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A Remarkably Simple Process for Monoprotecting Diols

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Abstract: *Lipase from pig pancreas (PPL) has been shown to catalyse selectively the hydrolysis of alkane-1,n-diol bis-acetates into the corresponding monoacetate.*

Despite an ostensible simplicity, selective protection of only one of the two chemically-equivalent hydroxy groups of polymethylene glycols -*i.e.* diols of general formula $HO-(CH_2)_n-OH$, **1**- remains an actual challenge, as attested by two recent publications.[1] Frequently, treatment of these diols with a stoechiometric amount of a reagent aimed at forming a derivative of the hydroxy functionality results in the formation of a 1/2/1 mixture of the unreacted diol, the monoprotected and the bis-protected derivative, respectively.[2]

Among the various tricks which have been devised to surpass this inherent statistical distribution, a common process involves the formation of the corresponding sodio monoalcoxide. Subsequent treatment by a silylating reagent has been claimed to deliver the monoprotected derivative in large excess.[3] With the lower members, prior transformation of the diol into a cyclic, symmetrical intermediate such as an acetal of p-anisaldehyde,[4a] a dibutylstannoxane,[4b] or a sulphite,[4c] followed by ring-opening attack of a suitable reagent has also proved to be very efficient.[5] However, whatever the method, the reagents appear to be more elaborate than both the product or the starting material.

Previously, we have shown that lipase-catalysed acylation of a C_{2v}-shaped tetraol proceeded to give the corresponding (*R,R*) *bis*-acetate with a high optical purity.[6] The noticeable stereoselectivity of this process was rationalised in supposing that acylation of the monoacetate, first formed as a mixture of *R* and *S* enantiomers with the former in excess, occurred with a stereoselectivity comparable to that observed in the first step: the minor monoacetate gave *mainly* a diastereomeric -*i.e. meso*- bis-acetate- whereas the major (*R*)-monoester led to the essentially-pure (*R,R*) bis-ester. Intriguingly, we failed to detect formation of any monoacetate in the process. This could have resulted from the improved lipophilic character of the transitory monoacetates, as compared with that of the starting diol: should any monoacetate be bound to the enzyme more tightly than the starting polyol, the rate of the second acylation step would be higher than the rate of the first one. Assuming that the same kinetic effect, resulting from dichotomy in lipophilicity of each individual substrate would take place in the related lipase-catalysed hydrolysis of bis-acetate of a 1,n-diol in aqueous media, it could be expected that formation of the corresponding monoacetate should be much faster than its subsequent hydrolysis, hence providing the basis for a selective acylation of diols. This has proved to be the case.

Bis-acetates **2**, prepared from diols **1** by using the conventional procedure (Ac_2O/AcONa, reflux; 91-95%), were stirred in a phosphate buffer in presence of PPL;[7] the pH being adjusted to *c.a.* 6.9 by periodic addition of a 1N aqueous sodium hydroxide solution. As soon as the theoretical amount (*i.e.* 1 eq.) of base was added, the hydrolysis was stopped by saturating the mixture with salt. The usual extraction process (CH_2Cl_2), followed by chromatography (silica gel; CH_2Cl_2/ether) then afforded the pure (NMR, TLC) monoester **3** (table).[8]

Table: $$\underset{\mathbf{2}}{\text{AcO-}(CH_2)_n\text{-OAc}} \xrightarrow[\text{pH 6.9 buffer}]{\text{PPL}} \underset{\mathbf{3}}{\text{AcO-}(CH_2)_n\text{-OH}}$$

Diacetate*	Time (hours)	Monoacetate, mass obtained (%)
2a, n=3	101	**3a**, 1.26g (82)**
2b, n=4	18	**3b**, 1.64g (95)
2c, n=5	23	**3c**, 1.62g (85)
2d, n=6	23	**3d**, 1.65g (79)
2e, n=8	24	**3e**, 1.18g (48)

* on a 13 mmol scale
** PPL (0.208 g) added after 55 h

Except in one case (n=8), the yield of isolated, pure product is high. For the lower homologue (n=3), the reaction was extraordinarily slow and brought to completion only after more enzyme was added. The yield in monoester remained acceptably high however.

Unsaturated diols gave similar results. For instance, the diacetate of butynediol **4** was converted, under the same conditions, into the corresponding monoacetate **5** in excellent yield (95%).

$$\underset{\mathbf{4}}{AcOCH_2{-}C{\equiv}C{-}CH_2OAc} \xrightarrow[\text{14 h}]{\text{PPL, pH 6.9}} \underset{\mathbf{5}\text{ (95\%)}}{AcOCH_2{-}C{\equiv}C{-}CH_2OH}$$

For comparison, the mono-TBDMS derivatives of diols **1b** and **1e** were prepared by treating the corresponding mono sodium salt (NaH (1 eq.), in THF) with *t*-butyldimethylsilyl chloride (TBDMSCl) according to reference 3a. Although the yields (89 and 46%, respectively) of these mono-protected derivatives rival those recorded above for the corresponding mono-acetates, the reagent and experimental conditions (*i. e.* NaH, TBDMS; anhydrous THF) required by this protection process are much more stringent than those involved in the enzymatic process.

The opportunity to exercise the synthetic potential of the enzymatic hydrolysis of diesters **2** arose when, during the course of another project, we needed to prepare an authentic sample of diphenylphosphinoxy derivatives **6b** and **6c**. Diols **1b** and **1c** were obvious starting materials and the hydrolysis of both bis-acetates

2b and **2c** was repeated on a larger scale (91 mmol). The crude monoacetates, almost pure in each case (TLC), were then transformed into the iodoesters **7** by using standard reagents. After filtration on silica gel (CH_2Cl_2), these iodides were converted, as indicated, into the targeted hydroxyalkyl diphenylphosphine oxides **6** in acceptable overall yield by sequential treatment with triphenylphosphine and sodium hydroxide.[9]

$$\begin{array}{ccccc} \text{AcO-}(CH_2)_n\text{-OAc} & \xrightarrow{1} & \text{AcO-}(CH_2)_n\text{-I} & \xrightarrow{2} & \text{HO-}(CH_2)_n\text{-P(O)Ph}_2 \\ \mathbf{2b\text{-}c}\ (n=4,\ 5) & & \mathbf{7b},\ 85\% & & \mathbf{6b},\ 88\%\ (75\%,\ \text{overall}) \\ & & \mathbf{7c},\ 81\% & & \mathbf{6c},\ 89\%\ (72\%,\ \text{overall}) \end{array}$$

1- a) PPL, pH 6.9 buffer; b) TosCl (1 eq.), pyridine; 0°C, 14h; c) NaI (3 eq.), acetone; reflux, 4h; 2- a) PPh_3 (1 eq.) toluene; reflux, 48h; b) 30% aqueous NaOH; reflux, 3h.

The same phosphine oxides could be obtained in a reduced number of steps, compared to the above process, by first preparing the bromohydrins **8**. Treatment of diols **1** by aqueous concentrated (48%) HBr solution in a two-phase system has been recommended in order to obtain these bromohydrins in good yield from diols.[10] Formation of the corresponding diphenylphosphine **9** by reacting **8** with the anion of diphenylphosphine, followed by hydrogen peroxide oxidation, would then provide **6**. Indeed, by using this heterogeneous bromination procedure, diols **1b** and **1c** gave, as shown, the corresponding bromohydrins **8b** and **8c** but in yields not exceeding 64% after distillation. Subsequent treatment by $Ph_2PLi/PhLi$[11] in THF gave effectively the phosphines **9b** and **9c**, respectively, which were eventually oxidised into **6b** and **6c** (34-36 %, overall).[12]

$$\begin{array}{ccccccc} \text{HO-}(CH_2)_n\text{-OH} & \xrightarrow{1} & \text{HO-}(CH_2)_n\text{-Br} & \xrightarrow{2} & \text{HO-}(CH_2)_n\text{-PPh}_2 & \xrightarrow{3} & \mathbf{6b\text{-}c} \\ \mathbf{1b\text{-}c}\ (n=3,4) & & \mathbf{8b},\ 64\% & & \mathbf{9b},\ 60\% & & 34\text{-}36\%,\ \text{overall} \\ & & \mathbf{8c},\ 55\% & & \mathbf{9c},\ 71\% & & \end{array}$$

1- 48% HBr/hexane, according to ref. 10a; 2- PPh_3 (1.5 eq.), Li (3 eq.), THF; r.t., 2h, then addition of **8**; r.t., overnight; 3- H_2O_2, acetone; 0°C, 1 h

In conclusion, as far as efficiency, reflected by the overall yield and simplicity of both reagent and experimental conditions are concerned, it thus appears that PPL-catalysed hydrolysis of bis-acetates of polymethyleneglycols can be considered as a convenient and useful process for preparing monosubstituted derivatives of diols **1**. The results presented herein illustrate further the potential of enzymes as clean substitutes for standard chemical reagents for mediating common, non-stereoselective functional group transformations.[13]

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5- For n=4, THF can be used (Mosset, P.; Grée, R.; Falck, J. R. *Synth. Commun.* **1989**, *19*, 645-658; Gruiec, R.; Noiret, N.; Patin, H. *Bull. Soc. Chim. Fr.* **1994**, *131*, 699-705. See also ref. 9a).

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7- Lipase from *Candida cylindracea*, another cheap enzyme, gave less satisfactory results.

8- The diacetate (13 mmol) was added to a stirred suspension of PPL (Fluka, 2-4 U/mg; 200 mg) in a pH=6.9 phosphate buffer (39 ml; prepared by dissolving KH_2PO_4 (1.83 g) and KOH (0.55 g) in water (98 ml)), in a 50 ml flask equipped with the electrode of a pH-meter (Tacussel). 1M NaOH was added periodically, as soon as the pH decrease exceeded *c.a.* 0.2 units. After the theoretical amount (*i.e.* 13 ml) of base was consumed, NaCl (20 g) and CH_2Cl_2 were added and the mixture was stirred for 2 hours further. Filtration on Celite (washing with ether; 4x20 ml) was followed by extraction of the aqueous layer (ether; 4x20 ml). After drying ($MgSO_4$), the solvents were evaporated and the residue was chromatographed (silica gel; CH_2Cl_2/ether) to afford the pure monoester. With n=8, a substantial amount of diol was also formed; possibly the extended lipophilicity of the chain outweighs any change resulting from substitution of an acetoxy residue by the hydroxy group and tends to reduce the difference in binding of both the bis- and the mono-acetate to the enzyme.

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12- Selected ^1H NMR (200MHz, $CDCl_3$) data: **3a**: 1.6-1.8 (m, 2H), 2.07 (s, 3H), 2.08-2.22 (m, O*H*), 3.71 (t, J=6Hz, 2H), 4.24 (t, J=6.1Hz, 2H); **3b**: 1.61-1.77 (m, 4H+ O*H*), 2.06 (s, 3H), 3.69 (t, J=6.1Hz, 2H), 4.11 (t, J=6.3Hz, 2H); **3c**: 1.38-1.50 (m, 2H+ O*H*), 1.53-1.74 (m, 4H), 2.05 (s, 3H), 3.65 (t, J=6.2Hz, 2H), 4.07 (t, J=6.5Hz, 2H); **3d**: 1.35-1.56 (m, 4H+ O*H*), 1.58-1.7 (m, 4H), 2.05 (s, 3H), 3.64 (t, J=6.4Hz, 2H), 4.06 (t, J=6.6Hz, 2H); **3e**: 1.3-1.4 (m, 8H+ O*H*), 1.53-1.72 (m, 4H), 2.04 (s, 3H), 3.63 (t, J=6.4Hz, 2H), 4.04 (t, J=6.6Hz, 2H); **5**: 1.81-2.04 (m, O*H*), 2.11 (s, 3H), 4.33 (t, J=1.8Hz, 2H), 4.72 (t, J=1.8Hz, 2H); **6b**: 1.63-1.49 (m, 4H), 2.23-2.37 (m, 2H), 2.86-2.91 (m, OH), 3.58-3.66 (m, 2H), 7.39-7.54 (m, 6H), 7.66-7.77 (m, 4H); **6c**: 1.46-1.67 (m, 6H), 1.76 (m, O*H*), 2.16-2.34 (m, 2H), 3.55-3.63 (m, 2H+ O*H*), 7.40-7.56 (m, 6H), 7.61-7.75 (m, 4H); **9b**: 1.49-1.57 (m, 2H), 1.63-1.73 (m, 2H), 2.03-2.11 (m, 2H), 3.63 (t, J=6.42Hz, 2H), 7.3-7.46 (m, 10H); **9c**: 1.47-1.55 (m, 6H), 2.02-2.09 (m, 2H), 3.6 (t, J=6.12Hz, 2H), 7.29-7.46 (m, 10H).

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