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Approaches to a Scaleable Synthesis of CH8757: A Potent Inhibitor of Matrix Metalloproteinases

Graham A. Frampton, Duncan R. Hannah, Neil Henderson, Ruth B. Katz,* Ian H. Smith, Neil Tremayne, Robert J. Watson, and Indrani Woollam

Celltech R & D, Granta Park, Great Abington, Cambridge CB1 6GS, United Kingdom

Abstract:

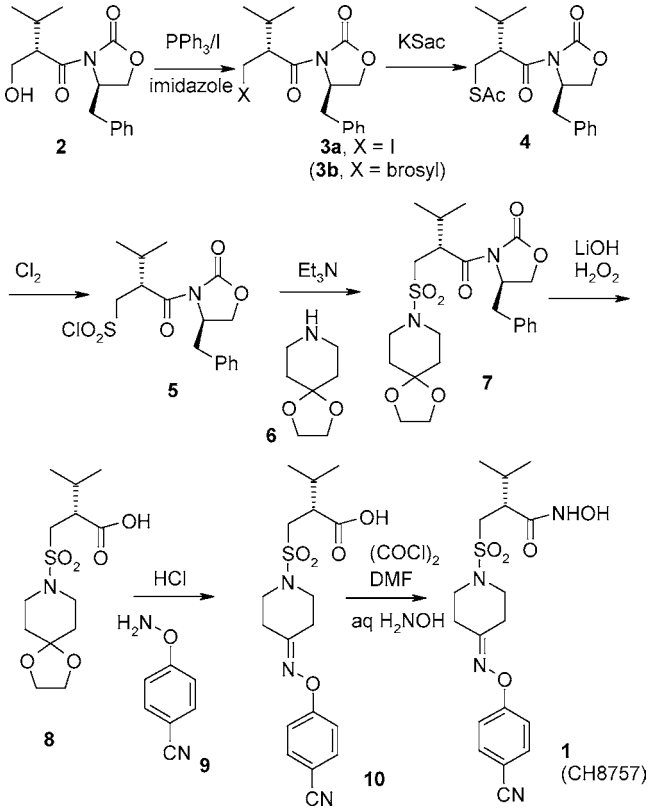
The synthesis of the matrix metalloproteinase (MMP) inhibitor CH8757 is described. The discovery route has been modified to incorporate a three-stage one-pot sequence using α,α,α-trifluorotoluene as solvent. The formation of the hydroxamic acid using oxalyl chloride is catalysed by DBU, thus avoiding the use of DMF, which may form the highly toxic byproduct, dimethylcarbamoyl chloride.

Investigation into inhibitors of matrix metalloproteinase (MMP) enzymes has been the subject of considerable pharmaceutical research, and a number of compounds have entered development as possible treatments for inflammatory conditions. We report here an investigation into a potential scale-up route for one of our active compounds, CH8757 (**1**).

The route used in research for preparation of CH8757 is shown in Scheme 1, via the iodide **3a**. As the basis for a potential scale-up route, two main issues needed to be addressed. First the conversion of the chiral intermediate **2** to the sulfonamide **7** was complicated by the fact that **3a** and **5** are viscous oils and **4** is a low-melting solid.

A second major issue involved the preparation of the hydroxamic acid, which was done using oxalyl chloride with DMF as a catalyst. This was felt to be pharmaceutically unacceptable due to the potential formation of the highly toxic dimethylcarbamoyl chloride.[1]

Scheme 1



Results and Discussion

One-Pot Preparation of Sulfonamide 7. The alcohol **2**[2] was prepared using Evans oxazolidinone chemistry.[3,4] In our early work,[2] this was converted to **7** via the iodide **3a**, using iodine, triphenylphosphine, and imidazole in toluene. Triphenylphosphine oxide is formed as a byproduct and could only be fully removed by filtration through silica gel. After solvent exchange into DMF, this was converted to thioacetate **4** by reaction with potassium thioacetate. An extractive work up into TBME (*tert*-butyl methyl ether) was necessary to isolate **4** as a viscous oil.

We found that the 4-bromophenylsulfonyl (brosyl) derivative **3b** could be used, instead of the iodide in conversion to the thioacetate, and was easily isolated as a crystalline solid. Initially the conversion to thioacetate was done as before in DMF. We wished to replace DMF with a solvent compatible with the chlorination to avoid solvent swaps. As the reaction required elevated temperatures, DCM was too volatile, and we wished to avoid solvents such as dichloroethane because of toxicity. After an extensive investigation, it was found that DMF could be replaced with α,α,α-trifluorotoluene (TFT) in the presence of triethylammonium bromide. The reaction could be worked up by simply washing with water.

The oxidative chlorination of **4** to give the sulfonyl chloride **5** and its coupling with **6** to give **7** had initially been done in DCM/water[5] but could also be done in TFT. After work-up the resulting solution of **5** in TFT could be used directly in the coupling reaction by addition to a solution of the amine **6** and triethylamine in DCM. The use of DCM here instead of TFT was necessary because of the poor solubility of the product in TFT. After work-up, the product

* To whom correspondence should be addressed. E-mail: Ruthkatz@celltechgroup.com.

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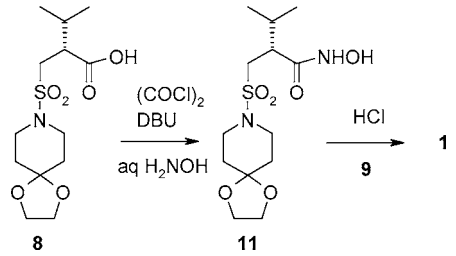
Scheme 2



7 could be crystallised from the remaining TFT once the DCM was removed.

This procedure is a considerable improvement to the previous process. The problems with isolation of the iodide and thioacetate were avoided. Three stages of chemistry could be done in the same solvent without isolation of the intermediates and with only aqueous washings between stages. Although the yield over the three stages (59%, 91% pure by HPLC peak area) was comparable to that from the previous procedure, the new method was much more suitable for scale-up.

Replacement of DMF in Oxalyl Chloride Reaction. Once the oxazolidinone **7** was hydrolyzed to **8**, two steps remained, introduction of the oxime ether and of the hydroxamic acid. Poor stability of the oxime ether functionality to conditions required to prepare the hydroxamic acid led us to prepare the hydroxamic acid first (Scheme 2).

The acid chloride formation was part of the penultimate step in the process. We were concerned about the toxicity of the potential dimethylcarbamoyl chloride byproduct and were determined to avoid the use of DMF as a catalyst. It was not possible simply to heat the acid with oxalyl chloride, as the dioxolane was unstable under these conditions. A number of literature precedents exist[6] where various organic bases, especially pyridine, have been used in catalytic amounts to promote formation of acid chlorides, especially with thionyl chloride, rather than oxalyl chloride. We screened a variety of bases in addition to pyridine. The results are shown in Table 1. Two of the bases, DMAP and DBU, gave reactions of acceptable rate and purity. DBU was selected for further investigation, as DMAP is rather more toxic.

Thus, the acid **8** was treated with 2 equiv of oxalyl chloride in THF in the presence of 0.06 equiv of DBU, at ambient temperature for 16 h. This was then added to a mixture of aqueous hydroxylamine and THF to give the desired hydroxamic acid **11**. The yield of **11** was 61%, 100% pure by HPLC using ELS detection, after a work-up which included recrystallisation from ethyl acetate.

The final step in the synthesis was achieved by hydrolysis of the dioxolane using aqueous HCl followed by treatment with **9**.[7] The product precipitated directly from the mixture and was isolated by filtration, giving **1** in a yield of 89%, with a purity of 98.8% and ee of > 98%.

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Table 1. **Comparison of bases as catalysts for acid chloride formation**

catalyst	rate,[a] purity
none	very slow, impure
DMF	fast, clean
pyridine	fast, impure
n-methyl morpholine	slow, clean
tetramethyl urea	slow, impure
DMAP	fast, clean
tert-butylammonium chloride	fast, moderate
triethylamine	slow, clean
DBU	fast, clean
DABCO	slowest
diisopropylamine	slow, clean
2,6-lutidine	slow, moderate

[a] Fast reactions were complete after approximately 4−5 h at room temperature; slow reactions after overnight stirring when the very slow reactions were still incomplete.

Conclusions

We have developed a scaleable route to the MMP inhibitor CH8757, with an excellent overall yield. The use of TFT as solvent for three of the steps without isolation of the intermediates is a significant improvement on the original discovery route, and avoided the need for chromatography. By replacing DMF with DBU, a catalyst in the formation of the acid chloride, the concomitant problem of toxicity was removed. We are confident that the new methodology for preparation of CH8757 will be suitable for large-scale synthesis.

Experimental Section

General. HPLC analyses were performed using a Gilson system, with a Phenomenex Luna C18 (2), 15 cm × 4.6 mm, 5 μm column, except for analysis of **5**, where a 25-cm column was used. Gradient elution was used with 0.1% TFA in acetonitrile/water mixtures. Detection was either at 210 nm, or using a Polymer Laboratories PL-ELS 1000 detector. ^{1}H NMR spectra were recorded on a 300 MHz Bruker Avance spectrometer. Starting materials and reagents were purchased commercially and used without purification. Mass spectroscopy data was obtained using a Finnigan LCQ Duo/HP1100 LC−MS system, ESI mode, Phenomenex Luna C18 (2), 10 cm × 4.6 mm, 5 μm column, running gradient elution with 0.1% formic acid in acetonitrile/water mixtures. Melting points were determined using a Mettler Toledo DSC 12E apparatus. All reactions were done under a nitrogen atmosphere.

4-Bromobenzenesulfonic Acid (*S*)-2-[1-((*R*)-4-Benzyl-2-oxo-oxazolidin-3-yl)methanoyl]-3-methylbutyl Ester (3b). A solution of **2** (10 g, 34 mmol), brosylchoride (9.65 g, 38 mmol) and DMAP (0.11 g, 0.86 mmol) in DCM (50 mL) was cooled in ice/water and treated with triethylamine (10.5 mL, 75.5 mmol). The reaction was quenched after 1 h by addition of 50 mL of water. After separation of the phases, the organic layer was washed with 1 M HCl (50 mL) and then water. The organic phase was concentrated to remove DCM, and TBME was added. The solid product was isolated by filtration. The brosylate **3b** was obtained in 75% yield, 98.8% pure (HPLC, 210 nm). ^{1}H NMR ($CDCl_3$) δ 7.78 (d,

2H), 7.69 (d, 2H), 7.15−7.40 (m, 5H), 4.65 (m, 1H), 4.46 (t, 1H), 4.26 (dd, 1H), 4.08−4.20 (m, 3H), 3.15 (dd, 1H), 2.72 (dd, 1H), 2.0 (m, 1H), 0.98 (d, 3H), 0.90 (d, 3H). Mass: 532, 534 (M+Na), mp: T_{onset} 88 °C, T_{max} 94 °C.

(*R*)-4-Benzyl-3-[(*R*)-2-(1,4-dioxa-8-aza-spiro[4.5]decane-8-sulfonylmethyl)-3-methyl-butanoyl]oxazolidin-2-one (7). A mixture of **3b** (10 g, 19.6 mmol), potassium thioacetate (4.5 g, 39.2 mmol), and tetraethylammonium bromide (2.0 g, 9.8 mmol) in TFT (100 mL) was heated to 40−50 °C overnight. The reaction was cooled and washed with water. (An aliquot was concentrated and characterised: ^{1}H NMR ($CDCl_3$) δ 7.2−7.35 (m, 5H), 4.65 (m,1H), 4.16 (d, 2H), 3.95 (m, 1H), 3.35 (m, 2H), 3.12 (dd, 1H), 2.76 (dd, 1H), 2.35 (s, 3H), 2.05 (m, 1H), 1.05 (d, 3H), 0.95 (d, 3H). Mass: 350 (M + 1), mp: T_{onset} 56 °C). The TFT solution of **4** (assume 19.6 mmol) was mixed with water (20 mL) and treated with chlorine (3 equiv) at 5−10 °C over 40 min. The layers were then separated, and the organic phase washed with water. The resulting solution of **5** was concentrated to approximately 50 mL, fresh TFT (50 mL) was charged, and the mixture was concentrated again. This was repeated once more, giving 59 g of TFT solution containing approximately 7 g of **5**, (An aliquot was concentrated, weighed, and characterised: ^{1}H NMR ($CDCl_3$) δ 7.15−7.36 (m, 5H), 4.65−4.75 (m, 2H), 4.47 (dd, 1H), 4.20 (d, 2H), 3.75 (dd, 1H), 3.43 (dd, 1H), 2.70 (dd, 1H), 2.20 (m, 1H), 1.15 (d, 3H), 0.95 (d, 3H)). A solution of **6** (2.9 mL, 23.5 mmol) and triethylamine (6.5 mL, 47.0 mmol) in DCM (35 mL) was cooled and treated with the above solution of **5** (assume 19.6 mmol), in TFT, maintaining the temperature below 10 °C. After a further 40 min, the organic phase was washed with water and a 10% citric acid solution. The DCM was removed and replaced with further TFT (35 mL), from which the product crystallised and was isolated by filtration. The product **7** was obtained in a 59% yield, 5.6 g (over three steps), 91.7% pure (approximately 5% of additional product remained in the liquors). ^{1}H NMR ($CDCl_3$) δ 7.2−7.35 (m, 5H), 4.67 (m, 1H), 4.40 (dd, 1H), 4.15 (d, 2H), 3.96 (s, 4H), 3.75 (dd, 1H), 3.50 (dd, 1H), 3.42 (m, 4H), 3.04 (dd, 1H), 3.70 (m,1H), 2.0 (m, 1H), 1.79 (m, 4H), 1.05 (d, 3H), 0.92 (d, 3H). Mass: 481 (M + 1), mp: T_{onset} 140.7 °C, T_{max} 148.2 °C.

(*R*)-2-(1,4-Dioxa-8-aza-spiro[4.5]decane-8-sulfonylmethyl)-*N*-hydroxy-3-methylbutyramide (11). To a solution of **8** (22 g, 68.5 mmol) and DBU (0.62 mL, 4.1 mmol) in THF (275 mL) at 22 °C was added oxalyl chloride (12 mL, 137 mmol) over 10 min. The mixture was stirred for 23 h. The resulting solution was cooled to 5 °C and added to a cooled mixture of aqueous H_2NOH (44 mL of a 50% solution, 720 mmol), and THF (110 mL). Vigorous gas evolution was observed. The resulting mixture was concentrated to remove THF and then extracted into DCM. After concentration to remove DCM, the product **11** was recrystallised from ethyl acetate, giving a yield of 61% (14.1 g), purity 100% (ELS detection). ^{1}H NMR (d_6-DMSO) δ 10.4 (br s, 1H), 8.75 (br s, 1H), 3.85 (s, 4H), 3.36 (dd, 1H), 3.11 (m, 4H), 2.95 (dd, 1H), 2.26 (m, 1H), 1.70 (m, 1H), 1.58 (m, 4 H), 0.80 (d, 6H). Mass: 337 (M + 1), mp: T_{onset} 148.4 °C, T_{max} 156.2 °C.

2-(*S*)-[4-(4-Cyano-phenoxyimino)piperidine-1-sulfonylmethyl]-*N*-hydroxy-3-methylbutyramide (1). A mixture of **11** (4.0 g, 12 mmol), 3 M HCl (14.4 mL, 43 mmol) and water (12 mL) was heated to 46 °C for 20 min and then cooled to 8 °C, and an additional 25 mL of water was added. The hydroxylamine **9** (1.6 g, 12 mmol) was added dropwise over 1 h as a solution in THF. Once the addition was complete, a further 20 mL of water was added. The CH8757 (**1**) was then isolated by filtration and washed to neutrality with water before drying. A yield of 89% (4.3 g), 98.8% purity (detection at 210 nm), ee > 98.0% was obtained. ^{1}H NMR (d_6-DMSO) δ 10.80 (br s, 1H), 9.10 (s, 1H), 8.10 (d, 2H), 7.55 (d, 2H), 3.75 (dd, 1H), 3.60 (m, 4H), 3.30 (dd, 1H), 3.04 (m, 2H), 2.75 (m, 2H), 2.56 (m, 1H), 2.00 (m,-1H), 1.01 (d, 6H). Mass: 409 (M + 1), mp: dec T_{onset} 177.6 °C. Chiral chromatography: Column, Chiralcel OD-H 5 μm + Chiralcel OD 10 μm (sequentially), 250 mm × 4.6 mm; mobile phase, solvent A: 1-propanol + 0.3% TFA + 0.2% diethylamine. Solvent B: heptane, isocratic, 30% A, wavelength, 254 nm; flow rate, 0.8 mL/min; retention times: (*S*)-isomer 14.9 min, (*R*)-isomer 17.5 min.

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