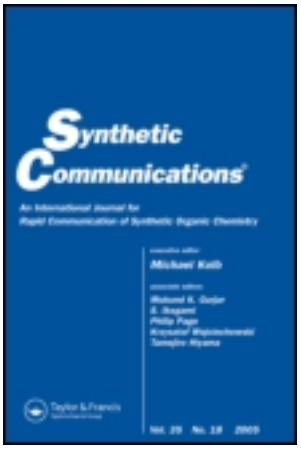

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Ying-Guang Zhu [a], Hong-Zhu Kan [a], Li-Qin Jiang [a] & Wen-Hao Hu [a]

[a] Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai, China

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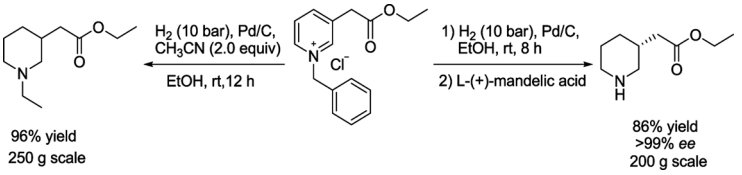
PRACTICAL AND SCALABLE SYNTHESIS OF ETHYL (*R*)-PIPERIDINE-3-ACETATE

Ying-Guang Zhu, Hong-Zhu Kan, Li-Qin Jiang, and Wen-Hao Hu

Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai, China

GRAPHICAL ABSTRACT



Abstract *A practical and scalable synthesis of ethyl (R)-piperidine-3-acetate was achieved from commercially available 3-pyridylacetic acid in 76% overall yield. The practical synthesis was demonstrated on 100-g scale. One-pot reductive N-ethylation of the pyridinium salt with acetonitrile gave an N-ethyl piperidine derivative.*

Keywords Ethyl (*R*)-piperidine-3-acetate; hydrogenation; L-(+)-mandelic acid; reductive *N*-ethylation; resolution

INTRODUCTION

Piperidine derivatives exhibit a broad range of biological activities such as antitumor, antiinflammatory, anxiolytic, and anti-epileptic activity.[1] For instance, optically active ethyl (*R*)-piperidine-3-acetate (*R*-**1**) is presented as a key skeleton in a number of bioactive compounds that are under active pharmaceutical research (Fig. 1).[2–4]

Because of its potential applications, many research groups have been studying the synthesis of (*R*)-**1** and its derivatives. It was reported that (*R*)-**1** was easily resolved from racemic **1** with L-(+)-mandelic acid in good yield.[5] However, preparation of racemic **1** required rather harsh reaction conditions and/or expensive reagents. For example, rhodium-catalyzed hydrogenation of ethyl 3-pyridylacetate (**6**) was reported to afford racemic **1** in good yields, but this procedure is not suitable for scale-up because of the expensive rhodium catalyst as well as elevated reaction

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Address correspondence to Wen-Hao Hu, Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China. E-mail: whu@chem.ecnu.edu.cn

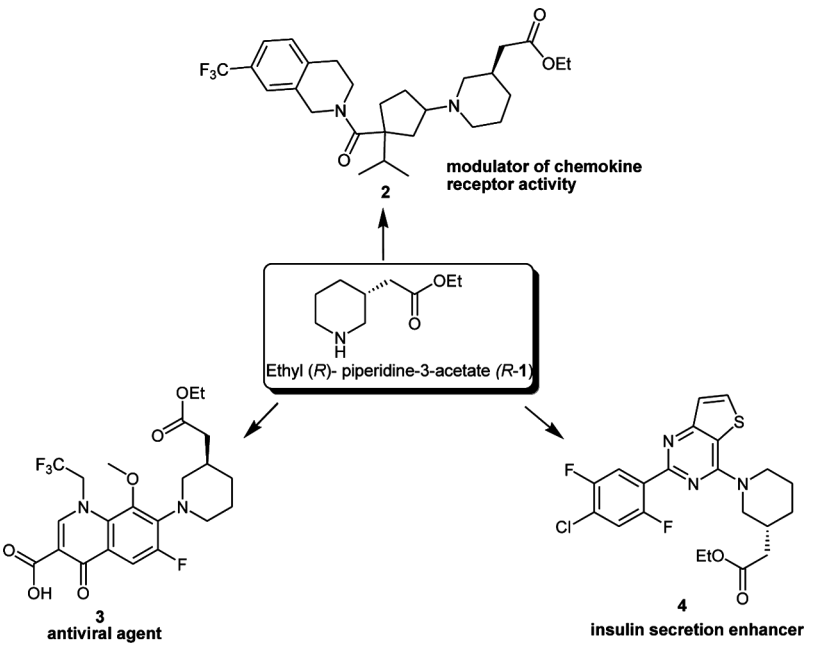
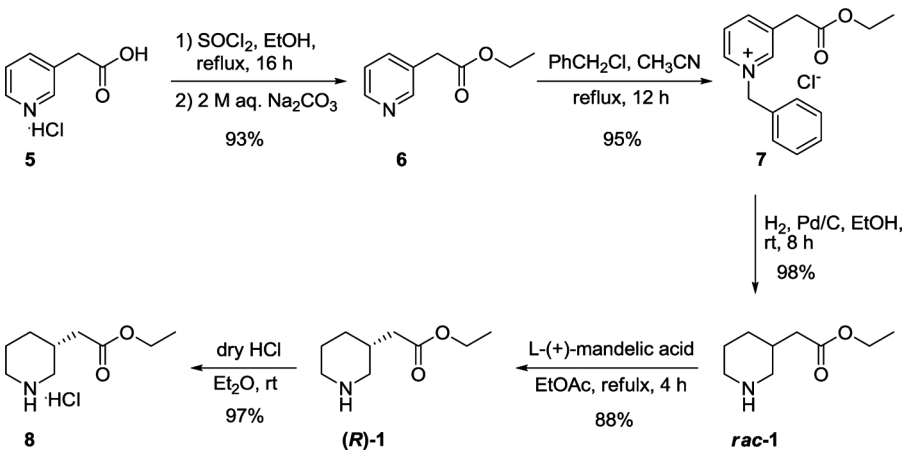


Figure 1. Selected illustrative examples of the importance of (*R*)-piperidine-3-acetate (**1**) motifs in drug discovery.

temperature and relatively long reaction time.[6] Alternatively, expensive PtO_2 also has been successfully used for the hydrogenation of **6**.[7] To avoid using the expensive rhodium and platinum catalysts,[8] reductions of some other pyridine derivatives such as corresponding *N*-oxide[9] or pyridinium salts[10] have been reported. For example, transfer hydrogenation of a pyridine *N*-oxide with ammonium formate in the presence of Pd/C was accomplished at room temperature.[9] We report here our efforts to achieve a practical and scalable synthesis of (*R*)-**1** under mild reaction conditions using 5% Pd/C as a catalyst. During the research, we found that CH_3CN can be used as a reductive *N*-ethylation reagent for the preparation of *N*-ethyl-piperidine-3-acetate (**9**). The modified practical and scalable procedures for the preparation of **1** and **9** have been demonstrated on a 100-g scale without using any column chromatographic purification during the whole processes.

RESULTS AND DISCUSSION

The synthetic route for the synthesis of (*R*)-**1** is outlined in Scheme 1. Commercially available 3-pyridylacetic acid hydrochloride (**5**) was used as the starting material. Esterification of **5** with $SOCl_2$ in ethanol gave **6** in 93% yield.[11] The challenge in the next step is to reduce the pyridine functionality under mild and practical reaction conditions. We first tried transfer hydrogenation of *N*-oxide of pyridine **6** in the presence of Pd/C catalyst according to a similar procedure reported in the literature.[9] Unfortunately, the reaction failed to give the desired piperidine *rac*-**1**. Instead,



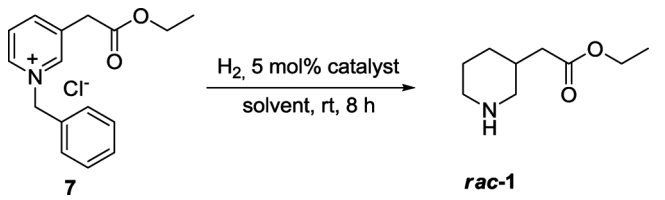
Scheme 1. Synthetic route of (R)-piperidine-3-acetate [(*R*)-**1**].

only the N-O bond was reduced back to the pyridine **6**. We were gratified to find that the reduction of **6** was successfully achieved through hydrogenation of corresponding *N*-benzyl pyridinium salt. Thus, treatment of **6** with benzyl chloride in acetonitrile gave the corresponding *N*-benzyl pyridinium salt **7** in 95% yield. Hydrogenation of **7** was carried out in EtOH under 10 bar H_2 pressure at room temperature in the presence of 5% Pd/C to cleanly afford the desired *rac*-**1** in 98% yield (Table 1, entry 3). Lower yield of the hydrogenation was observed when lower hydrogen pressure was applied (Table 1, entries 1 and 2). Other Pd catalysts such as $Pd(OAc)_2$ and $Pd(OH)_2/C$ were less effective than Pd/C in the hydrogenation (entries 4 and 5). Among the solvents screened, EtOH was found to be the best (entry 3 vs. entries 6–9). When using methanol as the solvent, a significant amount of transesterification product leading to methyl piperidine-3-acetate was obtained (entry 6).

The hydrogenation of **7** was successfully scaled up to 200 g with the same yield. During the process development for the scale-up, we found that residual solvent acetonitrile from the previous step has to be totally excluded before the hydrogenation. Otherwise, in the presence of CH_3CN, *N*-ethyl piperidine **9** was formed as a side product. Formation of **9** is proposed in Scheme 2. Hydrogenation of **7** should give *rac*-**1**. Nucleophilic addition of **1** to CH_3CN affords an amidine intermediate. Complete hydrogenation of the amidine intermediate results in *N*-ethyl piperidine **9** together with the formation of one molecule of NH_3. Similar reaction of *N*-ethylation from CH_3CN with both primary aromatic or aliphatic amines under Rh/C-catalyzed hydrogenation has been described in the literature before.[12]

This *N*-ethylation method is particularly attractive because those toxic and corrosive alkylating agents such as alkyl halides and carbonyl compounds are avoided. We decided to carry out a large-scale reaction to demonstrate the usefulness of the reaction. Thus, the one-pot reduction and *N*-ethylation of *N*-benzyl pyridinium salt **7** with 2 equiv. of CH_3CN was carried out on a 250-g scale under 10 bar H_2 pressure in the presence of Pd/C catalyst to afford *N*-ethyl piperidine **9** in 96% yield (Scheme 3).

Table 1. Reaction condition optimization for the hydrogenation of *N*-benzyl pyridinium salt **7**[a]

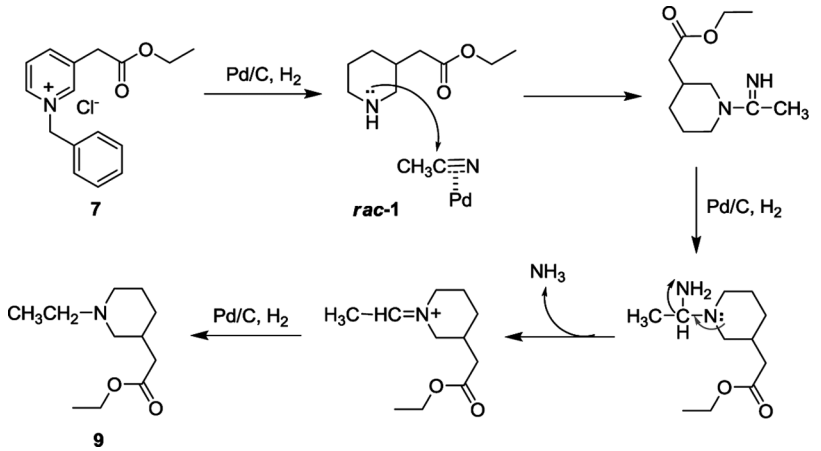


7 ***rac*-1**

Entry	H_2 (bar)	Solvent	Catalyst	Yield (%)[b]
1	1	EtOH	5% Pd/C	30
2	5	EtOH	5% Pd/C	75
3	10	EtOH	5% Pd/C	98
4	10	EtOH	$Pd(OAc)_2$	—
5	10	EtOH	5% $Pd(OH)_2/C$	42
6	10	MeOH	5% Pd/C	<10[c]
7	10	EtOAc	5% Pd/C	85
8	10	AcOH	5% Pd/C	89
9	10	THF	5% Pd/C	40

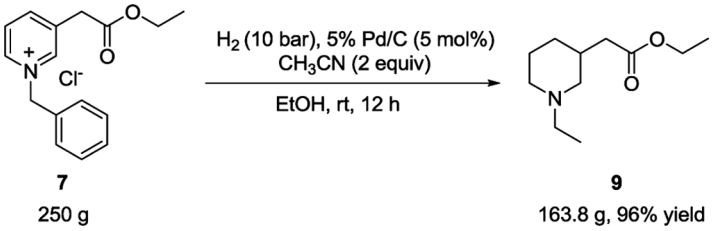
[a]The hydrogenation was carried out with 7 (1 g, 3 mmol) in the corresponding solvent (10 mL) at ambient temperature for 8 h in the presence of 5 mol% catalyst.
[b]Isolated yield.
[c]Methyl piperidine-3-acetate was isolated in 94% yield.

Finally, resolution of *rac*-**1** with L-(+)-mandelic acid was achieved in EtOAc to give (*R*)-**1** (>99% *ee*) in 88% yield according to a similar procedure reported in literature.[5] The optical purity of (*R*)-**1** was determined to be 99.2% *ee* by HPLC analysis. Under the same resolution conditions, (*S*)-**1** was also obtained in 81% yield with greater than 99% *ee* using D-(−)-mandelic acid as the resolution agent. For easy storage and transportation, oily **1** was converted to corresponding HCl salt form as a white solid.



7 ***rac*-1** **9**

Scheme 2. Proposed pathway for the formation of *N*-ethyl piperidine **9**.



Scheme 3. Scale-up of one-pot reduction and *N*-ethylation of **7**.

In conclusion, we have reported a practical and scalable synthesis of (*R*)-**1** from commercially available 3-pyridylacetic acid hydrochloride (**5**) in four steps with 76% overall yield. (*S*)-**1** can also be made similarly. The practical protocol was demonstrated on a 100-g scale. The key step in the synthesis is the successful hydrogenation of *N*-benzyl pyridinium salt of ethyl 3-pyridylacetate using relatively cheap Pd/C as a catalyst under mild reaction conditions. A one-pot reduction and *N*-ethylation of the *N*-benzyl pyridinium salt with acetonitrile was demonstrated on a large scale to give the corresponding *N*-ethyl piperidine derivative in good yield.

EXPERIMENTAL

All reagents were obtained commercially and were used without further purification unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500-MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS, $\delta = 0$ ppm) for ^{1}H NMR and deuteriochloroform ($CDCl_3$, $\delta = 77.00$ ppm) or deuteriodimethyl sulfoxide (DMSO-d_6, $\delta = 39.5$ ppm) for ^{13}C NMR spectroscopy. Mass spectra were recorded on a Bruker microTOF II mass spectrometer for both low-resolution and high-resolution mass spectra (HRMS). Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter. Melting points were determined with a Zeiss Axiolab microscope apparatus and are uncorrected.

Ethyl 3-Pyridylacetate (6)

$SOCl_2$(35 mL, 0.43 mol) was added to a solution of **5** (250.0 g, 1.44 mol) in EtOH (2.5 L) in 15 min at 0–5 °C. After completion of the addition, the reaction was heated under reflux for additional 16 h. EtOH was evaporated under reduced pressure. To the residue was added 2 M aqueous Na_2CO_3 (300 mL), and the resulting mixture was extracted with EtOAc (3×400 mL). The combined organic layers were washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give **6** as a colorless liquid (222.0 g, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (t, $J = 6.7$ Hz, 3 H), 3.62 (s, 2 H), 4.17 (q, $J = 6.7$ Hz, 2 H), 7.27–7.28 (m, 1 H), 7.64–7.65 (m, 1 H), 8.53 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.02, 38.39, 61.07, 123.27, 129.75, 136.67, 148.40, 150.27, 170.59. MS (ESI): $m/z = 165$ [M^+]. HRMS (ESI): m/z [$M + H$]$^+$ calcd. for $C_9H_{12}NO_2$: 166.0863; found: 166.0882.

1-Benzyl-3-ethoxycarbonylmethyl-pyridinium Chloride (7)

$PhCH_2Cl$ (185 mL, 1.61 mol) was added to a solution of **6** (222.0 g, 1.35 mol) in CH_3CN (2.3 L) at room temperature. The resulting mixture was stirred for 12 h under reflux. The reaction mixture was evaporated under reduced pressure to remove CH_3CN. The residue was washed with ether (2×400 mL) and completely dried in vacuo. *N*-Benzyl pyridinium salt **7** was obtained as a light yellow solid (372.5 g, 95% yield), mp 131–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (t, $J = 7.1$ Hz, 3 H), 3.99 (s, 2 H), 4.16 (q, $J = 7.1$ Hz, 2 H), 6.28 (s, 2 H), 7.36–7.38 (m, 3 H), 7.69–7.71 (m, 2 H), 7.92–7.95 (m, 1 H), 8.33 (d, $J = 7.9$ Hz, 1 H), 9.57 (d, $J = 5.9$ Hz, 1 H), 9.79 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.03, 37.26, 62.02, 64.24, 127.49, 129.60, 129.65, 129.95, 132.97, 135.86, 143.42, 145.72, 146.11, 168.92. MS (ESI): $m/z = 256$ $[M - Cl]^+$. HRMS (ESI): m/z $[M - Cl]^+$ calcd. for $C_{16}H_{18}NO_2$: 256.1332; found: 256.1332.

(±)-Ethyl 3-Piperidylacetate (*Rac*-1)

A mixture of **7** (200.0 g, 0.68 mol), EtOH (1.4 L), and 5% Pd/C (65.0 g) was stirred under 10 bar H_2 pressure at room temperature for 8 h. After completion of the hydrogenation, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was added to 2 M aqueous Na_2CO_3 (400 mL), and the resulting mixture was extracted with EtOAc (3×400 mL). The combined organic layers were washed with brine (400 mL), dried over Na_2SO_4, filtered, and concentrated to give racemic **1** as a colorless liquid (115.0 g, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08–1.09 (m, 1 H), 1.20 (t, $J = 7.1$ Hz, 3 H), 1.41–1.44 (m, 1 H), 1.58–1.61 (m, 1 H), 1.77–1.80 (m, 1 H), 1.86–1.89 (m, 1 H), 2.10–2.27 (m, 4 H), 2.47–2.49 (m, 1 H), 2.93 (d, $J = 12.1$ Hz, 1 H), 3.01 (d, $J = 12.1$ Hz, 1 H), 4.07 (q, $J = 7.1$ Hz, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.00, 21.48, 27.72, 29.97, 37.23, 43.02, 47.06, 59.89, 171.09. MS (ESI): $m/z = 171$ $[M^+]$. HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_9H_{18}NO_2$: 172.1332; found: 172.1339.

(*R*)-Ethyl Piperidine-3-acetate (*R*-1)

L-(+)-Mandelic acid (80 g, 0.53 mol) was added to a solution of *rac*-**1** (90.0 g, 0.53 mol) in EtOAc (800 mL). The resulting mixture was refluxed under stirring for 4 h. The resulting solution was allowed to cool to room temperature and stand at room temperature for an additional 12 h. The formed mandelic acid salt was filtered to give a white solid (160 g). The salt was recrystallized twice from EtOAc until enantiomeric excess (*ee*) of (*R*)-**1** free base reaches 99%. The mandelic acid salt was added to 2 M aqueous Na_2CO_3 (200 mL), and the resulting mixture was extracted with EtOAc (3×300 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated to give (*R*)-**1** as a yellow oil (39.6 g, 88% yield) with 99.2% *ee* determined by HPLC analysis (Daicel Chirapak AD-H, detection wavelength = 210 nm, flow rate = 1.0 mL/min, *n*-hexane/EtOH/diethylamine = 95:5:0.1, $t_R = 5.04$ min).

(*R*)-Ethyl Piperidine-3-acetate Hydrochloride (8)

Dry hydrogen chloride was continuously bubbled into a solution of (*R*)-**1** (39.6 g, 0.23 mol) in ether (300 mL) at 0 °C for 2 h until thin-layer chromatography

(TLC) showed the free base (*R*)-**1** was completely consumed. Then, the mixture was stirred for an additional 2 h at ambient temperature. The precipitated solid was isolated by filtration and dried to afford a white solid **8** (46.6 g, 97% yield), mp 132–134 °C. $[\alpha]_D^{20} - 9.7°$ (*c* 1.00, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.18 (t, $J = 7.1$ Hz, 3 H), 1.16–1.19 (m, 1 H, overlap), 1.64–1.68 (m, 1 H), 1.70–1.74 (m, 2 H), 2.10–2.13 (m, 1 H), 2.22–2.27 (m, 1 H), 2.32–2.36 (m, 1 H), 2.56 (t, $J = 11.9$ Hz, 1 H), 2.67–2.70 (m, 1 H), 3.13–3.16 (m, 2 H), 4.07 (q, $J = 7.1$ Hz, 2 H), 8.93 (br, s, 2 H). MS (ESI): $m/z = 207$ $[M^+]$. HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_9H_{18}ClNNaO_2$: 230.0918; found: 230.0930.

N-Ethyl-Piperidine-3-acetate (9)

In a 2-L autoclave, a mixture of **7** (250.0 g, 0.85 mol), CH_3CN (89.0 mL, 1.70 mol), EtOH (1.6 L), and 5% Pd/C (90.4 g) was stirred under 10 bar H_2 pressure at room temperature for 12 h. After completion of the hydrogenation, the catalyst was removed by filtration through a celite pad. The filtrate was concentrated under reduced pressure. H_2O (400 mL) and EtOAc (400 mL) were added to the resulting mixture. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 400 mL). The combined organic layers were washed with brine (400 mL), dried over Na_2SO_4, filtered, and concentrated to give **9** as a colorless liquid (163.8 g, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93–1.00 (m, 1 H), 1.07 (t, $J = 7.2$ Hz, 3 H), 1.25 (t, $J = 7.1$ Hz, 3 H), 1.56–1.69 (m, 3 H) 1.75–1.79 (m, 1 H), 1.84–1.88 (m, 1 H), 2.06–2.11 (m, 1 H), 2.20–2.23 (m, 2 H), 2.38 (q, $J = 7.2$ Hz, 2 H), 2.83–2.88 (m, 2 H), 4.13 (q, $J = 7.1$ Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.35, 15.63, 26.46, 32.25, 34.68, 40.92, 54.02, 54.91, 60.62, 61.58, 173.94. MS (ESI): $m/z = 199$ $[M^+]$. HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{11}H_{22}NO_2$: 200.1645; found: 200.1613.

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13. In view of the weak UV absorption, the optical purity of (*R*)-**1** was determined by HPLC analysis of corresponding *N*-benzyl derivative. The *N*-benzyl derived (*R*)-**1** (122 mg, 78% yield) was obtained by treatment of (*R*)-**1** (100 mg, 0.6 mmol) with benzyl chloride (75 mg,

0.6 mmol) in the presence of K_2CO_3 (165 mg, 1.2 mmol) in CH_3CN (5 mL) under reflux for 4 h. *N*-benzyl derived (*S*)-**1** was also made similarly. HPLC analysis results from the *N*-benzyl derivatives of (*R*)-**1** and (*S*)-**1**: (*R*)-**1**: 99.2% *ee*, retention time: $t_R = 5.04$ min; (*S*)-**1**: 100% *ee*, retention time: $t_R = 4.14$ min. Daicel Chirapak AD-H, detection wavelength = 210 nm, flow rate = 1.0 mL/min, *n*-hexane:EtOH:diethylamine = 95:5:0.1.