A Highly Diastereoselective Chloride-Mediated Dynamic Kinetic Resolution at Phosphorus On-Route to a Key Intermediate in the Synthesis of GSK2248761A

Alan Ironmonger, Mark Shipton, Fiona Slater, Pete Szeto, Matthew G. Unthank, François-René Alexandre, Catherine Caillet, Cyril B. Dousson

PII: S0040-4039(18)30461-1
DOI: https://doi.org/10.1016/j.tetlet.2018.04.018
Reference: TETL 49881

To appear in: *Tetrahedron Letters*

Received Date: 26 February 2018
Revised Date: 29 March 2018
Accepted Date: 9 April 2018

Please cite this article as: Ironmonger, A., Shipton, M., Slater, F., Szeto, P., Unthank, M.G., Alexandre, F-R., Caillet, C., Dousson, C.B., A Highly Diastereoselective Chloride-Mediated Dynamic Kinetic Resolution at Phosphorus On-Route to a Key Intermediate in the Synthesis of GSK2248761A, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.04.018

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A Highly Diastereoselective Chloride-Mediated Dynamic Kinetic Resolution at Phosphorus On-Route to a Key Intermediate in the Synthesis of GSK2248761A.

Alan Ironmonger[a, ∗], Mark Shipton[a, §], Fiona Slater[a], Pete Szeto[a], Matthew G. Unthank[c, §], François-René Alexandre[b, ‖], Catherine Caillet[b, ‖], and Cyril B. Dousson[b].

[a]*GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, United Kingdom.*
[b]*Merck & Co., Inc.,126 East Lincoln Avenue, Rahway, New Jersey 07065, USA.*[c] *Northumbria University. Department of Applied Sciences, Faculty of Health and Life Sciences, Newcastle upon Tyne, NE1 8ST, UK.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Asymmetric Synthesis
Chiral Phosphorus
Dynamic Kinetic Resolution
GSK2248761A
Phenylglycine methyl ester

ABSTRACT

A highly diastereoselective chloride-mediated dynamic kinetic resolution at phosphorus has been developed to access a key intermediate in the synthesis of GSK2248761A. This procedure utilises a soluble chloride source and a cheap readily available chiral auxiliary. The practicality of this transformation is demonstrated on a multi-gram scale.

GSK2248761A (Fosdevirine, IDX-899) **1** is an experimental Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) discovered by Idenix Pharmaceuticals and was in development for the treatment of HIV.[1] During our investigations towards an efficient scalable synthesis of **1** we desired an asymmetric synthesis to the key intermediate **2**, which we could insert into our current synthetic route.[2] We discovered that there were only a few methods to construct optically active phosphinate esters using techniques other than a classical resolution.[3] Mislow and co-workers first described the use of (−)-menthol as a chiral auxiliary that allowed the separation of diastereomers by fractional crystallization followed by further elaboration to optically active phosphine oxides and phosphinates.[4] We were able to prepare and separate by chromatography diastereomerically enriched menthyl phosphinate esters **3** and **4**, but our substrate proved unstable to the harsh transesterification conditions required to convert it into the desired

∗ Corresponding author. e-mail: alan.2.ironmonger@gsk.com

§ M.S. and M.U., are former GSK employees.

‖ C.C, F-R.A., and C.D. are former Idenix employees.