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

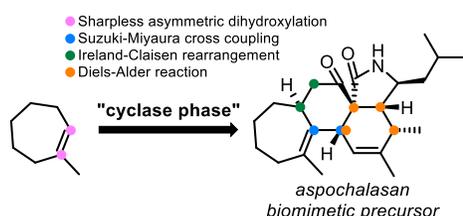
Oscar Gayraud,^{a,#} Benjamin Laroche,^{b,#} Nicolas Casaretto,^c and Bastien Nay^{*,a,b}

^a Laboratoire de Synthèse Organique, Ecole Polytechnique, CNRS, ENSTA, Institut Polytechnique de Paris, Palaiseau 91128, France

^b Unité Molécules de Communication et Adaptation des Microorganismes, Muséum National d'Histoire Naturelle, CNRS, Paris 75005, France

^c Laboratoire de Chimie Moléculaire, Ecole Polytechnique, CNRS, Institut Polytechnique de Paris, Palaiseau 91128, France

Supporting Information Placeholder



ABSTRACT: Aspochalasins are leucine-derived cytochalasins. Their complexity is associated to 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 bio-inspired 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 "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–non-ribosomal peptide synthetase (PKS-NRPS),^{13,14} and then cyclized before additional oxidative functionalizations.^{15,16} A two-phase bio-inspired 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}

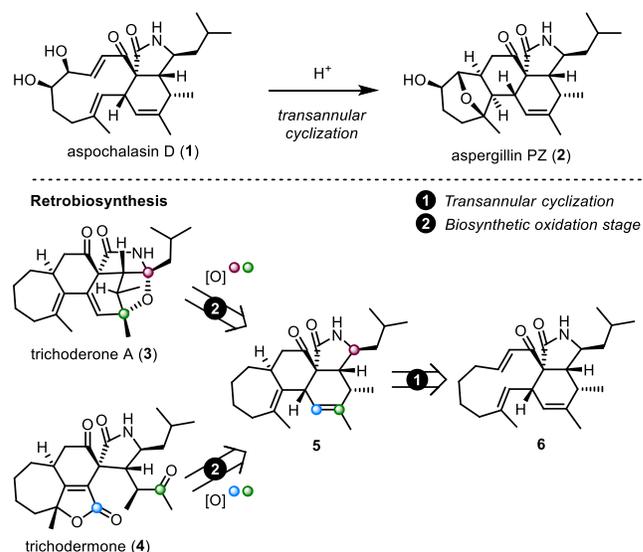
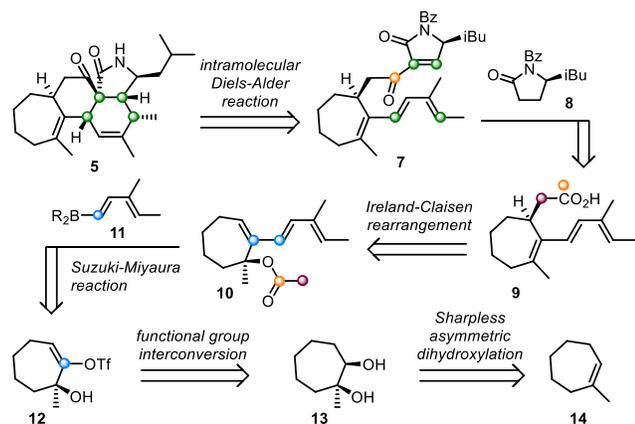


Figure 1. Structure of aspochalasin-related natural products **1-4** and retrosynthetic analysis of **3** and **4** highlighting precursor **5** for two-phase biomimetic synthesis.

Interestingly, oxygen-bridged trichoderone A (**3**)²⁴ and oxidatively cleaved trichoderone (**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 retrosynthetic 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 strategy towards complex aspochalasins and bio-inspired 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 constitutes a formal synthesis of trichoderone A (**3**). Above all, it provides the preliminary "cyclase" phase for future prospects on the second "oxidase" phase towards functionalized derivatives.

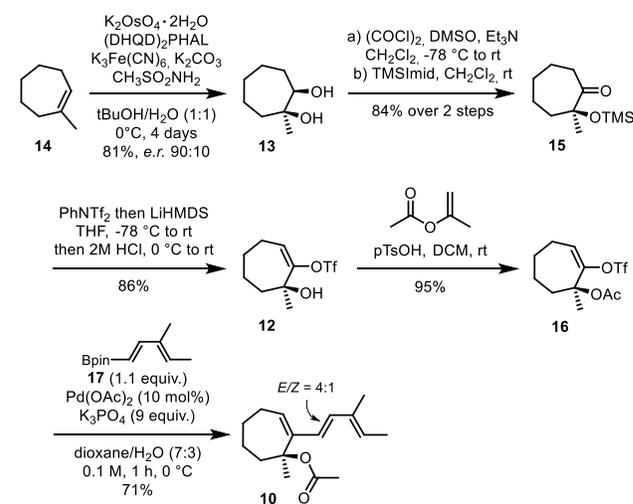
Retrosynthetically, compound **5** could be obtained by an intramolecular Diels-Alder reaction (IMDA), expectedly favoring the *endo* cycloadduct. The dienophile in IMDA substrate **7** can be installed in a two-stage manner involving the α -acylation of lactam **8** with carboxylic acid **9** after 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 rearrangement²⁷ 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-coupling²⁹ with dienyl boronate **11**. Finally, intermediate **12** could be synthesized from enantiomer-enriched *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. Retrosynthetic strategy towards intermediate **5**.



1-Methylcycloheptene **14** was available from a two-step literature sequence starting from commercial cycloheptanone (see Scheme S1 in the Supporting information).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 K₂O₈) combined with 1 equivalent of CH₃SO₂NH₂ in a 1:1 mixture of *t*BuOH/H₂O, diol **13** was promisingly obtained in 65% yield and an *e.r.* 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 *e.r.* (86:14). Finally, increasing the loadings of K₂O₈ (0.7 mol%) and of (DHQD)₂PHAL (1.75 mol%) resulted in good yields (81%) and *e.r.* (90:10) after 4 days. The reaction was easily reproducible and scalable (5-gram batches).

Scheme 2. Synthesis of Ireland-Claisen substrate **10**.



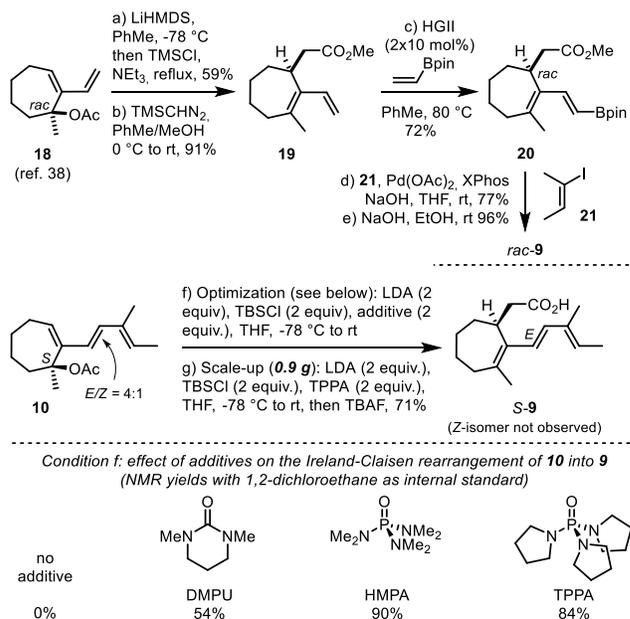
Diol **13** was then engaged in functional group manipulation towards enol triflate **16** (Scheme 2). The oxidation of the secondary alcohol was achieved by a Swern protocol, directly followed by the protection of the tertiary alcohol³⁵ in presence of 1-(trimethylsilyl)imidazole (TMSImid), affording **15** in 84% yield over two steps (11-gram scale). The enol triflation of **15** was performed by deprotonation with LiHMDS in presence of PhNTf₂. The tertiary alcohol was regenerated upon acidic treatment (HCl) at the end of the reaction, giving unprotected enol triflate **12** in 86% (5-gram 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 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, the yields dropping gradually from

95% to 52% when scaling-up from 1.4 g 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 in the Supporting information). The cross coupling performed well in the presence of Pd(OAc)₂ (10 mol%) and K₃PO₄ in a 7:3 dioxane/water mixture at 0 °C without ligand, providing triene **10** in 71% yield after one hour. In fact, the absence of ligand allowed 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 PCy₃, P(2-furyl)₃ or bis(diphenylphosphino)ferrocene (dppf) allowed the reaction to proceed in good yields (75-80%) and selectivities, these 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 metathesis³⁸ (Scheme 3, see also Scheme S3 in the Supporting information). Rearranged product **19** was successfully obtained in 59% yield after deprotonation by LiHMDS in toluene, followed by the addition of TMSCl/Et₃N and increasing the temperature to reflux. Diene **19** could also be engaged in additional transformations towards 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 procedure³⁹).

Scheme 3. The Ireland-Claisen rearrangement of branched allylic acetates **10** and **18**.

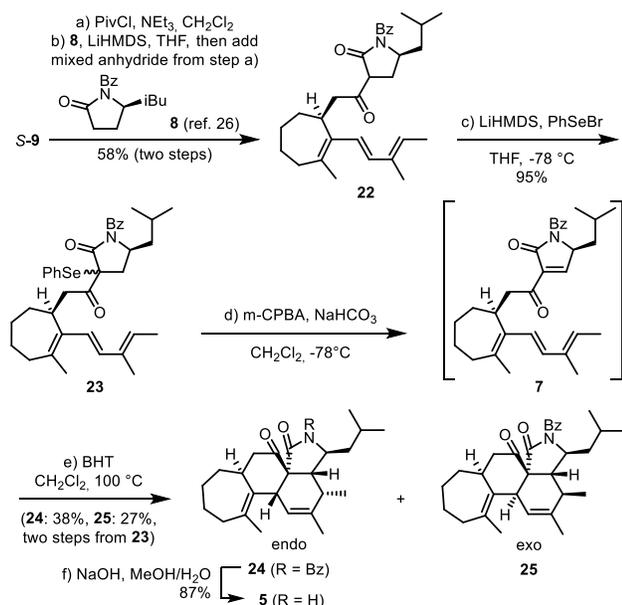


These preliminary results validated our rearrangement strategy, but the conditions were not directly transposable to triene substrate **10**. A screening of new conditions in presence of various bases (LiHMDS, LDA or LiTMP) and silyl reagents (TMSCl or TBSCl) in THF showed that in the absence of any 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 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 5 steps from *N*-Boc-L-leucine (see Scheme S4 in the Supporting information).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 presence of LiHMDS and reaction with PhSeBr. Oxidation and spontaneous elimination in presence of *m*-CPBA and NaHCO₃ in CH₂Cl₂ 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 CH₂Cl₂ was heated at 100 °C in a sealed tube, in 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 in the Supporting information 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

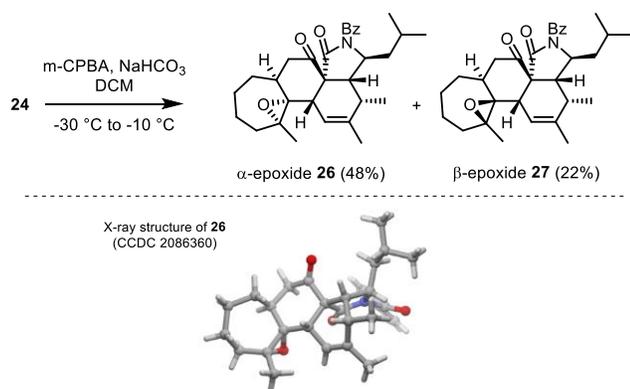
catalyst as previously reported for periconiasin derivatives.¹⁹ Finally, the lactam of cycloadduct **24** was deprotected under hydrolytic conditions to achieve the synthesis of biomimetic tetracyclic precursor **5**.

Scheme 4. Final steps towards 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%). 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.

Scheme 5. Epoxidation of **24** furnishing suitable crystals of **26** for X-ray analysis.



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" phase in the bio-inspired 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 bio-inspired diversity of aspochalasins for biological studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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

Crystal analysis of **26** (CIF)

Accession Codes

CCDC 2086360 (**26**) 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.

AUTHOR INFORMATION

Authors contributed equally to this work.

Corresponding Author

* Bastien Nay – E-mail: bastien.nay@polytechnique.edu

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