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Chemoenzymatic synthesis of a 1,2,3-triazolo-δ-lactone derivative

Abstract: The stereoselective synthesis of a 1,2,3-triazolo-δ-lactone (+)-**6** derived from a homoallyl alcohol (*S*)-(-)-**1** backbone was accomplished. 2-Thienyl-substituted allyl alcohol *rac*-**1** was efficiently resolved through enzymatic method with high ee (95%) and known stereochemistry. An enantiomerically enriched azidoalcohol (+)-**4** derived from a homoallyl alcohol was subjected to the Huisgen 1,3-dipolar cycloaddition reaction with diethyl acetylenedicarboxylate, followed by intramolecular cyclization of the corresponding cycloadduct (+)-**5**, to yield the 1,2,3-triazolo-δ-lactone derivative.

Keywords: azide-alkyne cycloaddition; enzymatic resolution; 2-azidoalcohol; 1,2,3-triazolo-δ-lactone.

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Introduction

Lactones are widely distributed in nature and play important roles in living organisms. The γ- and δ-lactones are the most common naturally occurring lactones. They are highly stable and show antimicrobial and cytotoxic activities [1, 2].

The chemistry of 1,2,3-triazole derivatives has gained interest over the past few years due to their wide range of applications in chemical, biological, medicinal, and materials science. The Huisgen 1,3-dipolar cycloaddition of azides and alkynes is the most efficient pathway for the synthesis of substituted 1,2,3-triazoles as chemotherapeutic agents [3–5], synthetic intermediates for bioactive compounds, agrochemicals, optical brighteners, photostabilizers, anticorrosive agents, and metal chelators [6–9]. The extraordinary stability toward metabolic transformations and aromatic nature of the triazole ring, along with its high dipole moment and H-bonding capability, makes it an important functionality as a connecting group [10–13].

The synthesis of compounds containing both δ-lactone and triazole rings attracts some interest because they are expected to possess important biological activities [14–18]. Moreover, the correlation between chirality and biological activity has become important in the pharmaceutical science [19]. Many applications have been focused on the chiral resolution of racemic substrates as the catalytic access to enantiomerically enriched chiral building blocks in organic syntheses [20].

We report here the enzymatic resolution of a 2-thienyl-substituted homoallylic alcohol and the synthesis of highly enantiomerically enriched 1,2,3-triazolo-δ-lactone derivative (+)-**6**.

Results and discussion

The key substrate *rac*-**1** was synthesized by the addition of allylmagnesium bromide to the commercially available 2-thienylcarbaldehyde [21] (Scheme 1).

The racemate *rac*-**1** was resolved by treatment with enzymes to produce the enantiomerically enriched homoallylic alcohol (*S*)-(-)-**1** and the ester (*R*)-(+)-**2** (Scheme 1). The enantiomeric resolution reactions were performed using various lipases with a 1:1 substrate/enzyme ratio and vinyl acetate as an acyl donor and solvent at 30°C.

The results of the enzymatic resolution of *rac*-**1** using Lipozyme, Novozyme 435, and *Candida rugosa lipase* (CRL) are summarized in Table 1. Lipozyme and Novozyme 435 gave good enantioselectivities varying between 74% and 95% ee. The enzyme CRL was not an adequate lipase for this resolution. Function c in Table 1 shows the velocity of the transformation of each enantiomer. The dimensionless enantiomeric ratio E can serve as a convenient measure of the enantioselectivity of an enzymatic resolution. Function E can be mathematically linked to the conversion c of the reaction and the optical purities of substrate and product, as indicated in Table 1. The value of E can be regarded as good in the range of 15–30 and

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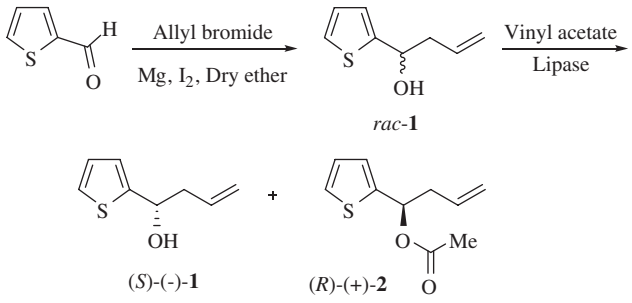
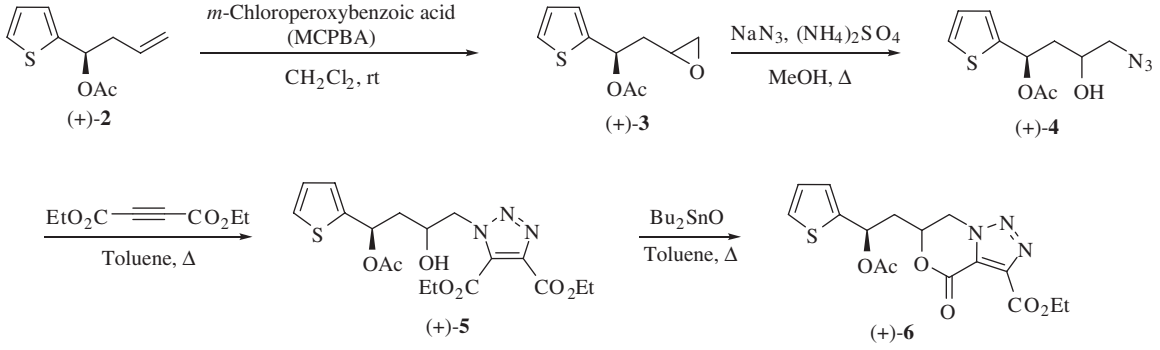


Scheme 1

Table 1 Enzymatic kinetic resolution of homoallylic alcohol *rac*-**1**.

Entry	Enzyme	Time (h)	Ester[a] ee_p[b] (%)	Alcohol[a] ee_s[b] (%)	c[c] (%)	E[d]
1	Lipozyme[e]	24	74 (*R*)	95 (*S*)	56	25
2	Novozyme 435[e]	48	90 (*R*)	81 (*S*)	47	55
3	CRL[e]	168	45 (*R*)	–	–	–

[a]The absolute configurations were found to be *S* for alcohol and *R* for ester by comparison of the optical rotations with the literature values [22, 23]. [b]Determined by HPLC analysis employing Daicel Chiralcel OJ-H column. [c]$c = ee_s/(ee_s+ee_p)$. [d]$E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$ [24]. [e]The reactions were carried out at 30°C.



Scheme 2

excellent when it exceeds 30. According to these analyses, Lipozyme shows good and Novozyme 435 excellent selectivities.

The absolute configuration of alcohol (-)-**1** was determined as *S* and that for ester (+)-**2** as *R*, by comparing the specific rotations with the literature values [22, 23].

The treatment of homoallyl ester (*R*)-(+)-**2** with *m*-chloroperoxybenzoic acid yielded the oxirane (+)-**3** (Scheme 2). Epoxide (+)-**3** was subjected to the reaction with NaN_3, which yielded vicinal azidoalcohol (+)-**4**. A 1,3-dipolar cycloaddition reaction of (+)-4 with diethyl acetylenedicarboxylate afforded a 1,2,3-triazole derivative (+)-**5**. Finally, intramolecular cyclization of (+)-**5** by treatment with dibutyltin oxide yielded the target 1,2,3-triazolo-δ-lactone (+)-**6** [14].

Conclusions

2-Thienyl-substituted allyl alcohol *rac*-**1** was successfully resolved by treatment with Lipozyme with high enantioselectivity (95% ee). The resultant enantiopure ester (*R*)-(+)-**2** was transformed into 1,2,3-triazolo-δ-lactone (+)-**6** in excellent yield.

Experimental

The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Bruker Spectrospin Advance DPX 400 spectrometer. Optical rotations were measured in a 10-cm cell using a Rudolph Research, Autopol III polarimeter. HPLC measurements were performed with a Thermo Separation Products P1500-SN-4000-UV2000 instrument, using a Chiralcel OJ-H analytical column (250×4.60 mm). HRMS spectra were recorded on an Agilent Technologies 6224 Accurate-Mass TOF LC/MS at the National Nanotechnology Research Center of Bilkent University (UNAM). Melting point was measured by Stuart SMP3 instrument. Flash column chromatography was performed on silica gel (60-mesh; Merck). The reactions were monitored by thin-layer chromatography (TLC) using Merck 0.2-mm silica gel 60 F_{254} analytical aluminum plates, visualized by UV light and polymolybden phosphoric acid in ethanol. All extracts were dried over anhydrous magnesium sulfate and solutions were concentrated under reduced pressure by using a rotary evaporator. Lipozyme and CRL were purchased from Aldrich and Novozyme 435 was donated by Novo Nordisk AS, Bagsverd, Denmark.

Enzymatic resolution of *rac*-1-(2-thienyl)but-3-en-1-ol (*rac*-1)

To 100 mg of *rac*-**1** in 3 mL of vinyl acetate was added 100 mg of the enzyme, and the mixture was shaken at 30°C. The reaction was

monitored by TLC. When nearly 50% conversion was observed, the mixture was filtered and the residue was concentrated *in vacuo*. The mixture was separated by flash chromatography using AcOEt/hexanes (1:5) as an eluent.

(*S*)-(-)-1-(2-Thienyl)but-3-en-1-ol [(*S*)-(-)-1]: This alcohol was obtained as a yellow oil; $[\alpha]_D^{31}$ = -20.1° (c = 1, CH_2Cl_2); 95% ee. The enantiomeric purity of the product was determined by HPLC analysis [Daicel Chiralcel OJ-H, *n*-hexane/*i*-PrOH (96:4), flow rate = 1 mL/min, λ = 230 nm, t_R = 15.0 min for the *S*-isomer, and t_R = 17.3 min for the *R*-isomer].

(*R*)-(+)-1-(2-Thienyl)but-3-enyl acetate [(*R*)-(+)-2]

This ester was obtained as a colorless oil; $[\alpha]_D^{31}$ = +46.3° (c = 1, CH_2Cl_2); 74% ee {Lit. [22]: $[\alpha]_D^{29}$ = +84° (c = 1, CH_2Cl_2); 91% ee}. The enantiomeric purity of the product was determined by HPLC analysis (Daicel Chiralcel OJ-H, *n*-hexane/*i*-PrOH 96:4, flow rate = 1 mL/min, λ = 230 nm, t_R = 8.5 min for the *S*-isomer, and t_R = 9.8 min for the *R*-isomer).

(+)-2-(Oxiran-2-yl)-1-(2-thienyl)ethyl acetate [(+)-3]

A solution of (+)-**2** (2 g, 10 mmol) in dichloromethane (50 mL) was cooled to 0°C, stirred, and treated slowly with *m*-chloroperoxybenzoic acid (15 mmol, 77%). The mixture was stirred at room temperature for 4 h, and the progress of the reaction was monitored by TLC. Then, the mixture was neutralized with a saturated solution of $NaHCO_3$ and extracted with dichloromethane (3×15 mL). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with a mixture of AcOEt/hexane (1:4).

The pure compound was obtained in 63% yield as a colorless oil; $[\alpha]_D^{25.2}$ = +93.2° (c = 1, CH_2Cl_2); ^{1}H NMR: δ 7.18–7.10 (m, 1H), 6.98–6.80 (m, 2H), 6.16–6.10 (m, 1H), 2.85–2.80 (m, 2H), 2.73–2.65 (m, 1H), 2.40–2.10 (m, 2H), 1.99 (s, 3H); ^{13}C NMR: δ 169.6, 142.7, 126.1, 125.5, 68.9, 48.8, 46.8, 39.6, 21.0. HRMS (ESI-TOF). Anal. Calcd for $C_{10}H_{12}O_3S$ $[M+Na]^+$: *m/z* 235.04103. Found: *m/z* 235.04512.

(+)-4-Azido-3-hydroxy-1-(2-thienyl)butyl acetate [(+)-4]

A solution of oxirane (+)-**3** (0.85 g, 4 mmol), NaN_3 (0.52 g, 8.0 mmol), and $(NH_4)_2SO_4$ (0.9 g, 6.8 mmol) in methanol (20 mL) was stirred and heated under reflux for 4 h. After the reaction was completed, as judged by TLC analysis, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography eluting with AcOEt/hexanes (1:3). The pure compound was obtained in 78% yield as a yellow oil; $[\alpha]_D^{31.8}$ = +92.6° (c = 1, CH_2Cl_2); ^{1}H NMR: δ 7.23–7.18 (m, 1H), 7.03–6.98 (m, 1H), 6.91–6.88 (m, 1H), 6.24 (dd, *J* = 3.3, and 10.3 Hz, 1H), 3.79–3.74 (m, 1H), 3.29–3.19 (m, 2H), 2.94 (bs, 1H), 2.25–2.11 (m, 1H), 1.97–1.91 (m, 1H); ^{13}C NMR: δ 147.3, 142.7, 126.8, 125.7, 125.0, 70.5, 68.1, 56.5, 41.8, 21.1. HRMS (ESI-TOF). Anal. Calcd for $C_{10}H_{13}N_3O_3S$ $[M+Na]^+$: *m/z* 278.05808. Found: *m/z* 278.06122.

(+)-Diethyl 1-[(4*R*)-4-acetoxy-2-hydroxy-4-(2-thienyl)-butyl]-1*H*-1,2,3-triazole-4,5-dicarboxylate ((+)-5)

To a stirred solution of azidoalcohol (+)-**4** (255 mg, 1 mmol) in toluene (10 mL), diethyl acetylene dicarboxylate (1.7 g, 10 mmol) was added. The mixture was stirred for 4 h and heated under reflux, then concentrated and the residue of the crude product was purified by flash chromatography eluting with AcOEt/hexanes (2:3). The pure compound was obtained in 75% yield as a yellow oil; $[\alpha]_D^{28.0}$ = +81.9° (c = 1, CH_2Cl_2); ^{1}H NMR: δ 7.21–7.19 (m, 1H), 7.01–6.96 (m, 1H), 6.90–6.86 (m, 1H), 6.23–6.19 (m, 1H), 4.67–4.53 (m, 2H), 4.39–4.30 (m, 4H), 4.06–4.02 (m, 1H), 2.20–2.12 (m, 1H), 1.97 (s, 3H), 1.93–1.86 (m, 1H), 1.32 (t, *J* = 7 Hz, 3H), 1.31 (t, *J* = 7 Hz, 3H); ^{13}C NMR: δ 171.2, 160.0, 159.0, 142.5, 139.5, 131.7, 126.7, 125.8, 125.6, 67.8, 66.8, 62.8, 61.8, 54.8, 41.6, 21.0, 14.1, 13.9. HRMS (ESI-TOF). Anal. Calcd for $C_{18}H_{23}N_3O_7S$ $[M+Na]^+$: *m/z* 448.11489. Found: *m/z* 448.11744.

Ethyl 6-[(*R*)-2-acetoxy-2-(2-thienyl)ethyl]-4-oxo-6,7-dihydro-4*H*-[1–3]triazolo[5,1-*c*][1, 4]oxazine-3-carboxylate [(+)-6]

Dibutyltin oxide (50 mg, 0.20 mmol) was added to a solution of triazole (+)-**5** (170 mg, 0.40 mmol) in 50 mL of dry toluene. The system, equipped with a Dean-Stark device, was heated under reflux for 1 h. The mixture was concentrated under reduced pressure, and the crude product was purified by flash chromatography using AcOEt/hexane (1:1) as eluent. The pure compound was obtained in 60% yield as white crystals; mp 100–102°C (dec); $[\alpha]_D^{26.0}$ = +45.0° (c = 1, CH_2Cl_2); ^{1}H NMR: δ 7.24–7.22 (m, 1H), 7.06–7.05 (m, 1H), 6.92–6.90 (m, 1H), 6.33–6.28 (m, 1H), 4.84–4.78 (m, 1H), 4.66–4.60 (m, 1H), 4.41–4.33 (m, 3H), 2.65–2.58 (m, 1H), 2.33–2.26 (m, 1H), 2.02 (s, 3H), 1.34 (t, *J* = 7 Hz, 3H); ^{13}C NMR: δ 169.7, 159.0, 152.6, 140.6, 127.1, 127.0, 126.3, 126.0, 125.0, 74.6, 67.3, 62.4, 49.0, 38.5, 21.1, 14.1. HRMS (ESI-TOF). Anal. Calcd for $C_{16}H_{17}N_3O_6S$ $[M+Na]^+$: *m/z* 402.07303. Found: *m/z* 402.07840.

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