Pergamon

Tetrahedron Letters 43 (2002) 683–685

TETRAHEDRON LETTERS

An enantioselective synthesis of sulphonamide hydroxamic acids as matrix metalloproteinase inhibitors

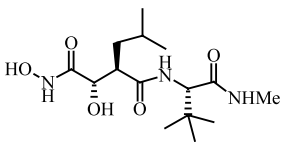
Robert J. Watson,* D. Batty, A. D. Baxter, D. R. Hannah, D. A. Owen and J. G. Montana

Celltech R & D Ltd, Granta Park, Abington, Cambridge CB1 6GS, UK

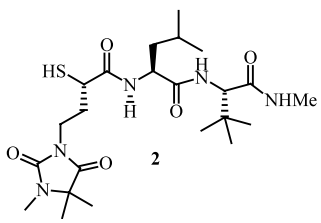
Received 12 September 2001; accepted 8 November 2001

Abstract—A high yielding and enantioselective synthesis of α-substituted hydroxamic acids as inhibitors of matrix metalloproteinases is described. © 2002 Published by Elsevier Science Ltd.

Excess proteolytic activity of matrix metalloproteinase enzymes (MMPs) has been implicated in a wide range of disease states including cancer,[1] arthritis[2] and inflammatory bowel disease.[3] In spite of the intense efforts within the pharmaceutical industry over the past decade, clinical development of MMP inhibitors has so far been disappointing, with problems of poor efficacy and unacceptable side effects.[4] Compounds such as Marimastat **1** have been shown to cause dose limiting joint pain in patients even at low doses, limiting the achievable efficacy of the drug.[5] However, the thiol BMS275291 **2** shows no such effects in man, even at high doses, indicating that MMP inhibitors with acceptable side effect profiles are achievable.[6]

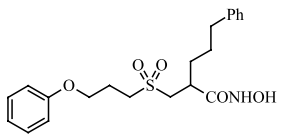


1

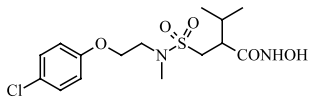


2

As part of our ongoing research, we recently disclosed a series of arylsulphonyl hydroxamic acids such as **3**[7] with good potency against the MMP enzymes and have developed from this, compound **4**, where the sulphone group has been replaced by a sulphonamide.



3



4

Compound **4** was prepared as shown in Scheme 1. The acrylate **5** was converted via the bromo ester **6** to the thioacetate **7** in excellent overall yield and this was efficiently converted into the key sulphonyl chloride **8** which was readily obtained in multigram quantities. Coupling with the commercially available amine and cleavage of the *tert*-butyl ester gave the acid **9**. Conversion to the desired hydroxamic acid **4** was achieved either by EDC mediated coupling with TBS-protected hydroxylamine, followed by deprotection with HCl in ether, or by formation of the acid chloride and reaction with aqueous hydroxylamine. Both methods gave excellent yields of the desired product.

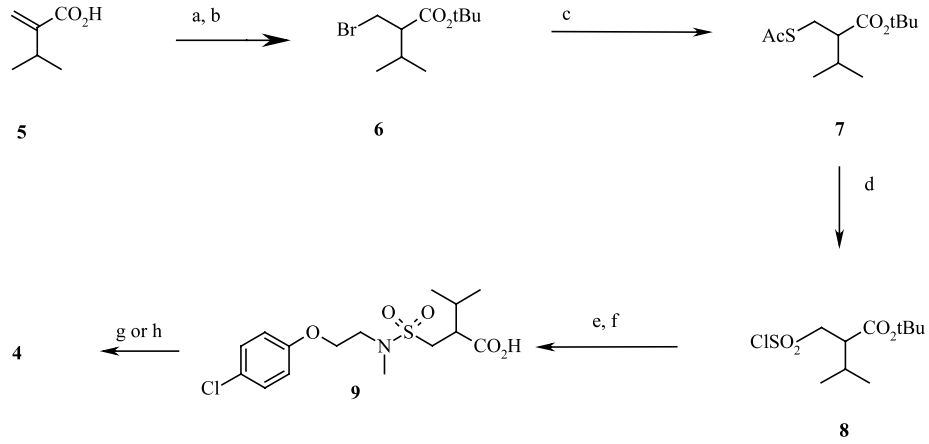
In order to progress compounds such as **4** we required a scaleable route by which to prepare this and related products in optically pure form. Optically active β-sulphonamido acids have previously been prepared by enzymic resolution of the analogous sulphonamido esters[8] but our objective was the preparation of an optically enriched sulphonyl chloride with which to prepare a range of sulphonamide products. Although Evans oxazolidinone chemistry is often the method of choice for the preparation of chiral α-substituted acids, its application to β-sulphonamido acids has not previously been described. Our development of an efficient route to such compounds is described in Scheme 2.

The titanium enolate of **10** was quenched with trioxane[9] to give the hydroxymethyl compound **11** in excellent

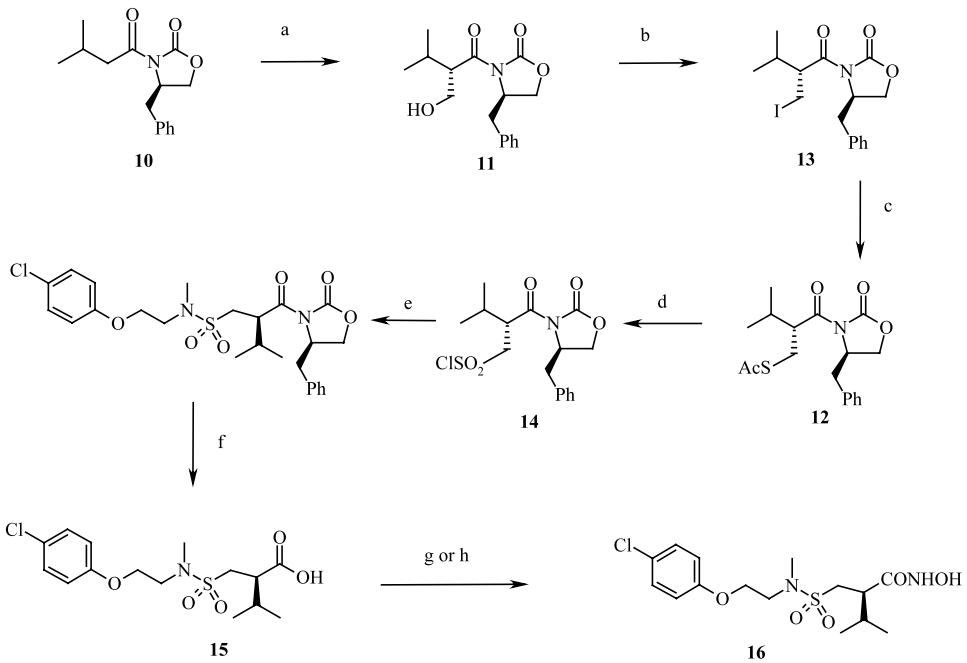
Keywords: MMP; hydroxamic acid; sulphonamide; oxazolidinone.

* Corresponding author.

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(01)02151-7



Scheme 1. *Reagents and conditions*: (a) HBr, AcOH, 90%; (b) isobutylene, H_2SO_4, 85%; (c) KSAc, DMF, 90%; (d) Cl_2, water, DCM, 90%; (e) 4-$ClC_6H_4O(CH_2)_2N(Me)H$, Et_3N, DCM, 95%; (f) TFA, DCM, 90%; (g) (i) H_2NOTBS, EDC, DCM, (ii) HCl, ether, DCM, 85%; (h) $(COCl)_2$, cat. DMF, DCM, then H_2NOH, aq. THF, 90%.



Scheme 2. *Reagents and conditions*: (a) $TiCl_4$, trioxane, Hunig's base, DCM, 0°C, 95%; (b) I_2, PPh_3, imidazole, toluene, reflux 1 h, 95%; (c) KSAc, DMF, rt, 3 h, 96%; (d) Cl_2, DCM, water, 0°C, 90%; (e) 4-$ClC_6H_4O(CH_2)_2N(Me)H$, Et_3N, DCM, 90%; (f) LiOH, H_2O_2, THF or EtOH, water, 85%; (g) H_2NOTBS, EDC, DCM, then HCl, ether 80%; (h) $(COCl_2)$, cat. DMF, DCM, then aq. H_2NOH, THF, water, 95%.

yield with no evidence of the other diastereomer. Several approaches to the preparation of the thioacetate **12** were investigated. Conversion of **11** to its methanesulphonate was efficient and gave crystalline material, however, reaction with potassium thioacetate in DMF proceeded slowly and gave by-products arising from attack of the nucleophile on the oxazolidinone ring. The analogous triflate reacted rapidly to give **12** along with several unidentified by-products. We were pleased to find that reaction of **11** with triphenylphosphine and iodine, while slow at room temperature, was rapid, clean and gave no racemisation in boiling toluene. Iodide **13** was easily obtained in sufficiently pure form by silica plug filtration, removing triphenylphosphine oxide and reacted smoothly to give the thioacetate **12** in excellent yield and optical purity.

Reaction of **12** with chlorine in a mixture of DCM and water at 0°C gave the sulphonyl chloride **14** in quantities up to 30 g as a viscous oil. This was then coupled with the required amine and cleaved under standard conditions to give the acid **15**. As we were concerned about racemisation in the conversion to the hydroxamic acid **16**, we initially employed EDC mediated coupling at low temperature with silyl protected hydroxylamine, followed by mild acidic cleavage of the silyl group. This

procedure gave **16** in 80% yield and >99.8% enantiomeric excess. Alternative conversion of **15** to the acid chloride followed by quenching with aqueous hydroxylamine gave a significantly improved yield of **16** with the e.e. still excellent at 99.5%.

In conclusion, we have developed a high yielding route to matrix metalloproteinase inhibitors with excellent optical purity. Further development of our series of chiral sulphonamide hydroxamic acids will be reported separately.

References

1. McCawley, L. J.; Matrisian, L. M. *Mol. Med. Today* **2000**, *6*, 149–156.
2. Elliott, S.; Cawston, T. *Drugs Aging* **2001**, *18*, 87–99.
3. Vaalamo, M.; Karjalainen-Lindsberg, M. L.; Puolakkainen, P.; Kere, J.; Saarialho-Kere, U. *Am. J. Pathol.* **1998**, *152*, 1005–1014.
4. Heath, E. I.; Grochow, L. B. *Drugs* **2000**, *59*, 1043–1055.
5. Montana, J. G.; Baxter, A. D. *Curr. Opin. Drug Discov. Res.* **2000**, *3*, 353–361.
6. Baxter, A. D.; Bird, J.; Bannister, R.; Bhogal, R.; Manallack, D. T.; Watson, R. J.; Owen, D. A.; Montana, J. G.; Henshilwood, J.; Jackson, R. C. In *Cancer Drug Discovery and Development*: *Matrix Metalloproteinase Inhibitors in Cancer Therapy*; Clandennin, N. J.; Appelt, K., Eds.; Humana Press: Totowa, NJ, USA, 2000; Vol. 8, pp. 193–221.
7. Baxter, A. D.; Bhogal, R.; Bird, J.; Keily, J. F.; Hannah, D. R.; Manallack, D. T.; Montana, J. G.; Nicholson, E. J.; Owen, D. A.; Pitt, W. R.; Watson, R. J.; Wills, R. E. *Bioorg. Med. Chem. Lett.* **2001**, in press.
8. Rosenberg, S. H.; Spina, K. P.; Condon, S. L.; Polakoswski, J.; Yao, Z. *J. Med. Chem.* **1993**, *36*, 460.
9. Saksena, A. K.; Girijavallabhan, V. M.; Wang, H.; Liu, Y.-T.; Pike, R. E.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *37*, 5657.