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Synthesis of Chiral Urethane N-Alkoxycarbonyl Tetramic Acids from Urethane N-Carboxyanhydrides (UNCAs)

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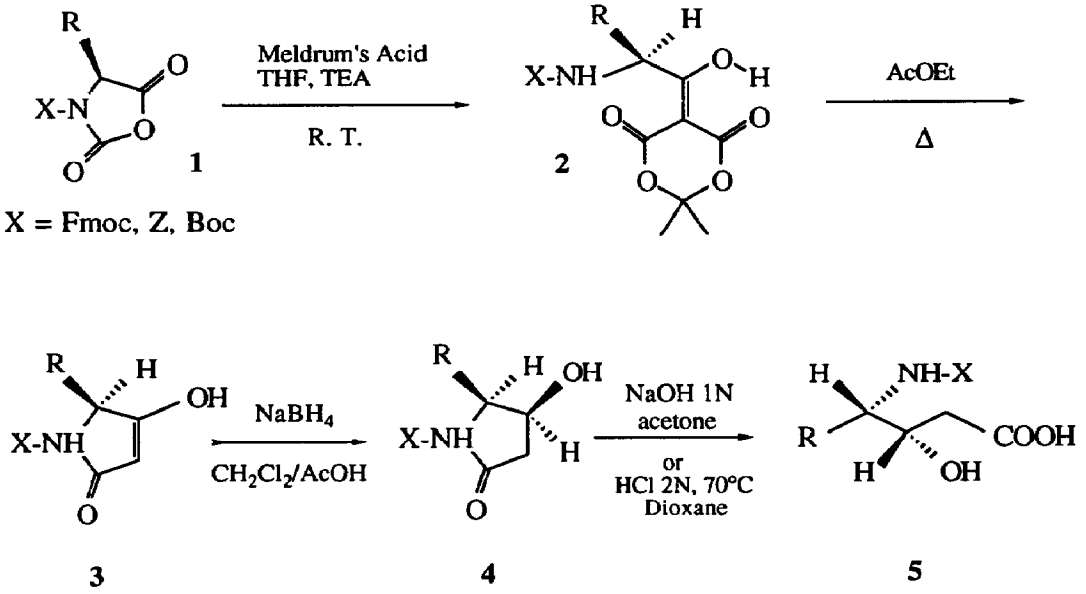
Abstract: The synthesis of chiral N-protected tetramic acid derivatives which are important precursors of β-hydroxy γ-amino acid under mild conditions is described. Reaction of urethane-N-carboxyanhydrides (UNCAs) with Meldrum's acid in the presence of a tertiary amine, followed by subsequent cyclisation produced tetramic acid derivatives. This procedure is applicable to Boc-, Fmoc- and Z- N-carboxyanhydrides.

Statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (AHMHA) is an unusual β-hydroxy γ-amino acid which was first discovered in pepstatin[1], a naturally occuring peptide antibiotic which functions as an unselective inhibitor of acid proteases such as renin, pepsin and cathepsin D. Statine analogs are also present in antiviral cytotoxic cyclodepsipeptides, didemnines A, B, C and nordidemnines A, B, C.[2]

Statine and β-hydroxy γ-amino acid have been widely used for the synthesis of inhibitors of aspartyl proteases such as renin, a key enzyme in the renin-angiotensin system, and HIV. These β-hydroxy γ-amino acids are recognized to mimic the transition state structure of the substrate when interacting with the enzymes. Only the β-hydroxy γ-amino acids of the *syn* configuration are generally believed to adopt a suitable conformation for such an interaction. Several syntheses of *syn*- and *anti*-statine and β-hydroxy γ-amino acids have been reported[3], mainly (i) by acylation of ester enolates or magnesium malonates with acylamino acid derivatives followed by diastereoselective reduction of the β-oxo esters; (ii) by stereoselective aldol condensation of ester enolates and α-alkoxycarbonylamino aldehydes. Stereospecific syntheses of *syn*-statine and statine analogs were reported via stereocontrolled reduction of tetramic acids[4-7]. The key step of these syntheses is the stereoselective reduction of the N-alkyloxycarbonyl tetramic acids **3**. In fact, the stereoselectivity of the reduction is very much dependent on the substitution on the nitrogen; reduction of N-unsubstituted tetramic

acids leads to a mixture of the epimeric alcohols **4**.[8] Optically pure tetramic acids are obtained from N-protected-amino acids, Meldrum's acid, 4-*N,N*-dimethylaminopyridine and isopropenyl chlorofomate[5]. The reaction conditions are rather elusive, and as reported by the authors, any change in the procedure leads to lower yields. Alternatively, enantiomerically pure tetramic acids are also accessible by hydrogenolytic deprotection of 4-(benzyloxycarbonyl)-3-oxocarboxylic acid esters[7]. Tetramic acids are also interesting intermediates for the synthesis of optically active γ-amino acid derivatives.[7]

Scheme 1. Synthesis of tetramic acids **3** and statine analogs **5** from UNCAs



We report herein on a simple and stereoselective synthesis of chiral tetramic acid derivatives **3a-j** (Scheme 1). The reaction of Meldrum's acid on the corresponding N-protected-N-carboxyanhydride **1** derivatives (UNCAs)[9] in the presence of a tertiary amine (triethylamine TEA, N,N-diisopropylethylamine DIEA, N-methylmorpholine NMM, etc.), readily afforded in a few minutes the adducts **2** in high yields. Any effort to purify these oily derivatives by column chromatography were unsuccessful. The crude materials were cyclized according to Jouin and Castro[5] and yielded the corresponding enantiomerically pure tetramic acid derivatives **3a-j** (Table 1). As previously described[5,9], diastereoselective reduction of tetramic acids **3** produced (4*S*, 5*S*)-N-alkoxycarbonyl-4-hydroxy-5-alkylpyrrolidin-2-ones **4** which after hydrolysis yielded statine and statine analogs **5**. The usefulness of this method was demonstrated by the synthesis of a series of tetramic acid **3a-j**

derivatives starting from Z, Boc and Fmoc N-protected-N-carboxyanhydrides (Table 1). They were identified by mass spectrometry, ^1H NMR spectroscopy and by comparison of their physical characteristics with those reported in the literature.

Table 1. Characterization of tetramic acid derivatives **3** from UNCAs **1**

Tetramic acid derivatives§	Yield* (%)	R_f(A)	R_f(B)	$[\alpha]_D^{20}$ (c = 1 MeOH)
Fmoc-L-Phe **3a**	84	0.45	0.57	+ 104
Fmoc-L-Leu **3b**	79	0.54		+ 66
Fmoc-L-Val **3c**	63	0.61	0.68	+ 44
Fmoc-L-Lys(Boc) **3d**	75	0.52	0.80	+ 46
Boc-L-Leu **3e**	87	0.58	0.72	+ 101
Boc-L-Phe **3f**	80	0.37	0.49	+ 205
Boc-L-Trp(For) **3g**	60	0.37	0.35	+ 113
Z-L-Phe **3h**	82	0.35	0.55	+ 150
Z-L-Leu **3i**	76	0.51		+ 44
Z-L-Val **3j**	80	0.75	0.57	+ 54

§ Identified by mass spectrometry and ^1H NMR spectroscopy (250 MHz); * Yields are expressed from the UNCAs; (A) Chloroform/methanol/acetic acid180/10/5; (B) Ethyl acetate/hexane/acetic acid 7/3/1.

In order to verify that the proposed method produced enantiomerically pure statine derivatives, the tetramic acids **3b** (R = *i*-Pr, X = Fmoc), **3e** (R = *i*-Pr, X = Boc) and **3i** (R = *i*-Pr, X = Z) were converted by stereoselective $NaBH_4$ reduction according to Jouin and Castro[5] into the Z-, Boc- and Fmoc- (4*S*,5*S*)-4-hydroxy-pyrrolidin-2-ones **4b**, **4e**, and **4i** (Table 2). Compounds **4e** and **4i** produced upon NaOH treatment Boc- and Z- *syn*-statines, while HCl treatment of compound **4b** led to Fmoc-*syn*-statine **5b**. These N-protected statines had $[\alpha]_D$ similar to that reported in the literature[5,7]. They were characterized by mass spectrometry and ^1H NMR spectroscopy.

Table 2. Characterization of N-protected statine derivatives **5**

Derivative 5	Yield (%)	Rf	$[\alpha]_D^{20}$ (c = 1 MeOH)	MH^+
Boc-L-Leu **5e**	65	0.50 (A)	+ 55	258
Fmoc-L-Leu **5b**	60	0.65 (B)	+ 42	379
Z-L-Leu **5i**	60	0.46 (B)	+ 58	292

Yields are expressed from the UNCAs; (A) Chloroform/methanol/acetic acid 180/10/5; (B) Dichloromethane/ethyl acetate 7/3.

In summary, chiral N-protected tetramic acid derivatives which are important precursors of statine and β-hydroxy γ-amino acid as well as of optically active γ-amino acid derivatives have been efficiently prepared in pure form from UNCAs and Meldrum's acid. These syntheses were performed in mild conditions, with high yields, at room temperature in a few minutes, with non-expensive reagents, providing a very attractive method of synthesis of N-protected tetramic acid derivatives.

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