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Tetrahedron Letters 46 (2005) 5005–5007
Tetrahedron Letters

Initial synthesis of UK-427,857 (Maraviroc)

David A. Price,* Simon Gayton, Matthew D. Selby, Jens Ahman, Sarah Haycock-Lewandowski, Blanda L. Stammen and Andrew Warren

Pfizer Global Research and Development, Sandwich Laboratories, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

Received 27 April 2005; accepted 19 May 2005
Available online 9 June 2005

Abstract—The initial synthesis of **UK-427,857** (Maraviroc) is described including the preparation of 4,4-difluorocyclohexanoic acid and amide coupling utilizing a polymer supported reagent.

UK-427,857 (Maraviroc) is a potent antagonist of the CCR5 receptor and is currently progressing through phase III clinical trials as a treatment for HIV (Fig. 1).[1] The structure includes a 4,4-difluorocyclohexyl unit, a phenylpropyl motif with a benzylic stereogenic centre and an equatorially disposed triazole in a tropane system. The synthesis of the required 1,2,4-triazole substituted tropane has been previously described.[2] This letter focuses on the challenges in preparing the required 4,4-difluorocyclohexanoic acid and the overall synthetic route used in the preparation of **UK-427,857** (Maraviroc) to underwrite initial studies.

The use of fluorine in molecules of pharmacological interest can profoundly alter their biological properties and there has been widespread research into methodologies for the introduction of this atom.[3] One of the most commonly used techniques is the conversion of carbon–oxygen functional groups into carbon–fluorine bonds by nucleophilic fluorinating sources. This transformation is routinely accomplished using diethylaminosulfur trifluoride (DAST) which is commercially available but does require careful handling due to its well-known thermal instability.[4] In our first attempts to use DAST to prepare the target acid **5**, we were disappointed to find that treatment of ketone **1** with 1.05 equiv of DAST in dichloromethane at 0 °C resulted in complete consumption of the starting material but gave an inseparable 1:1 mixture of the required difluoro compound **2** and the vinyl fluoride **3** in 85% yield. The formation of vinyl fluoride co-products from treatment of ketones with DAST is known in the literature and appears difficult to control.[5] Optimisation studies undertaken to influence the ratio of products including temperature, reagent stoichiometry and solvents were unsuccessful.

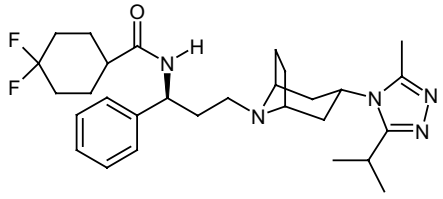

Figure 1. **UK-427,857** (Maraviroc).

The mixture of **2** and **3** was subjected to Upjohn conditions for dihydroxylation[6] and we were delighted to find that after the reaction overnight the required difluorocyclohexyl ester **2** could then be isolated in high purity by column chromatography.[7] The assumed product **4** from oxidation of the vinyl fluoride was never isolated and only identified by mass spectral evidence from the crude reaction mixture. Saponification of **2** gave the required 4,4-difluorocyclohexyl acid **5** which was recrystallised from cyclohexane to furnish an analytically pure material (Scheme 1).

With suitable quantities of **5** in hand, our attention turned to preparing multigram quantities of the phenylpropyl linker. The starting material was the commercially available chirally pure β-amino ester **6** which was protected in high yield.[8] The ester was then reduced

Keywords: Heterocycles; Triazoles; Amide; Tropane; Fluorination.
* Corresponding author. Tel.: +44 1304 644690; fax: +44 1304 651821; e-mail: david.a.price@pfizer.com

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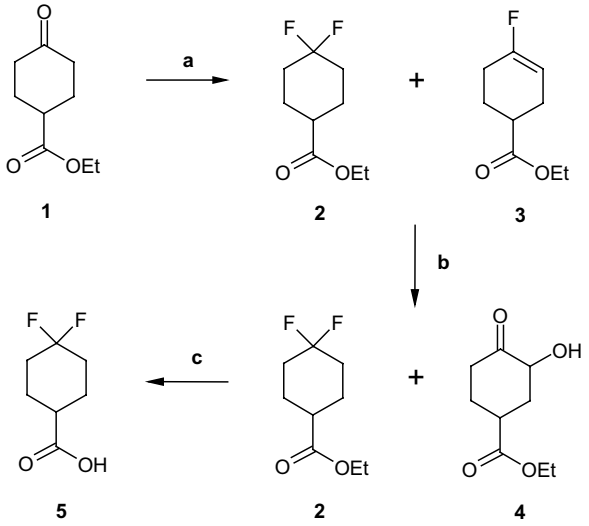
doi:10.1016/j.tetlet.2005.05.082

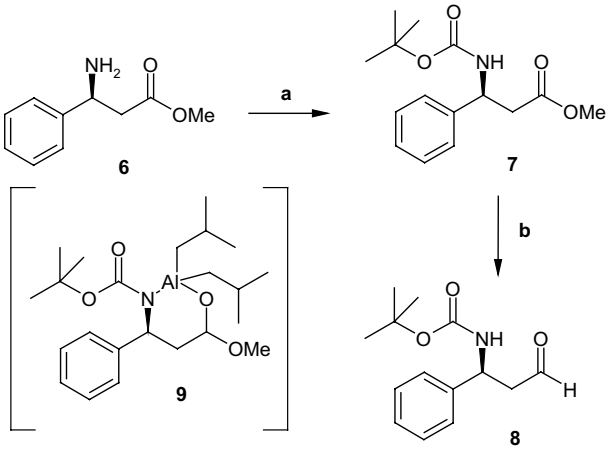


Scheme 1. Reagents and conditions: (a) DAST, 0 °C, CH_2Cl_2, 85% yield of 1:1 mixture; (b) OsO_4, NMO, acetone, water, 74% yield based on 1:1 mixture as starting material; (c) NaOH, THF, water, 65%.

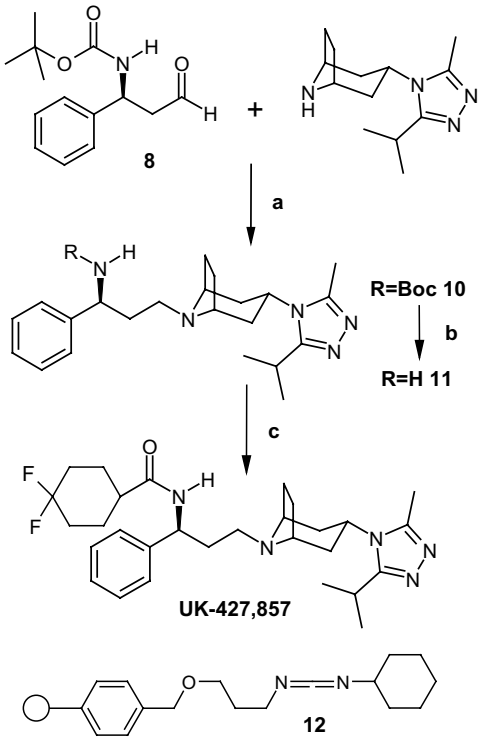
to the required aldehyde using 2 equiv of diisobutylaluminium hydride in dichloromethane. Over reduction to the alcohol is prevented by internal coordination of the aluminium to the nitrogen forming a six-membered chelate **9** that breaks up upon aqueous work-up liberating the aldehyde **8** (Scheme 2).

The optimised synthesis of the 1,2,4-triazole substituted tropane has been previously described and reductive amination with the aldehyde **8** furnished the key *tert*-butyl carbamate protected intermediate **10**. The *tert*-butyl carbamate was removed in high yield using 25% trifluoroacetic acid in dichloromethane to give the precursor **11**.

Previously in the project, high-throughput chemistry had been applied to template **11** to optimise rapidly the amide moiety of the series. The reagent of choice for performing this coupling with a variety of acids



Scheme 2. Reagents and conditions: (a) $(Boc)_2O$, aq $NaHCO_3$, 90%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 75%.



Scheme 3. Reagents: (a) $Na(AcO)_3BH$, CH_2Cl_2, 75%; (b) CF_3CO_2H, CH_2Cl_2, 95%; (c) **5**, **12**, CH_2Cl_2, 48%.

had been *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide. However, upon closer examination of the ^1H NMR spectra of a number of analogues it was apparent that trace amounts (typically <2 mol %) of the coupling reagent and associated adducts were contaminating the product after purification. This level of impurity was unacceptable in this synthesis as the material was underwriting key studies that could be influenced by minor impurities.

Alternative coupling agents were screened and the optimal conditions obtained were a slight excess of the acid **5** (1.1 equiv) and a polymer bound carbodiimide reagent **12** (2.0 equiv) in dichloromethane.[9] Once the reaction was complete, simple filtration and filtering through a pad of silica furnished **UK-427,857** (Maraviroc) which was recrystallised to analytical purity from toluene/hexane (Scheme 3).

In conclusion, we have described the initial synthetic route to **UK-427,857** (Maraviroc)[10] that was used to underwrite early evaluation. Subsequent synthetic improvements have been made and will be reported in further communications.

Acknowledgements

The authors wish to thank Andy Fowler for supplying and recommending the polymer supported reagent and Torren Peakman for his assistance with analysis of the ^1H spectra.

References and notes

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9. Purchased from Argonaut® catalogue number 800369.
10. The coupling reagent **12** (500 mg, 0.54 mmol) was added to a stirred solution of the amine **11** (100 mg, 0.27 mmol) and acid **5** (50 mg, 0.30 mmol) in dichloromethane (5 mL) at room temperature. After 1 h, the reaction mixture was filtered through a plug of silica washing with 10% methanol in dichloromethane (20 mL) to furnish **UK-427,857** (67 mg, 49%) as a white foam which was recrystallised from toluene/hexane (2:1) to yield a white solid, mp 197–198 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ = 7.36 (2H, m), 7.23 (3H, m), 6.61–6.48 (1H, br m), 5.15 (1H, dd, *J* 6.7 Hz, 6.7 Hz), 4.28 (1H, m), 3.33 (2H, m), 2.86 (1H, m), 2.48 (3H, s), 2.28 (2H, m), 2.18–1.61 (19H, m), 1.39 (6H, d, *J* 7.0 Hz); LRMS: *m/z* 514.4, MH^+; $C_{29}H_{41}F_2N_5O$ requires C, 67.75; H, 8.06; N, 13.54; Found C, 67.77; H, 8.00; N, 13.64.