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The first enzymatic resolution of quaternary α′-acetoxy α,β-unsaturated cyclohexenones and cyclopentenones

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Abstract—The enantioselective resolution of various quaternary α′-acetoxy α,β-unsaturated cyclohexenones and cyclopentenones was performed with the commercially available enzyme CCL in pH = 8.0 phosphate buffer. Various parameters that would affect the enantioselectivities were tested and the best enzymatic resolution conditions were found to afford the enantiomerically enriched quaternary acetoxylated substrates with high ee varying between 36% and 99%.

1. Introduction

A broad repertoire of chiral auxiliaries, reagents, and catalysts can be utilized for the reliable generation of tertiary stereocenters.[1] In contrast, the asymmetric construction of molecules with quaternary carbon stereocenters, that is, carbon stereocenters with four different non-hydrogen substituents, represents a very challenging and dynamic area in organic synthesis. The preparation of compounds with these centers with catalytic enantioselective reactions is also particularly demanding.[2] Tertiary alcohols and their derivatives containing tertiary C–O bonds are useful building blocks for many drugs and natural products, such as a prostaglandin analogue,[3] frontalin,[4] and a vitamin D_3 metabolite.[5] In comparison with the process for preparing optically active secondary alcohols, the synthesis of enantiomerically pure tertiary alcohols is still a challenging problem. The α-hydroxy carbonyl array is a common feature of many biologically important molecules and key intermediates in the synthesis of natural products.[6] Some of the biologically important compounds contain quaternary α-hydroxy carbonyl moieties, such as scyphostatin, which is the specific inhibitor of neutral sphingomyelinase,[7] and the anthracycline antitumor antibiotics adriamycin and daunomycin.[8]

The classical method for the preparation of optically active tertiary alcohols is via separation of their properly derivatized diastereomers.[9] Another common method involves multistep transformation from chiral pools of natural products, such as terpenes, amino acids, and carbohydrates.[10] Asymmetric synthesis by the addition of chiral organometallic reagents to unsymmetric ketones is a promising approach for obtaining optically active tertiary alcohols.[11] The catalytic asymmetric synthesis by dihydroxylation of 1,1-disubstituted olefins is so far the most effective method.[12] The catalytic asymmetric epoxidation of 1,1-disubstituted olefins followed by treatment with either a base or a nucleophile, leads to various tertiary alcohols.[13] In addition to these, several studies have also been directed toward the stereoselective synthesis of enantiomerically pure α-hydroxy ketones.[14] One direct method consists of the asymmetric oxidation of enolates.[15] However, microbial or enzymatic methods including lipases proved unsuccessful, since tertiary alcohols are usually too bulky to have access to the active sites of lipases.[16]

The lack of known syntheses of enantiomerically enriched quaternary α′-acetoxy-α,β-unsaturated cyclic ketones **2** prompted us toward the development of a new method. In connection with our work on the development of novel procedures for the manganese(III) acetate based direct oxidation of an alkyl substituted α′-position on cyclic α,β-unsaturated ketones **1**,[17] we herein report the enzymatic resolution of them into enantiomerically enriched forms. Over the course of our studies on all

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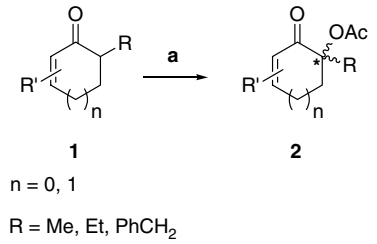


Scheme 1. Reagents and conditions: (a) $Mn(OAc)_3$, benzene, reflux.

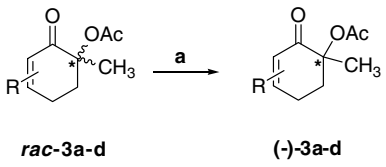
biotransformations, screening reactions were first completed with various hydrolases (i.e., PLE, CCL, HLE, and PPL) using a substrate:enzyme ratio from 1:1 to 1:0.5. Among the hydrolases studied, CCL proved suitable for the enantioselective hydrolysis of the substrates.

1.1. Synthesis of racemic substrates

α′-Substituted α,β-unsaturated cyclopentanones and cyclohexanones **1** were prepared from the corresponding α,β-unsaturated cyclic ketones using the slightly modified literature procedures,[18] with LDA and corresponding alkyl halides at −78 °C, which subsequently allowed us to react with $Mn(OAc)_3$. α′-Alkyl α,β-unsaturated cyclopentanones and cyclohexanones **1** (with dry benzene as the solvent) underwent selective oxidation with $Mn(OAc)_3$ to afford products **2** (Scheme 1).[17]

1.2. Enzymatic hydrolyses of racemic substrates

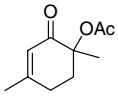
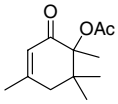
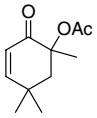
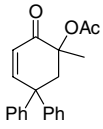
Various lipases (PLE, CCL, HLE, and PPL) were tested with all racemic substrates. It has been reported by us that (±)-6-acetoxy-3-methyl-2-cyclohexen-1-one can be resolved by PLE catalyzed hydrolysis to afford an enantiomerically enriched 6-hydroxy derivative with 95% ee.[19] Therefore, it was decided to examine the hydrolysis reaction of α′-substituted α′-acetoxy α,β-unsaturated cyclic ketones **2** by PLE, which is known for its broad substrate specificity and high stereoselectivity. (±)-6-Acetoxy-3,6-dimethyl-2-cyclohexen-1-one **3a** was chosen as a model compound and subjected to enzymatic resolution with PLE (Scheme 2). Treatment of the substrate in the absence of enzyme revealed that it does not undergo autohydrolysis. The enzymatic hydrolysis reaction was performed according to the following procedure. To a stirred solution of **3a** (100 mg) in phosphate buffer (pH 7.00, 10 mL), PLE (100 μL) was added in one portion and the reaction mixture stirred at 20 °C. The reaction was monitored by TLC. However, no hydrolysis was recorded after 156 h. Since the enantioselectivity of the enzymatic reactions depends on the pH, temperature and the addition of a co-solvent, screening reactions were performed by changing these parameters. The effect of temperature was examined by changing it from 14 to 28 °C. No change in the reaction was observed. Upon changing co-solvents (DMSO, *i*-propanol, *tert*-butyl methyl ether, and *n*-butanol), no new effect was recorded. It was decided to examine the effect of pH on the reaction. Substrate **3a** was subjected to pH 7.50 and pH 8.00 buffers in the absence of enzyme. It was observed that the substrate does not undergo any autohydrolysis between this pH range. Finally, substrate **3a** was subjected to enzymatic hydrolysis by the addition of 100 μL PLE in pH 7.50 and pH 8.00 buffers, respectively. It was recorded that in pH 8.00 buffer, the enzymatic hydrolysis started in 48 h. There was no hydrolysis at pH 7.50. Around 50% conversion was completed within 96 h in a pH 8.00 buffer system with PLE. The crude product was separated by flash column chromatography. (−)-6-Acetoxy-3,6-dimethyl-2-cyclohexen-1-one **2a** was obtained in 42% yield and 5% ee. Although the enantioselectivity was low, this first example showed that α′-substituted α′-acetoxy α,β-unsaturated cyclic ketones can be resolved by hydrolase type enzymes. From this, it was decided to examine the enzymatic hydrolysis reactions of the model compound **3a** with the other hydrolases like CCL, PPL, and HLE. The screening reactions were first performed to find out the optimum conditions in the hydrolysis reactions. All reactions were performed in a 1:0.5 substrate:enzyme molar ratio at pH 7.00. At this pH, no hydrolysis was recorded. The pH was increased to pH 8.00 by the addition of 1 M NaOH. The hydrolysis reactions of the substrate **3a** with CCL was completed within 78 h with 48% ee at 20 °C. No hydrolysis was recorded with PPL and HLE. When the pH was increased to 8.50, complete racemization of the substrate was recorded. Hence, the optimum pH in the hydrolysis should be pH 8.00. The temperature effect was also investigated. The temperature was changed from 14 to 28 °C, and the optimum temperature was found to be 20 °C for the enzyme CCL. Next, we focused on the enzymatic hydrolysis reactions with CCL and the optimum conditions found to be pH 8.00 buffer system, at 20 °C, with DMSO used as co-solvent. The substrate:enzyme molar ratio was changed from 1:0.5 to 1:1, and the ee increased to 99%. When the enzyme was used in a stoichiometric amount, the enantioselectivity increased. (−)-6-Acetoxy-3,6-dimethyl-2-cyclohexen-1-one **3a** was synthesized in 46% isolated yield in 99% ee at pH 8.00 buffer, at 20 °C. CCL, which is generally known for its stereoselectivity in the hydrolysis of secondary alcohols, appeared to be the best enzyme tested.



Scheme 2. Reagents and conditions: (a) Lipases, DMSO, pH = 8.00 phosphate buffer, 20 °C.

In order to examine the effect of substituents on the cyclohexenone ring system, various α′-methyl substituted α′-acetoxy cyclohexenones were subjected to hydrolysis by CCL. The results of enzymatic resolutions on different substrates are summarized in Table 1. The reaction was performed according to the following procedure: Substrate (100 mg) was added to pH 8.00 buffer (20 mL) in 1 mL of DMSO. CCL (100 mg) was then added to the solution and shaken for 96–148 h by TLC monitoring at 20 °C. The presence of substituents

Table 1.

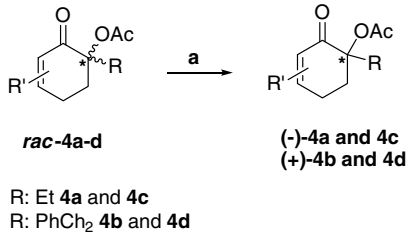
Entry	Substrate	3	Acetoxylated product	Time (h)	Yield (%)[a]	ee (%)[b]	$[\alpha]_D^{20}$
1		(±)-**3a**	(−)-**3a**	96	46	99	−13.1
2		(±)-**3b**	(−)-**3b**	108	51	62	−1.8
3		(±)-**3c**	(−)-**3c**	122	52	94	−42.2
4		(±)-**3d**	(−)-**3d**	136	48	73	−29.2

[a] Yields (%) are given as isolated yields.
[b] Enantiomeric excesses were determined by the Chiralcel ODH chiral column HPLC analysis.

at the fifth position, near the carbon atom of the stereogenic center, significantly decreases the enantioselectivity of the enzyme (entry 2). Substrates **3c** and **3d** (entries 3 and 4) were employed to test the effect of the substitution on the fourth carbon. In entry 3, substrate **3c** was resolved with 94% ee as high as substrate **3a**. In entry 4, a rapid decrease in enantioselectivity was observed (73% ee). This can be attributed to the solubility problem of the diphenyl substituted substrate.

The effects of the relatively bulkier substituents on the stereogenic center were examined by CCL hydrolysis of ethyl and benzyl substituted acetoxy cyclohexenones **4a–d** (Scheme 3). When the resolution of methyl substituted substrate **3a** was compared with ethyl and benzyl substituted substrates **4a** and **4b**, the bulkier ethyl and benzyl groups decreased the enantioselectivity to 71% and 61% ee, respectively (entries 1 and 2 in Table 2). A similar steric effect was observed for substrates **4c** and **4d** by comparing methyl substituted substrate **3b** as 45% and 36% ee, respectively.

Enzymatic resolution with CCL was also applied to α′-substituted 5-acetoxy cyclopentenones **5a–d** (Scheme 4). The results are summarized in Table 3. When the substituent was changed from methyl to either ethyl or benzyl



Scheme 3. Reagents and conditions: (a) CCL, DMSO, pH = 8.00 phosphate buffer, 20 °C.

(entries 1–3), the selectivity drastically decreased from 99% ee to 53% and 43% ee, respectively. In entry 4, (±)-5-acetoxy-2,3,5-trimethyl-2-cyclopenten-1-one **5d** afforded (−)-**5d** in 90% ee as expected.

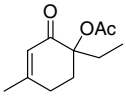
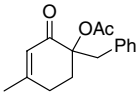
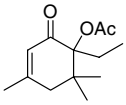
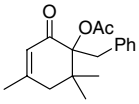
2. Conclusion

Herein, we have reported the first enzymatic resolutions of various quaternary α′-acetoxy-α,β-unsaturated cyclic ketones and have shown that the substituents on the quaternary and on the neighboring center drastically influence the enantioselectivity of the enzyme. Among the enzymes used under the hydrolysis conditions, CCL showed the best enantioselectivity. We have found out that the pH factor is crucial for high enantioselectivity. Commercially available and inexpensive enzyme CCL renders the process very attractive for large-scale preparations.

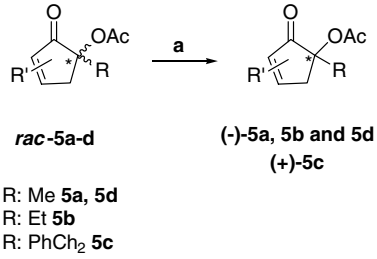
3. Experimental

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brucker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane. Apparent splittings are given in all cases. Infrared spectra were obtained from KBr pellets on a Mattson 1000 FT-IR spectrophotometer. Mass spectra were recorded on a Varian MAT 212. Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III polarimeter at 20 °C. HPLC measurements were performed with ThermoFinnigan Spectra System instrument. Separations were carried out on Chiralcel OD-H analytical column (250 × 4.60 mm) with hexane/2-propyl alcohol as eluent. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2-mm silica gel 60 F_{254} analytical aluminum plates. PLE (Pig

Table 2.

Entry	Substrate	4	Acetoxylated product	Time (h)	Yield (%)[a]	ee (%)[b]	$[\alpha]_D^{20}$
1		(±)-**4a**	(−)-**4a**	148	47	71	−12.5
2		(±)-**4b**	(+)-**4b**	142	48	61	+0.4
3		(±)-**4c**	(−)-**4c**	132	49	45	−3.2
4		(±)-**4d**	(+)-**4d**	138	45	36	+0.2

[a] Yields (%) are given as isolated yields.
[b] Enantiomeric excesses were determined by Chiralcel ODH chiral column HPLC analysis.



Scheme 4. Reagents and conditions: (a) CCL, DMSO, pH = 8.00 phosphate buffer, 20 °C.

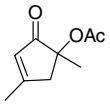
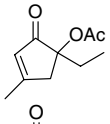
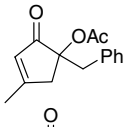
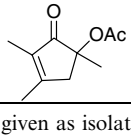
Liver Esterase) and HLE (Horse Liver Esterase) were purchased from Sigma as a suspension in ammonium sulfate solution (3.2 mol/L) and as a powder, respectively. CCL (Lipase, Type VII, from *Candida Rugosa*) and PPL (Lipase, Type II, from Porcine Pancreas) were purchased from Aldrich.

3.1. General procedure for the $Mn(OAc)_3$ oxidations of α′-alkyl α,β-unsaturated ketones (±)-3a–d, (±)-4a–d, and (±)-5a–d

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 cooled to room temperature and the α′-alkyl α,β-unsaturated (7.0 mmol) gradually added. The mixture was allowed to reflux until the dark brown color disappeared and also monitored by TLC. The reaction mixture was diluted with an equal amount of ethyl acetate and the organic phase washed with 1 M HCl, followed by saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by flash column chromatography using ethyl acetate/hexane as eluent.

Compounds **3a**–**d**, **4c**, and **5a**–**c** were synthesized and all are in accordance with the literature data.[17]

Table 3.

Entry	Substrate	5	Acetoxylated product	Time (h)	Yield (%)[a]	ee (%)[b]	$[\alpha]_D^{20}$
1		(±)-**5a**	(−)-**5a**	94	48	99	−33.6
2		(±)-**5b**	(−)-**5b**	100	52	53	−8.4
3		(±)-**5c**	(+)-**5c**	136	47	43	+1.2
4		(±)-**5d**	(−)-**5d**	98	46	90	−23.8

[a] Yields (%) are given as isolated yields.
[b] Enantiomeric excesses were determined by the Chiralcel ODH chiral column HPLC analysis.

3.1.1. (±)-6-Acetoxy-6-ethyl-3-methyl-2-cyclohexen-1-one (±)-4a. (0.97 g, 72%) as a colorless oil, R_f (EtOAc/hexane 1:4) 0.22; ν_{max} (neat) 3421, 2968, 1735, 1663, 1447 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.02 (1H, s, =C*H*), 2.71–2.82 (2H, m, =CCH_2), 2.38–2.47 (2H, m, CH_2COAc), 2.01 (3H, s, *Me*CO_2), 1.87 (3H, s, *Me*C=), 1.53–1.74 (2H, m, MeCH_2), 0.85 (3H, t, $J = 7$ Hz, *Me*CH_2); δ_C (100.6 MHz, $CDCl_3$) 208.0, 171.1, 158.1, 124.9, 81.3, 47.3, 37.4, 30.0, 27.8, 21.1, 19.2; HRMS (EI) M+, found 196.1098, $C_{11}H_{16}O_3$ requires 196.1100.

3.1.2. (±)-6-Acetoxy-6-benzyl-3-methyl-2-cyclohexen-1-one (±)-4b. (1.07 g, 59%) as a colorless oil, R_f (EtOAc/hexane 1:5) 0.32; ν_{max} (neat) 3012, 2961, 1730, 1652, 1493 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.34 (2H, d, $J = 6$ Hz, *Ph*), 7.19–7.26 (3H, m, *Ph*), 5.93 (1H, s, =C*H*), 3.58 (1H, d, $J = 14$ Hz, PhC$H_a$$H_b$), 3.19 (1H, d, $J = 14$ Hz, PhC$H_a$$H_b$), 2.80–2.83 (2H, m, =CC$H_2$), 2.28–2.34 (2H, m, C$H_2$COAc), 2.05 (3H, s, *Me*$CO_2$), 1.87 (3H, s, *Me*C=); δ_C (100.6 MHz, $CDCl_3$) 194.5, 170.2, 159.1, 135.3, 130.4, 128.2, 127.4, 126.9, 125.1, 85.8, 40.3, 37.6, 35.0, 24.2, 21.5, 15.0; HRMS (EI) M+, found 258.1254, $C_{16}H_{18}O_3$ requires 258.1256.

3.1.3. (±)-6-Acetoxy-6-benzyl-3,5,5-trimethyl-2-cyclohexen-1-one (±)-4d. (1.14 g, 57%) as a colorless oil, R_f (EtOAc/hexane 1:5) 0.31; ν_{max} (neat) 3014, 2950, 1734, 1652 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.31 (2H, d, $J = 7$ Hz, *Ph*), 7.15–7.24 (3H, m, *Ph*), 5.83 (1H, s, =C*H*), 3.68 (1H, d, $J = 14$ Hz, PhC$H_a$$H_b$), 2.92 (1H, d, $J = 14$ Hz, PhC$H_a$$H_b$), 2.56 (1H, d, $J = 18$ Hz, C$H_a$$H_b$), 2.31 (1H, d, $J = 18$ Hz, C$H_a$$H_b$), 2.05 (3H, s, *Me*$CO_2$), 1.93 (3H, s, =C*Me*), 0.94 (3H, s, C*Me*Me), 0.89 (3H, s, CMe*Me*); δ_C (100.6 MHz, $CDCl_3$) 196.2, 169.0, 153.1, 137.0, 131.6, 130.4, 127.7, 127.4, 126.3, 126.2, 125.3, 110.5, 86.8, 44.8, 41.2, 33.5, 24.5, 22.5; HRMS (EI) M+, found 286.1568, $C_{18}H_{22}O_3$ requires 286.1569.

3.1.4. (±)-5-Acetoxy-2,3,5-trimethyl-2-cyclopenten-1-one (±)-5d. (0.61 g, 48%) as a colorless oil, R_f (EtOAc/hexane 1:4) 0.17; ν_{max} (neat) 3018, 2400, 1735, 1672, 1521 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.80 (1H, d, $J = 18$ Hz, C$H_a$$H_b$), 2.32 (1H, d, $J = 18$ Hz, C$H_a$$H_b$), 2.01 (3H, s, *Me*$CO_2$), 1.88 (3H, s, =C*Me*CO), 1.82 (3H, s, *Me*C=), 1.16 (3H, s, *Me*COAc); δ_C (100.6 MHz, $CDCl_3$) 205.4, 173.1, 170.2, 127.8, 81.4, 46.3, 30.1, 23.8, 21.3, 20.0; HRMS (EI) M+, found 182.0942, $C_{10}H_{14}O_3$ requires 182.0943.

3.2. General procedure for CCL hydrolysis of 3a–d, 4a–d, and 5a–d

To a stirred solution of 100 mg substrate in 20 mL pH 8.00 phosphate buffer and 1 mL DMSO, 100 mg CCL was added in one portion and shaken at 20 °C. 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 as an eluent).

3.2.1. (−)-6-Acetoxy-3,6-dimethyl-2-cyclohexen-1-one (−)-3a. (46 mg, 46%) as a colorless oil; 99% ee $[\alpha]_D^{20} = -13.1$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 88:12), 1.0 mL/min flow rate, 254 nm $t_1 = 15.6$ min (major), $t_2 = 17.2$ min (minor).

3.2.2. (−)-6-Acetoxy-3,5,5,6-tetramethyl-2-cyclohexen-1-one (−)-3b. (51 mg, 51%) as a colorless oil; 62% ee $[\alpha]_D^{20} = -1.8$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 85:15), 1.0 mL/min flow rate, 254 nm $t_1 = 12.1$ min (major), $t_2 = 13.6$ min (minor).

3.2.3. (−)-6-Acetoxy-4,4,6-trimethyl-2-cyclohexen-1-one (−)-3c. (52 mg, 52%) as a colorless oil; 94% ee $[\alpha]_D^{20} = -42.2$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 90:10), 1.0 mL/min flow rate, 254 nm $t_1 = 14.5$ min (major), $t_2 = 16.9$ min (minor).

3.2.4. (−)-6-Acetoxy-6-methyl-4,4-diphenyl-2-cyclohexen-1-one (−)-3d. (48 mg, 48%) as a colorless oil; 73% ee $[\alpha]_D^{20} = -29.2$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 88:12), 1.0 mL/min flow rate, 254 nm $t_1 = 17.1$ min (minor), $t_2 = 20.4$ min (major).

3.2.5. (−)-6-Acetoxy-6-ethyl-3-methyl-2-cyclohexen-1-one (−)-4a. (47 mg, 47%) as a colorless oil; 71% ee $[\alpha]_D^{20} = -12.5$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 87:13), 1.0 mL/min flow rate, 254 nm $t_1 = 15.7$ min (major), $t_2 = 18.5$ min (minor).

3.2.6. (+)-6-Acetoxy-6-benzyl-3-methyl-2-cyclohexen-1-one (+)-4b. (48 mg, 48%) as a colorless oil; 61% ee $[\alpha]_D^{20} = +0.4$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 85:15), 1.0 mL/min flow rate, 254 nm $t_1 = 9.6$ min (major), $t_2 = 11.8$ min (minor).

3.2.7. (−)-6-Acetoxy-6-ethyl-3,5,5-trimethyl-2-cyclohexen-1-one (−)-4c. (49 mg, 49%) as a colorless oil; 45% ee $[\alpha]_D^{20} = -3.2$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 85:15), 1.0 mL/min flow rate, 254 nm $t_1 = 12.4$ min (major), $t_2 = 15.7$ min (minor).

3.2.8. (+)-6-Acetoxy-6-benzyl-3,5,5-trimethyl-2-cyclohexen-1-one (+)-4d. (45 mg, 45%) as a colorless oil; 36% ee $[\alpha]_D^{20} = +0.2$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 90:10), 1.0 mL/min flow rate, 254 nm $t_1 = 10.4$ min (major), $t_2 = 12.6$ min (minor).

3.2.9. (−)-5-Acetoxy-3,5-dimethyl-2-cyclopenten-1-one (−)-5a. (48 mg, 48%) as a colorless oil; 99% ee $[\alpha]_D^{20} = -33.6$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 90:10), 1.0 mL/min flow rate, 254 nm $t_1 = 6.9$ min (major), $t_2 = 9.8$ min (minor).

3.2.10. (−)-5-Acetoxy-5-ethyl-3-methyl-2-cyclopenten-1-one (−)-5b. (52 mg, 52%) as a colorless oil; 53% ee $[\alpha]_D^{20} = -8.4$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral col-

umn (*n*-hexane/2-propanol 90:10), 1.0 mL/min flow rate, 254 nm $t_1 = 8.4$ min (major), $t_2 = 10.7$ min (minor).

3.2.11. (+)-5-Acetoxy-5-benzyl-3-methyl-2-cyclopenten-1-one (+)-5c. (47 mg, 47%) as a colorless oil; 43% ee $[\alpha]_D^{20} = +1.2$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 85:15), 1.0 mL/min flow rate, 254 nm $t_1 = 5.9$ min (minor), $t_2 = 7.7$ min (major).

3.2.12. (−)-5-Acetoxy-2,3,5-trimethyl-2-cyclopenten-1-one (−)-5d. (46 mg, 46%) as a colorless oil; 90% ee $[\alpha]_D^{20} = -23.8$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 90:10), 1.0 mL/min flow rate, 254 nm $t_1 = 13.5$ min (major), $t_2 = 17.8$ min (minor).

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