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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>

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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>

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

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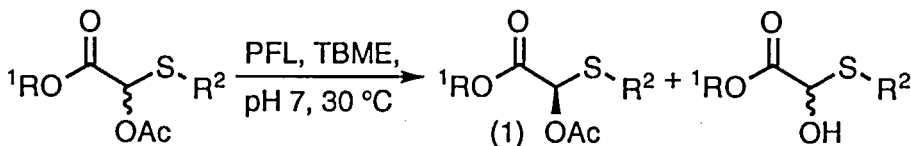
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A new method for the synthesis of cyclic and acyclic optically active S,O-acetals is reported, along with subsequent stereocontrolled transformations, culminating in a synthesis of the important antiviral nucleoside Lamivudine.

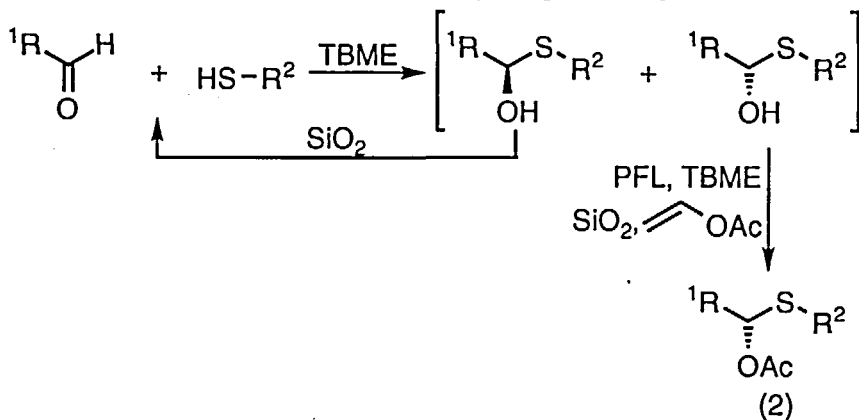
The enzymatic resolution of secondary alcohols by hydrolysis (or formation) of the corresponding acetates is a well established procedure.¹ We have recently developed new methods for the preparation of homochiral S,O-acetals by a novel enzymatic hydrolysis of a wide variety of α -acetoxy sulfides using *Pseudomonas fluorescens* lipase (PFL)² including a particularly novel SiO₂-catalysed dynamic kinetic resolution process (scheme 1).³

Scheme 1

Resolution by conventional enzymatic hydrolysis:

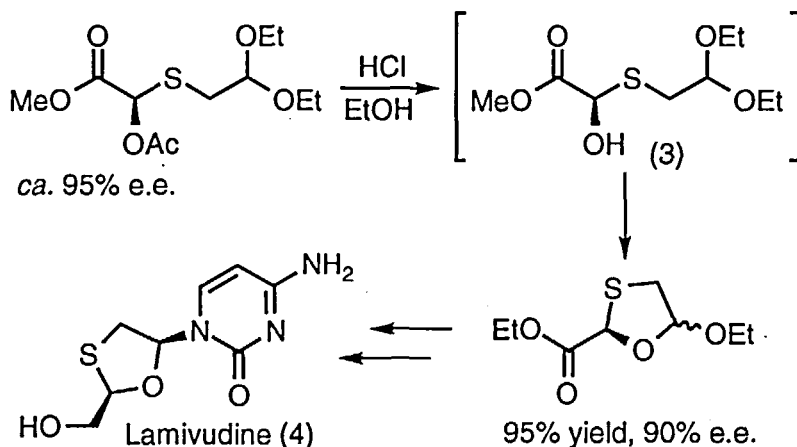


Enzymatic dynamic kinetic resolution of an epimerising hemithioacetal:



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.

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