ORGANIC LETTERS

2005
Vol. 7, No. 23
5325−5327

A Convergent Total Synthesis of Ustiloxin D via an Unprecedented Copper-Catalyzed Ethynyl Aziridine Ring-Opening by Phenol Derivatives

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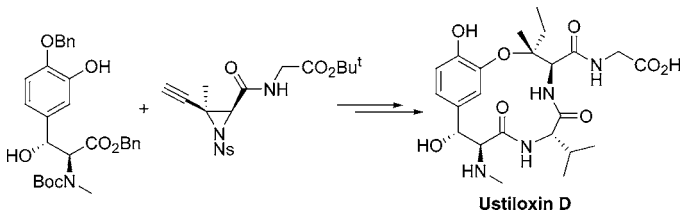
Received September 21, 2005

ABSTRACT



Ustiloxin D

The ustiloxins are a family of heterodetic cyclopeptides that have been isolated from the water extracts of false smut balls on the panicles of rice plants caused by the fungus *Ustilaginoidea virens*. A concise total synthesis of ustiloxin D has been achieved via an unprecedented ethynyl aziridine ring-opening of phenol derivatives. The longest linear sequence of the synthesis is 15 steps from commercially available compounds.

Ustiloxins[1] and phomopsins[2] are naturally occurring heterodetic peptides that are potent antimitotic agents.[3] Although isolated from distinct sources, these natural products share a similar 13-membered cyclic core structure with a unique chiral tertiary alkyl−aryl ether linkage (Figure 1). The stereocontrolled synthesis of tertiary alkyl−aryl ethers remains a challenge, especially in the presence of a vicinal stereogenic center. A goal of our program is to achieve the total synthesis of these intriguing molecules and to establish the minimum structural requirements for their antimitotic activity.

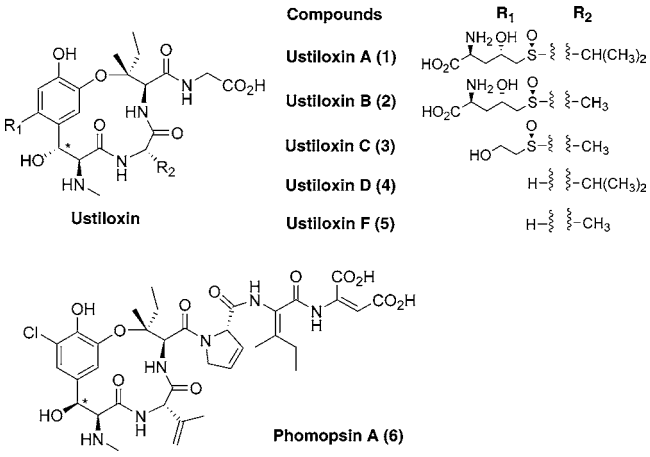


Figure 1. Structures of ustiloxins and phomopsin A.

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10.1021/ol052287g CCC: $30.25
Published on Web 10/12/2005

Two total syntheses of ustiloxin D (**4**) have been reported since its isolation in 1992.[4,5] The first total synthesis in our laboratory was accomplished in 31 steps utilizing a nucleophilic aromatic substitution (S_NAr) reaction to construct the chiral tertiary alkyl−aryl ether.[4] A 20-step synthesis by the Wandless group[5] used an Evans Al-catalyzed asymmetric aldol-type reaction,[6] as well as a Trost Pd-catalyzed asymmetric allylic *O*-alkylation (AAA) reaction[7] to build the chiral tertiary alkyl−aryl ether linkage.

To synthesize other ustiloxin congeners and their analogues for biological evaluation, a convergent and versatile second-generation approach was required. Moreover, the approach should be easily modifiable for the synthesis of phomopsin A. Our initial studies showed that a late-stage stereoselective tertiary alkyl−aryl ether formation was the key to a convergent route. Three types of reactions have been reported to form such a chiral tertiary ether motif, namely, the S_NAr reaction,[8] Mitsunobu-type reaction,[9,10] and AAA reaction.[7] However, our investigations indicated that the S_NAr and Mitsunobu reactions were highly substrate dependent and not suitable for late-stage synthesis. The asymmetric allylic *O*-alkylation reaction did not provide satisfactory results, although our model studies provided modest regio- and diastereoselectivity. Wandless also reported that the AAA reaction yielded a 2:1 ratio of inseparable diastereomers that were carried through all subsequent manipulations to the end of the synthesis.[5] As very limited methods exist to construct chiral tertiary alkyl−aryl ethers, a new method to build such a motif would not only be useful for the total syntheses of ustiloxin and phomopsin natural products but would also provide convenient access to other chiral tertiary alkyl ethers.

To this end, an unprecedented copper-catalyzed ethynyl aziridine ring-opening reaction by phenol derivatives was developed and optimized (Figure 2).[11] The new reaction

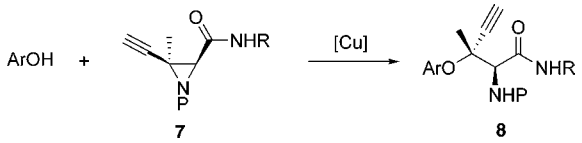

Figure 2. Copper-catalyzed ethynyl aziridine ring-opening by phenol derivatives.

affords tertiary alkyl−aryl ethers in a highly stereo- and regioselective fashion. Product **8** possesses the correct absolute configuration at the two chiral centers for ustiloxins and phomopsin A. More importantly, the ethynyl aziridine ring-opening reaction tolerates many functional groups and works with complex substrates.

A second-generation retrosynthetic analysis of ustiloxin D (**4**) is shown in Figure 3. The disconnection of the valine

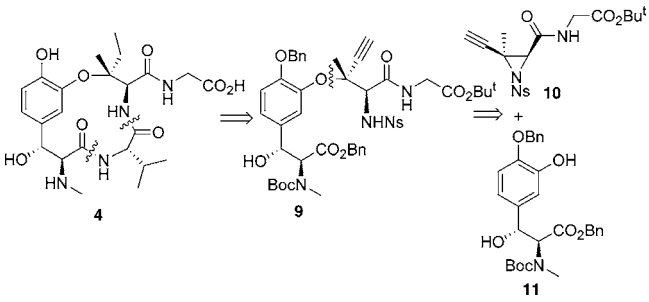

Figure 3. Second-generation retrosynthetic analysis.

residue from the ustiloxin macrocycle provides **9**. The advantage of this strategy is that this residue could be replaced by other amino acids to afford ustiloxin F (**5**) and other analogues. Further disconnection of **9** at the alkyl−aryl ether linkage provides two intermediates (**10** and **11**) of similar structural complexity. Both **10** and **11** could be synthesized rapidly from commercially available compounds. It should be mentioned that our early results, which were almost identical to those reported by Wandless,[5] provided all four diastereomers of **11** by an Evans aldol-type reaction.[6] The availability of these isomers makes the route modifiable for the synthesis of phomopsin A.

The synthesis of ethynyl aziridine **10** started from methyl ketone **12**, an intermediate in our previous total synthesis of ustiloxin D.[4,12,13] It was obtained in 60% yield by a four-step sequence from D-serine without chromatographic separation. Grignard addition of ethynylmagnesium bromide to **12** afforded chiral tertiary alcohol **13** in 80% yield with an 11:1 diastereomeric ratio. The amino alcohol was liberated by full deprotection with concentrated HCl, followed by selective protection of the primary amino group as its 2-nitrobenzenesulfonamide (Ns) in one pot. A one-step TEMPO-catalyzed oxidation protocol[14] directly oxidized the primary hydroxyl group of diol **14** to a carboxylic acid, which was coupled with glycine *tert*-butyl ester to provide dipeptide **15** in 85% over two steps without affecting the tertiary hydroxyl group. Mitsunobu reaction converted **15** to ethynyl aziridine **10** in 84% yield. The sequence for the preparation of aziridine **10** from D-serine was nine steps (Scheme 1).

The *p*-hydroxyl group of 3,4-dihydroxybenzaldehyde (**16**) was selectively protected as its benzyl ether,[15] followed by acylation of the *m*-hydroxyl group. Al-catalyzed asymmetric aldol-type reaction between aryl aldehyde **17** and 5-methoxy-2-(4-methoxyphenyl)oxazole (**18**) provided *cis*-oxazoline **19**

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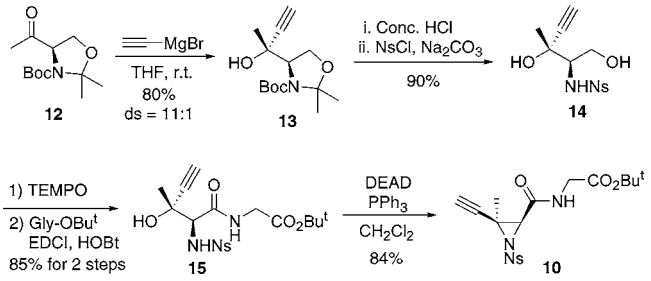
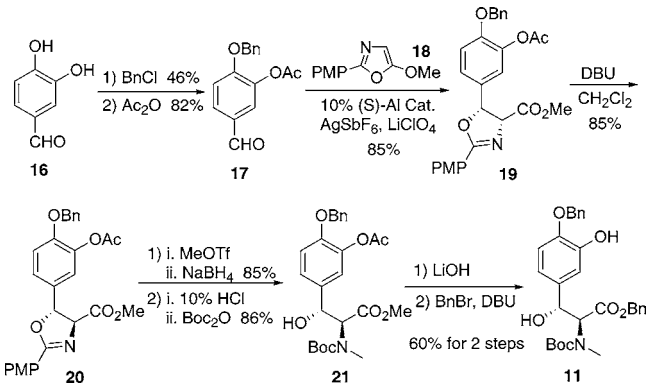
Scheme 1. Synthesis of Ethynyl Aziridine **10**



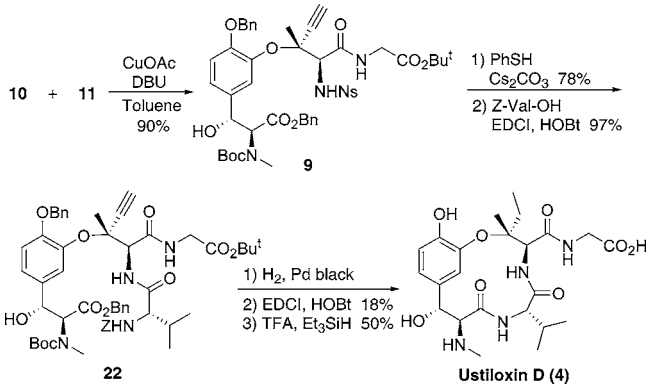
in 85% yield as a single enantiomer after recrystallization. DBU-mediated isomerization[6] afforded the *trans* isomer **20**. Iminium ion formation of **20** with methyl triflate followed by in situ $NaBH_4$ reduction at −78 °C introduced the *N*-methyl group required in ustiloxins.[16] Since diastereomers were formed upon reduction, the *p*-methoxybenzylidene was cleaved by 10% aqueous HCl, and the resulting secondary amine was protected as a Boc carbamate in one pot. Hydrolysis of the acetate and methyl ester of compound **21**, followed by selective formation of the benzyl ester, afforded the β-hydroxy tyrosine derivative **11** in a sequence of eight steps (Scheme 2).

Scheme 2. Synthesis of β-Hydroxy Tyrosine Derivative **11**



With compounds **10** and **11** in hand, the new ethynyl aziridine ring-opening reaction was successfully catalyzed by copper(I) acetate to provide the desired chiral tertiary alkyl−aryl ether **9** in 90% yield. The *o*-nosyl group was removed to afford the primary amine[17] in 78% yield. The amine was coupled with *Z*-valine using EDCI and HOBt to install all the required amino acid components for ustiloxin D. Palladium black catalyzed hydrogenolysis of **22** simultaneously removed the benzyl carbamate, benzyl ester, and benzyl ether and reduced the ethynyl group to the requisite ethyl group to afford the linear precursor, which underwent macrolactamization to provide the macrocycle in 18% yield for two steps. Cleavage of the Boc carbamate and *tert*-butyl ester by TFA in the presence of triethylsilane[18] completed the total synthesis of ustiloxin D (**4**) (Scheme 3).

Scheme 3. Synthesis of Ustiloxin D (**4**)



In conclusion, a concise total synthesis of ustiloxin D was achieved in 15 steps by the application of an unprecedented ethynyl aziridine ring-opening by a β-hydroxy tyrosine derivative. This approach is significantly more convergent than previous total syntheses, and it is also versatile for the synthesis of other congeners of ustiloxin and phomopsin natural products and their analogues.

Acknowledgment. We thank the NIH (CA-40081), Wyeth Research, and the University of Pennsylvania (Research Foundation) for financial support.

Note Added after ASAP Publication: There was an error in Scheme 2 in the version published ASAP October 12, 2005; the corrected version was published ASAP October 13, 2005.

Supporting Information Available: Experimental procedures and characterization data for compounds and intermediates in Scheme 3. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052287G

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