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First stereoselective acylation of a primary diol possessing a prochiral quaternary center mediated by lipase TL from *Pseudomonas stutzeri*

A. Pizzilli [a,†], R. Zoppi [b,†], P. Hoyos [b], S. Gómez [b], F.G. Gatti [b], M.J. Hernáiz [b,*], A.R. Alcántara [b,*]

[a] *Giulio Natta Politecnico di Milano, Department of Chemistry, Materials & Chemical Engineering, Piazza Leonardo Da Vinci 32, I-20133, Milan, Italy*
[b] *Biotransformations Group, Department of Organic and Pharmaceutical Chemistry, Pharmacy Faculty, Complutense University of Madrid, Plaza Ramón y Cajal s/n, Madrid, E-28040, Spain*

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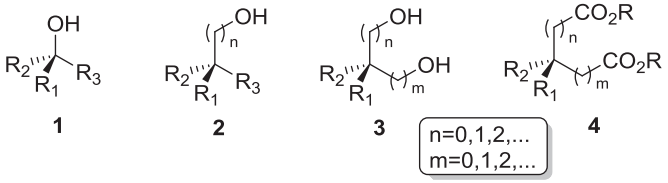
ABSTRACT

The first described acylation of a primary diol possessing a prochiral quaternary center catalyzed by lipase TL from *Pseudomonas stutzeri* is described. Optimized conditions were designed by testing different experimental conditions on model substrates (cyclopentylmethanol, cyclohexylmethanol, cyclopentane-1,1-diyldimethanol or cyclohexane-1,1-diyldimethanol) to find best organic solvent, optimal acyl donor and temperature, as well as the optimal substrates/enzyme ratio. Lipase TL resulted the best biocatalyst, while vinyl butyrate as acylating agent and a mixture of isooctane/THF 8/2, (v/v) resulted the best experimental conditions. Under these conditions, reaction were monitorized by chiral HPLC (diffraction index detector). The enantiomeric excess in the acylation of target substrate, (tetrahydro-2*H*-pyran-2,2-diyl)dimethanol, was measured by derivatization of monoesters with Mosher's *R*-MTPA-Cl, which also was useful to determine the *S* absolute configuration of the major reaction product of the lipase-catalyzed monoacylation.

1. Introduction

The stereoselective synthesis of molecules bearing a quaternary stereocenter is one of the most challenging tasks[1–6] of organic chemistry, being this situation particularly problematic for acyclic compounds, because of the high number of degrees of freedom associated to these structures;[4] thus, the enantioselective desymmetrization of either prochiral precursors or *meso* compounds is generally the most effective methodology.

Although the exquisite stereodiscrimination ability of enzymes is well known[7–11] and it has been recurrently reported,[12,13] especially in desymmetrization processes involving either *meso* or prochiral structures,[14,15] in most cases it has been applied to compounds possessing tertiary carbon chiral or prochiral centers, because most of the typical hydrolytic enzymes are unable to accept sterically hindered substrates bearing quaternary carbon atoms.[16] However, since the kinetic resolution of tertiary alcohols (Scheme 1, **1**) is becoming a fashionable trend in biocatalysis,[17–20] using mainly hydrolases or lyases, the most common strategy consists in using a spacer moiety for separating the bulky quaternary stereocenter from the point in which the enzyme is acting.



Scheme 1. Different compounds possessing quaternary centers recognized by enzymes.

Accordingly, some biocatalyzed resolutions of primary alcohols (Scheme 1, **2**) with remote quaternary stereocenters, either through enzyme-catalyzed acylation or hydrolysis, have been described.[21–33] In the same way, sterically crowded diesters (Scheme 1, **4**) have been enzymatically resolved as well.[34–37]

Perhaps one of the most attractive research area is the resolution of diols possessing quaternary carbon atoms (Scheme 1, **3**). For this type of compounds, two different cases must be considered,

* Corresponding authors. Tel.: +34 91 394 1820 (A.R.A.), +34 91 394 1821 (M.J.H.); fax: +34 91 394 1822; e-mail addresses: mjhernai@ucm.es (M.J. Hernáiz), andalcan@ucm.es (A.R. Alcántara).
† Both authors contributed equally to this work.

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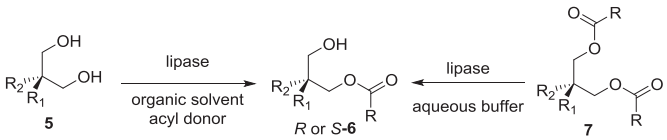
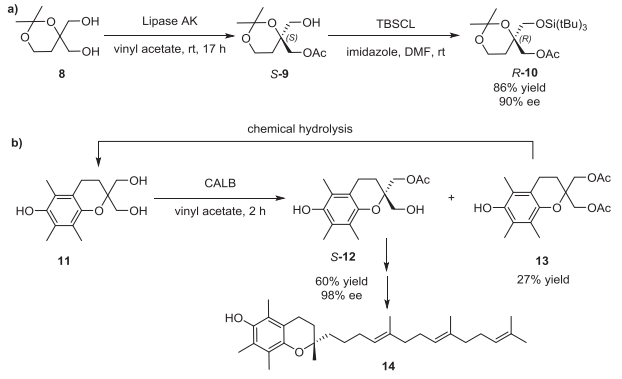
depending on the symmetry: *i*) 1,1-disubstituted 1,2-diols, molecules possessing a primary and a secondary hydroxyl group (n=0, m≠0) and *ii*) molecules having two primary hydroxyl groups (n≠0, m≠0).

However, for the second ones (Scheme 2, **5**), due to the fact that they do not possess any stereogenic center, conversion is not limited up to theoretical 50%, so that the enantiomeric composition of the product (*R* or *S*-**6**) is independent on the conversion, and thus the reaction may be run to completion. In that sense, different examples can be found in literature of desymmetrization of prochiral 2,2-disubstitued-1,3-diols generally through stereoselective mono-acylation of **5**[35,38–44] or less frequently by mono-hydrolysis of diesters **7**.[45,46] In all cases, conversion and enantiomeric excess values reported varied noticeably, as well as the absolute configuration of the monoester **6**.



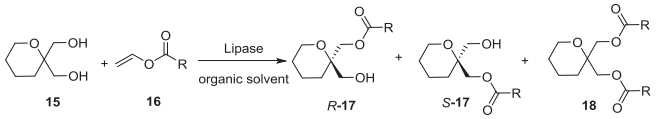
Scheme 2. Desymmetrization of prochiral 2,2-disubstitued 1,3-diols.

In this sense, Fukuyama and co-workers[41] reported the total synthesis of Leustroducsin, a colony stimulating factor inducer isolated from of *Streptomyces platensis* SANK 60191. In their strategy, the desymmetrization of the glycerol derivative **8** (Scheme 3, *a*) was catalyzed by lipase AK-mediated acylation. An ulterior protection of the monoacetate **9** with *tert*-butylchlorodimethylsilane yielded the *O*-protected monoalcohol *R*-**10** in good *ee* and high yield. Similarly, *S*-α-tocotrienol **14**, a very interesting molecule with many therapeutical effects,[47] has been prepared in 19% overall yield through a multistep synthesis[44,48] that involves the CALB-catalyzed acetylation of the bicyclic triol **11** (Scheme 3, *b*). The monoester *S*-**12** was obtained in 98% *ee* and 60% yield, which in principle could be increased, since the diester **13** (27%) can be easily recycled by a simple chemical hydrolysis. The assignation of the absolute configuration of *S*-**12** was also done through derivatization with Mosher's esters.[48]



Scheme 3. Some acylation of prochiral quaternary diols described in literature.

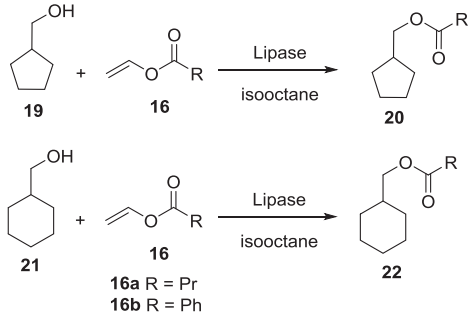
In this paper we report the first results obtained in the desymmetrization of a very simple prochiral 2,2-disubstitued 1,3-diol such as (tetrahydro-2*H*-pyran-2,2-diyl)dimethanol **15** (Scheme 4) through lipase-catalyzed acylation. This diol has been used as starting material in the preparation of different compounds for treating hair loss from the human scalp,[49] as well as for the synthesis of compounds useful as TNF-alpha inhibitors.[50] Thus, different parameters were studied in order to optimize the reaction, such as lipase nature, type of organic solvent, type of acyl donor, etc.



Scheme 4. Desymmetrization of (tetrahydro-2*H*-pyran-2,2-diyl)dimethanol **15**.

2. Results and discussion

Thus, as the first step in order to select the best conditions, the acylation of primary cycloalkyl methanols **19** and **20** with different vinyl esters **16** (Scheme 5) was carried out as a qualitative test to establish the best lipase (See Supplementary data).

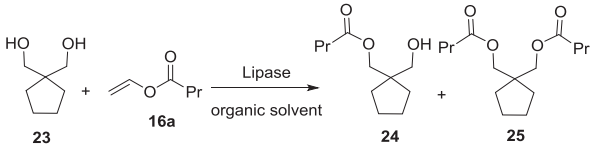


Scheme 5. Transesterification of primary alcohols **19** and **21**.

Biocatalysts tested in this test reactions were lipases from *Pseudomonas stutzeri* (lipase TL) *Alcaligenes* sp. (lipase QLC), *Candida rugosa*, Pig Pancreatic lipase and Amano lipase PS (see Supplementary data). Lipase TL and lipase QLC were apparently the best catalysts, while vinyl butyrate **16a** seemed to lead to better overall conversion after 24 h. These qualitative results were confirmed once the reaction was repeated after a shorter reaction time (200 min) for lipase TL, lipase QLC and *C. rugosa* lipase, also confirming the best performance of **16a** as acyl donor. Solvent tested were isooctane, THF and 2-MeTHF, being the first one the best.

In order to quantify the activity of lipases, acylation of cyclopentylmethanol **19** was used as test for determining the acyltransfer activity of Lipase TL, using isooctane as solvent. As a result of calculation, activity resulted in a value of 8.15×10^{-4} units mg^{-1}, defining one unit as the amount of enzyme necessary to synthesize 1 μmol of **20b** per minute under the described reaction conditions (see Supplementary data). This enzyme has been frequently used in our group, showing excellent results in many biotransformations.[51,52]

In a second step, all the information gathered up to this point about the catalytic performance of Lipase TL was applied to the acylation of a primary symmetrical diol such as the cyclopentane-1,1-diyldimethanol **23** (Scheme 6), for order to determining the best conditions for attempting the stereoselective monoacylation of our target molecule **15**. Nevertheless, a previous solubility problem had to be taken into account provided that **23** turned out to be



Scheme 6. Acylation of cyclopentane-1,1-diyldimethanol **23**.

insoluble in isooctane, the best organic solvent thus far, while THF proved to be the best option to solubilize **23**.

First reactions were then carried out using a low concentration of acyl donor in order to limit monoacylation of **23** (0.5/1, M/M) in different reaction media, ranging from 100% THF up to a binary mixture 80/20 isooctane/THF (v/v), the higher possible percentage of isooctane to ensure solubility of **23**. Nevertheless, very low conversions were obtained (not higher than 10% in the best case) as well as very low reaction rates, when using standard amount of lipase TL (10 mg). Thus, acyl donor ratio was increased from 0.5/1 up to 1.5/1, showing a clear improvement of reaction rate and conversion by increasing the amount of acyl donor. Finally, we doubled up the amount of lipase for accelerating reaction rate, and monitored the reaction upon a longer time (24 h) to control the relative amount of diacylation. As it can be seen in Fig. 1, the reaction rate is increased, although diacylated compound **25** becomes considerably noticeable at relatively short reaction times, avoiding the accumulation of **24** by a second entry of **24** at the lipase active site leading to diacylation, as described in our group in the acylation of prochiral 2-phenyl-1,3-propanediol.[53,54]

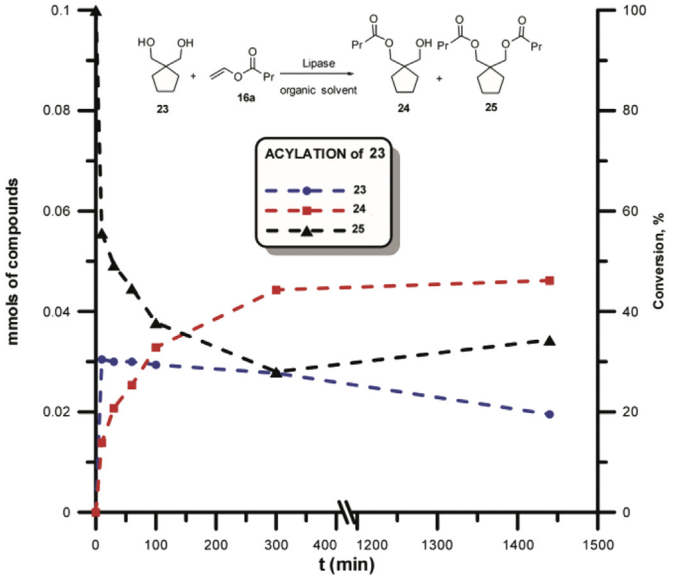
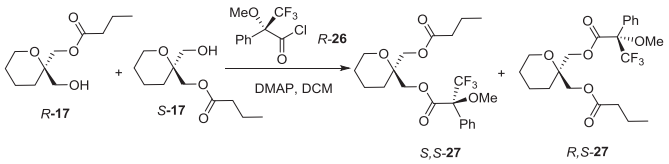


Fig. 1. Acylation of **23**. Experimental conditions as described in Experimental Section.

Finally, the acylation of the target prochiral substrate (tetrahydro-2*H*-pyran-2,2-diyl)dimethanol **15** was undertaken, as depicted in Scheme 4, considering all the previous results. Nevertheless, the chiral column used so far (Chiralcel OD-RH) could not properly separate *R*-**17** and *S*-**17**, so that HPLC analysis were only useful for determining overall conversion. Following the results obtained in the acylation of model substrate **23**, solvent used was a mixture of isooctane and THF (80/20 v/v), **16a** was added in a 1.5 M excess, and 20 mgs of lipase was used. Under these conditions, after 180 min no traces of **15** were detected, and 54% of conversion of monoester **17** and 46% of diester **18** were present at that mentioned reaction time at room temperature.

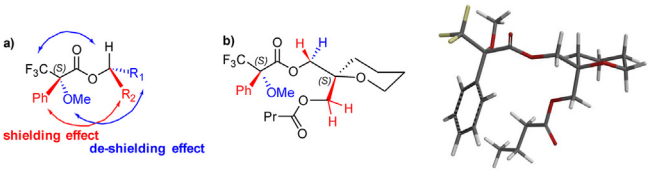
Raising up temperature to 37 °C (optimal for acylation of **18**) resulted in a decrease in the formation of monoester **17** (37%) and a concomitant increase in diester production (63%).

In order to determine the enantiopurity of monoester **17**, the same reactions carried out for analytical purposes were scaled-up five times and *R*-**17** and *S*-**17** were converted to the corresponding Mosher's esters *S*,*S*-**27** and *R*,*S*-**27**, as shown in Scheme 7.



Scheme 7. Derivatization of monester **17** by reaction with *R*-MTPA-Cl *R*-**26**.

Reaction yields were very similar (54% yield of **17**, at room temperature, and 42% yield at 37 °C), and the derivatization was done as described in Experimental Section. To measure the enantiomeric excess, the relative proportion of the signals between 4.3 and 4.0 ppm, corresponding to the methylene groups near the oxygen atom of the esters was analyzed. According to literature,[55] the preferred conformation of a *S*-Mosher's ester for secondary alcohols, keeping H, carbonyl and CF_3 group in a coplanar arrangement, is the one shown in Scheme 8, a).



Scheme 8. a) Preferred conformation for the *S*-Mosher's ester. b) Assumed minimum energy conformation of *S*,*S*-**27**.

In fact, if we extrapolate that model to *S*,*S*-diastereomer, (Scheme 8, b), the shielding effect of Ph group would affect more specifically those diasterotopic methylene hydrogens in red. In Fig. 2 we show an ampliation of the NMR spectra of Mosher's esters *S*,*S*-**27** and *S*,*R*-**27** obtained in the scaled reaction, as well as the chromatograms obtained in each case.

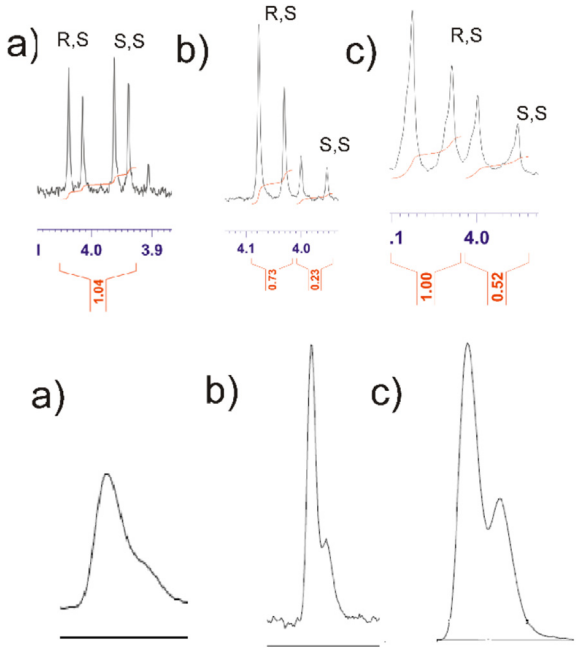
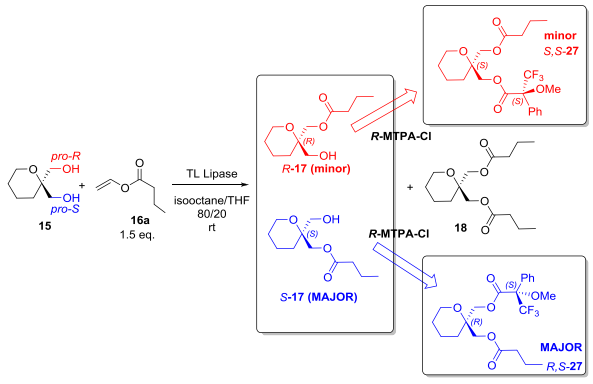


Fig. 2. NMR spectra of reaction obtained after derivatization and HPLC peak corresponding to reactions with chemically synthesized *rac*-**17** (a) and enzymatic reactions at room temperature (b) and 37 °C (c).

Considering integration for determining enantiomeric excess values, based on the signals at δ=4.01–4.04 and δ=3.96–3.94 (assigned to diastereotopic hydrogens at methylene closer to the *O*-MTPA moiety), it can be deduced that for acylation of **15** at room

temperature (Fig. 2, a), the *ee* value of monoester **17** is 53%, while increasing reaction temperature up to 37 °C (Fig. 2, b) not only has a deleterious effect on the yield, as commented previously, but also on the *ee* value, which is reduced to 44%.

On the other hand, for assigning the absolute configuration of the products, the higher intensity of signals at δ=3.96–3.94 and 4.30–4.28 (diasteromer *R,S*-**27**) compared to those other ones at δ=4.01–4.04 and 4.22–4.20 (*S,S*-**27**) indicates that *R,S*-**27** is the major component, so that the enzyme is primarily generating *S*-**17** with moderate ee, as schematized in Scheme 9.



Scheme 9. Stereochemical course of acylation of **15**.

This slightly higher acylation in the *pro-S* hydroxymethyl group of **15** is consistent with the reported *pro-S* preference of other lipases, as shown in Scheme 3. The higher enantiomeric excess described for those reported cases should be attributed to the higher rigidity of **8** and **11** compared to **15**, so different experiments are being conducted to prove the efficiency of lipase TL upon less flexible substrates.

To conclude, this is the first reported example of the use of lipase TL from *P. stutzeri* in the stereoselective acylation of prochiral primary diol possessing a quaternary stereo center. The results shown are opening the door for further application of this very interesting catalyst in the preparation of optically enriched building blocks.

3. Experimental section

3.1. General

Lipases from *P. stutzeri* (Lipase TL®) and immobilized lipase from *Alcaligenes* sp (Lipase QLC) were kindly donated by Meito & Sangyo Ltd, Japan. Lipases from *C. rugosa*, Amano Lipase PS and porcine pancreas were purchased from Sigma–Aldrich. All other reagents and solvents were obtained from Sigma–Aldrich and used as received.

NMR spectra were recorded on a Bruker AC-250 or Bruker AV 500 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to $CHCl_3$ (^{1}H: δ 7.27 ppm) and $CDCl_3$ (^{13}C: δ 77.0 ppm).

TLC was carried out on aluminium sheets precoated with silica gel; the spots were visualized under UV light (λ=254 nm). Column chromatography purifications were conducted on silica gel 60 (40–63 μm). All enzymatic reactions were monitored by HPLC. For reagents containing chromophoric groups, chiral HPLC analysis were performed on a chromatograph equipped with a Chiralcel-OD column and Diode Array detector; mobile phase: *n*-hexane/i-PrOH (98/2, v/v); flow rate: 0.6 mL/min. For the rest of compounds, HPLC analysis were performed on a chromatograph equipped with a Chiralcel-OD-RH column and a Refractive Index (RI) detector; mobile phase: H_2O/CH_3CN (60/40, v/v); flow rate: 0.6 mL/min.

3.2. Acylation procedures for diols

3.2.1. Chemical acylation of cyclopentane-1,1-diyldimethanol ***23***. To a stirred solution of triethylamine (1.5 mmol, 156 μL, *d*=0.727 g/mL) in dichloromethane (15 mL) at −78 °C, cyclopentane-1,1-diyldimethanol **23** (200 mg, 1.5 mmol) and butyryl chloride (2.25 mmol, 233.6 μL, *d*=1.026 g/mL) were added. The reaction was quenched after 3 h by addition of a phosphate buffer (pH 7.0). The organic materials were extracted with ether and combined extracts were dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1/6, v/v) to yield 159 mg of (1-(hydroxymethyl) cyclopentyl)methyl butyrate **24** (49.0%) and 19.5 mg of cyclopentane-1,1-diylbis(methylene) dibutyrate **25** (4.8%).

3.2.1.1. (1-(hydroxymethyl)cyclopentyl)methyl butyrate ***24***. ^{1}H NMR (250 MHz, $CDCl_3$): 4.05 (s, 2H), 3.35 (s, 2H), 2.85 (s, 1H), 2.36 (t, *J*=7.3 Hz, 2H), 1.75–1.58 (m, 6H), 1.49–1.37 (m, 4H), 0.90 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): 175.0, 68.2, 66.8, 48.3, 36.6, 32.3, 25.6, 18.9, 14.0. Anal. Calcd for $C_{11}H_{20}O_3$: C, 66.13%; H, 10.07%; found: C, 66.25%; H, 10.05%.

3.2.1.2. Cyclopentane-1,1-diylbis(methylene) dibutyrate ***25***. ^{1}H NMR (250 MHz, $CDCl_3$): 4.0 (s, 4H), 2.4 (t, *J*=7.4 Hz, 4H), 1.82–1.63 (m, 8H), 1.61–1.48 (m, 4H), 1.02 (t, *J*=7.4 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): 174.2, 67.7, 46.0, 36.6, 32.8, 25.6, 18.9, 14.1. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64%; H, 9.69%; found: C, 66.83%; H, 9.66%.

3.2.2. Enzymatic acylation of cyclopentane-1,1-diyldimethanol ***23***. Different amounts of vinyl butyrate **16a** and 0.1 mmol of cyclopentane-1,1-diyldimethanol **23** were dissolved in 1 mL of several organic solvents, and reactions were started at 37 °C by adding a fixed amount of lipase. The reactions were qualitatively followed by TLC (mobile phase *n*-hexane/ethyl acetate, 5/1, v/v). To quantify reaction conversion, aliquots of 20 μL were taken at different reaction times, microfiltered (0.2 nm), *re*-dissolved in 1 mL *n*-hexane, evaporated by speed-back and then dissolved again in a 500 μL mixture CH_3OH/CH_3CN (50/50, v/v), to be analyzed by HPLC (Chiralcel-OD-RH column, RI detector), using a mobile phase H_2O/CH_3CN (60/40, v/v) and toluene as internal standard (calibration curves for qualitative determination of **24** and **25** in Supplementary data); flow rate: 0.6 mL/min (tr: 6.7 min).

3.3. Chemical synthesis of (2-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)methyl butyrate 17 and (tetrahydro-2*H*-pyran-2,2-diyl)bis(methylene) dibutyrate 18

110 mg (0.75 mmol) of (tetrahydro-2*H*-pyran-2,2-diyl)dimethanol **15** and butyryl chloride (117 μL, 13 mmol, *d*=1.026 g/mL) were added to a stirred solution of triethylamine (0.75 mmol, 104 μL, *d*=0.727 g/mL) in dichloromethane (10 mL) at −78 °C. The reaction was quenched after 3 h at −78 °C by addition of a phosphate buffer (pH 7). The organic materials were extracted with ether and combined extracts were dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1/6, v/v) to yield 71.6 mg of (tetrahydro-2*H*-pyran-2,2-diyl)bis(methylene) dibutyrate **18** (33.4% yield).

Same reaction was carried out at 1 h with a 1/1 M ratio of butyril chloride and **15** to isolate racemic monoester **17** (46 mg, 48.1%).

3.3.1. (2-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)methyl butyrate ***17***. ^{1}H NMR (250 MHz, $CDCl_3$): 4.19 (s, 2H), 3.65 (t, *J*=5.3 Hz, 2H), 3.53 (s, 2H), 2.28 (t, *J*=7.5 Hz, 2H), 1.67–1.38 (m, 8H), 0.90 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): 174.3, 74.3, 64.6, 63.6, 62.7,

36.5, 27.3, 25.7, 19.0, 18.9, 14.0. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09%; H, 9.32%; found: C, 61.19%; H, 9.35%.

3.3.2. (Tetrahydro-2H-pyran-2,2-diyl)bis(methylene) dibutyrate ***18***. ^{1}H NMR (250 MHz, $CDCl_3$): 4.10 (dd, *J*=10.1 Hz, *J*=31.5 Hz, 4H), 3.65 (t, *J*=5.8 Hz, 2H), 2.25 (q, *J*=7.3 Hz, 4H), 1.68–1.41 (m, 10H), 0.87 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$): 173.8, 73.2, 64.2, 62.7, 36.5, 32.8, 28.0, 25.6, 18.8, 14.0. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91%; H, 9.15%; found: C, 63.05%; H, 9.13%.

3.4. Enzymatic acylation of (tetrahydro-2*H*-pyran-2,2-diyl) dimethanol 15

Different amounts of vinyl butyrate **16a** and 0.1 mmol of (tetrahydro-2*H*-pyran-2,2-diyl)dimethanol **15** were dissolved in 1 mL of several organic solvents, and reactions were started at room temperature by adding a fixed amount of lipase. The reactions were qualitatively followed by TLC (mobile phase *n*-hexane/ethyl acetate, 5/1, v/v). To quantify reaction conversion, aliquots of 20 μL were taken at different reaction times, microfiltered (0.2 nm), *re*-dissolved in 1 mL *n*-hexane, evaporated by speed-back and then dissolved again in a 500 μL mixture CH_3OH/CH_3CN (50/50), to be analyzed by HPLC (Chiralcel-OD-RH column, RI detector), using a mobile phase H_2O/CH_3CN (60/40, v/v) (calibration curves for qualitative determination of **17** and **18** in Supplementary data); flow rate: 0.6 mL/min (tr: 22.9 min).

Same reaction was carried out at five-fold scale to separate and analyse compounds *R*- and *S*-**17**.

3.5. Synthesis of Mosher's esters (*S,S*)-27 and (*R,S*)-27

18.9 mg (0.075 mmol) of *R*-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride (***R***)-**26** and 81.0 mg (0.05 mmol) of chemically synthesized ***rac*-17** were added to a stirred solution of DMAP (0.05 mmol, 6.12 mg) in dichloromethane (2.5 mL). The reaction was stopped and filtered after 5 h and concentrated under vacuum after TLC analysis showed the disappearance of the starting materials. The residue was purified by a Pasteur's pipette chromatography column on silica gel using dichloromethane as mobile phase, and then concentrated in vacuum, and NMR analysis were carried out. Similar protocol was carried out for derivatizing mixtures of *R*- and *S*-**17** obtained from enzymatic acylation.

*3.5.1. ((R,S)-and (S,S)-2-(((-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)methyl butyrate (R,S) and (S,S)-****27***. ^{1}H NMR (500 MHz, $CDCl_3$): 7.52 (d, *J*=5.0 Hz, 4H), 7.40 (m, 6H), 4.48 (t, *J*=11.4, 1H), 4.29 (d, *J*=11.4 Hz, 1H), 4.27 (t, *J*=11.4 Hz, 1H), 4.21 (d, *J*=11.4 Hz, 1H), 4.02 (d, *J*=11.4 Hz, 1H), 3.95 (d, *J*=11.4 Hz, 1H), 3.70 (t, *J*=5.4 Hz, 4H), 3.55–3.53 (2 x s, 6H), 2.29 (2 x t, *J*=7.4 Hz, 4H), 1.68–1.59 (m, 8H), 1.53–1.47 (m, 8H), 0.92 (2 x t, *J*=7.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): 173.4, 130.1, 128.8, 127.9, 127.8, 73.1 (*J*=27.9 Hz), 66.6, 63.8, 62.7, 55.8, 36.4, 28.0, 25.5, 19.0, 18.8, 18.8, 14.0.

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Supplementary data

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