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Enzymatic Resolution of α-Acetoxyethers: A New Approach to the Synthesis of Homochiral O,O-Acetals.

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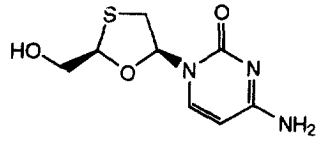
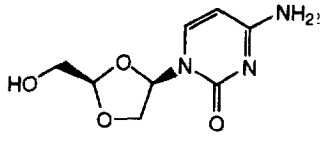
Abstract: A variety of α-acetoxyethers can be prepared by addition of an alcohol to a glyoxylate and *in situ* acetylation using acetyl chloride. They can then be resolved using *Pseudomonas fluorescens* lipase. Selectivity is highly dependent on the substrate, with high enantiomeric excesses achieved in most cases, with some notable exceptions. Use of alternative lipase enzymes helps overcome such limitations.

There is currently considerable pharmaceutical interest in nucleoside analogues due to their potential to act as antiviral, antibacterial, and anticancer agents.[1] Of particular interest to us are the 3,5-diheteronucleosides[2] such as Lamivudine (3TC™, **1**)[3] and dioxolane C **2**[4] which exhibit anti-HIV, anti-HBV and anti-cancer[5] activity. Because of the different activity and toxicity profiles of the two enantiomers of such compounds, highly enantioselective routes are required for their synthesis.[2-5]



Lamivudine™ (1)



Dioxolane C (2)

We have previously reported a synthetic route to Lamivudine where the key acetal chirality was introduced *via* a novel enzymatic hydrolysis of a racemic α-acetoxysulfide using *Pseudomonas fluorescens* lipase (PFL).[6] The preparation of homochiral secondary acetates by enzymatic resolution is a well established procedure, often giving very high selectivities with appropriate substrates.[7] There are a limited number of examples of enzymatic resolutions of O,O-stereogenic centres[8-10] however all these involve a specific substrate, and did not fully investigate the viability and generality of enzymatic resolution as a means of homochiral O,O-acetal synthesis. The potential of chiral acetals in stereocontrolled synthesis[11] and our previously developed α-acetoxysulfide methodology, led us to embark on a programme to extend this work to the equivalent α-acetoxyethers.

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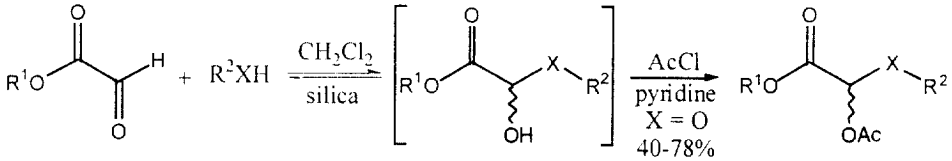
The α-acetoxyether substrates **5a** could be readily prepared *via* a convenient 'one-pot' procedure involving addition of an alcohol to methyl[12] or menthyl[13] glyoxylate followed by *in situ* acetylation of the intermediate hemiacetal (Scheme 1). This is analogous to the method we developed for α-acetoxysulfide **5b** synthesis which involved addition of a thiol to an aldehyde and subsequent acetylation of the resultant hemithioacetal intermediate using acetic anhydride in pyridine.[6] Comparison of equivalent α-acetoxy-sulfide and -ether systems revealed a general trend for lower yields in the case of the α-acetoxyethers, with more reactive acylating agents (acid chlorides) being required to give acceptable yields (see table). This suggests the position of equilibrium for formation of hemithioacetal **4b** lies further towards association than for hemiacetal **4a**, although both favour association rather than dissociation with glyoxylate precursors.



(3) X = O, S (4a) X = O (4b) X = S (see table) (5a) X = O (5b) X = S

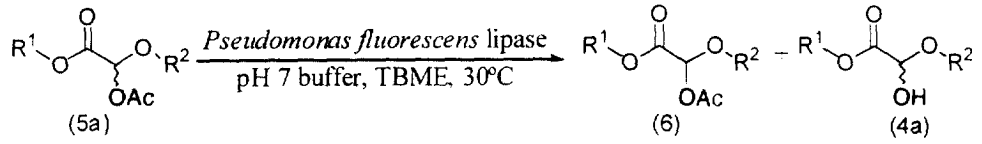
Scheme 1.

With these substrates in hand, we began to investigate the enzymatic hydrolysis reaction. *Pseudomonas fluorescens* lipase was employed due to its previous success in the resolution of α-acetoxysulfides. We were very pleased to observe that the switch from oxygen to sulfur did not alter the efficiency of the reaction in most cases, although with certain substrates there was a tendency for the reaction to proceed further than the optimum 50% conversion (table 1). It is worth noting the considerable variance in reaction timescale which ranges from <1hour (entry 6) to >10 hours (entries 7 and 12). The hemiacetal **4a** byproduct could clearly be seen in NMR spectra of the crude reaction mixtures, however on purification using column chromatography, only the resolved acetate and alcohol (from decomposition of **4a**) could be isolated.[14]

Excellent selectivity is observed with methyl esters (R^1 = Me) and a variety of ether substituents (R^2). There are however some particularly notable exceptions. When R^2 is a long alkyl chain, generally good selectivity is observed (entries 1,2 and 3), including those substrates containing a terminal alkene. However, the pentenyl substituted substrate (entry 5) gives anomalously low selectivity even though the reaction proceeds relatively quickly. Similar, but less dramatic results, are observed with the bromopropyl system (entry 5), although this is perhaps more understandable considering the combination of atom size and electronic effects of the bromine substituent. Cinnamyl (entry 6) and benzyl (entry 7) substituents are tolerated well, however with methylenecyclohexane, no reaction is observed even after prolonged reaction times. This may be due to a combination of steric effects and the enhanced hydrophobicity of the cyclohexyl group. High chemoselectivity is observed for acetate hydrolysis, even in the presence of multiple ester functionality (entry 8). Note also that diethylacetal groups remain intact under the mild reaction conditions (entries 9 and 12). Steric effects close to the α-acetoxyether chiral centre would appear to dramatically reduce the rate of hydrolysis as demonstrated by the isopropyl substituted substrate (entry 10).

As with most lipase catalysed resolutions the stereoselectivity of the hydrolysis can often be rationalised as being controlled by the relative sizes of the two groups either side of the reacting chiral acetate centre.[15] If the small methyl ester group is replaced with a much larger menthyl ester, then this would be expected to reverse the absolute stereochemistry at the chiral centre being resolved. The menthyl substitutent is useful in this case as it allows direct reading of diastereomeric purity by ^{1}H NMR without requiring shift

reagents or relying on other techniques. Use of a menthyl group also complicates the situation due to its chirality and inherent optical rotation, however the van't Hoff superposition principle suggests that the new acetal chiral centre contributes a negative rotation.[16]



(5a) (6) (4a)

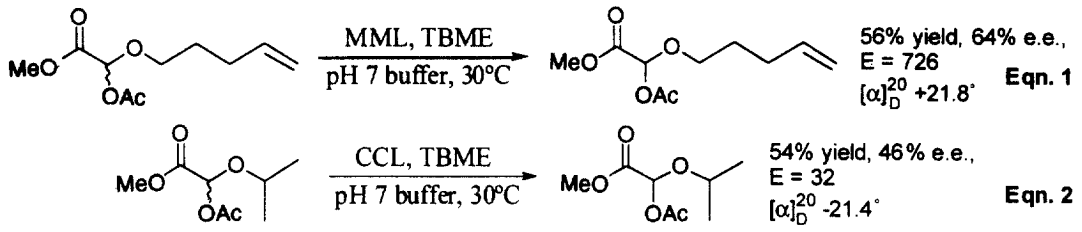
Entry	R^1O	R^2	Yield of (5a)	t (h)	Yield of (6)[b]	d.e. or e.e.[c] of (6) (%)	$[\alpha]^D_{20}$ (°)	E[f]
1	CH_3O	$-(CH_2)_7CH_3$	71	1.75	43	>95	-24.3	29
2	CH_3O	$-CH_2CH=CH_2$	58	9.4	32	>95	-31.5	16
3	CH_3O	$-(CH_2)_2CH=CH_2$	40	2.5	37	90	-24.7	25
4	CH_3O	$-(CH_2)_3CH=CH_2$	62	1.5	47	19	-8.8	1
5	CH_3O	$-(CH_2)_3Br$	43	4.6	43	53	+15.7	6
6	CH_3O	$-CH_2CH=CHPh$	75	0.8	39	>95	-39.1	145
7	CH_3O	$-CH_2Ph$	63	12.5	35	>95	+34.2	81
8	CH_3O	$-CH_2CO_2Et$	67	3.5	27	>95	-56.4	25
9	CH_3O	$-CH_2CH(OEt)_2$	66	9.0	37	>95	+21.4	145
10	CH_3O	$-CH(CH_3)_2$	49	n.r.[a]	---	---	---	---
11	CH_3O	$-CH_2c\text{-}C_6H_{11}$	59	n.r.[a]	---	---	---	---
12	L-Menthyl	$-CH_2CH(OEt)_2$	78	14.5	38	78[d]	-61.1 (-36.0)[e]	99
13	L-Menthyl	$-CH_2CH_3$	69	4.75	49	93[d]	-88.1 (-75.6)[e]	653

[a]n.r. = no reaction; [b]Standard conditions: 100mg substrate, phosphate buffer (pH7, 2ml), *tert*-butyl methyl ether (1ml), PFL (8-10mg), 30°C, time (h); [c]Determined by ^1H NMR using (+)-Eu(hfc)$_3$; [d]Determined by ^1H NMR; [e]Optical rotation of diastereomeric mixture; [f]$E=\{\ln[(1-c)(1-ee_s)]\}/\{\ln[(1-c)(1+ee_s)]\}$.

Table 1. Yields for α-acetoxyether formation and results of hydrolysis experiments.

At present, the absolute configurations of the products have not been unambiguously determined, a situation which is further confused by differing signs of optical rotations in the resolved products. Previous results had been much more consistent in their signs, although of course, differing substitutents can easily lead to significantly different optical rotations.

Although some substrates were not resolved efficiently, use of alternative lipase enzymes helps overcome such limitations. For example, the pentenyl substituted substrate (table 1, entry 4) is resolved with excellent efficiency using *Mucor miehei* lipase (MML) by methyl ester hydrolysis (scheme 2, eqn. 1). Similarly, the isopropyl substituted substrate (table 1, entry 10) is efficiently resolved using *Candida cylindracea* lipase (CCL) (scheme 2, eqn. 2).



Scheme 2.

In conclusion, we have demonstrated the enzymatic resolution of a broad range of α-acetoxyethers achieving very high levels of stereocontrol in many cases, and good to moderate yields. We are currently using this new chemistry in the synthesis of **2**, and are investigating the possibility of extending this methodology further to related systems, and developing new synthetic procedures involving the use of homochiral acetals.

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References.

1. Witczak, Z.T. *Curr. Med. Chem.*, **1995**, *1*, 392.
2. Qu, F.; Hong, J.H.; Du, J.; Newton, M.G.; Chu, C.K., *Tetrahedron*, **1999**, *55*, 9073 and refs. cited therein; Nguyen-Ba, N.; Brown, W.L.; Chan, L.; Lee, N.; Brasili, L.; Lafluer, D.; Zacharie, B. *Chem. Commun.*, **1999**, 1245 and refs. cited therein.
3. Coates, J.A.V.; Cammack, N.; Jenkinson, H.J.; Mutton, I.M.; Pearson, B.A.; Storer, R.; Cameron, J.; Penn, C.R. *Antimicrob. Agents and Chemotherap.*, **1992**, *36*, 202; Schinazi, R.F.; Chu, C.K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L.-S.; Beach, J.W.; Choi, W.-B.; Yeola, S.; Liotta, D.C. *Antimicrob. Agents and Chemotherap.*, **1992**, 672; Doong, S.-L.; Tsai, C.-H.; Schinazi, R.F.; Liotta, D.C.; Cheng, Y.-C. *Proc. Natl. Acad. Sci. USA*, **1992**, *88*, 8495.
4. Chu, C.K.; Beach, J.W.; Jeong, L.S.; Choi, B.G.; Comer, F.I.; Alves, A.J.; Schinazi, R.F. *J. Org. Chem.*, **1991**, *56*, 6503 and refs. cited therein.
5. Siu, L.L.; Attardo, G.; Izbicka, E; Lawrence, R; Cerna, C; Gomez, L.; Davidson, K.; Finkle, C.; Marsolais, C.; Rowinsky, E.K.; VonHoff, D.D. *Annals of Oncology*, **1998**, *9*, 885; Rabbani, S.A.; Harakidas, P.; Bowlin, T.; Attardo, G. *Cancer Res.*, **1998**, *58*, 3461.
6. Milton, J.; Brand, S.; Jones, M.F.; Rayner, C.M. *Tetrahedron Lett.*, **1995**, *36*, 6961; Milton, J.; Brand, S.; Jones, M.F.; Rayner, C.M. *Tetrahedron: Asymm.*, **1995**, *6*, 1903.
7. Roberts, S.M.; Wiggins, K.; Casy, G.; Phythian, S. *Preparative Biotransformations*, J. Wiley, Chichester, 1992; Davies, H.G.; Green, R.H.; Kelly, D.R.; Roberts, S.M. *Biotransformations in Preparative Organic Chemistry*, Best Synthetic Methods Series, Academic Press: London, 1992.
8. Chenevert, R.; Desjardins, M.; Gagnon, R. *Chem. Lett.*, **1990**, 33.
9. Van den Heuval, M.; Cuiper, A.D.; Van der Deen, H.; Kellogg, R.M.; Feringa, B.L. *Tetrahedron Lett.*, **1997**, *38*, 1655; Van der Deen, H.; Cuiper, A.D.; Hof, R.P.; Van Oerveren, A.; Feringa, B.L.; Kellogg, R.M. *J. Amer. Chem. Soc.*, **1996**, *118*, 3801.
10. Angelis, Y.S.; Smonou, I. *Tetrahedron Lett.*, **1997**, *38*, 8109.
11. Bull, S.D.; Correia, L.M.A.R.B.; Davies, S.G. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 2231 and refs. cited therein.
12. Kelly, T.R.; Schmidt, T.E.; Haggerty, J.G. *Synthesis*, **1972**, 544.
13. We are grateful to Dr. M.F. Jones of GlaxoWellcome (Stevenage) for providing the menthyl glyoxalate.
14. All new compounds were characterised by ^1H and ^{13}C NMR, IR, and mass spectra, and gave satisfactory elemental analysis and/or accurate mass spectra unless otherwise stated.
15. Cygler, M.; Grochulski, P.; Kazlauskas, R.J.; Schrag, J.D.; Bouthillier, F.; Rubin, B.; Serreqi, A.N.; Gupta, A.J. *J. Am. Chem. Soc.*, **1994**, *116*, 3180 and refs. cited therein.
16. Kondru, R.K.; Wipf, P.; Beratan, D.N. *J. Am. Chem. Soc.*, **1998**, *120*, 2204.