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An Easy Access to Partially Protected Enediyne Diols, Important Intermediates for Cyclic Systems, via PPL Catalysed Hydrolysis

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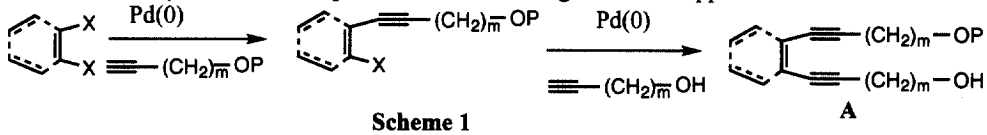
Abstract: Porcine Pancreatic Lipase (PPL)-catalysed hydrolysis of various enediyne diacetates led to partially protected diols that are synthetic precursors to cyclic systems, in yields ranging from 80-90%, after three cycles of hydrolysis.

For the synthesis of various cyclic azaenediynes,[1] we needed an access to the partially protected enediyne diols **A**. The usual route to such entities is *via* palladium(0)-catalysed monoeneyne coupling between *cis*-dihaloethylene[2] or benzene[3] and protected acetylenic alcohol, followed by another round of coupling with the corresponding free alcohol or *vice versa*. **(Scheme 1)** The main drawback of this protocol is the generation of some bis-coupled product in the first eneyne coupling step. An alternative approach would be to make the diol in a single step through a bis-coupling, protect both the hydroxyl groups and then selectively deprotect one of them. This may not only increase the overall yield but would also reduce the consumption of expensive palladium(0)- catalyst. Herein we report our result following the second approach.



Scheme 1

To test our proposition the various enediyne diacetates **1a-1d** , prepared from the corresponding diols, were subjected to PPL-catalysed hydrolysis. Interestingly, there was no formation of diol up to about 40-65% conversion (based on the consumption of substrate); only the monoacetates **2a-2d** were formed at this stage **(Table 1)**. The reaction was stopped, the monoacetate and the unreacted diacetate were separated. The recovered diacetate was recycled for PPL-catalysed hydrolysis to obtain more of the monoacetate. In this way the yield of the desired monoacetates could be increased upto 80-90% after three cycles of hydrolysis. It is pertinent to mention here that PPL has been used previously to prepare monoacetates of several diols including butyne-1,4-diol from their diacetates[4] in high yield.

To study the role of the triple bond on the kinetics of hydrolysis of the acetates, we made the diacetates **1e** and **1f** *via* sequential coupling of *cis*-dichloro ethylene or 1,2-dibromobenzene with homopropargyl and propargyl alcohols and subsequent acetylation. Both **1e** and **1f** showed very good regioselectivity on being subjected to PPL-catalysed hydrolysis. The acetate closer to the triple bond, i.e. the propargylic one underwent smooth hydrolysis leaving the distant ester intact. This was evident from a comparison of the ^{1}H NMR spectra of the diacetates with that of the hydrolysis products. For example the two proton singlet at δ 4.88 for the C-1 methylene in the diacetate **1e** shifted upfield, now appearing at δ 4.47 indicating hydrolysis

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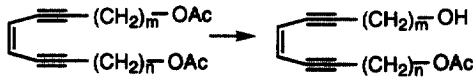
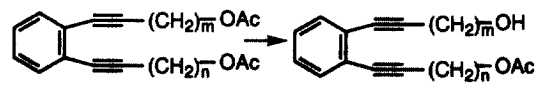
of C-1 acetate. The C-9 methylene protons have the same chemical shift in both the diacetate and the hydrolysis product. indicating no hydrolysis of the C-9 acetate. A similar observation was noted for the hydrolysis of **1f** (see **Table 1**). Interestingly, this regioselectivity is the reverse of what was observed[5] for PLE-catalysed hydrolysis of substrates containing an allylic and a β-alkoxy acetate. In that case, the rigidity imposed by a double-bond slowed down the hydrolysis of the allylic acetate.

In conclusion, we have achieved a simple chemoenzymatic method for the preparation of synthetically important partially protected enediyne alcohols. In addition, the importance of proximity of the triple bond in distinguishing between two regiochemically different acetates under PPL-catalysed hydrolytic conditions has also been demonstrated.



1a **m=n=1** **2a**
1b **m=n=2** **2b**
1e **m=1 n=2** **2e**



1c **m=n=1** **2c**
1d **m=n=2** **2d**
1f **m=1 n=2** **2f**

TABLE 1

Substrate	Extent of Hydrolysis(%) (Time of hydrolysis in h)	Monoacetate(% yield) (based on recovered diacetate)	Monoacetate(% yield) (after 3 cycles of hydrolysis)
1a	45 (20)	**2a** (95)	**2a** (80)
1b	45 (24)	**2b** (95)	**2b** (80)
1c	50 (20)	**2c** (96)	**2c** (84)
1d	50 (24)	**2d** (95)	**2d** (84)
1e	65 (30)	**2e** (97)	**2e** (90)
1f	65 (30)	**2f** (95)	**2f** (88)

Typical Experimental Procedure

The diacetate **1c** (200 mg), dissolved in acetone (15 ml) was treated with phosphate buffer (30 ml) and PPL (Fluka, 400 mg) and stirred at room temperature. The pH was kept at 7.8 by intermittent addition of 1N NaOH. After about 45% conversion, the mixture was filtered through celite and the filtrate extracted into ethyl acetate, dried and evaporated. The product monoacetate **2c** was isolated by column chromatography (Si-gel) (90 mg); δ_H ($CDCl_3$) 7.64-7.59 (2H, *m*, Ar-H), 7.48-7.42 (2H, *m*, Ar-H), 5.12 (2H, *s*, CH_2OAc), 4.73 (2H, *s*, CH_2), 2.33 (3H, *s*, $COCH_3$).

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