Enzymatic Resolution of (±)-2-*Exo*-7-*syn*-7-(1-propynyl)norbornan-2-ol, a Key Synthetic Intermediate for Jasmonoids

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Lipase-catalyzed resolution of 2-*exo*-7-*syn*-7-(1′-propynyl)norbornan-2-ol, a key synthetic intermediate for jasmonoids, was achieved using vinyl chloroacetate as an acyl donor.

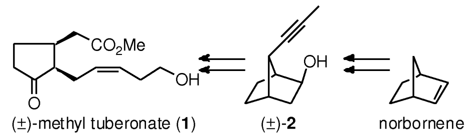
Key words: Enzymatic Resolution, Lipases, Transesterification, Chloroacetate, Bicyclo[2.2.1]heptan-2-ol

Introduction

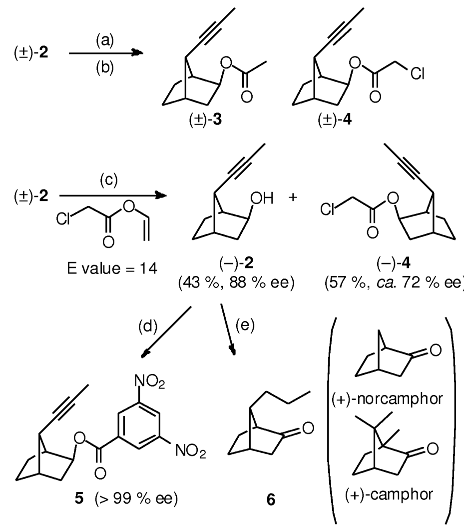
Jasmonoids are distributed as various biologically active compounds such as plant hormones [1] and perfumes [2], and sometimes show even therapeutic activity [3]. We have achieved the total synthesis of methyl tuberonate (**1**), a strong potato tuber-forming substance, in a racemic form [4] from norbornene (Scheme 1). In order to prepare the optically active product, we focused on the enzymatic resolution of the synthetic intermediate alcohols such as **2**. Enzymatic reaction has been one of the methods of choice to get optically active organic compounds under mild conditions [5]. Here we describe the results of the resolution of the sterically hindered alcohol (±)-**2**.

Results and Discussion

At first, transacetylation of (±)-**2** and hydrolysis of its acetate (±)-**3** were tried, however, neither proceeded using various commercial lipases and esterases. Then the more reactive chloroacetyl group was introduced. Transesterification of (±)-**2** with vinyl chloroacetate catalyzed by Chirazyme® L-9 (*Mucor miehei*, Roche) afforded (–)-**2** (88 % ee) and chloroacetate (–)-**4** at 57 % conversion (Scheme 2). The enantiomeric purity was determined by HPLC analysis of the corresponding MTPA ester, and the E value was calculated as 14. Enzymatic hydrolysis of (±)-**4** resulted in poor selectivity. The product (–)-**2** was further purified by recrystallization of its 3,5-dinitrobenzoate **5** up to > 99 % ee. The product of another run (–)-**2** (73 % ee) was converted into its saturated keto derivative **6** to determine the absolute configuration. The sign of optical rotation of **6** ($[\alpha]_D^{18}$ = +24° (*c* = 0.25, MeOH)) compared with those of (+)-norcamphor ($[\alpha]_D$ = +31°) and (+)-camphor [$[\alpha]_D^{20}$ = +54.9° (*c* = 5, EtOH)] revealed the stereochemistry as drawn in Scheme 2 [6]. The similar Cotton curves of **6** and (+)-camphor in the CD spectra also support this conclusion.



Scheme 1. Synthesis of (±)-methyl tuberonate (**1**).



Scheme 2. Enzymatic resolution of (±)-**2**. (a) Ac_2O, Py (99 %); (b) chloroacetyl chloride, Py, Et_2O (92 %); (c) Chirazyme® L-9, c.-f., C2, lyo., *i*-Pr_2O, 20 °C; (d) i. 3,5-dinitrobenzoyl chloride, pyridine, DMAP, Et_2O (quant.); ii. recrystallization from *i*-Pr_2O (58 %); (e) i. PDC, $CHCl_3$; ii. H_2, Pd-C, MeOH.

The alcohols **2** resolved in this experiment will be useful chiral building blocks for valuable compounds. The results also have exemplified a lipase-catalyzed transesterification of a rather hindered hydroxy group.

Experimental Section

General

Optical rotation: Horiba SEPA-300. NMR: Varian Gemini 2000 (300 MHz) and Varian Inova 500 (500 MHz). IR: Jasco Report-100. MS: Jeol JMS-700. HPLC: Hitachi L-6000 pump & Hitachi L-4200 UV/Vis detector. Column chromatography: Merck silica gel 60 (70 – 230 mesh).

(1S,2S*,4S*,7R*)-7-(1′-Propynyl)bicyclo[2.2.1]hept-2-yl acetate ((±)-**3**)*

To a solution of (±)-**2** (1.68 g, 11.2 mmol) in pyridine (3.4 g, 43 mmol) was added Ac_2O (4.08 g, 40.0 mmol) at 20 °C, and the mixture was stirred for 12 h at 20 °C, then diluted with Et_2O, dil. HCl (5 times), sat. aq. $NaHCO_3$ soln. and brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (hexane/EtOAc = 30 : 1) to give (±)-**3** (2.12 g, 99 %) as a colorless oil. – IR: ν = 3060 (s), 1730 (s, C=O), 1360 (m), 1245 (s, C–O), 1220 (m), 1080 (s), 1045 (m), 1020 (m) cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, J = 4.9 Hz, 1 H), 1.15 (d, J = 4.9 Hz, 1 H), 1.42 – 1.62 (m, 2 H), 1.81 (d, J = 2.4 Hz, 3 H, $CH_3C\equiv$), 1.85 – 1.9 (m, 1 H), 1.95 – 2.0 (m, 1 H), 2.03 (s, 3 H, $CH_3C{=}O$), 2.30 (m, 2 H), 2.41 (d, J = 4.1 Hz, 1 H), 4.58 (dd, J = 7.4, 3.6 Hz, 1 H, 2-H). – MS (EI): m/z = 117 $[M–AcOH–CH_3]^+$, 132 $[M–AcOH]^+$, 150 $[M+H–Ac]^+$, 177 $[M–CH_3]^+$, 192 M^+). – HRMS (EI): m/z = 192.1150 (calcd. 192.1150 for $C_{12}H_{16}O_2$, M^+).

(1S,2S*,4S*,7R*)-7-(1′-Propynyl)bicyclo[2.2.1]hept-2-yl chloroacetate ((±)-**4**)*

To a solution of (±)-**2** (150 mg, 0.999 mmol) and pyridine (0.50 g, 6.3 mmol) in dry Et_2O was added chloroacetyl chloride (339 mg, 2.98 mmol) at −20 °C. The mixture was stirred for 12 h at 20 °C, then diluted with Et_2O, washed with dil. HCl (5 times), sat. aq. $NaHCO_3$ soln. and brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (hexane/EtOAc = 30 : 1) to give (±)-**4** (209 mg, 0.922 mmol, 92 %) as a colorless oil. – IR: ν = 3100 (s), 1750 (s, C=O), 1720 (s, C=O), 1340 (m), 1310 (s), 1180 (s), 1070 (m), 1040 (m), 1045 (m), 1000 (m), 980 (m) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.1 – 1.2 (m, 2 H), 1.50 – 1.64 (m, 2 H), 1.79 (d, J = 1.5 Hz, 3 H, CH_3), 1.89 (dd, J = 13.5, 8.0 Hz, 1 H), 2.04 (dq, J = 13.5, 3.0 Hz, 1 H), 2.30 – 2.36 (m, 2 H), 2.46 (d, J = 4.5 Hz, 1 H), 4.03 (s, 2 H, CH_2Cl), 4.69 (dd, J = 7.5, 3.0 Hz, 1 H, 2-H). – MS (FAB): m/z = 133 $[M+H–ClCH_2COOH]^+$, 149 $[M–ClCH_2CO]^+$, 177 $[M–CH_3]^+$, 225, 227 M^+. – HRMS (FAB, NOBA+PEG+NaCl): m/z = 227.0835 (calcd. 227.0838 for $C_{12}H_{16}O_2{}^{37}Cl$, $[M]^+$).

*(–)-(1S,2S,4S,7R)-**3** (lipase-catalyzed transesterification)*

A suspension of (±)-**2** (150 g, 1.00 mmol), vinyl chloroacetate (0.30 mL, 0.36 g, 3.0 mmol, 3 eq.) and Chirazyme® L-9, c.-f., C2, lyo. (50 mg, 0.65 units) in *i*-Pr_2O (5 mL) was stirred at 20 °C for 6 h, and the mixture was filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 10 : 1) to give (–)-**3** [129 mg, 0.57 mmol, 57 %, $[\alpha]_D^{23} = -16.2°$ (c = 1.05, *i*-Pr_2O)] and (–)-**2** [65 mg, 0.43 mmol, 43 %, $[\alpha]_D^{23} = -8.1°$ (c = 0.93, *i*-Pr_2O)] as colorless oils.

HPLC Analysis of the MTPA esters

Column: Daicel Chiralcel® OD (4.6 × 250 mm); eluent: hexane/*i*-PrOH = 100 : 1, 1.0 mL min^{-1} at 20 °C; detection: 254 nm; t_R = 70 (80.1 %) and 9.5 (4.9 %) min: 88 % ee.

HPLC Analysis of the 3,5-DNB ester

Column: Daicel Chiralcel® OD (4.6 × 250 mm); eluent: hexane/*i*-PrOH = 9 : 1, 1.0 mL min^{-1} at 20 °C; detection: 254 nm; t_R = 28 (< 0.5 %) and 38 (> 99.5 %) min: > 99 % ee.

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