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Synthesis of chiral acetoxy lactones via the Baeyer–Villiger oxidation of cyclic aromatic acetoxy ketones

Ayhan S. Demir *, Asuman Aybey

Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

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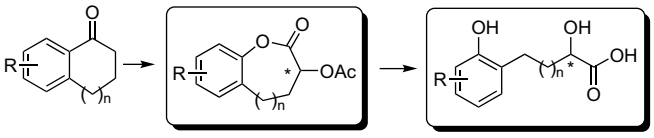
ABSTRACT

The α-acetoxylation of indanones and tetralones by using $Mn(OAc)_3$ followed by the enzyme catalyzed kinetic resolution of acetoxy ketones furnished both of the enantiomers of α-acetoxy ketones in good chemical and optical yields. The Baeyer–Villiger oxidation of α-acetoxy ketones with *m*-CPBA, CF_3SO_3H, and CH_2Cl_2, at rt gives the corresponding lactones without racemization. The acetoxy ketone moiety migrates selectively in order to form lactones. The mild hydrolysis of lactones affords phenolic α-hydroxycarboxylic acid derivatives.

1. Introduction

The Baeyer–Villiger (BV) oxidation of ketones represents a powerful methodology in synthesis for cleaving carbon–carbon bonds in an oxygen-insertion process. BV oxidation has been widely employed for the transformation of carbonyl compounds to the corresponding esters or lactones using peracids or hydrogen peroxide.[1,2] The chiral BV oxidation of cyclic ketones allows for rapid access to chiral lactones, which are valuable intermediates in organic chemistry. The biocatalytic equivalent to the above peracids is represented by monooxygenases, which are a sub-class of the oxygenase enzyme family in green processes.[3]

There are several methods for the BV oxidation of simple cycloalkanes, but to our best knowledge, much less attention has been paid to the synthetic applications of the BV oxidation of functionalized ketones, especially cyclic α-hydroxy ketones, which could be a straightforward route to the α-hydroxy lactones and α-hydroxyalkanoic acid derivatives. In the present paper, we report an effective chemoenzymatic synthetic approach to α-acetoxy ketones, their BV product lactones, and hydroxyalkanoic acid derivatives by the $Mn(OAc)_3$-mediated acetoxylation of cyclic aromatic ketones and BV oxidation followed by hydrolysis under mild conditions as shown in Scheme 1. These BV products and hydroxyalkanoic acid derivatives are either a precursor of some important biologically active compounds or they demonstrate biological activity.[4]



Scheme 1.

2. Results and discussion

In our ongoing work, we have published several papers on the $Mn(OAc)_3$-mediated direct acetoxylation and acyloxylation (carried out via metathesis of acetic acid with various carboxylic acids) of enones and aromatic ketones followed by the enzyme- and fungus-mediated resolution of acyloxy enones to obtain enantiomerically pure α-hydroxy ketones.[5,6]

As an initial reaction (Scheme 2), the oxidation of commercially available tetralone (**1a**) with $Mn(OAc)_3$ in cyclohexane or benzene was performed to obtain the desired 2-acetoxytetralone (**2a**) in 89% yield after purification of the crude product by column chromatography. Using similar procedures starting from the commercially available ketones α-actoxytetralone, indanone, and chromanone derivatives were synthesized in good to high yields as shown in Table 1. The direct synthesis of acetoxy enones **2a**–**g** under mild conditions from **1a**–**g** using $Mn(OAc)_3$ is an attractive alternative to the other (multistep) procedures for α-oxidation.[3a,7,17]

2.1. Baeyer–Villiger oxidation of α-acetoxy ketones

A large number of catalysts have been shown to be active in the oxidation of cycloalkanones to lactones using several oxidants but none of them describe the BV oxidation of aromatic ketones with electron rich substituents at the α-position. In most cases,

* Corresponding author. Fax: +90 312 210 3200.
E-mail address: asdemir@metu.edu.tr (A.S. Demir).

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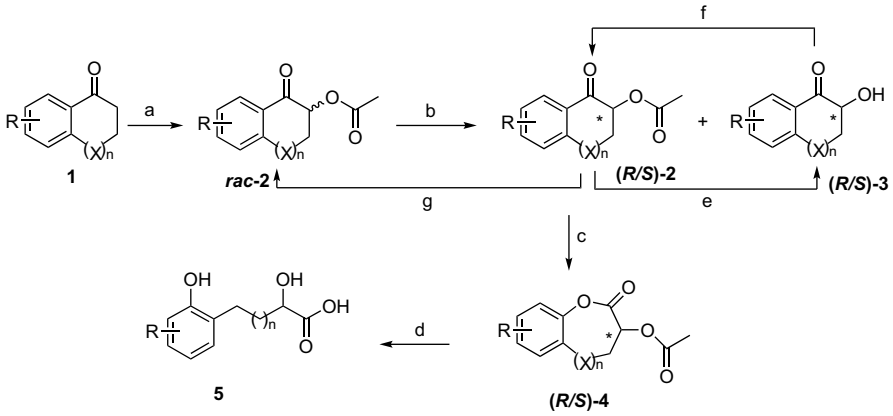
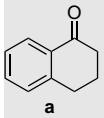
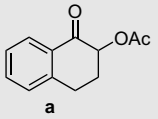
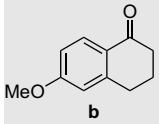
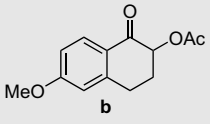
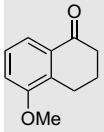
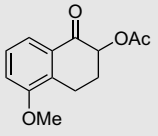
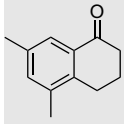
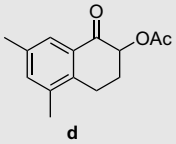
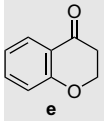
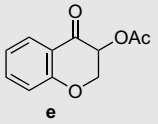
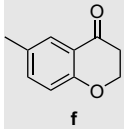
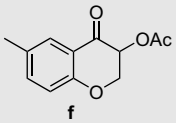
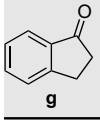
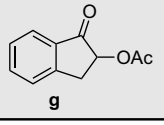


Scheme 2. (a) $Mn(OAc)_3$; (b) Enzymatic-kinetic resolution; (c) *m*-CPBA, CF_3SO_3H; (d) (K_2CO_3/MeOH);[17] (e) $Sc(OTf)_3$/MeOH/H_2O;[18c,d] (f) acetic anhydride/$Cu(OTf)_3$;[18a] (g) DBU in hexane/THF.[18b]

m-chloroperbenzoic acid is used as an oxidizing agent. In an initial reaction, the oxidation of **2a** was carried out with *m*-CPBA in $CHCl_3$, in which the reaction was monitored by TLC and no product formation was observed (48 h). To enhance the reactivity of *m*-chloroperbenzoic acid, the reagent is combined with an appropriate promoter, such as sulfonic acids, Nafion-H, CF_3COOH, hydrotalcite, $SnCl_4$, $Re(OTf)_3$, as well as trifluoromethanesulfonic acid.[8] As shown in Table 2, *m*-CPBA was used with various reagents for the BV oxidation of the acetoxylated products, in which the reactions were monitored by TLC: method A:[9] *m*-CPBA, $KHCO_3$, CH_2Cl_2, reflux (36–96 h); method B:[10] $NaBO_3 \cdot 4H_2O$, HCOOH, 0 °C (3–24 h); method C:[11] *m*-CPBA, PTSA, CH_2Cl_2, rt (10–24 h); method D:[12] *m*-CPBA, $Bi(OTf)_3$, CH_2Cl_2, 0 °C (48–96 h); method E:[13] *m*-CPBA, $CHCl_3$ (48 h); and method F:[14] *m*-CPBA, CF_3SO_3H, CH_2Cl_2, rt (15–45 min).

Table 1
$Mn(OAc)_3$-mediated acetoxylation of aromatic ketones

Aromatic ketones **1**	Acetoxy ketones **2**	Yield (%)
 **a**	 **a**	89[5a]
 **b**	 **b**	85[5a]
 **c**	 **c**	80
 **d**	 **d**	96
 **e**	 **e**	75[5b]
 **f**	 **f**	83
 **g**	 **g**	81[5a]

Depending on the reagents and conditions, most of the reactions furnished the desired products **4a**–**g** in moderate to high yields with the same regioselectivity (Scheme 2). According to the spectroscopic data, the acetoxy ketone group migrated in order to form the BV products and no other isomer was detected (GC, NMR, and GC–MS). Methods A and F work with all the compounds and method F: (*m*-CPBA, CF_3SO_3H (10 mol %), CH_2Cl_2, rt) gave the best yields (68–95%) in a short reaction time (15–45 min) compared to the other conditions. No product formation was observed by using method E.

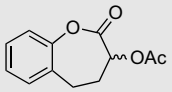
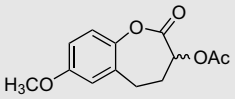
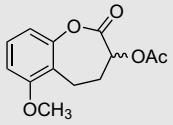
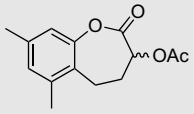
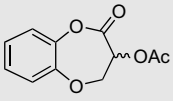
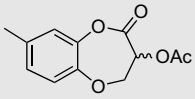
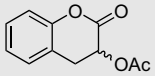
The enantiomerically pure α-acetoxy ketones and their respective BV products are interesting and important synthetic precursors for various compounds.[4,5] Therefore, we first attempted to perform the BV oxidation reaction with biocatalysts. BV oxidations can also be performed using enzymes (Baeyer–Villigerases). These biocatalysts enable one to reach very high enantioselectivity, and several examples demonstrating the possible preparative scale use of whole cell microorganisms, starting from either racemic or prochiral substrates, have been described.[3,16] The BV oxidation of **2b**, **2d**, and **2e** was carried out with cyclohexanone monooxygenase *Acinetobacter* sp. (EC 1.14.13.22) (CHMO, NADPH, DMSO/buffer (pH=8–9)) mainly unchanged starting material was isolated together with a trace amount of the hydrolysis product.

After unsuccessful biocatalytical BV reactions, we attempted the traditional well proven enzyme catalyzed kinetic resolution of the α-acetoxy ketones. We already published some preliminary results for the enzyme catalyzed kinetic resolution of acetoxy ketones.[5] In light of these preliminary results, acetoxy ketones are screened with enzymes for kinetic resolution.

Ester hydrolysis was investigated using commercially available enzymes: Amano PS, CCL (lipase from *Candida cylindracea*), PPL (Porcine pancreatic lipase), HPL (lipase from hog pancreas), WGL (lipase from wheat germ), MML (lipase from *Mucor miehei*), PRL (lipase from *Penicillium roqueforti*), RAL (Lipase from *Rhizopus arrhizus*), RNL (Lipase from *Rhizopus niveus*), PFL (lipase from *Pseudomonas fluorescens*), QLM (lipase from *Alcaligenes* sp.), AL (lipase from *Aspergillus*).

In a typical experiment, for enzymatic hydrolysis, the racemic acetates, **2a**–**g**, were dissolved in an appropriate organic solvent,

Table 2
The BV oxidation of α-acetoxy ketones

Acetoxy ketones **2**	Products **4**	Method A	Method B	Method C	Method D	Method E	Method F
		Yield (%)	Yield (%)	Yield (%)	Yield (%)	Yield (%)	Yield (%)
a	 **a**	60	—	20	—	—	90
b	 **b**	85	—	30	—	—	95
c	 **c**	65	—	40	—	—	90
d	 **d**	80	—	—	—	—	95
e	 **e**	35	40	25	65	—	68
f	 **f**	40	45	30	60	—	70
g	 **g**	55	—	—	—	—	70[15]

and then phosphate buffer (pH 7.0) (1:10) was added and the mixture was stirred at rt in the presence of an enzyme. The reaction was monitored by TLC, HPLC, and LC–MS with a chiral column using racemic acetate, and alcohol (synthesized from acetate with K_2CO_3/MeOH)[17] as references. When approximately 50% conversion was attained, the crude product was separated by flash column chromatography to afford acetate **2**, and alcohol **3** (Scheme 2).

All the enzymes achieved hydrolysis. Among them, Amano PS and WGL furnished the best results. All of the other enzymes give moderate ee (reaction time 48–120 h, ee: 25–52% for acetate 17–43% for alcohol; solvents: DMSO, toluene, dioxane, THF, acetonitrile, and xylene). In case of **2d** Amano PS and WGL showed reverse selectivity.

The BV oxidation of the acetoxy ketone (*S*)-**2** was carried out under the conditions as described for racemic acetoxy ketones. The careful monitoring of the ee value of the BV product **4a** showed that no racemization occurred during the oxidation. This procedure was applied to all of the acetoxy ketones and chiral BV products were obtained in 69–94% yields (Scheme 2). The results are summarized in Table 3. Under similar BV conditions as described by the acetate, the oxidation of chiral alcohol **3a** gave a mixture of the products, in which difficulties were produced by the separation and identification of the products. This reaction is under investigation. These difficulties can be overcome when the alcohols are converted to their acetate immediately after separation by flash column chromatography. Racemization-free acetylation of alcohols was carried out with acetic anhydride/$Cu(OTf)_3$ according to a procedure reported in the literature.[18a] The acetoxy ketone can be epimerized using DBU in hexane/THF.[18b] Likewise, racemization-free hydrolysis of chiral acetoxy ketone was carried out with $Sc(OTf)_3$/MeOH/H_2O

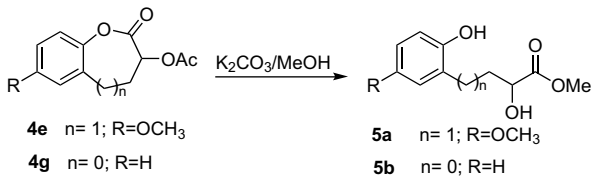
Table 3
Enzymatic-kinetic resolution and BV oxidation of α-acetoxy ketones

Enzymatic-kinetic resolution of α-acetoxy ketones				Baeyer–Villiger oxidation (method F)
α-Acetoxy ketone *rac*-**2**	Conditions	Acetate[a] **2**	Alcohol[a] **3**	BV product **4**
		ee (%), yield (%)	ee (%), yield (%)	ee (%), yield(%)
a	Amano PS buffer/ acetonitrile	(−)-(*S*)-**2a**[5a] 89, 45	(+)-(*R*)-**3a** 81, 36	**4a** 87, 89
b	Amano PS buffer/ toluene	(−)-**2b**[5a] 90, 35	**3b** 71, 39	**4b** 87, 93
c	Amano PS buffer/ toluene	(−)-**2c** 84, 40	**3c** 66, 41	**4c** 83, 90
d	Lipase from wheat germ buffer/DMSO	(+)-**2d** 85, 48	**3d** 81, 41	**4d** 85, 94
	Amano PS buffer/ toluene	(−)-**2d** 60, 45	41, 34	58, 91
e	Amano PS buffer/ toluene	(−)-(*S*)-**2e**[5b] 97, 36	(+)-(*R*)-**3e** 88, 38	**4e** 97, 69
f	Amano PS buffer/ toluene	(−)-**2f** 58, 45	**3f** 61, 41	**4f** 56, 71
g	Amano PS buffer/ acetonitrile	(+)-(*S*)-**2g**[5a] 86, 48	(−)-(*R*)-**3g** 81, 38	**4g**[15] 85, 73

[a] ee Values are determined via their acetate.

(Scheme 2).[18c,d] With this method, it was possible to obtain both enantiomers of the lactones.

The BV product lactones are starting materials for interesting α-hydroxycarboxylic acids with phenolic groups. As a representative, examples **4e** and **4g** are converted to the α-hydroxy esters **5a**, **5b** with K_2CO_3 in methanol. The reaction works under mild conditions at rt to form the products in 84–88% yield as shown in Scheme 3.



Scheme 3.

The results show that the $Mn(OAc)_3$-mediated acetoxylation of aromatic ketones followed by BV oxidation selectively furnishes lactones in good to high yields. By BV reactions, acetoxy ketone moiety migrates in order to form lactones. The lactones are also formed from the chiral α-acetoxy ketones without racemization. The chiral acetoxy ketones are synthesized via enzymatic-kinetic resolution. Enzyme-mediated hydrolysis of the acetoxy group provides hydroxy enone **4** and acetoxy enone **3** up to 97% enantiomeric excesses and in good chemical yields. In a representative example, lactones are converted to phenolic α-hydroxy esters **5a**,**b** in 84–88% yields. This method gives a simple new entry to the synthesis of lactones in order to form acetoxy ketones and their conversion to phenolic hydroxy esters, which are interesting intermediates for the synthesis of amino acids and other interesting compounds.

3. Experimental

3.1. General procedure for $Mn(OAc)_3$ oxidation

General procedures have been described previously.[5]

*3.1.1. 1,2,3,4-Tetrahydro-5-methoxy-1-oxonaphthalen-2-yl acetate (**2c**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **2c** (1.78 g, 80%) as a yellow solid. Mp 94–95 °C. IR (KBr): 3049, 2953, 1750, 1673, 1590, 1240, 1104, 940 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.6 (d, *J*=8.0 Hz, 1H), 7.27 (t, *J*=8.0 Hz, 1H), 7.0 (d, *J*=8.0 Hz, 1H), 5.48 (dd, *J*=13.7, 5.0 Hz, 1H), 3.87 (s, 3H), 3.24 (m, 1H), 2.84 (m, 1H), 2.07–2.30 (m, 2H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 169.6, 156.6, 132.7, 131.8, 127.4, 119.4, 114.4, 74.2, 55.5, 28.3, 21.8, 20.7. Anal. Calcd for $C_{13}H_{14}O_4$ (234.25): C, 66.66; H, 6.02. Found: C, 66.36; H, 5.87.

*3.1.2. 1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate (**2d**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **2d** (1.67 g, 96%) as a yellow solid. Mp 101–103 °C. IR ($CHCl_3$): 3447, 1693, 1608, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.6 (s, 1H), 7.1 (s, 1H), 5.4 (dd, *J*=13.7, 5.0 Hz, 1H), 2.80–3.0 (m, 2H), 2.34 (m, 1H), 2.27 (s, 3H), 2.21 (s,3H), 2.15 (s, 3H), 2.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 169.9, 138.2, 136.3, 136.2, 135.9, 131.7, 125.8, 74.2, 28.4, 25.0, 20.9, 19.3. Anal. Calcd for $C_{14}H_{16}O_3$ (232.28): C, 72.39; H, 6.94. Found: C, 72.33; H, 6.82.

*3.1.3. 3,4-Dihydro-6-methyl-4-oxo-2H-chromen-3-yl acetate (**2f**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **2f** (1.84 g, 83%) as a yellow oil. IR (neat): 3443, 1693, 1609, 1060, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.29 (d, *J*=8.4 Hz, 1H), 6.86 (d, *J*=8.4 Hz, 1H), 5.6 (dd, *J*=11.3, 5.5 Hz, 1H), 4.5 (dd, *J*=11.0, 5.5 Hz, 1H), 4.35 (dd, *J*=11.3, 11.0 Hz, 1H), 2.33 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.7, 169.3, 159.7, 137.6, 131.6, 127.4, 119.9, 117.8, 69.7, 68.6, 20.8, 20.6. Anal. Calcd for $C_{12}H_{12}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.31; H, 5.62.

3.2. General procedures for the Baeyer–Villiger oxidation of α-acetoxy ketones

Method A. A solution of α-acetoxy ketones **2a–g** (50 mg, 0.28 mmol) and $KHCO_3$ (35 mg, 0.35 mmol) in 10 mL CH_2Cl_2 were stirred, and commercial grade *m*-CPBA (80% activity, 61 mg, 0.35 mmol) was added to this mixture. The reaction mixture was stirred under reflux.

Method B. A solution of α-acetoxy ketone **2e** (50 mg, 0.24 mmol) in formic acid (0.5 mL, 98%) was stirred and cooled in an ice bath. Sodium perborate tetrahydrate (55 mg, 0.36 mmol, 90%) was added subsequently in small portions over a period of 6 h. Stirring was continued for another 2 h. The precipitate was filtered off and washed with ethyl acetate. The filtrate was diluted with water. Sodium metabisulphite was slowly added in order to quench the remaining peroxides. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $CaSO_4$ and concentrated in vacuo to dryness.

Method C. Baeyer–Villiger oxidation of **2c** (50 mg) with *m*-CPBA (217 mg) and *p*-toluenesulfonic acid (27 mg) in dichloromethane (5 mL) for 5 h gave a crude product.

Method D. To a mixture of an appropriate ketone (0.2 mmol) and $Bi(OTf)_3$ (5 mol %) in 10 mL of anhydrous dichloromethane at 0 °C commercial grade *m*-CPBA (80% activity, 69 mg, 0.4 mmol) was added, and the reaction mixture was stirred at rt. After the completion of the reaction, the catalyst was separated by simple filtration and the unreacted *m*-CPBA was decomposed by the addition of an aq $Na_2S_2O_3$ solution. The product was extracted using ethyl acetate, and all of the organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated to yield a crude product.

Method E. To a solution of α-acetoxy ketones (0.2 mmol) in 5 mL dry $CHCl_3$ commercial grade *m*-CPBA (80% activity, 69 mg, 0.4 mmol) was added, and the reaction mixture was stirred under reflux. Then, it was cooled to rt and extracted using ethyl acetate, and all the organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated to yield a crude product.

Method F. To a mixture of the starting material (0.2 mmol) and TfOH (3 mg, 0.02 mmol) in 10 mL of anhydrous CH_2Cl_2 at 0 °C, commercial grade *m*-CPBA (80% activity, 69 mg, 0.4 mmol) was added, and the mixture was stirred at rt. After the completion of the reaction, the excess of the reagent was decomposed by the addition of an aq $Na_2S_2O_3$ solution. Conventional workup and purification by silica gel column chromatography gave the desired esters or lactones.

*3.2.1. 2,3,4,5-Tetrahydro-2-oxobenzooxepin-3-yl acetate (**4a**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 5:1) to give **4a** (40 mg, 90%) as a colorless solid. Mp 67–68 °C. IR (KBr): 3461, 2953, 1782, 1738, 1450, 1384, 1169, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.16–7.33 (m, 4H), 5.08 (dd, *J*=10.4, 8.7 Hz, 1H), 3.05 (dt, *J*=13.6, 7.9 Hz, 1H), 2.71 (dt, *J*=14.0, 7.9 Hz, 1H), 2.28–2.48 (m, 2H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 168.1, 150.5, 129.5, 129.0, 128.9, 126.4, 119.7, 69.1, 32.3, 25.7, 20.5. Anal. Calcd for $C_{12}H_{12}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.36; H, 5.64.

*3.2.2. 2,3,4,5-Tetrahydro-7-methoxy-2-oxobenzooxepin-3-yl acetate (**4b**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **4b** (48 mg, 95%) as a semisolid. IR (KBr): 3445, 2949, 1769, 1738, 1494, 1380, 1163, 835 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, J=8.8 Hz, 1H), 6.71 (dd, J=8.8, 2.9 Hz, 1H), 6.63 (d, J=2.9 Hz, 1H), 4.99 (dd, J=10.5, 8.7 Hz, 1H), 3.73 (s, 3H), 2.96 (m, 1H), 2.57 (m, 1H), 2.19–2.37 (m, 2H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 168.3, 157.8, 144.4, 130.7, 120.9, 115.3, 112.8, 69.2, 55.7, 32.3, 26.4, 20.8. Anal. Calcd for $C_{13}H_{14}O_5$ (250.25): C, 62.39; H, 5.34. Found: C, 62.43; H, 5.41.

*3.2.3. 2,3,4,5-Tetrahydro-6-methoxy-2-oxobenzooxepin-3-yl acetate (**4c**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **4c** (45 mg, 90%) as a yellow solid. Mp 122–123 °C. IR (KBr): 3450, 2948, 1772, 1736, 1485, 1379, 1157, 784 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J=8.3 Hz, 1H), 6.81 (d, J=8.1 Hz, 1H), 6.74 (d, J=8.3 Hz, 1H), 5.03 (t, J=8.7 Hz, 1H), 3.85 (s, 3H), 3.26 (dd, J=13.9, 6.5 Hz, 1H), 2.60 (dt, J=13.9, 7.5 Hz, 1H), 2.21–2.43 (m, 2H), 2.1 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 167.6, 156.9, 151.5, 128.3, 117.9, 112.2, 108.2, 69.3, 55.8, 31.6, 20.4, 17.4. Anal. Calcd for $C_{13}H_{14}O_5$ (250.25): C, 62.39; H, 5.34. Found: C, 62.33; H, 5.43.

*3.2.4. 2,3,4,5-Tetrahydro-6,8-dimethyl-2-oxobenzooxepin-3-yl acetate (**4d**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 6:1) to give **4d** (36 mg, 95%) as an oily compound. IR (neat): 3441, 2940, 1768, 1743, 1448, 1376, 1076, 838 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (s, 2H), 4.91 (t, J=9.1 Hz, 1H), 2.65–2.84 (m, 2H), 2.24 (s, 3H), 2.23 (s, 3H), 2.12–2.31 (m, 2H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 168.2, 151.1, 138.2, 136.3, 129.1, 125.0, 118.3, 69.5, 30.1, 21.4, 21.3, 20.7, 19.6. Anal. Calcd for $C_{14}H_{16}O_4$ (248.27): C, 67.73; H, 6.50. Found: C, 67.56; H, 6.33.

*3.2.5. 3,4-Dihydro-2-oxo-2H-benzo[1,4]dioxepin-3-yl acetate (**4e**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 3:1) to give **4e** (30 mg, 68%) as a colorless solid. Mp 125–126 °C. IR (KBr): 3433, 2956, 1772, 1735, 1491, 1252, 1091, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.1 (m, 4H), 5.4 (t, J=8.5 Hz, 1H), 4.5 (d, J=8.0 Hz, 2H), 2.1 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 164.2, 145.7, 143.4, 126.5, 125.2, 121.5, 119.4, 72.9, 66.7, 19.4. Anal. Calcd for $C_{11}H_{10}O_5$ (222.19): C, 59.46; H, 4.54. Found: C, 59.52; H, 4.63.

*3.2.6. 3,4-Dihydro-8-methyl-2-oxo-2H-benzo[1,4]dioxepin-3-yl acetate (**4f**)*

The crude mixture was purified by column chromatography (hexane/AcOEt 3:1) to give **4f** (33 mg, 70%) as a yellow solid. Mp 107–108 °C. IR (KBr): 3447, 2944, 1792, 1751, 1403, 1274, 1091, 832 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, J=7.8 Hz, 2H), 6.88 (d, J=8.0 Hz, 1H), 5.36 (t, J=8.7 Hz, 1H), 4.40 (d, J=8.6 Hz, 2H), 2.28 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 165.5, 144.4, 144.0, 136.4, 127.0, 122.0, 120.8, 73.9, 67.8, 20.8, 20.0. Anal. Calcd for $C_{12}H_{12}O_5$ (236.07): C, 61.01; H, 5.12. Found: C, 61.33; H, 5.24.

3.3. General procedure for the lipase-catalyzed kinetic resolution of α-acetoxy ketones

Lipase was dissolved in potassium phosphate buffer (pH 7, 25 mL) and added to a solution of the pure substrate (200 mg) in organic solvent (5 mL) and the reaction mixture was stirred at rt. The reaction was monitored by TLC and HPLC and when 50% conversion was reached, the reaction was terminated by filtration.

*3.3.1. (−)-(S) 1,2,3,4-Tetrahydro-1-oxonaphthalen-2-yl acetate (**2a**)*

HPLC (Chiralcel OBH column, flow rate of 0.8 mL/min, hexane/*i*-propanol 9:1): t_R 26.1 for (−)-**2a**, 31.7 for (+)-**2a**. $[\alpha]_D$ −63.3 (*c* 0.57, CH_2Cl_2).

*3.3.2. (−)-1,2,3,4-Tetrahydro-6-methoxy-1-oxonaphthalen-2-yl acetate (**2b**)*

HPLC (Chiralcel OBH column, flow rate of 0.8 mL/min, hexane/*i*-propanol 9:1): t_R 45.6 for (−)-**2b**, t_R 66.8 for (+)-**2b**. $[\alpha]_D$ −200 (*c* 0.074, CH_2Cl_2).

*3.3.3. (−)-1,2,3,4-Tetrahydro-5-methoxy-1-oxonaphthalen-2-yl acetate (**2c**)*

HPLC (Chiralcel OBH column, flow rate of 0.8 mL/min, hexane/*i*-propanol 9:1): t_R 29.4 for (−)-**2c**, t_R 41.7 for (+)-**2c**. $[\alpha]_D$ −61 (*c* 0.32, $CHCl_3$).

*3.3.4. (+)-1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate (**2d**)*

HPLC (Chiralcel OBH column, flow rate of 0.5 mL/min, hexane/*i*-propanol 9:1): t_R 27.6 for (−)-**2d**, t_R 41.9 for (+)-**2d**. $[\alpha]_D$ 8.9 (*c* 0.36, CH_2Cl_2).

*3.3.5. (−)-1,2,3,4-Tetrahydro-5,7-dimethyl-1-oxonaphthalen-2-yl acetate (**2d**)*

HPLC (Chiralcel OBH column, flow rate of 0.5 mL/min, hexane/*i*-propanol 9:1): t_R 27.6. $[\alpha]_D$ −49.1 (*c* 0.81, CH_2Cl_2).

*3.3.6. (−)-(S)-3,4-Dihydro-4-oxo-2H-chromen-3-yl acetate (**2e**)*

HPLC (Chiralcel OD column, flow rate of 0.8 mL/min, hexane/*i*-propanol 9:1): t_R 12.1 for (−)-**2e**, t_R 13.2 for (+)-**2e**. $[\alpha]_D$ −63 (*c* 0.5, $CHCl_3$).

*3.3.7. (−)-3,4-Dihydro-6-methyl-4-oxo-2H-chromen-3-yl acetate (**2f**)*

HPLC (Chiralpak IA column, flow rate of 0.5 mL/min, hexane/*i*-propanol 9:1): t_R 15.9 for (+)-**2f**, t_R 18.9 for (−)-**2f**. $[\alpha]_D$ −19.5 (*c* 0.6, CH_2Cl_2).

*3.3.8. (+)-(S)-2,3-Dihydro-1-oxo-1H-inden-2-yl acetate (**2g**)*

HPLC (Chiralcel OD column, flow rate of 0.8 mL/min, hexane/*i*-propanol 95:5): t_R 21.1 for (−)-**2g**, t_R 23.3 for (+)-**2g**. $[\alpha]_D$ 16.2 (*c* 0.81, CH_2Cl_2).

3.4. General procedure for the hydrolysis of lactones

To 50 mg of starting compound in 10 mL MeOH, anhydrous K_2CO_3 (1:2 equivalent) was added. The mixture was stirred for 2 h at rt and monitored by TLC.

*3.4.1. Methyl 2-hydroxy-4-(2-hydroxy-5-methoxyphenyl)-butanoate (**5a**)*

Colorless semisolid (39 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.67–1.87 (m, 2H), 2.5 (m, 2H), 3.20 (s, 3H), 3.37 (s, 3H), 3.87 (dd, J=4.1 Hz, J=7.7 Hz, 1H), 6.60 (m, 2H), 6.69 (d, J=2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$+CCl_4): δ 181.5, 151.7, 150.2, 130.3, 129.5, 117.2, 111.6, 71.9, 56.3, 50.8, 34.7, 25.7. Anal. Calcd for $C_{12}H_{16}O_5$ (240.25): C, 59.99; H, 6.71. Found: C, 60.21; H, 6.55.

*3.4.2. Methyl 2-hydroxy-3-(2-hydroxyphenyl)propanoate (**5b**)*[19]

Colorless semisolid (42 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.84 (m, 1H), 3.06 (d, J=13.9 Hz, 1H), 3.50 (s, 3H), 4.23 (d, J=5.7 Hz, 1H), 6.75 (m, 2H), 7.15 (m, 2H). ^{13}C NMR (100 MHz,

$CDCl_3$+CCl_4): δ 180.7, 160.4, 131.6, 128.3, 125.3, 120.6, 113.5, 72.8, 35.4, 23.5.

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