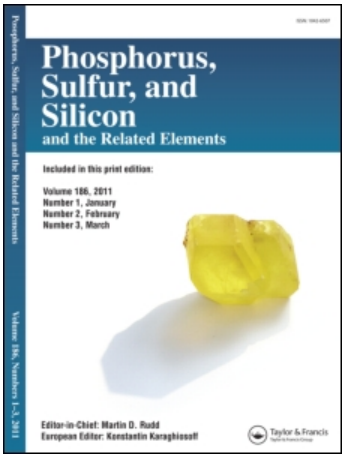


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

New Enantioselective Routes to Cyclic and Acyclic S,O-acetals; Enzymatic Resolution of α-Acetoxy Sulfides and Enantioselective Synthesis of the Antiviral Agent Lamivudine

Stephen Brand; John Milton; Martin F. Jones; Christopher M. Rayner

To cite this Article Brand, Stephen , Milton, John , Jones, Martin F. and Rayner, Christopher M.(1997) 'New Enantioselective Routes to Cyclic and Acyclic S,O-acetals; Enzymatic Resolution of α-Acetoxy Sulfides and Enantioselective Synthesis of the Antiviral Agent Lamivudine', Phosphorus, Sulfur, and Silicon and the Related Elements, 120: 1, 367 — 368
To link to this Article: DOI: 10.1080/10426509708545552
URL: http://dx.doi.org/10.1080/10426509708545552

Phosphorus, Sulfur, and Silicon, 1997, Vol. 120 & 121, pp. 367–368
Reprints available directly from the publisher
Photocopying permitted by license only

New Enantioselective Routes to Cyclic and Acyclic S,O-acetals; Enzymatic Resolution of α-Acetoxy Sulfides and Enantioselective Synthesis of the Antiviral Agent Lamivudine

STEPHEN BRAND[a], JOHN MILTON[a], MARTIN F. JONES[b] AND CHRISTOPHER M. RAYNER*[a]

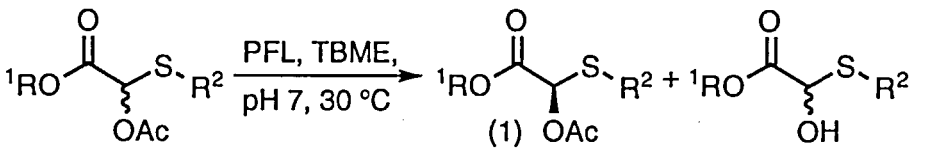
[a]*School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K.;* [b]*Process Research, Glaxo Research and Development Ltd., Gunnels Wood Road, Stevenage, Herts., SG1 2NY, U.K.*

A new method for the synthesis of cyclic and acyclic optically active S,O-acetals is reported, along with subsequent stereocontrolled transformations, culminating in a synthesis of the important antiviral nucleoside Lamivudine.

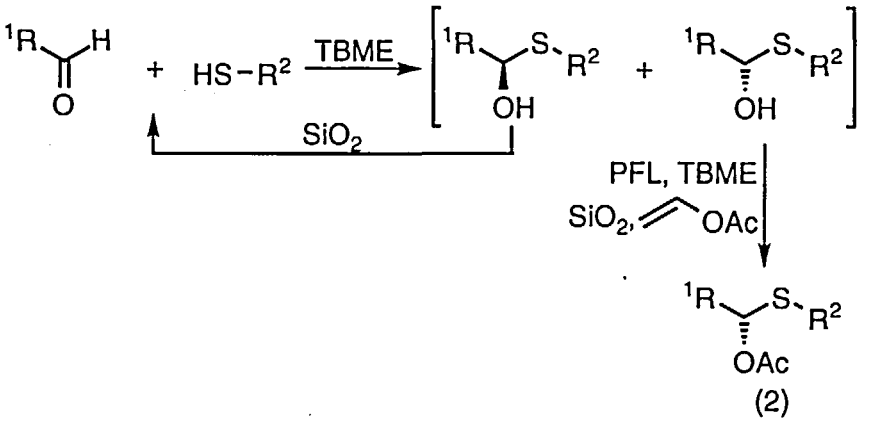
The enzymatic resolution of secondary alcohols by hydrolysis (or formation) of the corresponding acetates is a well established procedure.[1] We have recently developed new methods for the preparation of homochiral S,O-acetals by a novel enzymatic hydrolysis of a wide variety of α-acetoxy sulfides using *Pseudomonas fluorescens* lipase (PFL)[2] including a particularly novel SiO_2-catalysed dynamic kinetic resolution process (scheme 1).[3]

Scheme 1

Resolution by conventional enzymatic hydrolysis:

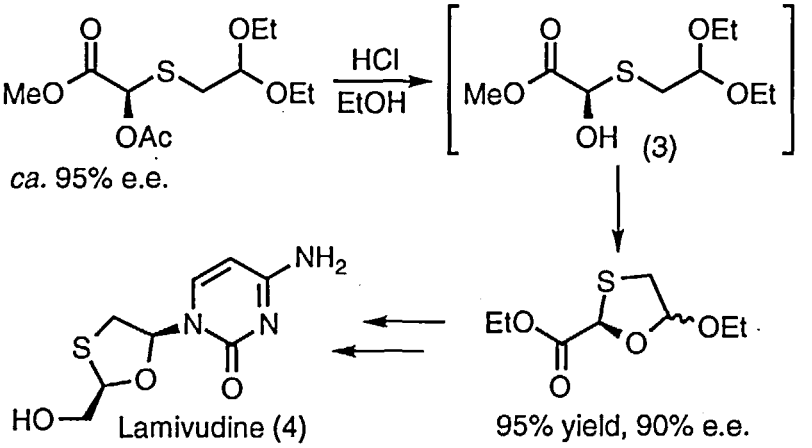


Enzymatic dynamic kinetic resolution of an epimerising hemithioacetal:



The α-acetoxy sulfides (1) and (2) can be prepared in high enantiomeric excess using this methodology (up to >95%e.e). Note that they allow access to both enantiomers of the α-acetoxy sulfide substrates. With appropriate substituents, they can also be converted into cyclic S,O-acetals with almost complete retention of stereochemical integrity *via* the configurationally stable hemithioacetal (3) (scheme 2).

Scheme 2.



We have now developed this methodology for use with a wide variety of substrates, and have demonstrated the synthetic utility of the optically active α-acetoxy sulfides produced, by the enantioselective synthesis of Lamivudine (4), an important antiviral nucleoside currently used in combination with AZT for the treatment of HIV infections (Epivir™).[3] Further investigations into the chemistry of α-acetoxy sulfides are currently underway.

REFERENCES

1. S.M. Roberts, K. Wiggins, G. Casy and S. Phythian, *Preparative Biotransformations,* J. Wiley, Chichester, 1992; b) H.G. Davies, R.H. Green, D.R. Kelly and S.M. Roberts, *Biotransformations in Preparative Organic Chemistry*, Best Synthetic Methods Series, Academic Press: London, 1992.
2. J. Milton, S. Brand, M.F. Jones and C.M. Rayner, *Tetrahedron Asymmetry*, 1995, **6**, 1903.
3. S. Brand, M.F. Jones and C.M. Rayner, *Tetrahedron Letters*, 1995, **36**, 8493.
4. J. Milton, S. Brand, M.F. Jones and C.M. Rayner, *Tetrahedron Letters*, 1995, **36**, 6961.