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Total Synthesis of Asperchalasine A

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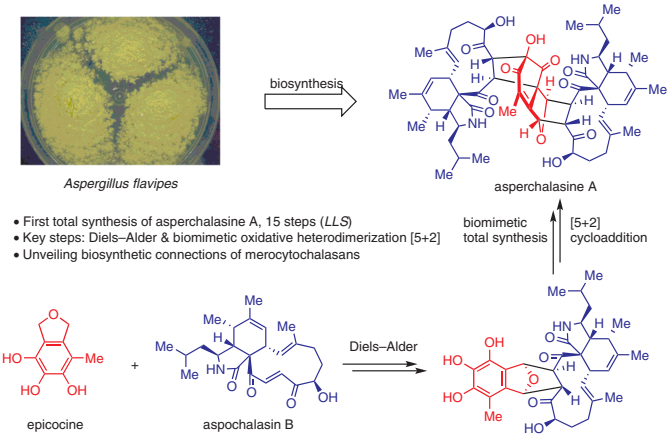

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Abstract Here we briefly reviewed recent synthetic progress toward cytochalasan trimer, asperchalasine A by Tang, Trauner and our group. This process features a highly stereoselective intermolecular Diels–Alder reaction and a HWE or RCM macrocyclization to establish the key monomer aspochalasin B. A late-stage biomimetic oxidative dearomatization of triphenol and subsequent [5+2] cycloaddition cascade furnished asperchalasine A. We anticipate that this key reaction could also be used for the synthesis of other merocytochalasans, and provide some insight into the biosynthetic connections of merocytochalasans.

Key words biomimetic synthesis, [5+2] cycloaddition, natural products, total synthesis, dimerization

1 Introduction

Cytochalasans are a large family of fungal metabolites (>400 members) possessing a highly substituted perhydroisoindolone scaffold first isolated in 1966.[1] They have a broad range of biological activities by targeting the actin cytoskeleton. In the past few decades, a series of total syntheses and biosynthesis of these fascinating natural products have been accomplished due to their intriguing structures and bioactivities, including Stork, Thomas, Vedejs, Trost, Weinreb, Tamm, Myers, Overman, and recently Tang.[2]

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Recently, the isolation of asperchalasine A by Zhang and co-workers in 2015 has triggered a burst of isolation of merocytochalasans, culminated in the discovery of asperchalasine A, epicochalasine A, aspergilasine A, asperflavipine A, amichalasine A and their congeners.[3] The first sandwich-shaped cytochalasan trimer, asperchalasine A[3a] (**1**) was isolated from the fermentation broth of *Aspergillus flaipes* (Figure 1). Biologically, asperchalasine A (**10**) specifi-

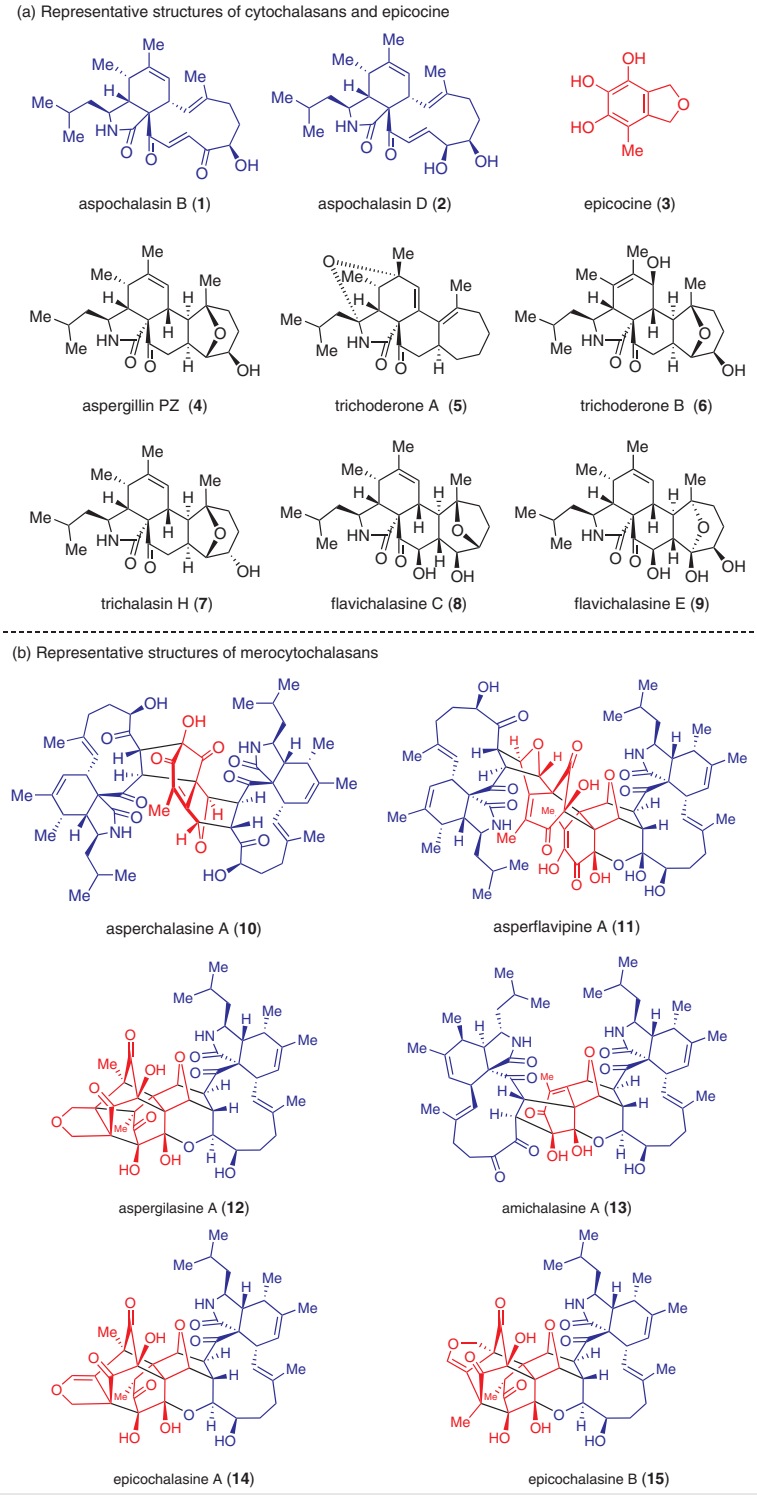


Figure 1 Representive structures of cytochalasans, epicocine, and merocytochalasans

cally induces significant G1-phase cell cycle arrest in cancer cell lines (RKO, HCT116, NB4, and HL60), making it a novel cytoskeletal inhibitor against cancer cells. Biosynthetically, asperchalasine A might be generated by incorporation of epicoccine (**3**, red part) with two molecules of aspochalasin B (**1**, blue part).

At the onset of isolation of merocytochalasans in 2015 the development of a scalable, practical, and collective synthetic route to merocytochalasans seemed an insurmountably difficult challenge. Inspired by their biosynthetic connections of merocytochalasans, and pioneering biomimetic synthesis of epicolactone by Trauner,[4] we were led to embark on a careful retrosynthetic analysis of asperhalasine A.

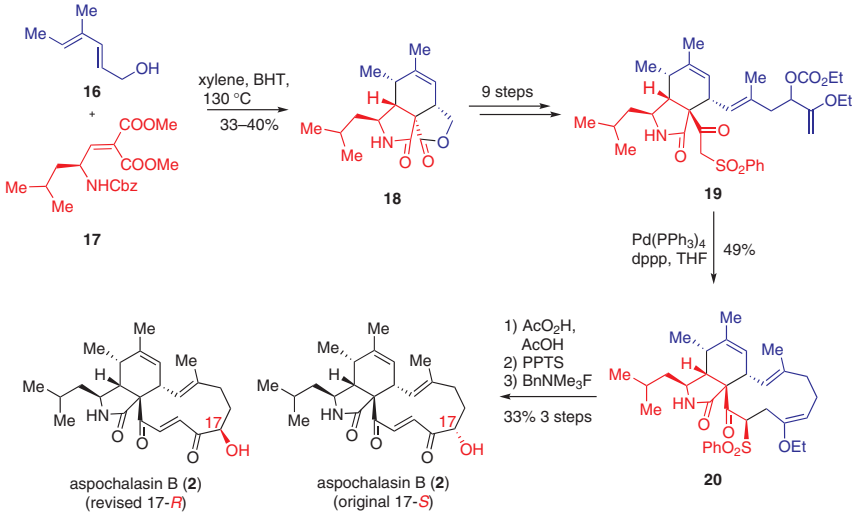
Key to the success of a chemical synthesis approach that would deliver all these merocytochalasans is a convergent and scalable route to key monomer aspochalasin B (**1**).

2 Total Synthesis of Aspochalasin B

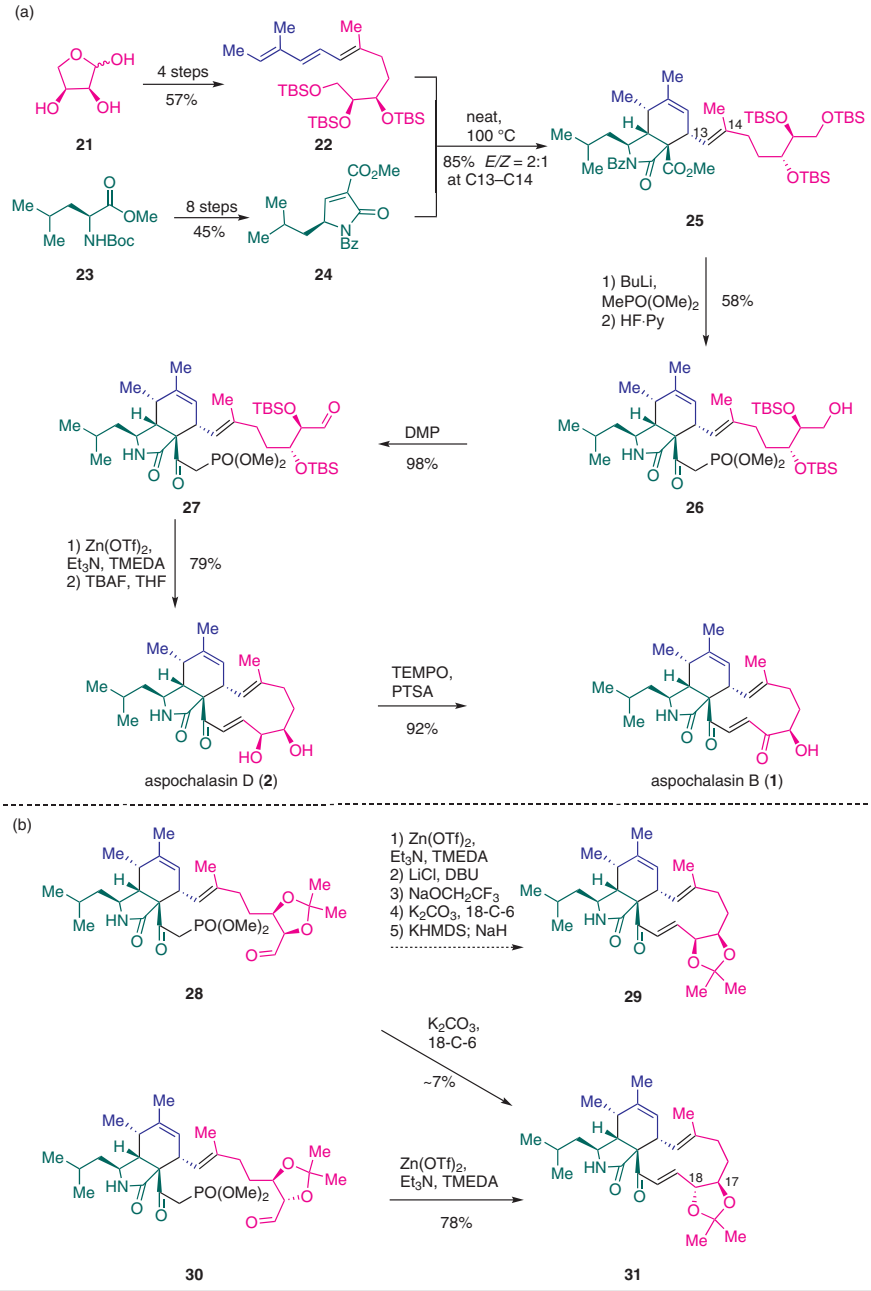
The first total synthesis of aspochalasin B (**1**) was accomplished by Trost in 19 steps from CBZ-leucine ester through an intermolecular Diels–Alder reaction and a palladium-catalyzed Tsuji–Trost macrocyclization (Scheme 1).[2j] Notably, the stereocenter of 17-OH of aspochalasin B was misassigned as 17-*S* at first.[5a] Although Trost reported the spectrum of their synthetic sample was identical with those of an authentic sample, the actually structure of their synthetic sample should be 17-*R* aspochalasin B, which was reisolated latter by other groups (**2**)[5b] and confirmed by our total synthesis.[6b]

In 2018, the Tang group, our group, and later the Trauner group reported the synthesis of aspochalasin B, the trimer asperchalasine A and related dimers, respectively.[6] In the aim of developing a convergent and scalable route to aspochalasin B, we designed a 11-step route by the assembly of three components of similar complexity.[6b] Notably, both triene segment **22** and dienophile **24** (Scheme 2, a) need to be enantiomerically pure, to avoid the possibility of diastereomerically mismatching in the Diels–Alder reaction. Triene segment **22** was prepared through two olefination reactions (Wittig and HWE) of triol **21** in four steps. While the dienophile **24** was readily prepared through commercially available *N*-Boc-L-leucine (**23**) in eight steps.

It is of note that dienophile **24** was very sensitive to acid and needed to be used immediately after flash chromatography purification. With both triene **22** and dienophile **24** in hand, we carried out the key intermolecular Diels–Alder reaction. A variety of Lewis acid promoters were examined, such as $BF_3{\cdot}OEt_2$, Et_2AlCl, TMSOTf, and $Eu(fod)_3$,[7] leading to the decomposition of triene **22** and dienophile **24**. To our delight, thermal conditions (neat, 100 °C) effectively assisted the Diels–Alder reaction and offered adduct **25**. We speculated that the regioselectivity was mainly induced by doubly activation of dienophile **24** with two electron-withdrawing groups on a single double bond. While, facial selectivity might be induced through an *endo* transition state with the triene **22** approaching from the less hindered face to avoid the repulsion of isobutanyl side chain of the dienophile **24**. Nucleophilic addition of lithium dimethyl methylphosphonate to the hindered methyl ester group of **25**, followed by selective desilyation and oxidation of the resulting primary alcohol with DMP furnished aldehyde **27** (56% yield from **25**). With this HWE macrocyclization precursor in hand, we found that $Zn(OTf)_2$, a mild Lewis acid, could effectively promote this macrocyclization in favor of intermolecular HWE olefination and no C-18 epimerized byproduct was detected.[2n] After global desilyation and se-



Scheme 1 Total synthesis of aspochalasin B by Trost



Scheme 2 Total synthesis of aspochalasins B and D by Deng

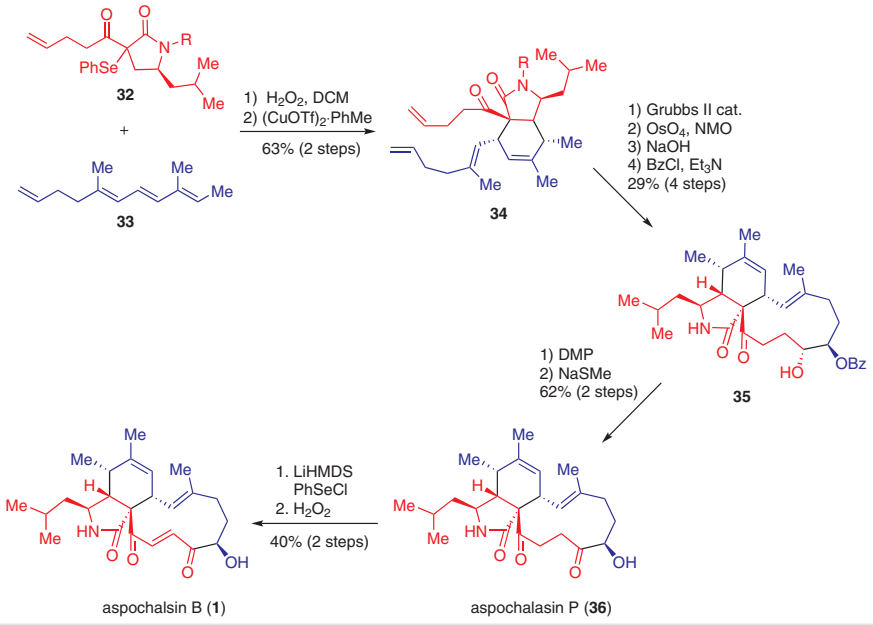
lective oxidation of the resulting allylic alcohol of aspochalasin D (**2**) with TEMPO and *p*-TsOH·H_2O,[8] the key monomer aspochalasin B (**1**), was prepared in decagram scale.

The protecting group of 17/18 hydroxy has a great influence on the efficiency of HWE macroolefination (Scheme 2, b). Actually, in our first-generation approach to aspochalasin B, HWE macroolefination precursor **28** was protected with acetonide, which however cannot be cyclized through HWE olefination using various conditions, such as $Zn(OTf)_2$, LiCl/DBU, [9a] $NaOCH_2CF_3$,[2n] K_2CO_3/18-C-6,[9b] KHMDS, and NaH, etc.

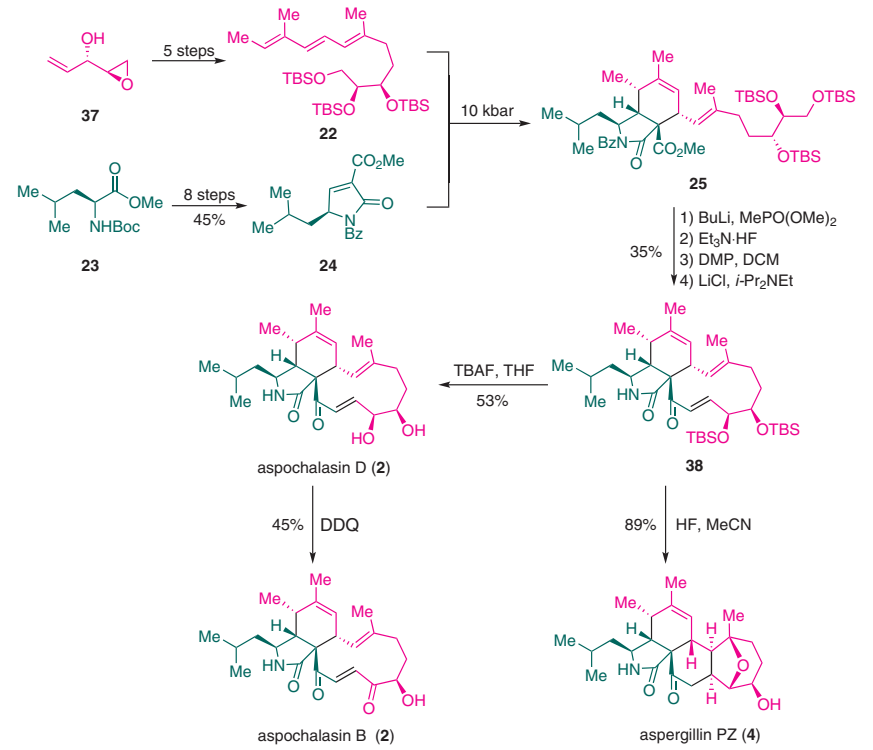
Only trace amount (7%) of **31** (18-*epi* of **29**) was obtained under the K_2CO_3/18-C-6 conditions. To confirm the result, we also prepared aldehyde **30**, which could be smoothly cyclized to **31** under the conditions of $Zn(OTf)_2$. At this point, we realized that the tethered protection group of 17/18 hydroxy, such as acetonide, could dramatically influence the conformation of cyclization precursor **28**, resulting in unfavorable conformation and extremely low

yield for cyclization. Based on these results, we switched the protecting group to TBS (**27**), which was albeit bulky but flexible, and at this time the HWE macrocyclization proceeded smoothly with high yield (Scheme 2, a).

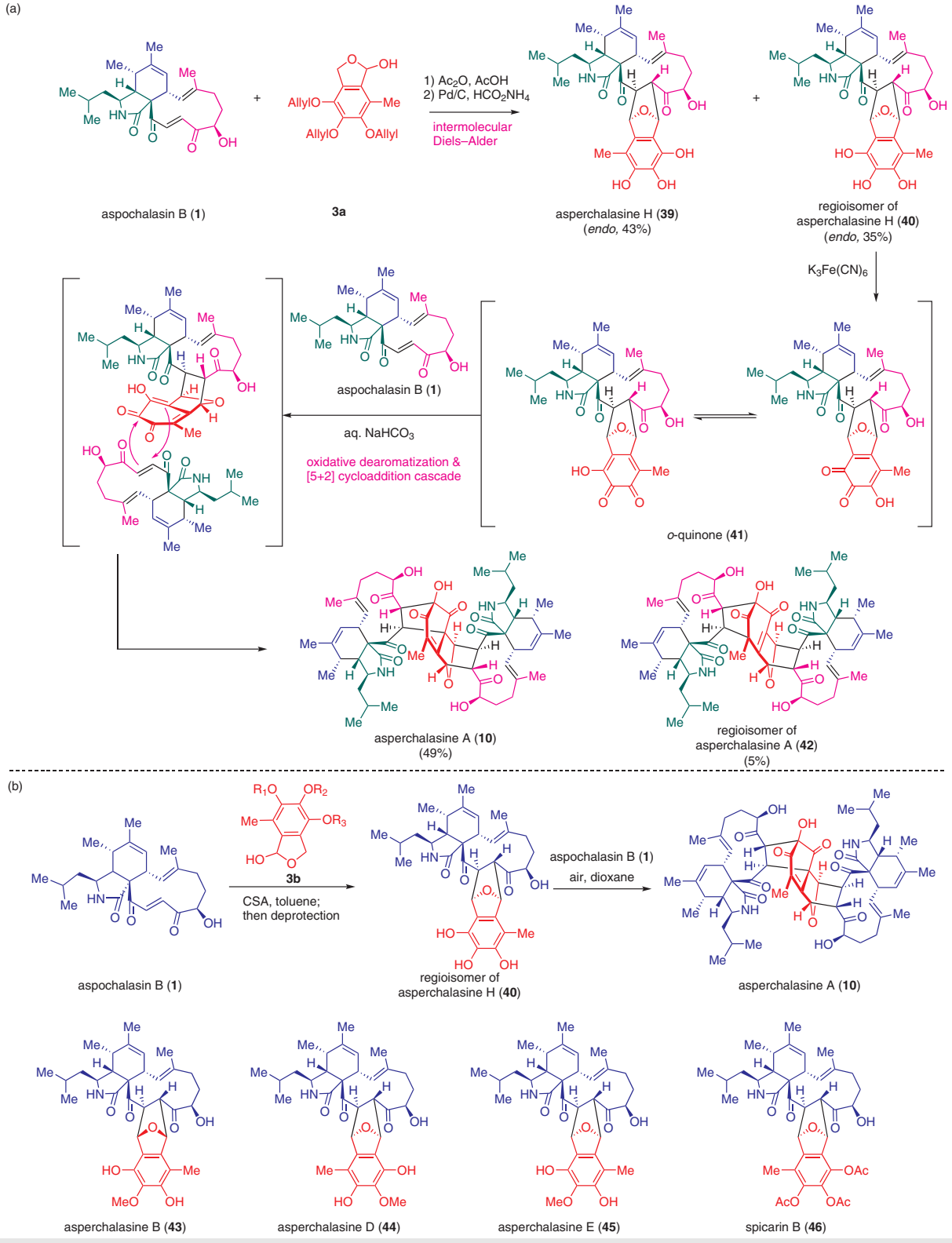
At the same time, Tang and co-workers reported their elegant synthesis of aspochalasin B through a different approach that combines both Diels–Alder reaction and RCM reaction (Scheme 3).[6a] Contrary to thermal promoted



Scheme 3 Total synthesis of aspochalasin B by Tang



Scheme 4 Total synthesis of aspochalasin B and aspergillin PZ by Trauner



Scheme 5 Total synthesis of asperchalasine A by Deng and Tang

Diels–Alder reaction by Deng, they found that $(CuOTf)_2$·PhMe initiated this reaction effectively and afforded **34** as a single adduct. After RCM reaction to construct the 11-membered macrocycle and subsequent three-step sequence to install the α-hydroxyl ketone, aspochalasin P (**36**) was readily prepared. Finally, aspochalasin B (**1**) was prepared through selenylation and subsequent oxidative elimination of aspochalasin P (**36**) in two steps.

About one month later, the Trauner group reported their elegant approach to aspochalasin B (**1**), aspochalasin D (**2**), and aspergillin PZ (**4**, Scheme 4).[6c] They also used triene **22** and dienophile **24** as Diels–Alder precursors, but in their synthesis, triene **22** was obtained via catalytic asymmetric epoxidation, and the intermolecular Diels–Alder reaction was achieved under high-pressure conditions.

More importantly, they realized the biomimetic conversion of aspochalasin B (**1**) into intricate pentacyclic aspochalasan aspergillin PZ (**4**), which was first synthesized by Overman in 28 steps.[10]

3 Total Synthesis of Asperchalasine A

With both aspochalasin B (**2**) and hemiacetal **16** readily prepared, we turned to explore the intermolecular Diels–Alder reaction. Both acidic and basic conditions can promote the isobenzofuran formation through 1,4-elimination of water or methanol in some precedents. We first tried basic conditions (MeLi) promoted elimination, and precursor methanol acetal of **3a** indeed afforded the desired diene with low conversion (40%).To our delight, acetic acid[11] turned out to be an efficient promoter for this 1,4-elimination, and the active diene was further captured in situ by dienophile aspochalasin B (**1**) to give two Diels–Alder adducts. These two adducts, after reductive deallylation (Pd/C, HCO_2NH_4)[12] turned out to be asperchalasine H (**39**) and its regioisomer **40**.[13] Notably, both asperchalasine H (**39**) and its regioisomer **40** are *endo* adducts, and no *exo* adducts were detected under these conditions.

The three protection groups of triphenol have a great influence on the *endo*/*exo* selectivity of the Diels–Alder reaction: When partially protected hemiacetal **3** was used, both *endo* and *exo* Diels–Alder adducts were obtained, and this phenomenon was also observed by Tang.[5a]

Then we turned to the final biomimetic cross-dimerization stage (Scheme 5, a). Based on the inspiration of the unique bicyclo[3.2.1]octadienone structure of asperchalasine A (**10**) we speculate that asperchalasine A (**1**) is formed through a base-promoted intermolecular Michael addition of *o*-quinone (**41**) to aspochalasin B (**1**) and subsequent intramolecular Aldol addition cascade after oxidation of the electron-rich aromatic ring of **40**. The active *o*-quinone **41** was readily obtained through oxidation of triphenol **40** with potassium ferricyanide and the subsequent Michael–aldol addition cascade proceeded smoothly under the conditions of sodium bicarbonate aqueous buffer, furnishing asperchalasine A (**10**) and its regioisomer **42** in 49% and 5% yield, respectively. We speculate that the regioisomer **42** might be another natural product not isolated yet. It is of note that there was a competition between homodimerization of the active intermediate *o*-quinone **41** and cross-dimerization of *o*-quinone **41** with aspochalasin B (**1**). In this case, we did not observe any homodimerized tetramers like asperflavipine A.

While, in Tang's synthesis of asperchalasine A (**10**), they also found that the steric effect of the isobenzofuran precursors played an important influence in controlling the *endo*/*exo* ratio of the Diels–Alder reactions (Scheme 5, b). After treatment of aspochalasin B (**1**) and hemiacetal **3b** with CSA and subsequent deprotection, they synthesized asperchalasines B, D, E, spicarin B, and the regioisomer of asperchalasine H (**40**), which after a biomimetic oxidative [5+2] cycloaddition afforded the desired asperchalasine A (**10**).

4 Conclusions

In summary, a brief review of recent synthetic progress toward aspochalasin B (**1**) and asperchalasine A (**10**) is discussed in this Synpact account. The key features of these route include: a highly stereoselective intermolecular Diels–Alder reaction and a HWE or RCM macrocyclization to establish the key monomer aspochalasin B (**1**); an intermolecular *endo*-selective Diels–Alder reaction and late-stage biomimetic oxidative dearomatization and subsequent [5+2] cycloaddition cascade to forge the caged bicyclo[3.2.1]octadienone ring system.

The total synthesis of aspochalasin B (**1**), aspergillin PZ (**4**), and asperchalasine A (**10**) opened the gate to other pentacyclic aspochalasans and merocytochalasans, for example, the most complex one: Asperflavipine A (**11**) might be generated by incorporation of two molecules of epicoccine (**4**, red part) with two molecules aspochalasin B through Diels–Alder reaction and [5+2] heterocycloaddition. While there still have been a lot of challenges *en route* to these congeners, for example: 1) How to realize the biomatic transformation of aspochalasin B (**1**) to other pentacyclic aspochalasans, such as trichoderones A (**6**), B (**7**), flavichalasines C (**8**), E (**9**)? 2) How to control the stereoselectivity (*endo*/*exo*) and regioselectivity of this Diels–Alder reaction? All these four isomers are needed for the synthesis of other merocytochalasans. 3) How to promote the desired [5+2] heterodimerization rather than homodimerization of *o*-quinones? Undoubtedly, these questions will be answered, and these biomimetic transformations will shed light to the biosynthesis pathway of cytochalasans in due course by synthetic chemists.

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