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The first enzymatic resolution of quaternary α-acetoxy α-substituted cyclic ketones

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Abstract—The enantioselective resolution of quaternary α-acetoxy α-substituted indanone and 1-tetralone derivatives was performed with commercially available enzyme CRL in pH = 8.0 phosphate buffer. Various parameters that would affect the enantoselectivities were tested, and the optimal enzymatic resolution condition was found to afford the enantiomerically enriched quaternary acetoxylated substrates with high ees (varied between 81% and 85%).

1. Introduction

The synthesis of optically active compounds with quaternary carbon stereocenters, that is, carbon stereocenters with four different non-hydrogen substituents, continues to be an exciting challenge in organic synthesis. Chiral tertiary α-hydroxy ketones and their derivatives containing tertiary C–O bonds are useful building blocks for many drugs and natural products. This is particularly true of the tetralone ring system where this structural unit is featured in the anthracycline antitumor antibiotics,[1] the phytoalexin lacinilene C,[2] the antitumor alkaloid camptothecin,[3] and the homoisoflavanone eucomol.[4] This unit is also used as a reagent for the deracemization of amino acids.[5]

Chiral tertiary α-hydroxy ketones have been prepared by the addition of Grignard reagents to α-keto ketals.[6] One of the most attractive methods involves the asymmetric oxidation of ketone enolates[7] and silyl enol ethers[8] using various chiral oxaziridines. The catalytic enantioselective oxidation of achiral α-substituted ketones has been achieved with molecular oxygen, by the use of chiral phase transfer catalysts derived from cinchona alkaloids[9] and by chiral monoaza-crown ethers.[10] Several microbial and enzymatic methods have been developed for the preparation of optically active secondary α-hydroxy and acetoxy ketones.[11] To the best of our knowledge, enzymatic resolution of tertiary α-hydroxy or acetoxy ketones has not yet been reported in the literature, since tertiary alcohols are usually too bulky to have access to the active sites of lipases.[12]

It is well known in the literature that $Mn(OAc)_3$ efficiently oxidizes aromatic ketones as well as enones[13], and as an extension of this method, we previously published the results of a regioselective oxidation method with $Mn(OAc)_3$ applied to various α′- and α-substituted α,β-unsaturated cyclic ketones[14a,14b] and cyclic aromatic ketones,[14b] respectively, to afford the corresponding substances with a quaternary α′- and α-acetoxy moiety. As an extension of the study, quaternary α′-acetoxy α,β-unsaturated cyclic ketones were subjected to enzymatic resolution.[14c] In connection with our work on the development of novel procedures for the direct oxidation of α-substituted indanone and tetralone derivatives with $Mn(OAc)_3$ in the synthesis of (±)-2-acetoxy-2-ethyl-1-indanone **2a**, (±)-2-acetoxy-2-acetyl-1-tetralone **2b**, and (±)-2-acetoxy-2-methyl-1-tetralone **2c**,[14b] we herein report the results of $Pb(OAc)_4$ mediated oxidation and subsequent CRL catalyzed enzymatic resolution of these into enantiomerically enriched forms.

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

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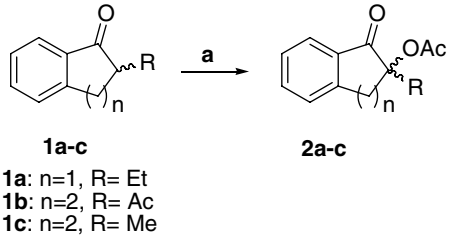
2. Synthesis of racemic substrates

Quaternary α-acetoxy α-substituted indanone and tetralone derivatives (±)-**2a**–**c** were prepared using our previously published method with $Mn(OAc)_3$[14b], and with $Pb(OAc)_4$. By using $Pb(OAc)_4$ as an oxidizing agent (with cyclohexane as the solvent), we improved slightly the yields of the oxidation products **2a**–**c** (Scheme 1). The results of the selective oxidation methods are shown in Table 1.

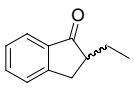
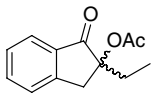
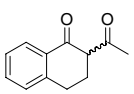
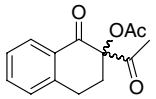
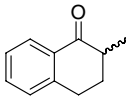
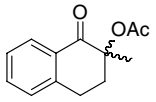
3. Enzymatic hydrolyses of racemic substrates

Various lipases (PLE, CRL, HLE, and PPL) were tested with all racemic substrates. Treatment of the substrates in the absence of an enzyme revealed that they do not undergo autohydrolysis. It was decided to examine the hydrolysis reaction of quaternary α-acetoxy cyclic ketones **2a**–**c** by PLE, which is known for its broad substrate specificity and high stereoselectivity. The enzymatic hydrolysis reaction was performed according to the procedure developed in our group (Scheme 2).[14c] To a stirred solution of **2a**–**c** (100 mg) in phosphate buffer (pH 8.00, 10 mL), with DMSO as a co-solvent, PLE (100 μL) was added in one portion and the reaction mixture stirred at 20 °C. The reaction was monitored by TLC. Among the racemic substrates, only (±)-2-acetoxy-2-methyl-1-tetralone **2c** afforded enzymatic hydrolysis. Around 50% conversion was completed within 96 h in the pH 8.00 buffer system with PLE. The crude product was separated by flash column chromatography. (−)-2-Acetoxy-2-methyl-1-tetralone **2c** was obtained in 48% yield and 7% ee. Absolute configuration of compound (−)-**2c** was assigned as (*R*) by comparison of its specific rotation with the literature data of the isolated (*S*)-(+)-2-hydroxy-2-methyl-1-tetralone.[7d] No hydrolysis was recorded with PPL and HLE. Next, we focused on the enzymatic hydrolysis reactions with CRL and found that the optimum conditions were a pH 8.00 buffer system, at 20 °C, with DMSO used as co-solvent. The substrate:enzyme ratio was changed from 1:0.5 to 1:1. When the enzyme was used in a stoichiometric amount, the enantioselectivity increased. (*R*)-(+)-2-Acetoxy-2-methyl-1-tetralone **2c** was synthesized in 45% isolated yield in 81% ee in pH 8.00 buffer, at 20 °C. CRL appeared to be the best enzyme tested.

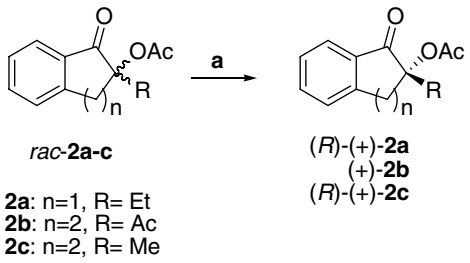


Scheme 1. Reagents and conditions: (a) $Pb(OAc)_4$, cyclohexane, reflux.

Table 1. Selective oxidation of α-substituted aromatic ketones

Entry	Reactant	Product	2	Time (h)	Yield (%)[a,b] with $Pb(OAc)_4$
1			*rac*-**2a**	12	52
2			*rac*-**2b**	12	68
3			*rac*-**2c**	12	67

[a] Yields (%) are given as the isolated yields.
[b] For $Mn(OAc)_3$ oxidation, see Ref. 14b.



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

Quaternary α-acetoxy indanone and tetralone derivatives (±)-2-acetoxy-2-ethyl-1-indanone **2a** and (±)-2-acetoxy-2-acetyl-1-tetralone **2b**, respectively, were subjected to hydrolysis by CRL. The results of the enzymatic resolutions on different substrates are summarized in Table 2. 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. CRL (100 mg) was then added to the solution and shaken for 72–136 h with TLC monitoring at 20 °C.

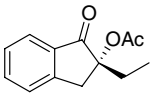
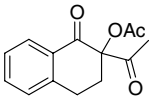
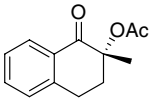
4. Conclusion

Herein, we have demonstrated the first enzymatic resolutions of quaternary α-acetoxy α-substituted cyclic ketones. Among the enzymes used in hydrolysis conditions, CRL showed the best enantioselectivity. We have found out that the pH factor was the critical point for high enantioselectivity. Commercially available and inexpensive enzyme CRL renders the process very attractive for large scale preparations.

5. 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 parts per million 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 spec-

Table 2. CRL resolution of α-substituted aromatic ketones

Entry	Substrate	Time (h)	Acetoxy pdt.[a]	Yield (%)[b]	Conversion (%)[c]	$[\alpha]_D^{20}$	ee (%)[d]
1	*rac*-**2a**	85	 (*R*)-(+)-**2a**	46	49	+14.8	83
2	*rac*-**2b**	72	 (+)-**2b**	49	50	+4.4	85
3	*rac*-**2a**	136	 (*R*)-(+)-**2c**	45	49	+2.6	81

[a] The absolute configurations of (+)-**2a** and (+)-**2c** were assigned as (*R*) by comparison of their specific rotations with the literature data Refs. 10 and 7d, respectively.
[b] Yields (%) are given as the isolated yields.
[c] Conversions were determined by the Thermo Hypersil-Keystone column HPLC analysis.
[d] Enantiomeric excesses were determined by the Chiralcel ODH chiral column HPLC analysis.

tra 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 Thermo Hypersil-Keystone analytical column (100 × 4.60 mm) and 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 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. CRL (Lipase, Type VII, from *Candida rugosa*) and PPL (Lipase, Type II, from Porcine Pancreas) were purchased from Aldrich. 2-Ethyl indanone **1a** and 2-acetyl tetralone **1b** were purchased from Aldrich. 2-Methyl tetralone **1c** was synthesized and is in accordance with the literature data.[14b]

5.1. General procedure for the $Pb(OAc)_4$ oxidations of α-substituted cyclic ketones (±)-1a–c

A mixture of $Pb(OAc)_4$ (5.00 g, 11.0 mmol) and the α-substituted 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 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.

5.1.1. (±)-2-Acetoxy-2-ethyl-indanone 2a. This (1.25 g, 52%) was obtained as a colorless oil, R_f (EtOAc/hexane 1:4) 0.31; ν_{max} (neat) 3410, 3019, 1724, 1609, 1466, 1257 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.71 (1H, d, $J = 8$ Hz, *Ar*), 7.53 (1H, t, $J = 8$ Hz, *Ar*), 7.30–7.33 (2H, m, *Ar*), 3.35 (1H, d, $J = 17$ Hz, CH_aH_b), 3.15 (1H, d, $J = 17$ Hz, CH_aH_b), 2.02 (3H, s, $MeCO_2$), 1.75–1.86 (1H, m, $MeCH_aH_b$), 1.63–1.72 (1H, m, $MeCH_aH_b$), 0.87 (3H, t, $J = 7$ Hz, $MeCH_2$); δ_C (100.6 MHz, $CDCl_3$) 202.8, 170.4, 149.8, 135.6, 135.3, 128.1, 126.2, 124.7, 85.1, 37.9, 30.1, 21.2, 8.0; *m/z* (EI) 220 (15), 219 (100), 160 (6), 159 (9); HRMS (EI) M^+, found 218.0937, $C_{13}H_{14}O_3$ requires 218.0943.

5.1.2. (±)-2-Acetoxy-2-acetyl-1-tetralone 2b. This (1.84 g, 68%) was obtained as a colorless oil, R_f (EtOAc/hexane 1:4) 0.41; ν_{max} (neat) 2254, 1794, 1709, 1662, 1363, 1095, 910, 753, 715 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.58 (1H, d, $J = 8$ Hz, *Ar*), 8.20 (1H, d, $J = 8$ Hz, *Ar*), 7.35–7.65 (2H, m, *Ar*), 2.79–3.02 (4H, m, CH_2CH_2), 2.26 (3H, s, $MeCO_2$), 2.23 (3H, s, *Me*CO); δ_C (100.6 MHz, $CDCl_3$) 210.3, 204.2, 198.7, 162.6, 143.6, 134.4, 129.0, 127.5, 112.5, 68.4, 32.5, 30.1, 26.3, 25.1; *m/z* (EI) 199 (42), 190 (14), 189 (100), 147 (17); HRMS (EI) M^+, found 246.0902, $C_{14}H_{14}O_4$ requires 246.0892.

5.1.3. (±)-2-Acetoxy-2-methyl tetralone 2c. This (1.61 g, 67%) was obtained as a white solid, mp 258–260 °C; R_f (EtOAc/hexane 1:3) 0.50; ν_{max} (neat) 2260, 1783, 1710, 1652, 1358 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.00 (1H, d, $J = 8$ Hz, *Ar*), 7.41 (1H, t, $J = 8$ Hz, *Ar*), 7.26 (1H, t, $J = 8$ Hz, *Ar*), 7.15 (1H, d, $J = 8$ Hz, *Ar*), 2.89–2.99 (3H, m, $CH_2CH_aH_bCMeOAc$), 2.00 (3H, s, $MeCO_2$), 1.97–1.99 (1H, m, $CH_2CH_aH_bCMeOAc$), 1.47 (3H, s, *Me*COAc); δ_C (100.6 MHz, $CDCl_3$) 195.2, 170.1, 142.4, 134.0, 131.6, 129.0, 128.8, 127.4, 81.3, 33.4, 27.3, 22.0, 21.7; HRMS (EI) M^+, found 218.0941, $C_{13}H_{14}O_3$ requires 218.0943.

5.2. General procedure for CRL hydrolysis of (±)-2a–c

To a stirred solution of 100 mg substrate in phosphate buffer (0.1 M, pH 8.00, 20 mL) and 1 mL DMSO, 100 mg

CRL 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 eluent).

5.2.1. (*R*)-(+)-2-Acetoxy-2-ethyl-indanone (*R*)-(+)-2a. This (46 mg, 46%) was obtained as a colorless oil; 83% ee $[\alpha]_D^{20} = +14.8$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 85:15), 1.0 mL/min flow rate, 254 nm $t_1 = 14.3$ min (minor), $t_2 = 15.4$ min (major).

5.2.2. (+)-2-Acetoxy-2-acetyl-1-tetralone (+)-2b. This (49 mg, 49%) was obtained as a colorless oil; 85% ee $[\alpha]_D^{20} = +4.4$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 85:15), 1.0 mL/min flow rate, 254 nm $t_1 = 12.7$ min (minor), $t_2 = 13.3$ min (major).

5.2.3. (*R*)-(+)-2-Acetoxy-2-methyl tetralone (*R*)-(+)-2c. This (45 mg, 45%) was obtained as a white solid; 81% ee $[\alpha]_D^{20} = +2.6$ (*c* 1.0, $CHCl_3$). Chiralcel OD-H chiral column (*n*-hexane/2-propanol 85:15), 1.0 mL/min flow rate, 254 nm $t_1 = 14.8$ min (minor), $t_2 = 16.2$ min (major).

Acknowledgments

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