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Stereoselective esterification of 2,6-dimethyl-1,7-heptanedioic acid, catalysed by *Candida rugosa* lipase

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Abstract

The immobilised *Candida rugosa* lipase (CRL) displayed *S*-preference for both stereogenic centres in this sequential esterification of 2,6-dimethyl-1,7-heptanedioic acid (**1**) (pure *meso* and *meso*: (±) mixture, 53/47) with *n*-butanol in cyclohexane at $a_w = 0.8$. The reaction was faster when short-chain primary *n*-alcohols was used and very slow, or even none reactive, when a long-chain alcohol was used.

Keywords: *Candida rugosa*; Esterification; Synthesis; Stereoselective; 2,6-Dimethyl-1,7-heptanedioic acid

1. Introduction

The number of articles published on the use of lipase as catalysts in organic chemistry have increased enormously during the last years [1]. Among them some deal with esterification of chiral methyl branched carboxylic acids catalysed by *Candida rugosa* lipase (CRL) [2]. These acids are useful building blocks, for instance in the synthesis of sex pheromones of pine sawfly species and we have during the years described several such syntheses [3].

Using a so-called double-*meso* trick [4] process, Chenevert and Desjardins [5] presented an enzymatic acetylation/desymmetrisation of the *meso*-2,6-dimethyl-1,7-heptanediol using *Pseudomonas cepacia* lipase as catalyst. The chiral *syn*- and/or *anti*-1,5-dimethylalkyl subunit is found in many insect pheromones, for instance in sex pheromones of several pine sawfly species (see Scheme 1) This *syn*-structural element has later been prepared employing the same enzymatic strategy as above to desymmetrise this *meso* compound and used it in the preparation the pheromone of the pine sawfly *Microdiprion pallipes* [6]. Our group has earlier described successful CRL-catalysed resolutions by esterification of 2- to 8-methylalkanoic acids and CRL was shown to be highly enantioselective even to remotely located stereocentres [3a,7]. Surprisingly, the enantiopreference of CRL was either *S* or *R* depending on the position of the methyl group in the carbon chain. To further investigate the enantiopreference of CRL we attempted to desymmetrise *meso*-2,6-dimethyl-1,7-heptanedioic acid (**1**) and also to simultaneously desymmetrise and resolve a *meso*/(±) mixture of 2,6-dimethyl-1,7-heptanedioic acid (**1**). We now wish to describe what constitutes to our knowledge, the first results that demonstrates this dioic acid to be a substrate for CRL in an esterification reaction in organic media.

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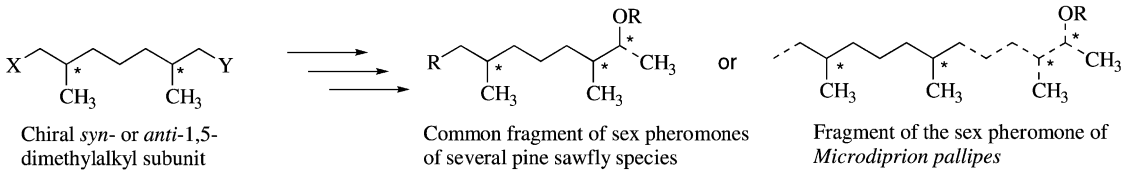


Scheme 1. Chiral *syn*- and/or *anti*-1,5-dimethylalkyl subunit of sex pheromones of pine sawfly species.

2. Experimental

Commercially available chemicals were used without further purification unless otherwise stated. *C. rugosa* lipase was purchased from Sigma–Aldrich and stored at 4 °C over dry silica gel. Macroporous polypropene Accurel EP 100, 350–1000 was obtained from Akzo Faser AG, Obernburg, Germany. Air sensitive reactions were carried out under anhydrous condition under argon atmosphere. Preparative liquid chromatography (LC) was performed on normal phase silica gel (Merck 60, 230–400 mesh, 0.040–0.063 mm) employing a gradient technique using an increasing concentration of distilled diethyl ether in distilled *n*-pentane or of distilled ethyl acetate in distilled cyclohexane (0 → 100%), as eluent. Thin layer chromatography which was performed on silica gel plates (Merck 60 F_{254}, pre-coated aluminium foil) eluted with ethyl acetate (20–40%) in cyclohexane and developed by spraying with vanillin/sulfuric acid in ethanol and heated at 120 °C. NMR spectra were recorded on a Bruker DMX 250 (250 MHz ^{1}H and 62.9 MHz ^{13}C) spectrometer using $CDCl_3$ as solvent and TMS as internal reference. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 1 dm cell. Mass spectra were recorded on a Saturn 2000 instrument, operating in the EI mode, coupled to a Varian 3800 GC instrument. Unless otherwise stated, conversions and purities were determined on a Varian 3400 GC instrument equipped with a capillary column (30 mm × 0.32 mm i.d.) coated with EC-1, d_f = 0.25 μm; carrier gas N_2 100 kPa, split ratio 40:1 (flow 1 ml/min) (GC programme: 120 °C/3 min, 8 °C/min, 260 °C). Boiling points are uncorrected and given as air-bath temperatures (mbar) in a bulb-to-bulb (Büchi-GKR-51) apparatus.

2.1. 2,6-Dimethyl-1,7-heptanedioic acid (1)

The dioic acid was synthesised according the published method [8] with modifications as follows: diethyl methylmalonate (71.4 g, 488 mmol) dissolved in dry THF (500 ml) was added to NaH (12.2 g, 0.292 mol) controlling the temperature between 0 and 10 °C. The solution was stirred at room temperature for 0.25 h and 1,3-dibromopropane (40.4 g, 0.200 mol) was added drop by drop and the mixture was refluxed overnight. The precipitate formed was dissolved when water (100 ml) was added, the aqueous layer was separated and extracted with diethyl ether (4 × 100 ml). The combined organic extracts were washed with NH_4Cl (sat. aq.), NaCl (sat. aq.) and dried ($MgSO_4$). After evaporation of the solvent and recrystallisation from cyclohexane 53.7 g of a crystalline material was obtained. This product was hydrolysed in the next step by refluxing overnight with KOH in MeOH (500 ml, 2.4 M) and water (50 ml). MeOH (300 ml) was added and the solvent was removed by evaporation which yielded a precipitate that was dissolved in water and washed with diethyl ether (4 × 100 ml). The aqueous layer was acidified with conc. HCl and the product acid obtained taken up in diethyl ether (2 × 150 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated to yield 31 g of crystals which was heated at 195 °C overnight. The remaining mixture was dissolved in diethyl ether and the precipitate was filtered off. The solvent was evaporated to yield 17.1 g (46%) of the pure title compound, 2,6-dimethylheptane-1,7-dioic acid (**1**) as a colourless solid after recrystallisation twice from water. ^{1}H NMR δ 1.17 (d, J = 7.0 Hz, 6H), 1.24–1.75 (m, 6H), 2.40–2.55 (m, 2H), 11.94 (bs, 2H). ^{13}C NMR δ 17.08, 17.27, 24.31, 25.17, 33.53, 33.98, 39.30, 39.79. Other spectral and an-

alytical data were similar to those in the literature of *meso*-(2*R*,6*S*)-2,6-dimethyl-1,7-heptanedioic acid [9]. The stereoisomeric composition of the dioic acid **1** was determined (*meso*: (±), 53/47) by GC (column EC-1) after derivatisation with (*R*)-1-phenylethylamine (>99.5% e.e.) to the corresponding bis-amide as described below. From this mixture pure *meso* compound was obtained by several recrystallisations from *n*-hexane/diethyl ether (2/1) [9]. Spectral and analytical data for the *meso* acid were similar to those in the literature of *meso*-(2*R*,6*S*)-2,6-dimethyl-1,7-heptanedioic acid [9]. Both this pure *meso* compound and the *meso*/(±) mixture were used as substrates in the CRL-catalysed esterification below.

2.2. General procedure for lipase-catalysed esterification of 2,6-dimethyl-1,7-heptanedioic acid

Exemplified by the esterification of the *meso*: (±) mixture (53/47) of the diacid **1**. The diacid (*meso*: (±), 53/47) from above (8.79 g, 46.8 mmol) was mixed with *n*-butanol (5.09 g, 68.8 mmol), diphenylether (internal standard, 3.7 g, 6 mg/ml) and $Na_2SO_4/Na_2SO_4{\cdot}10H_2O$ (2 eqv./1 eqv., $a_w = 0.8$) in cyclohexane (620 ml). The solution was stirred for 0.25 h before the enzyme, 21.1 g of immobilised [10] CRL (34 mg/ml) was added. The reaction mixture was stirred at room temperature to a conversion of 70% (i.e. 30% remaining dioic acid after 90.5 h). The enzyme was removed by filtration and the solid washed with CH_2Cl_2. After removal of the solvent by evaporation, the product mixture was dissolved in *n*-pentane (250 ml) and extracted with water (3 × 150 ml). The water phases were combined and the water removed by evaporation. After bulb-to-bulb distillation of the remaining oil 2.34 g of the 2,6-dimethylheptan-1,7-dioic acid (**1**) was obtained >98% pure by GC. The stereoisomeric composition was determined by GC (column EC-1) and the (2*R*,6*R*)-**1** dioic acid was found to contain 4% (2*S*,6*S*)-**1** and 35% *meso*-**1**. This dioic acid was then subjected to another cycle of esterification as above but to a conversion of 57% and after work up as above 1.02 g of (2*R*,6*R*)-2,6-dimethyl-1,7-heptanedioic acid >99.6% pure by GC was obtained, $[\alpha]_D^{25}$ −68.8 (c 0.930, CH_2Cl_2). The stereoisomeric composition was analysed by GC (column EC-1) and was found to be 93.5% (2*R*,6*R*)-**1** and 6.5% *meso*-**1**.

The organic phase from above, containing the monoester and the diester, was dried ($MgSO_4$) and the solvent was removed by evaporation to give 7.57 g of a mono-/diester mixture. This mixture was then subjected to another cycle of esterification as above to a total conversion of 36% (75 h). The enzyme was removed by filtration and washed with CH_2Cl_2 (100 ml), the solution was dried ($MgSO_4$) and the solvent removed by evaporation. The resulting oil was dissolved in pentane (100 ml) and extracted with Na_2CO_3 (2 × 60 ml, 15% aq.), the organic phase was dried ($MgSO_4$) and the solvent was removed by evaporation to give an oil which after LC gave 2.56 g of the diester (2*S*,6*S*)-**3**. IR (neat) 738, 1165, 1380, 1465, 1735, 2961 cm^{-1}. For determination of the stereochemical composition of this diester by GC (column EC-1) (2*S*,6*S*)-**3** was reduced to the corresponding diol followed by oxidation to the dioic acid and finally derivatisation to the bis-amide as below. The composition found was 67% (2*S*,6*S*)-**1**, 3% (2*R*,6*R*)-**1** and 30% *meso*-**1**.

The combined water phases from above were acidified (2 M HCl), extracted with diethyl ether (2 × 100 ml), the combined organic phases was dried ($MgSO_4$) and the solvent was removed by evaporation leaving an oil which after LC gave 3.18 g of the monoester (2*R*,6*S*)-**2**. The stereochemical composition was determined by GC (column EC-WAX) after derivatisation with (*R*)-1-phenylethylamine (>99.5% e.e.) as below and the stereoisomeric composition was 76% (2*R*,6*S*), 7% (2*R*,6*R*), 12% (2*S*,6*S*) and 5% (2*S*,6*R*). The stereochemical composition was also controlled by reducing to the corresponding *meso*-diol followed by oxidation to the dioic acid and finally derivatisation to bis-amide as below which was analysed by GC (column EC-1) 80% *meso*-**1**, 13% (2*S*,6*S*)-**1** and 7% (2*R*,6*R*)-**1**.

2.3. General procedure for reduction of (2*R*,6*R*)-*1*, (2*R*,6*S*)-*2* and (2*S*,6*S*)-*3* to the corresponding diols

Exemplified by the reduction of diester (2*S*,6*S*)-**3** to the (2*S*,6*S*)-diol. The diester (1.39 g, 4.65 mol) was dissolved in dry diethyl ether (5 ml) and added slowly to a solution of $LiAlH_4$ (0.18 g, 4.7 mol) in dry diethyl ether (6 ml). The reaction mixture was stirred at room temperature for 7 h. The reaction

was quenched with 2 M HCl and the water phase was extracted with diethyl ether (3 × 20 ml). The combined organic phases were dried ($MgSO_4$) and the solvent was removed by evaporation to give (2*S*,6*S*)-2,6-dimethyl-1,7-heptanediol in 73% yield. $[\alpha]_D^{25}$ +23.0 (c 0.831, CH_2Cl_2) The spectral data and analytical data were similar to those in the literature [11].

2.4. (2R,6R)-7-(t-Butyldimethylsiloxy)-2,6-dimethyl-1-heptanol

The (2*R*,6*R*)-2,6-dimethyl-1,7-heptanediol (0.114 g, 0.711 mmol) obtained as above but from (2*R*,6*R*)-**1**, *t*-butyldimethylsilyl chloride (0.163 g, 1.5 eqv.) and triethylamine was mixed, under argon, in dry THF (3.5 ml). The mixture was stirred at room temperature and after 72 h diethyl ether (2 ml) was added and the mixture was washed with HCl (3 ml, 1 M) and Na_2CO_3 (3 ml, 10% aq.). The organic phase was dried ($MgSO_4$), the solvent was removed by evaporation and the (2*R*,6*R*)-7-(*t*-butyldimethylsiloxy)-2,6-dimethyl-1-heptanol was obtained after LC as an oil pure by GC. $[\alpha]_D^{25}$ +10.2 (c 0.938, CH_2Cl_2). $[\alpha]_D^{25}$ +6.69 (c 0.065, CH_2Cl_2). IR 3345, 2928, 2857, 1472, 1463, 1388, 1361, 1257, 1099, 1037, 1006, 837, 775, 741, 668 cm^{-1}. Other spectral data and analytical data were similar to those in the literature [12].

2.5. General procedure for the oxidation of (2R,6R)-, (2S,6S)- and meso-2,6-dimethylheptan-1,7-diol to (2R,6R)-, (2S,6S)- or meso-2,6-dimethyl-heptan-1,7-dioic acid, respectively

The appropriate diol (0.027 g) was dissolved in dry acetone (2 ml) and 0.16 ml Jones reagent was added. After the disappearing of the orange/yellow colour an additional 0.08 ml Jones reagent was added. This procedure was repeated three times, with increasing time interval. After the last addition of Jones reagent the reaction mixture was stirred for additional 2.5 h. The reaction mixture was then filtered through a pad of Celite, and the solid was washed with CH_2Cl_2. The organic phase was extracted with Na_2CO_3 (2 × 4 ml, 10% aq.). The combined water phases were acidified (6 M HCl) and extracted with CH_2Cl_2 (2 × 6 ml). The combined organic phases were dried ($MgSO_4$), the solvent was removed by evaporation and the product dioic acid was used in the derivatisation procedure described below.

2.6. Determination of the stereoisomeric composition of (2R,6R)-*1*, (2R,6S)-*2* and (2S,6S)-*1* obtained from (2S,6S)-*3*

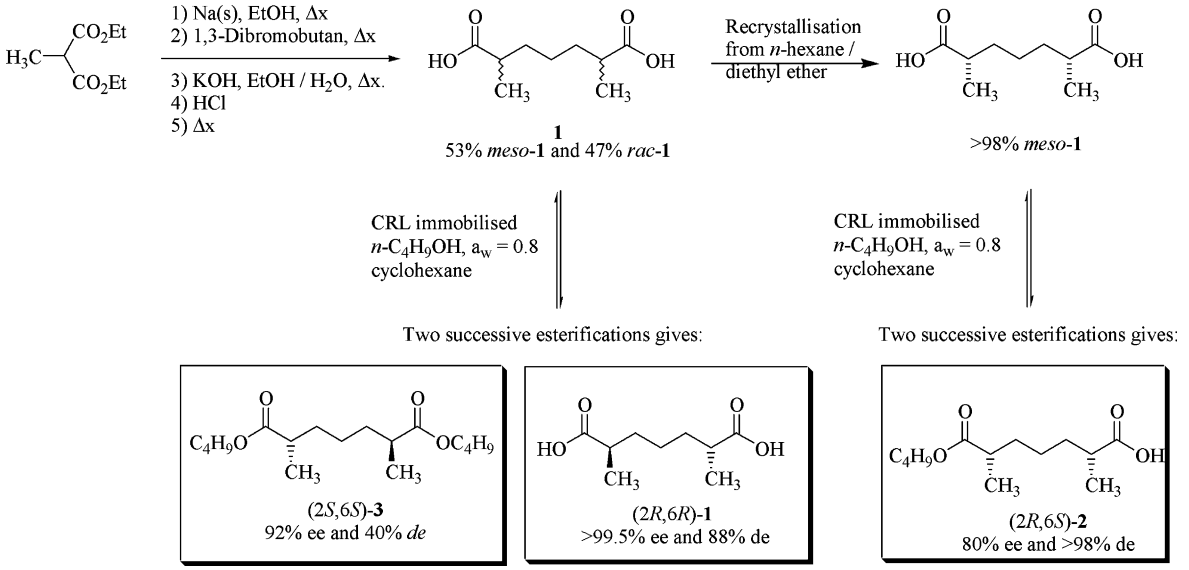
The dioicacids **1**, (2*R*,6*R*)-**1**, (2*S*,6*S*)-**1** or the monoester (2*R*,6*S*)-**2** (10 μl), distilled $SOCl_2$ (10 μl) and distilled dimethylformamide (10 μl), was dissolved in dry diethyl ether (1 ml). The mixture was shaken for 5 min. (*R*)-α-Phenylethylamine (20 μl) was added and the mixture was shaken for additional 10 min. To remove the HCl (g) formed, argon was blown over the mixture. The diethyl ether was evaporated and the remaining mixture was dissolved in 1–2 ml CH_2Cl_2. This solution was washed with water, Na_2CO_3, dried ($MgSO_4$) and finally analysed by GC.

The stereoisomeric composition of (2*S*,6*S*)-**1**, (2*R*,6*R*)-**1** and **1** was determined by GC (column EC-1, GC programme: 200 °C/10 min, 2 °C/min, 300 °C). Retention time (min.): 33.10 (2*R*,6*R*), 35.60 (2*S*,6*S*) and 35.00 (*meso*).

The stereochemical composition of the monoester (2*R*,6*S*)-**2** was determined by GC [30 m × 0.25 mm i.d., d_f = 0.25 μm, capillary column coated with EC-WAX, carrier gas He 16 psi, split ratio 30:1. (GC programme: isothermal 240 °C)]. Retention time (min.): 40.16 (2*R*,6*R*), 43.70 (2*S*,6*S*), 41.83 (2*R*,6*S*) and 44.61 (2*S*,6*R*).

3. Results and discussion

The 2,6-dimethyl-1,7-heptanedioic acid (**1**) used below was synthesised in good yield by a modified malonic ester synthesis [8] (see Scheme 2). The anion from diethyl methylmalonate was prepared from NaH and reacted with 1,3-dibromopropane yielding an tetraester which after base induced hydrolysis, decarboxylation and crystallisation yielded a *meso*/(±) mixture: 53/47 of **1**. From this mixture pure *meso* compound was obtained by several recrystallisations from *n*-hexane/diethyl ether (2/1) [9]. Both this pure *meso* compound and the *meso*/(±) mixture were used as substrates in the CRL-catalysed esterification below.



Scheme 2. The synthesis of and the kinetically desymmetrisation/resolution of the *meso* and *meso*/(±) mixture: 53/47 of 2,6-dimethyl-1,7-heptanedioic acid (**1**) using CRL as catalyst in esterification with *n*-butanol in cyclohexane.

In CRL-catalysed esterifications of methyl branched carboxylic acids reproducible results with high enantioselectivity is obtained when the a_w is controlled by adding a salt/hydrated salt pair e.g. $Na_2SO_4/Na_2SO_4{\cdot}10H_2O$ ($a_w = 0.8$) [13] and when the alcohol used is a long-chain *n*-alcohol in less than 1 molar equivalent per carboxylic unit [14]. Consequently, the 2,6-dimethyl-1,7-heptanedioic acid (**1**) (*meso*: (±), 53/47) was esterified with 1.5 molar equivalents of *n*-heptanol (0.75 molar equivalents per carboxylic unit) in cyclohexane at $a_w = 0.8$ catalysed by *C. rugosa* lipase (see Scheme 2).

In this case and using crude CRL at this relatively high water activity ($a_w = 0.8$) the lipase lost its catalytic activity and the reaction stopped. However, when using immobilised CRL the reaction ran smoothly even for several days. The use of CRL immobilised on polypropene has in some cases also been shown to positively influence the enantioselectivity [14]. Still, the reaction studied here was very slow and after several days the only product obtained was the monoester. Therefore, several primary alcohols were tested as nucleophiles in order to improve the rate of the reaction and the best result, a three time increased reaction rate was obtained with *n*-butanol or ethanol. When using long-chain *n*-alcohols, i.e. decanol, dodecanol, tetradecanol and hexadecanol no monoester or diester were formed after 3 weeks. Thus, when using *n*-butanol, 30% of the starting dioic acid remained after 90 h, at this point the reaction was stopped when the CRL was removed by filtration. The organic solution was shaken with water and the remaining substrate, the dioic acid (2*R*,6*R*)-**1** was isolated from the water phase. After distillation the dioic acid (2*R*,6*R*)-**1** was obtained and the stereoisomeric composition was analysed by GC after derivatisation with enantiomerically pure (*R*)-1-phenylethylamine to the corresponding bis-amide (see Section 2). This dioic acid (2*R*,6*R*)-**1** was found also to contain 4% (2*S*,6*S*)-**1** and 35% *meso*-**1**. To safely confirm the absolute configuration of this dioic acid it was esterified once more under CRL catalysis, now to 57% conversion (233 h) which resulted in (2*R*,6*R*)-**1** with >99.5% e.e. but still containing a small amount (6%) of *meso*-**1**. $[\alpha]_D^{25}$ −68.8 (c 0.930, CH_2Cl_2). $[\alpha]_D^{25}$ −20 (c 0.235, EtOH) [15]. This small amount of the *meso*-form is possible to remove by recrystallisation as the anilide according to the method used in Kipping [16].

The absolute configuration of the dioic acid (2*R*,6*R*)-**1** was established by reduction (basic or acidic hydrolysis of non-racemic 2-methyl alkanoic

esters and acids results in partly racemisation) [3] to the corresponding (2*R*,6*R*)-diol and then treating this with 1.5 molar equivalents of *t*-butyldimethylsilyl chloride to yield the known (2*R*,6*R*)-7-(*t*-butyldimethylsiloxy)-2,6-dimethyl-1-heptanol (see Section 2), $[\alpha]_D^{25}$ +10.2 (c 0.938, CH_2Cl_2) [12] $[\alpha]_D^{25}$ +6.69 (c 0.065, CH_2Cl_2). The lipase displayed *S*-preference for both stereogenic centres in this sequential esterification which is the normal preference of CRL for substrates as 2-methyl branched alkanoic acids [2,7,13,14]. However, results obtained from hydrolysis of 2-methyl branched diesters published by Ngooi et al. CRL shows *R*-preference [17] and recently, CRL was also demonstrated to display an amazing high *R*-preference in the esterification of 3-, 5- and 7-methyldecanoic acids [7b].

Remaining in the first organic phase from above esterification was a mixture found to be composed of 93.5% monoester (2*R*,6*S*)-**2**, 5.5% diester (2*S*,6*S*)-**3** and 1% dioic acid (2*R*,6*R*)-**1** after similar derivatisation and analysis as described previously (see Scheme 2). To obtain the monoester (2*R*,6*S*)-**2** in higher diastereomeric purity it is necessary to start with pure *meso*-form of the 2,6-dimethyl-1,7-heptandioic acid **1** in the esterification cycle. Recrystallisation of dioic acid **1** has been used to increase the *meso*/(±) ratio [9] and in our hands we obtained >98% *meso*-2,6-dimethyl-1,7-heptandioic acid **1**. Starting with this *meso* compound in an esterification sequence as above (but using a three folded amount of cyclohexane due to low solubility of this pure *meso* compound, *t*-butyl methyl ether was also tested as solvent but the stereoselectivity of the lipase then dropped to zero) gave after 3.5 h and a conversion of 12% the mono ester (2*R*,6*S*)-**2** in 66% e.e., $[\alpha]_D^{25}$ +2.5 (c 0.25, *n*-pentane). The enantiomeric (2*S*,6*R*)-monoester also produced (17%) should be a better substrate for CRL and react faster to the *meso*-diester then the (2*R*,6*S*)-**2** would. Thus, to increase the enantiomeric excess of the monoester (2*R*,6*S*)-**2** it was esterified once more in the same manner as previously but during 150 h and to a total conversion of 31%, the e.e. of the monoester was in this way increased to 80% e.e., $[\alpha]_D^{25}$ +3.6 (c 0.07, *n*-pentane). Thus, further optimisation of the reaction conditions is necessarily to improve the selectivity of CRL if the mono ester (2*R*,6*S*)-**2** is needed in higher enantiomeric purity.

4. Conclusions

In conclusion, we have shown that pure *meso* and a *meso*/(±) mixture of 2,6-dimethyl-1,7-heptandioic acid **1** are substrates in a CRL-catalysed esterification reaction and that the lipase show *S*-preference to both stereogenic centres in the substrates. Furthermore, using the presented method (2*S*,6*S*)- and (2*R*,6*R*)-dimethyl-1,7-heptanedioic acids are obtained moderate diastereomeric purities but in high or even very high enantiomeric purity, respectively, from a complex *meso*/(±) mixture of acid **1**. The mono ester of (2*R*,6*S*)-dimethyl-1,7-heptanedioic acids is also obtainable but in moderate enantiomeric purity from pure *meso*-2,6-dimethyl-1,7-heptandioic acid **1**.

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