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Novel Diastereoselective Acylation of 4-*C*-Hydroxymethyl-1,2-*O*-(1-methylethylidene)-3-*O*-(phenylmethyl)- α-D-pentofuranose: Effect of Lipases and Acylating Agents on Stereoselectivity

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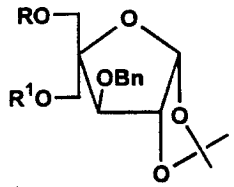
Abstract: Amano PS and CAL catalysed prochiral asymmetrization of the title compound **1** has been studied.

Being attractive building "chirons" in the synthesis of a wide variety of natural products like prostaglandins thromoboxanes, modified nucleosides and pheromones, carbohydrates have become a major focus of current biological research and targets of synthesis.[1,2]

However, a synthetically relevant problem faced in carbohydrate chemistry is the selective protection/ deprotection of nearly identical hydroxyl groups. Chemoenzymatic approaches including the use of lipases are among the favoured methods to carry out selective modifications on carbohydrates. We have employed the versatile 4-*C*-hydroxymethyl-1,2-*O*-(1-methylethylidene)-3-*O*-(phenylmethyl)-α-D-pentofuranose (**1**)[3] as a key intermediate towards the synthesis of modified nucleosides, as the attached hydroxymethyl group can be exploited for conversion into various functionalities as well as for the synthesis of bicyclo sugar derivatives which have recently been reported to be of immense importance in the antisense technology.[4] For further derivatization of **1**, we were interested in the selective protection of one of its two primary hydroxyl groups.

Our initial attempts for selective protection by chemical means however were not successful. Based on our earlier experience of carrying out stereoselective reactions using lipases,[5] a screening programme involving porcine pancreatic lipase (PPL), *Candida rugosa* lipase (CRL), *Pseudomonas cepacia* lipase (Amano PS) and *Candida antartica* lipase (CAL) for the preferential asymmetrization of the prochiral centre C-4 in **1** was undertaken. It was observed that using vinyl acetate as the acyl donor, PPL did not catalyse the reaction, while with CRL no clear cut selectivity was observed as both the monoacetylated compounds **2** and **3** along with the diacetate **4** were obtained. High diastereoselectivity was observed with both Amano PS and CAL and interestingly different monoacetylated epimers **2** and **3** were obtained, with Amano PS the acetylation occurs preferentially at C-1' hydroxyl affording **2** as major product (54% *de*, 63% conversion) while the latter yielded **3** as main product with *de* as high as 79% (optimised, 90% conversion). Repeated attempts to separate the epimers in each case failed. However the diastereomeric excess could be deduced from the difference in the integration values of the anomeric protons of both epimers as seen in their ^{1}H NMR spectra. The anomeric proton in the starting compound **1** (having C-4 prochiral centre) appeared as one doublet at δ 6.02 (J=4 .4 Hz), while the^{1}HMR spectra of both **2** and **3** exhibited two doublets for the C-1 proton of the two diastereomers in each of them at δ 6.03(J=4..3 Hz) and δ 5.96(J=4..4 Hz) respectively (Fig. 1.)



1 R = R^1 = H
2 R = H, R^1 = $COCH_3$
3 R = $COCH_3$, R^1 = H
4 R = R^1 = $COCH_3$
5 R = H, R^1 = $COCH_2CH_2CH_3$

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Further, on using 2,2,2-trifluoroethyl butyrate as an alternative acyl donor in the presence of CAL, a reversal of diastereoselectivity with the preferential acylation of the C-1' hydroxyl group was observed, yielding **5** as main product (50% *de*).

The comparison of spectra unambiguously permitted the tentative structure assignments to the epimers formed. It was observed that the protons of both C-1' and C-5 methylene groups of diol **1** appeared as a multiplet, one of the corresponding methylene protons shifted downfield on acylation, *i.e.* in compound **3** the C-1' methylene protons appeared as a broad singlet whilst the C-5 methylene protons appeared as two doublets at δ 4.23 and δ 4.29 (J = 11.7 Hz each). Furthermore the anomeric proton C-1 of **2** appeared at higher δ value (in $CDCl_3$, 300 MHz) at δ 6.03 compared to the corresponding proton in **3** which appeared at δ 5.96. Also the position of the acetyl group was unequivocally established by the significant NOE effect observed in H-3 on irradiation of H-1' in compound **3**.

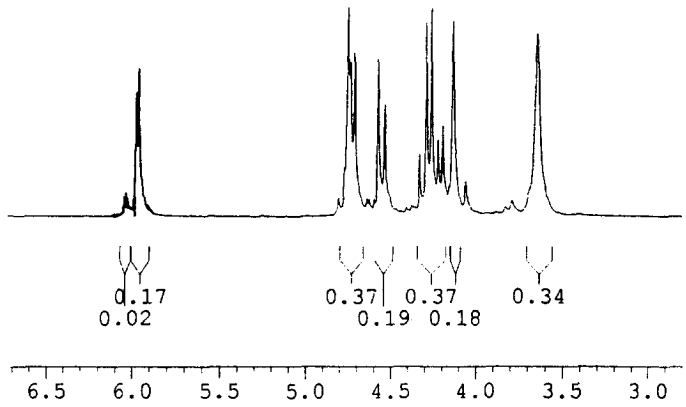

Figure 1: ^{1}H NMR spectrum of the product of CAL catalysed acetylation of **1**

In conclusion this study illustrates the complementary diastereoselectivity of Amano PS and CAL in organic solvents. Also the acylating agent has been seen to influence the stereochemical course of the enzymatic transesterification. The spectral characteristics observed may find applications in the characterization of similar compounds. Further studies to expand the scope and applications of this work in the synthesis of bicyclo nucleosides of therapeutic significance are in progress.

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6. General procedure: The diol 1 (100 mg) was incubated with the lipase (30 mg) in organic solvents (PPL/THF, CRL/DIPE, Amano PS/THF and CAL/DIPE) along with equimolar amount of the acylating agent in a controlled-temperature rotary shaker at 40-42°C. The reaction was monitored by HPLC and quenched by filtering off the enzyme followed by solvent evaporation at reduced pressure. The residue was chromatographed on silica to yield the acylated compound.