

Electronic Supplementary Information

Lipase-Catalyzed Domino Kinetic Resolution of α -Hydroxynitrones/ Intramolecular 1,3-Dipolar Cycloaddition: A Concise Asymmetric Total Synthesis of (–)-Rosmarinecine

Shuji Akai, Kouichi Tanimoto, Yukiko Kanao, Sohei Omura, and Yasuyuki Kita*

Graduate School of Pharmaceutical Sciences, Osaka University

1-6, Yamadaoka, Suita, Osaka 565-0871, Japan

E-mail: kita@phs.osaka-u.ac.jp, Fax: (+81) 6-6879-8229

Determination of optical purity and absolute structure of **9** and the recovered (*S*)-**6**

Optical purity of **9** and the recovered **6** was determined by HPLC using Daicel Chiralpak AD-H and Daicel Chiralpak AS, respectively. The absolute stereochemistry of (*S*)-**6** was determined by the modified Mosher method (Fig. 1), and the relative stereochemistry of **9** was determined by the nOe experiments (Fig. 2).

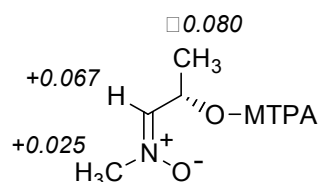


Figure 1. $\Delta\delta_{\text{H}}$ values ($\delta_{\text{S}} - \delta_{\text{R}}$) for the (*S*)- and (*R*)-MTPA esters of (*S*)-**6**.

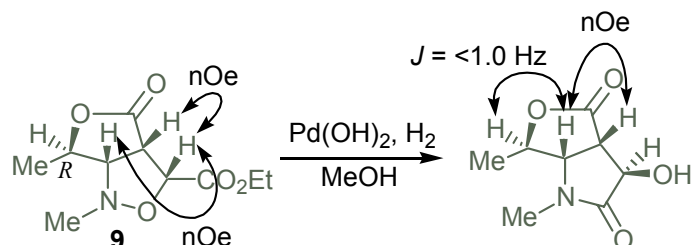


Figure 2. ^1H NMR data of **9** and its derivative.

A typical procedure for the enzymatic domino reaction: preparation of 5b from (±)-2 and 7b (Table 1, entry 5). A mixture of (±)-**2** (50 mg, 0.49 mmol), **7b** (159 mg, 0.74 mmol) and CAL-B (150 mg) in anhydrous MeCN (5 mL) was stirred at 5 °C for 12 h, filtered through a

Celite pad, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes–EtOAc 2:3 → EtOAc → CH₂Cl₂–MeOH 4:1) to give **5b** (67 mg, 60% yield, 91% ee) and (*S*)-**2** (14 mg, 28% yield, 96% ee). A recrystallization of **5b** (67 mg, 91% ee) from hexanes–EtOAc gave **5b** [45 mg, 40% from (±)-**2**, >99% ee]. The optical purity of **5b** was determined by HPLC using Daicel Chiralcel AD-H, and that of the recovered (*S*)-**2** determined using Daicel Chiralpak AS.

Ethyl (2a*R*, 3*S*, 6a*R*, 6b*R*)-2-Oxo-hexahydro-1,4-dioxo-4a-azacyclopenta[*cd*]pentalene-3-carboxylate (5b). White crystals, 99% ee; mp 117–118 °C; [α]_D²⁶ –53.4 (*c* 1.1, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ 1.33 (3H, t, *J* = 7.0 Hz), 2.39–2.46 (2H, m), 2.99–3.10 (1H, m), 3.75 (1H, dd, *J* = 6.0, 8.5 Hz), 3.79–3.84 (1H, m), 4.29 (2H, q, *J* = 7.0 Hz), 4.43 (1H, dd, *J* = 7.0, 8.5 Hz), 4.70 (1H, d, *J* = 6.0 Hz), 5.12 (1H, dd, *J* = 7.0, 13.5 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ 13.9, 32.4, 52.1, 54.5, 61.9, 71.5, 79.1, 83.1, 165.9, 174.0. IR (KBr): 1755 cm⁻¹. Anal. Calcd for C₁₀H₁₃NO₅: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.70; H, 5.68; N, 6.12.

(*S*)-3-Hydroxy-1-pyrroline *N*-Oxide (2). White crystals, 96% ee; mp 104–106 °C; [α]_D²⁴ –131.6 (*c* 1.3, CHCl₃) [lit.¹ 99% ee; mp 105–107 °C; [α]_D²¹ –136.4 (*c* 0.94, CHCl₃)].

A typical one-pot procedure for the preparation of 5b from (±)-2 and 3b (Table 1, entry 7).

Under a nitrogen atmosphere, a solution of **3b** (2.14 g, 14.8 mmol) in anhydrous acetone (25 mL) was added to an ice-cooled solution of ethoxyacetylene (2.48 mL, 30 mmol) and [RuCl₂(*p*-cymene)]₂ (45 mg, 0.074 mmol) in anhydrous acetone (50 mL) over 20 min. The reaction mixture was stirred at room temperature for 34 h and concentrated *in vacuo*. Acetonitrile (100 mL) was added and the mixture was cooled to 0 °C, and (±)-**2** (1.00 g, 9.9 mmol) and CAL-B (3.0 g) were successively added. The reaction mixture was stirred at 5 °C for 11 h, worked up and purified as mentioned above to give **5b** (1.31 g, 58% yield, 92% ee) and (*S*)-**2** (0.23 g, 23% yield, 95% ee). The first recrystallization of **5b** (1.31 g, 92% ee) from hexanes–EtOAc gave **5b** (0.66 g, >99% ee), and the second recrystallization of its mother liquid from hexanes–EtOAc gave another crop of **5b** (0.30 g, >99% ee). Thus, total 0.96 g (43% yield from (±)-**2**) of **5b** (>99% ee) was obtained.

Determination of optical purity of 5a and 14

Optical purity of **5a** was determined after its conversion to **14** (see Scheme 3), whose optical purity was determined using Daicel Chiralcel AD-H.

Reference

1) A. Goti, S. Cicchi, V. Fedi, L. Nannelli, and A. Brandi, *J. Org. Chem.*, 1997, **62**, 3119.