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Enzymatic Resolution of α,β-Diacetoxysulfides: Synthesis of Optically Active O,S-Acetals by Regiospecific Enantioselective Primary Acetate Hydrolysis

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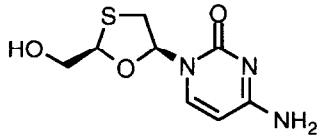
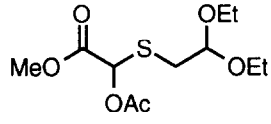
Abstract: α,β-Diacetoxy sulphides are precursors of chiral oxathiolanes and have been resolved by *Pseudomonas fluorescens* lipase catalysed hydrolysis. The resolution proceeds with complete regioselectivity for the primary acetate and excellent enantioselectivity in most cases.

We have previously demonstrated the synthetic utility of homochiral α-acetoxy sulfides in the synthesis of the antiviral agent Lamivudine (3TC™†, **1**).[1] This structurally interesting nucleoside analogue has been approved for the treatment of patients infected with HIV[2] as a combination therapy with AZT™† (Zidovudine) and is currently undergoing clinical trials for the treatment of hepatitis B.[3] Although the two enantiomers of (**1**) have similar potencies, the lower toxicity of the "unnatural" enantiomer means that enantioselective routes are of considerable importance. Chiral O,S-acetals have also aroused interest as stereocontrolling elements for 1,2- and 1,4-additions to α,β-unsaturated ketones[4] and in asymmetric epoxidation and aziridination,[5] and, in keeping with our continued interest in reactive organosulfur intermediates[6] has led us to consider improved alternative routes for their preparation.



Lamivudine **1**



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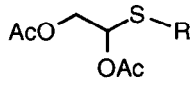
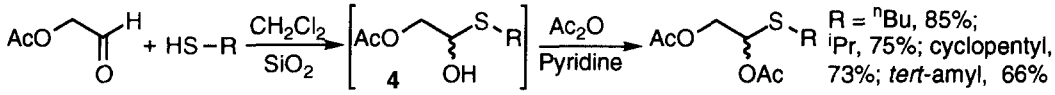


3

Our original route to Lamivudine employed an enzymatic resolution of α-acetoxy sulphide **2** followed by acid catalysed cyclisation of the derived configurationally stable hemithioacetal, to give an oxathiolane.[1] We envisaged that Lamivudine would be more conveniently accessed *via* a precursor which already contained a substituent in the correct oxidation level for the construction of the C-5' hydroxymethylene moiety. Thus we focused our attention upon the asymmetric synthesis of α,β-diacetoxy sulfides **3** and their subsequent synthetic manipulation. We had previously developed asymmetric routes to such compounds using a novel dynamic kinetic resolution by acetylation of an epimerising hemithioacetal **4**, although using *Pseudomonas fluorescens* lipase (PFL) this procedure gave rise to the undesired enantiomer for the synthesis of **1**.[7] We therefore attempted

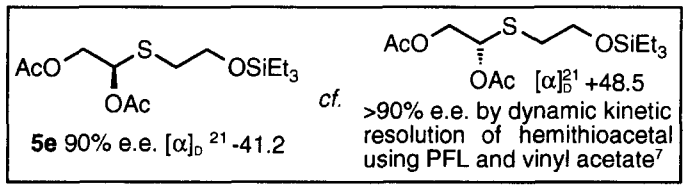
the resolution of α,β-diacetoxy sulfides by hydrolysis using PFL and entered into a systematic study of this interesting and potentially useful methodology with a variety of substrates with a view to a more expedient synthesis of resolved acyclic and cyclic O,S-acetals.

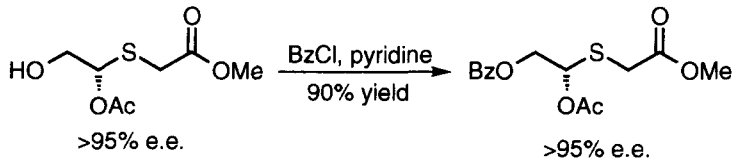
The racemic precursors were prepared in moderate to excellent yield by acetylation (Ac_2O, pyridine) of a hemithioacetal generated *in situ* from acetoxyacetaldehyde[8] and a thiol in the presence of silica gel. (scheme 1). Although acceptable yields could be obtained with all thiols studied, yields were generally lower for secondary and tertiary thiols presumably as a consequence of the lower thermodynamic stability of the hemithioacetal.



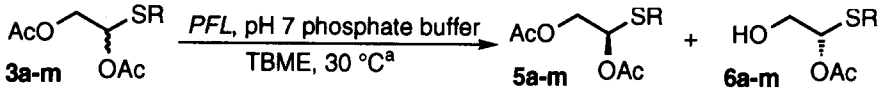
Scheme 1

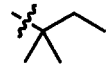
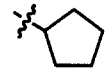
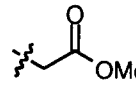
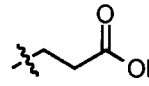
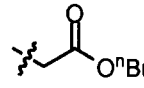
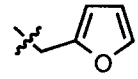
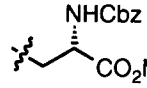
Our previous investigations into the resolution of related oxathioacetals had revealed the solvent dependency of PFL and suggested ^{t}BuOMe as a suitable medium.[9] Thus substrates were dissolved in ^{t}BuOMe and pH 7 phosphate buffer with PFL and the biphasic mixture was vigorously agitated to optimise interfacial contact. The results of these experiments are shown in the table. We observed only products resulting from regiospecific hydrolysis of the primary acetate to give the corresponding α-acetoxy-β-hydroxy sulphides, along with resolved starting material, both of which could be readily isolated. The resolution proceeded with excellent enantioselectivity (E) or diastereoselectivity in many cases, although contrary to our previous observations relating to secondary acetate hydrolysis, there was no clear relationship between enantioselectivity and the size of the sulphide substituent R. Comparison of optical rotations of the products with those of previous experiments[1] suggest that the lipase is selective for hydrolysis of the enantiomer with S absolute configuration.[10,11] An alternative synthesis of **5e** by esterification using our previously reported dynamic kinetic resolution procedure with PFL and vinyl acetate, gave the product with the R configuration, which is the opposite to that obtained using this methodology (see below).[7] This observation is consistent with a recently published study on the resolution of simple primary alcohols using PFL.[12] Importantly, the resolved diacetate products with suitable substitutents, now have the correct absolute configuration for the synthesis of the desired enantiomer of **1**.





Scheme 2



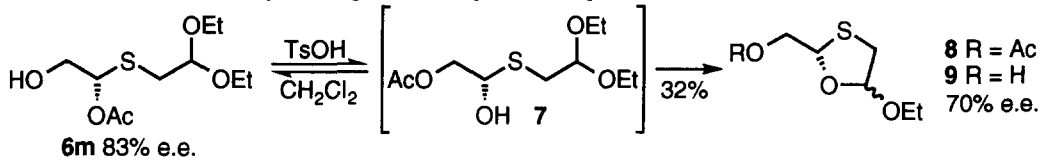
Entry	Substrate	R	Conv. (%)	Recovered diacetate 5		Monoacetate 6		E[d]
				Yield(%)	e.e. (%)	Yield(%)	e.e. (%)	
1	3a	$CH_3(CH_2)_3$	45[b]	50	57[c]	41	68[c]	9
2	3b	$(CH_3)_2CH$	39[b]	56	63[c]	34	96[c]	93
3	3c	$CH_3(CH_2)_7$	40[b]	57	75[c]	40	>96[c]	>100
4	3d	$Et_3SiO(CH_2)_3$	54[b]	43	88[c]	48	73[c]	18
5	3e	$Et_3SiO(CH_2)_2$	55[b]	42	90[c]	51	73[c]	20
6	3f		48[b]	49	86[c]	37	93[c]	74
7	3g		45[b]	53	69[c]	42	85[c]	25
8	3h		50[b]	46	89[c]	43	87[c]	42
9	3i		64[b]	34	85[c]	50	48[c]	7
10	3j		53[b]	45	89[c]	43	78[c]	24
11	3k		47[b]	50	47[c]	40	88[c]	37
12	3l		45[b]	51	80[b]	21	>96[b]	>100
13	3m	$(EtO)_2CHCH_2$	48[b]	51	76[c]	38	83[c]	27

[a]Standard conditions: 400mg substrate, phosphate buffer (pH 7, 4ml), solvent (4ml), *Pseudomonas fluorescens* lipase (6mg, ca. 260 Units), vigorous stirring, 30°C, 2-4h; [b]Determined by ^{1}H NMR; [c]Determined by ^{1}H NMR using (+)-Eu(hfc)$_3$; [d]E (enantioselectivity) = ln[(1-c)(1-ee$_s$)] / ln[(1-c)(1+ee$_s$)].[12]

Table: Results of Regiospecific Enzymatic Primary Acetate Hydrolyses

The monoacetates **6** could be reacylated without loss of stereochemical integrity (scheme 2), and as would be expected, the diacetates **5** were configurationally stable even after prolonged storage. Upon contact with silica gel, alcohols **6** underwent significant isomerisation to the corresponding hemithioacetals **7** (up to 20% in some cases) presumably by acid catalysed acetate migration. Such migrations are precedented in the hydrolyses of polyacetylated substrates[13] although in this instance decomposition could be minimised by

employing alumina in the purification procedure. This acid catalysed acetate migration could be exploited in a synthesis of a suitable precursor to oxathiolane nucleoside analogues (scheme 3). Thus treatment of acetal **6m** with *p*-toluene sulfonic acid (TsOH) induced acetate migration and subsequent cyclisation of the hemithioacetal onto the adjacent diethylacetal to give the desired oxathiolane as a mixture of acetate **8** and alcohol **9**.[14] Importantly, much of the stereochemical integrity of the thioacetal chiral centre is maintained throughout the reaction, and we are currently working to further optimise this process.



Scheme 3

In conclusion we have developed a simple synthesis and novel resolution of oxathioacetals by regioselective enzymatic hydrolysis of the primary acetate of α,β-diacetoxy sulfides. The data thus presented should assist further refinement of the binding model which predicts selectivity of *PFL* toward primary alcohols or the corresponding esters in which there is one or more heteroatom attached to the stereogenic centre.[15] We are now investigating new synthetic applications of these interesting chiral building blocks,[16] the results of which will be reported in due course.

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†3TC™ and AZT™ are registered trade marks of the Glaxo-Wellcome Group.

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