Enzymatic Kinetic Resolution of 2-Cyclohexen-1-ol Derivatives

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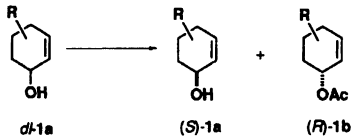
Synopsis. Optically active (*S*)-2-cyclohexen-1-ol derivatives and their enantiomeric (*R*)-acetates have been obtained in high enantiomeric excesses by enzymatic kinetic acetylation catalyzed by lipase AK.

Optically active 2-cyclohexen-1-ol derivatives are potentially useful substances for the synthesis of various bioactive compounds.[1] During the course of our synthetic study of (+)-dihydrocompactin,[2] we required a practical route for the preparation of optically pure 3-acetyl-2-cyclohexen-1-ol (**2a**).[3] Recent developments in biocatalytic resolution prompted us to describe our independent work on the efficient kinetic resolution of 2-cyclohexen-1-ol derivatives[4] *dl*-**1a** (Scheme 1) catalyzed by lipase AK from *Pseudomonas* sp.

Results and Discussion

Racemic 3-acetyl-2-cyclohexen-1-ol *dl*-(**2a**) was treated with vinyl acetate, lipase AK, and ground 4 Å molecular sieves in hexane[5] under various conditions. The progress of the reaction was monitored by thin layer chromatography (TLC) or ^{1}H NMR spectroscopy for the large scale reactions. As shown in Table 1, (*R*)-(+)-acetate (*R*)-(+)-**2b** was produced and the (*S*)-(−)-alcohol, (*S*)-(−)-**2a**, was recovered in satisfactory chemical and optical yields. When dry acetonitrile was used as a solvent, the highest selectivity (E=637)[6] was obtained. The reaction conditions employed in Entry 1 (Table 1, see Experimental) were the best for our practical preparative purpose.[7]

The enantiomeric excess of alcohol **2a** (Table 1, Entry 1) was determined by the ratio of the areas of two well-separated signals of the olefinic proton in the ^{1}H NMR spectrum of the diastereoisomeric (*R*)-(−)-2-methoxy-2-phenylacetate, **8**. The optical rotation value of enantiomerically pure alcohol **2a** was calculated from the (−)-rich alcohol **2a** (96% e.e., Entry 1); the enantiomeric excess of alcohol **2a** (Entries 2, 3, 4, and 5) was obtained by comparison of the optical rotation values. The enantiomeric excess of acetate **2b** was also determined by the optical rotation value. The (−)-rich alcohol **2a** (96% e.e., Entry 1) was acetylated and the observed optical rotation value of the resulting (+)-rich acetate **2b** (96% e.e.) was extrapolated to a value of 100% e.e. The absolute stereochemistry of alcohol **2a** was determined by the CD exciton chirality method.[8] Since the CD spectrum of allylic benzoate **9** prepared from the (−)-rich alcohol **2a** (36% e.e.) exhibited the first exciton CD Cotton effect with a negative sign ($\Delta\varepsilon$ −8.1 at 234 nm), the absolute stereochemistry of (−)-alcohol **2a** was established to be *S*.



Scheme 1.

With practical reaction conditions in hand, the procedure was applied to the enzymatic kinetic acetylation of some other racemic 2-cyclohexen-1-ol derivatives (**3a**, **4a**, **5a**, **6a**, and **7**). The results are listed in Table 1.

In all cases, the (*R*)-enantiomers were selectively acetylated as mentioned in the literature.[5] When the bulkiness of the substituents at C-3 increased from proton, methyl, acetyl, and 2-methyl-1,2-dioxolan-2-yl groups, the efficiencies of the resolution increased (Entries 1, 6, 7, and 8). On the contrary, bulkier substituents at C-4 had much influence in decreasing the rate of acetylation as well as stereoselectivity (Entries 6 and 10). The enantioselectivities of the acetylations of **3a**—**7** were determined by the ^{1}H NMR spectra of diastereomeric (*R*)-(−)-2-methoxy-2-phenylacetates **10** and **12** (Entries 6 and 9) or the optical rotations (Entries 7 and 8) (Fig. 1), and the absolute configuration of (*S*)-(−)-alcohol **3a** was determined to be *S* by the CD spectrum of benzoate **11** as discussed above (Entry 6 and Fig. 1).

The present kinetic acetylation can be applied easily to large scale preparations. The racemic alcohol *dl*-**5a** (20 g) was resolved almost quantitatively in 5.5 h.

In conclusion, we have shown that the high efficiency of the enzymatic kinetic resolution as well as the simplicity of operation by lipase AK in organic solvent provides a new practical alternative[3] for the preparation of optically active 2-cyclohexen-1-ol derivatives in high enantiomeric excesses.

Experimental

General IR spectra were recorded on a JASCO FT/IR 8300 spectrophotometer for solutions in carbon tetrachloride. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Bruker AC-250 (250 MHz), JEOL FX 90Q (90 MHz), or JEOL PMX-60 (60 MHz) instrument with tetramethylsilane as an internal standard. Optical rotations ($[\alpha]_D$) were determined on a JASCO DIP-4S polarimeter for solutions in chloroform. CD spectra were measured on a JASCO J-400X spectrophotometer. Ultraviolet spectra were obtained on a JASCO UVDEC-505 spectrophotometer. Lipase AK was obtained from Amano Pharmaceutical Co.

General Procedure of Kinetic Acetylation. To

Table 1. Enzymatic Kinetic Acetylation[a] of Various Racemic 2-Cyclohexen-1-ol Derivatives

Entry	Substrate	Time/h	Recovered alcohol				Produced acetate				E[c]
				Yield,[b]	e.e.(%),	$[\alpha]_D$		Yield,[b]	e.e.(%),	$[\alpha]_D$	
1	*dl*-**2a**	3.0	(*S*)-(−)-**2a**	44,	96[g]	−55.7	(*R*)-(+)-**2b**	47,	95[h]	+186	153
2[d]	*dl*-**2a**	3.0	(*S*)-(−)-**2a**	49,	91[h]	−52.4	(*R*)-(+)-**2b**	47,	95[h]	+188	124
3[e]	*dl*-**2a**	4.0	(*S*)-(−)-**2a**	64,	46[h]	−26.6	(*R*)-(+)-**2b**	30,	99[h]	+196	314
4[e]	*dl*-**2a**	6.0	(*S*)-(−)-**2a**	52,	76[h]	−43.9	(*R*)-(+)-**2b**	38,	97[h]	+191	148
5[f]	*dl*-**2a**	33.0	(*S*)-(−)-**2a**	48,	91[h]	−53	(*R*)-(+)-**2b**	41,	99[h]	+196	637
6	*dl*-**3a**	9.0	(*S*)-(−)-**3a**	40,	55[g]	−25.7	(*R*)-(+)-**3b**	55,	42[g]	+45.9	4.1
7	*dl*-**4a**	2.0	(*S*)-(−)-**4a**	37,	65[h]	−62.6	(*R*)-(+)-**4b**	37,	77[h]	+175	14.2
8	*dl*-**5a**	5.5	(*S*)-(−)-**5a**	50,	97[h]	−45.5	(*R*)-(+)-**5b**	43,	97[h]	+126	277
9	*dl*-**6a**	1.5	(*S*)-(+)-**6a**	46,	87[h]	+28.5	(*R*)-(−)-**6b**	40,	94[g]	+109	97
10	*dl*-**7**	3.0	No reaction								

a) At room temperature under nitrogen. b) Isolated yield. c) See Ref. 6. d) Without MS-4Å. e) 10 weight % of lipase AK was used. f) In dry acetonitrile. g) Determined by NMR. h) Determined by optical rotation.

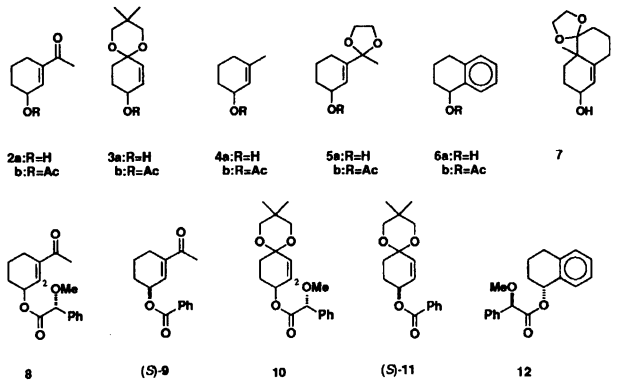


Fig. 1.

a stirred solution of racemic alcohol (ca. 100 mg) and vinyl acetate (2 ml) in hexane (10 ml) was added ground 4 Å molecular sieves (ca. 50 mg). After the mixture had been stirred at room temperature for 2 h, lipase Amano AK (ca. 50 mg) was added and the resulting suspension was stirred at room temperature under nitrogen. The reaction was monitored by TLC until almost 50% conversion and quenched by filtration of the enzyme and ground 4 Å molecular sieves. Evaporation of the solvent followed by preparative TLC or mplc separation (eluant: hexane/ethyl acetate=1) afforded the optically active acetate and alcohol.

For a preparative scale reaction, the racemic alcohol **5a** (20.0 g), vinyl acetate (80 ml), ground 4 Å molecular sieves (10 g), and lipase Amano AK (2.1 g) in hexane (1,000 ml) were treated in the same manner as above to give the optically active acetate (*R*)-**5b** (10.6 g, 43%, 97% e.e.) and alcohol (*S*)-**5a** (10.1 g, 50%, 97% e.e.).

Determination of the Enantiomeric Excess of Alcohol 2a. The e.e. values of alcohol **2a** (Entry 1) were determined by the integration of the ^{1}H NMR spectrum of ester **8** (vide infra). Since alcohol **2a** (96% e.e., Entry 1) had $[\alpha]_D^{22}$ −55.7° (*c* 0.233), the optical rotation value of the pure enantiomer of alcohol **2a** was calculated to be 58.1. Then, the e.e. values of alcohol **2a** (Entries 2, 3, 4, and 5) were determined by the optical rotation value.

Determination of the Enantiomeric Excess of Acetate 2b. The e.e.value of acetate **2b** was obtained by the optical rotation value; alcohol **2a** (96% e.e., Entry 1) was acetylated to give acetate **2b** ($[\alpha]_D^{23}$ −189.1°), and the optical rotation value of the pure enantiomer of acetate **2b** was calculated to be 197°.

The following spectroscopic data were observed for the optically active alcohols and acetates.

(*S*)-(−)-4,4-(2,2-Dimethyltrimethylene)dioxy-2-cyclohexen-1-ol (3a). Entry 6; $[\alpha]_D^{24}$ −25.7° (*c* 0.424) (55% e.e.); ^{1}H NMR (90 MHz) δ=0.96 (3H, s), 1.02 (3H, s), 1.68—2.02 (4H, m), 3.42—3.71 (4H, m), 5.15—5.27 (1H, m), 5.94 (1H, dd, J=10.5 and 2.5 Hz), and 6.17 (1H, d, J=10.5 Hz); IR 3600, 3448, 1684, and 1107 cm^{-1}. The e.e. value was obtained by integration of the ^{1}H NMR spectrum of ester **10** (vide infra).

(*R*)-4,4-(2,2-Dimethyltrimethylene)dioxy-2-cyclohexenyl Acetate (3b). Entry 6; $[\alpha]_D^{24}$ +45.9° (*c* 0.703) (42% e.e.); ^{1}H NMR (90 MHz) δ=0.95 (3H, s), 1.03 (3H, s), 1.75—2.18 (4H, m), 2.05 (3H, s), 3.41—3.71 (4H, m), 5.19—5.33 (1H, m), 5.86 (1H, dd, J=10.4 and 3.1 Hz), and 6.28 (1H, d, J=10.4 Hz); IR 1728, 1250, 1097, and 1048 cm^{-1}. The e.e. value was obtained by integration of the ^{1}H NMR spectrum of ester **10** after hydrolysis of acetate **3b** followed by esterification with (*R*)-(−)-2-methoxy-2-phenylacetic acid (vide infra).

(*R*)-3-Methyl-2-cyclohexenyl Acetate (4b). Entry 7; $[\alpha]_D^{23}$ +174.8° (*c* 1.16) (77% e.e.). The e.e. value was obtained by the optical rotation value of alcohol **4a**[9] after hydrolysis.

(*S*)-3-(2-Methyl-1,3-dioxanyl)-2-cyclohexenyl-1-ol (5a). Entry 8; $[\alpha]_D^{27}$ −45.5° (*c* 0.42) (98% e.e.); ^{1}H NMR (90 MHz) δ=1.45 (3H, s), 1.62—2.04 (7H, m), 3.80—3.98 (4H, m), 4.22—4.30 (1H, m), and 5.91—5.97 (1H, m); IR 3602, 1375, 1231, 1196, and 1042 cm^{-1}. The e.e. value was obtained by the optical rotation value of alcohol **2a** after deprotection of the acetal.

(*R*)-3-(Methyl-1,3-dioxolan-2-yl)-2-cyclohexenyl Acetate (5b). Entry 8; $[\alpha]_D^{27}$ +126° (*c* 0.426) (97% e.e.); ^{1}H NMR (90 MHz) δ=1.46 (3H, s), 2.05 (3H, s), 1.67—2.12 (6H, m), 3.81—4.0 (4H, m), 5.30—5.39 (1H, m), and 5.85—5.92 (1H, m); IR 1723, 1374, 1250, 1197, and 1040 cm^{-1}. The e.e. value was obtained by the optical rotation value of acetate **2b** after deprotection of the acetal.

(*R*)-1,2,3,4-Tetrahydro-1-naphthyl Acetate (6b). Entry 9; $[\alpha]_D^{24}$ +109.3° (*c* 1.137) (93% e.e.); ^{1}H NMR (90 MHz) δ=1.85—2.02 (4H, m), 2.08 (3H, s), 2.72—2.85 (2H, m), 6.0 (1H, t-like), and 7.09—7.26 (4H, m); IR 1724, 1378, and 1248 cm^{-1}. The e.e. value was obtained by integration of the ^{1}H NMR spectrum of ester **12** after hydrolysis of acetate **6b** followed by esterification with (*R*)-(−)-2-methoxy-2-phenylacetic acid (vide infra). Since the ^{1}H NMR spectrum (300 MHz) of ester **12** exhibited a proton on C-1 at 5.96 (0.967 H) and 6.04 (0.033 H) ppm, the e.e. value of acetate **6b** was calculated to be 93%.

(*S*)-3-Acetyl-2-cyclohexenyl (*R*)-2-Methoxy-2-phenylacetate (8). To a stirred solution of racemic 3-acetyl-2-cyclohexen-1-ol (**2a**) (57 mg, 0.41 mmol) in anhydrous dichloromethane (3 ml) was added *R*-(−)-2-methoxy-2-phenylacetic acid (76.5 mg, 0.46 mmol, 1.13 equiv), 4-(dimethylamino)pyridine (DMAP) (12.9 mg), and dicyclohexylcarbodiimide (DCC) (87.1 mg, 0.422 mmol, 1.04 molar amount) successively. After stirring at room temperature overnight, the resulting solution was poured into water. The products were extracted with ethyl acetate (30 ml×2), and the organic layer was washed with brine. Evaporation of the solvents followed by preparative TLC purification (eluant: hexane/ethyl acetate=1) afforded a diastereomeric mixture of ester **8** (114.5 mg, 98%); ^{1}H NMR (250 MHz) δ=1.42—2.07 (6H, m), 2.17 (1.5H, s), 2.27 (1.5H, s), 3.41 (3H, s), 4.77 (1H, s), 5.38—5.58 (1H, m), 6.33—6.45 (0.5H, m), 6.55—6.68 (0.5H, m), and 7.22—7.48 (5H, m); IR 1744, 1671, 1456, 1354, 1259, 1236, 1176, and 1115 cm^{-1}.

Alcohol **2a** (12.1 mg, Entry 1) was subjected to esterification. Without an aqueous work-up, ester **8** was isolated by preparative TLC (26.5 mg, 100%). The ^{1}H NMR spectra of **8** (250 MHz) exhibited the signal of C–2H in a ratio of 98 : 2.

(*S*)-3-Acetyl-2-cyclohexenyl Benzoate (9). To a stirred solution of 3-acetylcyclohex-2-en-1-ol (**2a**) (35.5 mg, 0.25 mmol, 36% e.e.) in anhydrous pyridine (1 ml) was added benzoyl chloride (0.1 ml) at 0 °C. After stirring for 30 min at that temperature, the resulting mixture was stirred at room temperature overnight. The product was extracted with ether (30 ml×2) and the organic layer was washed with brine. Evaporation of the ether followed by preparative TLC (eluant: hexane/ethyl acetate=1) and then mplc gave benzoate **9** (51.6 mg, 83%); UV (EtOH) λ_{max} 231.4 nm (ε 25300); CD (EtOH) λ_{ext} 234 nm ($\Delta\varepsilon$ −8.11); ^{1}H NMR (90 MHz) δ=1.6—2.3 (6H, m), 2.33 (3H, s), 5.73 (1H, m), 6.82 (1H, m), 7.3—7.6 (3H, m), and 8.0—8.2 (2H, m); IR 1713, 1671, 1452, 1316, 1272, 1259, 1236, 1113, and 1070 cm^{-1}.

4,4-(2,2-Dimethyltrimethylene)dioxy-2-cyclohexenyl (*R*)-2-Methoxy-2-phenylacetate (10). Ester **10** was prepared in the same manner as ester **8** (94%); ^{1}H NMR (250 MHz) δ=0.95 (3H, s), 1.01 (3H, s), 1.67—1.62 (2H, m), 1.98—1.81 (2H, m), 3.41 (3H, s), 3.63—3.44 (4H, m), 4.75 (1H, s), 5.3—5.35 (1H, m), 5.66 (0.5H, dd, *J*=10.3 and 3.3 Hz), 5.88 (0.5H, dd, *J*=10.3 and 3.3 Hz), 6.21 (0.5H, d, *J*=10.3 Hz), 6.29 (0.5H, d, *J*=10.3 Hz), and 7.45—7.32 (5H, m); IR 1742, 1178, and 1097 cm^{-1}.

Since the ^{1}H NMR spectrum (250 MHz) of ester **10**, derived from alcohol **3a** in Entry 6, exhibited signals of the C-2 proton at 5.66 (0.223 H) and 5.88 (0.777 H) ppm, the e.e. value of alcohol **3a** was calculated to be 55%.

(*S*)-4,4-(2,2-Dimethyltrimethylene)dioxy-2-cyclohexenyl Benzoate (11). Benzoate **11** was prepared in the same manner as benzoate **9** (90%); UV (EtOH) λ_{max} 229 nm (ε 13800); CD (EtOH) λ_{ext} 222 nm ($\Delta\varepsilon$ −5.88); ^{1}H NMR (90 MHz) δ=0.97 (3H, s), 1.04 (3H, s), 1.88—2.29 (4H, m), 3.44—3.74 (4H, m), 5.48—5.57 (1H, m), 5.99 (1H, dd, *J*=10.4 and 3.1 Hz), 6.34 (1H, br d, *J*=10.5 Hz), and 7.31—8.09 (5H, m); IR 1713, 1271, 1220, and 1095 cm^{-1}.

1,2,3,4-Tetrahydro-1-naphthyl (*R*)-2-Methoxy-2-phenylacetate (12). Ester **12** was prepared in the same manner as ester **8** (91%); ^{1}H NMR (250 MHz) δ=1.63—2.09 (4H, m), 2.68—2.87 (2H, m), 3.42 (3H, s), 4.77 (0.5H, s), 4.78 (0.5H, s), 5.96 (0.5H, t, *J*=5.1 Hz), 6.04 (0.5H, t, *J*=4.1 Hz), 6.98—7.45 (9H, m); IR 1740, 1259, 1178, and 1115 cm^{-1}.

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