OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Intramolecular Diels−Alder Cycloaddition Approach toward the *cis*-Fused $\Delta^{5,6}$-Hexahydroisoindol-1-one Core of Cytochalasins

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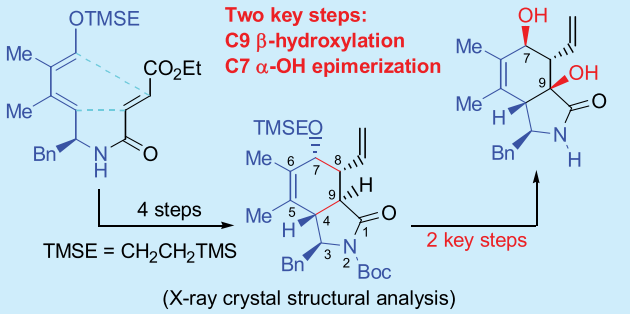
Supporting Information

ABSTRACT: Synthesis of the *cis*-fused $\Delta^{5,6}$-hexahydroisoindol-1-one core of cytochalasins B_2−B_5, K, Z_8, Z_9, Z_{12}−Z_{15}, and Z_{17} has been established starting from an intramolecular Diels−Alder reaction of the amide-tethered (8*E*)-1,3,8-nonatriene. The *trans*-fused 5/6-bicyclic adduct was then subjected to highly stereoselective C9-β-hydroxylation and epimerization of the C7-α-OH group.



Cytochalasans are a large family of fungal polyketide−amino acid hybrid metabolites possessing a common perhydroisoindol-1-one core.[1] The C3 group originates from amino acids and includes benzyl [cytochalasins **1**−**7** in Figure 1],[2−4] *p*-methoxybenzyl [pyrichalasins], (indol-3-yl)methyl [chaetoglobosins], 2-methylpropyl [aspochalasins], and methyl [alachalasins] groups.[1b] The perhydroisoindol-1-one core of cytochalasans is typically fused with a carbocycle (**10** in Scheme 1), lactone (**1**−**3** in Figure 1), and cyclic carbonate (**12**−**14** in Scheme 1), respectively, in various ring sizes. Cytochalasans possessing open-chains (**4**−**7** in Figure 1)[3] and spirocyclic/polycyclic scaffolds have been reported.[1c] Additional structural complexity has been observed in merocytochalasans arising from incorporation of epicoccine molecule(s) through dimerization or oligomerization.[1c,5] Cytochalasans are best known as microfilament-targeting molecules, exhibiting influence on cellular processes such as cell adhesion, intracellular motility, signaling, and cytokinesis.[1b,c] Studies have revealed two groups of cytochalasins, being cytotoxic and cytostatic.[6] This finding suggests potential use of cytostatic cytochalasins in cancer treatment. Other biological activities have been recognized for cytochalasans, including antibacterial,[7] antitumor,[8] immunomodulatory,[9] and phytotoxic activities,[8e,10] and inhibition of glucose transport[11] and HIV-1 protease.[12]

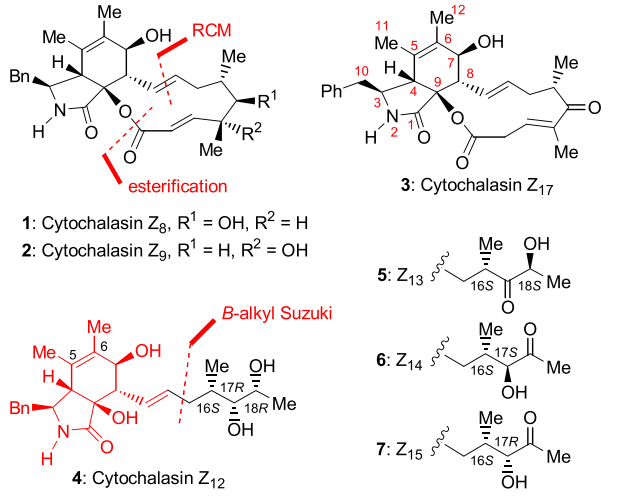


Figure 1. Cytochalasins possessing a $\Delta^{5,6}$-hexahydroisoindol-1-one core and a fused lactone (**1**−**3**) or a side chain (**4**−**7**).

The established biosynthesis of cytochalasins E (**13**) and K (**14**) is illustrated in Scheme 1,[13] featuring an intramolecular Diels−Alder (IMDA)[14] reaction of a 1,5-dihydropyrrol-2-one derivative **8** to form the adduct **9** in which a *cis*-$\Delta^{6,7}$-hexahydroisoindol-1-one core is fused with a carbocycle. Further enzymatic oxidation of **9** results in the proposed precytochalasin (**11a**) via ketocytochalasin (**10**).[15] Oxidation of **11a** to **12** takes place only for the C3-benzyl-substituted cytochalasans.[13] Epoxidation of the C6−C7 double bond in **12** gives **13**,[16] which is finally converted into **14**.[17] However, isoprecytochalasin (**11b**) is transformed into cytochalasin Z_{17} (**3**) via rosellichalasin (**16**) (see Scheme S1 in the Supporting Information).

Received: December 26, 2018

DOI: 10.1021/acs.orglett.8b04129
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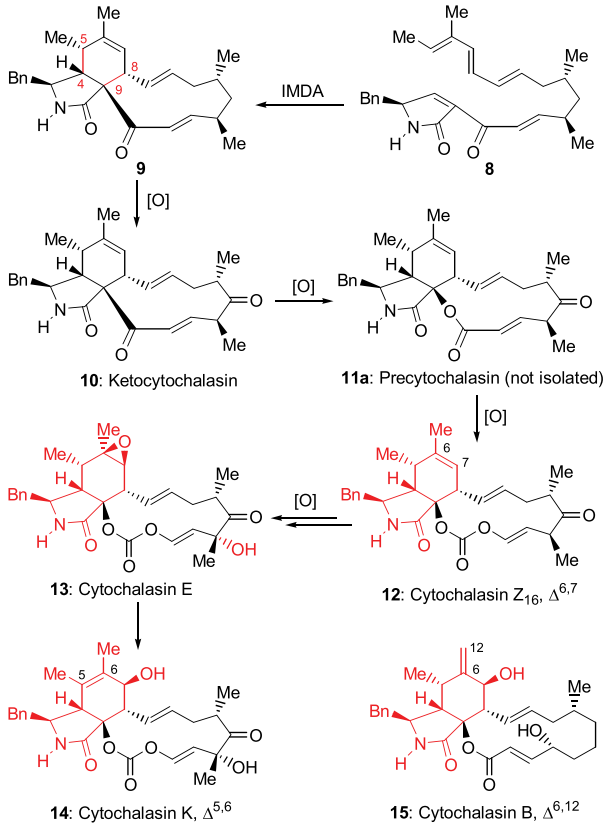
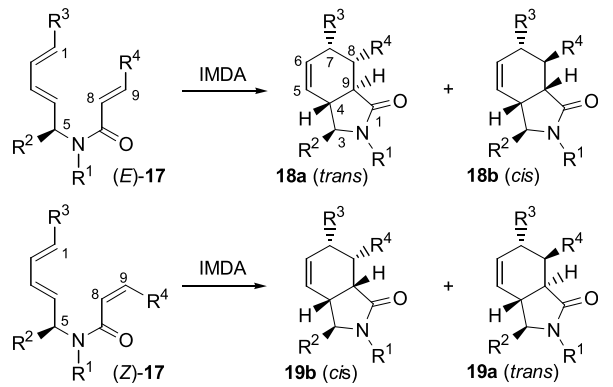
Scheme 1. Biosynthesis of Cytochalasins E and K



Compounds **12**–**15** represent the four main types of the *cis*-fused perhydroisoindol-1-one cores. Except for the $\Delta^{5,6}$-hexahydroisoindol-1-one core in **14**, total synthesis of cytochalasan congeners with the perhydroisoindol-1-one cores of **12**, **13**, and **15** has been reported by using both inter- and intramolecular Diels–Alder reactions (similar to **8** → **9**) as the key steps.[1b,18−20] We report here on a synthesis of the $\Delta^{5,6}$-hexahydroisoindol-1-one core, which would be derived from the indicated retrosynthetic bond disconnections for Z_8 (**1**),[2] Z_9 (**2**),[2] Z_{12}–Z_{15} (**4**–**7**),[3] and Z_{17} (**3**)[4] (Figure 1) via an IMDA reaction of the amide-tethered (8*E*)-1,3,8-nonatrienes (Scheme 2).[22] The same core structure is found in cytochalasins B_2–B_5 (Figure S1 in the Supporting Information)[21] and K (Scheme 1).[17] The key issues to be addressed are (a) installation of the C9-*β*-OH group; and (b) epimerization of the C7-*α*-OH group within the initially formed *trans*-fused 5/6-bicyclic adducts.[23]

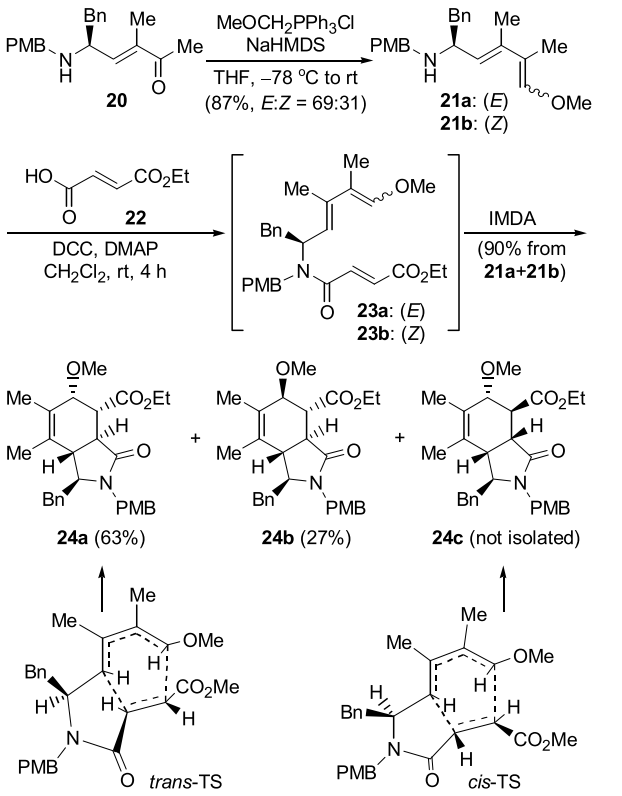
Scheme 2. IMDA Cycloaddition of 1,3,8-Nonatrienes 17



The parent amide-tethered 1,3,8-nonatriene **17** ($R^1 = R^2 = R^3 = R^4 = H$) was reported to undergo IMDA reaction at 190 °C to form a 46:54 mixture of **18a** and **18b**.[24,25b] From the C9-substituted (*E*)-**17** and (*Z*)-**17** ($R^2 = R^3 = H$; $R^4 = CO_2Me$, CO_2H, Ar), **18a** and **19a** were obtained as the major products in low to excellent diastereomeric ratios.[25] With an additional substituent at C1 or C5 position, high diastereoselectivity was observed for 1,9- and 5,9-disubstituted (*E*)-**17** and (*Z*)-**17** (R^2 = H or R^3 = H).[26] However, a 1,5,9-trisubstituted (*E*)-**17** afforded a 1:1 ratio of **18a** and **18b**.[27] Taking the adducts of (*E*)-**17** as the examples, inversion of stereochemistry at C7/C9 and C7/C8 of **18a** and **18b**, respectively, is required in order to synthesize **1**–**7** (Figure 1).

We first examined the IMDA reaction of **23a,b** derived from the dienyl amine **21a,b** and the acid **22** (Scheme 3). The Wittig

Scheme 3. IMDA Cycloaddition of Substrates 23a,b



olefination of **20** (see Scheme S2 in the Supporting Information) with excess Ph_3P = CHOMe gave a 69:31 inseparable mixture of **21a** and **21b** (87%); the latter were coupled with the acid **22** (DCC, DMAP) to form the trienyl amide **23a,b**. Spontaneous IMDA reaction of **23a,b** took place at room temperature to furnish three adducts **24a**–**c** in a ratio of 68:29:3 as estimated by ^{1}H NMR spectroscopy of the crude products. The compound **24a** (63%) should be the major adduct of (*E*)-**23a** formed via the *trans*-TS, while the minor adduct **24c** of (*E*)-**23a** would be formed via the *cis*-TS.[24] An analogous *trans*-TS should be considered for the formation of **24b** (27%) from (*Z*)-**23b**. The structures of **24a** and **24b** were assigned by comparison with a similar compound whose stereochemistry was determined by X-ray crystal structural analysis (*vide infra*).

The observed high diastereoselectivity of the IMDA reaction of both (*E*)-**23a** and (*Z*)-**23b** is very encouraging. Unfortunately, several attempted transformations (such as cleavage of

DOI: 10.1021/acs.orglett.8b04129
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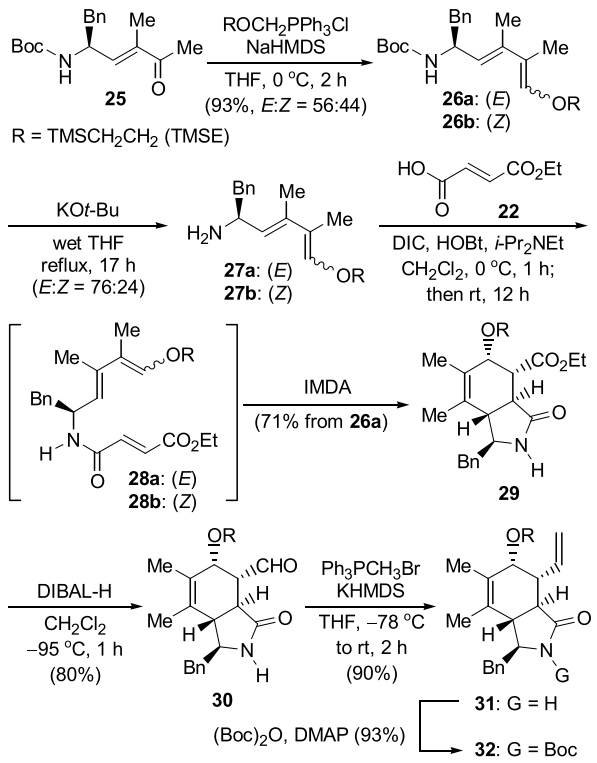
the methyl ether and reduction of the ester) of **24a,b** failed to form the expected products or afforded the byproducts due to elimination of the C7 methoxy group (see Scheme S4 in the Supporting Information). Next, we decided to explore the IMDA reaction of the N-unprotected substrates **28a,b** (Scheme 4). The Wittig olefination of **25** (see Scheme S3 in the

Scheme 4. Synthesis of *trans*-Fused Bicyclic Compounds



Supporting Information) using $Ph_3P{=}CHOTMSE$[28] gave a 56:44 inseparable mixture of (*E*)-**26a** and (*Z*)-**26b**, which were labile in $CDCl_3$ during NMR analysis and were prone to decompose to the corresponding ketone. Upon refluxing in THF in the presence of KO*t*-Bu,[29] the Boc group of **26a,b** was removed to afford the dienyl amines **27a,b** as a 76:24 *E*/*Z* mixture as analyzed by ^{1}H NMR spectroscopy, suggesting partial decomposition of the (*Z*)-isomer during the deprotection. The crude dienyl amines **27a,b** were then coupled with the acid **22** to give the amides **28a,b**, among which only (*E*)-**28a** spontaneously underwent the IMDA reaction to furnish the adduct **29** as a single diastereoisomer in 40% overall isolated yield from the mixed materials **26a,b** (71% overall yield based on the composition of **26a**). Presumably, the conjugated diene (*Z*)-**28b** did not prefer the *s-cis* conformation due to the bulky *O*-TMSE group, rendering its IMDA reaction difficult at room temperature. Because (*Z*)-**28b** was not recovered, it was assumed that decomposition of (*Z*)-**28b** occurred during the reaction or product purification. The stereochemistry of **29** was confirmed by X-ray crystal structural analysis of **32** (Figure 2); the latter was obtained via DIBAL-H reduction of **29** (80%), methylenation of **30** (90%), and N-Boc protection of **31** in MeCN (rt, 40 h; 93%).

Attempted cleavage of the TMSE group in **31** using CsF in HMPA at 120 °C or $BF_3{\cdot}OEt_2$ at 0 °C was unsuccessful due to nonselective attack of H_2O at C5 from both α and β faces as well as at C11−H of the allylic carbocation **S14** (Scheme 5; also see

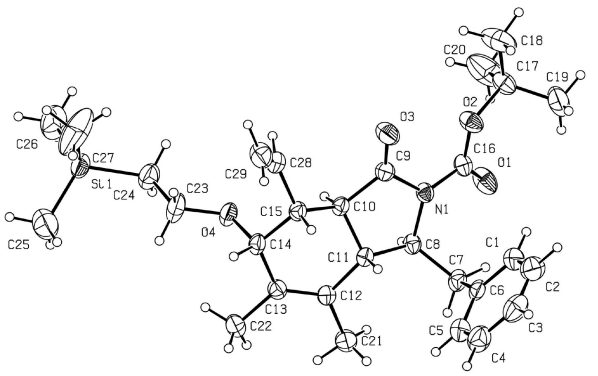
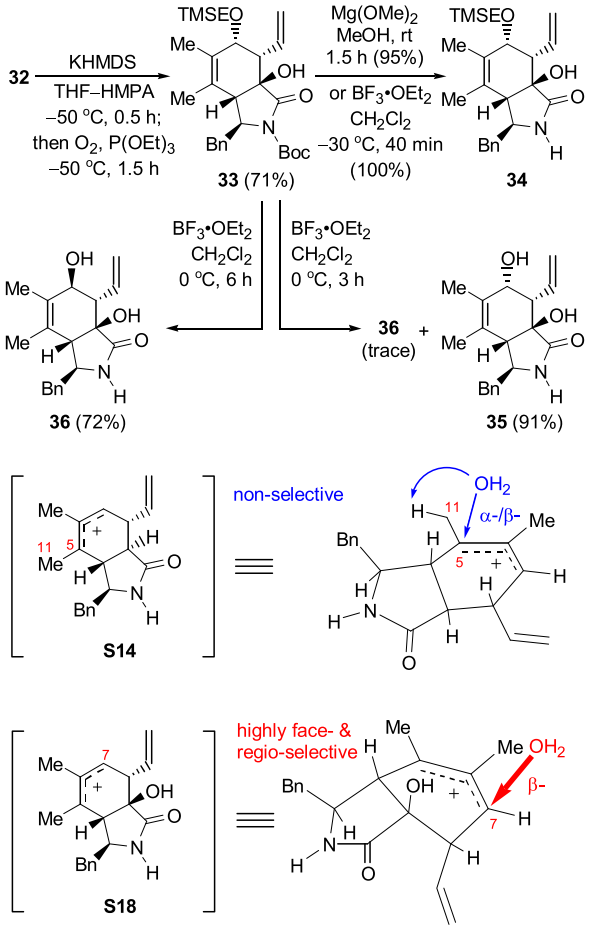


Figure 2. X-ray crystal structure of **32**.

Scheme 5. Synthesis of $\Delta^{5,6}$-Hexahydroisoindol-1-one



Scheme S5 in the Supporting Information). The results could be attributed to the nearly flat structure (analogous to **32** in Figure 2) of the *trans*-fused bicyclic skeleton of **S14**, which rendered the tetrasubstituted double bond at C5/C6 less stable than the trisubstituted one at C6/C7 due to higher ring strain. We envisaged that the *cis*-fused bicyclic skeleton of **33** would facilitate installation of the C7-OH group with the desired β configuration (Scheme 5).[30]

Thus, the C9-β-hydroxylation of **32** was carried out by exposing the lactam enolate to O_2 at −50 °C to give **33** in 71% yield. Removal of the Boc group in **33** using $Mg(OMe)_2$ in MeOH or $BF_3{\cdot}OEt_2$ at −30 °C gave **34**. It was found that concurrent cleavage of the Boc group and the TMSE ether in **33**

DOI: 10.1021/acs.orglett.8b04129
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could be achieved by exposure to $BF_3{\cdot}OEt_2$ at 0 °C for 3 h to afford **35** in 91% overall yield. It was pleasing that a trace amount of the diol **36** was detected. We assumed that the diol **36** should be formed from the *cis*-fused bicyclic allylic carbocation **S18** via highly face- and regioselective attack of H_2O; the convex shape of **S18** assured attack of H_2O from the β-face, while the regioselectivity was originated from the stability of the tetrasubstituted double bond at C5/C6.[31] Finally, upon treatment of **33** with $BF_3{\cdot}OEt_2$ at 0 °C for 6 h, the desired product **36** was obtained in 72% yield (Scheme 5; also see Scheme S5 in the Supporting Information). The ^{13}C NMR data of **36** are almost consistent with those of **4**[3] except for C5 (see Figure S2 in the Supporting Information).

In conclusion, we have established a concise synthesis of the common *cis*-fused $\Delta^{5,6}$-hexahydroisoindol-1-one core of cytochalasin B_2–B_5, K, Z_8, Z_9, Z_{12}–Z_{15}, and Z_{17} via an IMDA cycloaddition of the amide-tethered (8*E*)-1,3,8-nonatriene followed by highly stereoselective hydroxylation at C9 and epimerization of the allyl alcohol at C7. This synthetic strategy could be amended for synthesis of other cytochalasan congeners by replacing C3-Bn with other substituents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04129.

Experimental procedures, compound characterization data, and copies of original ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1588694 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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Laboratory of Asymmetric Catalysis and Synthesis is established under the Cheung Kong Scholars Program of The Ministry of Education of China. This work is supported in part by the National Natural Science Foundation of China (Grand No. 21172191). Mr. Jianming Gu of the X-ray crystallography facility of Zhejiang University is acknowledged for the assistance on crystal structural analysis.

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(31) One reviewer suggested an interesting possibility of a directing effect of C9-OH during the epimerization of C7-OH in **35**. However, at this stage there is no experimental evidence to support this proposal.

DOI: 10.1021/acs.orglett.8b04129
Org. Lett. XXXX, XXX, XXX−XXX