Asymmetric hydrogenation routes to β-amino-aldehydes

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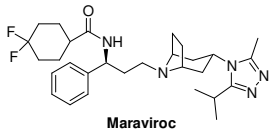
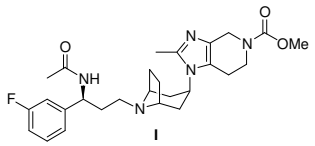
Introduction

Asymmetric hydrogenation is an established technology for the manufacture of intermediates for the pharmaceutical industry. Chirotech/Dowpharma has over ten years of experience in the development of asymmetric hydrogenation processes [1], many of which have been operated on 10's-100's Kg scale producing commercial quantities of valuable single enantiomer products.

Maraviroc is a potent antagonist of the CCR5 receptor developed by Pfizer and is currently in phase III clinical trials for HIV treatment [2]. A key intermediate in the synthesis of Maraviroc is a β-amino aldehyde currently prepared by reduction of a β-amino acid ester using DIBAL-H at -78 °C. Similar back-up candidates, such as **I** [3], are prepared using the same strategy. For long-term manufacture, this is not an ideal set of conditions owing to the need for expensive, cryogenic plant facilities. Application of asymmetric hydrogenation technology would provide a practical alternative. However, de-hydro-β-amino-acid esters are generally not ideal candidates for asymmetric hydrogenation owing to the different activity and selectivity displayed by the olefinic geometric isomers [4]. In collaboration with Pfizer we developed a route which would allow for the preparation of β-amino aldehydes by the asymmetric hydrogenation of an appropriately protected *N*-acyl enamide, which could be applied to Maraviroc and back-up candidates.



Maraviroc



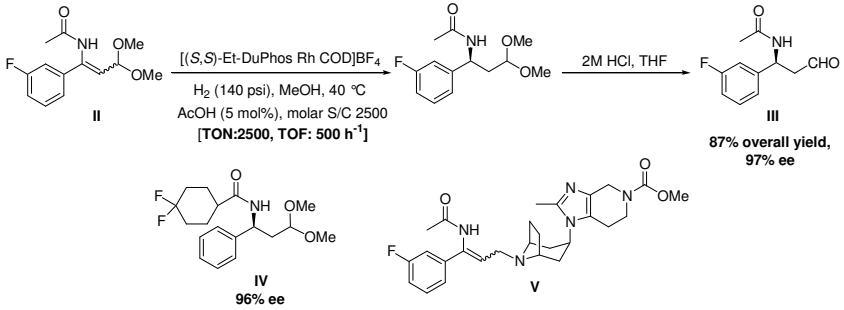
I

Materials and Methods

All chemicals were used as supplied. Hydrogenation reactions were performed in Parr vessels with de-oxygenated substrate and solvents. Catalysts were used as discrete isolated complexes, stored under nitrogen but manipulated in air for short periods. The catalysts were added as solutions prepared using de-oxygenated solvents in Schlenk apparatus.

Results and Discussion

A scalable synthesis of the *N*-acyl enamide **II** to ultimately provide **I** was developed from readily available starting materials. Investigations of the asymmetric hydrogenation of **II** indicated that an acetal group would be an ideal candidate for a masked aldehyde. The development of this chemistry which allowed for the preparation of the aldehyde **III** in 97% ee will be described in full, as will the work to produce the Maraviroc intermediate **IV** (**Scheme 1**). Late-stage hydrogenation of the fully functionalised intermediate **V** will also be described.



II **III** **IV** **V**

87% overall yield, 97% ee

96% ee

Scheme 1 Asymmetric hydrogenation substrates and products

Significance

This is the first report of the asymmetric hydrogenation of β-amino aldehyde acetals and provides access to pharmaceutical intermediates useful in the treatment of HIV. This methodology produces aldehydes, which are extremely versatile intermediates, and therefore could be widely applied in the pharmaceutical arena.

References

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3. Stupple, P. A. WO 2005/033107, Pfizer Inc.
4. Heller, D., Holz, J., Drexler, H.-J., Lang, J., Drauz, K., Krimmer, H. –P, and Börner, A. *J. Org. Chem.* 6816, 66 (2001).