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Chemoenzymatic enantioselective synthesis of 2-substituted glycerol derivatives

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ABSTRACT

2-Substituted glycerol derivatives **4a–g** were resolved by acylation with vinyl butyrate in the presence of lipases in organic media. The reverse reaction, the enzymatic hydrolysis of the corresponding butyrates **5a–g**, was also highly stereoselective and provided the opposite enantiomers. High enantioselectivities (ee >90%) and good isolated yields were obtained for all substrates using the appropriate lipase. *Pseudomonas cepacia* lipase or the closely related *Pseudomonas* sp. lipase were the most efficient enzymes for the resolution of substrates bearing smaller aliphatic groups. *Candida antarctica* lipase B was more suitable as the biocatalyst in the resolution of more sterically demanding aromatic substrates. 2-Benzylglycerol derivatives were resolved in the presence of *Rhizopus* sp. lipase.

1. Introduction

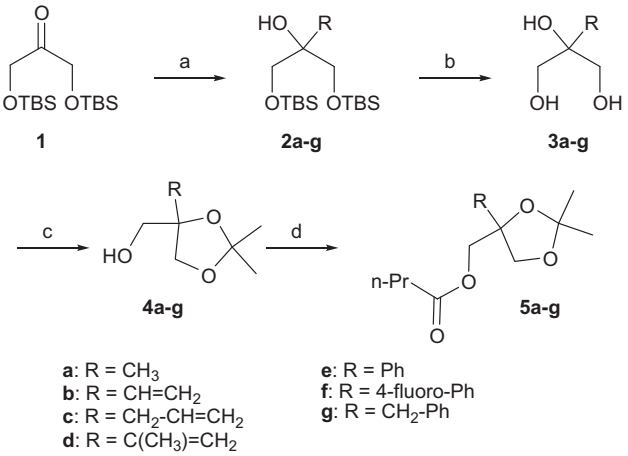
Glycerol (1,2,3-propanetriol) occurs naturally in many lipids in the form of phosphoric or fatty acid esters (glycerides). Traditionally, glycerol is commercially produced by several processes: soap manufacture, fatty acid or esters production, microbial fermentation, and chemical synthesis from propylene. Glycerol is utilized in many commercial products or can be converted into a variety of valuable chemicals or intermediates (dihydroxyacetone, epichlorohydrin, acrylic acid, etc). Glycerol is currently available in large surplus as a by-product in biodiesel production by the transesterification of vegetal oils with simple alcohols, such as methanol. Conversion of this abundant renewable resource into higher value-added chemicals has recently attracted much interest.[1–6]

Chiral tertiary alcohols are important frameworks frequently found in natural products and pharmaceuticals; however their enantioselective synthesis remains a significant challenge.[7–13] Desymmetrization of *meso* or resolution of chiral 2-substituted glycerol derivatives by chemical[14–17] or enzymatic[18–25] methods are valuable approaches to obtain optically active tertiary alcohols. Of particular interest is the chemoenzymatic preparation of enantiopure 2-methylglycerol derivatives reported by Wirz et al.[24] Herein we report the synthesis of both enantiomers of a series of 2-substitued-1,2-isopropylidene glycerols via enzymatic transesterification or hydrolysis.

2. Results and discussion

2.1. Substrates preparation

Substrates **4a–g** and **5a–g** were synthesized as outlined in Scheme 1. 1,3-Dihydroxyacetone bis-silyl ether **1** was prepared as described in the literature.[26] Grignard reactions with dihydroxyacetone derivative **1** in THF provided tertiary alcohols **2a–g** in high



Scheme 1. Reagents and conditions: (a) RMgX, THF; (b) *t*-Bu4NF, THF; (c) acetone, TsOH; (d) butyryl chloride, Et_3N, CH_2Cl_2.

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yields. Desilylation of **2a–g** with tetrabutylammonium fluoride (TBAF) afforded triols **3a–g**. 2-Methylglycerol **3a** was also prepared in one step by dihydroxylation of β-methallylic alcohol following a known procedure.[27] The diol functionality of **3a–g** was protected using acetone and *p*-toluenesulfonic acid (TsOH) to give acetals **4a–g**. Esters **5a–g** were obtained by acylation of **4a–g** with butyryl chloride in the presence of triethylamine.

2.2. Enzymatic kinetic resolutions

We examined both the acylation (transesterification) of alcohols **4a–g** and the hydrolysis of esters **5a–g** in the presence of commercially available lipases. The best reaction conditions reported for the resolution of **4a** were applied to the series of substrates.[24] The reactions were monitored by GC or HPLC on a chiral phase column allowing the simultaneous determination of conversion (*c*) and enantiomeric excesses (ee) of both product and remaining substrate. The reactions were stopped at conversion close to 50% and the *E* values were determined using Sih's method.[28]

The best results of the enzymatic hydrolysis of esters **5a–g** in a phosphate buffer (pH 7.5) are shown in Table 1. Excellent enantioselectivities (*E* >100) and good isolated yields were obtained for all substrates using the appropriate lipase. *Pseudomonas cepacia* lipase (PCL) or the closely related *Pseudomonas* sp. lipase (PSL) were the most efficient enzymes for the resolution of ester **5a–d** bearing smaller R groups (entries 1–4). *Candida antarctica* lipase B (CAL-B) was more suitable as the biocatalyst in the resolution of more sterically demanding substrates such as **4e**,**f** (entries 5 and 6). In the case of ester **5g**, *Rhizopus* sp. lipase (RSL) gave the best results. The absolute configurations of **4a–g** were determined by comparison or chemical correlation with compounds of known absolute configurations. In most cases, the (*R*)-ester was the faster-reacting enantiomer, yielding the (*S*)-alcohol in high ee and leaving the (*S*)-ester as an enantiomerically pure unreacted enantiomer (entries 1–4, 7). In contrast, CAL-B catalyzed the hydrolysis of the aromatic (*S*)-esters **5e**,**f** selectively.

The results of the lipase-catalyzed acylation of substrates **4a–g** using vinyl butyrate as the acyl donor in hexane are summarized in Table 2. The esterification of **4a–g** follows the same pattern as the hydrolysis of **5a–g** but the enantioselectivity ($46 < E < 126$) is lower (entries 1–7). The least satisfying result was obtained with alcohol **4g**; RSL showed good enantioselectivity but very low activity (entry 7). As expected, the transesterification of racemic alcohols **4a–g** and the hydrolysis of the corresponding racemic esters **5a–g** are complementary and lead to opposite enantiomers of both alcohol and ester. When both the alcohol and the corresponding ester are substrates for a hydrolase, acylation and hydrolysis are usually complementary and give the opposite enantiomers. Although acylation and hydrolysis represent reactions in opposite directions, the hydrolase favors the same enantiomer or the same prochiral group in both cases. While this empirical rule applies to kinetic resolutions and desymmetrizations, exceptions have been reported.[29]

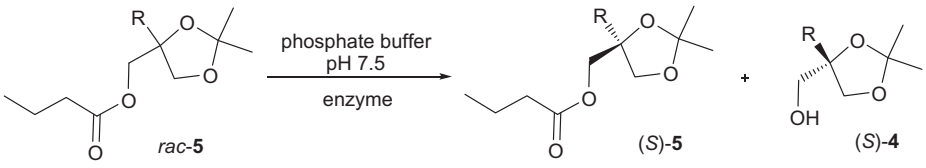
The title compounds are valuable synthons in asymmetric synthesis. For instance, compound **4c** has been used as a chiral building block for the synthesis of a number of natural products or biologically active compounds (Fig. 1) such as frontalin (insect pheromone), malyngolide (antibiotic), daunomycinone, and rhodomycinone derivatives (anthracyclinones, antitumor agents).[30] Ahn et al.[31] reported the stereoselective transformation of (*R*)-**4c** into 2-fluoroglycerol derivatives, en route to fluorinated nucleosides. Compound (*R*)-**4c** is usually prepared in low yields from D-lactose.[30] The present procedure provides both enantiomers of alcohols **4a–g** and esters **5a–g** in good yields with high enantiomeric excesses. Tertiary alcohols and their esters are poor substrates for most of the commercially available hydrolases presumably due to steric hindrance. Enzymes bearing the motif GGG(A)X (G = glycine, A = alanine, X = any amino acid) in the oxyanion binding pocket of their active site are active toward acetates of some tertiary alcohols.[7] In primary alcohols and their esters with an adjacent quaternary stereocenter bearing a protected alcohol, such as **4a–g** and **5a–g**, the hindered stereocenter lies further from the reactive group, and so lipase-catalyzed reactions are facilitated considerably and more general.[32]

3. Experimental

3.1. General

NMR spectra were recorded on a Varian Inova AS400 spectrometer (400 MHz). Infrared spectra were recorded on a Bomem MB-100 spectrometer. Optical rotations were measured using a JASCO DIP-360 digital polarimeter (c as grams of compound per 100 mL). High resolution mass spectra (HRMS) were obtained by chemical ionization (CI, NH_3) or electrospray ionization (ESI). Flash column chromatography was carried out using 40–63 μm (230–400 mesh) silica gel. *Pseudomonas* sp. lipase (PSL) and *P. cepacia* lipase (PCL,

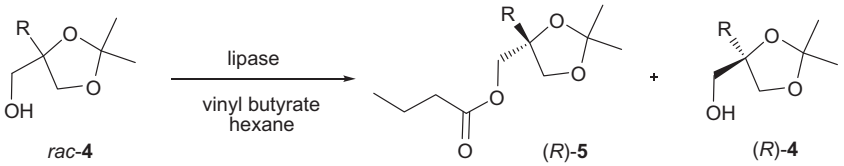
Table 1
Enzymatic resolution of **5a–g** using lipases under hydrolysis conditions



Entry	Substrate	Enzyme[a]	Time (h)	Alcohol **4**			Ester **5**			*E*
				Ee[b] (%)	Abs. conf.	Yield[c] (%)	Ee[b] (%)	Abs. Conf.	Yield[c] (%)	
1	**5a**	PCL	1	99	(*S*)	46	99	(*S*)	49	>200
2	**5b**	PSL	2	97	(*S*)	49	97	(*S*)	44	>200
3	**5c**	PCL	9	99	(*S*)	40	99	(*S*)	48	>200
4	**5d**	PSL	9	98	(*S*)	40	98	(*S*)	37	>200
5	**5e**	CAL-B	20	94	(*R*)	43	94	(*R*)	39	115
6	**5f**	CAL-B	52	94	(*R*)	41	94	(*R*)	41	115
7	**5g**	RSL	18	94	(*S*)	47	94	(*S*)	46	115

[a] PCL (*P. cepacia* lipase), PSL (*Pseudomonas* sp. lipase), CAL-B (*C. antarctica* lipase B), RSL (*Rhizopus* sp. lipase).
[b] Determined by GC or HPLC on a chiral phase.
[c] Isolated yield.

Table 2
Enzymatic resolution of **4a–g** using lipases under esterification conditions



Entry	Substrate	Enzyme[a]	Time (h)	Alcohol **4**			Ester **5**			*E*
				Ee[b] (%)	Abs. conf.	Yield[c] (%)	Ee[b] (%)	Abs. Conf.	Yield[c] (%)	
1	**4a**	PCL	24	98	(*R*)	40	93	(*R*)	39	126
2	**4b**	PCL	5	93	(*R*)	39	93	(*R*)	37	94
3	**4c**	PCL	10	99	(*R*)	40	85	(*R*)	42	63
4	**4d**	PCL	22	99	(*R*)	37	92	(*R*)	40	125
5	**4e**	CAL-B	1.25	92	(*S*)	46	92	(*S*)	44	78
6	**4f**	CAL-B	1	96	(*S*)	44	92	(*S*)	41	94
7	**4g**	RSL	648	80	(*R*)	48	90	(*R*)	42	46

[a] PCL (*P. cepacia* lipase), CAL-B (*C. antarctica* lipase B), RSL (*Rhizopus* sp. lipase).
[b] Determined by GC or HPLC on a chiral phase.
[c] Isolated yield.

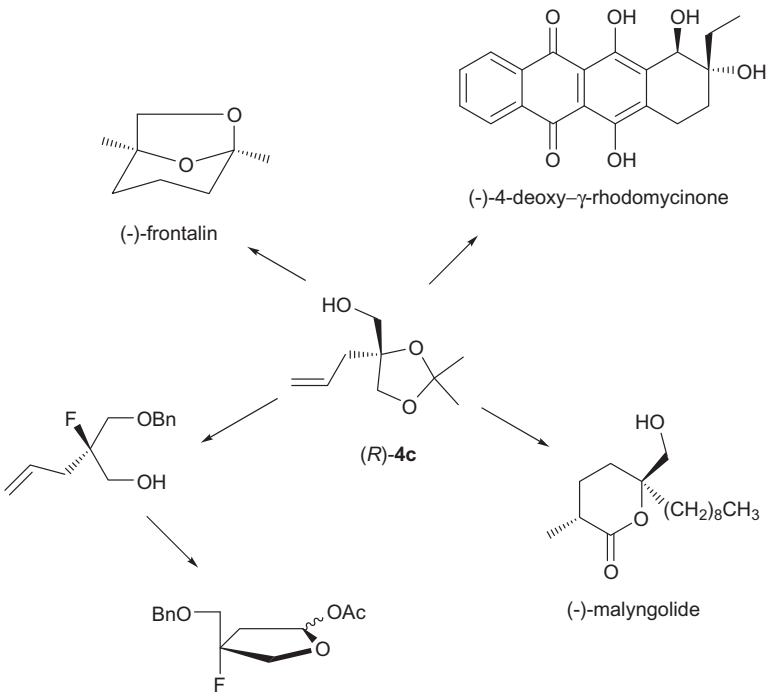


Figure 1. Natural products and biologically active compounds synthesized from (*R*)-**4c**.[30,31]

renamed *Burkholderia cepacia* lipase) were from Fluka-Aldrich-Sigma. *Rhizopus* sp. lipase (RSL, lipase F) was from Amano International Enzyme Co. and CAL-B (*Candida antarctica* lipase B (Chirazyme L2) was obtained from Boehringer Mannheim.

3.2. General procedure for the synthesis of alcohols 2a–g

To a solution of R-MgBr (66 mmol, 3 equiv) in anhydrous THF (130 mL) was added a solution of **1** (22 mmol, 1 equiv) in THF (15 mL). The mixture was stirred at room temperature and the progress of the reaction was monitored by TLC (hexane/AcOEt, 9:1). The reaction mixture was cooled to 0 °C, quenched with a 3 M HCl solution (29 mL), and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with satd $NaHCO_3$ (3 × 40 mL), water, and brine. The organic extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc, 95/5) to give a yellow oil (yields: 76–94%).

3.2.1. 1,3-Bis-[(*tert*-butyldimethylsilyloxy)methyl]-2-methylpropan-2-ol 2a

IR (neat) 3565, 3484, 2959–2862, 1472,1257,1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 12H), 0.90 (s, 18H), 1.10 (s, 3H), 2.58 (br s, 1H, OH), 3.40 (d, *J* = 9.3 Hz, 2H), 3.47 (d, *J* = 9.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.4, 20.9, 26.1, 66.6, 72.6; HRMS (ESI) Calcd for $C_{16}H_{39}O_3Si_2$ $(M+H)^+$: 335.2438. Found: 335.2432.

3.2.2. 1-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]but-3-en-2-ol 2b

IR (neat) 3566, 3094, 2956, 2930, 2858, 1472, 1258, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 12H), 0.88 (s, 18H), 3.48 (d, *J* = 9.5 Hz, 2H), 3.57 (d, *J* = 9.5 Hz, 2H), 5.18 (m, 1H), 5.41 (m, 1H),

5.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.5, 26.1, 65.8, 75.1, 115.0, 138.7. Spectroscopic data of compound **2b** are in agreement with that reported in the literature.[33]

3.2.3. 1-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]pent-4-en-2-ol 2c

IR (neat) 3566, 3484, 3077, 2955–2861, 1642, 1465, 1257, 1085 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 12H), 0.90 (s, 18H), 2.23 (m, 2H), 2.58 (br s, 1H, OH), 3.41 (d, J = 9.3 Hz, 2H), 3.50 (d, J = 9.3 Hz, 2H), 5.08 (m, 1H), 5.10 (m, 1H), 5.86–5.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.4, 26.1, 38.5, 65.1, 74.0, 118.0, 133.8; HRMS (ESI) Calcd for $C_{18}H_{41}O_3Si_2$ $(M+H)^+$: 361.2594. Found: 361.2539.

3.2.4. 1-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-methylbut-3-en-2-ol 2d

IR (neat) 3559, 2954, 2929, 2885, 2858, 1471, 1254, 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 12H), 0.86 (s, 18H), 1.77 (m, 3H), 3.53 (d, J = 9.5 Hz, 2H), 3.65 (d, J = 9.5 Hz, 2H), 4.89 (m, 1H), 4.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 18.4, 19.8, 26.0, 65.5, 76.4, 111.8, 146.3; HRMS (CI, NH_3) Calcd for $C_{18}H_{41}O_3Si_2$ $(M+H)^+$: 361.2594. Found: 361.2588.

3.2.5. 1,3-Bis-[(*tert*-butyldimethylsilyloxy)methyl]-2-phenylpropan-2-ol 2e

IR (neat) 3555, 3484, 3061, 3032, 2955–2857, 1601, 1470, 1256, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 12H), 0.88 (s, 18H), 3.15 (br s, 1H, OH), 3.72 (d, J = 9.4 Hz, 2H), 3.85 (d, J = 9.4 Hz, 2H), 7.24–7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.34, −5.30, 18.5, 26.1, 66.8, 75.5, 126.0, 127.3, 127.9, 142.8; HRMS (ESI) Calcd for $C_{21}H_{41}O_3Si_2$ $(M+H)^+$: 397.2594. Found: 397.2589.

3.2.6. 1,3-Bis-[(*tert*-butyldimethylsilyloxy)methyl]-2-(4-fluorophenyl)propan-2-ol 2f

IR (neat) 3356, 3020, 2967, 2900, 2876, 2845, 1661, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 12H), 0.87 (s, 18H), 3.12 (d, J = 7.6 Hz, 2H), 3.78 (d, J = 7.6 Hz, 2H), 6.98–7.02 (m, 2H), 7.50–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.5, 26.1, 66.7, 75.2, 114.6, 127.7, 139.1, 161.6; HRMS (ESI) Calcd for $C_{21}H_{39}O_3Si_2FNa$ $(M+Na)^+$: 437.2319. Found: 437.2310.

3.2.7. 1,3-Bis-[(*tert*-butyldimethylsilyloxy)methyl]-2-benzylpropan-2-ol 2g

IR (neat) 3559, 3064, 3030, 2954, 2929, 2885, 2858, 1471, 1254, 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 12H), 0.92 (s, 18H), 2.36 (s, 2H), 3.37 (d, J = 9.3 Hz, 2H), 3.45 (d, J = 9.3 Hz, 2H), 7.18–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.4, 26.1, 39.7, 64.7, 74.6, 126.4, 128.1, 130.9, 137.3; HRMS (CI, NH_3) Calcd for $C_{22}H_{43}O_3Si_2$ $(M+H)^+$: 411.2751. Found: 411.2743.

3.3. General procedure for the synthesis of triol 3a–g

To a solution of **2a–g** (12.5 mmol, 1 equiv) in THF (30 mL) was added a solution of tetrabutylammonium fluoride in THF (1 M, 38 mmol, 3 equiv). The mixture was stirred overnight at room temperature. The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc/hexane, 9:1 to pure EtOAc) to afford **3a–g**. All of the triols are known compounds that exhibited spectroscopic data identical to that reported in the literature.[15,16,20,34]

3.4. General procedure for the synthesis of acetals 4a–g

Triol **3a–g** (0.27 mmol, 1 equiv), *p*-toluenesulfonic acid (0.03 mmol, 0.1 equiv), and Na_2SO_4 (0.058 mmol, 0.2 equiv) were stirred in acetone at room temperature. The reaction was monitored by TLC (hexane/EtOAc, 70:30). The reaction was quenched by the addition of $NaHCO_3$ (24 mg, 0.28 mmol) and stirred for 15 min. The mixture was diluted with ethyl acetate (50 mL), washed with aqueous satd $NaHCO_3$ (30 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (hexane/EtOAc, 70:30) to give acetals **4a–g** as colorless oils (yields: 70–85%).

3.4.1. 2,2,4-Trimethyl-1,3-dioxolan-4-yl methanol 4a

IR (neat) 3463, 2986, 2936, 2874, 1457, 1372, 1251, 1213 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 3.47 (d, J = 11.3 Hz, 2H), 3.52 (d, J = 11.3 Hz, 2H), 3.73 (d, J = 8.6 Hz, 1H), 3.98 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 27.1, 27.3, 67.0, 71.2, 81.2, 109.8. Spectroscopic data are in agreement with that reported in the literature.[24]

3.4.2. (4-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl) methanol 4b

IR (neat) 3478, 3094, 2988, 2935, 2876, 1372, 1212, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.47 (s, 3H), 3.54 (m, 2H), 3.88 (d, J = 8.6 Hz, 1H), 4.07 (d, J = 8.6 Hz, 1H), 5.25 (d, J = 11.8 Hz, 1H), 5.41 (d, J = 14.8 Hz, 1H), 5.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 27.2, 66.1, 70.3, 84.1, 110.4, 116.0, 138.4. Spectroscopic data are in agreement with that reported in the literature.[15]

3.4.3. (2,2-Dimethyl-4-(prop-2-en-1-yl)-1,3-dioxolan-4-yl) methanol 4c

IR (neat) 3473, 3078, 2987, 2936, 2877, 1371, 1214, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.42 (s, 3H), 1.83 (br s, 1H, OH), 2.39 (m, 2H), 3.54 (m, 2H), 3.82 (d, J = 8.6 Hz, 1H), 3.89 (d, J = 8.6 Hz, 1H), 5.12 (m, 2H), 5.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 27.1, 39.9, 65.2, 69.3, 83.1, 109.5, 118.1, 133.8. Spectroscopic data are in agreement with that reported in the literature.[17]

3.4.4. (2,2-Dimethyl-4-(prop-1-en-2-yl)-1,3-dioxolan-4-yl) methanol 4d

IR (neat) 3481, 3097, 3084, 2988, 2939, 2877, 1371, 1213, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.48 (s, 3H), 1.77 (s, 3H), 3.58 (m, 2H), 3.97 (d, J = 8.6 Hz, 1H), 4.04 (d, J = 8.6 Hz, 1H), 4.99 (s, 1H), 5.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 26.0, 27.4, 65.9, 70.0, 86.5, 110.4, 112.6, 145.5. HRMS (CI, NH_3) Calcd for $C_9H_{17}O_3$ $(M+H)^+$: 173.1178. Found: 173.1174.

3.4.5. (2,2-Dimethyl-4-phenyl-1,3-dioxolan-4-yl) methanol 4e

IR (neat) 3404, 3061, 2922, 2851, 1637, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.57 (s, 3H), 3.63 (d, J = 11.6 Hz, 1H), 3.70 (d, J = 11.6 Hz, 1H), 4.15 (d, J = 8.5 Hz, 1H), 4.40 (d, J = 8.5 Hz, 1H), 7.28–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 27.2, 68.3, 71.5, 85.5, 110.3, 125.6, 127.5, 128.4, 143.0. Spectroscopic data are in agreement with that reported in the literature.[17]

3.4.6. [4-(4-Fluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl] methanol 4f

IR (neat) 3356, 3020, 2967, 2900, 2876, 1661, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.58 (s, 3H), 3.65 (m, 2H), 4.11 (d, J = 8.5 Hz, 1H), 4.38 (d, J = 8.5 Hz, 1H), 7.02–7.05 (m, 2H), 7.32–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 27.2, 68.2, 71.6, 85.2, 110.7, 115.5, 127.2, 127.3, 167.2. HRMS (CI, NH_3) Calcd for $C_{12}H_{15}O_3FNa$ $(M+Na)^+$: 249.0897. Found: 249.0909.

3.4.7. (4-Benzyl-2,2-dimethyl-1,3-dioxolan-4-yl) methanol 4g

IR (neat) 3387, 3064, 3030, 2985, 2925, 2853, 1603, 1153, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.41 (s, 3H), 1.64 (br s, 1H, OH), 2.94 (d, J = 13.6 Hz, 1H), 2.99 (d, J = 13.6 Hz, 1H), 3.47 (d, J = 11.2 Hz, 1H), 3.52 (d, J = 11.2 Hz, 1H), 3.85

(d, J = 8.6 Hz, 1H), 3.99 (d, J = 8.6 Hz, 1H), 7.22–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 27.5, 41.8, 65.3, 69.5, 83.8, 110.2, 126.9, 128.5, 130.8, 136.7. Spectroscopic data are in agreement with that reported in the literature.[17]

3.5. General procedure for the synthesis of butyrates 5a–g

To a solution of alcohol **4a–g** (0.28 mmol, 1 equiv) in anhydrous CH_2Cl_2 (2 mL) at 0 °C under a dry atmosphere were added anhydrous Et_3N (1.4 mmol, 5 equiv) and butanoyl chloride (0.34 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature and monitored by TLC (hexane/EtOAc, 90:10). The reaction mixture was quenched by the addition of water (5 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was washed with water (2 × 20 mL), satd $NaHCO_3$ (2 × 30 mL), dried over $MgSO_4$, and evaporated. The crude product was purified by flash chromatography (hexane/EtOAc, 95:5) to give esters **5a–g** as colorless oils (yields: 75–90%).

3.5.1. (2,2,4-Trimethyl-1,3-dioxolan-4-yl) methyl butanoate 5a

IR (neat) 2984, 2937, 2876, 1740, 1380, 1251, 1212, 1175, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.32 (s, 3H), 1.41 (s, 6H), 1.64 (m, 2H), 2.32 (t, J = 7.4 Hz, 2H), 3.72 (d, J = 8.7 Hz, 1H), 3.95 (d, J = 8.7 Hz, 1H), 4.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 18.3, 22.1, 26.4, 26.7, 35.7, 67.4, 71.4, 79.5, 109.4, 172.6. Spectroscopic data are in agreement with that reported in the literature.[24]

3.5.2. (4-Ethenyl-2,2-dimethyl-1,3-dioxolan-4-yl) methyl butanoate 5b

IR (neat) 3096, 2987, 2968, 2938, 2878, 1742, 1372, 1173, 1062 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.40 (s, 3H), 1.46 (s, 3H), 1.63 (m, 2H), 2.32 (t, J = 7.5 Hz, 2H), 3.84 (d, J = 8.7 Hz, 1H), 4.03 (d, J = 8.7 Hz, 1H), 4.05 (d, J = 11.2 Hz, 1H), 4.11 (d, J = 11.2 Hz, 1H), 5.22 (d, J = 9.6 Hz, 1H), 5.43 (d, J = 15.4 Hz, 1H), 5.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.6, 26.3, 27.1, 36.3, 66.7, 70.9, 82.0, 110.7, 116.0, 137.6, 173.4. HRMS (CI, NH_3) Calcd for $C_{12}H_{21}O_4$ $(M+H)^+$: 229.1440. Found: 229.1428.

3.5.3. (2,2-Dimethyl-4-(prop-2-en-1-yl)-1,3-dioxolan-4-yl) methyl butanoate 5c

IR (neat) 3079, 2984, 2868, 2877, 1742, 1381, 1177, 1064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3H), 1.41 (s, 6H), 1.65 (m, 2H), 2.33 (t, J = 7.4 Hz, 2H), 2.40 (m, 2H), 3.82 (d, J = 8.8 Hz, 1H), 3.89 (d, J = 8.8 Hz, 1H), 4.05 (s, 2H), 5.13 (m, 2H), 5.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 18.3, 26.4, 26.6, 35.7, 40.1, 65.8, 69.7, 81.1, 109.7, 118.1, 133.6, 172.5. HRMS (CI, NH_3) Calcd for $C_{13}H_{23}O_4$ $(M+H)^+$: 243.1596. Found: 243.1594.

3.5.4. [2,2-Dimethyl-4-(prop-1-en-2-yl)-1,3-dioxolan-4-yl] methyl butanoate 5d

IR (neat) 3084, 2986, 2968, 2938, 2877, 1742, 1381, 1177, 1064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 1.65 (m, 2H), 1.78 (s, 3H), 2.31 (t, J = 7.4 Hz, 2H), 3.96 (d, J = 8.8 Hz, 1H), 4.03 (d, J = 8.8 Hz, 1H), 4.15 (s, 2H), 4.96 (s, 1H), 5.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.6, 19.7, 25.9, 27.2, 36.3, 66.4, 70.3, 84.5, 110.6, 112.7, 144.4, 173.6. HRMS (CI, NH_3) Calcd for $C_{13}H_{23}O_4$ $(M+H)^+$: 243.1596. Found: 243.1594.

3.5.5. (2,2-Dimethyl-4-phenyl-1,3-dioxolan-4-yl) methyl butanoate 5e

IR (neat) 3101, 3006, 2965, 2878, 1740, 1370, 1221, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3H), 1.36 (s, 3H), 1.56 (s, 3H), 1.55–1.62 (m, 2H), 2.28 (t, J = 7.5 Hz, 2H), 4.12 (d, J = 8.7 Hz, 1H), 4.24 (s, 2H), 4.36 (d, J = 8.7 Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.5, 26.2, 27.2, 36.3, 68.5, 72.0, 83.7, 110.9, 125.7, 127.9, 128.5, 142.1, 173.6, HRMS (CI, NH_3) Calcd for $C_{16}H_{23}O_4$ $(M+H)^+$: 279.1596. Found: 279.1599.

3.5.6. [4-(4-Fluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl] methyl butanoate 5f

Crystallises on standing, mp. 50–52 °C; IR (neat) 3583, 2966, 2937, 2878, 1739, 1511, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 3H), 1.35 (s, 3H), 1.55 (s, 3H), 1.55–1.62 (m, 2H), 2.27 (t, J = 7.5 Hz, 2H), 4.09 (d, J = 8.7 Hz, 1H), 4.21 (s, 2H), 4.34 (d, J = 8.7 Hz, 1H), 7.02–7.07 (m, 2H), 7.34–7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.5, 26.1, 27.2, 36.3, 68.4, 71.9, 83.3, 110.0, 115.4, 127.5, 137.9, 162.5, 173.5. HRMS (CI, NH_3) Calcd for $C_{16}H_{21}O_4FNa$ $(M+Na)^+$: 319.1322. Found: 319.1320.

3.5.7. (4-Benzyl-2,2-dimethyl-1,3-dioxolan-4-yl) methyl butanoate 5g

IR (neat) 3064, 3031, 2965, 2936, 2876, 1740, 1176, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 6.7 Hz, 3H), 1.27 (s, 3H), 1.41 (s, 3H), 1.69 (m, 2H), 2.36 (t, J = 6.4 Hz, 3H), 2.95 (m, 2H), 3.88 (d, J = 8.6 Hz, 1H), 3.91 (d, J = 8.6 Hz, 1H), 3.97 (s, 2H), 7.21–7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.5, 26.8, 27.4, 36.4, 41.6, 66.2, 70.1, 81.7, 110.5, 127.0, 128.5, 130.8, 136.3, 171.4; HRMS (CI, NH_3) Calcd for $C_{17}H_{25}O_4$ $(M+H)^+$: 293.1753. Found: 293.1758.

3.6. Typical procedure for enzymatic reactions

3.6.1. Transesterification

To a solution of alcohol **4e** (80.5 mg, 0.39 mmol) in hexane (5.7 mL) were added vinyl butyrate (73 μL, 0.58 mmol, 1.5 equiv) and lipase B from *C. antarctica* (CAL-B, 400 units). The reaction course was monitored by chiral HPLC and when the conversion reached 50% (75 min), the reaction was quenched by filtration of the enzyme and the solvent evaporated. Flash chromatography of the residue with hexane/EtOAc (90:10–80:20) gave alcohol (*S*)-**4e** (37 mg, 46%, ee = 92%) and ester (*S*)-**5e** (48 mg, 44%, ee = 92%).

3.6.2. Hydrolysis

Ester **5e** (84 mg, 0.30 mmol) was suspended in a buffered aqueous solution (4.0 mL, phosphate pH 7.5). *C. antarctica* lipase B (400 units) was added and the pH maintained at its initial value by addition of 0.1 M aqueous NaOH. The reaction was monitored by chiral HPLC and stopped at the 50%-of-hydrolysis point (20 h). The aqueous mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated. Flash chromatography of the residue with hexane/EtOAc (90:10–80:20) gave alcohol (*R*)-**4e** (27 mg, 43%, ee = 94%) and ester (*R*)-**5e** (32.6 mg, 39%, ee = 94%).

3.6.3. Determination of the enantiomeric excess and absolute configuration

Compounds **4a–5a**: Chiral GC analysis on a Chiradex B-DM column; (*S*)-**4a** (from enzymatic hydrolysis, ee = 99%): $[\alpha]_D^{22} = -5.6$ (*c* 0.98, CH_2Cl_2), lit.[35] (*R*)-**4a**: $[\alpha]_D^{22} = +5.5$ (*c* 0.78, CH_2Cl_2); (*S*)-**5a** (from enzymatic hydrolysis, ee = 99%): $[\alpha]_D^{22} = -6.1$ (*c* 1.02, EtOH).

Compounds **4b–5b**: Chiral GC analysis on a Chiradex B-DM column; (*S*)-**4b** (from enzymatic hydrolysis, ee = 97%): $[\alpha]_D^{22} = -11.9$ (*c* 1.00, $CHCl_3$); the absolute configuration was established by correlation with 2-ethylglycerol monobenzyl ether of known absolute configuration.[36] Compound (*S*)-**5b** (from enzymatic hydrolysis, ee = 97%): $[\alpha]_D^{22} = +31.1$ (*c* 1.00, $CHCl_3$).

Compounds **4c–5c**: Chiral GC analysis on a Chiradex B-DM column; (*S*)-**4c** (from enzymatic hydrolysis, ee = 99%): $[\alpha]_D^{22} = +2.8$ (*c* 1.15, $CHCl_3$), lit.[37] (*R*)-**4c**: $[\alpha]_D^{22} = -3.0$ (*c* 3.00, $CHCl_3$); (*S*)-**5c** (from enzymatic hydrolysis, ee = 99%): $[\alpha]_D^{22} = -15.2$ (*c* 1.05, $CHCl_3$).

Compounds **4d–5d**: Chiral GC analysis on a Chiradex B-DM column; (*S*)-**4d** (from enzymatic hydrolysis, ee = 98%): $[\alpha]_D^{22} = -24.2$ (*c* 1.09, $CHCl_3$); the absolute configuration was established by correlation with 2-isopropenylglycerol monoacetate of known absolute configuration.[20] Compound (*S*)-**5d** (from enzymatic hydrolysis, ee = 98%): $[\alpha]_D^{22} = +29.1$ (*c* 1.30, $CHCl_3$).

Compounds **4e–5e**: Chiral HPLC analysis on a Chiralcel OJ-H column; (*R*)-**4e** (from enzymatic hydrolysis, ee = 94%): $[\alpha]_D^{22} = +5.9$ (*c* 1.03, $CHCl_3$), lit.[17] (*R*)-**4e**: $[\alpha]_D^{22} = +4.5$ (*c* 2.51, $CHCl_3$); (*R*)-**5e** (from enzymatic hydrolysis, ee = 94%): $[\alpha]_D^{22} = -18.7$ (*c* 1.00, $CHCl_3$).

Compounds **4f–5f**: Chiral HPLC analysis on a (*S*,*S*)Whelk-O1 column; (*S*)-**4f** (from enzymatic acylation, ee = 96%): $[\alpha]_D^{22} = -2.3$ (*c* 2.57, $CHCl_3$); the absolute configuration of **4f** was tentatively assigned by close similarity of its structure and chiral HPLC chromatogram with that of **4e**. Compound (*S*)-**5f** (from enzymatic acylation, ee = 92%): $[\alpha]_D^{22} = +17.9$ (*c* 1.51, $CHCl_3$).

Compounds **4g–5g**: Chiral HPLC analysis on a Chiralcel OJ-H column; (*S*)-**4g** (from enzymatic hydrolysis, ee = 94%): $[\alpha]_D^{22} = +7.7$ (*c* 1.65, $CHCl_3$), lit.[17] (*R*)-**4g**: $[\alpha]_D^{22} = -6.5$ (*c* 1.34, $CHCl_3$); (*S*)-**5g** (from enzymatic hydrolysis, ee = 94%): $[\alpha]_D^{22} = -10.9$ (*c* 1.00, $CHCl_3$).

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