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Asymmetrization of 2-methylpropane-1,3-diol by *Mucor miehei* lipase-catalyzed benzoylation in organic solvent

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Abstract—Asymmetrization of prochiral 2-methylpropane-1,3-diol by *Mucor miehei* lipase (MML)-catalyzed acylation with vinyl benzoate affords the corresponding (*S*)-monobenzoate (65% ee), which can be obtained enantiomerically pure in 40% yield from a sequential benzoylation procedure at 58% conversion of the diol to the corresponding dibenzoate.

2-Methylpropane-1,3-diol **1a** is the simplest *meso*-1,3-diol and its enantiomerically pure derivatives, such as monobenzyl ether **1b**,[1] constitute an important series of synthetically useful chiral building blocks (Fig. 1).

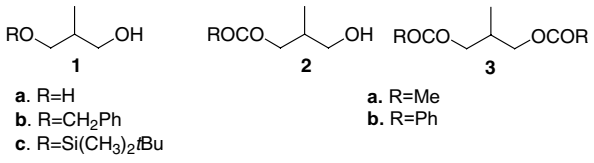
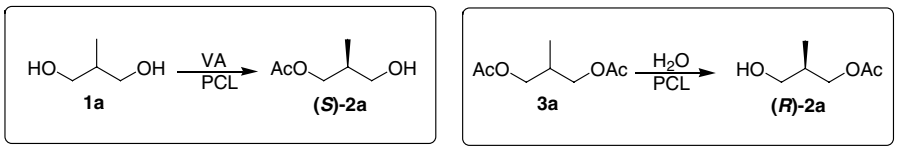


Figure 1.

The enantiotopic differentiation of the two primary hydroxy groups of the diol **1a** is one of the most fascinating challenges in asymmetric organic synthesis that has been only recently been achieved by chemical methods.[2,3] The enzymatic asymmetrization of prochiral substrates,[4] when applied to the diol **1a**, allow the formation of (*S*)-monoacetate **2a** by the *Pseudomonas cepacia* lipase (PCL)-catalyzed acetylation in chloroform,[5,6] whereas the opposite enantiomer (*R*)-acetate **2a** can be obtained by PCL-catalyzed hydrolysis of the prochiral diacetate **3a** (Scheme 1).[6,7]

The enantiomerically enriched monoacetate **2a** has been used as an intermediate in the preparation of the derivatives of 2-methylpropane-1,3-diol such as benzyl ether **1b**[1] or the silyl derivative **1c**.[8] However, chemical manipulation of a monoacetate such as **2a** may be complicated by the attitude of the acyl moiety to migrate towards the vicinal hydroxy group, an unfavourable side reaction encountered mainly in 1,2-diols[9] and observed also in the enzymatic preparation of monoacetate **2a**,[10] with the consequence that the final enantiomeric excess of the product can be considerably lowered. The above isomerization also occurs in the preparation of benzyl ether **1b** from the optically active acetate **2a** and so the experimental conditions for avoiding the side reaction had to be carefully studied.[1]

Differently from reactive esters such as acetyls, where partial isomerization may occur even during work-up, for a moderately reactive monoester such as benzoyl, the same equilibration is considerably slower.[9] Since a benzoate moiety is also more resistant than an aliphatic



Scheme 1.

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ester to several synthetic transformations,[11] we decided to investigate the enzymatic asymmetrization of diol **1a** in order to achieve the preparation of enantiomerically pure monobenzoate **2b**.

We recently reported that the selective enzymatic benzoylation of a primary group in 1,2-diols can be achieved using *Mucor miehei* lipase (MML) as the most suitable biocatalyst in an organic solvent and vinyl benzoate (VB) as acyl transfer.[12] The fastest reaction and the highest enantioselectivity were observed for propane-1,2-diol. This result showed that the size of the substrate might constitute a limiting factor for the activity of the enzyme.

On the basis of the above results, we thought that the simplest prochiral 1,3-diol **1a** could be a good substrate for the MML-catalyzed benzoylation and an enantiotopic asymmetrization could be expected. The benzoylation was carried out in the presence of MML and VB in *t*-butylmethyl ether, stopping the reaction before the formation of the dibenzoate **3b**. In 30 min we observed 84% conversion to monobenzoate **2b**,[13] whose configuration was established as (*S*) by comparison of its specific rotation with that reported for (***R***)-**2b**.[8] A 65% enantiomeric excess (ee) was established by ^{1}H NMR analysis of the ester obtained by reaction of enzymatically prepared (***S***)-**2b** with (*S*)-MTPACl.[14] However, the published specific rotation for (***R***)-(−)-**2b** obtained from 98% ee silyl derivative **1c** was considerably lower than the recorded value for the sample of (***S***)-(**+**)-**2b** obtained by MML-catalyzed asymmetrization of diol **1a**[15] (Scheme 2).

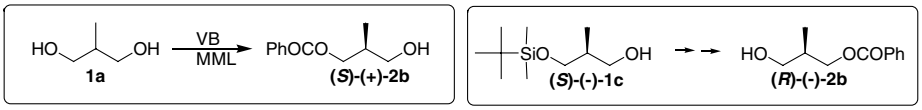
This discrepancy could be due to either low purity of the sample used to record the reported values or to migration of the benzoyl moiety that might have occurred at the stage of protection/deprotection required for the transformation of (***S***)-(−)-**1c** into (***R***)-(−)-**2b**.[8] The second point is especially important, in view of the assumed stability of the benzoate with respect to acyl migration towards vicinal hydroxy groups and, therefore, deserved a careful investigation. For this purpose, we prepared a sample of (*R*)-benzoate **2b** starting from methyl (2*R*)-3-hydroxy-2-methylpropionate (***R***)-**4** (Scheme 3).

According to described procedures,[16–18] the preparation of the enantiomerically pure compound (***S***)-**1c** from (*R*)-ester **4** was realized via the (*R*)-ester **5** and reduction of this intermediate with DIBAL. From the enantiomerically pure compound (***S***)-**1c**, after benzoylation/desilylation steps, an enantiomerically pure (>98% ee, as established by NMR of the MTPA ester) sample of (***R***)-(−)-**2b** could be prepared. The specific rotation recorded for this sample $[\alpha]_D = -8.0$, (*c* 1, MeOH) was considerably higher than the reported value[8] and the enantiomeric excess of the product confirms that the benzoate group is stable during the protection/deprotection, work-up and purification steps of the above synthetic route.

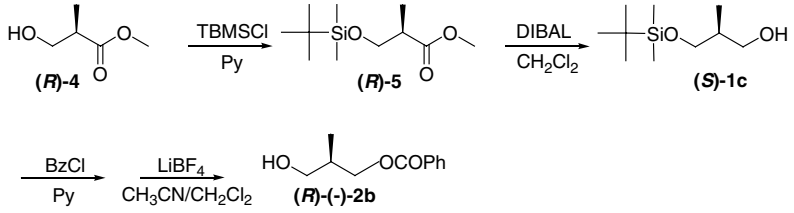
However, the enantiomeric purity of the (*S*)-benzoate **2b** formed by the MML-catalyzed asymmetrization of 1,3-diol **1a** was not satisfactory and we reinvestigated the enzymatic reaction in the presence of other lipases. Only the lipase from *Candida antarctica* (CAL) furnished similar result, but the reaction was much slower that the one catalyzed by MML.[19] We decided to study the sequential benzoylation of diol **1a**, that, according to similar reports on the enzymatic acetylation of 1,2-diols,[20] could furnish an enantiomerically pure monoester **2b**, should the esterification proceed to a >50% formation of diester.[21]

Considering also that the MML-catalyzed dibenzoylation of propane-1,2-diol was feasible and it enhanced the enantioselectivity of the monobenzoylation in raising the *E* value from 5.3 to 9.2,[22] we decided to study the sequential benzoylation of the diol **1a**. It was interesting to observe that in 1.5 h, the enzymatic dibenzoylation proceeded to 58% conversion with complete reaction of diol **1a**, so that enantiomerically pure (*S*)-**2b** was obtained in 40% yield after purification by flash chromatography (Scheme 4).[23]

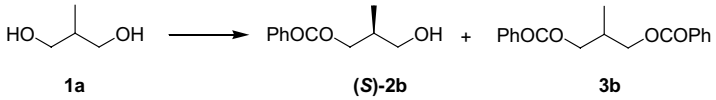
In conclusion, 2-methylpropane-1,3-diol **1a** can be asymmetrized by means of MML-catalyzed benzoylation with VB in *t*-butylmethyl ether to afford the (*S*)-monobenzoate **2b** with moderate enantioselectivity (65%). A sequential benzoylation of diol **1a** at 58% conversion to the dibenzoate **3b**, allowed the isolation of the



Scheme 2.



Scheme 3.



Scheme 4.

enantiomerically pure (*S*)-monobenzoate **2b**. A final remark should concern the usefulness of the benzoate as a protecting group in diol systems, where a monobenzoate is less prone to a migration side reaction that may lower the chemical or enantiomeric purity of the final product.

Acknowledgements

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13. In a typical procedure for MML-mediated benzoylation of **1a**, lipase (100 mg) was added to a solution of **1a** (1.0 mmol) and VB (1.2 mmol) in *t*-butylmethyl ether (10 mL). The mixture was allowed to react at room temperature under magnetic stirring with the progress of the reaction monitored by TLC (hexane/ethyl acetate, 80:20; v/v). GLC analyses were carried out on an HP-5 Hewlett Packard column (30 m × 0.32 mm; 0.25 mm ID, film thickness 0.25 μm). After 0.5 h, the reaction had reached 84% conversion and the enzyme filtered off and washed with methanol. The solvents were distilled under vacuum and flash chromatography (hexane/ethyl acetate, 80:20; v/v) afforded pure compound **2b** as a colourless oil (58% yield; 65% ee) $[\alpha]_D$ = +4.9 (*c* 1, MeOH).
14. The ee of the monobenzoate **2b** could not be established by HPLC analysis, using a Merck (*R*,*R*) Whelk-O1 column (4 mm × 25 cm). Ee was established by ^{1}H NMR analysis of the ester obtained by reaction of (***S***)-**2b** with (*S*)-MTPACl and by comparison with a sample of (*RS*)-monobenzoate **2b** prepared by partial benzoylation of **1a**. Significant signals corresponding to the Mosher derivative of the major enantiomer, (*S*)-1-benzoyloxy-2-methylpropan-3-ol (***S***)-**2b**: (500 MHz, $CDCl_3$) δ: 4.41 (1H, dd, *J* = 5.6 and 11.2 Hz, C*H*HO), 4.30 (1H, dd, *J* = 5.6 and 11.2 Hz, CH*H*O), 4.23–4.16 (2H, m, part AB of ABX system, CH_2O), 3.52 (3H, s, OCH_3), 2.41–2.34 (1H, m, C*H*CH_3), 1.04 (3H, d, *J* = 7.0 Hz, CH_3). Significant signals corresponding to the Mosher derivative of the minor (*R*)-enantiomer (***R***)-**2b**: ($CDCl_3$) δ: 4.38 (1H, dd, *J* = 5.6 and 11.2 Hz, C*H*HO), 4.32 (1H, dd, *J* = 5.6 and 11.2 Hz, CH*H*O), 4.24 (1H, dd, *J* = 5.6 and 11.2 Hz, C*H*HO), 4.15 (1H, dd, *J* = 5.6 and 11.2 Hz, C*H*HO), 3.52 (3H, s, OCH_3), 2.41–2.34 (1H, m, C*H*CH_3), 1.07 (3H, d, *J* = 7.0 Hz, CH_3).
15. In Ref. 8 it has been reported that the specific rotation of (***S***)-**(+)-2b** prepared by enzymatic resolution of (***RS***)-**2b** was +2.1 (*c* 1, MeOH, 84% ee), whereas for a sample of (***R***)-(−)-**2b** it was assumed to be 98% enantiomerically with a specific rotation of −2.5 (*c* 1, MeOH).
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19. Lipase from *Pseudomonas* sp. (Lipase PS 'Amano', 30 U/mg solid) and from *Candida cylindracea* (Lipase AYS 'Amano', 31.6 U/mg solid) were purchased from Amano Pharmaceutical. Lipase from *Candida antarctica* (Novozym 435®, acrylic resin supported lipase, 11.4 U/mg solid) was purchased from Novo Nordisk Bioindustrial Group. Lipase from *Mucor miehei* (Chirazyme® L-9, cf. C2, lyo, carrier-fixed lipase, 8 U/mg solid) was purchased from Roche Diagnostics GmbH. The enzymatic benzoylation with CAL was carried out as for MML; the reaction reached 68% conversion in 24 h with formation of 4% dibenzoate **3b**. After flash chromatography (hexane/ethyl acetate, 80:20; v/v) pure (***S***)-**2b** was obtained as a colourless oil (48% yield; 55% ee) $[\alpha]_D$ = +4.3 (*c* 1, MeOH). The reactions with PCL (20%, 72 h) and CCL (10%, 72 h) were too slow to be further examined.
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21. We have applied the sequential acetylation procedure to diol **1a** and obtained enantiomerically pure (***S***)-**2a**.[6]
22. The enzymatic dibenzoylation of propane-1,2-diol occurred in 40 h affording 62% of dibenzoate and 40% of unreacted monobenzoate. For other diols, the same procedure was very slow and enantioselectivity lower.[12]
23. The sequential benzoylation was carried out by adding MML (100 mg) to a solution of **1a** (1.0 mmol) and VB (2.4 mmol) in *t*-butylmethyl ether (10 mL). The mixture was allowed to react at room temperature under magnetic stirring and the progress of the reaction monitored by TLC and GLC. After 1.5 h the starting diol **1a** disappeared and 58% of dibenzoate **3b** was formed. After the usual work-up, pure compound (***S***)-**2b** was obtained after flash chromatography (40% yield); $[\alpha]_D$ = +7.9 (*c* 1, MeOH). A >98% ee was established by the NMR spectrum of MTPA derivative that showed no signal corresponding to (***R***)-**2b**.