Communication

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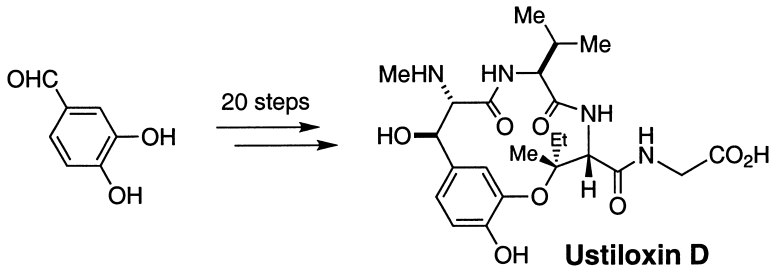

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Enantioselective Total Synthesis of Ustiloxin D

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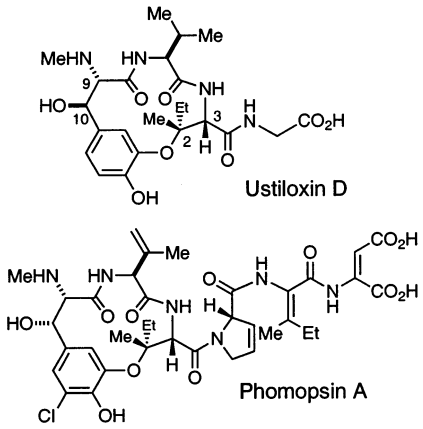
Ustiloxin D[1] and phomopsin A[2] (Chart 1) are potent antimitotic agents that bind to tubulin and interfere with cellular microtubule function.[3] To understand the molecular mechanisms by which mammalian cells monitor the integrity of their microtubules, we have been pursuing the synthesis of both natural products as well as synthetic variants designed to illuminate details of the mammalian spindle assembly checkpoint.[4]

Ustiloxin D and phomopsin A are representative members of a family of 13-membered macrolactams that possess a unique chiral tertiary alkyl−aryl ether linkage. The compounds differ in several respects, including the stereochemistry of the C10-benzylic hydroxyl group, the substituents on the aromatic ring, and the structure of the side chain attached to the macrocycle. Several groups have reported the syntheses of simplified ustiloxin analogues,[5,6] and the aryl sulfoxide substituent of ustiloxin A has been synthesized.[7] The Joullié group recently published the first total synthesis of ustiloxin D starting from D-serine, using a longest linear sequence of 31 steps.[8] Key steps in their synthesis include the use of a nucleophilic aromatic substitution reaction to construct the chiral tertiary alkyl−aryl ether,[4b] as well as Sharpless's asymmetric aminohydroxylation reaction to install the C10-benzylic hydroxyl group and the adjacent nitrogen functionality.[9,10] Herein we report the enantioselective synthesis of ustiloxin D with a longest linear sequence of 20 steps and using two new catalytic asymmetric reactions in the context of a total synthesis.

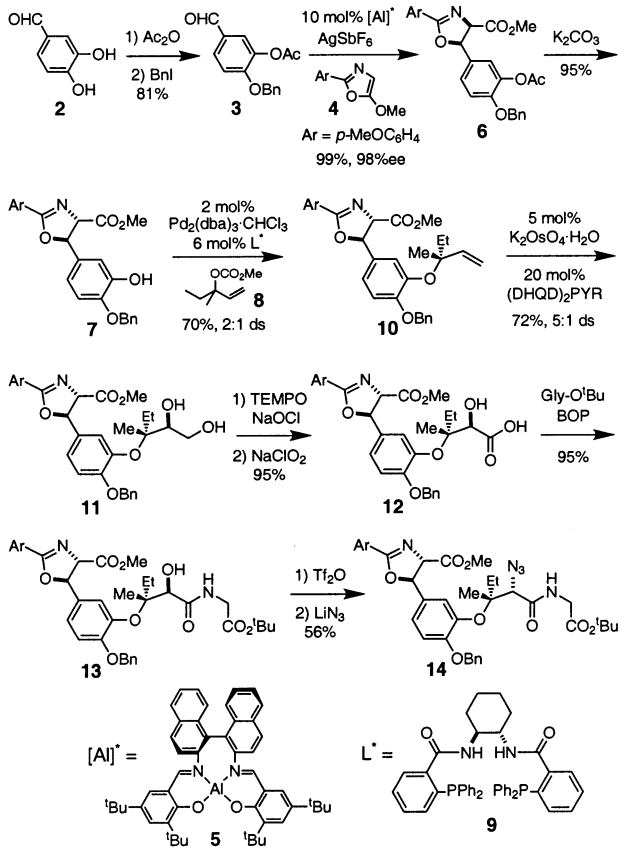
A requirement for our synthesis was to develop a strategy that allows us to access the natural products as well as unnatural variants of both the ustiloxin and phomopsin family members in order to provide sufficient quantities for our biological studies. During our previous studies, we discovered that the phomopsins could not be constructed by directly coupling the side chain to the macrolactam.[11] As a result, our present strategy incorporates the side chain before cyclization. Additionally, the use of Evans's new Al-catalyzed asymmetric aldol reaction between a benzaldehyde derivative and glycine enolate equivalent allows us to access both syn and anti products corresponding to the different stereochemistries at the benzylic hydroxyl group found in ustiloxins and phomopsins.[12] Finally, due to its high functional group tolerance, we used Trost's reaction between a phenol and a chiral π-allyl palladium complex to construct the chiral tertiary alkyl−aryl ether.[13] Taken together, these synthetic strategies allow us to use densely functionalized intermediates to realize an efficient synthesis of ustiloxin D.

The meta hydroxyl group of 3,4-dihydroxybenzaldehyde was selectively acetylated using acetic anhydride in excess sodium hydroxide, followed by benzylation at the para position to give protected benzaldehyde **3** (Scheme 1). The asymmetric aldol reaction was performed using oxazole **4**, 10% (*S*)-chiral aluminum catalyst **5**, and benzaldehyde **3** to provide *cis*-oxazoline **6** in 99% yield and 98% ee.[12] Treatment of **6** with K_2CO_3 in THF and methanol coincidently epimerized the methyl ester and hydrolyzed the aryl acetate to give the *trans*-oxazoline **7** in 95% yield. Reaction of phenol **7** with the π-allyl palladium precursor **8** in the presence of (*S*,*S*)-ligand **9** and $Pd_2(dba)_3$·$CHCl_3$ proceeded smoothly to give the key ether linkage in 70% yield as a 2:1 ratio of inseparable diastereomers. This mixture was carried through all subsequent steps to the end of the synthesis. We are currently exploring the use of

Chart 1. Ustiloxin D and Phomopsin A



Scheme 1



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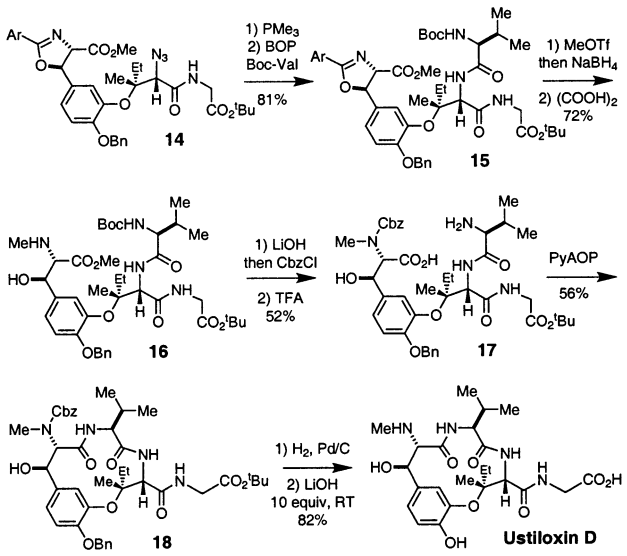
Scheme 2



nonracemic tertiary carbonate substrates to improve the selectivity of this transformation.

Sharpless's asymmetric dihydroxylation was used to set the C3 stereochemistry in 72% yield as a 5:1 ratio of diastereomers. Monosubstituted alkenes possessing allylic oxygenation are not generally the best substrates for this reaction,[14] and the $(DHQD)_2PYR$ ligand provided the best selectivity in our hands. The primary alcohol of **11** was selectively oxidized to the carboxylic acid in two steps, and the corresponding acid was coupled to Gly-O^{t}Bu to provide **13**. Activation of the secondary hydroxyl group as a trifluoromethanesulfonate, followed by treatment with anhydrous lithium azide in DMPU,[15] installed the C3 nitrogen functionality.

Reduction of azide **14** to the corresponding amine followed by coupling to Boc-valine provided **15** (Scheme 2). Treatment with methyl trifluoromethanesulfonate followed by $NaBH_4$ converted the oxazoline to the *N*-methyloxazolidine, which was then hydrolyzed to amino alcohol **16** upon treatment with mild acid. Careful treatment of **16** with 3 equiv of lithium hydroxide at 0 °C selectively hydrolyzed the methyl ester, which was followed by in situ protection of the secondary amine. The Boc group was selectively removed using 20% TFA (v/v) in dichloromethane at 0 °C to provide macrolactam precursor **17**. Slow addition of amino acid **17** to a DMF solution containing the coupling agent PyAOP[16] and Hunig's base provided macrocycle **18**. A two-step deprotection protocol, hydrogenolysis followed by basic hydrolysis, gave synthetic ustiloxin D, which proved to be identical to a sample of the natural product by spectroscopic analyses (^{1}H and ^{13}C NMR, HRMS, and specific rotation) as well as by TLC and HPLC analysis.

The enantioselective total synthesis of ustiloxin D has been achieved starting with 2,3-dihydroxybenzaldehyde. Three catalytic asymmetric reactions were employed to set the four stereocenters at C2, C3, C9, and C10. In particular, the use of Evans's Al-mediated aldol reaction is a highly flexible and enantioselective method to prepare the substituted phenylserine residues that possess the correct C10 stereochemistries for both ustiloxin and phomopsin family members. Furthermore, this reaction furnished the oxazoline product as a protecting group for the C9−C10 amino alcohol, and following 10 intervening transformations, our alkylative strategy for oxazoline deprotection delivered the desired *N*-methylated amine that is found in the natural product. Finally, the incorporation of the peptide side chain prior to macrocyclization will allow us to extend this strategy to the synthesis of more complex phomopsin family members.

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Supporting Information Available: Full characterization of natural and synthetic samples of ustiloxin D (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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