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Lipase-catalyzed kinetic resolution of α-hydroxymethylcycloalkanones with a quaternary carbon center. Chemoenzymatic synthesis of chiral pseudoiridolactones

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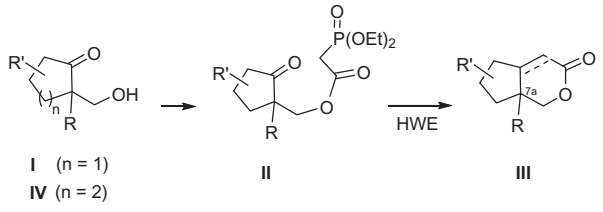
Dedicated to Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The resolution of α-alkyl-α-hydroxymethylcyclopentanones **1** and cyclohexanones **3** has been efficiently achieved by using lipase-catalyzed transesterification reactions with vinyl acetate as the acylating agent. The enantiomeric selectivities were dependent on both the ring size of the cycloalkanone and the bulk of the carbon group located at the stereogenic quaternary center. The resolved α-alkyl-α-hydroxymethylcyclopentanones **1** were used as enantiopure (or enantioenriched) precursors for the synthesis of the optically active pseudoiridolactones **6**–**7**.

1. Introduction

We recently described a new class of bicyclic δ-lactones **III**—referred to as pseudoiridolactones—which contain a carbon group at the bicyclic junction C-7a.[1] Thus, these iridoid-like δ-lactones **III** feature a chiral full-carbon quaternary carbon atom and were synthesized from racemic α-alkyl-α-hydroxymethyl-cyclopentanones **I** via an intramolecular Horner–Wadsworth–Emmons reaction (HWE) as the key step (Scheme 1).



I (n = 1)
IV (n = 2)
II
III

Scheme 1. Synthesis of pseudoiridolactones.

Numerous biologically important natural products contain such full-carbon quaternary carbon centers.[2] Among them, the terpenoids family has many representative examples.[3] Consequently, methodologies for creating these quaternary stereocenters have been a challenging area of research,[4] and enantioselective syntheses have been recently reviewed.[5] Chemoenzymatic strategies have been studied as well. Indeed, transformations based on enzymatic catalysis in organic solvents provide useful methods for the synthesis of chiral molecules with high enantiomeric purity.[6] In this field, lipases are the most frequently used catalysts, the advantage of which lies on their high stability, activity in organic solvents, and on their wide range of substrate specificities.[7] Thus, several lipase-catalyzed resolutions of primary alcohols containing chiral quaternary carbon centers have been investigated.[8–14] These examples concern the resolutions of 2-hydroxy-2-phenylalkanols,[8] 2-cyano-2-phenylhexanol,[9] a 4-hydroxymethyl-4-methylcyclohexenic taxol intermediate,[10] or tetronic acid derivatives[11] and the desymmetrization of prochiral 2,2-disubstituted 1,3-propanediols.[12] The resolution of hydroxymethyl cyclohexenone[13] and α-tetralones or α-indanones[14] was also successfully achieved.

Thus, in order to obtain these pseudoiridolactones **III** in an optically active form, we recently focused our attention to the lipase-catalyzed resolution of the above-mentioned α-alkyl-α-hydroxymethylcyclopentanones **I**. To the best of our knowledge, only few of them have been obtained in an enantiomerically pure form through the chemical separation of racemic diastereomers,[15] the asymmetric Carroll rearrangement,[16] the ozonolysis of chiral exomethylenecyclopentanes,[17] the lipase-mediated resolution of racemic diols,[18] or the catalytic asymmetric hydroxymethylation of silicon enolates.[19]

Our research reported herein was extended to the homologous cyclohexane-derived β-ketoalcohols **IV** ($n = 2$) which are also synthetically useful highly functionalized chiral synthons.[19]

2. Enzymatic resolution of β-ketoalcohols 1 and 3

2.1. Enzymatic resolution

We investigated the efficiency of some commercially available lipases to catalyze the transesterification of the last chiral β-ketoal-

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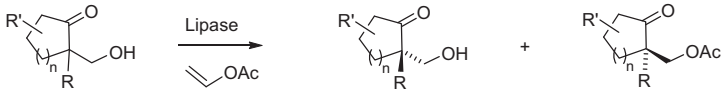
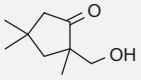
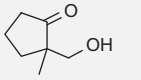
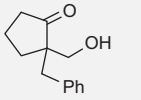
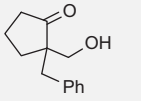
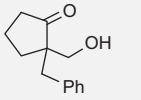
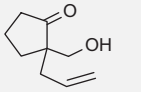
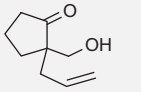
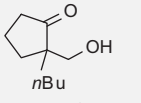
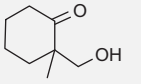
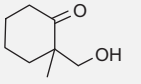
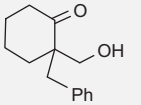
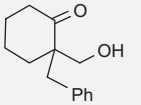
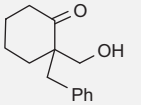
Table 1
Lipase-catalyzed transesterification of α-alkyl-α-hydroxymethylcycloalkanones **1** and **3**



1 (n = 1)
3 (n = 2)

1 (n = 1)
3 (n = 2)

2 (n = 1)
4 (n = 2)

Entry		Substrate **1**, **3**	Lipase[a]	Solvent	Time (h)	Conversion[c] (%)	Isolated yield[d] (%)		$[\alpha]_D^{20}$[e] (*R* or *S*)		ee (%)		*E*[g]
							1 (**3**)	**2** (**4**)	**1** (**3**)	**2** (**4**)	**1** (**3**)	**2** (**4**)[f]	
1	**1a**		Amano PS	Pentane	1	50	48	49	−79.1 (*S*)	+58.7 (*R*)	>99	>99	1050
2	**1b**		Amano PS	Pentane	3	45.3	50	46	−50.4 (*S*)	+87.8 (*R*)	82	>99	510
3	**1c**		Amano PS	Pentane, CH_2Cl_2, THF, $O(iPr)_2$	120	0							—
4	**1c**		Amano PS	Benzene	72	48	50	46	+34.0	−10.0	72	78	6
5	**1c**		Amano AK	Benzene	48	50	47	49	+81.4	−17.0	>99	>99	1057
6	**1d**		Amano PS	Pentane	96	0							
7	**1d**		Amano AK	Benzene	16	49.7	47	49	+38.0 (*R*)	−19.0 (*S*)	98	>99	922
8	**1e**		Amano AK	Benzene	17	50.2	48	49	+11.0	−12.5	>99	98	525
9	**3a**		Amano PS	Benzene	120	0							—
10	**3a**		Amano AK	Benzene	72	46	49	44	+67.0 (*S*)	−18.0 (*R*)	82	98	254
11	**3b**		Amano PS	Benzene	120	0							—
12	**3b**		Amano AK	Benzene	120	0							—
13	**3b**		Amano AK	Benzene[b]	11	50	45	47	+41.0 (*R*)	−19.0 (*S*)	98	98	458

[a] Reaction conditions: *rac*-**1** (1 mmol), vinyl acetate (3 mmol), and lipase (0.5–1 weight/weight of **1** or **3**) in the solvent (10 mL) were stirred at 20–25 °C.
[b] The transesterification was carried out at 65 °C.
[c] Conversion was calculated from the enantiomeric excess of the substrate **1**(**3**) (ee_s) and of the product **2**(**4**) (ee_p).[20]
[d] Yield of isolated product after flash chromatography.
[e] $[\alpha]_D^{20}$ were obtained in $CHCl_3$.
[f] The ee of acetates **2**(**4**) were obtained via their ^1H NMR spectra in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$.
[g] The enantiomeric ratio *E* was determined from the following equation: $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$, where ee_p = product ee, ee_s = substrate ee; $c = ee_s/(ee_s + ee_p)$%.[20]

cohols (±)-**1** and (±)-**3**. The kinetic resolutions were carried out with vinyl acetate as an acyl donor to give the acetates **2** and **4**, along with the unreacted alcohols **1** and **3** as shown in Table 1. The effects of the lipase, the solvent, and the temperature on the reactivity and selectivity of the reaction were evaluated.

The first lipase tested, Amano PS (*Pseudomonas cepacia*), was very efficient to resolve the α-methyl-substituted β-ketoalcohols **1a** and **1b** in pentane at room temperature (entries 1 and 2). On the contrary, it turned out to be inefficient to acylate **1c**, whatever the solvent used (pentane, CH_2Cl_2, THF, or diisopropylether) (entry 3). The transesterification was very slow and poorly enantioselective in benzene (entry 4). Then, another lipase, Amano AK (*Pseudomonas fluorescens*), was tested. The transesterification was also slow to achieve a 50% conversion, but was efficient after 48 h (entry 5). Similar results were obtained with the β-ketoalcohol **1d**. The lipase Amano PS was unreactive with **1d** (entry 6), while the reaction with lipase Amano AK gave a good resolution in benzene after 16 h (entry 7). The β-ketoalcohol **1e** was similarly resolved by the lipase Amano AK in benzene (entry 8). Thus, the efficiency of resolution of the chiral β-ketoalcohols **1** strongly depends on the bulk of the substituent of the quaternary carbon atom.

The resolution of the homologous α-hydroxymethylcyclohexanones **3a**–**b** was then studied with the same lipases. Unlike ketoalcohols **1a** and **1c**, the β-ketoalcohols **3a** and **3b** were unreactive with the lipase Amano PS (compare entries 1/9 and 4/11), which demonstrates that the efficiency of the resolution depends on the ring size of the cycloalkanone. The β-ketoalcohol **3a** was resolved by the lipase Amano AK in benzene (entry 10). Moreover, the β-ketoalcohol **3b** was unreactive in benzene at room temperature (entry 12), but heating the reaction mixture at 65 °C allowed the transesterification reaction to be achieved with a good enantioselectivity (entry 13).

2.2. Determination of the enantiomeric excess

Several means were used to determine the enantiomeric excess (ee) of the β-ketoalcohols **1**(**3**) and the acetates **2**(**4**).

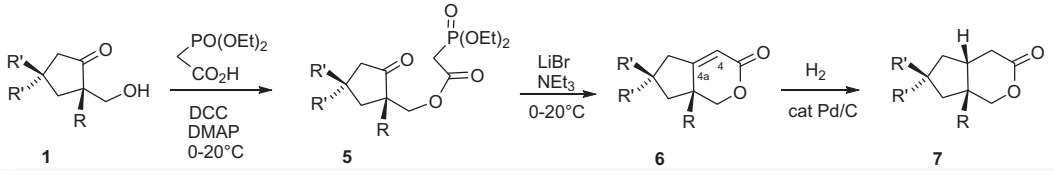
The ee of β-ketoalcohol (−)-**1a** was determined via its ^{1}H NMR spectrum in the presence of 50% of the chiral shift reagent (+)-Eu(hfc)$_3$.[21] Indeed, the methyl groups located at the quaternary carbon center of both enantiomers were well resolved (Table 1, entry 1). However, this procedure could not be extended to the other β-ketoalcohols **1b**–**e**. The ee (82%) of β-ketoalcohol (−)-**1b** was obtained by gas chromatography on a chiral column 'β-cyclodextrine' (Table 1, entry 2). The ee (>99%) of β-ketoalcohol (+)-**1d** was determined by using ^{31}P NMR after reaction of this β-ketoalcohol with the derivatizing Anderson-Shapiro reagent [(+)-2-chloro-4(*R*),5(*R*)-dimethyl-2-oxo-1,3,2-dioxaphospholane] (Table 1, entry 7).[22] For the other β-ketoalcohols **1c**,**e** and **3a**,**b**, the ee determination was obtained after their transformation into their acetates (**2c**,**e** and **4a**,**b**, respectively, which were prepared by a DMAP, catalyzed acetylation in dichloromethane). For these acetates, the ^{1}H NMR spectra in the presence of 40–50% of the chiral shift reagent Eu(hfc)$_3$ gave an easy separation of the acetate methyl groups Table 1, entries 5, 8, 10, 13. This last NMR procedure was also used for the ee determination of all the acetates **2** and **3** obtained directly from the lipase-catalyzed transesterification reactions.

The configurations of the unreacted β-ketoalcohol **1**(**3**) and of the acetates **2**(**4**) given in Table 1 were established by comparison with the known enantiomeric forms of several β-ketoalcohols **1**(**3**): (−)-(*S*)-**1a**,[15] (+)-(*R*)-**1b**,[19a] (+)-(*R*)-**1d**,[16] (−)-(*R*)-**3a**,[13b] and (−)-(*S*)-**3b**.[19] The enantioenriched β-ketoalcohol (+)-**1c** is known,[19b] but its configuration is uncertain.

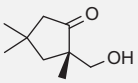
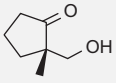
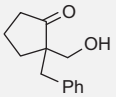
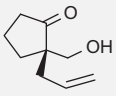
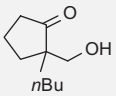
3. Synthesis of the chiral pseudoiridolactones 6 and 7

With the optically active α-alkyl-α-hydroxymethyl-cyclopentanones **1** in hands (with ee = 82–99%), we could synthesize the chiral pseudoiridolactones **6** and **7** through the methodology already described (Table 2).[1] The esterification of β-ketoalcohols **1** to phosphonoacetates **5** was performed by reaction with phosphonoacetic acid in the presence of dicyclohexylcarbodiimide DCC (74–92% yield). The Horner–Wadsworth–Emmons reaction was achieved under

Table 2
Synthesis of pseudoiridolactones **6**-**7** from the α-alkyl-α-hydroxymethylcyclopentanones **1**



1 **5** **6** **7**

Entry	**1**	ee (%) (*R* or *S*)	β-Ketoalcohol **1**	**5** Yield[a] (%)	$[\alpha]_D^{20}$[b]	**6** Yield[a] (%)	$[\alpha]_D^{20}$[b]	**7** Yield[a] (%)	$[\alpha]_D^{20}$[b]
1	(−)-**1a**	>99 (*S*)		92	−38.5	86	+208.9	97	+82.0
2	(−)-**1b**	82 (*S*)		74	−32.4	80	+184.4	96	+28.6
3	(+)-**1c**	99		90	+30.1	81	+52.4	94	−34.0
4	(+)-**1d**	98 (*R*)		78	+28.5	84	+83.4	93[c]	−27.0
5	(+)-**1e**	99		76	−16.0	80	+101.0	97	+26.4

[a] Yield of isolated product after flash chromatography.
[b] $[\alpha]_D^{20}$ were obtained in $CHCl_3$ (c ~1).
[c] The fully saturated lactone **7f** is obtained in place of lactone **7d**.

mild conditions (LiBr, NEt_3 at 0–20 °C) to give the unsaturated bicyclic-δ-lactones **6** (80–86% yield). Finally, catalytic hydrogenation of the C-4/C-4a double bond gave the pseudoiridolactones **7** (93–97% yield). Of course, in the case of the δ-lactone **6d**, the catalytic hydrogenation gave directly the fully saturated pseudoiridolactone **7f** in place of pseudoiridolactone **7d** (Table 2, entry 4). As these transformations do not involve the quaternary carbon atom, the configuration of this carbon was retained within molecules **5**–**7**.

4. Conclusion

The kinetic resolution of various α-alkyl-α-hydroxymethylcyclopentanones **1** and cyclohexanones **3** was performed by a lipase-catalyzed transesterification with vinyl acetate as the acylating agent in organic solvents with an enantiomeric ratio E superior to 250. The efficiency of the resolution was dependent on the ring size of the substrate and on the bulkiness of the carbon group on the quaternary α-carbon atom. The enantiopure (or enantioenriched) α-alkyl-α-hydroxymethylcyclopentanones **1** so obtained were the precursors of the optically active pseudoiridolactones **6**–**7**.

5. Experimental

5.1. Methods and materials

Dichloromethane and ether were distilled from calcium hydride and stored under nitrogen. Thin-layer chromatography (TLC) was performed using precoated Kieselgel 60 F_{254} plates (Merck). Detection was done by UV (254 nm) followed by charring with 4% *p*-anisaldehyde, 5% acetic acid, and 5% sulfuric acid in 86% ethanol. Flash chromatography was performed on Silica Gel 60 (40–63 μm, Merck) and refers to the procedure of Still.[24] IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer and obtained from thin films on NaCl plates for oils. ^{1}H and ^{13}C NMR spectra were respectively recorded at 300 MHz and 75 MHz on a Bruker DRX 300. ^{1}H and ^{13}C NMR chemical shifts were obtained in $CDCl_3$ and reported in ppm relative to $CHCl_3$ (^{1}H: δ = 7.26) and $CDCl_3$ (^{13}C: δ = 77.16) as internal standards, respectively. Multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) are reported in hertz. Optical rotation was measured with a Perkin–Elmer 141 polarimeter. PE refers to petroleum ether and EE to ethyl ether.

Lipases Amano PS (*P. cepacia*) and Amano AK (*P. fluorescens*) were supplied by Amano Pharmaceutical Co. Ltd, Japan. The shift reagent Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate],[21] (+)-Eu(hfc)$_3$, and the derivatizing agent (+)-2-chloro-4(*R*),5(*R*)-dimethyl-2-oxo-1,3,2-dioxaphospholane[22] were purchased from Aldrich and Fluka, respectively.

The racemic 2-hydroxymethyl-2,4,4-trimethylcyclopentanone **1a**,[1b] 2-hydroxymethyl-2-methylcyclopentanone **1b**,[1b] 2-hydroxymethyl-2-benzylcyclopentanone **1c**,[1b] 2-hydroxymethyl-2-allylcyclopentanone **1d**,[1b] 2-hydroxymethyl-2-butylcyclopentanone **1e**,[1b] and 2-hydroxymethyl-2-benzylcyclohexanone **3b**[1b] were synthesized following literature procedures.

5.2. Synthesis of 2-hydroxymethyl-2-methylcyclohexanone 3a

2-Hydroxymethyl-2-methylcyclohexanone **3a** was prepared through the reduction of the diethylketal of the known ethyl 1-methyl-2-oxocyclohexanecarboxylate[23] as follows.

5.2.1. Ethyl 1-methyl-(2,2-ethylenedioxy)cyclohexanecarboxylate[23]

A solution of ethyl 1-methyl-2-oxocyclohexanecarboxylate[23] (1.16 g, 6.3 mmol), ethyleneglycol (700 mg, 7.9 mmol), and PTSA (80 mg, 0.31 mmol) in toluene (30 mL) was refluxed in a round-bottomed flask equipped with a Dean–Stark system. After completion of the reaction, toluene was evaporated and Et_2O (20 mL) was added. The organic solution was washed twice with 5% aqueous $NaHCO_3$ (2 × 6 mL) and 5% aq NaCl (2 mL). The resulting aqueous phases were extracted with ether (2 × 10 mL). The combined organic phases were dried over $MgSO_4$. After evaporation of the solvents, the crude oil was purified by flash chromatography (PE/EE 60:40) to give the β-ketal-ester as a colorless oil (1.42 g, 98%). R_f = 0.50 (PE/EE 50:50). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.15 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 3.90–3.98 (m, 4H, OCH_2CH_2O), 2.02–2.10 (m, 1H, $C_qCH_aH_b$), 1.85–1.89 ($C_qCH_aH_b$), 1.50–172 (m, 4H, 2 × CH_2), 1.35–1.46 (m, 2H, CH_2), 1.26 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.25 (s, 3H, C_qCH_3).

5.2.2. 2-Hydroxymethyl-2-methylcyclohexanone 3a[25]

Step 1: The above-mentioned ketal-ester (1.42 g, 6.22 mmol) was slowly added to a stirred suspension of lithium aluminum hydride (260 mg, 6.85 mmol) in ether (10 mL) stirred at 0 °C under a nitrogen atmosphere. After 1 h, the hydrolysis of the reaction mixture was performed by adding successively H_2O (282 μL), a 5% NaOH solution (282 μL), and then water (2 × 282 μL). The mixture was stirred for 0.5–1 h until a white precipitate appeared. This solid was filtered on a sintered glass filter. The organic phase was evaporated under vacuum to give a crude β-ketal-alcohol as a yellow oil (quantitative yield) which was used directly in the next step.

Step 2: 2 M HCl (1.8 mL) was added to a solution of the crude β-ketal-alcohol in ether (10 mL) at room temperature. After stirring for 2 h, the organic phase was successively washed with saturated $NaHCO_3$ (5 mL), then brine before drying over anhydrous Na_2SO_4. After evaporation of the solvent, purification by flash chromatography (PE/EE 60:40) afforded the already known[25] 2-hydromethyl-2-methylcyclohexanone **3a** (804 mg, 92%). R_f = 0.20 (PE/EE 50:50). IR (neat): 3420, 2940, 1700, 1450, 1310, 1120, 1040, 900, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.56 (d, ^2J = 11.4 Hz, 1H, CH_aH_bOH), 3.42 (d, ^2J = 11.4 Hz, 1H, CH_aH_bOH), 2.63 (t, ^3J = 7.1 Hz, 1H, C_qCH_2), 2.45 (dd, ^2J = 14.3 Hz, ^3J = 6.2 Hz, 1H, CH_aH_b–CO), 2.27 (dd, ^2J = 14.3 Hz, ^3J = 4.6 Hz, 1H, CH_aH_b–CO), 1.55–1.85 (m, 5H, 2 × CH_2 and OH), 1.19 (s, 3H, C_qCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 218.5 (C=O), 69.4 (CH_2OH), 50.5 (C_q), 39.4 (CH_2–CO), 35.9 ($CqCH_2$), 27.7, 21.1 and 20.6 (3 × CH_2).

5.3. General procedure for the lipase-catalyzed asymmetric transesterification of β-ketoalcohols 1 and 3

The racemic β-ketoalcohol **1** (or **3**) (1 mmol) and vinyl acetate (3 mmol) were dissolved in the appropriate organic solvent (10 mL/mmol). The lipase (0.5–1 weight/weight of **1** or **3**) was then added. The reaction mixture was stirred at the defined conditions and was monitored by TLC and gas chromatography. When the maximum conversion was reached, the reaction was terminated by filtration over Celite, eluting with ether. The acetate **2** (or **4**) and the recovered β-ketoalcohol **1** (or **3**) were separated by flash chromatography over silica (petroleum ether/diethyl ether 50:50).

5.3.1. 2-Acetoxymethyl-2,4,4-trimethylcyclopentanone 2a

Following the general transesterification procedure, a mixture of β-ketoalcohol **1a** (200 mg, 1.28 mmol), vinyl acetate (330 mg, 3.84 mmol), and the crude enzyme Amano PS (128 mg) in pentane (15 mL) was stirred at 25 °C for 1 h. Purification by flash chromatography gave the acetate **2a** (125 mg, 49%) and the recovered alcohol **1a** (96 mg, 48%).

Acetate (+)-(*R*)-**2a**: R_f = 0.45 (PE/EE 50:50); $[\alpha]_D^{20} = +58.7$ (*c* 1.05, $CHCl_3$); ee >99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.95 (d, ^2J = 10.7 Hz, 1H, CH_aH_b–OAc), 3.90 (d, ^2J = 10.7 Hz, 1H, CH_aH_b–OAc), 2.25 (d, ^2J = 17.3 Hz, 1H, (C-5)H_aH_b), 2.17 (d, ^2J = 17.3 Hz, 1H, (C-5)H_aH_b),

2.02 (s, 3H, CO–CH_3), 1.98 (d, ^2J = 13.6 Hz, 1H, (C-3)H_aH_b), 1.68 (d, ^2J = 13.6 Hz, 1H, (C-3)H_aH_b), 1.14 (s, 3H, *gem*-CH_3), 1.12 (s, 3H, *gem*-CH_3), 1.11 (s, 3H, (C-2)CH_3). ^{13}C NMR(75 MHz, $CDCl_3$) δ: 224.0 (C-1, *C*=O), 171.3 (*C*=O, ester), 70.1 (*C*H_2–OAc), 55.0 (C-5), 52.1 (C-2), 39.5 (C-3), 30.3 (*gem*-*C*H_3), 30.2 (*gem*-*C*H_3), 21.5 (*C*H_3–CO), 17.4 (C-4), 16,4 ((C-2)*C*H_3).

Ketolcohol (−)-(*S*)-**1a**: $[\alpha]_D^{20} = -79.1$ (*c* 1.00, $CHCl_3$), ee >99%.

5.3.2. 2-Acetoxymethyl-2-methylcyclopentanone 2b

Following the general transesterification procedure, a mixture of β-ketoalcohol **1b** (657 mg, 5.13 mmol), vinyl acetate (1.32 g, 15.4 mmol), and the crude enzyme Amano PS (400 mg) in pentane (40 mL) was stirred at 25 °C for 3 h. Purification by flash chromatography gave the acetate **2b** (402 mg, 46%) and the recovered alcohol **1b** (328 mg, 50%).

Acetate (+)-(*R*)-**2b**: R_f = 0.38 (PE/EE 50:50); $[\alpha]_D^{20} = +87.8$ (*c* 1.02, $CHCl_3$), ee >99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.05 (d, ^2J = 10.8 Hz, 1H, CH_aH$_b$–OAc), 3.45 (d, ^2J = 10.8 Hz, 1H, CH$_a$$H_b$–OAc), 2.2–2.4 (m, 2H, 5-H), 2.01 (s, 3H, CO–CH_3), 1.7–1.8 (m, 4H, 4H, 3-H and 4-H), 1.01 (s, 3H, (C-2)CH_3). ^{13}C NMR(75 MHz, $CDCl_3$) δ: 220.9 (C-1, *C*=O), 171.2 (*C*=O, ester), 68.2 (*C*H_2–OAc), 48.6 (C-2), 38.3 (C-5), 33.7 (C-3), 21.2 (*C*H_3–CO), 20.0 (*C*H_3), 19.1 (C-4).

Ketoalcohol (−)-(*S*)-**1b**: $[\alpha]_D^{20} = -50.4$ (*c* 1.0, $CHCl_3$), ee = 82% determined by gas chromatography using a Shimadzu GC-14A chromatograph equipped with a chiral capillary column Cyclodex βtm (60 m × 0.25 mm ID × 0.25 μ film): N_2 carrier gas (~1 cm^3 min^{-1}); temperature program from 40 °C to 200 °C at 5 °C min^{-1}; t_R((+)-**1b**) = 30.5 min, and t_R((−)-**1b**) = 31.2 min.

5.3.3. 2-Acetoxymethyl-2-benzylcyclopentanone 2c[26]

Following the general transesterification procedure, a mixture of β-ketoalcohol **1c** (120 mg, 0.59 mmol), vinyl acetate (152.2 mg, 1.77 mmol), and the enzyme *P. fluorescens* AK (59 mg) in benzene (8 mL) was stirred at 25 °C for 48 h. Purification by flash chromatography gave the acetate **2c** (68 mg, 47%) and the recovered alcohol **1c** (49 mg, 49%).

Acetate (−)-**2c**: R_f = 0.40 (PE/EE 50:50); $[\alpha]_D^{20} = -17$ (*c* 1.1, $CHCl_3$); ee >99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.1–7.40 (m, 5H, H_{arom}), 4.09 (s, 2H, CH_2–OAc), 2.88 (d, ^2J = 13.4 Hz, 1H, CH_aH$_b$–Ph), 2.69 (d, ^2J = 13.4 Hz, 1H, CH$_a$$H_b$–Ph), 2.06 (s, 3H, CO–C$H_3$), 1.50–2.20 (m, 6H, 3 × CH_2).

Ketoalcohol (+)-**1c**: $[\alpha]_D^{20} = +81.4$ (*c* 1.00, $CHCl_3$), ee >99%.

5.3.4. 2-Acetoxymethyl-2-allylcyclopentanone 2d

Following the general transesterification procedure, a mixture of β-ketoalcohol **1d** (100 mg, 0.65 mmol), vinyl acetate (167.7 mg, 1.95 mmol), and *P. fluorescens* AK (65 mg) in benzene (6 mL) was stirred at 25 °C for 16 h. Purification by flash chromatography gave the acetate **2d** (60 mg, 47%) and the recovered alcohol **1d** (49 mg, 49%).

Acetate (−)-(*S*)-**2d**: R_f = 0.42 (PE/EE 50:50); $[\alpha]_D^{20} = -19$ (*c* 1.01, $CHCl_3$); ee = 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.70 (ddt, $^3J_{trans}$ = 17.3 Hz, $^3J_{cis}$ = 9.6 Hz, 1H, ^3J = 7.5 Hz, C*H*=CH$_2$), 5.13 (d, $^3J_{trans}$ = 17.3 Hz, 1H, C=C*H*H), 5.09 (dt, $^3J_{cis}$ = 9.6 Hz, $^4J_{allyl}$ = 1.0 Hz, 1H, C=CH*H*), 4.09 (d, ^2J = 10.9 Hz, 1H, CH_aH$_b$–OAc), 4.03 (d, ^2J = 10.9 Hz, 1H, CH$_a$$H_b$–OAc), 2.22–2.30 (m, 4H, CH_2–CO and CH_2–CH=CH$_2$), 2.10–2.20 (m, 4H, 2 × CH_2), 2.03 (s, 3H, CO–CH_3).

Ketoalcohol (+)-(*R*)-**1d**: $[\alpha]_D^{20} = +38$ (*c* 1.05, $CHCl_3$); ee = 98%.

5.3.5. 2-Acetoxymethyl-2-butylcyclopentanone 2e

Following the general transesterification procedure, a mixture of β-ketoalcohol **1e** (900 mg, 5.3 mmol), vinyl acetate (1.38 g, 15.9 mmol), and lipase Amano AK (530 mg) in benzene (50 mL) was stirred at 25 °C for 17 h. Purification by flash chromatography gave the acetate **2e** (548 mg, 49%) and the recovered alcohol **1e** (433 mg, 48%).

Acetate (−)-**2e**: R_f = 0.40 (PE/EE 50:50); $[\alpha]_D^{20} = -12.5$ (*c* 1.0, $CHCl_3$); ee = 99%. ^{1}H NMR(300 MHz, $CDCl_3$) δ: 4.20 (d, ^2J = 10.7 Hz, 1H, CH_aH$_b$–OAc), 4.02 (d, ^2J = 10.7 Hz, 1H, CH$_a$$H_b$–OAc), 2.10 (s, 1H, CO–C$H_3$), 2.0–2.03 (m, 1H, C(5)*H*H), 1.55–1.85 (m, 1H + 4H, C(5)H*H* and 2 × CH_2), 1.32 (t, ^3J = 7.1 Hz, 2H, C(2)CH_2), 1.18 (m, 4H, 2 × CH_2), 0.90 (t, ^3J = 6.6 Hz, 3H, CH_3).

Ketoalcohol (+)-**1e**: $[\alpha]_D^{20} = +11$ (*c* 1.0, $CHCl_3$); ee = 99%.

5.3.6. 2-Acetoxymethyl-2-methylcyclohexanone 4a[27]

Following the general transesterification procedure, a mixture of β-ketoalcohol **3a** (100 mg, 0.7 mmol), vinyl acetate (181 mg, 2.1 mmol), and lipase *P. fluorescens* AK (70 mg) in benzene (5 mL) was stirred at 20 °C for 72 h. Purification by flash chromatography gave the acetate **4a** (56 mg, 44%) and the recovered alcohol **3a** (49 mg, 49%).

Acetate (−)-(*R*)-**4a**: R_f = 0.44 (PE/EE 50:50); $[\alpha]_D^{20} = -18$ (*c* 1.09, $CHCl_3$); ee = 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.20 (d, ^2J = 11.1 Hz, 1H, CH_aH$_b$–OAc), 4.14 (d, ^2J = 11.1 Hz, 1H, CH$_a$$H_b$–OAc), 2.42–2.45 (m, 1H, (C-6)*H*H), 2.06 (s, 3H, CO–CH_3), 1.75–1.93 (m, 7H, (C-6)H*H* and 3 × CH_2), 1.17 (s, 3H, (C-2)CH_3).

Ketoalcohol (+)-(*S*)-**3a**: $[\alpha]_D^{20} = +67$ (*c* 1.01, $CHCl_3$); ee = 82%.

5.3.7. 2-Acetoxymethyl-2-benzylcyclohexanone 4b

Following the general transesterification procedure, a mixture of β-ketoalcohol **3b** (109 mg, 0.5 mmol), vinyl acetate (129 mg, 1.5 mmol), and lipase *P. fluorescens* AK (50 mg) in benzene (5 mL) was stirred at 65 °C for 18 h. Purification by flash chromatography gave the acetate **4b** (59 mg, 45%) and the recovered alcohol **3b** (51 mg, 47%).

Acetate (−)-(*S*)-**4b**: R_f = 0.50 (PE/EE 50:50); $[\alpha]_D^{20} = -19$ (*c* 1.05, $CHCl_3$); ee = 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22–7.26 (m, 5H, H_{arom}), 4.78 (d, ^2J = 11.5 Hz, 1H, CH_aH$_b$–OAc), 4.51 (d, ^2J = 11.5 Hz, 1H, CH$_a$$H_b$–OAc), 3.38 (d, ^2J = 13.7 Hz, 1H, CH_aH$_b$–Ph), 3.10 (d, ^2J = 13.7 Hz, 1H, CH$_a$$H_b$–Ph), 2.77 (t, ^3J = 6.6 Hz, 2H, CH_2–CO), 2.39 (s, 3H, CO–CH_3), 1.90–1.96 (m, 6H, 3 × CH_2).

Ketoalcohol (+)-(*R*)-**3b**: $[\alpha]_D^{20} = +40$ (*c* 1.03, $CHCl_3$); ee >99%.

6. Synthesis of the pseudoiridolactones 6–7

The synthesis of the optically active pseudoiridolactones **6**–**7** was achieved as previously described for the racemic form of these same pseudoiridolactones.[1b] The yields and the optical rotations $[\alpha]_D^{20}$ (~1, $CHCl_3$) are given in Table 2. Their spectroscopic data are all given in Ref. 1b.

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