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Chemoenzymatic synthesis of α′- and α-acetoxylated cyclic ketones

Cihangir Tanyeli,* Engin Turkut and İdris Mecidoğlu Akhmedov

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

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Abstract—α,β-Unsaturated and saturated cyclic ketones were selectively oxidized at the α′- and α-positions using $Mn(OAc)_3$ and $Pb(OAc)_4$, respectively, resulting in high chemical yields. The resultant racemic α′- and α-acetoxylated substrates were resolved into corresponding enantiomerically enriched α′- and α-hydroxylated and acetoxylated compounds with 96–98% ee via PLE hydrolysis. The absolute configurations of α′-acetoxy-α,β-unsaturated cyclic ketones were determined by transforming them into the corresponding saturated α-acetoxy cyclic ketones of known absolute configuration.

1. Introduction

Synthetic methods for the selective oxidation of common functional groups occupy a central position in the syntheses of various complex natural products. In particular, the utilities of (±)-2-hydroxy and (±)-2-acetoxy cyclic ketones are appealing synthons[1] and several syntheses are already known.[2] Furthermore, α′-acetoxy-α,β-unsaturated cyclic ketones are also important in synthetic methodologies. The acetate group can serve as a useful protective group for the hydroxy functions in the α-hydroxy ketones.[3,4] The α-acetoxy ketones can be prepared in various ways, which include the reaction of α-bromo ketones with carboxylate ions,[5] the oxidation of morpholine enamine with thallium(III) triacetate,[6] anodic oxidation of enol acetates in acetic acid,[7] $Cu(acac)_2$ catalyzed insertion reactions of α-diazo ketones with carboxylic acids[2e] and the solvolytic reaction of α-keto triflate in acetic acid or formic acid.[8] Currently there are only a few methods that deal with the direct preparation of α-acetoxy ketones. These involve the oxidation of ketones with lead(IV) tetraacetate,[9] the oxidation of ketones with manganese(III) triacetate in acetic acid[10] and the oxidation of aromatic ketones with a hypervalent iodine reagent followed by solvolysis in acetic acid in the presence of silver carbonate.[11]

In addition to this, several studies have also been directed to the stereoselective synthesis of enantiomerically pure α-hydroxy ketones:[12] One direct method consists of the asymmetric oxidation of enolates.[13–15] Thus, by using enantiomerically pure *N*-sulfonyloxaziridines, Davis et al.[13] were able to achieve good to excellent enantioselectivities in reagent controlled asymmetric oxidations of prochiral enolates. On the other hand, in the chiral auxiliary approach, the diastereoselective oxidation of chiral enolates has been performed using oxidants such as achiral sulfonyloxaziridines, dibenzyl peroxydicarbonate and Vedejs' MoOPH reagent.[14] Along these lines, an important addition was devised by Sharpless et al.;[15] indeed, these authors have shown that α-hydroxy ketones in high enantiomeric excess can be obtained by the well-established osmium-catalyzed asymmetric dihydroxylation (AD)[16] of the corresponding enol ethers or silyl enol ethers.[15]

The lack of known syntheses of enantiomerically enriched α′-acetoxy-α,β-unsaturated cyclic ketones prompted us towards the development of a new method. In connection with our work on the development of novel procedures for the direct oxidation of α,β-unsaturated and saturated cyclic ketones with $Mn(OAc)_3$[17] and $Pb(OAc)_4$, respectively, in the synthesis of (±)-5-acetoxy-2-cyclopentenone **1a**, (±)-6-acetoxy-2-cyclohexenone **1b** and (±)-2-acetoxycyclopentanone **3a**, (±)-2-acetoxycyclohexanone **3b**, we herein report the enzymatic resolution of them into enantiomerically enriched forms. Over the course of our study on all biotransformations, screening reactions were first completed with various hydrolases (i.e., PLE, CCL, HLE and PPL) using a substrate:enzyme ratio from 1:1 to 1:0.5. Among the hydrolases studied, PLE proved suitable for the enantioselective hydrolysis of the substrates. The

* Corresponding author. Tel.: +90-312-210-32-22; fax: +90-312-210-12-80; e-mail: tanyeli@metu.edu.tr

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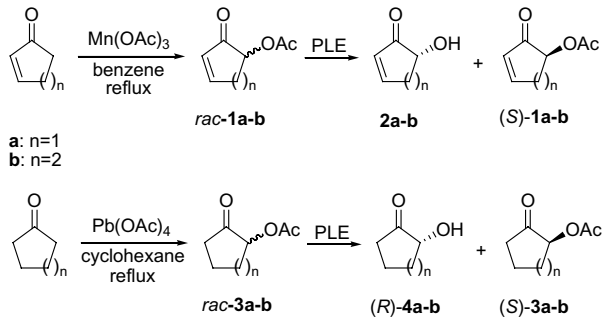


Scheme 1.

observed preliminary results proved promising and prompted us to undertake a thorough catalytic study. PLE-catalyzed reactions of acetoxylated substrates (±)-**1a** and **b** and (±)-**3a** and **b** afforded hydroxylated (*R*)-(−)-**4a**, (*R*)-(+)-**4b** and acetoxylated (*S*)-(+)-**1a**, (*S*)-(−)-**1b**, (*S*)-(+)-**3a**, (*S*)-(−)-**3b** (Scheme 1).

2. Results and discussion

2.1. Synthesis of racemic substrates 1a and b and 3a and b

Racemic **1a** and **b** were obtained in 65% and 72% chemical yields, respectively, using a manganese(III) acetate oxidation method by refluxing α,β-unsaturated cyclic enones (1:1 molar ratio) in benzene under a Dean–Stark trap for 8 h.[17] The $Mn(OAc)_3$ method did not afford the desired α-acetoxylated products **3a** and **b** with saturated cyclic ketones. Thus, we improved the known literature $Pb(OAc)_4$[9] procedure applied for saturated ketones in which acetic acid or benzene is used as the solvent with low chemical yield. In our modified procedure, saturated cyclic ketones were refluxed with $Pb(OAc)_4$ (1:2 molar ratio) in cyclohexane under an argon atmosphere for 12 h to afford racemic **3a** and **b** in 62% and 92% chemical yields, respectively.

2.2. Enzymatic hydrolyses of racemic substrates 1a and b and 3a and b

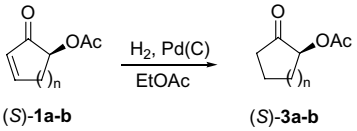
Various lipases (PLE, CCL, HLE and PPL) were tested with all racemic substrates **1a** and **b** and **3a** and **b**. Among these lipases, PLE gave the best results whereas the other lipases afforded poor chemical yields and ees (<10% ee). The first bioconversion was performed using PLE according to the following general procedure. To a stirred solution of **1a** (500 mg) in phosphate buffer (pH 7.00, 50 mL), PLE (100 μL) was added in one portion and the reaction mixture stirred at 20 °C in a pH stat unit. The conversion was monitored by TLC. After 5 h, (+)-5-acetoxy-2-cyclopentenone **1a** was obtained with 96% ee in 45% chemical yield (Table 1, entry 1). The next attempt involved substrate **1b** using PLE under the same conditions as above. (−)-6-Acetoxy-2-cyclohexenone **1b** was obtained with 97% ee in 46% isolated yield (entry 2). 5-Hydroxy-2-cyclopentenone **2a** and 6-hydroxy-2-cyclohexenone **2b** were not isolated in enantiomerically enriched forms. This is presumably due to the fast racemization and/or rearrangement of α′-hydroxylated cyclic enones as observed in our previous work.[18]

The bioconversion of (±)-2-acetoxycyclopentanone **3a** afforded (+)-2-acetoxycyclopentanone **3a** and (−)-2-hydroxycyclopentanone **4a** with 98% and 99% ee in 47% and 44% isolated yields, respectively (entry 3). In the last example, we attempted to hydrolyze (±)-2-acetoxycyclohexanone **3b** using the same enzyme, which afforded (−)-2-acetoxycyclohexanone **3b** with 96% ee and (+)-2-hydroxycyclohexanone **4b** with 99% ee (entry 4).

2.3. Absolute configuration determinations

The absolute configurations of acetoxylated and hydroxylated saturated cyclic ketones **3a** and **b** and **4a** and **b** were determined by comparing the sign of their specific rotations (at the same concentration and in the same solvent) with those in the literature. According to these results, (−)-2-hydroxycyclopentanone **4a**[19a] and (+)-2-hydroxycyclohexanone **4b**[19b] have (*R*)-configurations, whereas (+)-2-acetoxycyclopentanone **3a**[19a] and (−)-2-acetoxycylohexanone **3b**[19c] have (*S*)-configurations.

In the absolute configuration determinations of α′-acetoxylated cyclic enones **1a** and **b**, they were transformed into the corresponding saturated cyclic ketones **3a** and **b** by H_2, Pd(C). According to these transformations results, both (+)-5-acetoxy-2-cyclopentenone **1a** and (−)-6-acetoxy-2-cyclohexenone **1b** have (*S*)-configurations (Scheme 2).



Scheme 2.

Table 1

Entry	Substrate	Time (h)	Acetoxy pdt.	Yield (%)[a]	$[\alpha]_D^{20}$	Ee (%)[b]	Hydroxy pdt.	Yield (%)[a]	$[\alpha]_D^{20}$	Ee (%)[c]
1	(±)-**1a**	5	(*S*)-(+)-**1a**	45	+60.3	96	—	—	—	—
2	(±)-**1b**	3	(*S*)-(−)-**1b**	46	−88.7	97	—	—	—	—
3	(±)-**3a**	8	(*S*)-(+)-**3a**	47	+61.6	98	(*R*)-(−)-**4a**	44	−42.2	99
4	(±)-**3b**	7	(*S*)-(−)-**3b**	45	−87.5	96	(*R*)-(+)-**4b**	39	+14.1	99

[a] Yields (%) are given as the isolated yields.
[b] Enantiomeric excess values are determined by the Chiralcel ODH chiral column HPLC analysis.
[c] Enantiomeric excess values are determined by the Phenomenex Chirex (*S*)-LEU and (*R*)-NEA chiral column HPLC analysis.

3. Conclusion

Herein, we have improved the direct regioselective oxidations of α,β-unsaturated and saturated cyclic ketones using $Mn(OAc)_3$ and $Pb(OAc)_4$, respectively, in good yields and have shown that enantiomerically enriched forms of (*S*)-**1a**–**b**, (*S*)-**3a**–**b** and (*R*)-**4a**–**b** can be obtained through enzymatic hydrolyses of racemic substrates **1a** and **b** and **3a** and **b**. Among the enzymes used in hydrolysis conditions, PLE showed the best enantioselectivity. The absolute configurations of both **1a** and **b** were determined by transforming them into the corresponding saturated derivatives **3a** and **b**, respectively, with H_2/Pd(C) in EtOAc. Commercially available and inexpensive enzyme PLE used in catalytic levels, renders the process very attractive for large scale preparations.

4. Experimental

^1H NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane. IR spectra were obtained from a Perkin–Elmer Model 1600 series FT-IR spectrometer and are reported in cm^{-1}. Optical rotations were measured in $CHCl_3$ and MeOH solution in a 1 dm cell using a Bellingham & Stanley P20 polarimeter at 20 °C. Mass spectra were recorded on a Varian MAT 212. PLE (Pig Liver Esterase) and HLE (Horse Liver Esterase) were purchased from Sigma as a suspension in ammonium sulfate solution (3.2 mol/L) and as a powder, respectively. CCL (Lipase, Type VII, from *Candida Rugosa*) and PPL (Lipase, Type II, from Porcine Pancreas) were purchased from Aldrich.

4.1. General procedure for the $Mn(OAc)_3$ oxidation of α,β-unsaturated ketones 1a and b

A mixture of $Mn(OAc)_3$ (3.25 g, 14.0 mmol) in benzene (150 mL) was refluxed for 45 min using a Dean–Stark trap. The mixture was then cooled to room temperature and enone (7.0 mmol) gradually added. The mixture was allowed to reflux until the dark brown colour disappeared and also monitored by TLC. The reaction mixture was diluted with ethyl acetate (150 mL) and the organic phase washed with 1 M HCl (150 mL), saturated $NaHCO_3$ (150 mL) and brine (150 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product mixture was separated by flash column chromatography using ethyl acetate/hexane (1:3) as eluent to afford product **1a** or **b**.

4.1.1. (±)-5-Acetoxy-2-cyclopentenone 1a. (0.64 g, 65%) as a colourless oil; R_f (EtOAc/hexane 1:3) 0.38; ν_{max} (neat) 1743, 1635 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.76–7.78 (1H, m, C*H*=CHCO), 6.34–6.36 (1H, m, CH=C*H*CO), 5.20 (1H, dd, *J* 3, 7 Hz, C*H*OAc), 3.21–3.29 (1H, m, C$H_a$$H_b$CHOAc), 2.66–2.73 (1H, ddd, *J* 3, 5, 19 Hz, $CH_a$$H_b$CHOAc), 2.22 (3H, s, *Me*CO_2); δ_C (100.6 MHz, $CDCl_3$) 202.5, 174.2, 169.1, 129.3, 75.2, 40.4, 21.2; HRMS (EI): M^+, found 140.0468. $C_7H_8O_3$ requires 140.0473.

4.1.2. (±)-6-Acetoxy-2-cyclohexenone 1b. (0.77 g, 72%) as a colourless oil; R_f (EtOAc/hexane 1:2) 0.26; ν_{max} (neat) 1732, 1677, 1608 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.87–6.92 (1H, m, C*H*=CHCO), 5.98–6.02 (1H, m, CH=C*H*CO), 5.30 (1H, dd, *J* 5, 8 Hz, C*H*OAc), 2.47–2.51 (2H, m, CH_2CH=CH), 2.19–2.23 (1H, m, C$H_a$$H_b$CHOAc), 2.11 (3H, s, *Me*CO_2), 2.02–2.09 (1H, m, $CH_a$$H_b$CHOAc); δ_C (100.6 MHz, $CDCl_3$) 194.4, 170.5, 150.3, 128.9, 73.9, 28.9, 25.9, 21.2; HRMS (EI): M^+, found 154.0632. $C_8H_{10}O_3$ requires 154.0630.

4.2. General procedure for the $Pb(OAc)_4$ oxidation of saturated ketones 3a and b

A mixture of $Pb(OAc)_4$ (5.00 g, 11.0 mmol) and cyclic ketone (11.0 mmol) in cyclohexane (50 mL) was allowed to reflux for 12 h and monitored by TLC. The reaction mixture was diluted with cyclohexane (50 mL) and the organic phase washed with water (100 mL), brine (100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product mixture was separated by flash column chromatography using ethyl acetate/hexane (1:2) as eluent to afford product **3a** or **b**.

4.2.1. (±)-2-Acetoxycyclopentanone 3a. (0.96 g, 62%) as a colourless oil; R_f (EtOAc/hexane 1:2) 0.47; ν_{max} (neat) 1753, 1744 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.99 (1H, t, *J* 10 Hz, C*H*OAc), 2.23–2.37 (2H, m, CH_2CO), 2.07–2.20 (2H, m, CH_2CHOAc), 2.01 (3H, s, *Me*CO_2), 1.69–1.88 (2H, m, C$H_2$$CH_2$CHOAc); δ_C (100.6 MHz, $CDCl_3$) 212.6, 170.3, 75.7, 35.1, 28.4, 20.2, 17.4; HRMS (EI): M^+, found 141.0552. $C_7H_9O_3$ requires 141.0552.

4.2.2. (±)-2-Acetoxycyclohexanone 3b. (1.58 g, 92%) as a colourless oil; R_f (EtOAc/hexane 1:2) 0.51; ν_{max} (neat) 1750, 1720, 1230 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.05–5.14 (1H, m, C*H*OAc), 2.41–2.48 (1H, m, C$H_a$$H_b$CO), 2.27–2.38 (1H, m, $CH_a$$H_b$CO), 2.19–2.26 (1H, m, C$H_a$$H_b$COAc), 2.08 (3H, s, *Me*$CO_2$), 1.98–2.06 (1H, m, $CH_a$$H_b$COAc), 1.85–1.95 (1H, m, C$H_a$$H_b$$CH_2$CO), 1.63–1.77 (2H, m, C$H_2$$CH_2$CHOAc), 1.48–1.62 (1H, m, $CH_a$$H_b$$CH_2$CO); δ_C (100.6 MHz, $CDCl_3$) 204.8, 170.4, 76.9, 41.1, 33.4, 27.5, 24.1, 21.1; HRMS (EI): M^+, found 156.0784. $C_8H_{12}O_3$ requires 156.0786.

4.3. General procedure for enzymatic hydrolyses of 1a and b and 3a and b

To a stirred solution of 500 mg *rac*-**1a**–**b** or *rac*-**3a**–**b** in 50 mL pH 7.00 phosphate buffer, 100 μL PLE was added in one portion and the reaction mixture stirred at 20 °C

in a pH stat unit. The conversion was monitored by TLC. The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash column chromatography (EtOAc/hexane 1:3).

4.3.1. (*S*)-(+)-5-Acetoxy-2-cyclopentenone (*S*)-(+)-1a. (0.23 g, 45%) as a colourless oil; 96% ee $[\alpha]_D^{20} = +60.3$ (*c* 0.2, $CHCl_3$).

4.3.2. (*S*)-(−)-6-Acetoxy-2-cyclohexenone (*S*)-(−)-1b. (0.23 g, 46%) as a colourless oil; 97% ee $[\alpha]_D^{20} = -88.7$ (*c* 0.5, MeOH).

4.3.3. (*S*)-(+)-2-Acetoxycyclopentanone (*S*)-(+)-3a. (0.24 g, 47%) as a colourless oil; 98% ee $[\alpha]_D^{20} = +61.6$ (*c* 1.57, $CHCl_3$), lit.[19a] $[\alpha]_D^{20} = +61.0$ (*c* 2.0, $CHCl_3$).

4.3.4. (*R*)-(−)-2-Hydroxycyclopentanone (*R*)-(−)-4a. (0.15 g, 44%) as a colourless oil; 99% ee $[\alpha]_D^{20} = -42.2$ (*c* 1.2, $CHCl_3$), lit.[19a] $[\alpha]_D^{20} = -38.4$ (*c* 1.2, $CHCl_3$); ν_{max} (neat) 3153, 1790, 1721 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.99 (1H, t, *J* 10 Hz, C*H*OH), 3.12–3.16 (1H, br s, O*H*), 2.26–2.40 (2H, m, CH_2CO), 2.06–2.18 (1H, m, CH_aH_bCHOH), 1.91–2.05 (1H, m, CH_aH_bCHOH), 1.56–1.83 (2H, m, CH_2CH_2CO); δ_C (100.6 MHz, $CDCl_3$) 218.8, 76.2, 34.4, 31.0, 16.7; HRMS (EI): M^+, found 100.0520. $C_5H_8O_2$ requires 100.0524.

4.3.5. (*S*)-(−)-2-Acetoxycyclohexanone (*S*)-(−)-3b. (0.23 g, 45%) as a colourless oil; 96% ee $[\alpha]_D^{20} = -87.5$ (*c* 0.2, MeOH), lit.[19c] for (*R*)-(+)-**3b** $[\alpha]_D^{20} = +89.3$ (*c* 1.0, MeOH).

4.3.6. (*R*)-(+)-2-Hydroxycyclohexanone (*R*)-(+)-4b. (0.14 g, 39%) as a colourless oil; 99% ee $[\alpha]_D^{20} = +14.1$ (*c* 0.5, $CHCl_3$), lit.[19d] for (*R*)-(+)-**3b** $[\alpha]_D^{20} = +13.4$ (*c* 0.5, $CHCl_3$); ν_{max} (neat) 3146, 1790, 1716 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.00–4.15 (1H, m, C*H*OH), 2.8 (1H, br s, O*H*), 2.46–2.55 (1H, m, CH_aH_bCO), 2.35–2.45 (1H, m, CH_aH_bCO), 2.24–2.34 (1H, m, CH_aH_bCHOH), 2.01–2.10 (1H, m, CH_aH_bCHOH), 1.35–1.88 (4H, m, CH_2CH_2); δ_C (100.6 MHz, $CDCl_3$) 211.7, 75.7, 39.8, 37.1, 27.9, 23.8; HRMS (EI): M^+, found 114.0680. $C_6H_{10}O_2$ requires 114.0681.

4.4. Hydrogenation of (*S*)-1a and (*S*)-1b

To a stirred solution of (*S*)-**1a** (0.20 g) in EtOAc (20 mL), Pd(C) (10 mg) was added and stirred at room temperature under a hydrogen atmosphere for 3 h. The filtration of the mixture followed by evaporation of the solvent in vacuo quantitatively afforded (*S*)-**3a**. The same procedure was applied for the transformation of (*S*)-**1b** into (*S*)-**3b**. All spectroscopic data of the products are in accordance with (*S*)-**3a** and (*S*)-**3b**, respectively.

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