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Chemoenzymatic Synthesis of (Protected) Psymberic Acid

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Two alternative approaches to the side-chain of psymberin (**1**), psymberic acid (**5**), have been developed starting from either racemic or enantiopure acetal **6**. A five-step chemoenzymatic route provided the PMB-protected acid (*S*,*S*)-**16** required for the coupling that should ultimately lead to the natural product **1**.

Introduction

In 2004 psymberin (**1**) (***Ps****ammocinia*, ***symb****iont*, *ped****erin***) was isolated from the marine sponges *Psammocinia* sp. and *Ircinia ramose* off the coast of Papua New Guinea by two independent research groups.[1,2] Its structural resemblance to other cytotoxins of the pederin family [e.g. pederin (**2**), mycalamide A (**3**) and the non-natural psympederin (**4**)], which are known to have strong antitumour properties, also suggested cytotoxic activity. Screening showed that psymberin (**1**) shows remarkable cytostatic activity against multiple human cancer cell lines with an LC_{50} in nanomolar concentrations.[1,3] The very high biological activity, the lack of natural availability and its challenging chemical structure has made psymberin (**1**) an attractive target for total synthesis.[4] Its unique structure contains nine stereogenic centres and consists of a central pyran core, a dihydroisocoumarin unit and an unsaturated acyclic side-chain. The stereochemical assignment of the stereogenic centres relied on the use of multidimensional ^1H and ^{13}C NMR techniques, whereas the absolute and relative configurations were based on homology to other pederins; stereogenic centres were also characterized by the comparison of optical rotations and biogenetic origin. However, the stereochemistry at C-4 of the unsaturated amide side-chain initially remained undefined.[1] Finally, the first total synthesis by De Brabander and co-workers in 2005 led to the complete structural assignment of psymberin (**1**) with the (4*S*) configuration.[4a] Other approaches to assign the configuration of the amide side-chain were conducted by chemical correlation[5] and natural product degradation.[6] In addition, the central pyran core, the dihydroisocumarin unit and coupling strategies have received considerable attention;[7–9] apart from the procedures reported for the total syntheses,[4] a number of publications have dealt with alternative routes,[10,11] including a formal synthesis of psymberin (**1**).[12] Encouraged by its high biological activity, a possible biological precursor[13] (seco-psymberin) and a hybrid[14] [psympederin (**4**)] were synthesized and tested for their biological activity. Furthermore, just recently a series of analogues were synthesized; their structure–activity relationships (SAR) were investigated by modifying the unsaturated amide side-chain of psymberin (**1**; Figure 1).[15]

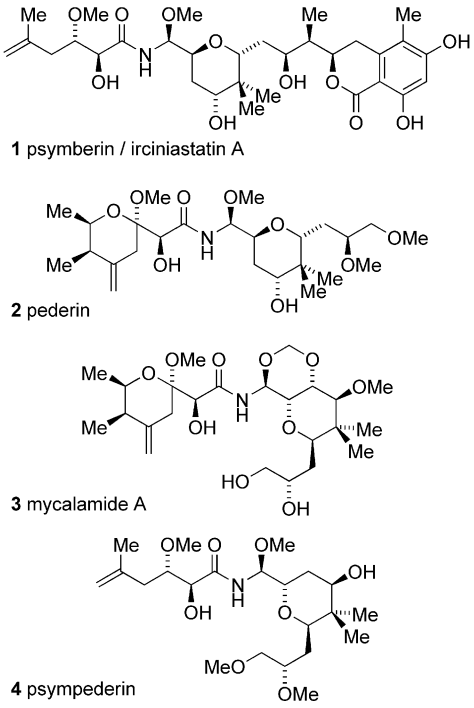

Figure 1. Members of the pederin family.

In this paper we focus on the side-chain of psymberin (**1**) and of the non-natural psympederin (**4**), psymberic acid (**5**), providing a detailed conclusion to our preliminary report.[16] We present an alternative chemoenzymatic route to the side-chain with a highly diastereoselective aldol reaction

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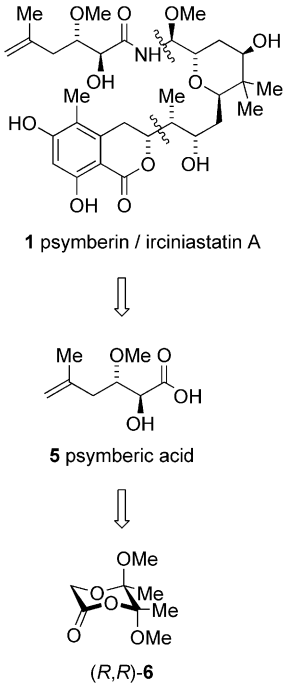
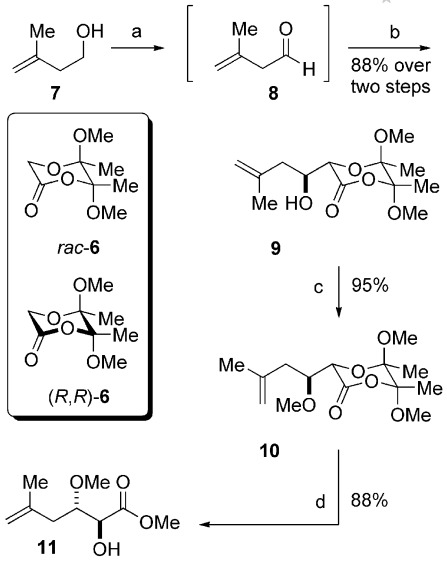
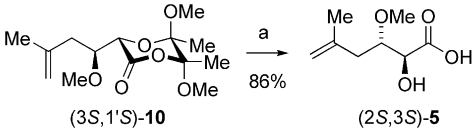
as a key step. To establish the absolute and relative configurations, Ley and co-workers' butane 2,3-diacetal protected glycolic acid **6** was used, which provided *anti*-2,3-dihydroxy esters after deprotection (Scheme 1).[17a–17c]



Scheme 1. Retrosynthetic analysis of psymberin (**1**).



Scheme 2. Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, 0 °C; (b) LiHMDS to **6**, THF, –78 °C, then precooled **8**, 88% over two steps; (c) 1,8-bis(dimethylamino)naphthalene, Me_3OBF_4, CH_2Cl_2, room temp., 95%; (d) CSA, MeOH, room temp., 88%.



Scheme 3. Reagents and conditions: (a) 1 N HCl in THF, 3 d, room temp. (86%).

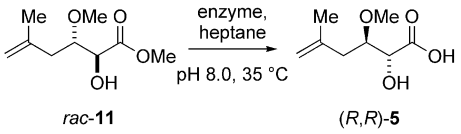
Results and Discussion

We started our synthetic endeavour with the oxidation of the commercially available primary alcohol **7** to the corresponding aldehyde **8** using Dess–Martin periodinane[18a,18b] (Scheme 2). Compound **8** could not be stored and was directly employed in the subsequent transformation without further purification. Thus, the crude aldehyde **8** was precooled and then added to the enolate of protected glycolic acid **6** at –78 °C to form exclusively the *anti*-aldol product **9** in 88% yield (over two steps). Because standard techniques for the *O*-methylation did not work, we utilized 1,8-bis(dimethylamino)naphthalene (proton sponge) and the Meerwein salt to furnish the desired product **10** in high yield (95%).

In analogy to a procedure described in the literature,[17b] the deprotection with camphorsulfonic acid (CSA) was straightforward (88% yield), resulting in either the racemic methyl ester *rac*-**11** or the enantiomerically pure ester (*S*,*S*)-**11**, depending on the glycolic acid anion equivalent used. The sequence described was performed by starting from acetal *rac*-**6** as well as from the pure enantiomer (*R*,*R*)-**6**. Psymberic acid [(2*S*,3*S*)-**5**] itself could also be obtained directly by the convenient hydrolysis of the diacetal (3*S*,1′*S*)-**10** starting from (*R*,*R*)-**6** (Scheme 3; 86%).

Next, it was necessary to set up an analytical base for the enzymatic kinetic resolution of the racemic methyl ester *rac*-**11** to furnish the acid (2*S*,3*S*)-**5**. The starting material **11** as well as the product **5** (after treating the acids with small portions of CH_2N_2) could be separated by HPLC on a chiral stationary phase. Enzyme-screening was then performed in a biphasic system on an analytical scale in order to find an appropriate hydrolase that might be suitable for the enantioselective hydrolysis.[19] After defined periods of time, small aliquots were taken from the reaction mixture, and the enantiomeric excess of the product mixture was determined. Although a moderate enantiomeric excess for the substrate was obtained (Scheme 4), the main drawback was that various side-reactions, for example, transesterification, occurred. The fact that the tested biocatalysts unfortunately retained in all cases the desired (*S*,*S*) enantiomer **11**, and with poor enantioselectivity (*E* value), rendered the route impractical for preparative purposes.

With respect to the envisaged coupling strategy, the alcohol function requires protection to avoid the side-reactions mentioned above for the transformation of the ester *rac*-**11**. For the task at hand, silyl protecting groups seemed to be one logical choice. Under standard conditions (Scheme 5) the desired products *rac*-**12** (TES protection) and *rac*-**13** (TPS protection) were obtained in non-optimized yields of 80 and 74%, respectively. However, no baseline separation of either pair of enantiomers was obtained

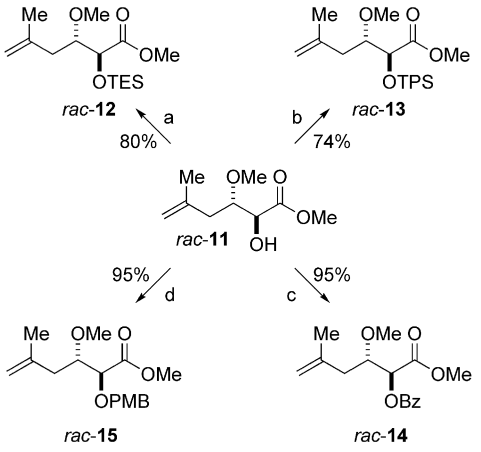


rac-**11** (*R*,*R*)-**5**

Entry	Enzyme[19]	*ee* (*S*,*S*)-**11**	*ee* (*R*,*R*)-**5**	*E*
1	CAL-B	32%	0.5%	1.2
2	PLE	19%	3.3%	1.2
3	lipase PS	14%	2.3%	1.1
4	CRL	14%	3.4%	1.2
5	PPL	16%	0.4%	0

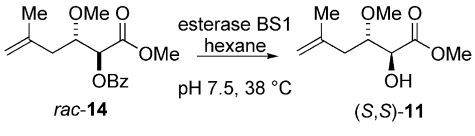
Scheme 4. Enzymatic kinetic resolution of the methyl ester *rac*-**11** in a biphasic system [potassium phosphate buffer (pH = 8.0)/*n*-heptane] at 35 °C after 24 h (analytical scale).

(HPLC analysis). As an alternative, the benzoyl protecting group was introduced (*rac*-**14**; 95% yield from *rac*-**11**), because it has already been successfully applied in the total synthesis by De Brabander and co-workers;[4a] otherwise, acetates or long-chain fatty acids would have been the preferred choice as better selectivity would have been expected.[21,22]



Scheme 5. Reagents and conditions: (a) imidazole, TESCl (TES = Et_3Si), CH_2Cl_2, 0 °C, 80%; (b) imidazole, CH_2Cl_2, 0 °C, TPSCl (TPS = *t*$BuPh_2Si$), 74%; (c) BzCl (Bz = benzoyl), NEt_3, DMAP, CH_2Cl_2, 0 °C, 95%; (d) PMBBr (PMB = *p*-methoxybenzyl), *n*Bu_4NI, DMF, NaH, –50 °C, 95%.

The screening of 24 different hydrolases[19] was only moderately successful. Although none of the lipases used was active towards the substrate, some esterases [esterase E3 (Roche diagnostics) and esterase BS1 (Codexis)] showed conversion, albeit with only poor selectivity. By using the esterase from *Bacillus subtilis* strain BS1 (Codexis) on a preparative scale, enantiomerically highly enriched starting material (>99% *ee*) could be isolated in 31% yield (56% conversion; Entry 1, Scheme 6), but subsequent analysis showed that the wrong enantiomer, (*R*,*R*)-**14**, was obtained. Next, we focused our attention on the isolation of the alcohol (*S*,*S*)-**11**; low conversion was achieved (31%, Entry 2), and no significant accumulation of the desired product could be detected.



rac-**14** (*S*,*S*)-**11**

Entry	Conversion	*ee* (*S*,*S*)-**11**	*ee* (*R*,*R*)-**14**
1	56%[a]	77%	>99%
2	31%	>99%	45%

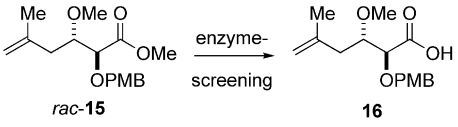
[a] Isolated product in 31% yield.

Scheme 6. Kinetic resolution of *rac*-**14**.

We assumed that the alcohol (*S*,*S*)-**11** was further converted into the hydroxy acid (*S*,*S*)-**5**, but we failed to isolate it directly from the reaction mixture or after derivatization (esterification with TMS-diazomethane). As described above, a similar observation was made when using the unprotected psymberic ester *rac*-**11** as the substrate in the kinetic resolution.

Finally, the PMB protecting group proved to be appropriate for furnishing the desired natural (*S*,*S*) enantiomer. When introducing the PMB group through the use of the corresponding trichloroacetimidate, ether *rac*-**15** was obtained in only a moderate yield (up to 62%). Different conditions (temperature, solvents) and acids for the activation were tested (CSA, $BF_3{\cdot}Et_2O$, TfOH, PPTS),[20] but due to a number of byproducts, isolation of pure ether *rac*-**15** turned out to be a major problem. Eventually, the use of 4-methoxybenzyl bromide in the presence of *n*Bu_4NI gave the desired product *rac*-**15** in a respectable yield (95%; Scheme 5). After establishing the analytical tool for determining the enantiomeric excess (HPLC), the substrate was tested for its suitability in enzymatic kinetic resolution. Again different lipases and esterases[19] were tested (20 in total) in an aqueous two-phase system (potassium phosphate buffer/*n*-heptane), but no conversion of the substrate *rac*-**15** was detected after 24 h. To enhance the conversion rate we decided to repeat the enzyme-screening in an aqueous one-phase system with the main focus on esterases as they are known to be more suitable for converting simple alcohols and complex acids.[21,22] Moreover, we increased the enzyme/substrate ratio to a five-fold excess to ensure conversion. Under these conditions most of the esterases showed activity towards the substrate *rac*-**15** (Scheme 7). Samples taken after 2 and 24 h allowed us not only to assess the conversion, but also to determine the enantiomeric excess of the preferentially converted ester **15**. Because the enzymes esterase 001 and esterase BS3 (both from Codexis) showed the highest activity and enantioselectivity, we repeated the biotransformation on a preparative scale to assign the configuration by comparison of the obtained analytical data with those reported in the literature.[6]

It was ascertained that the named enzymes hydrolysed the desired (*S*,*S*) enantiomer of *rac*-**15** to give the natural PMB-protected psymberic acid (*S*,*S*)-**16**. We repeated the hydrolysis at different temperatures using esterase BS3[19] (Entries 1 and 2 in Scheme 8). Because it was found that at 40 °C the enantiomeric purity of (*S*,*S*)-**16** was not satisfac-



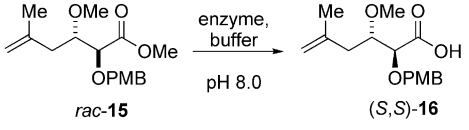
rac-**15** **16**

Entry	Enzyme[19]	*ee* (2 h) [sub.]	*ee* (24 h) [sub]	Substrate configuration
1	BS2	57%	[a]	(*S*,*S*)-**15**
2	BS3	73%	>99%	(*R*,*R*)-**15**
3	003	38%	>99%	(*R*,*R*)-**15**
4	001	79%	>99%	(*R*,*R*)-**15**
5	004	4%	0%	–
6	SD	3%	3%	–
7	PLE	61%	[a]	(*R*,*R*)-**15**
8	RO	2%	5%	–
9	PPL	1%	5%	–
10	CRL	2%	5%	–

[a] Both enantiomers were completely hydrolysed after 24 h.

Scheme 7. Enzymatic hydrolysis of ester *rac*-**15** performed in an aqueous one-phase system (analytical scale).

tory (83% *ee*), we lowered the temperature to 30 °C. Although the enantiomeric excess of the product was enhanced to 89% it still was too low for our purpose. The use of the esterase 001[19] (Entry 3 in Scheme 8) finally gave the desired acid (*S*,*S*)-**16** with high optical purity (*ee* ca. 98%) and in good yield (47%; $E > 100$). Increasing the reaction



rac-**15** (*S*,*S*)-**16**

Entry	Temp.	Time	*ee* (*R*,*R*)-**15**	*ee* (*S*,*S*)-**16**	*E*
1	30 °C	26 h	~ 96 %	~ 89 %	67
2	40 °C	16 h	> 95 %	> 83 %	48
3	25 °C	65 h	> 94 %	~ 98 %	> 100

Scheme 8. Kinetic resolution of the PMB-protected psymberic acid methyl ester (*rac*-**15**) on a preparative scale (Entries 1 and 2: esterase BS3; Entry 3: esterase 001).

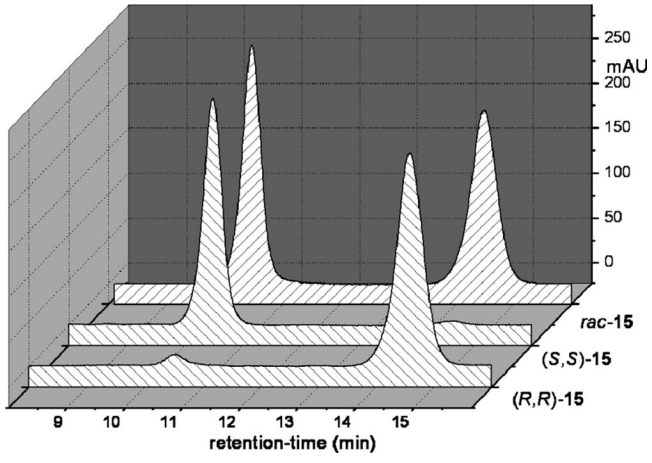


Figure 2. HPLC trace [column = Chiracel OD-H (4.6 × 250 mm), flow = 0.7 mL/min (*n*-heptane/*i*PrOH = 98:2)] of the kinetic resolution of ester *rac*-**15** at the end of the reaction [line 1: unreacted substrate *rac*-**15**; line 2: from product (*S*,*S*)-**16** after derivatization] and the remaining substrate (*R*,*R*)-**15** (line 3).

temperature to 30–40 °C did unfortunately not enhance the conversion rate and hence shorten the reaction time, but led to denaturation of the enzyme; the reaction stopped in both cases at low conversion. Subsequent addition of small portions of the enzyme also did not significantly improve the reaction. Figure 2 displays the HPLC trace of the kinetic resolution of *rac*-**15** performed on a preparative scale. A small amount of the product (*S*,*S*)-**16** was treated with diazomethane (in diethyl ether) to furnish the ester (*S*,*S*)-**15**, thus determining its optical purity.

Conclusions

We have developed two alternative routes to the acid side-chain of psymberin (**1**). Starting from acetal (*R*,*R*)-**6**, we obtained the unprotected psymberic acid (**5**) in three steps in an overall yield of 72%. The biocatalytic route furnished the PMB-protected coupling partner **16**. Racemic methyl ester *rac*-**15** could be obtained in a five-step sequence from *rac*-**6** in 69% yield. The ultimate kinetic resolution was optimized ($E > 100$) and gave the desired product with high selectivity (*ee* ca. 98%) and in a respectable yield (47%). Thus, another key intermediate in the synthesis of a chemoenzymatic natural product has been prepared.

Experimental Section

General: All starting materials were purchased from commercial suppliers and used as received, unless stated otherwise. All solvents were dried by common methods prior to use; THF was freshly distilled from sodium/benzophenone and methanol from calcium hydride. The hydrolases were used as non-immobilized powders as purchased.[19] Preparative chromatographic separations were performed by column chromatography on Merck silica gel 60 (0.063–0.200 μm). Solvents for flash chromatography (PE/EtOAc) were distilled before use. PE refers to the fraction with a boiling point in the range 40–60 °C. Celite® refers to Celite 545 (0.02–0.1 mm) purchased from Sigma–Aldrich. TLC was carried out on precoated plastic sheets (Polygram® SIL G/UV, Macherey–Nagel) with detection by UV (254 nm) and/or by staining with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. sulfuric acid (60 mL), H_2O (940 mL)]. Optical rotations were measured at 20 °C with a Perkin–Elmer 241 MC Polarimeter against the sodium D line. ^1H and ^{13}C NMR spectra were recorded at 20 °C with a Bruker Avance/DRX 600 spectrometer in $CDCl_3$ with TMS as an internal standard. Chemical shifts are given in ppm relative to Me_4Si (^1H NMR: $\delta = 0$ ppm) or to the resonance of $CDCl_3$ (^{13}C NMR: $\delta = 77.0$ ppm).

3-(1′-Hydroxy-3′-methylbut-3′-en-1′-yl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one (*rac*-9): Dess–Martin periodinane[18] (4.46 g, 10.5 mmol) was added in one portion to a stirred solution of alcohol **7** (906 mg, 10.5 mmol) in wet CH_2Cl_2 (21 mL) at 0 °C. The mixture was stirred at room temp. overnight followed by quenching with saturated aqueous $Na_2S_2O_3$ solution (150 mL) and half-saturated aqueous $NaHCO_3$ solution (150 mL). After effervescence had ceased, the mixture was extracted four times with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered under dry nitrogen and precooled to –78 °C. The aldehyde **8** was kept in solution until used. Meanwhile, lithium bis(trimethyl-

silyl)amide (1.0 M in THF, 5.52 mL, 5.52 mmol) was added dropwise to a stirred solution of *rac*-**6** (1.00 g, 5.26 mmol) at –78 °C in THF (15 mL). After stirring for 10 min, the precooled aldehyde solution (ca. 40 mL) was added in one portion. The mixture was stirred for a further 10 min, followed by the addition of acetic acid (664 mg, 11.1 mmol). The solution was then warmed to room temp. The mixture was concentrated under reduced pressure and purified by flash column chromatography (eluent: petroleum ether/ethyl acetate, 90:10) to furnish the aldol product **9** (1.28 g, 4.67 mmol, 89%) as a white crystalline solid. R_f = 0.25 (petroleum ether/ethyl acetate, 80:20). M.p. 59–63 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.43 (s, 3 H, Me), 1.51 (s, 3 H, Me), 1.80 (s, 3 H, CH_2=C*Me*), 2.36 (dd, $^3J_{2'a,1'}$ = 4.2, $^2J_{2'a,2'b}$ = 14.8 Hz, 1 H, 2′-H_a), 2.46 (dd, $^3J_{2'b,1'}$ = 8.9, $^2J_{2'b,2'a}$ = 14.9 Hz, 1 H, 2′-H_b), 3.22 (d, $^3J_{3,1'}$ = 2.6 Hz, 1 H, 3-H), 3.34 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 4.18 (d, $^3J_{OH,1'}$ = 2.9 Hz, 1 H, OH), 4.21 (m, 1 H, 1′-H), 4.89 (br., 2 H, 4′-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 16.9 (Me at C-5), 17.9 (Me at C-6), 22.7 (Me at C-3′), 39.6 (C-2′), 49.2 (OMe at C-5), 50.3 (OMe at C-6), 70.8 (C-3), 74.4 (C-1′), 98.2 (C-5), 104.9 (C-6), 113.2 (C-4′), 142.0 (C-3′), 167.1 (C-2) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 3502, 2949, 1742 (C=O), 1379, 1030 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 219 (2) [M – C_4H_7]$^+$, 116 (94) [$C_6H_{12}O_2$]$^+$, 101 (100) [$C_5H_9O_2$]$^+$. $C_{13}H_{22}O_6$ (274.31): calcd. C 56.92, H 8.08; found C 56.99, H 8.08.

(–)-(3*S*,5*R*,6*R*,1′*S*)-3-(1′-Hydroxy-3′-methylbut-3′-en-1′-yl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-one [(3*S*,5*R*,6*R*,1′*S*)-9]: The pure enantiomer was prepared according to the procedure reported for the racemic mixture, starting from (*R*,*R*)-**6**. $[\alpha]_D^{20}$ = –161 (*c* = 0.78, $CHCl_3$).

5,6-Dimethoxy-3-(1′-methoxy-3′-methylbut-3′-en-1′-yl)-5,6-dimethyl-1,4-dioxan-2-one (*rac*-10): 1,8-Bis(dimethylamino)naphthalene (947 mg, 4.42 mmol; proton sponge) and Me_3OBF_4 (436 mg, 2.95 mmol) were added in one portion to a stirred solution of aldol product *rac*-**9** (808 mg, 2.95 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temp. overnight. Subsequently, small portions of the proton sponge and Me_3OBF_4 were added every 12 h, until the reaction was complete (as judged by TLC). In total, 3.0 equiv. of base and 2.2 equiv. of the methylating reagent were used over a period of 3 d. Afterwards, the mixture was filtered through a plug of Celite®, concentrated under reduced pressure and purified by flash column chromatography (eluent: petroleum ether/ethyl acetate, 90:10). The ether *rac*-**10** was obtained as a clear, colourless liquid (809 mg, 2.80 mmol, 95%). R_f = 0.44 (petroleum ether/ethyl acetate, 80:20). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.43 (s, 3 H, Me), 1.49 (s, 3 H, Me), 2.98 (s, 3 H, CH_2=C*Me*), 2.12 (dd, $^3J_{2'a,1'}$ = 3.6, $^2J_{2'a,2'b}$ = 14.8 Hz, 1 H, 2′-H_a), 2.57 (ddd, $^4J_{2'b,4'H}$ = 0.8, $^3J_{2'b,1'}$ = 9.6, $^2J_{2'b,2'a}$ = 14.8 Hz, 1 H, 2′-H_b), 3.33 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.46 (s, 3 H, 1′-OMe), 3.87 (ddd, $^3J_{1',3}$ = 2.4, $^3J_{1',2'a}$ = 3.7, $^3J_{1',2'b}$ = 9.6 Hz, 1 H, 1′-H), 4.45 (d, $^3J_{3,1'}$ = 2.4 Hz, 1 H, 3-H), 4.82 (br., 2 H, 4′-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 16.9 (Me at C-5), 17.9 (Me at C-6), 22.7 (Me at C-3′), 38.8 (C-2′), 49.1 (OMe at C-5), 49.8 (OMe at C-6), 58.2 (OMe at C-1′), 71.1 (C-3), 80.8 (C-1′), 98.3 (C-5), 105.2 (C-6), 112.8 (C-4′), 142.5 (C-3′), 167.8 (C-2) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 2948, 1748 (C=O), 1379, 899 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 116 (100) [$C_6H_{12}O_2$]$^+$, 101 (93) [$C_5H_9O_2$]$^+$. $C_{14}H_{24}O_6$ (288.34): calcd. C 58.32, H 8.39; found C 58.35, H 8.39.

(–)-(3*S*,5*R*,6*R*,1′*S*)-5,6-Dimethoxy-3-(1′-methoxy-3′-methylbut-3′-en-1′-yl)-5,6-dimethyl-1,4-dioxan-2-one [(3*S*,5*R*,6*R*,1′*S*)-10]: The pure enantiomer was prepared according to the procedure reported for the racemic mixture, albeit starting from (3*S*,5*R*,6*R*,1′*S*)-**9**. $[\alpha]_D^{20}$ = –182 (*c* = 0.9, $CHCl_3$).

Methyl 2-Hydroxy-3-methoxy-5-methylhex-5-enoate (*rac*-11): In analogy to a literature procedure,[17b] ether **10** (1.43 g, 4.96 mmol) was diluted with dry MeOH (20 mL), and, after 5 min, *rac*-camphorsulfonic acid was added (1.21 g, 5.21 mmol). Stirring was continued at room temp. for 15 h. After full conversion (as judged by TLC), the mixture was extracted four times with CH_2Cl_2 (4 × 10 mL) against saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography (eluent: petroleum ether/ethyl acetate, 85:15) afforded the ester *rac*-**11** as a clear liquid (817 mg, 4.37 mmol, 88%). The data are in full agreement with those reported in the literature.[6] R_f = 0.19 (petroleum ether/ethyl acetate, 80:20). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.78 (s, 3 H, Me), 2.22 (ddd, $^4J_{4a,6}$ = 0.8, $^3J_{4a,3}$ = 6.0, $^2J_{4a,4b}$ = 14.5 Hz, 1 H, 4-H_a), 2.37 (ddd, $^4J_{4b,6}$ = 0.8, $^3J_{4b,3}$ = 7.4, $^2J_{4b,4a}$ = 14.5 Hz, 1 H, 4-H_a), 2.96 (d, $^3J_{OH,2}$ = 5.2 Hz, 1 H, OH), 3.45 (s, 3 H, OMe), 3.68 (ddd, $^3J_{3,2}$ = 2.8, $^3J_{3,4a}$ = 6.1, $^3J_{3,4b}$ = 7.5 Hz, 1 H, 3-H), 3.81 (s, 3 H, COO*Me*), 4.39 (dd, $^3J_{2,3}$ = 2.7, $^3J_{2,OH}$ = 5.2 Hz, 1 H, 2-H), 4.80 (br., 1 H, 6-H_a), 4.84 (br., 1 H, 6-H_b) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 22.7 (Me at C-5), 37.9 (C-4), 52.5 (COO*Me*), 58.3 (OMe at C-3), 71.8 (C-2), 81.4 (C-3), 113.3 (C-6), 141.8 (C-5), 173.0 (C-1) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 3463 (OH), 2951, 1735 (C=O), 1439, 1217, 1101 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 99 (100) [$C_6H_{11}O$]$^+$. $C_9H_{16}O_4$ (188.22): calcd. C 57.43, H 8.57; found C 57.22, H 8.49. The enantiomers were separated on an analytical scale by HPLC: Chiracel OD-H (4.6 × 250 mm), flow = 0.4 mL/min, λ = 202 nm, solvent: *n*-heptane/isopropyl alcohol 96:4, R_t [(*S*,*S*)-**11**] = 11.63 min and R_t [(*R*,*R*)-**11**] = 13.73 min. A small sample (1 μL) of the product (*S*,*S*)-**16** (see below) was treated with diazomethane solution in diethyl ether to determine the *ee* through its ester.

(+)-(2*S*,3*S*)-2-Hydroxy-3-methoxy-5-methylhex-5-enoic Acid [(*S*,*S*)-5]: The diacetal (3*S*,5*R*,6*R*,1′*S*)-**10** (100 mg, 0.35 mmol) was placed in a reaction flask and diluted with THF (1.5 mL) before a 1 N aqueous HCl stock solution (500 μL) was added. The mixture was stirred at room temp. for 3 d before it was diluted with water (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 50:50 + 1 vol.-% acetic acid) gave the desired acid (*S*,*S*)-**5** (52 mg, 0.30 mmol, 86%) as a clear liquid. The data obtained are in full agreement with those reported in the literature.[5] R_f = 0.23 (petroleum ether/ethyl acetate/acetic acid 49.5:49.5:1). $[\alpha]_D^{22}$ = +21.6 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.80 (s, 3 H, CH_2=C*Me*), 2.31 (dd, $^3J_{4a,3}$ = 5.4, $^2J_{4a,4b}$ = 14.6 Hz, 1 H, 4-H_a), 2.42 (dd, $^3J_{4b,3}$ = 7.5, $^2J_{4b,4a}$ = 14.5 Hz, 1 H, 4-H_b), 3.49 (s, 3 H, OMe), 3.74 (ddd, $^3J_{3,2}$ = 4.0, $^3J_{3,4a}$ = 5.3, $^3J_{3,4b}$ = 7.6 Hz, 1 H, 3-H), 4.41 (d, $^3J_{2,3}$ = 3.9 Hz, 1 H, 2-H), 4.84 (br., 1 H, 6-H_a), 4.88 (br., 1 H, 6-H_b) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 22.8 (Me at C-5), 37.5 (C-4), 58.1 (OMe at C-3), 70.9 (C-3), 81.0 (C-2), 114.0 (C-6), 141.2 (C-5), 174.5 (C-1) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 3408 (OH), 2934, 1724 (C=O), 1444, 1216, 1095, 892 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 118 (100) [$C_4H_6O_4$]$^+$.

Methyl 3-Methoxy-5-methyl-2-(triethylsilyloxy)hex-5-enoate (*rac*-12): Imidazole (309 mg, 4.53 mmol) was added to a stirred solution of alcohol *rac*-**11** (776 mg, 4.12 mmol) in dry CH_2Cl_2 (6 mL). After the base had dissolved completely, the solution was cooled to 0 °C, and chlorotriethylsilane (622 mg, 4.12 mmol) was added dropwise through a syringe. The mixture was warmed to room temp. overnight, filtered through a plug of Celite® and concentrated under reduced pressure. Flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 98:2) afforded the protected

alcohol *rac*-**12** as a colourless liquid (990 mg, 3.62 mmol, 80%). R_f = 0.73 (petroleum ether/ethyl acetate, 95:5). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.62 (q, $^3J_{1',2'}$ = 7.4 Hz, 6 H, 1′-H), 0.96 (t, $^3J_{2',1'}$ = 7.7 Hz, 9 H, 2′-H), 1.78 (s, 3 H, Me), 2.28 (d, $^3J_{4,3}$ = 6.5 Hz, 2 H, 4-H), 3.39 (s, 3 H, OMe), 3.6 (ddd, $^3J_{3,2}$ = 4.3, $^3J_{3,4a}$ = 5.4, $^3J_{3,4b}$ = 7.0 Hz, 1 H, 3-H), 3.74 (s, 3 H, COO*Me*), 4.29 (d, $^3J_{2,3}$ = 4.3 Hz, 1 H, 2-H), 4.81 (br., 2 H, 6-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 4.6 (C-1′), 6.7 (C-2′), 22.8 (Me at C-5), 38.9 (C-4), 51.8 (COO*Me*), 58.4 (OMe at C-3), 73.5 (C-3), 82.1 (C-2), 112.8 (C-6), 142.5 (C-5), 172.6 (C-1) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 2954, 2878, 1750 (C=O), 1365, 1111, 725 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 302 (1) $[M]^+$, 273 (21) $[M - C_2H_5]^+$, 99 (100) $[C_6H_{11}O]^+$. $C_{15}H_{30}O_4Si$ (302.48): calcd. C 59.56, H 10.00; found C 59.19, H 9.87.

Methyl 2-(*tert*-Butyldiphenylsilyloxy)-3-methoxy-5-methylhex-5-enoate (*rac*-13): Imidazole (111 mg, 1.63 mmol) was added to a stirred solution of alcohol *rac*-**11** (279 mg, 1.48 mmol) in dry CH_2Cl_2 (3 mL). After the base had dissolved completely, the solution was cooled to 0 °C, and *tert*-butylchlorodiphenylsilane (428 mg, 1.56 mmol) was added dropwise through a syringe. The mixture was warmed to room temp. overnight, filtered through a plug of Celite® and concentrated under reduced pressure. Flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 98:2) afforded the protected alcohol *rac*-**13** as a colourless oil (469 mg, 1.10 mmol, 74%). R_f = 0.56 (petroleum ether/ethyl acetate, 85:5). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.12 (s, 9 H, C*Me*$_3$), 1.70 (s, 3 H, Me), 2.24 (ddd, $^4J_{4a,6}$ = 0.6, $^3J_{4a,3}$ = 4.3, $^2J_{4a,4b}$ = 15.3 Hz, 1 H, 4-H$_a$), 2.36 (ddd, $^4J_{4b,6}$ = 0.7, $^3J_{4b,3}$ = 8.7 H, $J_{4b,4a}$ = 15.3 Hz, 1 H, 4-H$_b$), 3.29 (s, 3 H, OMe), 3.47 (s, 3 H, COO*Me*), 3.58 (ddd, $^3J_{3,2}$ = 3.0, $^3J_{3,4a}$ = 4.3, $^3J_{3,4b}$ = 8.7 Hz, 1 H, 3-H), 4.35 (d, $^3J_{2,3}$ = 3.0 Hz, 1 H, 2-H), 4.72–4.77 (m, 2 H, 6-H), 7.32–7.46 (m, 6 H, arom. H), 7.65–7.70 (m, 4 H, arom. H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 19.4 (*C*Me$_3$), 22.7 (Me at C-5), 26.8 (C*Me*$_3$), 38.9 (C-4), 51.5 (COO*Me*), 58.2 (OMe at C-3), 73.9 (C-3), 82.4 (C-2), 112.6 (C-6), 127.5 (arom. CH), 127.6 (arom. CH), 129.8 (arom. CH), 133.0 (arom. CH), 133.1 (arom. C$_{ipso}$), 136.1 (arom. CH), 142.4 (C-5), 171.8 (C-1) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 3073, 2932, 2858, 1759 (C=O), 1428, 1106, 700 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 369 (31) $[M - C_4H_9]^+$, 99 (56) $[C_6H_{11}O]^+$. $C_{25}H_{34}O_4Si$ (426.62): calcd. C 70.38, H 7.99; found C 70.27, H 8.03.

1,3-Dimethoxy-5-methyl-1-oxohex-5-en-2-yl Benzoate (*rac*-14): NEt_3 (23.9 mg, 0.24 mmol), BzCl (33.2 mg, 0.24 mmol) and DMAP (2.39 mg, 0.02 mmol) were added to a stirred solution of alcohol *rac*-**11** (37 mg, 0.19 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was warmed to room temp. overnight. Because no complete conversion was detected (TLC), the mixture was cooled to 0 °C, and additional small portions of NEt_3 (19.8 mg, 0.19 mmol), BzCl (27.5 mg, 0.19 mmol) and DMAP (2.39 mg, 0.02 mmol) were added. After complete conversion (as judged by TLC), the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (2 mL) and extracted three times with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography on silica (eluent: petroleum ether/ethyl acetate, 98:2) gave the desired diester as a clear liquid (53 mg, 0.18 mmol, 95%). The spectroscopic data obtained are in full agreement with those reported in the literature.[4a,8,10] R_f = 0.15 (*n*-pentane/ethyl acetate, 98:2). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.80 (s, 3 H, CH_2=C*Me*), 2.41 (dd, $^3J_{4a,3}$ = 5.1, $^2J_{4a,4b}$ = 14.6 Hz, 1 H, 4-H$_a$), 2.52 (dd, $^3J_{4b,3}$ = 8.1, $^2J_{4b,4a}$ = 14.6 Hz, 1 H, 4-H$_b$), 3.50 (s, 3 H, OMe), 3.79 (s, 3 H, COO*Me*), 3.92 (ddd, $^3J_{3,2}$ = 2.7, $^3J_{3,4a}$ = 5.2, $^3J_{3,4b}$ = 8.1 Hz, 1 H, 3-H), 4.86 (br., 2 H, 6-H), 5.55 (d, $^3J_{2,3}$ = 2.7 Hz, 1 H, 2-H), 7.47 (m$_c$, 2 H, arom. H), 7.60 (m$_c$, 1 H, arom. H), 8.10 (m$_c$, 2 H, arom. H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 22.7 (Me at C-5), 39.1 (C-4), 52.4 (COO*Me*), 58.3 (O*Me* at C-3), 73.3 (C-2), 79.5 (C-3), 113.5 (C-6), 128.5 (arom. CH), 129.3 (arom. C$_{ipso}$), 130.0 (arom. CH), 133.5 (arom. CH), 141.5 (C-5), 165.8 (C-1′), 168.6 (C-1) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 2955, 2929, 1724 (C=O), 1602, 1263, 1110, 893 cm^{-1}. MS (ESI): *m*/*z* (%) = 315 (100) $[M + Na]^+$. The enantiomeric excess was determined by HPLC: column = Chiracel OD-H (4.6 × 250 mm), flow = 0.5 mL/min, λ = 225 nm, solvent: *n*-heptane/isopropyl alcohol 95:5, R_t [(*S*,*S*)-**14**] = 14.4 min and R_t [(*R*,*R*)-**14**] = 16.8 min.

(+)-(2*S*,3*S*)-1,3-Dimethoxy-5-methyl-1-oxohex-5-en-2-yl Benzoate [(*S*,*S*)-14]: The (*S*,*S*) enantiomer was prepared according to the procedure reported for the racemic mixture. $[\alpha]_D^{20}$ = +15 (*c* = 0.16, $CHCl_3$).

Methyl 3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enoate (*rac*-15): *n*Bu_4NI (196 mg, 0.53 mmol) was added in one portion to a stirred solution of *p*-methoxybenzyl bromide (801 mg, 3.99 mmol) in DMF (12 mL). The mixture was stirred at room temp. for 2 h and was then cooled to –50 °C. Then methyl psymberate (*rac*-**11**) (500 mg, 2.66 mmol) was added through a syringe, followed by solid NaH (80.0 mg, 3.32 mmol). Stirring was continued for 20 h allowing the mixture to warm to room temp. After completion of the reaction (as judged by TLC), the mixture was extracted four times with CH_2Cl_2 (4 × 10 mL) against saturated aqueous $NaHCO_3$ solution, dried with $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent purification with flash column chromatography (eluent: petroleum ether/ethyl acetate, 95:5) gave the product *rac*-**15** as a colourless oil (778 mg, 3.79 mmol, 95%). The data are in full agreement with those reported in the literature.[6] R_f = 0.54 (petroleum ether/ethyl acetate, 80:20). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.74 (s, 3 H, Me), 2.30 (dd, $^3J_{4a,3}$ = 4.8, $^2J_{4a,4b}$ = 14.6 Hz, 1 H, 4-H$_a$), 2.35 (dd, $^3J_{4b,3}$ = 7.8, $^2J_{4b,4a}$ = 14.6 Hz, 1 H, 4-H$_b$), 3.34 (s, 3 H, OMe at C-3), 3.66 (ddd, $^3J_{3,2}$ = 4.5, $^3J_{3,4a}$ = 4.7, $^3J_{3,4b}$ = 7.8 Hz, 1 H, 3-H), 3.76 (s, 3 H, COO*Me*), 3.80 (s, 3 H, OMe), 4.05 (d, $^3J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 4.40 (d, $^2J_{1'a,1'b}$ = 11.5 Hz, 1 H, 1′-H$_a$), 4.65 (d, $^2J_{1'b,1'a}$ = 11.5 Hz, 1 H, 1′-H$_b$), 4.76 (br., 1 H, 6-H$_a$), 4.80 (br., 1 H, 6-H$_b$), 6.87 (d, $^3J_{3',4'}$ = 8.6 Hz, 2 H, arom. H), 7.28 (d, $^3J_{4',3'}$ = 8.6 Hz, 2 H, arom. H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 22.8 (Me at C-5), 39.0 (C-4), 51.9 (COO*Me*), 55.3 (OMe), 58.2 (OMe at C-3), 72.3 (C-1′), 79.0 (C-3), 80.8 (C-2), 113.0 (C-6), 113.8 (arom. CH), 129.4 (arom. C$_{ipso}$), 129.8 (arom. CH), 142.2 (C-5), 159.4 (arom. C$_{ipso}$), 171.6 (C-1) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 2937, 2836, 1746 (C=O), 1613, 1514, 1247, 1103, 1033, 821 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 308 (4) $[M]^+$, 253 (6) $[C_{13}H_{17}O_5]^+$, 207 (43), 187 (8) $[C_9H_{15}O_4]^+$, 121 (100) $[C_8H_9O]^+$, 99 (5) $[C_6H_{11}O]^+$. $C_{17}H_{24}O_5$ (308.37): calcd. C 66.21, H 7.84; found C 66.43, H 7.94.

Representative Procedure for the Enzyme-Screening (*rac*-11, *rac*-14, *rac*-15): A sample (1 mL) was removed from a stock solution of the enzyme (1 mg/mL) and added to the substrate (2 mg in *n*-heptane, 1 mL) in a 2 mL Eppendorf vial. The mixture was vigorously shaken with a Thermomix at 40 °C and 1400 rpm. After defined periods of time (1, 2, 6 and 24 h), aliquots (15 μL) were taken from the organic layer, diluted with *n*-heptane (300 μL) and extracted against saturated aqueous $NaHCO_3$ solution (500 μL). After effervescence had ceased and the layers separated, a sample (150 μL) was removed from the organic phase and analysed by HPLC (injection volume: 5 μL).

Enzymatic Kinetic Resolution of Methyl 3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enoate (*rac*-15): The esterase 001 (48 mg, 3.2 U/mg) was added to a stirred solution of *rac*-**15** (109 mg,

0.35 mmol) in potassium phosphate buffer (10 mL of a 100 mM solution; pH = 8.0) at room temp. The reaction was monitored (pH electrode) and the pH kept constant (at pH 8.0) by adding small amounts of a 1 N NaOH stock solution. Small samples were taken to determine the *ee* of the substrate (*R*,*R*)-**15**. After 65 h, the reaction was complete. The reaction mixture was diluted with a saturated aqueous $NaHCO_3$ solution (50 mL) and extracted three times with petroleum ether (3 × 10 mL), acidified to pH = 2.0 with a 2 N aqueous HCl solution and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The pale-yellow oil was further purified by flash column chromatography with a gradient (eluent: petroleum ether/ethyl acetate, 80:20 to 50:50 + 1 vol.-% acetic acid) to yield the ester (*R*,*R*)-**15** (52 mg, 0.17 mmol, 49%) and the acid (*S*,*S*)-**16** (49 mg, 0.17 mmol, 47%) as colourless oils. The spectroscopic data for (*R*,*R*)-**15** are in agreement with those reported for the racemic compound *rac*-**15** (see above): $[\alpha]_D^{29}$ = +53 (*c* = 0.4, $CHCl_3$; *ee* > 94%) and $[\alpha]_D^{29}$ = +58 (*c* = 0.3, $CHCl_3$; *ee* >99%) {ref.[6] $[\alpha]_D^{29}$ = –57 [*c* = 0.7, $CHCl_3$; for the (*S*,*S*) enantiomer]}. The data for (*S*,*S*)-**16** are full in agreement with those reported in literature.[6] R_f = 0.18 (petroleum ether/ethyl acetate/acetic acid, 49.5:49.5:1). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.74 (s, 3 H, Me), 2.26 (dd, $^3J_{4a,3}$ = 5.5, $^2J_{4a,4b}$ = 14.5 Hz, 1 H, 4-H_a), 2.41 (dd, $^3J_{4b,3}$ = 7.9, $^2J_{4b,4a}$ = 14.4 Hz, 1 H, 4-H_b), 3.42 (s, 3 H, OMe), 3.75 (ddd, $^3J_{3,2}$ = 3.0, $^3J_{3,4a}$ = 5.5, $^3J_{3,4b}$ = 8.0 Hz, 1 H, 3-H), 3.81 (s, 3 H, OMe), 4.15 (d, $^3J_{2,3}$ = 3.0 Hz, 1 H, 2-H), 4.57 (d, $^2J_{1'a,1'b}$ = 11.3 Hz, 1 H, 1′-H_a), 4.68 (d, $^2J_{1'b,1'a}$ = 11.3 Hz, 1 H, 1′-H_b), 4.81 (br., 2 H, 6-H), 6.89 (d, $^3J_{3',4'}$ = 8.7 Hz, 2 H, arom. H), 7.29 (d, $^3J_{4',3'}$ = 8.7 Hz, 2 H, arom. H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25 °C): δ = 22.7 (Me at C-5), 38.5 (C-4), 55.3 (OMe), 58.4 (OMe at C-3), 72.9 (C-1′), 78.3 (C-3), 80.9 (C-2), 113.5 (C-6), 114.0 (arom. CH), 128.7 (arom. C_{ipso}), 129.9 (arom. CH), 141.6 (C-5), 159.7 (arom. C_{ipso}), 173.1 (C-1) ppm. IR (ATR, film): $\tilde{\nu}_{max}$ = 2936, 2837, 1723 (C=O), 1612, 1586, 1513, 1247, 1103, 1032, 820 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 121 (100) $[C_8H_9O]^+$, 99 (70) $[C_6H_5O]^+$. The enantiomeric excess was determined by HPLC: A small sample (1 μL) of the product (*S*,*S*)-**16** was treated with diazomethane solution in diethyl ether to yield the ester **15**; column = Chiracel OD-H (4.6 × 250 mm), flow = 0.7 mL/min, λ = 202 nm, solvent: *n*-heptane/isopropyl alcohol, 98:2, R_t [(*S*,*S*)-**15**] = 10.80 min and R_t [(*R*,*R*)-**15** = 15.55 min]. $[\alpha]_D^{27}$ = –24.4 (*c* = 0.62, $CHCl_3$; *ee* 98%) {ref.[6] $[\alpha]_D^{27}$ = –25.9 [*c* = 1.1, $CHCl_3$; for the (*S*,*S*) enantiomer]}.

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[19] Enzymes used and their suppliers: Codexis: esterase BS1 (*Bacillus subtilis*), esterase BS2 (*Bacillus subtilis*), esterase BS3 (*Bacillus subtilis*), esterase SD (*Streptomyces diastatochromogenes*), esterase 001, esterase 003, esterase 004, and pig liver esterase (PLE). Fluka: *Candida antarctica* lipase B (CAL-B), hog pancreas lipase (PPL), amano lipase PS (*Burkholderia cepacia*), *Rhizopus oryzaea* esterase (RO), *Rhizopus oryzaea* lipase, and *Candida rugosa* lipase (CRL). Roche diagonostics: esterase E1 (pig liver esterase), lipase L1 (*Burkholderia cepacia*), lipase L3 (*Candida rugosa*), lipase L5 (*Candida antarctica* lipase A), lipase L8 (*Thermomyces lanuginosa*), and lipase L10 (*Alcaligenes sp.*).
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