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A new and efficient chemoenzymatic route to both enantiomers of α′-acetoxy and α′-hydroxy-α-methoxy cyclic enones

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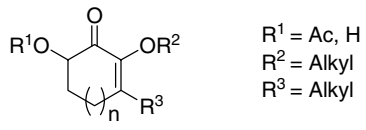
Abstract—A chemoenzymatic synthesis of both enantiomers of the pharmacologically interesting α′-acetoxy and α′-hydroxy-α-methoxy cyclic enones starting from α-hydroxy cyclic enones is described. Protection of 1,2-diketones, manganese(III) acetate-mediated acetoxylation followed by enzyme-mediated hydrolysis of α′-acetoxy enones gives acetoxy enones **3a–d** and hydroxy enones **4a–d** with high enantiomeric excesses (up to 99%) and good yields. The transesterification of *rac*-**4b** in the presence of DMAP afforded (+)-**4b** and (−)-**3b** in high enantiomeric excesses (91–94%) and good chemical yields.

1. Introduction

Chiral cyclic polyoxygenated compounds, such as **A** (Fig. 1), are important structural units in many biologically active compounds and are also important synthons for the asymmetric synthesis of natural products.[1] It is, therefore, of considerable interest to develop efficient methods for the preparation of these compounds in enantiomerically pure forms.

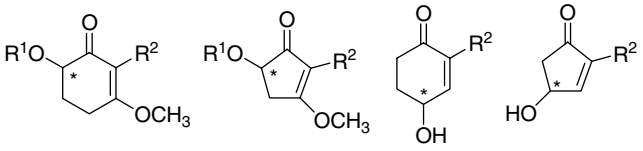
A few examples have been published for the preparations of these compounds in racemic form,[1,2] but no examples have given enantiopure products. In our ongoing work, we have published several papers concerning the $Mn(OAc)_3$-mediated direct acetoxylation and acyloxylation of cyclic enones followed by the enzymatic- and fungus-mediated resolution of acyloxy enones to obtain enantiomerically pure α-hydroxy ketones (Fig. 2).[3]



R^1 = Ac, H
R^2 = Alkyl
R^3 = Alkyl

A

Figure 1.



R^1= H, Ac; R^2 = H, Me, CH_2OH

Figure 2.

Due to the multifunctional nature of chiral α′-acetoxy and α′-hydroxy-α-methoxy cyclic enones, they can take part in several stereoselective transformations. This led us to explore a chemoenzymatic method for obtaining them in their enantiomerically pure forms, and we report herein an efficient chemoenzymatic route to the three-step synthesis of both enantiomers of **3** and **4**, starting from 3-alkyl-2-hydroxy-cyclic enones **1a–d**, which are representative examples for the simple enantioselective synthesis of α′-acetoxy and α′-hydroxy-α-methoxy cyclic enones.

2. Result and discussion

1,2-Diketones **1a** and **1b** were synthesized according to the literature procedure starting from the corresponding

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enones[2a,4] while **1c** and **1d** are commercially available compounds. 1,2-Diketones were converted to the 3-methoxy-2-methyl cyclic enones **2a–d** using a procedure already reported in the literature.[2,5] As an initial reaction (Scheme 1), oxidation of enone **2a–d** with manganese(III) acetate in benzene was performed to obtain the desired α′-acetoxy enones, *rac*-**3a–d**, in 88–95% yield after purification by column chromatography.[6]

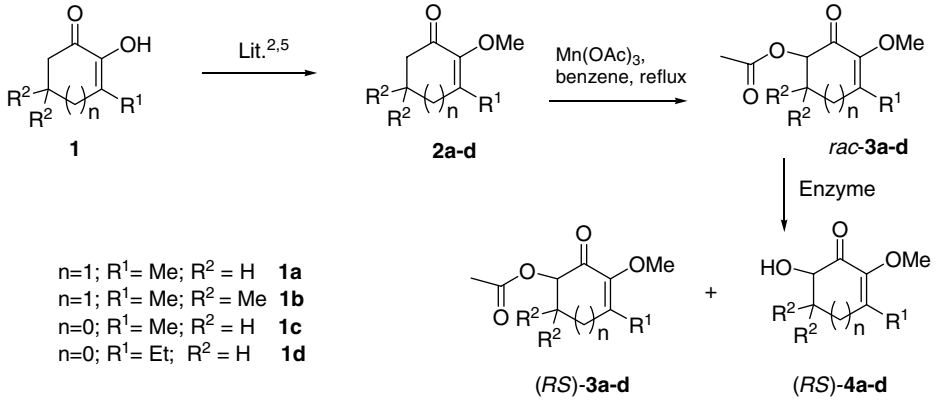
Lipase type enzymes are used extensively for the synthesis of enantiomerically pure compounds via the resolution of racemic mixtures. The high stereoselectivity in organic media and their low cost make them very useful catalysts for enantioselective resolution.[7]

Based on preliminary information available to us from our previous work with biocatalyst-mediated reactions,[3e–k] we tested a series of enzymes for screening the enantioselective hydrolysis of acetoxy enone *rac*-**3a**. As shown in Table 1, 11 enzymes showed activity as measured by the hydrolysis of *rac*-**3a** at pH 7 in toluene with high ee. For the kinetic resolution step, the following conditions provided the best results.

In a typical experiment, for the enzymatic hydrolysis, the racemic 4-methoxy-3-methyl-2-oxocyclohex-3-enyl acetate, *rac*-**3a**, was dissolved in toluene, then phosphate buffer (pH 7.0) was added and the mixture stirred at room temperature in the presence of the enzyme. The reaction was monitored by TLC analysis and HPLC with a chiral column using *rac*-**3a**, and *rac*-**4a** (synthesized from *rac*-**3a**).[3j,k] Careful monitoring of the reactions with TLC and HPLC provided the acetoxy enone (−)-**3a** (25–97% ee) and hydroxy enone (+)-**4a** (57–90% ee) (Table 1). For a preparative scale synthesis of (−)-**3a**, CCL was used, and when an approximately 50% conversion was attained, the crude product was separated by flash column chromatography to provide (−)-4-methoxy-3-methyl-2-oxocyclohex-3-enyl acetate, (−)-**3a** in 44% yield. For the preparative scale synthesis of (+)-**4a**, *Mucor miehei* lipase was used and the product obtained in 46% yield. The enzyme preferentially transformed the (+)-enantiomer.

For the enantioselective hydrolysis of acetoxy enone *rac*-**3b**, we tested a series of enzymes at various pH values (5, 7, 9) and solvents (toluene, THF, acetonitrile, DMSO). As shown in Table 2, only toluene and DMSO at pH 7 provided results with high enantiomeric excesses for hydroxyl enone (60–99% ee). *Aspergillus* exhibited a high enantioselectivity for the hydroxy enone and this enzyme was used for preparative scale synthesis of **4b** (>99% ee, 48% yield). The enzyme preferentially transformed the (+)-enantiomer.

We next examined the transesterification of *rac*-**4b** under various conditions. As shown in Scheme 2, asymmetric transesterification of *rac*-**4b** was carried out with several



Scheme 1.

Table 1. Enzymatic hydrolysis of 3-methoxy-4-methyl-2-oxocyclohex-3-enyl acetate *rac*-**3a** in toluene[a]

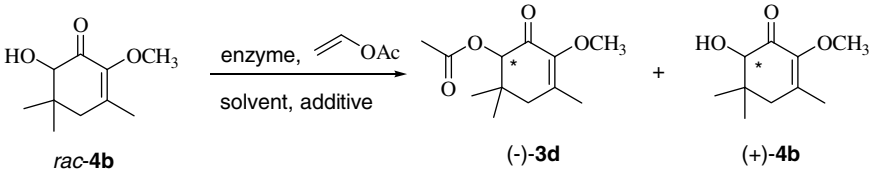
Entry	Enzyme	Reaction time	Acetate ee[b] (%)	Alcohol ee[b] (%)	Conversion[8] (%)	E[8]
1	*Aspergillus*	20 h	25	57	30	4.6
2	Amano PS	18 h	83	85	49	31
3	QLM	22 h	69	61	53	8.3
4	Lipase PL	22 h	70	73	49	13
5	Lipase TL	2 d	64	70	48	10
6	*Pseudomonas fluorescens*	4 d	78	88	47	37
7	*Mucor miehei*	8 d	85	90	49	51
8	*Rhizopus arrhius*	10 d	59	75	44	12
9	Porcine Pancrease	7 d	88	83	51	31
10	*Candida cylindracea*	4 d	97	86	53	55
11	Lipase AL	10 d	66	68	49	10

[a] All hydrolyses of *rac*-**3a** were carried out in toluene/buffer pH = 7.
[b] Enantiomeric excesses were determined by HPLC equipped with an appropriate chiral column using racemic compounds as references.

Table 2. Enzymatic hydrolysis of 3-methoxy-4,6,6-trimethyl-2-oxocyclohex-3-enyl acetate (*rac*-**3b**)

Entry	Enzyme	Reaction time (d), solv., pH	Conversion[8] (%)	Acetate ee[a] (%)	Alcohol ee[a] (%)	E[8]
1	Hog pancrease	32, DMSO, 7	40	48	72	9.8
2	*Rhizopus niveus*	42, DMSO, 7	37	35	60	5.6
3[b]	*Rhizopus niveus*	15, THF, 7	—	—	—	—
4[b]	*Rhizopus niveus*	15, CH_3CN, 7	—	—	—	—
5	*Aspergillus*	15, DMSO, 7	13	11	76	8.2
6[b]	*Aspergillus*	15, THF, 7	—	—	—	—
7[b]	*Aspergillus*	15, CH_3CN, 7	—	—	—	—
8	*Aspergillus*	5, Toluene, 7	42	73	>99	>200
9	*Aspergillus*	18, Toluene, 5	27	31	83	14
10	*Aspergillus*	20, Toluene, 9	51	78	74	15

[a] Enantiomeric excesses were determined by HPLC equipped with an appropriate chiral column using racemic compounds as references.
[b] No reaction was observed.



Scheme 2.

lipases in either various solvents (DMSO, toluene, acetonitrile, hexane) or without solvent. In all cases, only trace amounts of the products were formed.

It is known that addition of crown ethers, amino alcohols, and bases affects the hydrolysis of esters, and that addition of bases also enhances the rate of transesterification with use of enzymes in apolar organic solvents.[9] Enzyme mediated transesterification was carried out using several bases (DMAP, 2,4-lutidine, 2,6-lutidine, and pyridine). Among those bases examined, DMAP, in particular, which is the most basic of these additives, considerably enhanced the reaction rate.

In the transesterification of *rac*-**4b**, only lipase TL displayed any reactivity toward *rac*-**4b** in the presence of DMAP (5 equiv). In regards to the ee of the remaining substrate (+)-**4b** (91–94%) and that of the product (−)-**3b** (57–76%), lipase TL was only the promising lipase employed in the transesterification of *rac*-**4b** in hexane. Lipase TL in hexane at room temperature was applied for the preparative synthesis of (−)-**3b** (43%). The enzyme preferentially transformed the (−)-enantiomer (Table 3).

The enantioselective hydrolysis of 4-methoxy-3-methyl-2-oxocyclopent-3-enyl acetate (*rac*-**3c**) was investigated with several available enzymes in solvents (DMSO, THF) at pH 7. Careful monitoring of the reactions by TLC and HPLC provided the acetoxy enone (+)-**3c** (15–87% ee) and hydroxy enone (−)-**4c** (25–96% ee). Amano PS (in THF and DMSO) and CCL (in THF) exhibited high enantioselectivity for acetoxy enone (86–87% ee), and CCL (in DMSO, THF), PLE and Amano PS (in DMSO) exhibited high enantioselectivity for hydroxy enone (82–96% ee) (Table 4). All enzymes preferentially recognized the (−)-enantiomer of *rac*-**3c**.

As shown in Table 4, CCL exhibited solvent dependent substrate selectivity for the hydroxyl- and acetoxy enone, and this enzyme in THF was used for preparative scale synthesis of (+)-**3c** (47%) and the same enzyme was used in DMSO for the preparative scale synthesis of (−)-**4c** (42%).

Under the above mentioned conditions, as described for *rac*-**3c**, the enantioselective hydrolysis of 3-ethyl-4-methoxy-2-oxocyclopent-3-enyl acetate *rac*-**3d** was screened with various enzymes in different solvents (DMSO, toluene, acetonitrile, hexane, THF) at pH 7. CCL in DMSO exhibited high enantioselectivity for hydroxy enone (99% ee) (Table 5). PLE exhibited high enantioselectivity for the hydroxy enone in THF (95% ee) and high enantioselectivity for the acetoxy enone in DMSO (93% ee). All enzymes preferentially recognized the (−)-enantiomer of *rac*-**3d**. Preparative scale synthesis

Table 3. Transesterification of 6-hydroxy-2-methoxy-3,5,5-trimethylcyclohex-2-en-1-one *rac*-**4b**

Entry	Enzyme	Solvent	Additive	Reaction time (d)	Acetate ee[a] (%)	Alcohol ee[a] (%)	Conversion[8] (%)	E[8]
1	Lipase TL	Hexane	DMAP (rt)	2	76	91	54	22
2	Lipase TL	Hexane	DMAP (5 °C)	4	57	94	62	12
3	Lipase TL	—	DMAP	2	73	93	56	21

[a] Enantiomeric excesses were determined by HPLC equipped with an appropriate chiral column using racemic compounds as references.

Table 4. Enzymatic hydrolysis of 3-methoxy-4-methyl-2-oxocyclopent-3-enyl acetate (*rac*-**3c**)

Entry	Enzyme	Reaction time (h)	Solvent	Acetate ee[a] (%)	Alcohol ee[a] (%)	Conversion[8] (%)	E[8]
1	CCL	6	DMSO	15	96	14	56
2	PLE	41	DMSO	63	83	43	20
3	Amano PS	1	DMSO	87	85	51	34
4	CCL	21	THF	87	82	51	28
5	Amano PS	1	THF	86	67	56	13
6	PLE	82	THF	32	25	56	2.2

[a] Enantiomeric excesses were determined by HPLC equipped with an appropriate chiral column using racemic compounds as references.

Table 5. Enzymatic hydrolysis of 4-ethyl-3-methoxy-2-oxocyclopent-3-enyl acetate *rac*-**3d**

Entry	Enzyme	Reaction time (min)	Solvent	Acetate ee[a] (%)	Alcohol ee[a] (%)	Conversion[8] (%)	E[8]
1	CCL	85	DMSO	79	99	44	>200
2	PLE	85	DMSO	93	52	64	10
3	Amano PS	25	DMSO	61	41	60	4.3
4	PPL	85	DMSO	50	79	39	13
5	PLE	110	THF	51	95	35	64
6	Amano PS	25	THF	75	55	58	7.5
7	PLE	52 h	THF	12	28	30	2

[a] Enantiomeric excesses were determined by HPLC equipped with an appropriate chiral column using racemic compounds as references.

of acetoxy enone was carried out by using PLE in DMSO (50%) and preparative scale synthesis of hydroxyl enone was carried out by using PLE in THF (42%).

3. Conclusion

These results show that manganese(III) acetate-mediated acetoxylation of protected 1,2-diketones followed by enzyme-mediated hydrolysis of the acetoxy group provides hydroxy enones **4a–d**, and acetoxy enones **3a–d** with high enantiomeric excesses (up to 99%) and in good chemical yields. This method provides a simple new entry to the synthesis of cyclic hydroxy enones, which are important precursors for pharmacologically interesting compounds. As we reported earlier for related systems, racemization free interconversion of acetate to alcohol and vice versa gives additional flexibility to this method.[3j,k]

4. Experimental

4.1. Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (^{1}H: $\delta = 7.27$), $CDCl_3$ (^{13}C: $\delta = 77.0$) and CCl_4 (^{13}C: $\delta = 96.4$) as internal standards. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light ($\lambda = 254$ nm). Enantiomeric excesses were determined by HPLC analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column, as described in the experimental part. Optical rotations were measured with a Krüss P3002RS automatic polarimeter.

4.2. General procedure for the α′-acetoxylation of α,β-unsaturated ketones[6]

A solution of 8 mmol α,β-unsaturated ketone and 12 mmol $Mn(OAc)_3$ in 30 mL benzene/AcOH (10:1) was stirred at reflux (Dean–Stark apparatus), during which the dark brown color of $Mn(OAc)_3$ disappeared over time, which was also monitored by GC–MS and TLC. After all starting material was consumed, the reaction mixture was diluted with ether and washed with brine. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. If necessary, the crude products were purified by column chromatography using EtOAc/hexane as eluent. In some cases, direct filtering of the reaction mixture through a pad of silica provided pure acetoxy enones.

4.3. 3-Methoxy-4-methyl-2-oxocyclohex-3-enyl acetate 3a[2a]

Brown solid (1.46 g, 92%), mp 91.2–92.3 °C; IR (KBr): $\nu = 1745$, 1693, 1638 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 3H, CH_3), 2.09 (ddd, $J = 5.3$, 11.8, 25.1 Hz, 1H, CH_2, H-5), 2.17 (s, 3H, $COCH_3$), 2.21 (m, 1H, CH_2, H-5), 2.41 (m, 1H, CH_2, H-4), 2.59 (m, 1H, CH_2, H-4), 3.66 (s, 3H, OCH_3), 5.28 (dd, $J = 5.3$, 13.3 Hz, 1H, CH, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 20.7, 27.9, 28.4, 59.5, 73.5, 143.8, 147.9, 169.6, 188.9.

4.4. 3-Methoxy-4,6,6-trimethyl-2-oxocyclohex-3-enyl acetate 3b

Yellow semi-solid (1.71 mg, 95%); IR (KBr): $\nu = 1742$, 1686, 1630, 1239 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.87 (s, 3H, CH_3), 2.13 (d, $J = 18.1$ Hz, 1H, CH_2), 2.19 (s, 3H, $COCH_3$), 2.54 (d, $J = 18.1$ Hz, 1H, CH_2), 3.63 (s,

3H, OCH_3), 5.15 (s, 1H, CH, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 19.8, 20.5, 27.3, 37.4, 44.2, 59.3, 80.6, 140.4, 147.3, 169.8, 188.5. Anal. Calcd for $C_{12}H_{18}O_4$ (226.27): C, 63.70; H, 8.02. Found: C, 63.51; H, 7.98.

4.5. 3-Methoxy-4-methyl-2-oxocyclopent-3-enyl acetate *rac*-3c[2a]

Colorless oil (130 mg, 88%), IR ($CHCl_3$): $v = 1668$, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H, CH_3), 2.08 (s, 3H, $COCH_3$), 2.24 (d, $J = 17.4$ Hz, 1H, H-4), 2.76 (dd, $J = 6.7$, 17.5 Hz, 1H, H-4), 3.85 (s, 3H, OCH_3), 5.00 (dd, $J = 2.6$, 6.8 Hz, 1H, H-5) ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.7, 34.2, 57.2, 69.3, 149.5, 150.0, 169.1, 195.7.

4.6. 4-Ethyl-3-methoxy-2-oxocyclopent-3-enyl acetate *rac*-3d

Colorless oil (144 mg, 91%), IR ($CHCl_3$): $v = 1714$, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.0 (t, $J = 7.5$ Hz, 3H, CH_3), 2.08 (s, 3H, $COCH_3$), 2.30 (d, $J = 7.3$ Hz, 1H, H-4), 2.40 (m, 2H, CH_2), 2.88 (dd, $J =$ 6.7, 17.7 Hz, 1H, H-4), 3.80 (s, 3H, OCH_3), 5.05 (dd, $J = 2.7$, 6.7 Hz, 1H, H-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2, 20.7, 21.7, 32.5, 58.2, 70.2, 150.0, 156.3, 170.3, 197.3. Anal. Calcd for $C_{10}H_{14}O_4$ (198.22): C, 60.59; H, 7.12. Found: C, 60.31; H, 7.34.

4.7. General procedure for the lipase-catalyzed kinetic resolution

Lipase (200–300 mg) was dissolved in phosphate buffer (pH 7, 30 mL) and added to a solution of the pure substrate (0.5 mmol) in solvent (3 mL) and the reaction mixture left to stir at rt. Conversion was monitored by TLC and HPLC up to 50%. After filtration the filtrate was extracted with dichloromethane, dried over $MgSO_4$, concentrated, and purified by column (*n*-hexane/ethyl acetate, 4:1).

4.8. General procedure for the lipase-catalyzed transesterification in the presence of additives

To a stirred solution of *rac*-6-hydroxy-2-methoxy-3,5,5-trimethylcyclohex-2-en-1-one *rac*-**4b** (0.5 mmol), vinyl acetate (10 mmol) and 2.5 mmol DMAP in hexane (10 mL) were added in one portion and the reaction mixture was stirred at rt. The reaction was monitored by TLC up to 50%. After filtration, the filtrate was extracted with dichloromethane, dried over $MgSO_4$, and concentrated.

4.9. (−)-3-Methoxy-4-methyl-2-oxocyclohex-3-enyl acetate (−)-3a

Brown solid, mp 91.2–92.3 °C (44 mg, 44% yield), $[\alpha]_D^{20} = -140$ (*c* 0.5, $CHCl_3$) for 97% ee; HPLC: Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 90:10, flow 0.8 mL min^{-1}, 20 °C, R_f for (−)-**3a**: 12.73 min; (+)-**3a**: 20.48 min.

4.10. (+)-3-Methoxy-4,6,6-trimethyl-2-oxocyclohex-3-enyl acetate (+)-3b

Yellow semi-solid (49 mg, 43% yield), $[\alpha]_D^{25} = -39.5$ (*c* 0.6, $CHCl_3$) for 76% ee; HPLC: Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 98:2, flow 0.8 mL min^{-1}, 20 °C, R_f for (+)-**3b**: 18.57 min; (−)-**3b**: 23.72 min.

4.11. (+)-6-Hydroxy-2-methoxy-3-methylcyclohex-2-en-1-one (+)-4a

Colorless oil (36 mg, 46% yield), $[\alpha]_D^{20} = +81.6$ (*c* 0.2, $CHCl_3$) for 90% ee; HPLC: Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 90:10, flow 0.8 mL min^{-1}, 20 °C, R_f for (−)-**4a**: 9.21 min; (+)-**4a**: 11.43 min. IR (KBr): $v = 3472$, 1677, 1635, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (ddd, $J = 5.24$, 12.24, 25.7 Hz, 1H, CH_2, H-4), 1.95 (s, 3H, CH_3), 2.34 (m, 2H, CH_2, H-5), 2.55 (m, 1H, CH_2, H-4) 3.63 (s, 1H, OH), 3.69 (s, 3H, OCH_3), 4.09 (dd, $J = 5.4$, 13.5 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 22.7, 33.4, 59.52, 73.7, 144.1, 148.3, 198.6. Anal. Calcd for $C_8H_{12}O_3$ (156.18): C, 61.52; H, 7.74. Found: C, 61.68; H, 7.88.

4.12. (+)-6-Hydroxy-2-methoxy-3,5,5-trimethylcyclohex-2-en-1-one (+)-4b

Colorless oil (44 mg, 48% yield), $[\alpha]_D^{25} = +111$ (*c* 0.3, $CHCl_3$) for 99% ee; HPLC: Chiralcell OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 99:1 flow 0.8 mL min^{-1}, 20 °C, R_f for (+)-**4b**: 12.42 min; (−)-**4b**: 14.47 min. IR (KBr): $v = 3414$, 1670, 1643, 1283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.88 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.12 (d, $J = 18.1$ Hz, 1H, CH_2, H-4), 2.49 (d, $J = 18.1$ Hz, 1H, CH_2, H-4), 3.61 (br s, 1H, OH), 3.69 (s, 3H, OCH_3), 3.90 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 18.0, 27.7, 39.3, 44.1, 59.4, 80.2, 143.2, 146.7, 195.2. Anal. Calcd for $C_{10}H_{16}O_3$ (184.23): C, 65.19; H, 8.75. Found: C, 65.43; H, 8.91.

4.13. (+)-3-Methoxy-4-methyl-2-oxocyclopent-3-enyl acetate (+)-3c[2a]

Colorless oil (43 mg, 47%) $[\alpha]_D^{20} = +10.6$ (*c* 0.8, $CHCl_3$) for 87% ee; IR ($CHCl_3$); HPLC: Chiralcell AD column, UV detection at 254 nm, eluent: hexane/2-propanol = 98:2, flow 0.3 mL min^{-1}, 20 °C, R_f: for (−)-**3c**: 36.17 min; (+)-**3c**: 46.83 min.

4.14. (+)-4-Ethyl-3-methoxy-2-oxocyclopent-3-enyl acetate (+)-3d

Colorless oil (49.5 mg, 50%) $[\alpha]_D^{20} = +32.1$ (*c* 1, $CHCl_3$) for 93% ee. HPLC: Chiralcell AD column, UV detection at 254 nm, eluent: hexane/2-propanol = 96:4, flow 0.3 mL min^{-1}, 20 °C, R_f: for (−)-**3d**: 22.31 min; (+)-**3d**: 25.05 min.

4.15. (−)-5-Hydroxy-3-methyl-2-methoxy-2-cyclopentene-1-one (−)-4c[10,11]

Colorless oil (30 mg, 42%) $[\alpha]_D^{20} = -9.6$ (c 0.8, $CHCl_3$) for 96% ee; HPLC: Chiralcell AD column, UV detection at 254 nm, eluent: hexane/2-propanol = 98:2, flow 0.3 mL min^{-1}, 20 °C, R_f: for (−)-**4c**: 75.48 min; (+)-**4c**: 69.53 min. IR ($CHCl_3$): $\nu = 3023$, 1667, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H, CH_3), 2.30 (d, $J = 17.2$, 1H, H-4), 2.70 (dd, $J = 6.55$, 17.3 Hz, 1H, H-4), 3.85 (s, 3H, OCH_3), 4.05 (dd, $J = 7.07$, 19.4 Hz, 1H, H-5).

4.16. (+)-3-Ethyl-5-hydroxy-2-methoxy-2-cyclopentene-1-one (+)-4d

Colorless oil (33 mg, 42%), $[\alpha]_D^{20} = +15.2$ (c 0.8, $CHCl_3$) for 95% ee; HPLC: Chiralcell AD column, UV detection at 254 nm, eluent: hexane/2-propanol = 96:4, flow 0.3 mL min^{-1}, 20 °C, R_f: for (−)-**4d**: 46.7 min; (+)-**4d**: 49.95 min. IR ($CHCl_3$): $\nu = 3017$, 1669, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, $J = 7.5$ Hz, 3H, CH_3), 2.28 (dd, $J = 6.6$, 17.3 Hz, 1H, H-4), 2.30 (d, $J = 7.5$ Hz, 1H, H-4), 2.40 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.02 (dd, $J = 2.5$, 6.5 Hz, 1H, H-5) ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 21.8, 33.9, 57.8, 69.9, 96.2, 156.1, 202.9. Anal. Calcd for $C_8H_{12}O_3$ (156.18): C, 61.52; H, 7.74. Found: C, 661.33; H, 7.86.

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References

1. (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **2000**, *122*, 3785; (b) Urban, M.; Sarek, J.; Klinot, J.; Korinkova, G.; Hajduch, M. *J. Nat. Prod.* **2004**, *67*, 1100; (c) Holtz, E.; Koehler, V.; Appel, B.; Langer, P. *Eur. J. Org. Chem.* **2005**, 532; (d) Landais, Y.; Vincent, J. M. *Synthesis* **2004**, 647; (e) Koike, T.; Murata, K.; Ikariya, T. *Org. Lett.* **2000**, *2*, 3833; (f) Schneider, D. F.; Viljoen, M. S. *Tetrahedron* **2002**, *58*, 5307; (g) Schneider, D. F.; Viljoen, M. S. *Synth. Commun.* **2002**, *32*, 1285; (h) Schneider, D. F.; Viljoen, M. S. *Synth. Commun.* **1997**, *27*, 3349; (i) Munkombwe, N. M.; Maswabi, T.; Hughes, N. A. *Phytochemistry* **1997**, *45*, 1217; (j) Davies, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919.
2. (a) Demir, A. S.; Saatçioglu, A. *Synth. Commun.* **1993**, *23*, 571; (b) Demir, A. S.; Jeganathan, A. *Synthesis* **1992**, 235.
3. (a) Demir, A. S.; Sayrac, T.; Watt, D. S. *Synthesis* **1990**, 1119; (b) Demir, A. S.; Jeganathan, A.; Watt, D. S. *J. Org. Chem.* **1989**, *54*, 4020; (c) Demir, A. S.; Gercek, Z.; Reis, O.; Duygu, A. N.; Arikan, E. *Tetrahedron* **1999**, *55*, 2441; (d) Demir, A. S.; Çamkerten, N.; Akgün, H.; Tanyeli, C.; Mahasneh, A. S.; Watt, D. S. *Synth. Commun.* **1990**, *20*, 2279; (e) Demir, A. S.; Hamamci, H.; Doganel, F.; Camkerten, N.; Aksoy-Cam, H. *Turkish J. Chem.* **2000**, *24*, 141; (f) Demir, A. S.; Aybey, A.; Sesenoglu, Ö.; Polat, F. *Tetrahedron: Asymmetry* **2003**, *14*, 1489; (g) Demir, A. S.; Fındık, H.; Köse, E. *Tetrahedron: Asymmetry* **2004**, *15*, 777; (h) Gercek, Z.; Karakaya, D.; Demir, A. S. *Tetrahedron: Asymmetry* **2005**, *16*, 1743; (i) Demir, A. S.; Senocak, D. *Tetrahedron: Asymmetry* **2004**, *15*, 2641; (j) Demir, A. S.; Sesenoglu, O. *Org. Lett.* **2002**, *4*, 2021; (k) Demir, A. S.; Sesenoglu, O. *Tetrahedron: Asymmetry* **2002**, *13*, 667.
4. (a) Ponaras, A. A. *Tetrahedron Lett.* **1980**, *21*, 4803; (b) Rissafi, B.; Rachiqi, N.; Louzi, A. E.; Loupy, A.; Petit, A.; Fkih-Tetouani, S. *Tetrahedron* **2001**, *57*, 2761.
5. (a) Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B. *J. Am. Chem. Soc.* **1986**, *108*, 2662; (b) Wenkert, E.; Golob, N. F.; Sathe, S. S.; Smith, R. A. J. *Synth. Commun.* **1973**, *3*, 205.
6. Demir, A. S.; Reis, Ö.; Igdir, A. C. *Tetrahedron* **2004**, *60*, 3427.
7. (a) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis—Regio- and Stereoselective Biotransformations*; Wiley-VCH: Weinheim, 1999; (b) Liese, A.; Seelbach, K.; Wandrey, C. *Industrial Biotransformations*; Wiley-VCH: Weinheim, 2000; (c) Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Springer: Berlin, 2000.
8. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294, E values are calculated using the program 'Selectivity' by K. Faber and H. Hoenig, http://www.cis.TUGraz.at/orgc/.
9. Aoyagi, Y.; Saitoh, Y.; Ueno, T.; Horiguchi, M.; Takeya, K.; Robert, M.; Williams, R. M. *J. Org. Chem.* **2003**, *68*, 6899.
10. Hesse, G.; Enner, F.; Hertel, H. *Liebigs Ann. Chem.* **1957**, *609*, 57.
11. According to ^1H NMR spectra slow, isomerization of this product to 2,3-dihydroxy-4-methylcyclopent-2-enone at rt is observed; this subject is currently under investigation.