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A highly efficient chemoselective synthesis of 3,5-diketoesters by lipase-catalyzed transesterification: application to the resolution of secondary alcohols

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Abstract

A large number of 3,5-diketoesters have been synthesized by an immobilized lipase-catalyzed transesterification reaction. Excellent yields and chemoselectivity were observed. The immobilized lipase could be reused without significant loss of activity up to three reaction cycles. The same enzyme system has been used for resolution of secondary alcohols. Overall good chemical and optical yield were observed.

Keywords: 3,5-Diketoesters; Enzymatic transesterification; Thermostable lipase; Enantioselectivity

1. Introduction

Many of the aromatic compounds found in nature arise from acetate via poly-β-carbonyl intermediates. 3,5-Diketo acids and their esters are one such class of compound which act as a important intermediates for the biosynthesis of many polyketide-derived aromatic natural products [1]. The acids and the corresponding esters can be prepared by hydrolysis of triacetic lactone and other 4-hydroxy-2-pyrones [2–8] and are relatively stable at room temperature. Whereas chemical synthesis of methyl and ethyl 3,5-dioxohexanoates have been published, the synthesis of allylic, propargylic, and benzylic poly-β-ketoesters are not represented in the chemical literature. Cordova and Janda [9] reported the synthesis of several β-ketoesters by CAL-B catalyzed transesterification at low pressure (10 Torr) and at 40 °C. The use of low pressure allowed easy removal of MeOH and EtOH generated from the starting β-ketoesters, making the reaction irreversible and preventing inhibition of lipase by MeOH and EtOH. Generally, the reactions were carried out in a rotary evaporator or in a vacuum oven which needs continuous attention when the reaction time is long. In this paper, we describe the lipase-catalyzed transesterification reaction of 3,5-diketoesters with numerous alcohols having different functionality (Scheme 1) at atmospheric pressure and 50 °C. A set of immobilized lipases was used as the transesterifying agent.

The resolution of secondary alcohols is a very important organic transformation in the area of asymmetric synthesis and numerous chemical and biochemical methods for resolution are well documented in the literature for the above process, still new reports are coming in the literature addressing various issues of the above process. In this article, we also describe how resolution of secondary alcohols can be achieved via transesterification with 3,5-diketoesters using immobilized lipase.

2. Results and discussion

2.1. Enzyme preparation

The immobilization of lipases allows for their recycling and reuse in a continuous fashion. Sol–gel encapsulation has proven to be a particularly easy and useful way to immobilize enzymes. We have followed the method developed by Reetz et al. [10]. It involves the acid or base catalyzed hydrolysis of alkoxy silanes in the presence of enzyme. Mechanistically, the silane precursor undergoes hydrolysis and cross-linking

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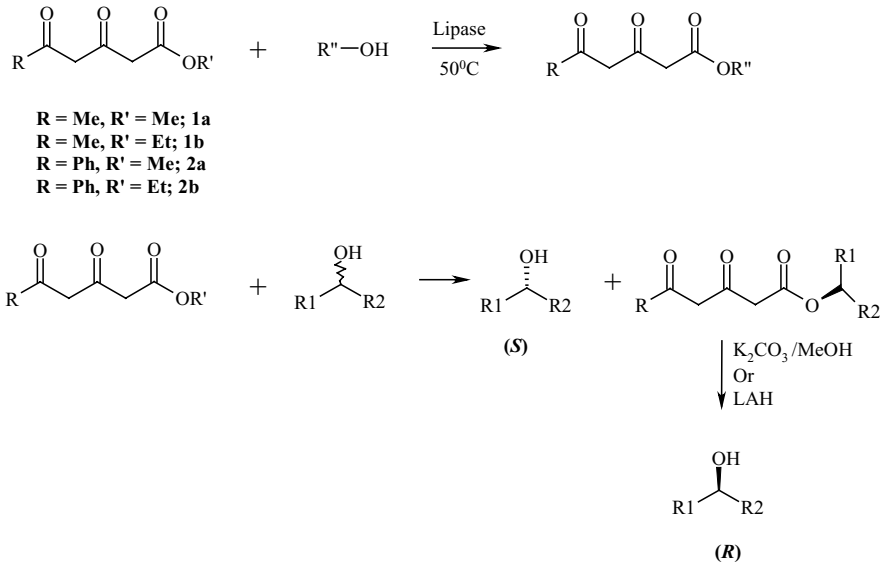


Scheme 1. Transesterification of 3,5-diketoesters with lipase.

condensation with formation of a SiO_2 matrix in which the enzyme is encapsulated [11].

$$\mathrm{RSi(OMe)_3} + \underset{\text{(TMOS)}}{\mathrm{Si(OMe)_4}} \xrightarrow[\text{lipase}]{\text{hydrolysis}} \text{Immoblized lipase} \quad (\mathrm{R} = {}^{n}\mathrm{C_3H_7}\ \text{(PTMS)},\ \mathrm{R} = {}^{n}\mathrm{C_4H_9}\ \text{(BTMS)},\ \mathrm{R} = {}^{i}\mathrm{C_4H_9}\ \text{(}i\text{BTMS)})$$

The gel precursor was prepared from a mixture of tetramethylorthosilicate (TMOS) and alkyltrimethoxysilanes of the type $RSi(OMe)_3$ having non-hydrolysable alkyl groups. In their original work Reetz et al. had observed an alkyl effect, i.e. enhancement of lipase activity upon using $RSi(OMe)_3$ in the series Me < Et < ^{n}Pr < ^{n}Bu. In our experiments, we have used mainly three alkyltrimethoxysilanes PTMS, BTMS, and ^{i}BTMS. PVA was used as an additive, and may have a stabilizing effect on lipase [12]. CRL and WGL both were immobilized on the above procedure. PPL was immobilized on celite and hyflosupercel support by adsorption [13,14]. Where as CAL-B immobilized on macroporus acrylic resin was available from commercial source.

The transesterifications were performed using different primary alcohols and secondary alcohols as acyl acceptors and 3,5-diketosters (**1a–b**, **2a–b**) as acyl donors. The reaction was performed under an argon atmosphere and at 50 °C, at atmospheric pressure (see Section 4) without solvent. The reaction was run at temperatures ranging from 40 to 80 °C, however, the best yield was obtained at 50 °C in almost all cases. We also carried out the reaction at low pressure, but the yield and rate of reaction remained unaltered. Increasing the reaction temperature drastically reduces the yield, whereas at room temperature (25 °C) the reaction time was greatly increased.

2.2. Transesterification of primary alcohols

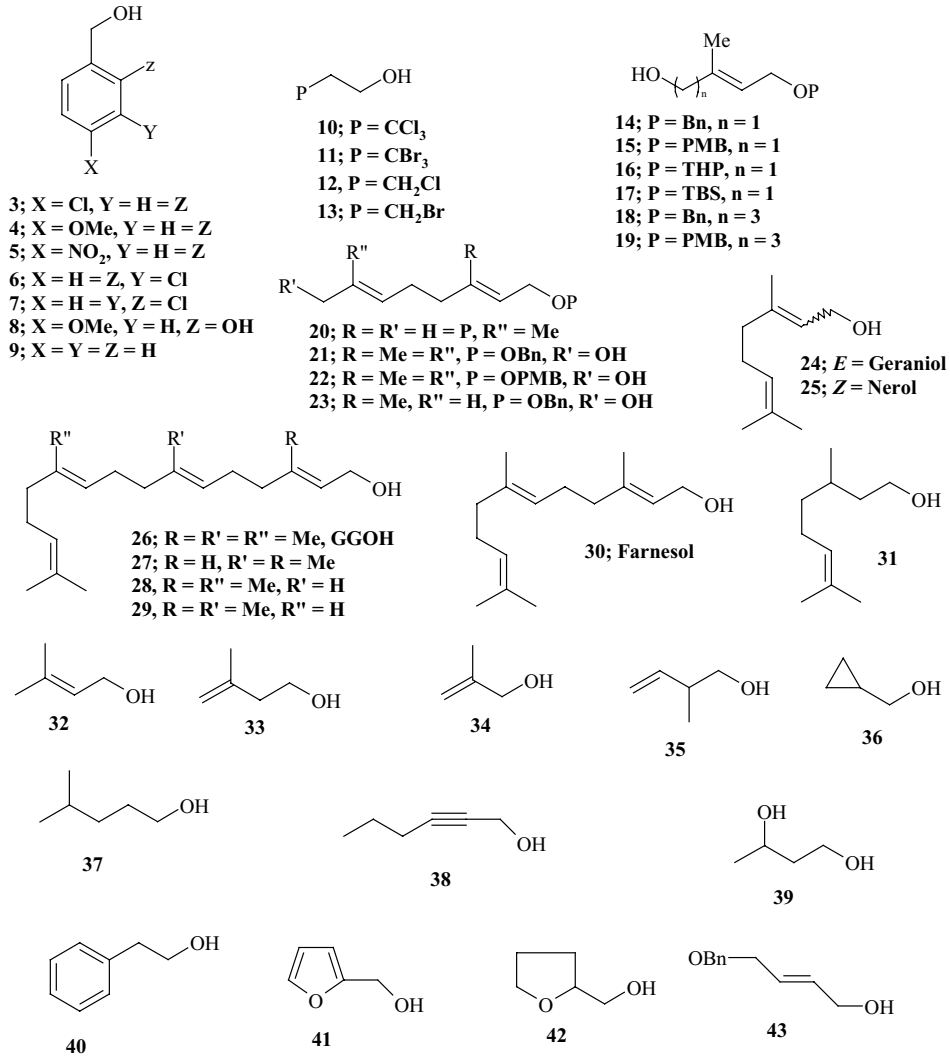
A large set of structurally diverse primary alcohols (**3–43**, Scheme 2) was tested for the transesterification reaction. Based on these results, the following observations and conclusions were made.

(1) The best yield of transesterification was observed with CAL immobilized on macroporus acrylic resin and CRL entrapped in a sol–gel matrix (all the three alkyltrimethoxysilane/TMOS, Table 1). In Table 1, the chemical yield and reaction time for the transesterification reaction of benzyl alcohol and 3,5-diketoesters (**1a**, **2a**) with different lipase systems is included. It was observed that lipase from porcine pancreas (immobilized on celite and hyflosupercel) and wheat germ lipase took longer reaction times and moderate chemical yields were also observed compared with the CAL-B and CRL catalyzed reactions.

Table 1
Transesterification of benzylalcohol (9) with different lipase systems

Entry	Lipase	Support for immobilization	Time (h)	Yield (%)
1	CAL[a]	Macroporus acrylic resin	10.5	83
2	CRL[b]	Gel (TMOS:PTMS, 1:5)	10	82
3	PPL[c]	Celite	16	32
4	PPL	Hyflosupercel	17	36
5	WGL[d]	Gel (TMOS:PTMS, 1:5)	14	52

[a] *Candida antarctica* lipase (lipolase, recombinant *Candida antarctica* was obtained from Sigma Co.).
[b] *Candida rugosa* lipase (type VII, crude was obtained from Sigma Co.).
[c] Porcine pancreatic lipase (crude, type II was obtained from Sigma Co.).
[d] Wheat germ lipase (type I, lyophilized powder was obtained from Sigma Co.).



Scheme 2. Set of primary alcohols for transesterification reaction.

(2) High chemoselectivity was observed in the transesterification of **8**. Exclusive formation of one product indicates chemoselectivity for alkyl alcohols compared to phenols. Chemoselectivity between primary and secondary alcohols was also examined in the case of **39**. It was observed that the primary alcohol reacts faster but, after some time the secondary alcohol begins to react.

(3) Substitution pattern in the aromatic ring largely affects the rate of the reaction. It was observed that the presence of –OH and –Cl groups at *o*-, *m*-, and *p*-positions have a minor effect on the reaction rate, whereas the presence of a *p*-OMe group enhances the reaction rate as observed in the case of 4-methoxy benzyl alcohol (Table 2). The polar *p*-NO_2 group was found to be an unfavorable substituent as 4-nitrobenzyl alcohol reacted extremely slow. It is suggested that the non-polar environment of the acyl binding pocket in the active site of lipase does not allow a polar –NO_2 group in its vicinity.

(4) It was observed that aliphatic alcohols containing Cl, Br, CCl_3, and CF_3 substituents (**10**–**13**) were very poor substrates as compared to their non-halogenated counterparts (Table 2). Probably, there are unfavorable interactions between the π-electron system of the tryptophan (or some other residue inside the pocket) and the halogen containing groups [15].

(5) Alcohols having *E*-geometry reacted faster than the *Z* counterparts as observed in the case of geraniol and nerol. Geraniol reacts 2.5 times faster than nerol under same reaction conditions, whereas all *trans* farnesol (**30**), all *trans* geranyl-geraniol (**26**) and nor-methyl all *trans* geranyl-geraniol (**27**–**29**) react rapidly (Table 2).

(6) Alcohols containing several protecting groups, e.g. benzyl, *p*-methoxybenzyl, tetrahydropyranyl, tert-butyldimethylsilyl (**14**–**19**, **21**–**23**, **43**) are good substrates for the transesterification reaction (Table 2), indicating that the enzyme system is compatible with different functional groups.

Table 2
Transesterification reaction with lipase[a] of 3,5-diketoesters[b]

Entry	Substrate	Time (h)	Yield (%)
1	**3**	9.5	78
2	**4**	8	82
3	**5**	16	55
4	**8**	9	84
5	**9**	10	80
6	**12**	20	5
7	**14**	10	82
8	**15**	10.5	76
9	**18**	12	72
10	**19**	10	62
11	**20**	9.5	80
12	**21**	10.5	83
13	**22**	14	80
14	**23**	12.5	76
15	**24**	8	82
16	**25**	18	84
17	**26**	7	85
18	**28**	9	82
19	**30**	10	78
20	**31**	12	84
21	**32**	8	88
22	**33**	9	86
23	**34**	10	68
24	**35**	13	82
25	**36**	14	72
26	**37**	24	78
27	**38**	12.5	83
28	**39**	14	58
29	**40**	10	78
30	**41**	10	92
31	**42**	11	84
32	**43**	14.5	73

[a] CAL immobilized on macroporus acrylic resin and CRL immobilized on sol–gel matrix (derived from different silane) were used as transesterification reagent. PPL immobilized on celite, hyflosupercel and WGL immobilized on sol–gel matrix gave poor results.

[b] All four 3,5-diketoesters (**1a–b**, **2a–b**) provided almost same result in terms of yield and reaction time.

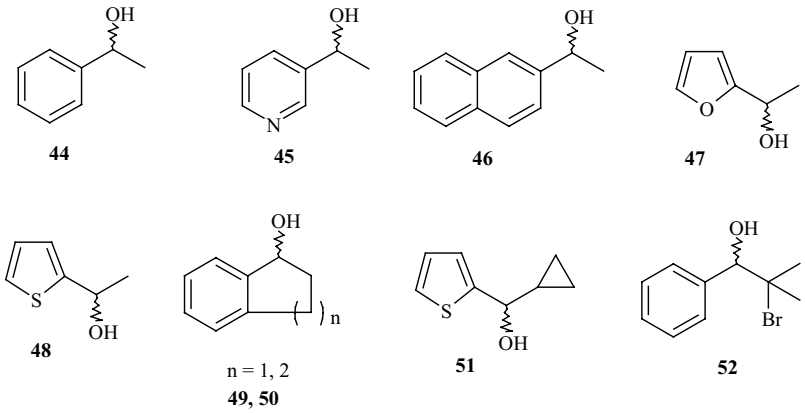
(7) We have not studied the enantioselectivity of the transesterification reaction for alcohols **31**, **35**, and **42**.
(8) In almost all the cases, the final product is rich in enol isomers as determined by NMR (^{1}H and ^{13}C).

2.3. Resolution of secondary alcohols

Based on the preliminary results obtained in the lipase-catalyzed transesterification reaction of primary alcohols with diketoestes, a set of secondary alcohols (**44**–**52**) was chosen for the resolution experiment (Scheme 3). The selected lipases are CRL and CAL-B as both provided excellent chemical yield in the transesterification reaction of primary alcohols. In a typical resolution process, the racemic alcohols were treated with immobilized lipase and 3,5-diketoesters (see Section 4 for details) at 50 °C for the desired reaction time. The reaction was monitored by TLC after certain intervals. After the usual workup unreacted alcohol and esterified alcohols were separated by preparative TLC. It was already well established that (*R*)-enantiomer of the alcohol reacts faster with enzyme (mainly lipase from Candida source) in a transesterification reaction. In our case also the same effect was observed, and we also determined the absolute configuration of both the alcohols using NMR and optical rotation measurement. The (*R*)-alcohols were released from the ester by hydrolysis with K_2CO_3/MeOH or reduction with LAH. Hence, both the enantiomers were obtained with easy separation. The reaction temperature of 50 °C allowed easy removal of MeOH and EtOH generated from the starting 3,5-diketoesters, making the reaction irreversible and preventing inhibition of lipase by MeOH and EtOH. An empirical rule to predict which enantiomer of secondary alcohols reacts faster in lipase (Candida type) catalyzed reaction was proposed by Bornscheuer and Kazlauskas [16]. The rule is based on the size of the substituents and suggest that lipases distinguish between enantiomeric secondary alcohols primarily by comparing the sizes of two substituents. All of our substrates (**44**–**50**) fit perfectly into the model. The best enzyme system for the resolution was CAL-B and CRL (sol–gel matrix), where as PPL and WGL both lead to poor *E* values. The excellent enantioselectivity ("*E*" value) observed with CAL-B can be best explained as it is a pure recombinant immobilized preparation of a thermostable lipase. Where as the other three lipases are immobilized forms of commercial mixtures of isoforms. Hence, these enzyme mixtures (exclude CRL) lead to poor enantioselectivity when compared to the pure recombinant enzyme. The reason why immobilized (sol–gel matrix) form of CRL-isoenzymes show good enantioselectivity is unclear to us. Among the transesterifying agents all the diketoesters react equally well.

2.4. Determination of enantiomeric excess and configuration from NMR

The enantioselectivity for the transesterification reaction of secondary alcohols were measured by NMR. After the transesterification experiment, slow reacting alcohol and the fast reacting alcohol (released from the ester) were both derivatized with optically pure *ortho*-fluoroaryllacticacids and their NMR spectra was recorded. Being diastereomeric in nature the ester shows clear differences in chemical shift (ppm) between certain pairs of protons in the ^{1}H NMR spectrum. The integral ratio of a particular protons in the spectra of diastereomeric esters derived from alcohols (enantiomerically rich with one isomer) determines the enantioselectivity of the reaction. The chiral derivatized agent *ortho*-fluorinatedaryllacticacids were easily prepared from easily available starting materials [17]. The optical purity of synthesized CDA was analyzed as reported earlier using NMR [18]. The alcohols were derivatized with FAC acid by treatment with EDCI/DMAP at 0 °C [19]. No racemization was observed under the above mentioned



Scheme 3. Set of secondary alcohols used in the resolution experiment.

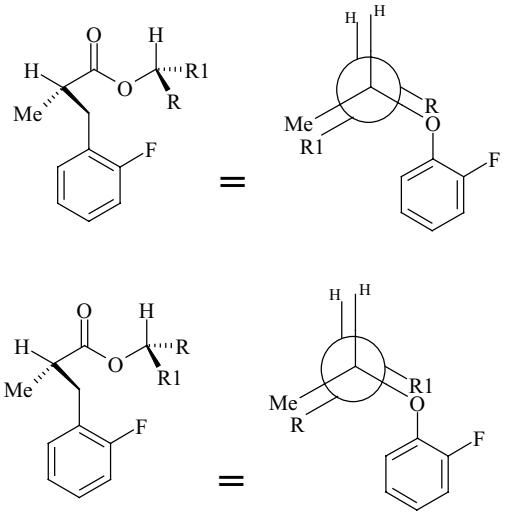
Table 3
Transesterification of **44**–**52** with **1a** and CAL-B

Entry	Alcohol	Conversion (C)	Time (h)	*R*-ester		*S*-alcohol		*E*[b]
				e.e.$_p$[a]	Yield (%)	e.e.$_s$[a]	Yield (%)	
1	**44**	**49**	10	95	48	90	42	130
2	**45**	**50**	12	92	42	94	39	81
3	**46**	**49**	10.5	96	40	93	41	163
4	**47**	**48**	14	95	40	90	49	114
5	**48**	**48**	16	90	38	84	44	50
6	**49**	**49**	10	96	45	91	45	164
7	**50**	**48**	10	96	46	88	45	145
8	**51**	**49**	18	72	40	70	32	13
9	**52**	**43**	20	40	35	31	30	3.2

[a] e.e.$_s$ was calculated by NMR.
[b] Enantioselectivities of the reaction (*E*) [24] were determined using the "Selectivity" program developed by K. Faber, H. Hönig, and A. Kleewein, (http://www.cis.TUGraz.at/orgc/).

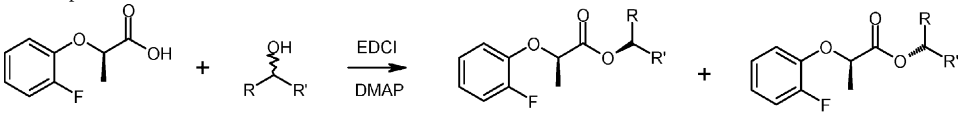
reaction conditions. The chemical and optical yields for the resolution experiment are listed in Table 3. Excellent enantioselectivity (*E* value) was observed in all cases, except for alcohols **51** and **52** where a contributing factor may be the similar size of two groups in these alcohols (Table 3).

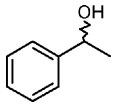
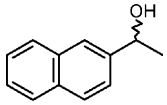
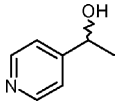
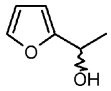
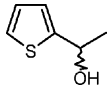
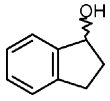
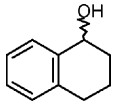
A model for the determination of the absolute configurations of alcohols has been reported previously [20] by preparing diastereomeric FAC esters. In this method, alcohols obtained in the resolution experiment, were derivatized with a single enantiomer of FAC (mainly *R*, due to low cost in preparation). The conformations of the diastereomeric esters are represented in an extended Newman projection formula (Scheme 4). It was shown by X-ray analysis and supported by NMR spectroscopy that the α-hydrogen of the FAC-acid as well as the α-hydrogen of the secondary alcohol is eclipsed with the carbonyl oxygen of ester (Scheme 4). The group eclipsing the aromatic ring (from FAC) experiences a ring current effect, and is therefore, shifted upfield in the proton-NMR spectrum. Consequently, in a pair of diastereomeric esters, one of the diastereomers will have the resonance of the R substituent shifted upfield and that of the R^1 substituent shifted downfield compared with the corresponding substituents of the other diastereomers. Excellent agreement was observed by comparing the NMR spectra of diastereomeric esters of alcohols



Scheme 4. Extended Newman projections of *O*-arylated lactic esters.

Table 4
NMR spectral data for the diastereomeric esters formed from the alcohols with *R*-FAC[a]



Entry	Alcohol	$\Delta\delta$ (–OC*H*RR′)	$\Delta\delta$ (–C*H*FAC)	$\Delta\delta$ (–*Me*FAC)	$\Delta\delta$[b] (other)
1		0.015	−0.015	−0.032	0.07 (–*Me*CHPh), −0.07 (aromaticzone)
2		0.072	0.056	0.03	0.122 (−*Me*CHNap)
3		0.016	0.01	0.015	0.095 (–*Me*CHPyr), −0.08, −0.2 (pyridine ring proton)
4		0.015	−0.016	−0.032	0.058 (–*Me*CHFur), −0.06 (furan ring proton)
5		0.012	−0.018	No separation	−0.06 (thiophene ring proton)
6		−0.06	No separation	−0.031	No separation
7		−0.048	0.011	No separation	No separation

[a] Only significant peaks for which baseline separation was observed are included.
[b] Chemical shift difference in ppm between *R*,*R* and *R*,*S* diastereomers recorded at room temperature at 500 MHz ($CDCl_3$).

(**44**–**48**, Table 4). This model cannot be applied to alcohols **49** and **50**, due to their compact structure where the phenyl ring is fused to the carbocycle. The configurational assignment for these two alcohols was made comparing the optical rotation value with the literature value.

3. Conclusion

In conclusion we have reported an efficient and chemoselective lipase-catalyzed transesterification reaction of 3,5-diketoesters. The recovery, reusability, and thermo stability of lipase, avoidance of bulk solvents make this process interesting for future application. Our initial results on the resolution of secondary alcohols also showed promising results, seven out of the nine tested alcohol shows excellent enantioselectivity in the resolution experiment. Further studies on resolution of amine, desymmetrization of meso diols by applying the above methodology are in progress and will be communicated in due course.

4. Experimental

4.1. Enzyme preparation

Lipase from *Candida rugosa*, wheat germ, and porcine pancreas (Crude) was available commercially from Sigma Co., USA. PPL was immobilized on celite and hyflosupercel by adsorption techniques. Whereas CRL and WGL were immobilized by entrapment in hydrophobic sol–gel matrix. The gel was prepared by efficient mixing of tetramethoxysilane (TMOS) and alkyl (^{n}Pr, ^{n}Bu, ^{i}Bu) trimethoxysilane. The method of immobilization is described as follows:

(a) *Immobilization of PPL on celite*: Celite 545 (2 g) was washed with deionized water and 0.1N phosphate buffer (pH 7.0) and then added to a solution of 0.5 g PPL in 10 ml of a 0.1N phosphate buffer. The mixture was spread on a watch glass and left to dry at room temperature with occasional mixing until visibly dry. It was further dried in vacuum desiccators. The water content of the enzyme, calculated by comparison of its weight

before and after heating at 110 °C for 24 h, was approximately 1.5% (w/w).

(b) *Immobilization of PPL on hyflosupercel*: Crude PPL (3 g) was suspended in 0.06N (pH 7.0) phosphate buffer and immediately treated with hyflosupercel (10 g). The suspension was magnetically stirred for 30 min at RT and then allowed to stand still overnight. The resulting suspension was frozen at −20 °C while gently stirring manually. The frozen mixture was then lyophilized at 10^{-2} mbar. The resulting solid was removed from the flask, gently ground, and further dried at 10^{-2} mbar in a desiccator over P_2O_5. Yield = 13.4 g. Thus, 1 g of immobilized enzyme corresponds to 0.22 g of crude PPL.

(c) *Immobilization of CRL and WGL on sol–gel matrix*: Crude enzyme 12.5 mg was suspended in 1 ml water, shaken for 15 min and centrifuged to remove insoluble components. The supernatant (400 μl) was added to a mixture of aq. NaF (1 M, 100 μl added), PVA (MW 15,000, 4% (w/w) in water, 200 μl added), and water (164 μl, to give a ratio total water/silane = 8). The solution was shaken and PTMS (875 μl, 5 mmol) was added followed by TMOS (148 μl, 1 mmol). The reaction mixture was vigorously shaken for 5 s on a vortex mixer and then gently shaken by hand. After about 30 s, when the mixture formed a clear homogeneous solution and warmed up, it was placed in an ice bath until gelation occurs (5 min). The reaction vessel was left to stand closed for 24 h, then it was opened and the gel was air dried at 37 °C for 3 days. The white gel was crushed in a mortar, shaken with 10 ml of water for 3 h, then filtered and washed with water, acetone, and hexane. After drying for 24 h at 35 °C, 450 mg of immobilized lipase was obtained.

Lipase from *Candida antarctica* (CAL-B) immobilized on macroporus acrylic resin was obtained from NOVO Nordisk.

4.2. Chemicals

3,5-Diketoesters were prepared as reported earlier [21–23]. 3,5-Dioxo-hexanoic acid methyl/ethyl esters (**1a**–**b**) were prepared from dehydroacetic acid and magnesium methylate/ethylate. 3,5-Dioxo-5-phenylpentanoic acid methyl/ethyl esters (**2a**–**b**) were prepared by Claisen condensation of *N*,*N*-dimethyl benzamide with acetoacetate dianion. Alcohols (**14**–**23**, **26**–**29**, **43**) used in the transesterification were synthesized from easily available starting material. All remaining alcohols were obtained from commercial suppliers.

4.3. Reaction conditions

Unless stated otherwise, lipase-catalyzed alcoholysis was carried out as follows. In a typical transesterification the alcohols (50 mg) and 3,5-diketoester (100 mg) were mixed with immobilized enzyme (50 mg). The reaction flask was kept in an argon atmosphere with magnetic stirring for 8–16 h at 50 °C, and then CH_2Cl_2 was added followed by filtration. The organic layer was evaporated and the final product was purified by preparative TLC. The solid residue was washed with CH_2Cl_2 and dried in a vacuum desiccator. It can be reused without significant loss of activity for three cycles. Chemical yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

4.4. Selected spectral (^1H and ^{13}C NMR in $CDCl_3$) data

4.4.1. 3,5-Dioxo-hexanoic acid benzyl ester

δ_H: 7.5–7.4 (m, 5H), 5.65 (s, 1H), 5.2 (s, 2H), 3.5 (s, 2H), 2.1 (s, 3H). δ_C: 190.313, 187.188, 167.603, 135.544, 128.870, 128.809, 128.539, 100.698, 67.521, 49.557, 24.528.

4.4.2. 3,5-Dioxo-hexanoic acid 4-nitro-benzyl ester

δ_H: 8.2 (d, J = 7.0 Hz, 2H), 7.6 (d, J = 7.0 Hz, 2H), 5.7 (s, 1H), 5.3 (s, 2H), 3.45 (s, 2H), 2.1 (s, 3H). δ_C: 190.188, 187.168, 167.325, 142.128, 131.0, 128.597, 124.022, 100.761, 65.730, 45.178, 24.428.

4.4.3. 3,5-Dioxo-hexanoic acid 4-methoxy-benzyl ester

δ_H: 7.3 (d, J = 6.8 Hz, 2H), 6.9 (d, J = 6.8 Hz, 2H), 5.6 (s, 1H), 5.2 (s, 2H), 3.9 (s, 3H), 3.5 (s, 2H), 2.1 (s, 3H). δ_C: 190.3, 187.2, 167.6, 159.9, 130.4, 127.6, 114.17, 100.6, 67.2, 55.5, 45.3, 24.0.

4.4.4. 3,5-Dioxo-hexanoic acid 4-methyl-pentyl ester

δ_H: 5.65 (s, 1H), 4.1 (t, J = 7.0 Hz, 2H), 3.5 (s, 2H), 2.1 (s, 3H), 1.7 (m, 2H), 1.65 (m, 1H), 1.32 (m, 2H), 1.0 (d, J = 6.8 Hz, 6H). δ_C: 190.264, 187.432, 167.817, 100.662, 66.195, 45.378, 35.058, 27.856, 26.563, 26.529, 24.537, 22.645.

4.4.5. 3,5-Dioxo-hexanoic acid phenethyl ester

δ_H: 7.4–7.2 (m, 5H), 5.6 (s, 1H), 4.4 (t, J = 7.2 Hz, 2H), 3.4 (s, 2H), 3.0 (t, J = 7.2 Hz, 2H), 2.1 (s, 3H). δ_C: 190.350, 187.245, 167.667, 137.693, 129.116, 128.725, 126.850, 100.718, 66.049, 45.305, 35.129, 24.557.

4.4.6. 3,5-Dioxo-hexanoic acid furan-2-ylmethyl ester

δ_H: 7.4 (s, 1H), 6.4 (d, 2H), 5.65 (s, 1H), 5.1 (s, 2H), 3.5 (s, 2H), 2.1 (s, 3H). δ_C: 190.284, 187.108, 167.417, 149.073, 143.617, 111.302, 110.838, 100.653, 58.983, 45.005, 24.485.

4.4.7. 3,5-Dioxo-hexanoic acid 3-methyl-but-2-enyl ester

δ_H: 5.65 (s, 1H), 5.35 (t, J = 8.2 Hz, 1H), 4.6 (d, J = 8.2 Hz, 2H), 3.45 (s, 2H), 2.1 (s, 3H), 1.8 (s, 3H), 1.75 (s, 3H). δ_C: 190.323, 187.353, 167.754, 139.926, 118.220, 100.683, 62.478, 45.232, 25.912, 24.523, 18.190.

4.4.8. 3,5-Dioxo-hexanoic acid 3,7-dimethyl-oct-6-enyl ester

δ_H: 5.65 (s, 1H), 5.1 (m, 1H), 4.2 (m, 2H), 3.45 (s, 2H), 2.1 (s, 3H), 2.0 (m, 2H), 1.75 (s, 3H), 1.7 (s, 3H), 1.6–1.2 (m, 5H), 1.0 (d, $J = 6.8$ Hz, 3H). δ_C: 190.280, 187.408, 167.831, 131.571, 124.674, 100.663, 64.355, 45.370, 37.114, 35.466, 29.626, 25.894, 25.560, 24.538, 19.530, 17.838.

4.4.9. 3,5-Dioxo-hexanoic acid 2-methyl-but-3-enyl ester

δ_H: 5.75 (m, 1H), 5.6 (s, 1H), 5.1 (m, 2H), 4.1 (m, 2H), 3.35 (s, 2H), 2.5 (m, 1H), 2.1 (s, 3H), 1.1 (d, $J = 7.0$ Hz, 3H). δ_C: 190.266, 187.311, 167.693, 139.842, 115.521, 100.727, 69.441, 45.3, 37.083, 24.334, 16.469.

4.4.10. 3,5-Dioxo-hexanoic acid 2-methyl-allyl ester

δ_H: 5.65 (s, 1H), 5.0 (s, 2H), 4.6 (s, 2H), 3.4 (s, 2H), 2.1 (s, 3H), 1.75 (s, 3H). δ_C: 190.377, 187.190, 167.424, 139.554, 113.966, 100.741, 68.929, 45.528, 24.551, 19.612.

4.4.11. 3,5-Dioxo-hexanoic acid (E)-3,7-dimethyl-octa-2,6-dienyl ester

δ_H: 5.65 (s, 1H), 5.4 (m, 1H), 5.1 (m, 1H), 4.65 (t, $J = 8.0$ Hz, 2H), 3.36 (s, 2H), 2.0–2.2 (m, 7H), 1.78 (s, 3H), 1.75 (s, 3H), 1.6 (s, 3H). δ_C: 190.332, 187.373, 167.782, 143.192, 132.115, 123.838, 117.905, 100.690, 62.592, 45.294, 39.702, 26.450, 25.867, 24.570, 17.877, 16.690.

4.4.12. 3,5-Dioxo-hexanoic acid (2E,6E)-3,7,11-trimethyl-dodeca-2,6,10-trienyl ester

δ_H: 5.65 (s, 1H), 5.4 (m, 1H), 5.1 (m, 2H), 4.7 (d, $J = 8.0$ Hz, 2H), 3.35 (s, 2H), 2.1 (s, 3H), 2.0 (m, 8H), 1.8–1.6 (s, 12H). δ_C: 190.349, 187.352, 167.792, 143.240, 135.715, 131.531, 124.483, 123.735, 117.918, 100.688, 62.606, 45.284, 39.878, 39.717, 26.897, 26.377, 25.891, 24.581, 17.881, 16.709, 16.205.

4.4.13. 3,5-Dioxo-hexanoic acid (2E,6E)-8-benzyloxy-3,6-dimethyl-octa-2,6-dienyl ester

δ_H: 7.2–7.5 (m, 5H), 5.65 (s, 1H), 5.5 (m, 1H), 5.4 (m, 1H), 4.54 (s, 2H), 4.5 (s, 2H), 4.05 (d, $J = 10.2$ Hz, 2H), 3.4 (s, 2H), 2.2–2.4 (m, 2H), 2.1 (s, 3H), 1.7 (s, 6H). δ_C: 109.4, 187.3, 167.7, 139.9, 138.6, 130.0, 128.8, 128.6, 128.0, 127.7, 121.4, 100.7, 72.3, 71.5, 66.7, 45.3, 39.0, 26.2, 24.6, 16.7, 14.2.

4.4.14. 3,5-Dioxo-hexanoic acid (E)-6-(4-methoxy-phenoxy)-4-methyl-hex-4-enyl ester

δ_H: 7.28 (d, $J = 6.8$ Hz, 2H), 6.8 (d, $J = 6.8$ Hz, 2H), 5.65 (s, 1H), 5.42 (m, 1H), 4.55 (s, 2H), 4.16 (t, $J = 7.2$ Hz, 2H), 4.0 (d, $J = 8.0$ Hz, 2H), 3.85 (s, 3H), 3.35 (s, 2H), 2.1 (s, 3H), 2.0–2.1 (m, 2H), 1.8 (m, 2H), 1.65 (s, 3H). δ_C: 190.356, 187.416, 167.817, 159.340, 139.009, 130.703, 129.658, 121.953, 114.039, 100.734, 72.030, 66.406, 65.253, 55.253, 45.292, 35.775, 26.710, 26.438, 16.6.

4.4.15. 3,5-Dioxo-hexanoic acid (E)-2-methyl-4-phenoxy-but-2-enyl ester

δ_H: 7.4–7.2 (m, 5H), 5.7 (m, 1H), 5.65 (s, 1H), 4.6 (s, 2H), 4.55 (s, 2H), 4.1 (d, $J = 8.0$ Hz, 2H), 3.4 (s, 2H), 2.1 (s, 3H), 1.7 (s, 3H). δ_C: 190.386, 187.235, 167.513, 138.304, 133.755, 128.820, 128.667, 128.061, 125.571, 100.734, 72.635, 70.140, 66.224, 45.370, 24.580, 14.422.

4.4.16. 3,5-Dioxo-hexanoicacid-4-(tertbutyl-dimethyl-silanyloxy)-2-methylbut-2-enyl ester

δ_H: 5.68 (m, 1H), 5.6 (s, 1H), 4.6 (s, 2H), 4.25 (d, $J = 9.0$ Hz, 2H), 3.7 (s, 2H), 3.4 (s, 2H), 2.1 (s, 3H), 1.7 (s, 3H), 0.9 (s, 9H), 0.05 (s, 6H). δ_C: 190.3, 187.1, 167.5, 130.8, 129.4, 100.9, 70.4, 59.9, 45.3, 44.2, 26.1, 24.6, 18.6, 14.3, −4.9.

4.4.17. 3,5-Dioxo-hexanoic acid (E)-4-benzyloxy-but-2-enyl ester

δ_H: 7.4–7.3 (m, 5H), 5.9 (m, 2H), 4.7 (d, $J = 8.0$ Hz, 2H), 4.5 (s, 2H), 4.1 (d, $J = 8.0$ Hz, 2H), 3.4 (s, 2H), 2.1 (s, 3H). δ_C: 190.371, 187.397, 167.812, 138.232, 131.786, 128.597, 127.919, 127.821, 126.061, 100.749, 72.634, 69.853, 65.538, 45.538, 24.570.

4.4.18. 3,5-Dioxo-hexanoic acid (E)-7-methyl-octa-2,6-dienyl ester

δ_H: 5.8 (m, 1H), 5.65 (s, 1H), 5.6 (m, 1H), 4.6 (d, $J = 8.0$ Hz, 2H), 3.35 (s, 2H), 2.1 (s, 3H), 1.75 (s, 3H), 1.65 (s, 3H). δ_C: 190.331, 187.258, 167.539, 137.046, 132.326, 123.817, 123.563, 100.689, 66.389, 45.287, 32.631, 27.605, 25.856, 24.557, 17.914.

4.4.19. 3,5-Dioxo-hexanoic acid cyclopropylmethyl ester

δ_H: 5.65 (s, 1H), 4.0 (d, $J = 8.4$ Hz, 2H), 3.35 (s, 2H), 2.1 (s, 3H), 1.2 (m, 1H), 0.6 (m, 2H), 0.3 (m, 2H). δ_C: 190.335, 187.463, 167.936, 101.323, 70.627, 45.617, 24.894, 9.941, 3.511, 9.812.

4.4.20. 3,5-Dioxo-hexanoic acid 3-methyl-but-3-enyl ester

δ_H: 5.62 (s, 1H), 4.8 (s, 1H), 4.75 (s, 1H), 4.25 (t, $J = 7.2$ Hz, 2H), 3.38 (s, 2H), 2.4 (t, $J = 7.2$ Hz, 2H), 2.1 (s, 3H), 1.75 (s, 3H). δ_C: 190.271, 187.359, 167.740, 141.539, 112.752, 100.719, 63.781, 45.325, 36.711, 24.545, 22.622.

4.4.21. 3,5-Dioxo-hexanoic acid 4-hydroxy-3-methoxy-benzyl ester

δ_H: 7.3 (m, 1H), 7.0 (s, 1H), 6.8 (m, 1H), 5.6 (s, 1H), 5.1 (s, 2H), 3.9 (s, 3H), 3.4 (s, 2H), 2.1 (s, 3H). δ_C: 190.385, 187.188, 167.646, 146.940, 145.863, 128.719, 120.769, 115.034, 110.662, 100.722, 67.253, 56.182, 45.272, 24.566.

4.4.22. 3,5-Dioxo-hexanoic acid hex-2-ynyl ester

δ_H: 5.6 (s, 2H), 4.75 (s, 2H), 3.4 (s, 2H), 2.25 (m, 2H), 2.1 (s, 3H), 1.6–1.4 (m, 4H), 0.9 (t, $J = 7.0$ Hz, 3H). δ_C: 190.280, 187.004, 167.147, 100.670, 88.465, 53.957, 45.018, 30.594, 24.523, 22.080, 18.617, 13.742.

4.4.23. 3,5-Dioxo-hexanoic acid (2E,6E,10E)-7,11,15-trimethyl-hexadeca-2,6,10,14-tetraenyl ester

δ_H: 5.7 (m, 2H), 5.65 (s, 1H), 5.1 (m, 3H), 4.4 (d, J = 8.0 Hz, 2H), 3.35 (s, 2H), 2.1 (s, 3H), 2.2–2.0 (m, 12H), 1.8–1.6 (s, 12H). δ_C: 190.358, 187.265, 167.265, 137.118, 136.007, 135.193, 131.481, 124.567, 124.338, 123.534, 123.311, 100.711, 66.549, 45.281, 39.921, 39.889, 32.675, 27.522, 26.955, 26.803, 25.914, 24.588, 17.884, 16.271, 16.212.

4.4.24. 3,5-Dioxo-hexanoic acid tetrahydro-furan-2-ylmethyl ester

δ_H: 5.65 (s, 1H), 4.25 (dd, J = 13.0 Hz, 6.0 Hz, 1H), 4.18 (m, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 3.8 (m, 1H), 3.4 (s, 2H), 2.1 (s, 3H), 2.0 (m, 1H), 1.9 (m, 2H), 1.6 (m, 1H). δ_C: 190.341, 187.201, 167.761, 100.743, 76.465, 68.697, 67.509, 45.123, 28.105, 25.863, 24.575.

4.4.25. 3,5-Dioxo-5-phenyl-pentanoic acid benzyl ester

δ_H: 7.9 (d, J = 7.0 Hz, 2H), 7.65–7.3 (m, 8H), 6.3 (s, 2H), 5.3 (s, 2H), 3.6 (s, 2H). δ_C: 189.695, 182.087, 167.582, 135.544, 134.245, 132.795, 128.888, 128.876, 128.709, 128.468, 127.431, 96.894, 67.652, 46.237.

4.4.26. 3,5-Dioxo-5-phenyl-pentanoic acid 4-nitro-benzyl ester

δ_H: 8.3 (d, J = 6.8 Hz, 2H), 8.0 (d, J = 7.0 Hz, 2H), 7.7–7.4 (m, 5H), 6.4 (s, 1H), 5.4 (s, 2H), 3.6 (s, 2H). δ_C: 189.351, 182.912, 167.684, 142.023, 134.330, 132.646, 131.089, 128.884, 128.678, 127.346, 124.022, 96.984, 66.387, 46.237.

4.4.27. 3,5-Dioxo-5-phenyl-pentanoic acid 4-methoxy-benzyl ester

δ_H: 7.88 (d, J = 7.0 Hz, 2H), 7.65 (t, J = 7.0 Hz, 1H), 7.52 (t, J = 7.0 Hz, 2H), 7.35 (d, J = 6.8 Hz, 2H), 6.9 (d, J = 6.8 Hz, 2H), 6.25 (s, 1H), 5.2 (s, 2H), 3.8 (s, 3H), 3.55 (s, 2H). δ_C: 189.424, 182.733, 167.711, 159.987, 134.184, 132.879, 130.569, 128.876, 127.327, 114.209, 127.668, 96.851, 67.363, 55.481, 46.167.

4.4.28. 3,5-Dioxo-5-phenyl-pentanoic acid phenethyl ester

δ_H: 7.9 (d, J = 7.0 Hz, 2H), 7.6–7.4 (m, 3H), 7.2–7.0 (m, 5H), 6.3 (s, 1H), 4.4 (t, J = 6.8 Hz, 2H), 3.5 (s, 2H), 3.0 (t, J = 6.8 Hz, 2H). δ_C: 189.279, 182.856, 167.679, 137.666, 134.278, 132.897, 129.117, 128.915, 128.772, 127.350, 126.801, 97.015, 66.149, 46.112, 35.164.

4.4.29. 3,5-Dioxo-5-phenyl-pentanoic acid furan-2-ylmethyl ester

δ_H: 7.9 (d, J = 6.9 Hz, 2H), 7.6–7.4 (m, 4H), 6.45 (d, J = 15 Hz, 2H), 6.3 (s, 1H), 5.2 (s, 2H), 3.55 (s, 2H). δ_C: 189.115, 182.811, 167.467, 149.088, 143.662, 134.229, 132.876, 128.875, 127.349, 11.574, 110.848, 96.873, 59.094, 45.866.

4.4.30. 3,5-Dioxo-5-phenyl-pentanoic acid 3-methyl-but-2-enyl ester

δ_H: 7.9 (d, J = 7.0 Hz, 2H), 7.6–7.4 (m, 3H), 6.35 (s, 3H), 5.4 (t, J = 8.4 Hz, 2H), 4.7 (d, J = 8.4 Hz, 2H), 3.6 (s, 2H), 1.8 (s, 3H), 1.75 (s, 3H). δ_C: 189.451, 182.813, 167.787, 140.095, 134.330, 132.838, 128.884, 127.313, 118.241, 96.935, 62.586, 46.111, 26.056, 18.266.

4.4.31. 3,5-Dioxo-5-phenyl-pentanoic acid 2-methyl-allyl ester

δ_H: 7.95 (d, J = 7.0 Hz, 2H), 7.6–7.35 (m, 3H), 6.35 (s, 1H), 5.1 (s, 2H), 4.6 (s, 2H), 3.6 (s, 2H), 1.8 (s, 3H). δ_C: 189.239, 182.870, 167.439, 139.583, 134.264, 132.894, 128.828, 127.324, 113.730, 96.969, 68.859, 46.049, 19.671.

4.4.32. 3,5-Dioxo-5-phenyl-pentanoic acid 3-methyl-but-3-enyl ester

δ_H: 7.9 (d, J = 7.0 Hz, 2H), 7.6–7.4 (m, 3H), 6.3 (s, 1H), 4.8 (s, 1H), 4.75 (s, 1H), 4.3 (t, J = 7.2 Hz, 2H), 3.5 (s, 2H), 2.4 (t, J = 7.2 Hz, 2H), 1.8 (s, 3H). δ_C: 189.437, 182.742, 167.739, 141.529, 134.262, 132.870, 128.898, 127.311, 112.717, 96.978, 63.846, 43.147, 36.734, 22.651.

4.4.33. 3,5-Dioxo-5-phenyl-pentanoic acid (E)-3,7-dimethyl-octa-2,6-dienyl ester

δ_H: 7.9 (d, J = 7.0 Hz, 2H), 7.6–7.4 (m, 3H), 6.34 (s, 1H), 5.45 (m, 1H), 5.18 (m, 1H), 4.75 (d, J = 8.4 Hz, 2H), 3.5 (s, 2H), 2.2–2.0 (m, 4H), 1.81 (s, 3H), 1.74 (s, 3H), 1.65 (s, 3H). δ_C: 189.465, 182.807, 167.790, 143.286, 134.327, 132.836, 132.489, 128.884, 127.314, 123.850, 117.914, 96.937, 62.610, 46.135, 39.728, 26.463, 25.880, 17.892, 16.729.

4.4.34. 3,5-Dioxo-5-phenyl-pentanoic acid 3,7-dimethyl-oct-6-enyl ester

δ_H: 7.9 (d, J = 7.0 Hz, 2H), 7.6–7.4 (m, 3H), 6.36 (s, 1H), 5.1 (m, 1H), 4.25 (m, 2H), 3.56 (s, 2H), 2.0 (m, 2H), 1.7 (s, 3H), 1.6 (s, 3H), 1.5 (m, 1H), 1.4 (m, 2H), 1.2 (m, 2H), 0.92 (d, J = 7.0 Hz, 3H). δ_C: 189.494, 182.779, 167.947, 134.296, 132.851, 128.819, 127.308, 127.205, 124.686, 96.924, 64.333, 46.201, 37.139, 35.507, 29.653, 25.913, 25.569, 19.552, 17.850.

4.4.35. 3,5-Dioxo-5-phenyl-pentanoic acid (2E,6E)-3,7,11-trimethyl-dodeca-2,6,10-trienyl ester

δ_H: 7.9 (d, J = 6.8 Hz, 2H), 7.6–7.4 (m, 3H), 6.3 (s, 1H), 5.47 (m, 1H), 5.2 (m, 2H), 4.74 (d, J = 8.0 Hz, 2H), 3.5 (s, 2H), 2.2–2.0 (m, 8H), 1.8 (s, 3H), 1.75 (s, 3H), 1.65 (s, 3H). δ_C: 189.475, 182.794, 167.795, 143.325, 135.723, 134.322, 132.837, 131.540, 128.884, 127.314, 124.498, 123.744, 117.919, 96.929, 62.605, 46.120, 39.887, 39.737, 26.905, 26.384, 25.912, 17.901, 16.748, 16.220.

4.4.36. 3,5-Dioxo-5-phenyl-pentanoic acid hex-2-ynyl ester

δ_H: 7.9 (d, J = 6.8 Hz, 2H), 7.6–7.4 (m, 3H), 6.3 (s, 1H), 4.78 (s, 2H), 3.56 (s, 2H), 2.2 (t, J = 7.0 Hz, 2H),

1.6 (m, 2H), 0.9 (t, $J = 7.0$ Hz, 3H). δ_C: 189.069, 182.763, 167.153, 134.226, 132.891, 128.890, 127.333, 96.898, 88.358, 73.741, 54.0, 45.846, 22.0, 20.914, 13.634.

4.4.37. 3,5-Dioxo-5-phenyl-pentanoic acid 4-methyl-pentyl ester

δ_H: 7.9 (d, $J = 7.0$ Hz, 2H), 7.6–7.4 (m, 3H), 6.3 (s, 1H), 4.2 (t, $J = 7.0$ Hz, 2H), 3.6 (s, 2H), 1.75 (m, 2H), 1.7 (m, 1H), 1.3 (m, 2H), 0.9 (d, $J = 6.0$ Hz, 6H). δ_C: 189.768, 182.735, 167.032, 134.284, 132.779, 128.875, 127.427, 96.894, 66.203, 46.278, 35.062, 27.679, 26.564, 22.645.

4.4.38. 3,5-Dioxo-5-phenylpentanoic-acid-cyclopropylmethyl ester

δ_H: 7.9 (d, $J = 7.0$ Hz, 2H), 7.4–7.6 (m, 3H), 6.35 (s, 1H), 4.1 (d, $J = 10.2$ Hz, 2H), 3.55 (s, 2H), 1.2 (m, 1H), 0.6 (m, 2H), 0.3 (m, 2H). δ_C: 189.6, 182.7, 167.9, 134.3, 132.8, 128.8, 127.3, 96.9, 70.5, 46.1, 9.9, −3.5.

4.4.39. 3,5-Dioxo-hexanoic acid (R)-1-phenyl-ethyl ester

δ_H: 7.5–7.3 (m, 5H), 5.95 (q, $J = 6.6$ Hz, 1H), 5.6 (s, 1H), 3.4 (s, 2H), 2.1 (s, 3H), 1.65 (d, $J = 6.6$ Hz, 3H). δ_C: 190.334, 187.303, 167.048, 141.215, 128.814, 128.738, 128.415, 100.670, 74.053, 45.521, 24.548, 22.155.

4.4.40. 3,5-Dioxo-hexanoic acid (R)-1-naphthalen-2-yl-ethyl ester

δ_H: 7.9–7.65 (m, 4H), 7.6–7.4 (m, 3H), 6.18 (q, $J = 6.5$ Hz, 1H), 5.55 (s, 1H), 3.42 (s, 2H), 2.05 (s, 3H), 1.7 (d, $J = 6.5$ Hz, 3H). δ_C: 190.299, 187.291, 167.057, 138.547, 133.346, 128.723, 128.592, 128.250, 127.863, 126.567, 126.506, 125.393, 124.214, 100.615, 73.884, 45.599, 24.477, 22.139.

4.4.41. 3,5-Dioxo-hexanoic acid (R)-1-pyridin-4-yl-ethyl ester

δ_H: 8.6 (d, $J = 8.6$ Hz, 2H), 7.5 (d, $J = 8.6$ Hz, 2H), 5.9 (q, $J = 6.6$ Hz, 1H), 5.65 (s, 1H), 3.48 (s, 2H), 2.1 (s, 3H), 1.6 (d, $J = 6.6$ Hz, 3H). δ_C: 190.679, 187.935, 166.300, 150.3, 128.948, 120.856, 100.704, 72.112, 45.432, 24.509, 22.018.

4.4.42. 3,5-Dioxo-hexanoic acid (R)-1-furan-2-yl-ethyl ester

δ_H: 7.45 (s, 1H), 6.35 (s, 2H), 6.05 (q, $J = 6.6$ Hz, 1H), 5.6 (s, 1H), 3.38 (s, 2H), 2.1 (s, 3H), 1.67 (d, $J = 6.6$ Hz, 3H). δ_C: 190.237, 187.214, 167.021, 153.06, 142.909, 110.512, 108.528, 100.557, 66.58, 45.298, 24.515, 18.22.

4.4.43. 3,5-Dioxo-hexanoic acid (R)-1-thiophen-2-yl-ethyl ester

δ_H: 7.35 (m, 1H), 7.1 (m, 1H), 7.0 (m, 1H), 6.26 (q, $J = 6.6$ Hz, 1H), 5.58 (s, 1H), 3.35 (s, 2H), 2.1 (s, 3H), 1.7 (d, $J = 6.6$ Hz, 3H). δ_C: 190.286, 187.164, 166.980, 143.880, 126.888, 126.062, 125.841, 100.632, 69.131, 45.402, 24.541, 22.048.

4.4.44. 3,5-Dioxo-hexanoic acid (S)-indan-1-yl ester

δ_H: 7.45 (m, 1H), 7.37–7.2 (m, 3H), 6.3 (m, 1H), 3.35 (s, 2H), 3.15 (m, 1H), 2.9 (m, 1H), 2.57 (m, 1H), 2.18 (m, 1H), 2.1 (s, 3H). δ_C: 190.201, 187.443, 167.795, 144.729, 140.703, 129.49, 127.028, 125.849, 125.066, 100.649, 79.952, 45.463, 32.358, 30.964, 24.535.

4.4.45. 3,5-Dioxo-hexanoic acid (S)-(1,2,3,4-tetrahydro-naphthalen-1-yl) ester

δ_H: 7.35–7.1 (m, 4H), 6.1 (m, 1H), 3.35 (s, 2H), 2.9 (m, 1H), 2.78 (m, 1H), 2.1 (s, 3H), 2.0–1.8 (m, 4H). δ_C: 190.128, 187.536, 167.469, 138.238, 134.136, 129.810, 129.382, 128.632, 126.399, 100.663, 71.744, 45.690, 29.161, 29.097, 24.520, 18.907.

4.4.46. (R)-2-(2-Fluoro-phenoxy)-propionicacid

$[\alpha]_d$ ^{25}: Ref. [19]; δ_H: Ref. [19]; δ_C: 176.497, 153.456 (d, $J = 245.0$ Hz), 145.254 (d, $J = 11.0$ Hz), 124.619 (d, $J = 4.0$ Hz), 123.368 (d, $J = 7.1$ Hz), 117.974, 116.983 (d, $J = 18.4$ Hz).

4.4.47. (R)-2-(2-Fluoro-phenoxy)-propionicacid (S)-1-phenyl-ethyl ester

δ_H: 7.5–7.25 (m, 5H), 7.14 (m, 1H), 6.95 (m, 2H), 6.85 (m, 1H), 5.9678 (q, $J = 6.5$ Hz, 1H), 4.809 (q, $J = 6.8$ Hz, 1H), 1.695 (d, $J = 6.8$ Hz, 3H), 1.5132 (d, $J = 6.5$ Hz, 3H). δ_C: 171.187, 153.228 (d, $J = 246.0$ Hz), 145.781 (d, $J = 10.5$ Hz), 141.075, 128.778, 128.323, 126.312, 124.384 (d, $J = 3.9$ Hz), 122.609 (d, $J = 7.0$ Hz), 117.135, 116.764 (d, $J = 18.0$ Hz), 74.615, 73.606, 22.124, 18.676.

4.4.48. (R)-2-(2-Fluoro-phenoxy)-propionicacid (R)-1-phenyl-ethyl ester

δ_H: 7.35 (m, 3H), 7.24 (m, 2H), 7.1 (m, 1H), 6.98 (m, 2H), 6.88 (m, 1H), 5.9532 (q, $J = 6.5$ Hz, 1H), 4.8237 (q, $J = 6.8$ Hz, 1H), 1.6635 (d, $J = 6.8$ Hz, 3H), 1.5828 (d, $J = 6.5$ Hz, 3H). δ_C: 171.190, 153.243 (d, $J = 244.6$ Hz), 145.782 (d, $J = 10.3$ Hz), 141.079, 128.665, 128.179, 126.2, 124.442 (d, $J = 3.7$ Hz), 122.623 (d, $J = 7.0$ Hz), 117.253, 116.776 (d, $J = 18.4$ Hz), 74.510, 73.670, 22.293, 18.641.

4.4.49. (R)-2-(2-Fluoro-phenoxy)-propionicacid (S)-1-naphthalen-2-yl-ethyl ester

δ_H: 7.9–7.7 (m, 4H), 7.58–7.4 (m, 3H), 7.1 (m, 1H), 6.96 (m, 2H), 6.84 (m, 1H), 6.133 (q, $J = 6.5$ Hz, 1H), 4.8381 (q, $J = 6.8$ Hz, 1H), 1.7106 (d, $J = 6.8$ Hz, 3H), 1.5968 (d, $J = 6.5$ Hz, 3H). δ_C: 171.224, 153.216 (d, $J = 246.2$ Hz), 145.776 (d, $J = 10.6$ Hz), 138.397, 133.321, 133.284, 128.661, 128.276, 127.88, 126.527, 126.428, 125.346, 124.367 (d, $J = 3.8$ Hz), 124.151, 122.603 (d, $J = 7.0$ Hz), 117.117, 116.764 (d, $J = 18.3$ Hz), 74.638, 73.726, 22.113, 18.702.

4.4.50. (R)-2-(2-Fluoro-phenoxy)-propionicacid (R)-1-naphthalen-2-yl-ethyl ester

δ_H: 7.9–7.8 (m, 4H), 7.55 (m, 2H), 7.4 (m, 1H), 7.15 (m, 1H), 7.0–6.9 (m, 3H), 6.189 (q, $J = 6.5$ Hz, 1H), 4.9108 (q, $J = 6.8$ Hz, 1H), 1.741 (d, $J = 6.8$ Hz, 3H), 1.7101 (d, $J = 6.5$ Hz, 3H). δ_C: 171.321, 153.264 (d, $J = 246.1$ Hz), 145.906 (d, $J = 10.5$ Hz), 138.503, 133.346, 133.287, 128.627, 128.352, 127.912, 126.509, 126.435, 125.329, 124.555 (d, $J = 4.0$ Hz), 124.107, 122.659 (d, $J = 7.0$ Hz), 117.112, 116.853 (d, $J = 18.6$ Hz), 74.658, 73.797, 22.346, 18.769.

4.4.51. (R)-2-(2-Fluoro-phenoxy)-propionicacid (S)-1-pyridin-4-yl-ethyl ester

δ_H: 8.6 (d, $J = 7.8$ Hz, 2H), 7.25 (d, $J = 7.8$ Hz, 2H), 7.14 (m, 1H), 6.95 (m, 2H), 6.83 (m, 1H), 5.8796 (q, $J = 6.6$ Hz, 1H), 4.8548 (q, $J = 6.8$ Hz, 1H), 1.6889 (d, $J = 6.8$ Hz, 3H), 1.4684 (d, $J = 6.6$ Hz, 3H). δ_C: 171.013, 153.288 (d, $J = 246.4$ Hz), 150.323, 149.844, 145.593 (d, $J = 10.6$ Hz), 124.453 (d, $J = 3.9$ Hz), 122.954 (d, $J = 7.0$ Hz), 120.770, 117.425, 116.892 (d, $J = 18.5$ Hz), 74.666, 71.905, 21.850, 18.658.

4.4.52. (R)-2-(2-Fluoro-phenoxy)-propionicacid (R)-1-pyridin-4-yl-ethyl ester

δ_H: 8.56 (d, $J = 7.7$ Hz, 2H), 7.14 (m, 1H), 7.07 (d, $J = 7.7$ Hz, 2H), 7.0 (m, 2H), 6.88 (m, 1H), 5.888 (q, $J = 6.6$ Hz, 1H), 4.8712 (q, $J = 6.8$ Hz, 1H), 1.7036 (d, $J = 6.8$ Hz, 3H), 1.563 (d, $J = 6.6$ Hz, 3H). δ_C: 171.086, 153.164 (d, $J = 246.2$ Hz), 150.237, 149.778, 145.661 (d, $J = 10.4$ Hz), 124.522 (d, $J = 3.6$ Hz), 122.831 (d, $J = 7.0$ Hz), 120.720, 117.025, 116.913 (d, $J = 18.5$ Hz), 74.386, 71.972, 21.973, 18.697.

4.4.53. (R)-2-(2-Fluoro-phenoxy)-propionicacid (S)-1-furan-2-yl-ethyl ester

δ_H: 7.44 (m, 1H), 7.1 (m, 1H), 6.95 (m, 2H), 6.85 (m, 1H), 6.38 (m, 2H), 6.0603 (q, $J = 6.7$ Hz, 1H), 4.7684 (q, $J = 6.8$ Hz, 1H), 1.6758 (d, $J = 6.8$ Hz, 3H), 1.5775 (d, $J = 6.7$ Hz, 3H). δ_C: 171.181, 153.206 (d, $J = 246.2$ Hz), 152.888, 145.723 (d, $J = 10.4$ Hz), 142.824, 124.392 (d, $J = 3.8$ Hz), 122.63 (d, $J = 7.0$ Hz), 117.525, 116.75 (d, $J = 18.4$ Hz), 110.505, 108.322, 74.637, 66.23, 18.741, 18.201.

4.4.54. (R)-2-(2-Fluoro-phenoxy)-propionicacid (R)-1-furan-2-yl-ethyl ester

δ_H: 7.36 (m, 1H), 7.1 (m, 1H), 6.96 (m, 2H), 6.88 (m, 1H), 6.3 (m, 2H), 6.045 (q, $J = 6.7$ Hz, 1H), 4.78355 (q, $J = 6.8$ Hz, 1H), 1.643 (d, $J = 6.8$ Hz, 3H), 1.6353 (d, $J = 6.7$ Hz, 3H). δ_C: 171.280, 153.328 (d, $J = 246.1$ Hz), 152.877, 145.677 (d, $J = 10.7$ Hz), 142.829, 124.417 (d, $J = 3.6$ Hz), 122.761 (d, $J = 7.0$ Hz), 117.138, 116.772 (d, $J = 18.6$ Hz), 110.507, 108.33, 74.646, 66.362, 18.626, 18.198.

4.4.55. (R)-2-(2-Fluoro-phenoxy)-propionicacid (S)-1-thiophen-2-yl-ethyl ester

δ_H: 7.3 (m, 1H), 7.1–7.0 (m, 2H), 7.0–6.9 (m, 3H), 6.87–6.81 (m, 1H), 6.2707 (q, $J = 6.6$ Hz, 1H), 4.7838 (q, $J = 6.8$ Hz, 1H), 1.69 (d, $J = 6.8$ Hz, 3H), 1.6455 (d, $J = 6.6$ Hz, 3H). δ_C: 171.110, 153.183 (d, $J = 246.4$ Hz), 145.727 (d, $J = 10.6$ Hz), 143.175, 126.885, 125.978, 125.786, 124.408 (d, $J = 3.8$ Hz), 122.619 (d, $J = 6.9$ Hz), 117.047, 116.766 (d, $J = 18.6$ Hz), 74.459, 68.918, 21.889, 18.620.

4.4.56. (R)-2-(2-Fluoro-phenoxy)-propionicacid (R)-1-thiophen-2-yl-ethyl ester

δ_H: 7.27 (m, 1H), 7.1 (m, 2H), 7.03–6.94 (m, 3H), 6.9 (m, 1H), 6.253 (q, $J = 6.6$ Hz, 1H), 4.7961 (q, $J = 6.8$ Hz, 1H), 1.6987 (d, $J = 6.8$ Hz, 3H), 1.6452 (d, $J = 6.6$ Hz, 3H). δ_C: 117.189, 153.307 (d, $J = 246.0$ Hz), 145.704 (d, $J = 10.4$ Hz), 143.735, 126.861, 126.762, 125.806, 124.43 (d, $J = 3.8$ Hz), 122.73 (d, $J = 7.0$ Hz), 117.444, 116.788 (d, $J = 18.6$ Hz), 74.529, 68.829, 22.049, 18.546.

4.4.57. (R)-2-(2-Fluoro-phenoxy)-propionicacid (S)-indan-1-yl ester

δ_H: 7.4 (m, 1H), 7.38–7.31 (m, 2H), 7.25 (m, 1H), 7.1 (m, 1H), 7.0–6.95 (m, 2H), 6.9 (m, 1H), 6.3526 (m, 1H), 4.8085 (q, $J = 6.8$ Hz, 1H), 3.13 (m, 1H), 2.9 (m, 1H), 2.52 (m, 1H), 2.0 (m, 1H), 1.7058 (d, $J = 6.8$ Hz, 3H). δ_C: 171.921, 153.275 (d, $J = 246.5$ Hz), 145.793 (d, $J = 10.4$ Hz), 144.763, 140.673, 129.442, 127.027, 125.835, 125.108, 124.429 (d, $J = 3.8$ Hz), 122.668 (d, $J = 6.9$ Hz), 117.274, 116.81 (d, $J = 18.5$ Hz), 79.535, 74.557, 32.235, 30.396, 18.705.

4.4.58. (R)-2-(2-Fluoro-phenoxy)-propionicacid (R)-indan-1-yl ester

δ_H: 7.27 (m, 3H), 7.23 (m, 1H), 7.1 (m, 1H), 7.02 (m, 1H), 6.97 (m, 1H), 6.91 (m, 1H), 6.2906 (m, 1H), 4.8123 (q, $J = 6.8$ Hz, 1H), 3.1 (m, 1H), 2.9 (m, 1H), 2.55 (m, 1H), 2.15 (m, 1H), 1.6745 (d, $J = 6.8$ Hz, 3H). δ_C: 171.980, 153.278 (d, $J = 246.1$ Hz), 145.754 (d, $J = 10.6$ Hz), 144.589, 140.558, 129.423, 127.0, 125.816, 125.086, 124.41 (d, $J = 4.0$ Hz), 122.677 (d, $J = 6.9$ Hz), 117.328, 116.793 (d, $J = 18.4$ Hz), 79.654, 74.584, 32.352, 30.38, 18.71.

4.4.59. (R)-2-(2-Fluoro-phenoxy)-propionicacid-(S)-(1,2,3, 4-tetrahydro-naphthalen-1-yl) ester

δ_H: 7.3–7.1 (m, 4H), 7.08 (m, 1H), 6.99 (m, 1H), 6.94 (m, 1H), 6.88 (m, 1H), 6.1167 (m, 1H), 4.8131 (q, $J = 6.8$ Hz, 1H), 2.88 (m, 1H), 2.86 (m, 1H), 2.8–2.75 (m, 2H), 1.97 (m, 1H), 1.88–1.85 (m, 1H), 1.6946 (d, $J = 6.8$ Hz, 3H). δ_C: 171.6, 153.144 (d, $J = 246.1$ Hz), 145.778 (d, $J = 10.6$ Hz), 138.270, 133.966, 129.819, 129.384, 128.589, 126.373, 124.394 (d, $J = 3.8$ Hz), 122.543 (d, $J = 7.0$ Hz), 116.932, 116.808 (d, $J = 18.5$ Hz), 74.428, 71.133, 29.124, 29.082, 18.705, 18.684.

4.4.60. (R)-2-(2-Fluoro-phenoxy)-propionicacid(S)-(1,2,3,4-tetrahydro-naphthalen-1-yl) ester

δ_H: 7.25 (m, 1H), 7.18–7.1 (m, 4H), 7.03 (m, 1H), 6.94 (m, 2H), 6.069 (m, 1H), 4.8238 (q, $J = 6.8$ Hz, 1H), 2.88 (m, 1H), 2.78 (m, 1H), 2.05 (m, 2H), 1.98 (m, 1H), 1.85 (m, 1H), 1.6891 (d, $J = 6.8$ Hz, 3H). δ_C: 171.686, 153.248 (d, $J = 246.2$ Hz), 145.145.77 (d, $J = 10.6$ Hz), 138.148, 133.992, 129.474, 129.296, 128.435, 126.291, 124.533 (d, $J = 3.7$ Hz), 122.635 (d, $J = 7.0$ Hz), 117.383, 116.116.8 (d, $J = 18.6$ Hz), 74.635, 71.528, 29.188, 29.09, 18.984, 18.777.

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References

[1] T.M. Harris, C.M. Harris, Tetrahedron 33 (1977) 2159–2185.
[2] J.N. Collie, J. Chem. Soc. 59 (1891) 179–189.
[3] J.N. Collie, J. Chem. Soc. 59 (1891) 607–617.
[4] J.N. Collie, J. Chem. Soc. 63 (1893) 329–337.
[5] J.N. Collie, J. Chem. Soc. 91 (1907) 1806–1813.
[6] F. Sproxton, J. Chem. Soc. 89 (1906) 1186–1190.
[7] W.B. Mors, O.R. Gottilieb, C.J. Djerassi, J. Am. Chem. Soc. 79 (1957) 4507–4511.
[8] R.F. Witter, E. Stotz, J. Biol. Chem. 176 (1948) 485.
[9] A. Cordova, K.D. Janda, J. Org. Chem 66 (2001) 1906–1909.
[10] M.T. Reetz, A. Zonta, J. Simpel Kamp, Biotechnol. Bioeng. 49 (1996) 527–534.
[11] A. Ghanem, V. Schurig, Tetrahedron: Asymmetry 14 (2003) 2547–2555.
[12] M.T. Reetz, P. Tielmann, W. Wiesenhöfer, W. Könen, Adv. Synth. Catal. 345 (2003) 717–728.
[13] L. Banfi, G. Guanti, R. Riva, Tetrahedron: Asymmetry 6 (1995) 1345–1356.
[14] D. Bianchi, P. Cesti, E. Battistel, J. Org. Chem. 53 (1988) 5531–5534.
[15] B.H. Hoff, L. Ljones, A. Rønstad, T. Anthpnsen, J. Mol. Catal. B: Enzym. 8 (2000) 51–60.
[16] U.T. Bornscheuer, R.J. Kazlauskas, Hydrolases in Organic Synthesis (Regio- and Stereoselective Biotransformations), Wiley–VCH, Weinheim, 1999, p. 65.
[17] A. Heumann, R. Faure, J. Org. Chem. 58 (1993) 1276–1279.
[18] A. Heumann, A. Loutfi, B. Ortiz, Tetrahedron: Asymmetry 6 (1995) 1073–1076.
[19] J.S. Yadav, S. Nanda, Tetrahedron: Asymmetry 12 (2001) 3223–3234.
[20] L. Tottie, C. Moberg, A. Heumann, Acta Chem. Scand. 47 (1993) 492–499.
[21] G. Sollade, L. Gresso-Kempf, Tetrahedron: Asymmetry 7 (1996) 2371–2379.
[22] G. Sollade, N. Husser, Tetrahedron: Asymmetry 6 (1995) 2679–2682.
[23] M. Yamaguchi, K. Shibato, H. Nakashina, T. Minami, Tetrahedron 44 (1988) 4767–4775.
[24] C.S. Chen, Y. Fujimoto, G. Girdaukas, C.J. Sih, J. Am. Chem. Soc. 104 (1982) 7294–7299.