A Stereospecific Elimination to Form Dehydroamino Acids: Synthesis of the Phomopsin Tripeptide Side Chain

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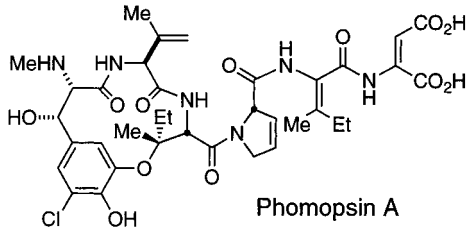
An increasing interest in α,β-dehydroamino acids has developed in recent years based both on their importance as commodity chemicals and their presence in biologically active natural products. Efficient methods for the asymmetric hydrogenation of α,β-dehydroamino acids allow access to a wide variety of unnatural amino acids.[1] Dehydroamino acids are also found in many natural products including the antrimycins, tentoxin, and the phosphatase inhibitors microcystin and nodularin.[2] Unsaturated amino acids introduce elements of conformational rigidity as well as changes in reactivity due to the presence of an alkene.[3] In this report, we describe an efficient and stereoselective method for the synthesis of α,β-dehydroamino acids from readily available β-hydroxyamino acids.

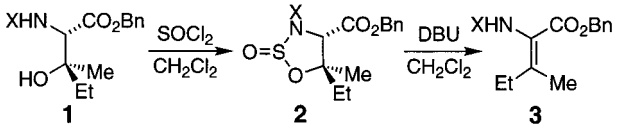
These findings grew out of research directed toward the total synthesis of phomopsin A, which is a fungal metabolite that binds to microtubules (Chart 1).[4] Our synthetic approach required a

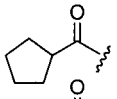
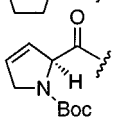
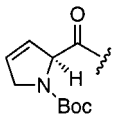
Chart 1



method to stereoselectively prepare (*E*)-dehydroisoleucine. A variety of methods exist for the synthesis of dehydroamino acids, and they have been reviewed recently.[3c,5] Some of these approaches introduce unsaturation using elimination reactions such as the dehydration of β-hydroxyamino acids as well as N-chlorination followed by dehydrochlorination. Alternative methods utilize condensation reactions (e.g., the Horner−Wadsworth−Emmons reaction of phosphorylglycine esters) to form the double bond. These methods generally rely on thermodynamic control to dictate the alkene geometry. If there is no strong thermodynamic preference or if the desired product is not the thermodynamically favored isomer, the existing synthetic methods are often ineffective. Others have used these methods to synthesize dehydroisoleucine, and the most efficient method provided a 3:2 mixture of *E* and *Z* isomers.[6]

Table 1. Dehydroamino Acids from Tertiary Alcohols

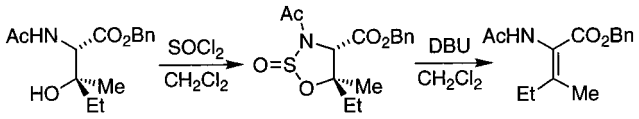


Entry	X	Isolated yield (%) 1→2	2→3
1	Ac	77	79
2		70	96
3		83	77
4	Boc	91	84
5	Ac	77	82 [a]
6		75	83 [a]

[a] The (2*S*,3*S*) substrate was used providing (*E*) **3**.

Enantiomerically pure β-hydroxy-α-amino acids are readily accessible using Sharpless' methods,[7] and thus we chose dehydration as our preferred synthetic strategy. We observed that treatment of an *N*-acyl-β-hydroxyamino ester with thionyl chloride led to formation of cyclic sulfamidites. The diastereomeric products, arising from two configurations at sulfur, were separated and isolated. Treatment of either diastereomer with base resulted in elimination of SO_2 to yield the α,β-dehydroamino ester (Scheme 1). The more oxidized cyclic sulfamidates have previ-

Scheme 1



ously been used as substrates for nucleophilic substitution reactions.[8] Recently, direct nucleophilic ring openings of cyclic sulfamidites derived from amino alcohols have been reported.[9] However, neither cyclic sulfamidites nor sulfamidates have been directly employed as substrates for elimination reactions.

Tertiary alcohols can be difficult to functionalize and stereoselectively eliminate due to steric crowding and a propensity to undergo E1 elimination reactions. In our hands, tosylation and mesylation of β-hydroxyisoleucine could only be achieved in low yields, and subsequent elimination reactions led to complex mixtures of products. However, Table 1 shows the results for the

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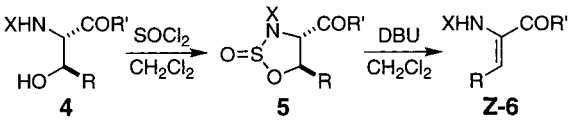
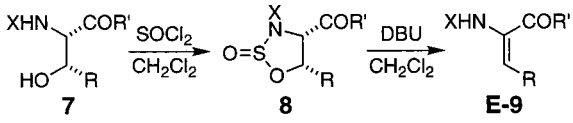
Table 2. Dehydroamino Acids from Secondary Alcohols



	Substrate			Isolated yield (%)		
				Method A		Method B
Entry	X	R	R'	4→5	5→6	4→6
1	Cbz	Ph	OMe	100	91	95
2	Cbz	Me	OBn	85	96	87
3	Boc	Me	OBn	81	72	82
4	Fmoc	Me	OBn	96	69 [a]	47
5	Bz	Me	OMe	39	53	83
6	CF_3CO	Me	OBn	72	35	55
7	Piv	Me	OBn	59	65	60
8	Cbz	Me	NH-Ala-OMe	89	0 [b]	66



	Substrate			Isolated yield (%)		
				Method A		Method B
Entry	X	R	R'	7→8	8→9	7→9
9	Cbz	Ph	OMe	92	60	80
10	Cbz	Me	OBn	62	54	82

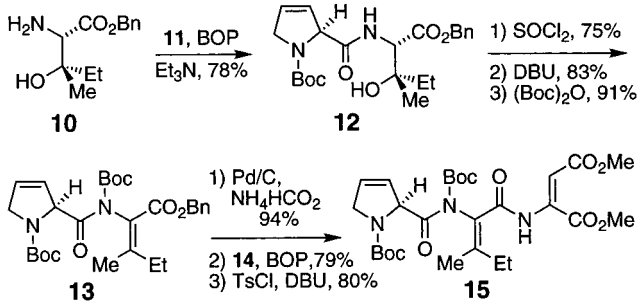
[a] The Fmoc group was removed and the amine was obtained. [b] By using the two-step procedure the cyclic sulfamidite was isolated, but the intermediate underwent hydrolysis upon treatment with base.

elimination of tertiary β-hydroxyamino esters to β,β-disubstituted dehydroamino esters via sulfamidite intermediates. This reaction is highly stereoselective, which facilitates the synthesis of either the *E* or *Z* isomer of dehydroisoleucine depending upon the configuration of the initial β-hydroxyamino ester (Table 1, entries 3 and 6). Only products derived from antiperiplanar elimination have been observed, and molecular modeling of both diastereomeric sulfamidite intermediates (Table 1, entry 1) reveals H−C_α−C_β−O bond angles of 150−154°.

This method is also suitable for the elimination of secondary alcohols, and results using threonine and hydroxyphenylalanine derivatives are shown in Table 2. Preliminary investigations led to the development of two experimental methods. Using a two-step procedure, the intermediate sulfamidites are isolated, purified by chromatography, and then treated with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU).[10] An alternative procedure is a one-pot protocol that requires an excess of base. Acyl groups with various steric and electronic characteristics are tolerated on the nitrogen atom, and entry 8 demonstrates that this method may be used for dipeptide substrates. The high degree of stereoselectivity is especially noteworthy in the case of (*E*)-dehydrophenylalanine (entry 9).[11] Cyclic sulfamidites may also be effectively used to synthesize dehydroalanine derivatives.[12]

We used this method to synthesize the tripeptide side chain of phomopsin A (Scheme 2). The benzyl ester of β-hydroxyisoleucine (**10**) was coupled to *N*-Boc-dehydroproline (**11**) to provide dipeptide **12**. Formation of the cyclic sulfamidite was followed by stereoselective elimination to yield the didehydrodipeptide, which was subsequently protected with Boc anhydride to provide **13**. Transfer hydrogenolysis liberated the free carboxylic acid without reduction of dehydroproline. The carboxylic acid was then coupled to dimethyl β-hydroxyaspartate (**14**), and subsequent dehydration provided the desired protected tripeptide (**15**), which will be further elaborated to phomopsin A.

Scheme 2



We have developed an efficient and stereospecific method to synthesize trisubstituted and tetrasubstituted α,β-dehydroamino acids from β-hydroxyamino acid derivatives. The requisite substrates are readily available, and high to moderate yields of the desired dehydroamino acid derivatives are obtained. Cyclic sulfamidites provide an effective solution to the problem of stereoselectively synthesizing α,β-dehydroamino acids.

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Supporting Information Available: Experimental procedures and characterization data are provided (PDF). This material is provided free of charge via the Internet at http://pubs.acs.org.

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(10) Bases other than DBU have been used for the two-step procedure with similar success. Tetramethylguanidine, 1,5-diazabicyclo[4,3,0]non-5-ene, and potassium *tert*-butoxide efficiently convert sulfamidites to the corresponding alkenes (data not shown).

(11) Excellent yields of (*E*)-dehydrophenylalanine derivatives may also be obtained by treating the intermediate cyclic sulfamidite with $RuCl_3$ and $NaIO_4$ to form the cyclic sulfamidate, which stereoselectively provides the desired product upon treatment with DBU.

(12) Treatment of Cbz-serine-benzyl ester with thionyl chloride using the one-step procedure provided 74% yield of the α,β-dehydroamino ester.