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Combination of stereospecific dihydroxylation and enzyme catalyzed enantioselective resolution for synthesis of enantiopure vicinal diols

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Abstract

By employing a combination of stereospecific osmium catalyzed dihydroxylation of selected alkenes, and enantioselective lipase catalyzed kinetic resolution, nine alkenes were converted into nine enantiopure vicinal diols and nine enantiopure hydroxy butanoates.

Keywords: Dihydroxylation; Kinetic resolution; Novozym 435; Novozym 735; Enantiopure building blocks

1. Introduction

Several natural products contain an α-alkyl-α,β-dihydroxy carboxylic acid subunit [1–6]. Chiral building blocks containing one tertiary and one secondary hydroxy group can be synthesized from alkenes by a combination of stereospecific dihydroxylation and lipase catalyzed kinetic resolution. When the molecules produced in the dihydroxylation step contain two stereocentra, not all four stereoisomers will be produced in the same reaction. Since this reaction is stereospecific, the *E*-isomer of the alkene will give two of the four stereoisomers, an enantiomeric pair, and the *Z*-isomer will give two other stereoisomers, the other enantiomeric pair. Separation of the enantiomers can be achieved by kinetic resolution via transesterification catalyzed by hydrolytic enzymes. If the dihydroxy product contains one secondary and one tertiary hydroxy group, the subsequent enzyme catalyzed reaction will give a relatively simple product mixture consisting of hydroxy esters, since most hydrolases react much faster with a secondary centre. However, some hydrolases, like Lipase A from *Candida antarctica*, CAL-A, (in immobilized form, Novozym 735), have been reported to be active also at tertiary centres [7–10]. This sequence of reactions has previously been employed to convert dimethyl citraconate [(*Z*)-**1**] and dimethyl mesaconate [(*E*)-**1**] into enantiopure (2*S*,3*R*)-**2**, (2*R*,3*R*)-**2** and the corresponding enantiopure butanoates (2*R*,3*S*)-**3** and (2*S*,3*S*)-**3**, respectively [11]. Reduction give rise to branched tetritols which have been detected in large quantities as aerosols in the atmosphere above the Amazonian rain forest [12]. They are claimed to be formed by photo-oxidation of isoprene expelled from the trees. If this is correct, they should be formed as a mixture of stereoisomers.

2. Results and discussion

Methyl angelate [(*Z*)-**4**], methyl tiglate [(*E*)-**4**], 2-methyl-2-butene (**5**), methyl 3,3-dimethylacrylate (**6**), ethyl (*E*)-β-methylcinnamate [(*E*)-**7**] were purchased as carboxylic esters or synthesized from the corresponding carboxylic acids. The benzyl ethers (*Z*)-**8** and (*E*)-**8** were synthesized from (*Z*)-**4** and (*E*)-**4**, respectively by reduction of the carboxylic ester group, and reaction with benzyl chloride in NaOH-solution with tetrabutylammonium hydrogensulphate as phase transfer catalyst in high yield. The racemic diols (2*R**,3*R**)-**9**, (2*R**,3*S**)-**9**, (3*R**)-(**10**), (2*R**)-(**11**), (2*R**,3*S**)-**12**, (2*R**,3*S**)-**13** and (2*R**,3*R**)-**13** were obtained from the corresponding alkenes by stereospecific dihydroxylation in high yields (Scheme 1).

Osmium-catalyzed oxidation is the most reliable and efficient method for synthesis of vicinal diols from alkenes. We found it practical to use an immobilized variant of the osmium catalyst since it can easily be separated from the product and also be reused. Triosmium dodecacarbonyl, $Os_3(CO)_{12}$, was immobilized in mesoporous Al-MCM-41 material (Os-Al-MCM-41) by chemical vapor deposition [13]. The *cis*-dihydroxylations were performed using Os-Al-MCM-41 under Upjohn conditions. Addition of citric acid increased the reaction rate [14]. Reactions performed in the presence of 1 equiv. (−)-mandelic acid, in order to induce enantioselectivity, did not result in a sig-

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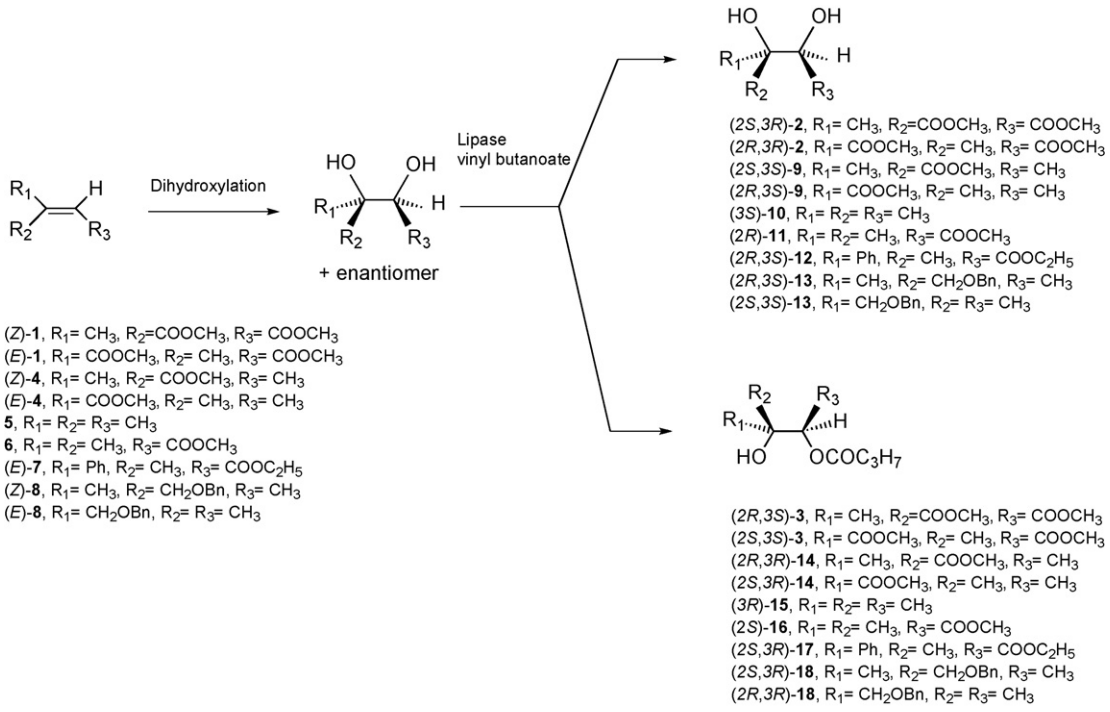

Scheme 1.

nificant ee of the product. However, the yields obtained, were similar to reactions performed with $K_2OsO_2(OH)_4$ as catalyst.

The racemic diols **9**–**13** were resolved by lipase catalyzed kinetic resolution. In order to find the conditions that gave the highest enantioselectivity, *E*-value, the reactions were performed with four industrial lipases as catalysts; in hexane or toluene and with vinyl butanoate as acyl donor. The reactions were monitored with chiral GLC-analyses, and *E*-values were calculated to give the values shown in Table 1. The four different lipases showed the same enantiopreference at the secondary centres ($R_3 \neq H$ in Scheme 1) in esterification reactions for all of the substrates, in accordance with the Kazlauskas rule [15]. Indeed, when *E*-values of resolutions are high, the enantiopreference can be used to determine absolute configurations of the products of a kinetic resolution [16]. Moreover, when the configurations of the secondary centres were known, the configurations of the tertiary centres in **9**, **12** and **13** of the remaining diols, and in the butanoates **14**, **17** and **18** were also proven, since the dihydroxylations were stereospecific.

The size of the substituents at the secondary centre is the primary selection factor for obtaining high *E*-values. CAL-B usually gives high selectivity when the stereocenter carries a large or bulky group and a small group, as in the case of **9**, **10** and **13** (see Table 1) [17]. When the small substituent was a carboxylic ester group, as in **2** and **12**, the conversion rate was quite low, presumably because of bad fit of this group into the stereospecifity pocket in the active site [18]. It is worthy to notice that, in most cases, the large group at the secondary centre, has priority over the small group, with respect to *R/S*-nomenclature, which means that the *R*-enantiomer is the fastest reacting. However, this is not the case for **2**, **11** and **12**, where the *S*-form is the faster reacting enantiomer.

Less is known about the active site of CAL-A and the interaction with the substrate, mainly because less work has been

Table 1
E-values and configurations obtained in small scale transesterifications of 2*R**,3*R**-**2**, 2*R**,3*S**-**2**, 2*R**,3*R**-**9**, 2*R**,3*S**-**9**, 3*R**-**10**, 2*R**-**11**, 2*R**,3*S**-**12**, 2*R**,3*S**-**13** and 2*R**,3*R**-**13**

Substrate	CAL-A	CAL-B	RML	TL IM	Remaining alcohol	Product (butanoate)
2*R**,3*R**-**2**	140	–	128	8	2*R*,3*R*-**2**	2*S*,3*S*-**3**
2*R**,3*S**-**2**	20	–	33	14	2*S*,3*R*-**2**	2*R*,3*S*-**3**
2*R**,3*R**-**9**	3	>200	>200	200	2*S*,3*S*-**9**	2*R*,3*R*-**14**
2*R**,3*S**-**9**	3	>200	>200	65	2*R*,3*S*-**9**	2*S*,3*R*-**14**
3*R**-**10**	4	175	9	10	3*S*-**10**	3*R*-**15**
2*R**-**11**	4	1	19	3	2*R*-**11**	2*S*-**16**
2*R**,3*S**-**12**	120	–	>200	65	2*R*,3*S*-**12**	2*S*,3*R*-**17**
2*R**,3*S**-**13**	4	>200	200	28	2*R*,3*S*-**13**	2*S*,3*R*-**18**
2*R**,3*R**-**13**	5	>200	200	36	2*S*,3*S*-**13**	2*R*,3*R*-**18**

The following lipases were used: Novozym 735 (Lipase A from *Candida antarctica*, CAL-A), Novozym 435 (Lipase B from *Candida antarctica*, CAL-B), Lipozyme RM IM (lipase from *Rhizomucor miehei*, RML) or Lipozyme TL IM (lipase from *Thermomyces lanuginosa*, TLIM).

Table 2
Transesterification reactions of alcohols **9–13**

Substrate	Lipase	Conv. (%)	Produced esters		Remaining diols	
			ee_P	$[\alpha]_D^{20}$	ee_S	$[\alpha]_D^{20}$
(2*R**,3*S**)-**9**	CAL-B	50	99.9	+22.3 (c 1.0, $CHCl_3$)	99.9	+1 (c 1.0, $CHCl_3$)
(2*R**,3*R**)-**9**	CAL-B	50	99.8	−21.5 (c 1.0, $CHCl_3$)	99.9	+12.3 (c 1.0, $CHCl_3$)
10	CAL-B	50.5	95.1	−6.7 (c 1.5, Et_2O)	97.1	+6.9 (c 1.5, Et_2O)
11	RML	47.2	79.8	−13.7 (c 0.6, $CHCl_3$)	71.3	−6 (c 0.8, $CHCl_3$)
(2*R**,3*S**)-**12**	RML	49.9	99.9	+13.6 (c 2.5, $CHCl_3$)	99.5	−14.0 (c 2.5, $CHCl_3$)
(2*R**,3*S**)-**13**	CAL-B	50.0	99.9	−18.4 (c 2.5, $CHCl_3$)	99.9	+9.2 (c 2.5, $CHCl_3$)
(2*R**,3*R**)-**13**	CAL-B	50.0	99.9	−16 (c 2.5, $CHCl_3$)	99.9	−8.2 (c 2.5, $CHCl_3$)

performed with CAL-A as catalyst, and unpublished X-ray structure. CAL-A did not show the same high selectivity when the small substituent at the secondary centre was a methyl group as in **9**, **10**, **11** and **13**. Carboxylic methyl or ethyl esters gave higher *E*-values, as shown for **2** and **12**. Recently it has been reported that CAL-A shows high selectivity when the substrates are more bulky [19,20]. The relative configuration was also observed to be important for the selectivity in the transesterification reaction of **2**. The reason for the low *E*-value of the 2*R**,3*S**-**2** pair was due to high rate of reaction for the slow reacting enantiomer as compared to 2*R**,3*R**-**2** [11]. The same effect was also observed when TL IM was used as catalyst, also in the resolution of (2*R**,3*S**)-**9** and (2*R**,3*R**)-**9**. RML showed the same tendency as CAL-B, except in the conversion of **2** and **12** where both rate of conversion and enantioselectivity were higher.

The optimized reactions conditions were used in scaled-up reactions in which the diols and butanoates were separated by chromatography. Enantiomeric excesses and optical rotations are given in Table 2.

3. Conclusions

Osmium catalyzed dihydroxylation of selected alkenes gave racemic dihydroxy compounds with one tertiary and one secondary stereocenter. An immobilized variant of the osmium catalyst was used since it could be easily separated from the reaction mixture and also be reused. Triosmium dodecacarbonyl, $Os_3(CO)_{12}$ was immobilized in mesoporous Al-MCM-41 material (Os-Al-MCM-41) by chemical vapor deposition. Addition of citric acid increased the reaction rate. However, use of enantiopure (−)-mandelic acid did not result in enantioselection. Subsequent transesterifications utilizing the secondary alcohol function, catalyzed by either Novozym 435 or 735, gave satisfactory *E*-values. Nine alkenes were converted into nine enantiopure vicinal diols and nine enantiopure hydroxy butanoates.

4. Experimental

4.1. General

Lipases, Novozym 735 (solution of Lipase A from *C. antarctica*, CAL-A), Novozym 435 (immobilized Lipase B from *C. antarctica*), Lipozyme RM IM (lipase from *Rhizomucor miehei*, RML) and Lipozyme TL IM (lipase from *Thermomyces lanuginosa*, TL IM) were from Novozymes. The transesterification reactions were performed at 30 °C in an Infors MINITRON Shaker Incubator. The produced esters and the unreacted substrate were separated by flash chromatography with Versaflash system from Supelco with versaPak silica cartridge 40 mm × 150 mm or 40 mm × 75 mm. Optical rotations were determined using a Perkin–Elmer 243B Polarimeter, concentrations are in g/100 mL.

4.2. Lipase immobilization

Novozym 735 was immobilized on magnetic particles (2.8 mm diameter, surface 5 m^2/g). The particles (500 mg) were mixed with 1,1-carbonyldiimidazole (405 mg, 2.5 mmol) in acetone (15 mL) for 4 h. After washing with acetone (3× 20 mL, 3× 1 h), phosphate buffer (15 mL, pH 7, 0.1 M) and Novozym 735 (4 mL) were added. The mixture was stirred for 20 h, solvent was decanted, and the particles were washed with buffer before drying.

4.3. Analyses

Chiral analyses of the transesterification reactions were performed on Varian 3400 gas chromatograph equipped with a chiral CP Chirasil Dex CB column (25 m, 0.25 mm i.d. and 0.32 μm film thickness), column pressure 8 psi, split flow 60 mL/min.

Temperature programs for analysis of the various racemates are given in Table 3.

Chiral analyses of (2*R**,3*R**-**2**) and (2*R**,3*S**-**2**) have been described [11].

NMR spectra were recorded in $CDCl_3$ solutions using Bruker DPX 300 and 400 instruments. Chemical shifts are in ppm relative to TMS and coupling constants in Hz. Enantiomeric ratios (*E*) were calculated using the computer program *E and K calculator version* 2.03 [21].

4.4. Dihydroxylations

4.4.1. Method 1

The alkene (0.5 g) and citric acid (0.75 mol equiv.) were dissolved in 10 mL of a 1:1 mixture of *tert*-butyl alcohol and water. The osmium containing material, Os-Al-MCM-41

Table 3
Temperature programs and retention times (t_R) for GLC-analyses of **9–18**

Temperature programs	Alcohols, t_R (min)	Butanoates, t_R (min)
95 °C (10 min), 95–115 °C (4 °C/min), 115–180 °C (10 °C/min)	7.8 (2*S*,3*S*)-**9**: 8.1 (2*R*,3*R*)-**9**	16.2 (2*S*,3*S*)-**14**: 16.5 (2*R*,3*R*)-**14**
90–115 °C (4 °C/min), 115–180 °C (10 °C/min)	6.0 (2*R*,3*S*)-**9**: 7.0 (2*S*,3*R*)-**9**	7.8 (2*R*,3*S*)-**14**: 8.1 (2*S*,3*R*)-**14**
85–89 °C (1 °C/min), 89 °C (2 min), 89–95 °C (1.5 °C/min)	4.5 (3*S*)-**10**: 4.9 (3*R*)-**10**	9.1 (3*S*)-**15**: 10.4 (3*R*)-**15**
90–115 °C (4 °C/min), 115–180 °C (10 °C/min)	5.8 (2*R*)-**11**: 6.2 (2*S*)-**11**	8.3 (2*R*)-**16**: 8.5 (2*S*)-**16**
145 °C (30 min)	13.1 (2*R*,3*S*)-**12**: 13.8 (2*S*,3*R*)-**12**	19.09 (2*R*,3*S*)-**17**: 19.32 (2*S*,3*R*)-**17**
80–130 °C (10 °C/min), 130–170 °C 1.5 °C/min (1 min)	22.1 (2*R*,3*S*)-**13**: 22.3 (2*S*,3*R*)-**13**	29.0 (2*R*,3*S*)-**18**: 29.2 (2*S*,3*R*)-**18**
80–130 °C (10 °C/min), 130–170 °C 1.5 °C/min (1 min)	18.1 (2*S*,3*S*)-**13**: 18.7 (2*R*,3*R*)-**13**	30.8 (2*S*,3*S*)-**18**: 31.2 (2*R*,3*R*)-**18**

(50 mg) was added followed by 4-methyl-morpholine *N*-oxide (1.1 mol equiv.). The reaction was stirred at room temperature for 15 h before the catalyst was filtered off. *tert*-Butyl alcohol was evaporated and the aqueous residue was extracted with Et_2O (4× 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give the diol.

4.4.2. Method 2

The alkene (0.5 g) and citric acid (0.75 mol equiv.) were dissolved in 10 mL of a 1:1 mixture of *tert*-butyl alcohol and water. Potassium osmate (5 mg, ca. 0.2 mol%) was added followed by 4-methyl-morpholine *N*-oxide (1.1 mol equiv.). The reaction was stirred at room temp for 15 h before Na_2SO_3 (0.3 g) was added. The reaction mixture was further stirred for 1 h. *tert*-Butyl alcohol was evaporated before the aqueous residue was extracted with Et_2O (4× 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give the diol.

4.5. Racemic dihydroxy compounds

4.5.1. (2R*,3R*)-Methyl-2,3-dihydroxy-2-methylbutanoate [(2R*,3R*)-9]

Methyl angelate [(*Z*)-**4**] gave (2*R**,3*R**)-**9** 0.6 g, 4.05 mmol, ^{1}H NMR: δ 3.81 (q, *J* 6.4 Hz, 1H), 3.81 (s, OCH_3), 3.49 (s, 1H, OH), 2.08 (s, 1H, OH), 1.45 (s, CH_3), 1.16 (d, *J* 6.4, CH_3), ^{13}C NMR: δ 175.9, 77.4, 72.3, 52.9, 22.3, 17.7.

4.5.2. (2R*,3S*)-Methyl-2,3-dihydroxy-2-methylbutanoate [(2R*,3S*)-9]

Methyl tiglate [(*E*)-**4**] gave (2*R**,3*S**)-**9** 0.61 g, 4.12 mmol, ^{1}H NMR: δ 3.95 (q, *J* 6.4 Hz, 1H), 3.82 (s, OCH_3), 3.41 (s, 1H, OH), 2.11 (s, 1H, OH), 1.33 (s, CH_3), 1.23 (d, *J* 6.4 Hz, CH_3), ^{13}C NMR: δ 177.2, 77.0, 72.0, 53.4, 22.1, 17.1.

4.5.3. 2-Methyl-2,3-butanediol (10)

2-Methyl-2-butene (**5**) gave **10** 0.64 g, 6.15 mmol, ^{1}H NMR: δ 3.62 (q, 1H), 2.1 (br s, 2H, OH), 1.21 (s, CH_3), 1.16 (s, CH_3), 1.15 (d, CH_3), ^{13}C NMR: δ 17.8, 23.0, 26.7, 73.3, 74.4.

4.5.4. Methyl 2,3-dihydroxy-3-methylbutanoate (11)

Methyl 3,3-dimethylacrylate (**6**) gave **11** 0.55 g, 3.72 mmol, ^{1}H NMR: δ 3.99 (s, 1H), 3.83 (s, OCH_3), 2.75 (br s, 2H, OH), 1.30 (s, CH_3), 1.22 (s, CH_3), ^{13}C NMR: δ 173.6, 76.6, 72.1, 52.4, 25.7, 25.0.

4.5.5. (2R*,3R*)-Ethyl 2,3-dihydroxy-3-phenylbutanoate [(2R*,3R*)-12]

Ethyl (*E*)-β-methylcinnamate [(*E*)-**7**] gave (2*R**,3*R**)-**12** 0.47 g, 2.1 mmol, ^{1}H NMR: δ 1.60 (s, CH_3), 3.33 (br s, OH), 3.44 (br s, OH), 4.34 (d, *J* 6.1 Hz, 1H), 7.23–7.29 (1H), 7.30–7.37 (2H), 7.44–7.48 (2H), 1.16 (t, *J* 7.1 Hz, CH_3), 4.15 (q, *J* 7.1 Hz, CH_2), ^{13}C NMR: δ 13.98, 25.75, 61.96, 75.72, 77.68, 125.26 (2C), 127.32, 128.09 (2C), 143.92, 172.64.

4.5.6. (2R*,3S*)-1-(Benzyloxy)-2-methylbutane-2,3-diol [(2R*,3S*)-13]

(*Z*)-1-Benzyloxy-2-methyl-2-butene [(*Z*)-**8**] gave (2*R**,3*S**)-**13** 0.52 g, 2.48 mmol, ^{1}H NMR: δ 1.15 (s, CH_3), 1.20 (d, *J* 6.6 Hz, CH_3), 2.75 (br s, OH), 3.2 (br s, OH), 3.4–3.7 (2H, CH_2), 3.71 (q, *J* 6.6 Hz, 1H), 4.57 (d, *J* 5.3 Hz, 2H), ^{13}C NMR: δ 17.54 (C5), 21.03 (C4), 73.54 (C3), 73.67 (C2), 73.85 (C1), 75.15 (CH_2), 127.76 (2C), 127.96 (1C), 128.54 (2C), 137.60 (1C).

4.5.7. (2R*,3R*)-1-(Benzyloxy)-2-methylbutane-2,3-diol [(2R*,3R*)-13]

(*E*)-1-Benzyloxy-2-methyl-2-butene [(*E*)-**8**] gave (2*R**,3*R**)-**13** 0.49 g, 2.33 mmol, ^{1}H NMR: δ 1.06 (s, CH_3), 1.10 (d, *J* 6.4 Hz, CH_3), 2.90 (br s, 2 OH), 3.37–3.48 (2H, CH_2), 3.83 (q, *J* 6.4 Hz, 1H), 4.53 (q, 2H), 7.23–7.39 (5H, Bn), ^{13}C NMR: δ 17.19 (C4), 19.66 (C5), 71.83 (C3), 74.12 (C1), 74.27 (C2), 77.28, 128.11, 128.32, 128.92, 138.02.

4.6. Small scale transesterifications

A typical small scale reaction contained 20 mg of the substrate in hexane or toluene (3 mL), immobilized lipase (20 mg) and vinyl butanoate (3 equiv.). The reactions were monitored by chiral GLC analyses.

4.7. Scaled-up transesterification reactions

4.7.1. Lipase catalyzed transesterification of (2R*,3S*)-9

Methyl (2*R**,3*S**)-2,3-dihydroxy-2-methylbutanoate [(2*R**,3*S**)-**9**] (0.51 g, 3.4 mmol) and vinyl butanoate (1.51 g, 13.8 mmol) were dissolved in toluene (25 mL). Novozym 435 (0.1 g) was added. The reaction was stopped at 50% conversion. The enzyme was filtered off and washed with Et_2O (10 mL) and the combined organic phases were concentrated under reduced pressure. Ester

and alcohol were separated by flash chromatography, eluent system: (EtOAc:hexane, 1:4), (2*R*,3*S*)-**9**, 94.0 mg, 0.634 mmol, 99.9% ee, ^{1}H NMR: δ 3.95 (q, *J* 6.4 Hz, 1H), 3.82 (s, 3H, –OCH_3), 3.41 (s, 1H, OH), 2.11 (s, 1H, OH), 1.33 (s, CH_3), 1.23 (d, *J* 6.4 Hz, CH_3); ^{13}C NMR: δ 177.2, 77.0, 72.0, 53.4, 22.1, 17.1. $[\alpha]_D^{20}$ + 1 (c 1, $CHCl_3$), (2*S*,3*R*)-**14**, 255 mg, 1.17 mmol, 99.9% ee, ^{1}H NMR: δ 5.09 (q, *J* 6.4 Hz, 1H), 3.72 (s, 3H, OCH_3), 1.33 (s, CH_3), 1.25 (d, *J* 6.4 Hz, CH_3), butanoyl-part: 0.90 (CH_3), 2.25 (CH_2), 1.60 (CH_2); ^{13}C NMR: δ 175.6, 172.5, 76.1, 73.9, 52.9, 36.2, 21.6, 18.3, 18.2, 13.5, $[\alpha]_D^{20}$ + 22.3 (c 1, $CHCl_3$).

4.7.2. Lipase catalyzed transesterification of (2R*, 3R*)-9

Methyl (2*R**,3*R**)-2,3-dihydroxy-2-methylbutanoate [(2*R**,3*R**)-**9**] (0.7 g, 4.72 mmol) and vinyl butanoate (1.62 g, 14.2 mmol) were dissolved in hexane (20 mL) and Novozym 435 (0.1 g) was added. The reaction was stopped at 50% conversion. The enzyme was filtered off and washed with Et_2O (10 mL) and the combined organic phases were concentrated under reduced pressure. Ester and alcohol were separated by flash chromatography. Eluent system: CH_2Cl_2:MeOH, 95:5, (2*S*,3*S*)-**9**, 0.285 g, 1.92 mmol, 99.9% ee, ^{1}H NMR: δ 3.81 (q, *J* 6.4 Hz, 1H), 3.81 (s, OCH_3), 3.49 (br s, 1H, OH), 2.08 (br s, 1H, OH), 1.45 (s, CH_3), 1.16 (d, *J* 6.4 Hz, CH_3), ^{13}C NMR: δ 175.9, 77.4, 72.3, 52.9, 17.7, $[\alpha]_D^{20}$ + 12.3 (c 1.0, $CHCl_3$). Lit. [22] +8.7 (c 0.6 $CDCl_3$), (2*R*,3*R*)-**14**, 0.350 g, 1.60 mmol, 99.8% ee, ^{1}H NMR: δ 5.12 (q, *J* 6.4 Hz, 1H), 3.81 (s, OCH_3), 3.34 (s, 1H), 1.40 (s, CH_3), 1.20 (d, *J* 6.4 Hz, CH_3), butanoyl-part: 0.95 (CH_3), 1.67 (CH_2), 2.32 (CH_2), ^{13}C NMR: δ 175.3, 173.0, 76.2, 73.4, 53.1, 36.3, 22.1, 18.5, 14.9, 13.6, $[\alpha]_D^{20}$ − 21.5 (c 1.0, $CHCl_3$).

4.7.3. Lipase catalyzed transesterification of 10

2-Methyl-2,3-butanediol (**10**) (0.45 g, 4.3 mmol) and vinyl butanoate (2.25 g, 19.7 mmol) were dissolved in toluene (20 mL) and Novozym 435 (100 mg) was added. The reaction was monitored on a chiral GLC-column and stopped at 50.5% conversion. The enzyme was filtered off and washed with Et_2O before the combined organic solvents were evaporated. Alcohol and butanoate were separated by flash chromatography, eluent system: (CH_2Cl_2:MeOH, 95:5), (3*S*)-**10**, 159 mg, 1.39 mmol, 97.1% ee, ^{1}H NMR: δ 3.62 (q, 1H), 2.1 (br s, 2H, OH), 1.21 (s, CH_3), 1.16 (s, CH_3), 1.15 (d, CH_3). ^{13}C NMR: δ 17.8, 23.0, 26.7, 73.3, 74.4. $[\alpha]_D^{20}$ + 6.9 (c 1.5, Et_2O), Lit. [23] +9.0 (c 1.5 Et_2O), (3*R*)-**15** 0.30 g, 1.72 mmol, 95.1% ee, ^{1}H NMR: δ 1.15–1.20, 4.79, butanoyl-part: 0.95 (CH_3), 1.61 CH_2), 2.30 (CH_2); ^{13}C NMR: δ 76.46, 72.12, 26.29, 24.71, 14.89, 173.30, 36.54, 18.56, 13.66. $[\alpha]_D^{20}$ − 6.7 (c 1.5, Et_2O).

4.7.4. Lipase catalyzed transesterification of 11

Methyl 2,3-dihydroxy-3-methylbutanoate (**11**) (0.15 g, 1.0 mmol) and vinyl butanoate (1.08 g, 9.46 mmol) were dissolved in hexane (15 mL) and Lipozyme RM IM (0.16 g) was added. The reaction was stopped at 50% conversion. The enzyme was filtered off and washed with Et_2O (10 mL) and the combined organic phases were concentrated under reduced pressure. Ester and alcohol were separated by flash chromatography, (2*R*)-**11**, 0.065 g, 0.44 mmol, 71.3% ee, ^{1}H NMR: δ 3.99 (s, 1H), 3.83 (s, OCH_3), 2.75 (br s, 2H, OH), 1.30 (s, CH_3), 1.22 (s, CH_3), ^{13}C NMR: δ 173.6, 76.6, 72.1, 52.4, 25.7, 25.0 $[\alpha]_D^{20}$ − 6.0 (c 0.8, $CHCl_3$). Lit. [24] +26 ($CHCl_3$) for (2*S*)-**11**, (2*S*)-**16**, 0.10 g, 0.46 mmol, 79.8% ee, ^{1}H NMR: δ 4.90 (s, 1H), 3.80 (s, OCH_3), 1.35 (s, CH_3), 1.22 (s, CH_3), butanoyl-part: 1.00 (CH_3), 2.40 (CH_2), 1.60 (CH_2). ^{13}C NMR: δ 173.0, 169.5, 78.3, 76.8, 52.6, 36.0, 32.1, 26.1, 18.6, 13.7, $[\alpha]_D^{20}$ − 13.7 (c 0.6, $CHCl_3$).

4.7.5. Lipase catalyzed transesterification of (2R*,3S*)-12

The ethyl ester (2*R**,3*S**)-**12** (0.5 g. 2.2 mmol) and vinyl butanoate (1.27 g, 11.1 mmol) were dissolved in hexane (25 mL) and immobilized Lipozyme RM IM (0.1 g) was added. The reaction was stopped at 49.9% conversion. The enzyme was filtered off and washed with Et_2O (10 mL) and the combined organic phases were concentrated under reduced pressure. Ester and alcohol were separated by flash chromatography. (2*R*,3*S*)-**12**, 0.2 g, 0.45 mmol, 99.9% ee, ^{1}H NMR: δ 1.60 (s, CH_3), 3.33 (br s, OH), 3.44 (br s, OH), 4.34 (d, *J* 6.1 Hz, 1H), 7.23–7.29 (1H), 7.30–7.37 (2H), 7.44–7.48 (2H), 1.16 (t, *J* 7.1 Hz, CH_3), 4.15 (q, *J* 7.1 Hz, CH_2), ^{13}C NMR: δ 13.98, 25.75, 61.96, 75.72, 77.68, 125.26 (2C), 127.32, 128.09 (2C), 143.92, 172.64. $[\alpha]_D^{20}$ − 14 (c 2.5, $CHCl_3$), (2*S*,3*R*)-**17**, 0.32 g, 1.09 mmol, 99.5% ee, ^{1}H NMR: δ 1.63 (s, CH_3), 3.30 (s, OH), 5.28 (s, 1H), 7.23–7.49 (5H, Bn), 1.12 (t, *J* 7.1 Hz, CH_3), 4.12 (q, *J* 7.1 Hz, 2H), butanoyl-part: 2.31 (CH_2), 1.58 (CH_2), 0.87 (CH_3). ^{13}C NMR: δ 13.43, 13.86, 18.23, 26.72, 35.78, 61.61, 75.02, 77.99, 124.97 (2C), 127.31, 128.11 (2C), 144.01, 168.56 (C=O), 172.46 (C=O). $[\alpha]_D^{20}$ + 13.6 (c 2.5, $CHCl_3$).

4.7.6. Lipase catalyzed transesterification of (2R*,3S*)-13

The diol (2*R**,3*S**)-**13** (0.3 g, 1.4 mmol) and vinyl butanoate (0.81 g, 7.14 mmol) were dissolved in hexane (15 mL) and Novozym 435 (0.1 g) was added. The reaction was stopped at 50% conversion. The enzyme was filtered off and washed with Et_2O (10 mL) and the combined organic phases were concentrated under reduced pressure. Ester and alcohol were separated by flash chromatography. (2*R*,3*S*)-**13**, 0.095 g, 0.45 mmol, 99.9% ee, ^{1}H NMR: δ 1.15 (s, CH_3), 1.20 (d, *J* 6.6 Hz, CH_3), 2.75 (br s, OH), 3.2 (br s, OH), 3.4–3.7 (2H, CH_2), 3.71 (q, *J* 6.6 Hz, 1H), 4.57 (d, *J* 5.3 Hz, 2H), ^{13}C NMR: δ 17.54 (C5), 21.03 (C4), 73.54 (C3), 73.67 (C2), 73.85 (C1), 75.15 (CH_2), 127.76 (2C), 127.96 (1C), 128.54 (2C), 137.60 (1C). $[\alpha]_D^{20}$ 9.2 (c 2.5, $CHCl_3$), (2*S*,3*R*)-**18**, 0.18 g, 0.64 mmol, 99.9% ee, ^{1}H NMR: δ 1.16 (s, 3H, CH_3), 1.23 (d, *J* 6.6 Hz, CH_3), 2.8 (br s, 1H, OH), 3.25–3.30, 3.40–3.43 (CH_2), 4.52 (q, *J* 12.1 Hz, 2H), 5.00 (q, *J* 6.6 Hz, 1H), 7.25–7.36 (5H, Ph), butanoyl-part: 0.92 (CH_3), 1.60 (CH_2), 2.21 (CH_2), ^{13}C NMR: δ 13.95 (C4), 19.36 (C5), 72.26 (C3), 72.28 (C2), 73.46 (C1), 74.27 (CH_2), 127.76 (2C), 127.77 (1C), 128.43 (2C), 137.77 (1C), 172.72 (C=O), 13.64, 18.47, 36.49, $[\alpha]_D^{20}$ − 18.4 (c 2.5, $CHCl_3$).

4.7.7. Lipase catalyzed transesterification of (2R*,3R*)-13

The diol (2*R**,3*R**)-**13** (0.3 g, 1.4 mmol) and vinyl butanoate (0.81 g, 7.14 mmol) were dissolved in hexane (15 mL) and

Novozym 435 (0.1 g) was added. The reaction was stopped at 50% conversion. The enzyme was filtered off and washed with Et_2O (10 mL) and the combined organic phases were concentrated under reduced pressure. Ester and alcohol were separated by flash chromatography, (2*S*,3*S*)-**13**, 0.104 g, 0.5 mmol, 99.9% ee, ^{1}H NMR: δ 1.06 (s, CH_3), 1.10 (d, *J* 6.4 Hz, CH_3), 2.90 (br s, 2 OH), 3.37–3.48 (2H, CH_2), 3.83 (q, *J* 6.4 Hz, 1H), 4.53 (d, 2H), 7.23–7.39 (5H, Ph), ^{13}C NMR: δ 17.19 (C4), 19.66 (C5), 71.83 (C3), 74.12 (C1), 74.27 (C2), 77.28, 128.11, 128.32, 128.92, 138.02. $[\alpha]_D^{20}$ − 8.2 (c 2.5, $CHCl_3$), (2*R*,3*R*)-**18**, 0.17 g, 0.61 mmol, 99.9% ee, ^{1}H NMR: δ 1.16 (s, CH_3), 1.18 (d, *J* 6.4 Hz, CH_3), 3.30–3.43 (2H, CH_2), 4.52 (d, *J* 4.0 Hz, 2H), 5.09 (q, *J* 6.4 Hz, 1H), 7.25–7.37 (5H, Ph), butanoyl-part: 2.25 (CH_2), 1.63 (CH_2), 0.93 (CH_3). ^{13}C NMR: δ 14.87 (C4), 20.01 (C5), 73.20 (C3), 73.55 (C1), 73.76 (C2), 74.97 (CH_2), 127.71 (2C), 127.76 (1C), 128.42 (2C), 137.83 (1C), 173.21 (C=O), 36.43, 18.49, 13.63. $[\alpha]_D^{20}$ − 16 (c 2.5, $CHCl_3$).

4.8. Synthesis of unsaturated alcohols

4.8.1. (Z)-1-Benzyloxy-2-methyl-2-butene [(Z)-8]

Methyl angelate [(*Z*)-**4**] (4.6 g, 40.4 mmol) was dissolved in dry Et_2O (20 mL), $LiAlH_4$ (1.6 g, 42.2 mmol) was added and the reaction was stirred for 4 h. Water (5 mL) was added under vigorous stirring. The organic and the water phases were separated. The water phase was extracted with Et_2O (3× 20 mL). The organic phases were combined, dried over $MgSO_4$ and evaporated to yield (*Z*)-2-methylbut-2-en-1-ol (3.38 g, 39.3 mmol) ^{1}H NMR: δ 1.63 (d, *J* 6.8 Hz, CH_3), 1.78 (CH_3), 2.7 (br s, OH), 4.12 (s, 2H, CH_2), 5.35 (q, *J* 6.8 Hz, 1H), ^{13}C NMR: δ 12.72 (C4), 21.04 (C5), 60.58 (C1), 121.94 (C3), 134.77 (C2).

(*Z*)-2-Methylbut-2-en-1-ol (1.0 g, 11.6 mmol) and benzyl chloride (1.5 g, 11.9 mmol) were stirred vigorously in NaOH:water (20 mL, 50% NaOH pellets (w/v)) and tetrabutylammonium hydrogensulphate (0.1 g, 0.29 mmol) for 6 h. The water phase was extracted with Et_2O (3× 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness, (*Z*)-**8**, 2.02 g 11.5 mmol, ^{1}H NMR: δ 1.60 (d, *J* 6.8 Hz, CH_3), 1.78 (m, CH_3), 4.02 (s, CH_2), 4.45 (s, OCH_2), 5.46 (q, *J* 6.8 Hz, 1H), 7.22–7.39 (5H, Ph), ^{13}C NMR: δ 13.12 (C4), 21.65 (C5), 67.89 (C1), 71.64 (CH_2), 123.70 (C3), 127.49 (1C), 127.72 (2C), 128.32 (2C), 132.63 (C2), 138.67 (1C).

4.8.2. (E)-1-Benzyloxy-2-methyl-2-butene, [(E)-8]

Methyl tiglate [(*E*)-**4**] (4.0 g, 35.1 mmol) was dissolved in dry Et_2O (20 mL), $LiAlH_4$ (1.4 g, 36.8 mmol) was added and the reaction was stirred for 4 h. Water (5 mL) was added under vigorous stirring. The organic and the water phases were separated. The water phase was extracted with Et_2O (3× 20 mL). The organic phases were combined, dried over $MgSO_4$ and evaporated to yield (*E*)-2-methylbut-2-en-1-ol, 2.92 g, 33.4 mmol, ^{1}H NMR: δ 1.61 (d, *J* 6.8 Hz, CH_3), 1.65 (s, CH_3), 3.96 (s, CH_2), 5.47 (q, *J* 6.8 Hz, 1H), ^{13}C NMR: 13.37, 13.61, 68.92, 120.63, 135.81.

(*E*)-2-Methylbut-2-en-1-ol (1.0 g, 11.6 mmol) and benzyl chloride (1.5 g, 11.9 mmol) were stirred vigorously in NaOH:water, (20 mL, 50% NaOH pellets (w/v)) and tetrabutylammonium hydrogensulphate (0.1 g, 0.29 mmol) for 6 h. The water phase was extracted with Et_2O (3× 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness, (*E*)-**8**, 2.0 g 11.4 mmol, ^{1}H NMR: δ 1.62 (d, *J* 6.8 Hz, CH_3), 1.67 (m, CH_3), 3.88 (br s, CH_2), 4.42 (s, CH_2), 5.50 (br q, *J* 6.8 Hz, 1H), 7.20–7.36 (5H, Ph), ^{13}C NMR: δ 13.64 (C4), 14.10 (C5), 71.93, 76.80, 123.11 (C3), 127.91, 128.17, 128.78, 133.38, 139.16.

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