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First asymmetric synthesis of CJ-14877 and its enantiomer and their interleukin-1β inhibitory activities

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ABSTRACT

A potent antiinflammatory methyl picolinate alkaloid CJ-14877 [(+)-**1**] and its enantiomer (−)-**1** were synthesized in two steps starting from commercially available methyl 5-bromopicolinate. The synthesis includes microwave-assisted *Suzuki* coupling reaction and *Sharpless* asymmetric dihydroxylation.

A methyl picolinate derivative having a C_3 unit on C-5, CJ-14877 [(+)-**1**], and its family (**2–4**) are potent cytokine inhibitors isolated from a fermentation broth of a fungus basidiomycetes (Fig. 1).[1] Isolation of (+)-**1** was reported also from a culture filtrate of a fungus, *Hirsutella nivea* BCC 2594, a pathogen of insects.[2] These compounds are shown to inhibit lipopolysaccharide (LPS)-induced production of interleukin-1β without decreasing the leucine uptake.[1] However, the structure–activity relationship is not known yet. To obtain new antiinflammatory drugs of this series, we studied synthesis of (+)-**1**. We established a facile two step synthesis of (+)-**1** and its enantiomer (−)-**1**, by the synthetic strategy shown in Scheme 1: stereoselective preparation of (+)-**1** and its enantiomer (−)-**1** by *Sharpless* asymmetric dihydroxylation[3] of compound **5**, which may be obtained via *Suzuki* coupling reaction[4] between (*E*)-prop-1-enylboronic acid with commercially available methyl 5-bromopicolinate (**6**).[5]

The present paper reports detailed procedure of this method. First, the *Suzuki* coupling reaction of **6** with (*E*)-prop-1-enylboronic acid (**7**) was carried out under several reaction conditions (Table 1). A mixture of **6** and **7** was heated at 80 °C for 0.5 h under an Argon atmosphere to give the corresponding coupling product **5** in 84% yield (entry 6). Prolonged reaction time gave no further improvement in the yield (entries 7 and 8). Recently, microwave has come to be used as an efficient heating procedure.[6] A microwave-assisted Suzuki coupling reaction was described by Sharma et al.,[7] which we applied to the present scheme. When the reaction mixture was heated by means of microwave at 140 °C for 5 min, the reaction proceeded to give the corresponding coupling product **5** in 87% yield (entry 15).[8] When (*Z*)-prop-1-enylboronic acid (**8**) was employed as the substrate, the coupling product **9** was obtained in 93% yield (entry 16). By the *Sharpless* asymmetric dihydroxylation (AD) of the coupling product **5** using AD-mix-α,[9] diol (+)-**1** was obtained in quantitative yield,[10] whose spectral and physical data were identical to those of natural (+)-**1**. The

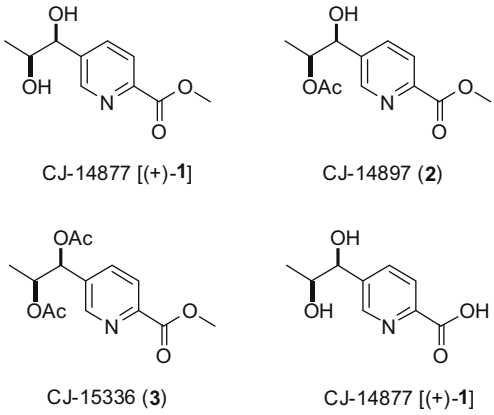

Figure 1. Natural cytokine production inhibitors CJ-14877 [(+)-**1**] and their analogues.

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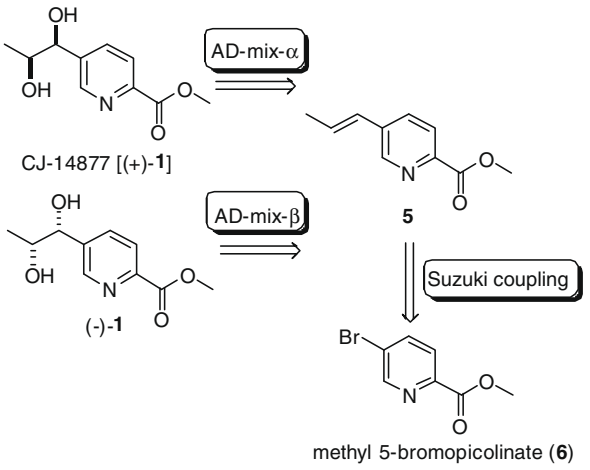
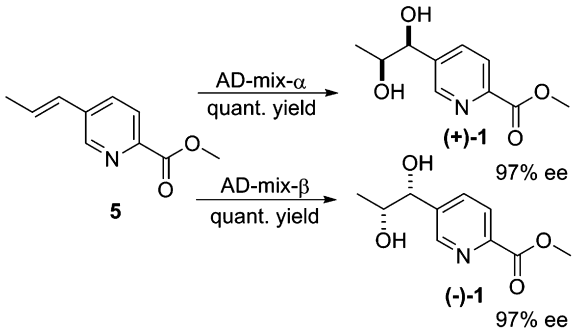


Scheme 1. Synthetic strategy for preparation of (+)-**1** and its enantiomer (−)-**1** from **6**.



Scheme 2. Asymmetric dihydroxylation of **5**.

enatiomeric excess of this product was calculated by using the chiral column OD-HPLC system and was shown to be 97% ee.[11]

Table 2
IL-1β production inhibitory activity (%) induced with LPS

Compounds	Concentration (μM)			
	0.01	0.1	1.0	10
(+)-**1**	−9.5	13.8	39.6	49.8
(−)-**1**	9.1	4.3	10.6	−7.5

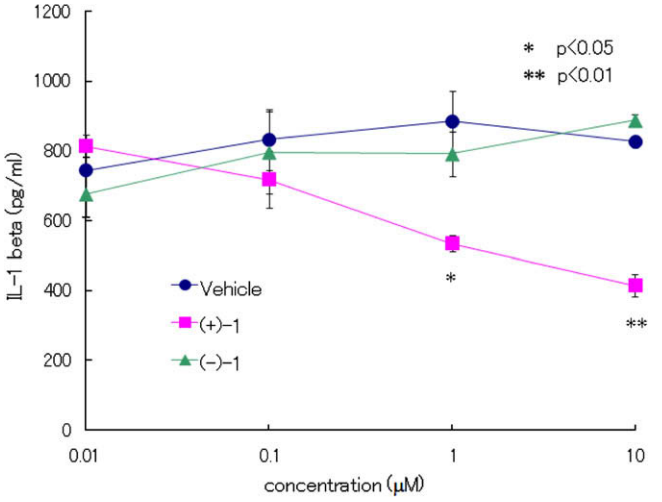
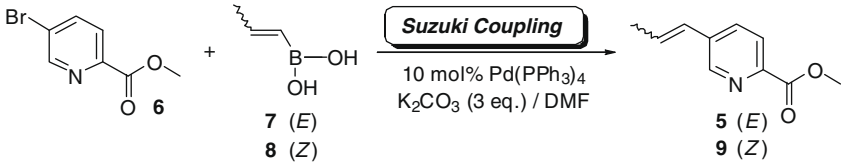


Figure 2. Effect of (+)-**1** and its enantiomer (−)-**1** on IL-1β production induced with LPS (100 ng).

When AD-mix-β[9] was employed as an oxidant in the dihydroxylation reaction of **5**, instead of AD-mix-α, the enatiomer (−)-**1** was obtained also in very high yield and with very high enantiomeric excess (Scheme 2).

The both of CJ-14877 [(+)-**1**] and its enantiomer [(−)-**1**] were evaluated for inhibitory activities of LPS-stimulated IL-1β production by human PBMC.[12] The results was shown in Table 2 and Figure 2. CJ-14877 [(+)-**1**] inhibited IL-1β production depending

Table 1
Palladium-mediated coupling reactions of methyl 5-bromopicolinate (**6**) with (*E*)- or (*Z*)-prop-1-enylboronic acids (**7** or **8**)



Entries[a]	Boronic acids (3.0 equiv)	Reaction temp (°C)	Reaction time (h)	Products	Yields (%)
1	7	rt	5	5	70 (12)[b]
2	7	rt	24	5	65 (15)[b]
3	7	50	1	5	58 (28)[b]
4	7	50	5	5	87
5	7	50 (MW)[c]	5 min	5	20 (61)[b]
6	7	80	0.5	5	84
7	7	80	1	5	85
8	7	80	5	5	85
9	7	80 (MW)[c]	5 min	5	43 (46)[b]
10	7	80 (MW)[c]	5 min × 2	5	53 (26)[b]
11	7	120 (MW)[c]	5 min	5	73 (20)[b]
12	7	120 (MW)[c]	10 min	5	88 (5)[b]
13	7	120 (MW)[c]	5 min × 2	5	87
14	7	130 (MW)[c]	5 min	5	80 (5)[b]
15	7	140 (MW)[c]	5 min	5	87 (1)[b]
16	8	140 (MW)[c]	5 min	9	93

[a] Ref. 8.
[b] The yields in parenthesis means the recovery of the starting material.
[c] MW: microwave irradiation.

on the substrate level and the inhibition ratio was 49.8% at 10 μM. On the other hand, its enantiomer [(−)-**1**] showed no IL-1β production inhibitory activity at 10 μM. That indicated that the stereochemistry on C-7 and C-8 of compound **1** are important on the activity.

In summary, an effective and facile two step synthesis of CJ-14877 ((+)-**1**) and its enantiomer [(−)-**1**] from commercially available methyl 5-bromopicolinate (**6**) was successfully established for the first time. Preparation of a series of synthetic analogues is now in progress.

Acknowledgments

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References and notes

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5. Methyl 5-bromopicolinate (**5**) was purchased from Combi-Blocks Co. (Cat. No. CA-4117). The starting material can also be prepared by the procedure reported by Song et al. (*J. Org. Chem.* **2001**, *66*, 605.).
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7. Sharma, A. K.; Gowdahalli, K.; Krzeminski, J.; Amin, S. *J. Org. Chem.* **2007**, *72*, 8987.
8. *General procedure for microwave-assisted Suzuki coupling reaction*: A mixture of methyl 5-bromopicolinate (0.02 g, 0.093 mmol), (*E*)-prop-1-enylboronic acid (0.023 g, 0.28 mmol), $Pd(PPh_3)_4$ (0.01 g, 0.0093 mmol), K_2CO_3 (0.039 g, 0.28 mmol), and dry DMF (1.0 mL) was heated at 140 °C by using a microwave apparatus (at 2.45 GHz, Discover, CEM Co., North Carolina, USA) for 5 min. After dilution with H_2O (10 mL), the mixture was extracted with AcOEt (10 mL × 3), and the extract was washed with H_2O (10 mL × 3), dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oily residue, which was purified by MPLC (hexanes:AcOEt = 1:2). The yield of the resulting coupling product **5** was 85%. Compound **5**: Colorless amorphous solid, mp 67–68 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (1H, d, 2.0), 8.02 (1H, d, 8.2), 7.71 (1H, dd, 8.2, 2.0), 6.48–6.36 (2H, m), 3.96 (3H, s), 1.91 (3H, d, 5.0). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (s), 147.6 (d), 145.6 (s), 136.6 (s), 132.9 (d), 131.3 (d), 126.8 (d), 125.0 (d), 52.7 (q), 18.7 (q). IR (film): ν_{max} 1738 (C=O), 1708 (C=C) cm^{-1}. HRMS (ESI): Calculated for $C_{10}H_{12}NO_2$ (M^++H): 178.0868. Found: 178.0860. Compound **9**: Colorless viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (1H, d, 1.7), 8.11 (1H, d, 6.6), 7.74 (1H, dd, 6.6, 1.7), 6.44 (1H, m), 6.05 (1H, dq, 9.4, 5.8), 4.01 (3H, s), 1.93 (3H, dd, 5.8, 1.4). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7 (s), 150.0 (d), 145.4 (s), 136.7 (s), 136.4 (d), 131.6 (d), 125.6 (d), 124.7 (d), 52.8 (q), 14.8 (q). IR (film): ν_{max} 1741 (C=O), 1721 (C=C) cm^{-1}. HRMS (ESI): Calculated for $C_{10}H_{12}NO_2$ (M^++H): 178.0868. Found: 178.0870.
9. AD-mix-α and -β (Cat. No. 392758-10G and 392766-10G) were purchased from Aldrich Co. (MI).
10. *General procedure for Sharpress asymmetric dihydroxylation*: A mixture of compound **5** (0.03 g, 0.169 mmol), AD-mix-α (0.237 g, 0.169 mmol), and $AcNH_2$ (0.016 g, 0.169 mmol) in ^{t}BuOH–H_2O (1:1, 2.1 mL) was stirred at room temperature for 6 h. After addition of satd Na_2SO_3 (10 mL), the mixture was extracted with AcOEt (10 mL × 3), and the extract was dried over $MgSO_4$, filtered, and evaporated in vacuo to give an oily residue, which was purified by MPLC ($CHCl_3$/MeOH = 15:1) to give (+)-**1** in a quantitative yield. The spectral and physical data of the product were identical to those of natural CJ-14877 reported by Ichikawa et al.[1]
11. The percentage of enantiomeric excess (% ee) values of (+)- and (−)-**1** were calculated on the basis of HPLC analysis. (Analytical conditions: column: CHIRALCEL OD-H (Daisel Co., Ltd, 0.46 × 15 cm), elution: *n*-hexane–^{i}PrOH (85:15), at flow rate of 0.6 mL/min, detection: UV (270 nm)). Retention time (t_R): 29.0 min for [(+)-**1**]; 33.6 min for [(−)-**1**].
12. Human peripheral blood mononuclear cells (PBMC) in RPMI1640 medium containing 10% fetal bovine serum were cultured with various concentration of the compounds in the presence of 100 ng/ml lipopolysaccharides (LPS, *E. coli* B4) for 24 h. The human IL-1β concentration in the culture supernatant was measured by ELISA in accordance with the protocol of the manufacturer (eBioscience, Inc.).