Asymmetric Total Synthesis of (+)-Pepluanol A. *J. Am. Chem. Soc.* **2021**, *143*, 11934–11938.

(10) For general reviews on IEDDA reactions, see: (a) Jiang, X.; Wang, R. Recent Developments in Catalytic Asymmetric Inverse-Electron-Demand Diels–Alder Reaction. *Chem. Rev.* **2013**, *113*, 5515–5546. (b) Foster, R. A. A.; Willis, M. C. Tandem inverse-electron-demand hetero-/retro-Diels–Alder reactions for aromatic nitrogen heterocycle synthesis. *Chem. Soc. Rev.* **2013**, *42*, 63–76. (c) Knall, A. C.; Slugovc, C. Inverse electron demand Diels–Alder (iEDDA)-initiated conjugation: a (high) potential click chemistry scheme. *Chem. Soc. Rev.* **2013**, *42*, 5131–5142. (d) Oliveira, B. L.; Guo, Z.; Bernardes, G. J. L. Inverse electron demand Diels–Alder reactions in chemical biology. *Chem. Soc. Rev.* **2017**, *46*, 4895–4950. (e) Zhang, J.; Shukla, V.; Boger, D. L. Inverse Electron Demand Diels–Alder Reactions of Heterocyclic Azadienes, 1-Aza-1,3-Butadienes, Cyclopropenone Ketals, and Related Systems. A Retrospective. *J. Org. Chem.* **2019**, *84*, 9397–9445.

(11) For reviews on 2-pyrones in IEDDA reactions, see: (a) Cai, Q. The [4 + 2] Cycloaddition of 2-Pyrone in Total Synthesis. *Chin. J. Chem.* **2019**, *37*, 946–976. (b) Huang, G.; Kouklovsky, C.; de la Torre, A. Inverse-Electron-Demand Diels-Alder Reactions of 2-Pyrones: Bridged Lactones and Beyond. *Chem. Eur. J.* **2021**, *27*, 4760–4788. (c) Si, X.-G.; Zhang, Z.-M.; Cai, Q. Asymmetric Inverse-Electron-Demand Diels–Alder Reactions of 2-Pyrones by Lewis Acid Catalysis. *Synlett* **2021**, *32*, 947–954. (d) Xu, M.; Cai, Q. Progress of Catalytic Asymmetric Diels-Alder Reactions of 2-Pyrones. *Chin. J. Org. Chem.* **2022**, *42*, 698–713.

(12) For examples, see: (a) Böhm, A.; Bach, T. Radical Reactions Induced by Visible Light in Dichloromethane Solutions of Hünig's Base: Synthetic Applications and Mechanistic Observations. *Chem. Eur. J.* **2016**, *22*, 15921–15928. (b) Das, M. K.; Dinda, B. K.; Bisai, V. A unified approach to sesquiterpenes sharing trimethyl(*p*-tolyl) cyclopentanes: Formal total synthesis of (±)-laurokamurene B. *Tetrahedron Lett.* **2019**, *60*, 2039–2042. (c) Harned, A. M.; Stoltz, B. M. Development of a catalytic enantioselective synthesis of the guanacastepene and heptemerone tricyclic core. *Tetrahedron* **2019**, *75*, 3166–3177.

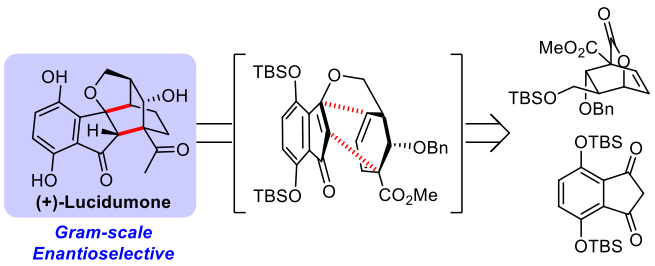
(13) Huang, G.; Guillot, R.; Kouklovsky, C.; Maryasin, B.; de la Torre, A. Diastereo- and Enantioselective Inverse-Electron-Demand Diels-Alder Cycloaddition between 2-Pyrones and Acyclic Enol Ethers. *Angew. Chem. Int. Ed.* **2022**, *Accepted*, e202208185. Doi: 10.1002/anie.202208185.

(14) For recent examples by other groups, see: (a) Liang, X.-W.; Zhao, Y.; Si, X.-G.; Xu, M.-M.; Tan, J.-H.; Zhang, Z.-M.; Zheng, C.-G.; Zheng, C.; Cai, Q. Enantioselective Synthesis of Arene cis-Dihydrodiols from 2-Pyrones. *Angew. Chem. Int. Ed.* **2019**, *58*, 14562–14567. (b) Si, X.-G.; Zhang, Z.-M.; Zheng, C.-G.; Li, Z.-T.; Cai, Q. Enantioselective Synthesis of cis-Decalin Derivatives by the Inverse-Electron-Demand Diels–Alder Reaction of 2-Pyrones. *Angew. Chem. Int. Ed.* **2020**, *59*, 18412–18417. (c) Xu, M.-M.; You, X.-Y.; Zhang, Y.-Z.; Lu, Y.; Tan, K.; Yang, L.; Cai, Q. Enantioselective Synthesis of Axially Chiral Biaryls by Diels–Alder/Retro-Diels–Alder Reaction of 2-Pyrones with Alkynes. *J. Am. Chem. Soc.* **2021**, *143*, 8993–9001. (d) Xu, M.-M.; Yang, L.; Tan, K.; Chen, X.; Lu, Q.-T.; Houk, K. N.; Cai, Q. An enantioselective ambimodal cross-Diels–Alder reaction and applications in synthesis. *Nat. Catal.* **2021**, *4*, 892–900. (e) Lu, Y.; Xu, M.-M.; Zhang, Z.-M.; Zhang, J.; Cai, Q. Catalytic Asymmetric Inverse-Electron-Demand Diels–Alder Reactions of 2-Pyrones with Indenes: Total Syntheses of Cephanolides A and B. *Angew. Chem. Int. Ed.* **2021**, *60*, 26610–26615. (f) Zhang, F.; Ren, B.-T.; Zhou, Y.; Liu, Y.; Feng, X. Enantioselective construction of cis-hydroindole scaffolds via an asymmetric inverse-electron-demand Diels–Alder reaction: application to the formal total synthesis of (+)-minovincine. *Chem. Sci.* **2022**, *13*, 5562–5567.

(15) The 2-pyrone substrate was prepared according to a known procedure: Corey, E. J.; Watt, D. S. Total synthesis of (±)-α- and (±)-β-copaenes and ylangenes. *J. Am. Chem. Soc.* **1973**, *95*, 2303–2311.

(16) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. A novel ketone synthesis by a palladium-catalyzed reaction of thiol esters and organozinc reagents. *Tetrahedron Lett.* **1998**, *39*, 3189–3192.

(17) (a) Bechara, W. S.; Pelletier, G.; Charette, A. B. Chemoselective synthesis of ketones and ketimines by addition of organometallic reagents to secondary amides. *Nat. Chem.* **2012**, *4*, 228–234. (b) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide activation: an emerging tool for chemoselective synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899–7925.



Gram-scale
Enantioselective