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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1705–1708

Lipase-catalyzed alcoholysis of diol dibenzoates: selective enzymatic access to the 2-benzoyl ester of 1,2-propanediol and preparation of the enantiomerically pure (*R*)-1-*O*-benzoyl-2-methylpropane-1,3-diol

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Received 16 February 2005; accepted 16 March 2005

Abstract—Enzymatic debenzoylation of 1,2-propanediol dibenzoate with 1-octanol has been studied in organic solvent using lipases from different sources. In general a slow, highly regioselective alcoholysis in diisopropyl ether affords exclusively a monoester benzoylated at the secondary hydroxy group although the reaction proceeds with low enantioselectivity. In the presence of *Pseudomonas cepacia* lipase absorbed onto celite, a faster reaction allows the preparation of the 2-benzoyl ester of (*R*)-1,2-propanediol (82% ee) and the enantiomerically pure (*R*)-1-*O*-benzoyl-2-methylpropane-1,3-diol (>98% ee).
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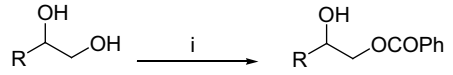
1. Introduction

The selective protection of polyhydroxy compounds still remains a challenge in organic synthesis.[1] Considering an ester as the protecting group of an alcohol, the selective acylation or deacylation can be chemically achieved only by a few methods including microwave heating.[2] The biocatalytic approach using enzymes has been adopted for the introduction/removal of acyl groups, such as acetates,[3] but aliphatic esters are not sufficiently stable for synthetic manipulations. An additional disadvantage of the above using protecting groups is constituted by the fact that migration towards a vicinal hydroxy group frequently occurs under a variety of experimental conditions.[4–6] This unfavourable side reaction is much slower for moderately reactive monoesters, such as benzoates that present the additional advantage to be more resistant to several synthetic transformations.[1] We have recently reported (Scheme 1) that the selective enzymatic benzoylation of the primary hydroxy group of 1,2-diols can be obtained with lipase from *Muchor miehei* (MML) in an organic solvent and vinyl benzoate (VB) as an acyl transfer agent.[7]



R = CH_3; C_4H_9; C_8H_{17}; Ph; CH_2Ph; $CH=CH_2$

Scheme 1. Reagents: (i) MML, VB, *tert*-butyl methyl ether (*t*BuOMe).

We have started to study the enzymatic deacylation of dibenzoates of 1,2-diols by alcoholysis, a reaction that should preferably occur at the primary benzoate moiety, thus allowing the preparation of the 2-monobenzoate that, at present, can be hardly obtained by selective chemical procedures.[8]

2. Results and discussion

2.1. Lipase-catalyzed debenzoylation of 1-*O*,2-*O*-dibenzoylpropane-1,2-diol 1

The dibenzoate of 1,2-propanediol **1** [1-*O*,2-*O*-dibenzoylpropane-1,2-diol] was selected as substrate to set up the experimental conditions of lipase-catalyzed debenzoylation in diisopropyl ether (DIPE), a solvent that has been frequently used in alcoholysis procedures.[9,10] Other solvents, such as hexane, toluene, chloroform, tetrahydrofuran and *tert*-butyl methyl ether

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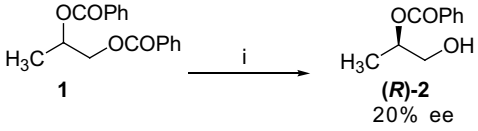
doi:10.1016/j.tetasy.2005.03.019

were used but with DIPE, the reaction rates were the most satisfactory. On the basis of our recent report on the enzymatic benzoylation of 1,2-diols,[7] we selected MML as the biocatalyst for the alcoholysis process. After preliminary experiments, an enzyme/substrate ratio of 1 g/mmol was selected, since higher amount of lipase produced only marginal beneficial effects and were not practical from a preparative point of view. Using 1-butanol as the deacylating agent (4.4 mmol/mmol substrate), the reaction proceeded to 40% conversion in 7 days. In an attempt to improve yields and lower reaction times, other nucleophiles (water, ethanol, 1-butanol, 1-octanol, 1-dodecanol, benzyl alcohol, 2-phenylethanol) were examined within 7 days reaction. 1-Octanol carried out the fastest alcoholysis affording in 7 days the expected monobenzoate **2** (75% yield). Conversely from the unstable acetate of secondary hydroxy group in 1,2-diols[11,12] monobenzoate **2** was a stable product that did not show favour to migrate during the purification by silica gel chromatography or on standing at room temperature.

As a general comment on the MML-catalyzed debenzoylation, it should be pointed out that the alcoholysis proceeds with high regioselectivity and constitutes as the first example of an enzymatic preparation of a 1,2-diol protected as benzoate at the secondary hydroxy group (Scheme 2). In order to determine the stereochemical outcome of the enzymatic reaction and the enantiomeric excess of the product, reference samples of (*RS*)-**2** and (*R*)-**2** were prepared by a conventional protection/deprotection sequence. Starting from commercial (*RS*)-**2** and (*R*)-**1**, selective protection of the primary hydroxy group as *t*-butyldimethylsilyl ether,[13] benzoylation of the secondary hydroxy group, and removal of the silyl group[14] afforded required standards. HPLC analysis using a chiral column (see Experimental section) allowed us to obtain 20% ee and establish an (*R*)-configuration for the enzymatically prepared monobenzoate **2**. Interestingly, the same HPLC analysis was unsuccessful in resolving the enantiomers of (*RS*)-1-*O*-benzoyl ester of propane-1,2-diol. MTPA esters of (*RS*)-**2** and enzymatically prepared monobenzoate **2** were obtained by reaction with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl].[15] ^{1}H NMR analysis confirmed the enantioselectivity and stereochemical outcome of the enzymatic reaction. Other lipases such as pPL (from porcine pancreas), CCL (from *Candida cylindracea*) and CAL (from *Candida antarctica*) were then examined and it was concluded that they were neither more active nor more enantioselective than MML. Interestingly, only lipase from *Pseudomonas* sp. (PSL) showed a good enantioselectivity (78% ee), although the (*R*)-monobenzoate **2** was obtained in only 20% yield after 14 days at room temperature.



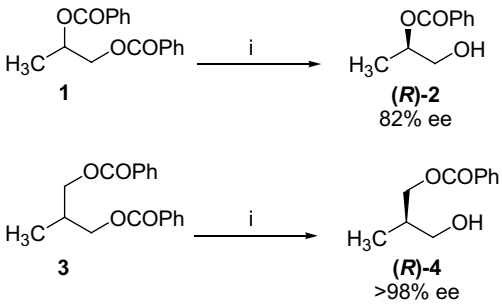
Scheme 2. Reagents: (i) MML, 1-octanol, DIPE.

2.2. *Pseudomonas* species lipase absorbed onto celite as a biocatalyst for enantioselective debenzoylation

The observed enantioselectivity of the reaction catalyzed by PSL prompted us to study experimental conditions that would accelerate the process. It turned out that PSL absorbed onto celite[16] (30% w/w, enzyme/substrate ratio 1.2 g/mmol, corresponding to 0.36 g of PSL/mmol) catalyzed, at room temperature, the debenzoylation at an extent of 33% in 2 days, although the enantioselectivity remained substantially unaffected (82% ee). Furthermore, when compared to the MML-catalyzed alcoholysis (92% conversion to monobenzoate **2** in 14 days), the complete conversion with PSL/celite was obtained in 6 days. Generally, a positive effect on activity, stability and selectivity of absorbed[17] or immobilized[18] lipases has already been demonstrated. We then applied the PSL/celite-mediated alcoholysis to the asymmetrization of 1-*O*,2-*O*-dibenzoyl-2-methylpropane-1,3-diol **3**. In the presence of PSL/celite, 50% conversion was achieved in 2 days and the enantiomerically pure (*S*)-monobenzoate **4** was obtained (>98% ee). Conversely for all other native lipases, complete conversion could be reached with PSL/celite in 14 days, but the enantioselectivity of the reaction was lower (45% ee). We also carried out the same reaction with MML and found that in 10 days, 30% conversion was reached, obtaining an enantiomerically pure product (>98% ee). The enantiomeric excess and (*R*)-configuration was established by analyzing the NMR spectra of the MTPA ester of monobenzoate **4** prepared by enzymatic debenzoylation and comparing the resonances with those described for (*S*)-**4**.[19] Results on the debenzoylation of dibenzoates **1** and **3** with PSL/celite are illustrated in Scheme 3.

3. Conclusions

The preliminary data on the lipase-catalyzed debenzoylation indicate that PSL/celite may allow a biocatalytic preparation of 2-*O*-benzoylpropane-1,2-diol **2** and 82% ee can be reached. The debenzoylation process can be probably extended to other 1,2-diol dibenzoates and we are actively exploring other applications of this enzymatic reaction. Furthermore, the deacylation of the dibenzoate **3**, which affords enantiomerically pure (*R*)-**4** is an example of enantioselective enzymatic desymmetrization.[20] This latest result is complementary to the MML-catalyzed benzoylation of 2-methylpropane-1,3-



Scheme 3. Reagents: (i) PSL/celite, 1-octanol, DIPE.

diol that affords enantiomerically pure (*S*)-**4**.[19] Both enantiomers of monobenzoate **4** are important chiral building blocks derived from *meso*-2-methylpropane-1,3-diol[21] and are now available as enantiomerically pure synthons by a biocatalytic approach.

4. Experimental

4.1. General

Optical rotations were measured on a Perkin–Elmer 241 polarimeter (sodium D line at 25 °C). Melting points were obtained using a Stuart Scientific SMP3 instrument and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-500 spectrometer operating at 500.13 MHz and are referenced to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.24 ppm; coupling constants (*J*) are given in hertz. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated plates with a fluorescent indicator. Flash chromatography[22] was performed using Merck silica gel 60 (230–400 mesh) using appropriate mixtures of petroleum ether and ethyl acetate as eluants. The progress of all reactions, column chromatography and compound purity were monitored by TLC, GLC and/or HPLC. GLC analyses were carried out using a Hewlett Packard GC System HP6890 with a HP-5 Hewlett Packard column (30 m × 0.32 mm; 0.25 mm ID, film thickness 0.25 μm). HPLC analyses were carried out using a Perkin Elmer HPLC instrument with a Series 200 UV/vis detector operating at 240 nm using a chiral Merck (*R*,*R*) Whelk-O1 column (4 mm × 25 cm). All reagents were obtained from commercial sources and used without further purification. Porcine pancreas lipase (24 U/mg solid) was purchased from Fluka. Lipases from *Pseudomonas* sp. (Lipase PS 'Amano', 30 U/mg solid) and from *C. cylindracea* (Lipase AYS 'Amano', 31.6 U/mg solid) were purchased from Amano Pharmaceutical. Lipases from *C. antarctica* (Novozym 435®, acrylic resin supported lipase, 11.4 U/mg solid) and *Mucor miehei* (Chirazyme® L-9,c.-f., C2, lyo, carrier-fixed lipase, 8 U/mg solid) were purchased from Novo Nordisk and Roche Diagnostics GmbH, respectively.

4.2. (*RS*)-2-*O*-Benzoylpropane-1,2-diol 2

To a solution of (*RS*)-1,2-propanediol (1.0 g; 13.14 mmol) in pyridine (10 mL), *tert*-butyldimethylchlorosilane (2.9 g; 19.24 mmol) was added. The mixture was allowed to react under continuous stirring at room temperature and the progress of the reaction monitored by TLC (petroleum ether/AcOEt 7:3) and GC. At the end of reaction, the 1-silyl derivative was purified by silica gel column chromatography (petroleum ether/AcOEt 7:3) and reacted with benzoyl chloride (2.7 g; 19.24 mmol) in pyridine (10 mL) at 0–5 °C. After stirring overnight, addition of 1 M HCl and work-up afforded the 1-*O*-silyl,2-*O*-benzoyl derivative that was used for the next step without purification. A solution of 1 M lithium tetrafluoroborate in CH_3CN (25.0 mL) was slowly added to the solution of the above compound in CH_2Cl_2–CH_3CN (1:1, 40 mL). The reaction was stirred at room temperature overnight and then evaporated at reduced pressure to give a crude product that was purified by flash chromatography on silica gel. Elution with petroleum ether/AcOEt (9:1) afforded title compound **2** (40% isolated yield, colourless oil). Chiral HPLC (hexane/isopropanol 98:2) t_R = 20.9 min for (*S*)-**2** and 22.5 min for (*R*)-**2**. ^{1}H NMR ($CDCl_3$) δ 8.04 (2H, d, *J* = 7.0 Hz, H-*ortho*), 7.55 (1H, t, *J* = 7.0 Hz, H-*para*), 7.42 (2H, dd, *J* = 7.0 and 7.0 Hz, H-*meta*), 5.23 (1H, ddq, *J* = 3.5, 6.3 and 6.3 Hz, H-1), 3.79 (1H, dd, *J* = 3.5 and 11.9 Hz, H-2a), 3.74 (1H, dd, *J* = 6.3 and 11.9 Hz, H-2b), 1.36 (3H, d, *J* = 6.3 Hz, CH_3).

4.3. (*R*)-2-*O*-Benzoylpropane-1,2-diol (*R*)-2

(*R*)-**2** was chemically prepared from the commercially available enantiomerically pure (*R*)-1,2-propanediol **1** (Fluka, Switzerland) as previously described for (*RS*)-**2**; $[\alpha]_D^{25} = -18.6$ (*c* 1, $CHCl_3$). Chiral HPLC (hexane/isopropanol 98:2) t_R = 22.5 min. Significative signals corresponding to the Mosher derivative of (*R*)-**2**: ($CDCl_3$) δ 5.43–5.37 (1H, m, C*H*OCOPh), 4.52–4.46 (2H, m, part AB of ABX system, CH_2O), 3.48 (3H, s, OCH_3), 1.36 (3H, d, *J* = 7.0 Hz, CH_3).

4.4. MML-mediated alcoholysis of 1-*O*,2-*O*-dibenzoylpropane-1,2-diol 1

The substrate (1.0 mmol), 1-octanol (4.4 mmol) and lipase (1.0 g) were suspended in DIPE (10 mL). The mixture was allowed to react at room temperature under magnetic stirring and the progress of the reaction monitored by TLC (petroleum ether/AcOEt 8:2) and GLC (160 °C for 5 min; 30 °C/min to 280 °C for 15 min; t_R = 4.5 min for monobenzoate, t_R = 10.4 min for dibenzoate). At the end of reaction, the enzyme was filtered off and washed with methanol, the solvents were distilled under vacuum and the product purified by flash chromatography. Elution with petroleum ether/AcOEt (9:1) afforded monobenzoate **2** as a colourless oil (0.122 g, 68% for the MML catalyzed reaction at 75% conversion). At 30% conversion, (*R*)-**2** (ee 20%) was obtained in 28% yield; $[\alpha]_D^{25} = -3.6$ (*c* 1, $CHCl_3$). Significative signals corresponding to the Mosher derivative of the minor enantiomer (40%), (*S*)-**2**: (500 MHz, $CDCl_3$) δ 5.43–5.37 (1H, m, C*H*OCOPh), 4.52 (1H, dd, *J* = 3.3 and 11.8 Hz, C*H*HO), 4.46 (1H, dd, *J* = 6.1 and 11.8 Hz, CH*H*O), 3.50 (3H, s, OCH_3), 1.39 (3H, d, *J* = 7.0 Hz, CH_3). For the signals corresponding to the Mosher derivative of the major enantiomer (60%) (*R*)-**2** see Section 4.3.

4.5. PSL/celite-mediated alcoholysis of 1-*O*,2-*O*-dibenzoylpropane-1,2-diol 1 and 1-*O*,3-*O*-dibenzoyl-2-methylpropane-1,3-diol 3

The substrate (1.0 mmol), 1-octanol (4.4 mmol) and lipase (1.2 g) were suspended in DIPE (10 mL). The mixture was allowed to react at room temperature under magnetic stirring and the progress of the reaction monitored by GLC. The enzyme was filtered off and

washed with methanol, the volatiles were distilled under vacuum and the product was purified by flash chromatography.

4.5.1. (*R*)-2-*O*-Benzoylpropane-1,2-diol (*R*)-2. $[\alpha]_D^{25} = -15.4$ (*c* 1, $CHCl_3$). ^1H NMR of the Mosher ester of enzymatically prepared **2** showed two singlets at 3.50 ppm [9%, (*S*)-2] and 3.48 ppm [91%, (*R*)-2] corresponding to resonances of the three hydrogen atoms of the OCH_3 group of MTPA [82% ee for (*S*)-4].

4.5.2. (*R*)-1-*O*-Benzoyl-2-methylpropane-1,3-diol (*R*)-4. $[\alpha]_D^{25} = -8.0$ (*c* 1, MeOH); lit:[19] $[\alpha]_D^{25} = +7.9$ (*c* 1, MeOH) for enantiomerically pure (*S*)-4; ^1H NMR ($CDCl_3$) δ 8.02 (2H, d, $J = 7.0$ Hz, H-*ortho*), 7.54 (1H, t, $J = 7.0$ Hz, H-*meta*), 7.42 (2H, dd, $J = 7.0$ and 7.0 Hz, H-*para*), 4.35 (1H, dd, $J = 5.4$ and 11.2 Hz, C*H*HOBz), 4.28 (1H, dd, $J = 6.3$ and 11.2 Hz, CH*H*OBz), 3.60 (1H, dd, $J = 5.4$ and 11.2 Hz, C*H*HOH), 3.56 (1H, dd, $J = 6.3$ and 11.2 Hz, CH*H*OH), 2.23 (1H, br s, O*H*), 2.14–2.08 (1H, m, C*H*CH_3), 1.04 (3H, d, $J = 7.0$ Hz, CH_3). For the configuration and evaluation of the ee, analysis of the ^1H NMR spectrum of the MTPA ester of enzymatically prepared (*R*)-4 was performed as reported for (*S*)-**4**.[19]

Acknowledgements

This work was financially supported by Università degli Studi di Milano (Fondi FIRST).

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