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Diastereoselective Synthesis of *N*-Protected β-Amino-α-hydroxyacids (Norstatines) from Urethane *N*-Carboxyanhydrides (UNCAs)†

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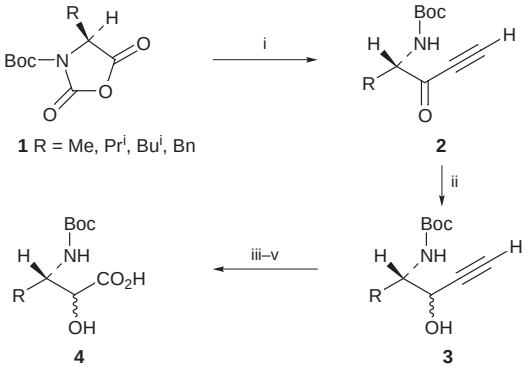
β-Amino-α-hydroxyacids (norstatines) are prepared from urethane *N*-protected carboxyanhydrides (UNCAs); the key step is the diastereoselective reduction of a keto-acetylenic compound, which lead is, with *syn* diastereoselectivity, to the corresponding propargylic alcohol.

The development of new synthetic routes to unusual amino acids has attracted considerable recent interest. In particular, the naturally occurring peptides bestatin and amastatin discovered by Umezawa[1] contain a β-amino-α-hydroxyacid moiety (norstatine). These peptides were shown to be potent inhibitors of aminopeptidases.[2] Furthermore, norstatine-related compounds have been reported to be HIV protease[3] and renin inhibitors.[4] β-Amino-α-hydroxyacids are thereby interesting synthetic targets since norstatine acts as a transition state mimic of peptide bond hydrolysis.

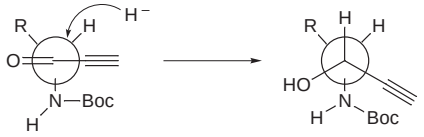
We have been involved in the study of the reactivity of urethane *N*-protected carboxyanhydrides (UNCAs). UNCAs are very reactive and were used with success for the synthesis of various amino acid derivatives such as β-amino-alcohols,[5] statine derivatives[6] and α-amino-aldehydes.[7] We have previously described a general method for the preparation of norstatines from *N*-protected aminoaldehydes.[8] The key step was the reaction of ethynylmagnesium bromide with *N*-protected aminoaldehydes to afford propargylic alcohols with *syn* diastereoselectivity. We propose here an alternative route to prepare norstatines from UNCAs **1** (Scheme 1). The interest in this method is to allow the preparation of both *syn* or *anti* diastereomers, according to the reduction conditions used for the keto-acetylenic derivative.



Scheme 1 i, H−C≡C−MgBr, THF, −60 °C; ii, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C; iii, dihydropyran, PPTS, CH_2Cl_2; iv, $NaIO_4$, $RuCl_3$, CH_3CN/CCl_4, H_2O; v, H_3O^+.

We studied first the reactivity of urethane *N*-protected carboxyanhydrides **1** towards ethynylmagnesium bromide. To avoid a possible double addition of the acetylide on the carbonyl group, the reaction was run at low temperature (−60 to −40 °C) and we noticed that UNCAs are reactive enough to yield to the corresponding keto-acetylenics **2** in acceptable yields (Table 1).

In a second approach, we have examined the stereoselective reduction of compounds **2** with Luche's reagent.[9] We assumed that reduction under these conditions led, with non-chelation control, to the *syn* propargylic alcohols **3** (Scheme 2).



Scheme 2

To confirm the supposed *syn* diastereoselectivity of the reduction leading to the (2*S*, 3*S*)-norstatines, we have converted the propargylic alcohol **3a** into the corresponding oxazoline derivative **5** after reaction with 2,2-dimethoxypropane (Scheme 3).

Table 1 Preparation of norstatines **4** from *N*-protected *N*-carboxyanhydride (UNCAs)

UNCA (**1**)	Keto-acetylenic compound **2** (% yield)	Propargylic alcohol **3** (% yield)	Norstatine **4** (% yield)
Boc-Ala-NCA (**1a**)	72	96 (*syn*/*anti*: 80/20)	58
Boc-Phe-NCA (**1b**)	41	95 (*syn*/*anti*: 72/28)	65
Boc-Leu-NCA (**1c**)	62	97 (*syn*/*anti*: 70/30)	60
Boc-Val-NCA (**1d**)	60	–	–

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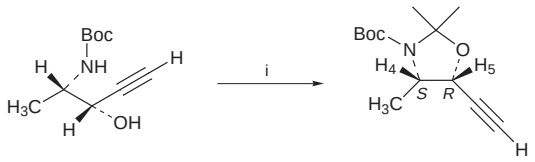
† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



3a 5

Scheme 3

The relative configuration of **5** was assigned on the basis of the ^{1}H NMR coupling constant between H4 and H5. The mixture of stereoisomers was quantified by the distinguishable signals.

The *N*-protected *β*-amino-*α*-hydroxyalkanoic acids **4** were synthesized as shown in Scheme 1. Alcohols **3** were then protected by tetrahydropyranylation in quantitative yields before oxidative cleavage. Oxidation of these intermediates into acids (norstatines) was achieved using the $RuCl_3/NaIO_4$ method[10] in 58–65% yields.

In summary, we have demonstrated a convenient diastereoselective synthesis of norstatines from UNCAs. The procedure described in this paper allows the preparation of (2*S*, 3*S*)-norstatines. The interest in this methodology is to allow the preparation of both (2*S*, 3*S*)- and (2*R*, 3*S*)-norstatines with the reducing agent used here.

Experimental

The following procedure is representative. To a stirred solution of ethynylmagnesium bromide in THF (6.0 mmol) was added under nitrogen atmosphere at −60 °C, a solution of UNCA (5 mmol) in THF (10 ml). The reaction mixture was stirred for 4 h between −60 and −40 °C and then quenched with NH_4Cl (10 ml). The product was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give an oil which was purified by chromatography on silica gel. The keto-acetylenic compound **2a** was obtained in 72% yield; mp 66–67 °C, $[\alpha]_D^{20}$ − 35.7 (*c*, 1.0, methanol); ν/cm^{-1} (KBr) 3398, 3213, 2084, 1690, 1378, 1166; δ_H (200 MHz, $CDCl_3$) 1.42 (d, 3 H, $J = 7$ Hz), 1.45 (s, 9 H), 3.37 (s, 1 H), 4.42 (qxd, 1 H, $J = J' = 7$ Hz), 5.12 (s large, 1 H).

Alcohol **3a**.—Major diastereomer (80%): δ_H (300 MHz, $CDCl_3$) 1.22 (d, 3 H, $J = 7$ Hz), 1.45 (s, 9 H), 2.47 (d, 1 H, $J = 2.1$ Hz), 3.55 (s large, 1 H), 3.75–4.05 (m, 1 H) 4.40 (dxd, 1 H, $J = 2.4$ Hz, $J' = 2.1$ Hz), 4.77 (s large, 1 H). Minor diastereomer (20%): distinct signals δ 4.35 (dxd, 1 H, $J = 5.5$ Hz, $J' = 2.1$ Hz).

Oxazoline Derivative **5**.—On the basis of the ^{1}H NMR coupling constant (5.4 Hz) and molecular modelling study using the program SYBYL v. 5.1 (Tripos Associates, St Louis, MO) (torsion between H4 and H5 = 29°) we suggest for the main diastereomer a *syn* stereochemistry and a 4*S*, 5*R* relative stereochemistry at C4 and C5, assuming that the chiral centre of the UNCA was fixed. For the minor diastereomer, the measured coupling constant (3.3 Hz) and the torsion between H4 and H5 (100°) suggest an *anti* stereochemistry.

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