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An improved synthesis of the broad spectrum matrix metalloprotease inhibitor marimastat

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Abstract

A considerably shortened synthesis of the broad spectrum matrix metalloproteinase (MMP) inhibitor marimastat has been achieved by a direct hydroxylamino ring opening of a key acetonide intermediate.

Keywords: matrix metalloproteinase (MMP); hydroxylamino ring opening; marimastat synthesis.

The hydroxamic acid marimastat (**1**)[1] (Fig. 1) is a broad spectrum inhibitor of the matrix metalloproteinase (MMP) family of enzymes. Matrix metalloproteinase enzymes (including collagenases, gelatinases, stromelysins, and matrilysin) are involved in tissue remodelling and destruction.[2] Over-expression of members of this enzyme family has been implicated in human conditions such as rheumatoid and osteoarthritis,[3] asthma,[4] and a variety of different cancers.[5] Matrix metalloproteinase inhibitors such as marimastat are already reported to be in clinical trials for the treatment of some of the above conditions.[6,7]

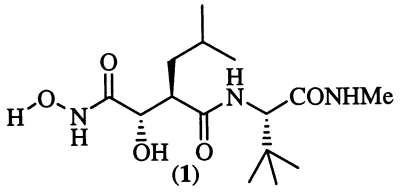

Figure 1.

The synthesis of marimastat reported by British Biotechnology Ltd[1] starts with a stereocontrolled alkylation of an (*S*)-diisopropyl malate dianion. There is evidence[8] to suggest that the stereocontrol achieved in this reaction arises from a cyclic intermediate (**2**) formed by chelation

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between the lithium enolate and the adjacent hydroxyl group (Fig. 2). This gives rise to the diisopropyl esters hindering one approach of the electrophile, and stereoinduction as high as 10:1 (*R:S*) has been achieved.

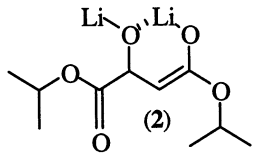
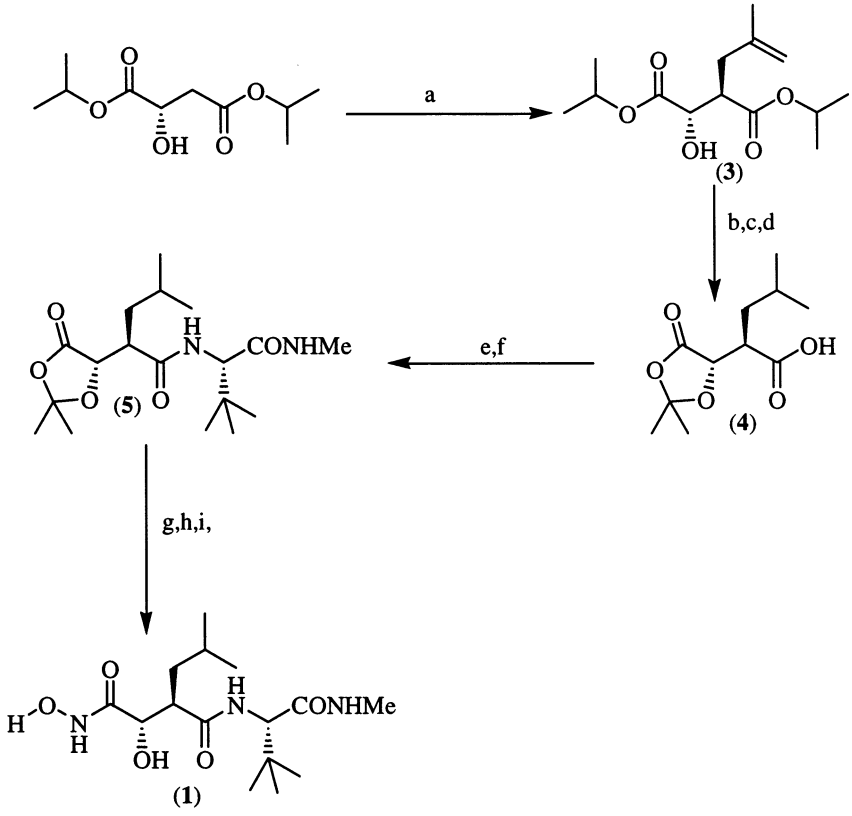


Figure 2.

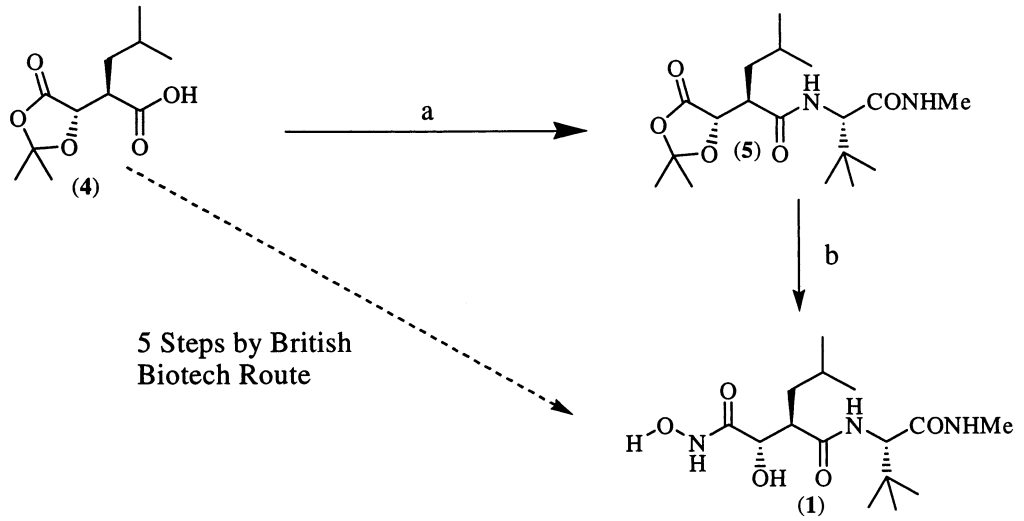
Hydrogenation of the alkene (**3**) (Scheme 1), followed by saponification of the esters and acetonide formation yielded the carboxylic acid (**4**). Carbodiimide coupling with pentafluorophenol gave the activated ester in 58% yield, which was displaced with L-*tert*-leucine methylamide to give amide (**5**). Acetonide deprotection, followed by EDC coupling with *O*-benzylhydroxylamine and protecting group removal gave the hydroxamic acid marimastat (**1**).



Scheme 1. (a) LDA, THF, methallyl iodide 49%; (b) EtOH, Pd–C, H_2, 98%; (c) KOH, dioxane, 99%; (d) 2,2-dimethoxypropane, tosic acid, 100%; (e) EDC, DCM, pentafluorophenol, 58%; (f) L-*tert*-leucine methylamide, DMF; (g) THF, 2 M HCl; (h) EDC, BnO–NH_2, DCM; (i) EtOH, Pd–C, H_2

In our improved synthesis (*S*)-diisopropylmalate was again used as the starting material, with conversion to the acid **4** proceeding smoothly in comparable yields to those reported in the literature.[1] Our first modification (Scheme 2) to the synthesis was to couple acid **4** directly with

L-*tert*-leucine methylamide using EDC to give a 60% yield of pure amide (**5**), after trituration in diethyl ether. This removed the need to proceed via the activated pentafluorophenyl ester, and any extra purification associated with that coupling step, hence improving the yield.



Scheme 2. (a) DCM, EDC, L-*tert*-leucine methylamide, 60%; (b) H_2NOH, THF, 93%

In our hands previous syntheses of marimastat had suffered from variable yields in the final three steps,[9] leading to poor overall yields and relatively poor purity of the final product. We found the overall yields for these three steps from acetonide (**5**) to marimastat (**1**) varied from 7 to 15%. Literature examples[10] suggested that the acetonide (**5**) could provide a reactive electrophilic centre for direct attack of hydroxylamine. A small scale experiment using aqueous hydroxylamine in DMF provided marimastat directly from **5**, product isolation being achieved by dilution of the reaction mixture with water, followed by filtration. The product purity was excellent by LC,[11] LCMS and high field NMR, and the chemical yield (35%) was better than that achieved using the reported route.[1] A significant improvement in yield was achieved by using THF as the reaction solvent, followed by evaporation of the reaction mixture to low volume, before collection of the product by filtration and washing with water. In this case, the yield was increased to 93%,[12] with a purity of 99.6–99.8%.

A stereospecific synthesis of marimastat has been achieved. The first improvement employs a direct coupling between acid **4** and L-*tert*-leucine methylamide removing the need to proceed via the activated pentafluorophenyl ester. The second improvement relies on a key acetonide ring opening step which has been optimised to give a 93% yield, with excellent purity of the final compound. This adaptation of the previously reported route reduces the number of synthetic steps from nine to six. This not only significantly reduces the amount of time required to perform this synthesis, but also increases the overall yield of marimastat from amide (**5**) from 7–15 to 93%.

Acknowledgements

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9. Yields for conversion from acetonide (**4**) to marimastat are not reported in Ref. 1.
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11. Purity determined on a PHENOMENEX LUNA 5μ C18 column, using acetonitrile and pH 2.2 water as the mobile phase, and detection at 210 nm.
12. Optimised method: Acetonide (**5**) (12 g, 34 mmol) was taken up in tetrahydrofuran (50 ml) and aqueous hydroxylamine (12 ml, 170 mmol) was added. The reaction was heated to reflux for 1 hour before being allowed to cool, and diluted with water (20 ml). The tetrahydrofuran was removed in vacuo and the slurry filtered. The filter pad was washed with water (10 ml), and then dried in vacuo to yield the desired product as a white solid (10.1 g, 93%).