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First example of hydrolytic kinetic resolution of acrylate of secondary alcohols by lipase Amano AK

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ABSTRACT

Lipase Amano AK is found to be extremely efficient catalyst for hydrolytic kinetic resolution of acrylates of secondary alcohols in aqueous phosphate buffer at pH 7.0. Both aliphatic and benzylic secondary alcohols show good to excellent *E* values.

1. Introduction

In recent years, enzymes [1] are finding huge applicability in the manufacture of a wide range products, *viz.* drugs, agro-pharmaceuticals, organic fine chemicals and plastics [2] because of their easy commercial availability and high catalytic efficiency. Among the enzymes, lipases are used very often in organic synthesis because of their excellent selectivities. They catalyze hydrolysis, esterification, *trans*-esterification including alcoholysis on a broad range of substrates due to their ability to change their conformation depending on the substrate structure (induced fit enzyme) [3]. Especially, lipases are suited for the kinetic resolution of secondary alcohols due to their exceptional stability and enantioselectivity in both water and organic solvents, besides being environmentally friendly.

The α,β-unsaturated lactone [4] is one of the most important functionalities present in a wide spectrum of naturally occurring compounds that display diverse pharmacological properties, such as antitumor, antimicrobial, and antifungal. The synthesis of α,β-unsaturated lactones can be achieved by ring closing metathesis (RCM) of acrylates of secondary alcohol with unactivated olefin terminal [5]. The stereoselectivity of the acrylate terminal can be achieved in two pathways, *viz.* by esterification of chiral secondary alcohol, derived from non-enzymatic stereoselective reactions, with α,β-unsaturated acid chlorides [6], or through enzymatic kinetic resolution of acrylates of secondary alcohols (Scheme 1).

While surfing the literature, we have observed that the enzymatic esterification of olefin-tethered secondary alcohols to synthesize enantiomerically pure α,β-unsaturated ester is finding scant attention, albeit being very promising. In spite of having tremendous potential, there are only a few reports [7] on synthesis of chiral α,β-unsaturated esters by enzymatic *trans*- esterification of racemic secondary alcohols with α,β-unsaturated vinyl esters. But, no report is available for enzymatic hydrolysis of α,β-unsaturated esters leading to chiral alcohol, unlike the enzymatic hydrolysis of the acetate of secondary alcohols. It is a fact that in most of the kinetically controlled enzymatic reactions, equilibrium shift towards the right with slightest change in the reaction conditions. Therefore, both enzymatic esterification and hydrolysis are important pathways to achieve enantiomeric alcohol with high ee-values. In order to develop an efficient method for the synthesis enantiomerically pure acrylates and secondary alcohol, we are reporting for the first time, the lipase Amano AK catalyzed enzymatic kinetic hydrolysis of acrylates of secondary alcohols to achieve good to excellent enantioselectivity.

2. Experimental

2.1. General

All reagents were commercially available and used without further purification. Most of the alcohols were synthesized by $NaBH_4$ reduction of coommercially available ketones purchased

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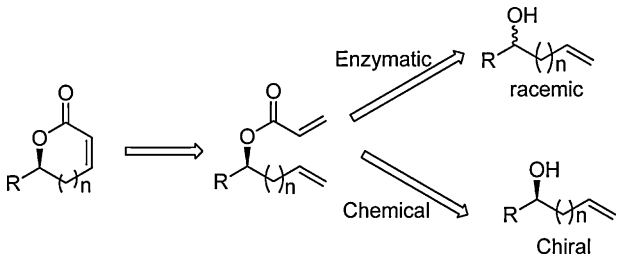

Scheme 1.

from Sigma Aldrich and acrylated with acryloyl chloride and DBU/triethylamine as per literature procedure [6a]. The alcohol derivatives for entry 6, 7 and 8 were synthesized by Grignard reaction with their corresponding aldehydes. All acrylates were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. The IR spectra were recorded on a Perkin Elmer spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker AC-400 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on an Waters M515 series equipped with a chiral column (Chiralcel AD-H and Chiralcel OD-H), using mixtures of *n*-hexane/isopropyl alcohol (IPA) as mobile phase, at 25 °C. For column chromatography, we employed Merck silica gel 60–120 mesh.

2.2. General procedure for the synthesis of acrylates

A mixture of the secondary alcohol (2 mmol) and triethylamine (3 mmol) was dissolved in 20 mL dichloromethane and cooled to 0 °C. Then acryloyl chloride (5 mmol) was added drop wise to the reaction mixture and allowed to stir overnight. Upon completion, the reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with dichloromethane and aqueous NH_4Cl solution, dried over Na_2SO_4 and concentrated in a rotavapor. The residual oil is purified by column chromatography (silica gel, EtOAc/Hexane). The acrylates are characterized by ^{1}H NMR, ^{13}C NMR.

2.2.1. 1-Phenylethyl acrylate

Purification by column chromatography using hexane and ethyl acetate in 9:1 ratio to achieve 1-phenylethyl acrylate as a colorless liquid (yield 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, J = 6.8 Hz, 3H), 5.78 (dd, J = 10.4 Hz, 1.6 Hz, 1H), 5.93 (q, J = 6.4 Hz, 1H), 6.11 (dd, J = 17.6 Hz, 10.4 Hz, 1H) 7.28 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 72.7, 126.0, 127.9, 128.6, 130.7, 141.5, 165.4 ppm.

2.2.2. 1-(4-Methoxyphenyl)ethyl acrylate

Purification by column chromatography using hexane and ethyl acetate in 9:1 ratio to achieve 1-(4-methoxyphenyl)ethyl acrylate as a colorless liquid (yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, J = 6.4 Hz, 3H), 3.58 (s, 3H), 5.59 (dd, J = 10, 1.2 Hz, 1H), 5.72 (q, J = 6.4 Hz, 1H), 5.91 (dd, J = 17.2, 10 Hz, 1H), 6.19 (dd, J = 17.6, 1.2 Hz, 1H), 6.70 (d, J = 8 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 55.3, 113.8, 127.6, 128.8, 130.7, 133.6, 165.5 ppm.

2.2.3. 1-(4-Chlorophenyl) ethyl acrylate

Purification by column chromatography using hexane and ethyl acetate in 9:1 ratio to achieve 1-(4-chlorophenyl)ethyl acrylate as a colorless liquid (yield 88%). ^{1}H NMR (400 MHz, $CDCl_3$): 0.55 (d, J = 6.8 Hz, 3H), 5.88 (dd, J = 27 Hz, 6.4 Hz, 1H), 5.84 (q, J = 6.4 Hz, 1H), 6.05 (dd, J = 17.2, 10.4 Hz, 1H), 6.34 (dd, J = 17.2, 0.8 Hz, 1H), 7.23 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 71.7, 127.5, 128.4, 128.5, 128.7, 131.0, 133.6, 140.1, 165.3 ppm.

2.2.4. 1-(3-Nitrophenyl) ethyl acrylate

Purification by column chromatography using hexane and ethyl acetate in 9:1 ratio to achieve 1-(3-nitrophenyl)ethyl acrylate as a colorless liquid (yield 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (d, J = 6.4 Hz, 3H) 5.88 (d, J = 10 Hz, 1H) 6.01 (q, J = 6.4 Hz, 1H), 6.15 (dd, J = 17.2 Hz, 10 Hz, 1H), 6.44 (d, J = 18 Hz, 1H), 7.52 (t, J = 8 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 8.14 (d, J = 8 Hz, 1H), 8.23 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 71.4, 121.1, 123.0, 128.3, 129.7, 131.8, 132.4, 143.9, 165.3 ppm.

2.2.5. 1-(4-Methyl phenyl)ethyl acrylate

Purification by column chromatography using hexane and ethyl acetate in 9:1 ratio to achieve 1-(4-methylphenyl)ethyl acrylate as a colorless liquid (yield 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (d, J = 6.8 Hz, 3H), 2.34 (s, 3H), 5.81 (dd, J = 10.4, 1.2 Hz,1H), 5.93 (q, J = 6.4 Hz, 1H), 6.17 (dd, J = 17.2, 10.4 Hz, 1H), 6.41 (dd, J = 17.6, 1.2 Hz, 1H), 7.164 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 22.1, 72.4, 126.1, 128.8, 129.1, 130.7, 138.1, 165.5 ppm.

2.2.6. 1-Phenylbutyl acrylate

Purification by column chromatography using hexane and ethyl acetate in 12:1 ratio to achieve 1-phenylbutyl acrylate as a colorless liquid (yield 73%). ^{1}H NMR (400 MHz,$CDCl_3$): δ 0.92 (t, J = 14.8, 7.2 Hz, 3H), 1.31 (m, 2H), 1.86 (m, 2H), 5.81 (t, J = 2.4 Hz, 1H), 5.83 (d, J = 0.8 Hz, 1H), 6.15 (dd, J = 21.2, 10.4 Hz, 1H), 6.41 (d, J = 21.6 Hz, 1H), 7.30 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 18.7, 38.4, 76.0, 126.4, 127.8, 128.4, 128.7, 130.7, 140.7, 165.5 ppm.

2.2.7. 1-(4-Bromophenyl)allyl acrylate

Purification by column chromatography using hexane and ethyl acetate in 12:1 ratio to achieve 1-(4-bromophenyl)allyl acrylate as a colorless liquid (yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25 (t, J = 16.8 Hz, 2H), 5.83 (dd, J = 10.4, 1.2 Hz, 1H), 5.91–5.98 (m, 1H), 6.13 (dd, J = 17.2, 10.4 Hz, 1H), 6.24 (d, J = 5.6 Hz, 1H), 6.41 (dd, J = 17.2, 1.2 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 75.6, 117.5, 122.2, 128.2, 128.9, 131.7, 135.6, 137.8, 165 ppm.

2.2.8. 1-[(E)-2-Phenylvinyl]but-3-enyl acrylate

Purification by column chromatography using hexane and ethyl acetate in 12:1 ratio to achieve 1-[(E)-2-phenylvinyl]but-3-enyl acrylate as a colorless liquid (yield 66%). ^{1}H NMR: δ 2.53 (m, 2H), 5.09–5.16 (m, 2H), 5.56 (q, J = 6.6 Hz, 1H), 5.75–5.85 (m, 2H), 6.11–6.21 (m, 2H), 6.43 (dd, J = 17.4, 1.4 Hz, 1H), 6.64 (d, J = 16.0 Hz, 1H), 7.24–7.39 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.1, 73.9, 118.2, 126.6, 126.9, 128.0, 128.5, 128, 6, 130.8, 132,7, 133.0, 136.2, 165.4 ppm.

2.2.9. Octan-2-yl acrylate

Purification by column chromatography using hexane and ethyl acetate in 20:1 ratio to achieve octan-2-yl acrylate as a colorless liquid (yield 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (t, J = 6 Hz, 3H), 1.09–1.60 (m, 13H), 4.85–4.93 (m, 1H), 5.71 (dd, J = 10, 1.2 Hz, 1H), 6.02 (dd, J = 17.2, 10.4 Hz, 1H), 6.3 (d, J = 16.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 19.9, 22.5, 25.3, 29.1, 31.7, 35.8, 71.3, 129.1, 130.1, 165.9 ppm.

2.2.10. Octan-3-yl acrylate

Purification by column chromatography using hexane and ethyl acetate in 20:1 ratio to achieve octan-3-yl acrylate as a colorless liquid (yield 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71–0.81 (m, 6H), 1.18 (m, 6H), 1.41–1.55 (m, 4H), 4.80 (m, 1H), 4.84 (dd, J = 10.4, 1.2 Hz, 1H), 6.02 (dd, J = 17.6, 10.4 Hz, 1H), 6.3 (dd, J = 17.6, 1.2 Hz,