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Synthesis of a Biomimetic Tetracyclic Precursor of Aspochalasins and Formal Synthesis of Trichoderone A

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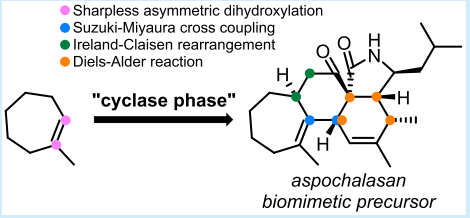
ABSTRACT: Aspochalasins are leucine-derived cytochalasins. Their complexity is associated with a high degree of biosynthetic oxidation, herein inspiring a two-phase strategy in total synthesis. We thus describe the synthesis of a putative biomimetic tetracyclic intermediate. The constructive steps are an intramolecular Diels−Alder reaction to install the isoindolone core of cytochalasins, whose branched precursor was obtained from a stereoselective Ireland−Claisen rearrangement performed from a highly unsaturated substrate. This also constitutes a formal synthesis of trichoderone A.



The bioinspired two-phase synthesis paradigm first relies on the construction of a minimally oxidized natural product skeleton, often referred to as the "cyclase phase".[1] This intermediate is then engaged in a second stage involving functional decorations, also called the "oxidation phase" when it comes to selective oxidative functionalization, which aims to produce the final natural products. Highly complex natural products have been achieved by this strategy,[1−9] with Baran's recent two-phase synthesis of Taxol standing as a feat in such approaches.[10] While these examples most often concern terpenoids, biosynthetic oxidative functionalizations are ubiquitous. Cytochalasins obey the same logic,[11,12] with a core skeleton being first constructed by a hybrid polyketide synthase−nonribosomal peptide synthetase (PKS-NRPS)[13,14] and then cyclized before additional oxidative functionalizations.[15,16] A two-phase bioinspired strategy to synthesize complex cytochalasins is thus conceivable if we can efficiently access a precursor with a low functionalization pattern.

Owing to their reputed biological activities,[17−19] cytochalasins have often been targeted in total synthesis.[20] In particular, aspochalasins (e.g., **1**)[21] are 11-membered macrocyclic compounds incorporating a typical fused isoindolone (Figure 1). During the biosynthesis, a transannular cyclization of the macrocycle can result in tetracyclic 7/6/6/5 fused skeletons, while additional oxygenated decorations can be installed.[22] This is exemplified by aspergillin PZ (**2**),[23] recently synthesized by Trauner though a biomimetic cyclization strategy.[20o]

Interestingly, oxygen-bridged trichoderone A (**3**)[24] and oxidatively cleaved trichodermone (**4**)[25] could be derived from a common biosynthetic intermediate (**5**) after late-stage oxidative functionalizations (Figure 1), with **5** possibly arising from biosynthetic precursor **6** after transannular cyclization. This retrobiosynthetic hypothesis differs from the previously suggested deoxygenative route that makes aspochalasin D (**1**) a precursor of **3** and **4**.[20q,25] Thus, a two-phase biomimetic

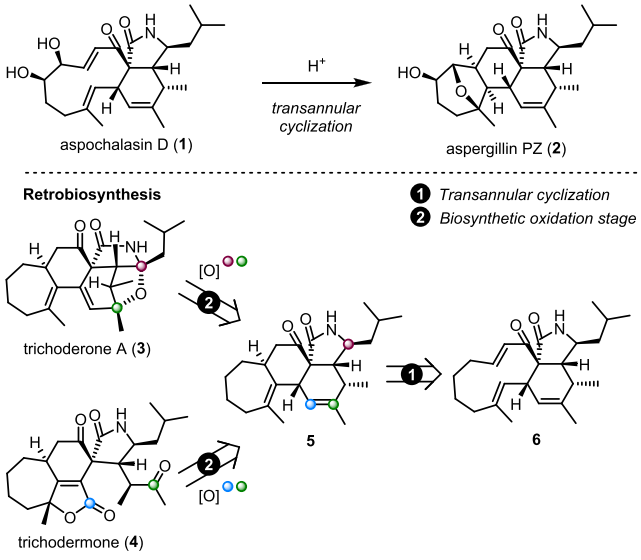


Figure 1. Structure of aspochalasin-related natural products **1**−**4** and retrobiosynthetic analysis of **3** and **4** highlighting precursor **5** for two-phase biomimetic synthesis.

strategy toward complex aspochalasins and bioinspired analogues, involving extensive oxidations, could be envisaged if precursor **5** can be synthesized, as we report herein. After the recent impressive work of Puno, Deng and co-workers on the divergent synthesis of aspochalasins,[20q] our work also

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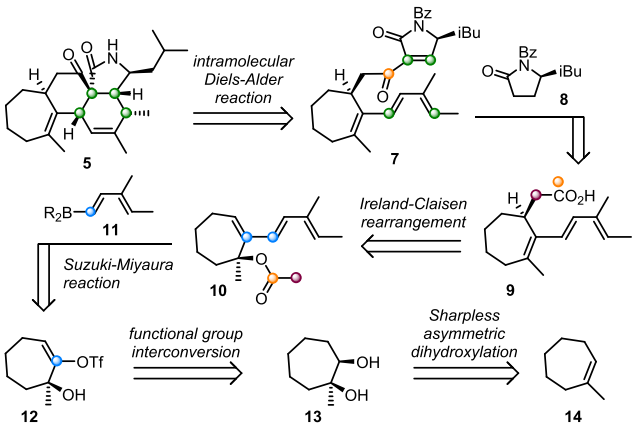
constitutes a formal synthesis of trichoderone A (**3**). Above all, it provides the preliminary "cyclase" phase for future prospects on the second "oxidase" phase toward functionalized derivatives.

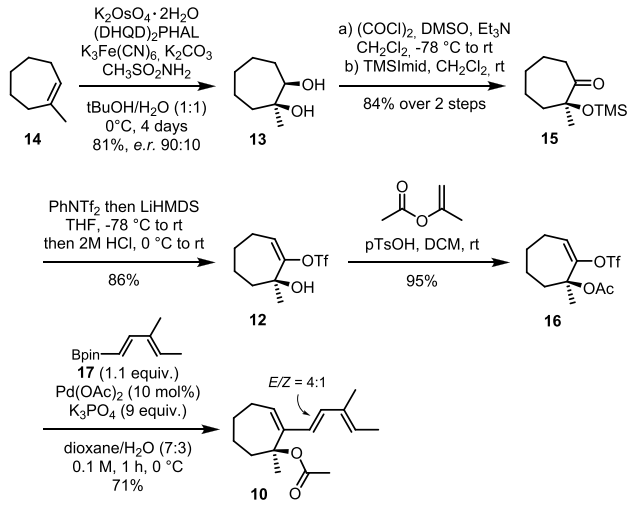
Retrosynthetically, compound **5** could be obtained by an intramolecular Diels–Alder reaction (IMDA), expectedly favoring the *endo* cycloadduct. The dienophile in IMDA substrate **7** can be installed in a two-stage manner involving the α-acylation of lactam **8** with carboxylic acid **9** after activation as a mixed anhydride, followed by a selenide-mediated oxidation of the α-position. Lactam **8** is accessible on a decagram scale from L-leucine.[26] Compound **9** could be stereoselectively delivered by an Ireland–Claisen rearrangement[27] of allylic acetate **10**, enabling the transfer of stereochemistry from the chiral acetate.[28] In fact, this allylic acetate is also a sensitive triene, and as far as we know, the Ireland–Claisen rearrangement has never been applied to such highly unsaturated substrate. This reaction would however allow an asymmetric access to acid **9**, foreseeing an enantioselective synthesis of acetate precursor **10**. The triene moiety could be installed on enol triflate **12** by a Suzuki–Miyaura sp^2–sp^2 cross-coupling[29] with dienyl boronate **11**. Finally, intermediate **12** could be synthesized from enantioenriched *syn*-diol **13**, which was envisioned to be obtained from 1-methylcycloheptene **14** through a Sharpless asymmetric dihydroxylation.[30] This reaction was expected to provide a reliable entry to secure an asymmetric synthesis of compound **5** (Scheme 1).

Scheme 1. Retrosynthetic Strategy toward Intermediate 5



1-Methylcycloheptene **14** was available from a two-step literature sequence starting from commercial cycloheptanone (see Scheme S1).[31] It was submitted to a Sharpless asymmetric dihydroxylation to access diol **13** (Scheme 2). Since this reaction had not been described on alkene **14**, we relied on ligand guidelines to choose the most appropriate conditions[32] and on the reported dihydroxylation of 1-methylcyclohexene or 1-phenylcycloheptene using the ligand $(DHQD)_2PHAL$ [dihydroquinidine-1,4-phthalazinediyl diether].[33] In the presence of commercially available AD-mix-β (involving 1 mol % of $(DHQD)_2PHAL$ and 0.4 mol % of K_2OsO_4) combined with 1 equiv of $CH_3SO_2NH_2$ in a 1:1 mixture of *t*BuOH/H_2O, diol **13** was promisingly obtained in 65% yield and an er of 84:16 at room temperature (after 3 days),[34] which were respectively improved to 69% and 90:10 at 0 °C (after 7 days as the reaction was slowed down at this temperature). The anthraquinone ligand $(DHQD)_2AQN$ [dihydroquinidine anthraquinone-1,4-diyl diether], also proposed for trisubstituted olefins, was evaluated giving a better NMR yield (88%) but a lower er (86:14). Finally, increasing the loadings of K_2OsO_4 (0.7 mol %) and of $(DHQD)_2PHAL$ (1.75 mol %) resulted in good yields (81%) and er (90:10) after 4 days. The reaction was easily reproducible and scalable (5 g batches).

Scheme 2. Synthesis of Ireland–Claisen Substrate 10



Diol **13** was then engaged in functional group manipulation toward enol triflate **16** (Scheme 2). The oxidation of the secondary alcohol was achieved by a Swern protocol, directly followed by the protection of the tertiary alcohol[35] in the presence of 1-(trimethylsilyl)imidazole (TMSImid), affording **15** in 84% yield over two steps (11 g scale). The enol triflation of **15** was performed by deprotonation with LiHMDS in the presence of $PhNTf_2$. The tertiary alcohol was regenerated upon acidic treatment (HCl) at the end of the reaction, giving unprotected enol triflate **12** in 86% (5 g scale). Significant difficulties were observed with the acetylation of the tertiary alcohol, in view of the Ireland–Claisen rearrangement. The reaction was ineffective in most classical conditions, but finally succeeded in the presence of isopropenyl acetate under acid catalysis (*p*TsOH), to give acetate **16** in 95% (1.4 g scale). Unfortunately, these conditions were hardly scalable, as the yields dropped gradually from 95% to 52% when scaling up from 1.4 to 10 g (this problem was solved by running the reaction in multiple flasks).

The final step to Ireland–Claisen substrate **10** involved a Suzuki–Miyaura cross coupling between triflate **16** and dienylboronate **17** (easily available from tiglic aldehyde through a boron–Wittig strategy recently reported by Morken;[36] see Scheme S2). The cross coupling performed well in the presence of $Pd(OAc)_2$ (10 mol %) and K_3PO_4 in a 7:3 dioxane/water mixture at 0 °C without ligand, providing triene **10** in 71% yield after 1 h. In fact, the absence of ligand allowed us to perform the reaction on a 1.6 g scale, providing **10** as a 4:1 mixture of *E* and *Z* isomers, respectively, supposedly formed through triene isomerization under the reaction conditions (the undesired *Z* isomer was eliminated during the next step, possibly due to lower reactivity attributed to a steric clash during the Ireland–Claisen rearrangement). Although electron-rich ligands like PCy_3, $P(2\text{-furyl})_3$, or bis(diphenylphosphino)ferrocene (dppf) allowed the reaction to proceed in good yields (75–80%) and selectivities, these

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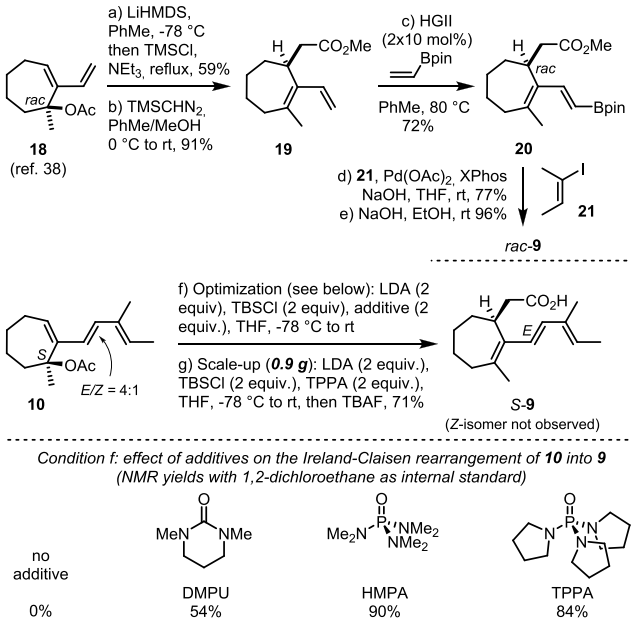
Org. Lett. 2021, 23, 5755–5760

conditions were hardly reproducible when scaling up the reaction.

Only a few examples of Ireland−Claisen rearrangements have been performed on branched allylic systems bearing conjugated substituents at position 2, like acetate **10**. In 2006, Diver and co-workers were able to perform tandem enyne metatheses giving products with the branched 2-vinylallylic acetate topology like ours, which were engaged in the Ireland−Claisen rearrangement.[37] We first attempted this rearrangement on simplified substrate **18** previously obtained in a racemic form from enyne metathesis[38] (Scheme 3, see also Scheme S3). Rearranged product **19** was successfully obtained in 59% yield after deprotonation by LiHMDS in toluene, followed by the addition of TMSCl/Et_3N and increasing the temperature to reflux. Diene **19** could also be engaged in additional transformations toward triene **9** (racemic form), through a sequence of cross metathesis with pinacol vinylboronate and a Suzuki−Miyaura cross-coupling with iodoolefin **21** (available from the corresponding bromoolefin by applying Klapars and Buchwald procedure[39]).

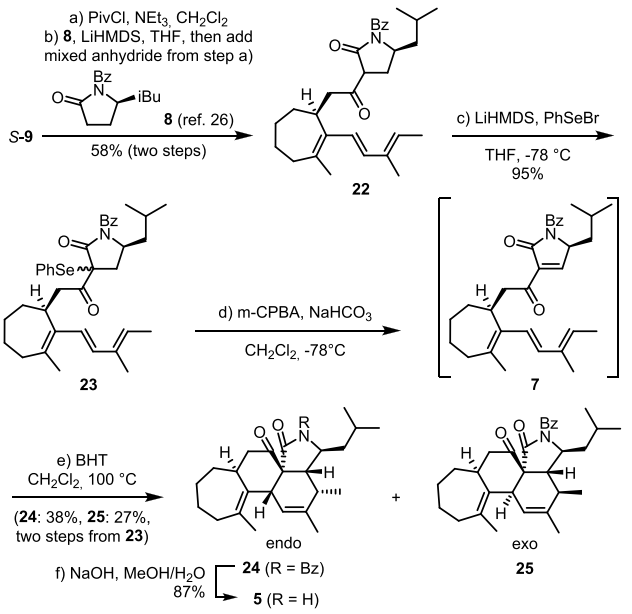
Scheme 3. Ireland−Claisen Rearrangement of Branched Allylic Acetates 10 and 18



These preliminary results validated our rearrangement strategy, but the conditions were not directly transposable to triene substrate **10**. A screening of new conditions in the presence of various bases (LiHMDS, LDA, or LiTMP) and silyl reagents (TMSCl or TBSCl) in THF showed that in the absence of any additive the couple LiTMP/TBSCl was the best to afford partial conversion of starting material **10**, giving 32% of **9**. In fact, the use of an additive was crucial for the success of the reaction in the presence of LDA. HMPA and the less toxic TPPA (Scheme 3) were the most effective, furnishing **9** in 90 and 84% yields, respectively. The rearrangement performed well at room temperature in THF. Although the carboxylic acid could be directly obtained on small-scale reactions (0.2 mmol), the same conditions on a larger scale (3.6 mmol) afforded a mixture of the TBS ester and the acid, which needed an additional treatment with TBAF, leading to acid *S*-**9** in 71%.

Carboxylic acid *S*-**9** was next coupled to γ-lactam **8** (Scheme 4), which is available in five steps from *N*-Boc-L-leucine (see Scheme S4).[26] To do so, *S*-**9** was activated as a mixed pivaloyl anhydride and added to deprotonated, benzoyl-protected γ-lactam **8**, giving α-acyl-γ-lactam **22** in 58% (two steps). These conditions proved superior to the more classical activation of *S*-**9** as an acyl imidazole by treatment with carbonyldiimidazole.[20] To install the dienophile, intermediate **22** was converted into selenide **23** in 95% yield by deprotonation in the presence of LiHMDS and reaction with PhSeBr. Oxidation and spontaneous elimination in the presence of *m*-CPBA and $NaHCO_3$ in CH_2Cl_2 at −78 °C released the IMDA substrate **7**, which was too unstable to be isolated. After reductive and basic treatment of this reaction mixture to eliminate any trace of oxidant and acid, a solution of **7** in CH_2Cl_2 was heated at 100 °C in a sealed tube, in the presence of BHT as a radical scavenger, to furnish *endo* cycloadduct **24** in 38% yield and *exo* product **25** in 27% yield after purification (see Scheme S5 for details on structure analysis). It was not possible to improve this reaction, especially by any catalytic process involving a Lewis acid or the Schreiner's catalyst as previously reported for periconiasin derivatives.[19] Finally, the lactam of cycloadduct **24** was deprotected under hydrolytic conditions to achieve the synthesis of biomimetic tetracyclic precursor **5**.

Scheme 4. Final Steps toward Tetracyclic Precursor 5



An epoxidation of **24** could selectively be achieved on the cycloheptene ring, furnishing a 2:1 stereoisomeric mixture of separable epoxides **26** (48%) and **27** (22%). The major isomer **26** (α-epoxide) could be crystallized for X-ray analysis (Scheme 5). Above all, based on Puno's and Deng's recent work,[20q] this new synthetic strategy provides a formal synthesis of trichoderone A (**3**), which can be formed from **5** upon air oxidation, through allylic peroxidation and oxidative cyclization.

In conclusion, we were able to perform the synthesis of a key synthetic precursor (**5**) of tetracyclic aspochalasan natural products and derivatives, the structure of which could be confirmed by X-ray analysis of an epoxide product (**26**).[40] Compound **5** constitutes a good entry to perform the "oxidase"

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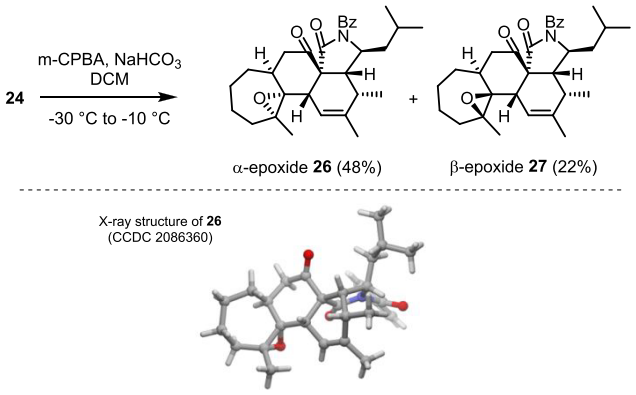
Scheme 5. Epoxidation of 24 Furnishing Suitable Crystals of 26 for X-ray Analysis



phase in the bioinspired synthesis of natural products such as trichoderone A (**3**) and trichodermone (**4**). In particular, this work constitutes a formal synthesis of **3**.[20q] Additional oxidations can be envisaged on precursor **5**, either in a total synthesis perspective or to synthesize a bioinspired diversity of aspochalasins for biological studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01922.

Additional schemes, synthetic procedures and copies of NMR spectra (PDF)

Accession Codes

CCDC 2086360 contains 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 emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

#O.G. and B.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C−H Oxidations. *Nature* **2009**, *459*, 824−828. (b) Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. Total Synthesis of Eudesmane Terpenes: Cyclase Phase. *Tetrahedron* **2010**, *66*, 4738−4744. (c) Ishihara, Y.; Baran, P. S. Two-Phase Terpene Total Synthesis: Historical Perspective and Application to the Taxol® Problem. *Synlett* **2010**, *2010*, 1733−1745.

(2) Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. Two-Phase Synthesis of (−)-Taxuyunnanine D. *J. Am. Chem. Soc.* **2014**, *136*, 4909−4912.

(3) Jin, Y.; Yeh, C.-H.; Kuttruff, C. A.; Jørgensen, L.; Dünstl, G.; Felding, J.; Natarajan, S. R.; Baran, P. S. C−H. Oxidation of Ingenanes Enables Potent and Selective Protein Kinase C Isoform Activation. *Angew. Chem., Int. Ed.* **2015**, *54*, 14044−14048.

(4) Yuan, C.; Jin, Y.; Wilde, N. C.; Baran, P. S. Short, Enantioselective Total Synthesis of Highly Oxidized Taxanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 8280−8284.

(5) Chu, H.; Smith, J. M.; Felding, J.; Baran, P. S. Scalable Synthesis of (−)-Thapsigargin. *ACS Cent. Sci.* **2017**, *3*, 47−51.

(6) Kuroda, Y.; Nicacio, K. J.; da Silva, I. A., Jr.; Leger, P. R.; Chang, S.; Gubiani, J. R.; Deflon, V. M.; Nagashima, N.; Rode, A.; Blackford, K.; Ferreira, A. G.; Sette, L. D.; Williams, D. E.; Andersen, R. J.; Jancar, S.; Berlinck, R. G. S.; Sarpong, R. Isolation, Synthesis and Bioactivity Studies of Phomactin Terpenoids. *Nat. Chem.* **2018**, *10*, 938−945.

(7) Hung, K.; Condakes, M. L.; Novaes, L. F. T.; Harwood, S. J.; Morikawa, T.; Yang, Z.; Maimone, T. J. Development of a Terpene Feedstock-Based Oxidative Synthetic Approach to the *Illicium* Sesquiterpenes. *J. Am. Chem. Soc.* **2019**, *141*, 3083−3099.

(8) Wein, L. A.; Wurst, K.; Angyal, P.; Weisheit, L.; Magauer, T. Synthesis of (−)-Mitrephorone A via a Bioinspired Late Stage C−H Oxidation of (−)-Mitrephorone B. *J. Am. Chem. Soc.* **2019**, *141*, 19589−19593.

(9) Berger, M.; Knittl-Frank, C.; Bauer, S.; Winter, G.; Maulide, N. Application of Relay C−H Oxidation Logic to Polyhydroxylated Oleanane Triterpenoids. *Chem.* **2020**, *6*, 1183−1189.

(10) (a) Kanda, Y.; Ishihara, Y.; Wilde, N. C.; Baran, P. S. Two-Phase Total Synthesis of Taxanes: Tactics and Strategies. *J. Org. Chem.* **2020**, *85*, 10293−10320. (b) Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Murthy Appala, V. R.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. S. Two-Phase Synthesis of Taxol. *J. Am. Chem. Soc.* **2020**, *142*, 10526−10533.

(11) Scherlach, K.; Boettger, D.; Remme, N.; Hertweck, C. The Chemistry and Biology of Cytochalasans. *Nat. Prod. Rep.* **2010**, *27*, 869−886.

(12) Skellam, E. The Biosynthesis of Cytochalasans. *Nat. Prod. Rep.* **2017**, *34*, 1252−1263.

(13) Fujii, R.; Minami, A.; Gomi, K.; Oikawa, H. Biosynthetic Assembly of Cytochalasin Backbone. *Tetrahedron Lett.* **2013**, *54*, 2999−3002.

(14) (a) Song, Z.; Bakeer, W.; Marshall, J. W.; Yakasai, A. A.; Khalid, R. M.; Collemare, J.; Skellam, E.; Tharreau, D.; Lebrun, M.-H.; Lazarus, C. M.; Bailey, A. M.; Simpson, T. J.; Cox, R. J. Heterologous

Expression of the Avirulence Gene ACE1 from the Fungal Rice Pathogen *Magnaporthe Oryzae*. *Chem. Sci.* **2015**, *6*, 4837−4845. (b) Zhang, H.; Hantke, V.; Bruhnke, P.; Skellam, E. J.; Cox, R. J. Chemical and Genetic Studies on the Formation of Pyrrolones During the Biosynthesis of Cytochalasans. *Chem. - Eur. J.* **2021**, *27*, 3106−3113.

(15) Ishiuchi, K.; Nakazawa, T.; Yagishita, F.; Mino, T.; Noguchi, H.; Hotta, K.; Watanabe, K. Combinatorial Generation of Complexity by Redox Enzymes in the Chaetoglobosin A Biosynthesis. *J. Am. Chem. Soc.* **2013**, *135*, 7371−7377.

(16) Hu, Y.; Dietrich, D.; Xu, W.; Patel, A.; Thuss, J. A. J.; Wang, J.; Yin, W.-B.; Qiao, K.; Houk, K. N.; Vederas, J. C.; Tang, Y. A Carbonate-Forming Baeyer-Villiger Monooxygenase. *Nat. Chem. Biol.* **2014**, *10*, 552−554.

(17) Cooper, J. A. Effects of Cytochalasin and Phalloidin on Actin. *J. Cell Biol.* **1987**, *105*, 1473−1478.

(18) Carruthers, A.; Helgerson, A. L. Inhibitions of Sugar Transport Produced by Ligands Binding at Opposite Sides of the Membrane. Evidence for Simultaneous Occupation of the Carrier by Maltose and Cytochalasin B. *Biochemistry* **1991**, *30*, 3907−3915.

(19) Zaghouani, M.; Gayraud, O.; Jactel, V.; Prévost, S.; Dezaire, A.; Sabbah, M.; Escargueil, A.; Lai, T.-L.; Le Clainche, C.; Rocques, N.; Romero, S.; Gautreau, A.; Blanchard, F.; Frison, G.; Nay, B. Multifaceted Study on a Cytochalasin Scaffold: Lessons on Reactivity, Multidentate Catalysis, and Anticancer Properties. *Chem. - Eur. J.* **2018**, *24*, 16686−16691.

(20) (a) Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. Total Synthesis of Cytochalasin B. *J. Am. Chem. Soc.* **1978**, *100*, 7775−7777. (b) Stork, G.; Nakamura, E. A Simplified Total Synthesis of Cytochalasins via an Intramolecular Diels-Alder Reaction. *J. Am. Chem. Soc.* **1983**, *105*, 5510−5512. (c) Thomas, E. J.; Whitehead, J. W. F. Cytochalasan Synthesis: Total Synthesis of Cytochalasin H. *J. Chem. Soc., Chem. Commun.* **1986**, *9*, 727−728. (d) Dyke, H.; Sauter, R.; Steel, P.; Thomas, E. J. Cytochalasan Synthesis: Total Synthesis of Cytochalasin G. *J. Chem. Soc., Chem. Commun.* **1986**, *18*, 1447−1449. (e) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. A. Sulfur-Mediated Total Synthesis of Zygosporin E. *J. Am. Chem. Soc.* **1988**, *110*, 4822−4823. (f) Trost, B. M.; Ohmori, M.; Boyd, S. A.; Okawara, H.; Brickner, S. J. Palladium-Catalyzed Synthesis of Macrocycles. A Total Synthesis of (−)-Aspochalasin B. *J. Am. Chem. Soc.* **1989**, *111*, 8281−8284. (g) Merifield, E.; Thomas, E. J. Cytochalasan Synthesis: Total Synthesis of Cytochalasin D. *J. Chem. Soc., Chem. Commun.* **1990**, *6*, 464−466. (h) Merifield, E.; Thomas, E. J. Total Synthesis of Cytochalasin D: Total Synthesis and Full Structural Assignment of Cytochalasin O. *J. Chem. Soc., Perkin Trans. 1* **1999**, *22*, 3269−3283. (i) Haidle, A. M.; Myers, A. G. An Enantioselective, Modular, and General Route to the Cytochalasins: Synthesis of L-696,474 and Cytochalasin B. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 12048−12053. (j) Canham, S. M.; Overman, L. E.; Tanis, P. S. Identification of an Unexpected 2-Oxonia[3,3]Sigmatropic Rearrangement/Aldol Pathway in the Formation of Oxacyclic Rings. Total Synthesis of (+)-Aspergillin PZ. *Tetrahedron* **2011**, *67*, 9837−9843. (k) Tian, C.; Lei, X.; Wang, Y.; Dong, Z.; Liu, G.; Tang, Y. Total Syntheses of Periconiasins A−E. *Angew. Chem., Int. Ed.* **2016**, *55* (24), 6992−6996. (l) Zaghouani, M.; Kunz, C.; Guédon, L.; Blanchard, F.; Nay, B. First Total Synthesis, Structure Revision, and Natural History of the Smallest Cytochalasin: (+)-Periconiasin G. *Chem. - Eur. J.* **2016**, *22*, 15257−15260. (m) Bao, R.; Tian, C.; Zhang, H.; Wang, Z.; Dong, Z.; Li, Y.; Gao, M.; Zhang, H.; Liu, G.; Tang, Y. Total Syntheses of Asperchalasines A−E. *Angew. Chem., Int. Ed.* **2018**, *57*, 14216−14220. (n) Long, X.; Ding, Y.; Deng, J. Total Synthesis of Asperchalasines A, D, E, and H. *Angew. Chem., Int. Ed.* **2018**, *57*, 14221−14224. (o) Reyes, J. R.; Winter, N.; Spessert, L.; Trauner, D. Biomimetic Synthesis of (+)-Aspergillin PZ. *Angew. Chem., Int. Ed.* **2018**, *57*, 15587−15591. (p) Zeng, Z.; Chen, C.; Zhang, Y. Enantioselective Total Synthesis of Periconiasin A. *Org. Chem. Front.* **2018**, *5*, 838−840. (q) Wu, H.; Ding, Y.; Hu, K.; Long, X.; Qu, C.; Puno, P.-T.; Deng, J. Bioinspired Network Analysis Enabled Divergent Syntheses and Structure Revision of Pentacyclic Cytochalasans. *Angew. Chem., Int. Ed.* **2021**, *60*, 15963−15971.

(21) Keller-Schierlein, W.; Kupfer, E. Stoffwechselprodukte von Mikroorganismen. 186. Mitteilung. Über die Aspochalasine A, B, C und D. *Helv. Chim. Acta* **1979**, *62*, 1501−1524.

(22) Wei, G.; Tan, D.; Chen, C.; Tong, Q.; Li, X.-N.; Huang, J.; Liu, J.; Xue, Y.; Wang, J.; Luo, Z.; Zhu, H.; Zhang, Y. Flavichalasines A−M, Cytochalasan Alkaloids from *Aspergillus Flavipes*. *Sci. Rep.* **2017**, *7*, 42434.

(23) Zhang, Y.; Wang, T.; Pei, Y.; Hua, H.; Feng, B. Aspergillin PZ, a Novel Isoindole-Alkaloid from *Aspergillus Awamori*. *J. Antibiot.* **2002**, *55*, 693−695.

(24) Ding, G.; Wang, H.; Li, L.; Chen, A. J.; Chen, L.; Chen, H.; Zhang, H.; Liu, X.; Zou, Z. Trichoderones A and B: Two Pentacyclic Cytochalasans from the Plant Endophytic Fungus *Trichoderma Gamsii*. *Eur. J. Org. Chem.* **2012**, *2012*, 2516−2519.

(25) Ding, G.; Wang, H.; Li, L.; Song, B.; Chen, H.; Zhang, H.; Liu, X.; Zou, Z. Trichodermone, a Spiro-Cytochalasan with a Tetracyclic Nucleus (7/5/6/5) Skeleton from the Plant Endophytic Fungus Trichoderma Gamsii. *J. Nat. Prod.* **2014**, *77*, 164−167.

(26) Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T. A.; Eissenstat, M. A. Facile Stereoselective Synthesis of γ-Substituted γ-Amino Acids from the Corresponding α-Amino Acids. *Tetrahedron* **1997**, *53*, 12867−12874.

(27) Ireland, R. E.; Mueller, R. H. Claisen Rearrangement of Allyl Esters. *J. Am. Chem. Soc.* **1972**, *94*, 5897−5898.

(28) (a) Ziegler, F. E. The Thermal, Aliphatic Claisen Rearrangement. *Chem. Rev.* **1988**, *88*, 1423−1452. (b) Enders, D.; Knopp, M.; Schiffers, R. Asymmetric [3.3]-Sigmatropic Rearrangements in Organic Synthesis. *Tetrahedron: Asymmetry* **1996**, *7*, 1847−1882. (c) Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. New Aspects of the Ireland and Related Claisen Rearrangements. *Tetrahedron* **2002**, *58*, 2905−2928.

(29) Miyaura, N.; Suzuki, K. Y. A. A New Stereospecific Cross-Coupling by the Palladium-Catalyzed Reaction of 1-Alkenylboranes with 1-Alkenyl or 1-Alkynyl Halides. *Tetrahedron Lett.* **1979**, *20*, 3437−3440.

(30) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. Asymmetric Dihydroxylation via Ligand-Accelerated Catalysis. *J. Am. Chem. Soc.* **1988**, *110*, 1968−1970. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement. *J. Org. Chem.* **1992**, *57*, 2768−2771.

(31) Barbier, M.; Hügel, M. F. Synthèses dans la série de l'acide céto-9 décène-2 trans oique ("substance royale"). *Bull. Soc. Chim. Fr.* **1961**, *28*, 951−954.

(32) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 275−307.

(33) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483−2547.

(34) Enantiomeric ratios (er) were measured by chiral HPLC after benzoylation of the secondary alcohol (see the Supporting Information for details).

(35) Any attempt to shorten this route, especially by introducing the acetate group before the enol triflation, proved ineffective.

(36) (a) Coombs, J. R.; Zhang, L.; Morken, J. P. Synthesis of Vinyl Boronates from Aldehydes by a Practical Boron−Wittig Reaction. *Org. Lett.* **2015**, *17*, 1708−1711. (b) Liu, X.; Deaton, T. M.; Haeffner, F.; Morken, J. P. A Boron Alkylidene−Alkene Cycloaddition Reaction: Application to the Synthesis of Aphanamal. *Angew. Chem., Int. Ed.* **2017**, *56*, 11485−11489.

(37) Clark, D. A.; Kulkarni, A. A.; Kalbarczyk, K.; Schertzer, B.; Diver, S. T. Tandem Enyne Metathesis and Claisen Rearrangement: A Versatile Approach to Conjugated Dienes of Variable Substitution Patterns. *J. Am. Chem. Soc.* **2006**, *128*, 15632−15636.

https://doi.org/10.1021/acs.orglett.1c01922
Org. Lett. 2021, 23, 5755−5760

(38) Laroche, B.; Detraz, M.; Blond, A.; Dubost, L.; Mailliet, P.; Nay, B. Ring-Closing Enyne Metathesis of Terminal Alkynes with Propargylic Hindrance. *J. Org. Chem.* **2015**, *80*, 5359−5363.
(39) Klapars, A.; Buchwald, S. L. Copper-Catalyzed Halogen Exchange in Aryl Halides: An Aromatic Finkelstein Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 14844−14845.
(40) Gayraud, O.; Laroche, B.; Casaretto, N.; Nay, B. Synthesis of a Biomimetic Tetracyclic Precursor of Aspochalasins Al-lowing a Formal Synthesis of Trichoderone A. *ChemRXiv* **2021**, DOI: 10.26434/chemrxiv.14748840.

https://doi.org/10.1021/acs.orglett.1c01922
Org. Lett. 2021, 23, 5755−5760