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Title Total Synthesis of Asperchalasines A, D, E and H

Xianwen Long[+,a,b], Yiming Ding[+,a] and Jun Deng[*,a]

This paper is dedicated to the 80th anniversary celebration of Kunming Institute of Botany, Chinese Academy of Sciences.

Abstract: The first total syntheses of cytochalasan dimers asperchalasines A, D, E and H have been accomplished. The key steps of the synthesis include a highly stereoselective intermolecular Diels-Alder reaction and a HWE macrocyclization to establish the key monomer aspochalasin B and an intermolecular Diels-Alder reaction followed by a biomimetic oxidative heterodimerization via 5+2 cycloaddition to furnish asperchalasine A. The synthetic efforts provide insight into the biosynthetic pathway of cytochalasan dimers and enables the further study of their biological properties.

Cytochalasans are a large family of fungal metabolites (> 300 members) with intriguing structures and bioactivity.[1] They exhibit a broad range of biological activities, including immunomodulatory,[2] cytotoxic,[3] and nematicidal activities,[4] and has attracted considerable attention from the synthetic community.[5] In 2015, the first subclass cytochalasan dimers, asperhalasines A, B, D, E and H（Figure **1**）,[6] were isolated by Zhang and co-workers from the culture broth of *Aspergillus flaipes*. Structurally, **1** possesses an unprecedented 13-oxatetracyclo[7.2.1.1^{2,5}.0^{1,6}]tride-8,12-dione core containing as many as 20 stereogenic centers, which might be biosynthetically generated by the fusion of two aspochalasins B (**6**) to an epicoccine. Biologically, **1** selectively induces G1-phase cell cycle arrest in fast-dividing cancner cells, making it a novel cytoskeletal inhibitor against cancner cells. Herein, we report the first asymmetric total synthesis of asperchalasine A (**1**).

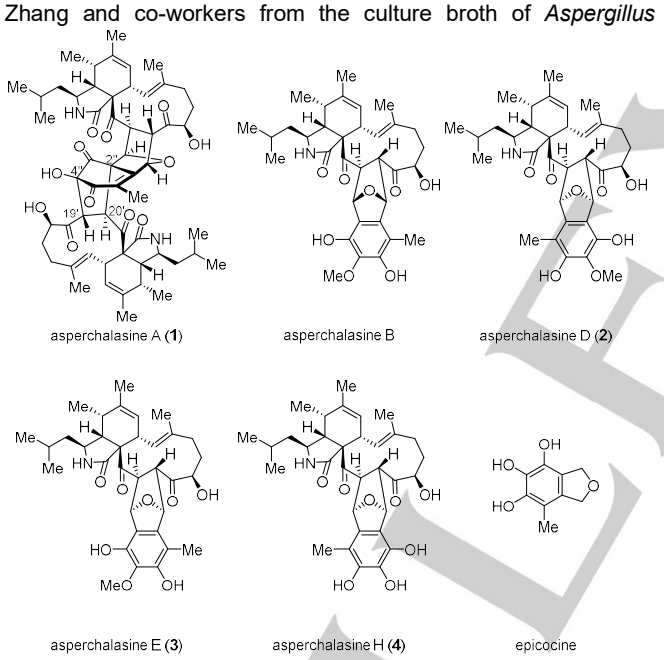
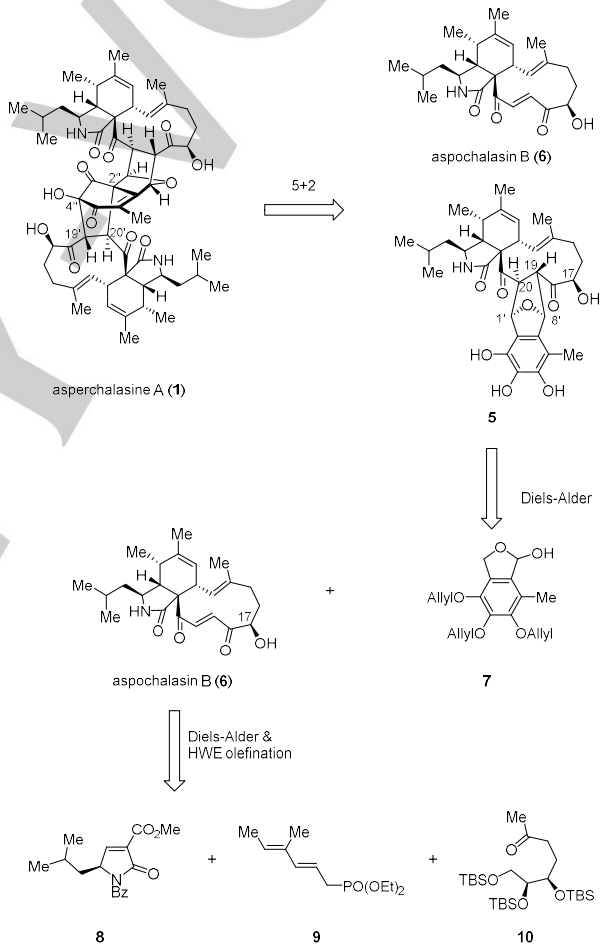


Figure 1. Asperchalasines A, B, D, E, H and epicocine.



Scheme 1. Retrosynthetic Analysis of Asperchalasine A.

We first undertook a retrosynthetic analysis of asperchalasines A (**1**), as illustrated in Scheme **1**. It's likely that asperchalasine A is formed biosynthetically through the union of two aspochalasins B and one epicoccine. Inspired by this biosynthetic hypothesis, the initial disconnection takes place at the C19'–C4'' and C20'–C2'' bond to provide aspochalasin B (**6**) and **5**, which could be further disassembled in a retro-Diels-Alder reaction to give aspochalasin B and hemi-acetal **7**. Aspochalasin B could be assembled from three fragments **8**–**10** through an intermolecular Diels-Alder reaction and a Horner-Wadsworth-Emmons (HWE) macrocyclization. Previously, Trost

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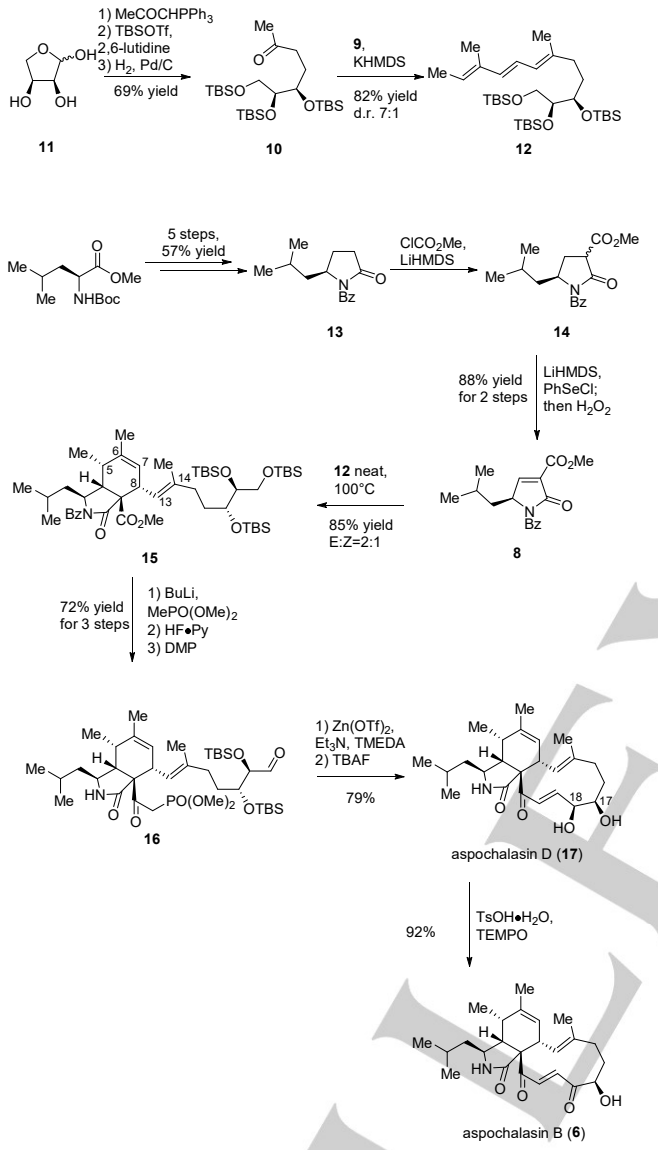
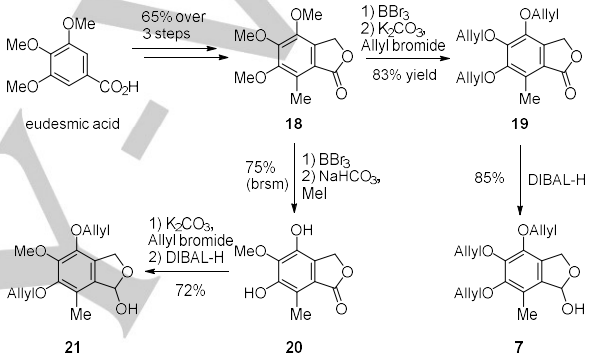
and co-workers[5j] reported first total synthesis of aspochalasin B in 1989 and Myers and co-workers[5n] reported their elegant total synthesis of cytochalasin B using HWE macrocylization stragety in 2004. Here, we report a concise and scalable approach to aspochalasin B, which in turn enabled a rapid synthesis of asperchalasine A and other dimers in this family.



Scheme 2. Total Synthesis of Aspochalasin B.

Our synthesis commenced with a stereospcific construction of the triene segment **12** (Sheme **2**). Hemi-acetal **11** was obtained in 70% yield from L-Arabinose through a known three-step sequence.[7] Wittig olefination (with reagent 1-(Triphenylphosphoranylidene)-2-propanone), followed by tert-butyldimethylsilyl ethers protection of tri-ol and hydrogenation of the resulting double bond furnished methyl-ketone **10** in 69% yield. Coupling of this methyl-ketone to the dienyl phosphonate **9**[8] using KHMDS as base, gave the conjugated triene (**12**) with good overall efficiency (82%, *E*:*Z*= ~7:1). We then constructed the dienophile **8**. The lactam **13** was readily prepared from *N*-boc-L-leucine (5 steps, 57% yield).[9] C-Acylation of **13** with methyl chloroformate provided methyl ester **14**. After sequential selenylation and oxidative elimination, **14**[10] was converted into the doubly activated dienophile **8** (88% yield for 2 steps), which was unstable[11] and was used immediately. With both **8** and **12** in hand, we examined a variety of conditions for the intermolecular Diels-Alder reaction. Lewis acid promoters such as: $BF_3{\cdot}OEt_2$, Et_2AlCl, TMSOTf, $Eu(fod)_3$[12] led to decomposition of diene **12**. To our delight, heating a mixture of **8** and **12** (neat, 100℃) furnished Diels-Alder products **15** and its C13-C14 isomer in 85% yield from **14** (*E*:*Z* = ~2:1,). The regioselectivity was mainly induced by electron donating effect of 5, 6-dimethyl groups and facial selectivity was controlled by a thermal *endo* transition state with the triene approaching from the less hindered face of the dienophile **8**. The C13-C14 cis/trans isomerization was mainly caused by thermodynamic equilibration which was also observed by Thomas group in their intramolecular Diels-Alder reaction.[5g-h] Addition of lithium dimethyl methylphosphonate[13] to the hindered methyl ester group of **15**, followed by selectively deprotection

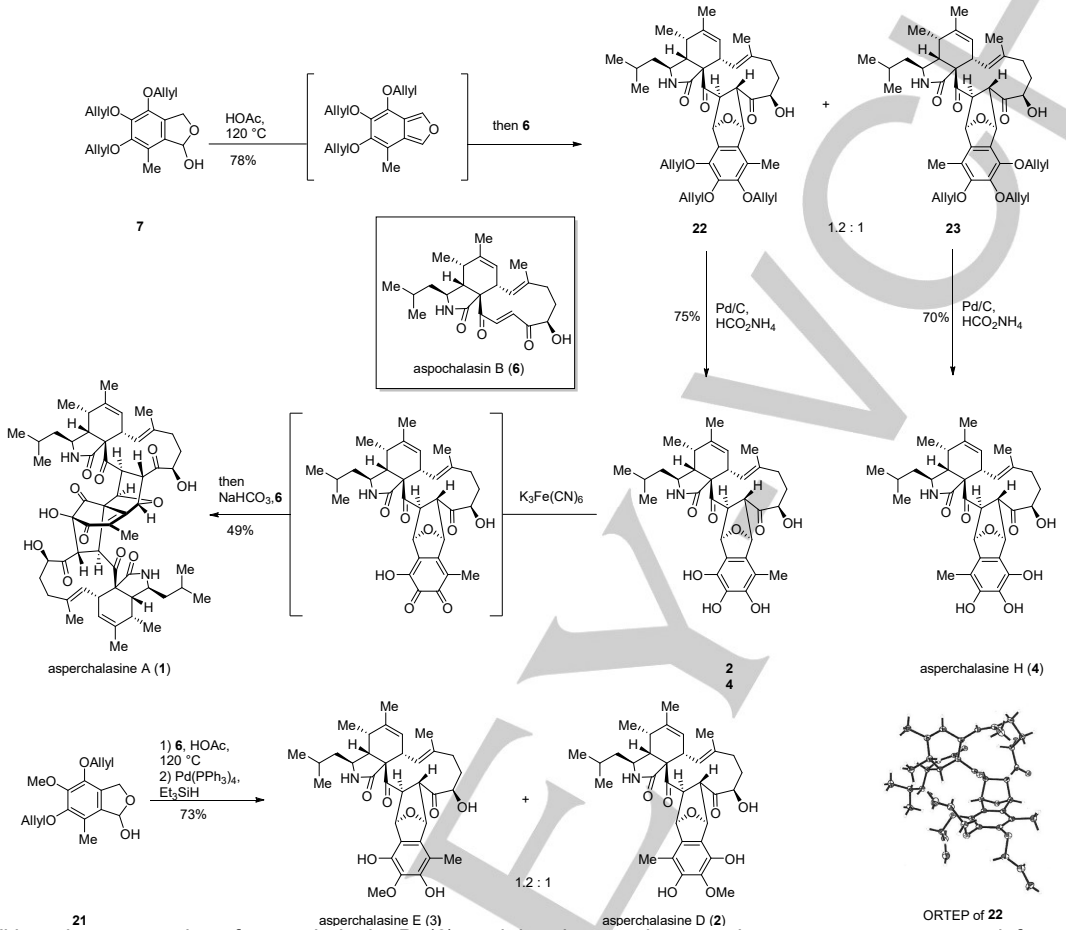


Scheme 3. Construction of hemi-acetal **7** and **21**.

and oxidation of the resultant primary alcohol with Dess-Martin periodinane furnished aldehyde **16** (72% yield for 3 steps) as a substrate for HWE macrocyclization. Various macrocylization conditions, such as KHMDS, NaH, LiBr/Et_3N,[14a] K_2CO_3/18-crown-6,[9b] $NaOCH_2CF_3$[5n] were examined, which failed to provide the resulting 11-membered enone and, in some cases, led to epimerization of the C-18 stereogenic center. To our delight, the use of $Zn(OTf)_2$,[15] a mild Lewis acid promoted macrocyclization in favor of intermolecular HWE olefination and minimal epimerization at C-18.[16, 5n] After hydrolysis of the *tert*-butyldimethylsilyl ether with TBAF and selective oxidation of the allylic alcohol with TEMPO and *p*-$TsOH{\cdot}H_2O$,[17] we achieved the syntheses of aspochalasin D (**17**) and aspochalasin B (**6**), in overall 79% and 72% respectively.

Subsequently, we prepared diene precursors **7** and **21** (Scheme **3**). Known compound **18** [18] arising from eudesmic acid was subjected to a sequence of global demethylation, allylation and partial reduction of lactone **19** with DIBAL-H, to give hemi-acetal **7** as precursor of diene (71% yield for 3 steps). Another hemi-acetal **21** was prepared similarly from mono-methylated lactone **20**[19] through allylation and partial reduction (54% yield for 4 steps).

Scheme 4. Total Synthesis of asperchalasines A, D, E and H.



With a large quantity of aspochalasin B (**6**) and hemi-acetal **7** in hand, we investigated the proposed biomimetic, intermolecular Diels-Alder reaction. Upon treatment with HOAc, hemi-acetal **7** underwent an 1, 4-elimination of water to generate the active diene, which was trapped in situ by dienophile aspochalasin B[20] to give exclusively *endo*-Diels-Alder adducts **22** and its regioisomer **23** in 78% yield. No other diastereomeric isomers were detected. The structure of adduct **22** was determined by X-ray crystallographic analysis (Scheme **4**). Both cycloadducts were subjected to deallylation[21] (Pd/C, HCO_2NH_4) to furnish **24** and asperchalasine H (**4**) respectively.[22] Then we entered the final stage of the synthesis. Inspired by Zhang's biosynthetic hypothesis[7a] and Trauner's elegant biomimetic synthesis of epicolactone,[19, 23] we propose that asperchalasine A is formed through a reaction cascade initiating with oxidation of the electron-rich aromatic ring in **24**, followed by an intermolecular Michael addition of the resulting quinone to **6** and intramolecular aldol cyclization. Treatment of **24** with potassium ferricyanide led to facile oxidation of the electron-rich aromatic ring to yield the corresponding *o*-quinone, which was unstable and trapped by another molecule of aspochalasin B (**6**) in the presence of sodium bicarbonate to furnish the formal [5+2] adduct asperchalasine A (**1**) in 49% yield. Due to the poor selectivity of direct methylation (K_2CO_3/MeI) of asperchalasine H (**4**) and **24**, we turned to preinstalled mono-methylated hemi-acetal **21**. To our delight, mono-methylated hemi-acetal **21** underwent the same sequence used for asperchalasine H(**4**) synthesis to render asperchalasines D (**2**) and E (**3**) in 73% overall yield. The spectra and physical properties of **1, 2, 3, 4, 6, 17** were identical to those reported for their naturally occurring counterparts, respectively.

In summary, we have accomplished the first total synthesis of asperchalasines A, D, E and H. The monomer aspochalasin B (**6**) was prepared through an intermolecular Diels-Alder cycloaddition and HWE macrocyclization. Acid promoted *endo*-selective Diels-Alder reaction of **6** and **7** and subsequent oxidative heterodimerization of **24** and **6** furnished asperchalasines A, D, E and H. The reported synthetic strategy is applicable to construct other structurally more complex cytochalasan dimers, and in turn facilitate the investigation of their mechanism of cell cycle arrest in cancer cell lines.

Acknowledgements

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Keywords: total synthesis • biomemitic synthesis • asperchalasines • 5+2 • Diels-Alder

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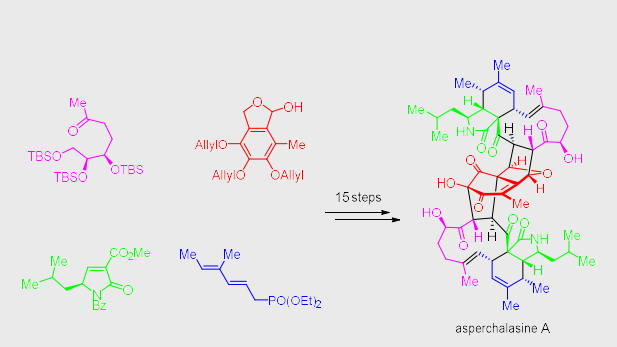

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