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Five-Component Synthesis of Marimastat Analogues

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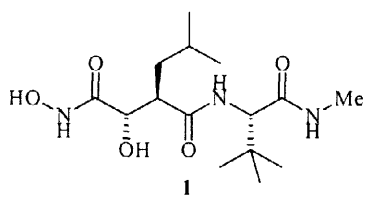
Abstract: The synthesis of analogues of the matrix metalloproteinase (MMP) inhibitor marimastat has been achieved in one-pot by a two step procedure involving an Ugi four-component reaction followed by hydroxylaminolysis of an acetonide.

Keywords: Enzyme inhibitors, hydroxamic acids, Ugi reaction

The hydroxamic acid derivative marimastat (**1**) is an inhibitor of the matrix metalloproteinase (MMP) family of enzymes [1]. Over expression of these zinc dependent enzymes (eg. the collagenases, stromelysins, gelatinases and matrilysin) has been implicated in the pathogenesis of human diseases that involve tissue remodelling and / or destruction. Marimastat and other MMP inhibitors are in clinical trials for the treatment of cancer [2]. These compounds are characterised by possessing a zinc binding group (eg. -CONHOH, -CO_2H, -SH) and substituents which bind to the enzyme sub-sites.



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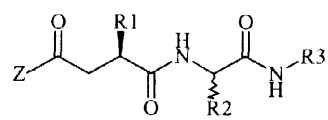

2 Z = OtBu, **3** Z = OH, **4** Z = NHOH

There is considerable interest in methods for the parallel synthesis of MMP inhibitors [3] and we have recently reported the preparation of succinyl derivatives **2** *via* an Ugi four-component condensation (amine + aldehyde + carboxylic acid + isonitrile) [4]. In this procedure ammonia was employed as the amine component and the carboxylic acid component was a mono protected chiral succinic acid derivative. A subsequent deprotection step provided carboxylic acid derivatives **3** which are MMP inhibitors with moderate to good potency. However, the corresponding hydroxamic acids **4** tend to be more potent MMP inhibitors. These could be prepared either by a two step procedure involving coupling with O-benzylhydroxylamine and subsequent catalytic hydrogenolysis, or the less efficient direct coupling with hydroxylamine. The former process was not amenable to parallel synthesis in contrast to the latter process for which product purification was achieved by automated reverse phase preparative HPLC. In this letter we report a one-pot five-component preparation of hydroxamic acid based MMP inhibitors that feature an α-hydroxy substituent as in marimastat **1**. The procedure involves in the first step the Ugi reaction of an alkylated malate acetonide derivative **5** [5], ammonia, an aldehyde **6**, and an isonitrile **7** in methanol. In the second step methanolic hydroxylamine (5 equivalents) is added to open up the acetonide and furnish the hydroxamic acid [6]. A dilute solution of HCl in methanol is added to destroy unreacted noxious isonitrile [4], the solvent evaporated and the residue purified by automated reverse phase preparative HPLC to give the desired products in modest yields as 1:1 mixtures of diastereoisomers at the new chiral centre (Table).

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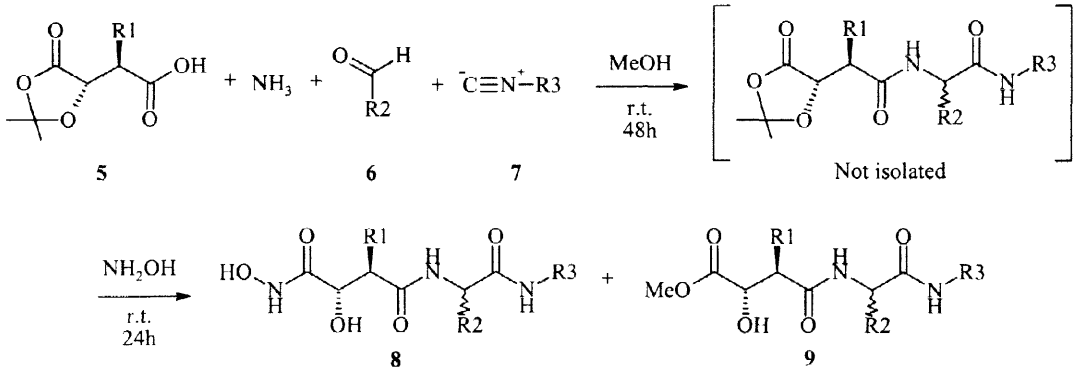

5 6 7 8 9

In a preferred procedure one equivalent of ammonia is first reacted with 1.25 equivalents of aldehyde to preform the imine prior to addition of 1.25 equivalents each of acetonide **5** and isonitrile **7**. This minimises the extent of the competing ammonia catalysed formation of the methyl ester **9** which is the main product when excess ammonia (2.5 equivalents) is employed. Subsequent addition of hydroxylamine is required since introduction at the same time as the Ugi components leads to complex reaction products.

Table: Preparation of α-hydroxy hydroxamic acid derivatives **8**

Compound	R1	R2	R3	% Yield [7]
8a	$-CH_2iPr$	-tBu	-tBu	73
8b	$-CH_2iPr$	-tBu	$-C_6H_{11}$	26
8c	$-CH_2iPr$	-tBu	$-CH_2CO_2Me$	17
8d	$-CH_2iPr$	$-CMe_2allyl$	-iPr	13
8e	$-CH_2iPr$	$-CMe_2allyl$	-nBu	14
8f	$-CH_2CH{=}CHPh$	-tBu	C_6H_{11}	26
8g	$-CH_2CH{=}CHPh$	-tBu	-nBu	36
8h	$-CH_2CH{=}CHPh$	-tBu	$-CH_2Ph$	40
8i	$-CH_2CH{=}CHPh$	$-CMe_2allyl$	-tBu	36
8j	$-CH_2CH{=}CHPh$	$-CMe_2allyl$	$-CH_2Ph$	45

In conclusion, a rapid synthesis of marimastat analogues has been achieved which is suitable for the preparation of MMP inhibitor libraries by parallel methods [8].

References and Notes

[1] Brown P, Whittaker M. Biotech Médecine, 1998, 9, 11-16.

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[4] Floyd CD, Harnett LA, Miller A, Patel S, Saroglou L, Whittaker M. Synlett, 1998, 637-639.

[5] Seebach D, Aebi J, Wasmuth D. Org. Synth. Coll. VII, 153-159.

[6] Synthesis of α-hydroxy hydroxamic acids via hydroxylaminolysis of acetonides, Todd R, Courtney S. Unpublished results.

[7] Yields are given following purification by automated reverse phase preparative HPLC (except **8a**:- precipitated from ether/water) and the compounds which were obtained as 1:1 mixtures of diastereoisomers gave satisfactory analytical and spectral data.

[8] The compounds **8** in the Table are active MMP inhibtiors:- eg. **8e** inhibited human recombinant collagenase-1, stromelysin-1 and 72kDa gelatinase with IC_{50} values of 10 nM, 60 nM and 3 nM respectively.