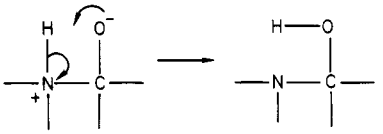
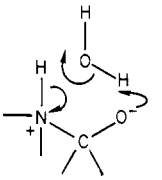
portant point here is that if severely bent N/H/N geometries are readily generated in intramolecular reactions, then nonlinear transfer probably contributes to intermolecular reactions as well.[10] Assumptions of linearity in the latter may therefore be suspect.

The MINDO/3 calculations on $NH_2CH_2NH_3^+$ relate to the "proton switch" mechanism of tetrahedral intermediates:



Such a mechanism has been proposed for ester aminolyses, amide hydrolyses, and enzyme-catalyzed mechanisms.[11-13] It appears from the high activation energy associated with our 1,3-shift that the mechanism, taken literally, is not favorable. If, however, one or more solvent or buffer species intervene according to a Grunwald-Meiboom mechanism,[14] then compressing the N/C/N angle would no longer be necessary, and rates of 10^6-10^8 s^{-1} are possible.



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Communications

Stereospecific Synthesis of α,β-Dehydroamino Acids from β-Hydroxy α-Amino Acid Derivatives

Summary: A series of protected β-hydroxy α-amino acids have been converted stereospecifically to their dehydro derivatives by treatment with (diethylamino)sulfur trifluoride and pyridine, threo isomers giving rise to the *Z* derivatives and erythro isomers to the *E* derivatives.

Sir: Dehydroamino acids have recently become a topic of increasing interest as important constituents of many fungal metabolites with antibiotic or phytotoxic properties such as nisin and subtilin.[1,2] In addition, dehydroamino acids are versatile precursors for the asymmetric synthesis of amino acids and peptides.[3-5]

Several syntheses of dehydroamino acids have been reported,[2] the most general of which involves β elimination from β-functionalized α-amino acids. For exammple, β-hydroxy α-amino acids have been converted to their unsaturated analogues via base treatment of their *O*-tosyl or β-chloro derivatives.[6,7] Alternatively, β-mercapto α-amino acids have been oxidized to the corresponding sulfoxides and then subjected to thermal elimination.[8] Direct methods involving dehydration of protected β-hydroxy α-amino acids with several dehydrating agents have also been reported.[9,10] However, mixtures of geometrical isomers (*E* and *Z*) have been obtained. Recently the use of disuccinimido carbonate for the dehydration of threonine to the *Z* isomer has also been reported.[11]

In this paper we describe a one-step, stereospecific and efficient method for the preparation of α,β-dehydroamino acids from protected β-hydroxy α-amino acids using (diethylamino)sulfur trifluoride (DAST) with pyridine as the dehydrating agent. Although DAST is generally employed for fluorinating alcohols with a minimum of side reactions,[12] a few instances involving extensive dehydration have been reported.[13,14] We have thus investigated dehydration of β-hydroxy amino acid derivatives with DAST, and we have found that in the presence of a base such as

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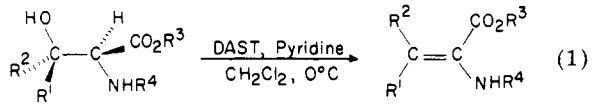
Table I. Preparation of Dehydroamino Acids from β-Hydroxy Amino Acid Derivatives Using (Diethylamino)sulfur Trifluoride and Pyridine

reactant	product[a]	yield,[b] %	mp, °C	NMR ($CDCl_3$)[c] β-H (s)	NMR ($CDCl_3$)[c] α-H (s)	R_f[d]
Z-Ser-OBz (1a)	Z-ΔAla-OBz (2a)	75	46-48	5.83 (s), 6.25 (s)		0.66
Z-Thr-OBz (1b)	(Z)-Z-ΔAbu-OBz (2b)	90	58-59[e]	6.79 (q, J = 7.2)	1.80 (d, J = 7.2)	0.39
Z-Allothr-OBz (1c)	(E)-Z-ΔAbu-OBz (2c)	90	46-47	6.92 (q, J = 7.1)	2.08 (d, J = 7.1)	0.50
threo-Z-3-OHLeu-OBz (1d)	(Z)-Z-ΔLeu-OBz (2c)	90	72-73[e]	6.52 (d, J = 10.3)	2.67 (m, J = 10.3, 6.6)	0.47
erythro-Z-3-OHLeu-OBz (1e)	(E)-Z-ΔLeu-OBz (2e)	80	30-31	6.60 (d, J = 10.2)	3.33 (m, J = 10.2, 6.7)	0.58
Boc-Thr-OEt (1f)	(Z)-Boc-ΔAbu-OEt (2f)	70[f]	31-33	6.67 (q, J = 7.2)	1.80 (d, J = 7.2)	0.49
Boc-Allothr-OEt (1g)	(E)-Boc-ΔAbu-OEt (2g)	65	oil	6.77 (q, J = 7.7)	2.06 (d, J = 7.7)	0.65

[a] IR and mass spectra and C, H, and N microanalysis were in accord with product structure. [b] Isolated purified yields. [c] NMR spectra were recorded on a 80-MHz Varian FT-80A spectrometer by using FT techniques; the chemical shifts are given in δ reltaive to internal Me_4Si and the J values are given in hertz. [d] Measured on silica TLC plates by using EtOAc/hexane (1:3 v/v) as the eluent; solvent migration was 6.5 cm. [e] Recrystallization solvent was ether-*n*-hexane. [f] 15% starting material was recovered.

pyridine dehydrated amino acids are obtained in high yields (eq 1). The method has been applied to derivatives



(1)

1 2

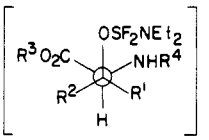
	R¹	R²	R³	R⁴
a	H	H	CH_2Ph	CO_2CH_2Ph
b	Me	H	CH_2Ph	CO_2CH_2Ph
c	H	Me	CH_2Ph	CO_2CH_2Ph
d	$CHMe_2$	H	CH_2Ph	CO_2CH_2Ph
e	H	$CHMe_2$	CH_2Ph	CO_2CH_2Ph
f	Me	H	CH_2Me	CO_2CMe_3
g	H	Me	CH_2Me	CO_2CMe_3

of serine, threonine (threo and erythro), and 3-hydroxyleucine (threo and erythro).[15] Benzyloxycarbonyl and *tert*-butoxycarbonyl groups were used as the nitrogen protective groups and benzyl and ethyl groups as the carboxyl protective groups. The experimental procedure is illustrated below for the preparation of (Z)-*N*-(benzyloxycarbonyl)-2,3-dehydro-2-aminobutyric acid benzyl ester (**2b**) from *N*-(benzyloxycarbonyl)threonine benzyl ester (**1b**).

A solution of **1b** (343 mg, 1 mmol) and pyridine (0.8 mL, 1 mmol) in dry CH_2Cl_2 (2 mL) is added dropwise to a solution of DAST (0.13 mL, 1 mmol) in CH_2Cl_2 (2 mL) at 0 °C over a few minutes. The reaction solution is stirred for 0.5 h at 0 °C, washed with 5% $NaHCO_3$, and concentrated in vacuo. The residue is chromatographed on silica gel with 10% EtOAc in hexane as the eluent to give pure **2b** in 90% yield. Similarly, dehydroamino acids **2a,c–g** have been prepared from the corresponding hydroxy amino acids **1a,c–g**. The results of these experiments are given in Table I.

The assignment of configuration of products **2b–g** and their stereochemical purity were determined by NMR spectroscopy, which differentiates between the *E* and *Z* isomers. Inspection of the NMR spectra of our crude reaction products indicated the sole formation of the *Z* isomers from *threo*-β-hydroxy α-amino acid derivatives and of the corresponding *E* isomers from *erythro*-hydroxy precursors. The purity of the reaction products was further confirmed by TLC analysis, since *E* and *Z* isomers show different R_f values on silica (Table I).

The stereospecific formation of (Z)-dehydroamino acids from *threo*-hydroxy amino acids and (E)-dehydroamino acids from *erythro*-hydroxy amino acids is compatible with an E2 elimination process. Since DAST is known to react with alcohols to give $ROSF_2NEt_2$ derivatives,[12] the reaction is likely to involve formation of intermediate **3**, followed by trans elimination from an antiperiplanar conformation.



3

The high stereospecificity of this reaction may be attributed to the good leaving ability of the OSF_2NEt_2 group in what apparently is a concerted mechanism and to the mild reaction conditions, which preclude product isomerization. No isomerization was thus observed when the syntheses of the thermodynamically less favored (E)-dehydroamino acids **2c,e,g** were performed, although *E* to *Z* isomerizations are often encountered under classical dehydration conditions.[7,16]

These results demonstrate the usefulness of DAST/pyridine as a powerful dehydrating agent for the stereospecific preparation of dehydroamino acids. Expansion of this method to direct synthesis of dehydropeptides is under current investigation.

Registry No. **1a**, 21209-51-8; **1b**, 16597-50-5; **1c**, 84500-41-4; **1d**, 84500-42-5; **1e**, 84500-43-6; **1f**, 84500-44-7; **1g**, 84500-45-8; **2a**, 59524-07-1; (*Z*)-**2b**, 84520-34-3; (*E*)-**2c**, 84500-46-9; (*Z*)-**2c**, 84520-50-3; (*E*)-**2e**, 84500-47-0; (*Z*)-**2f**, 84500-48-1; (*E*)-**2g**, 84500-49-2; (diethylamino)sulfur trifluoride, 38078-09-0; pyridine, 110-86-1.

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