Regular Article

Stereo-Selective Preparation of Tenaic Acid, *trans*-(2*S*,6*S*)-Piperidine-2,6-dicarboxylic Acid, *via* Anodic Oxidation and Cobalt-Catalyzed Carbonylation

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Tenaic acid (piperidine-2,6-dicarboxylic acid) is a naturally occurring imino acid that comprises three stereoisomers due to its two asymmetric centers at C2 and C6. The configuration of natural tenaic acid is reported to correspond to *trans*-(2*S*,6*S*). However, a few studies are focused on the stereospecific synthesis of *trans*-(2*S*,6*S*)-tenaic acid. The present study investigates a convenient synthetic method that includes regio-specific anodic oxidation and stereospecific cobalt-catalyzed carbonylation to obtain *trans*-(2*S*,6*S*)-tenaic acid. Methyl (*S*)-*N*-benzoyl- α -methoxy-pipecolate, the key intermediate that displays a structure that corresponds to an intermediate (*N*- α -hydroxyalkyl amide) of intramolecular amidocarbonylation, was obtained *via* an anodic oxidation of methyl (*S*)-*N*-benzoyl-pipecolate. Subsequently, cobalt-catalyzed carbonylation converted the methyl (*S*)-*N*-benzoyl- α -methoxy-pipecolate to *trans*-(2*S*,6*S*)-*N*-benzoyl-tenaic acid dimethyl ester in good optical purity (>95% enantiomeric excess (ee)) and modest yield (63%). Finally, de-protection occurred *via* acidic hydrolysis to obtain *trans*-(2*S*,6*S*)-tenaic acid. The stereochemistry of synthesized tenaic acid was confirmed as corresponding to *trans*-(2*S*,6*S*) by comparing its physical properties with those of a *cis*-*meso*-isomer and those of a *trans*-(2*S*,6*S*)-isomer that were reported in previous studies.

Key words tenaic acid; piperidine-2,6-dicarboxylic acid; stereoisomer; amidocarbonylation; anodic oxidation; carbonylation

Tenaic acid (also termed as piperidine-2,6-dicarboxylic acid) is a naturally occurring imino acid derivative that was isolated from a red alga, *Porphyra tenera*,¹⁾ which comprises three stereoisomers, namely, *trans*-(2*S*,6*S*)-, *trans*-(2*R*,6*R*)-, and *cis*-*meso*-isomers due to two asymmetric centers at C2 and C6 (Fig. 1). A study by Kawauchi *et al.* reported that the stereochemistry of natural tenaic acid corresponded to *trans*.¹⁾ Additionally, *cis*-*meso*-isomers of tenaic acid derivatives are readily obtained by platinum(IV) oxide (PtO₂) or palladium on carbon (Pd/C) catalyzed hydrogenation of piperidine-2,6-dicarboxylic acid derivatives, respectively.^{2–4)} Mitsakos *et al.* reported on dihydrodipicolinate synthase inhibition activity as a biological activity of tenaic acid.⁵⁾

However, stereoselective total synthesis of an optically active *trans*-isomer was not achieved until a study by Waserman *et al.* who synthesized a *trans*-(2*S*,6*S*)-isomer by multistep reactions and determined the absolute stereochemistry of natural tenaic acid as corresponding to *trans*-(2*S*,6*S*).⁶⁾ Ohtani *et al.* obtained optically pure *trans*-(2*R*,6*R*)- or *trans*-(2*S*,6*S*)-isomers *via* a photocatalytic reaction with activated cadmium sulfide (CdS) particles by using (*R*,*R*)- or (*S*,*S*)-2,6-diaminopimelic acid as the starting material wherein the mechanism resembles a possible biosynthetic pathway.^{7–9)} However, optically active 2,6-diaminopimelic acid is expen-

sive. The following two procedures have been reported for synthesizing a racemate. Chrystal *et al.* synthesized racemic tenaic acid derivative *via* α,α' -dibromination of pimeric acid followed by cyclization using liquid ammonia.²⁾ Einhorn *et al.* synthesized racemic *N*-*tert*-butoxycarbonyl-tenaic acid dimethyl ester *via* alkylation of the dianion of *N*-*tert*-butoxycarbonyl iminodiacetic acid dimethyl ester with diiodopropane.¹⁰⁾ Additionally, Chrystal *et al.* separated *cis*-*meso*-isomer and racemic *trans*-isomer by using fractional precipitation of racemic mixture of tenaic acid diamide.²⁾ However, it is essential to develop additional facile and practical synthesis methods with respect to *trans*-tenaic acid.

Conversely, cobalt-catalyzed amidocarbonylation was developed by Wakamatsu *et al.* in our laboratories as a useful method for the synthesis of *N*-acyl- α -amino acids (**6**) from amide (**4**), aldehyde (**5**), and carbon monoxide (CO)^{11–13)} (Chart 1). Dicobalt octacarbonyl [Co₂(CO)₈] functions as the catalyst precursor. The first step of the amidocarbonylation involves a nucleophilic addition of the amide (**4**) to the aldehyde (**5**) with the formation of an *N*- α -hydroxyalkyl amide (**7**), which eliminates the hydroxide ion (OH[−]) to form the corresponding *N*-acylimine cation (**8a**) or *N*-acyl-iminium ion (**8b**). An active catalyst species, tetracarbonylcobaltate [Co(CO)₄][−], forms a corresponding alkyl cobalt complex (**9**) with the *N*-acylimine

Fig. 1. Structures of Stereoisomers of Tenaic Acid

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Chart 1. Cobalt-Catalyzed Amidocarbonylation of Amides with Aldehydes

Reagents: (a) CO/H₂ (13.7 MPa), Co₂(CO)₈ in acetone; (b) CH₂N₂ in CH₃OH–Et₂O.

Chart 2. Synthesis of Tenuic Acid *via* Hydroformylation–Intramolecular Amidocarbonylation

cation (**8a**) in a nucleophilic substitution. CO insertion transforms alkyl cobalt complex (**9**) into an acyl cobalt complex (**10**). This product (**10**) forms *N*-acyl-α-amino acid (**6**) *via* an intermolecular nucleophilic attack of water on the acyl bond. The intramolecular formation of an oxazolone derivative (**11**) with subsequent hydrolysis also seems possible.^{12,13} In addition to original cobalt-catalyzed amidocarbonylation, Beller developed palladium-catalyzed amidocarbonylation for the synthesis of numerous *N*-acyl-α-amino acid derivatives.¹⁴

The scope of application range of this reaction is significantly broadened with its combination with other reactions to yield intermediates that are similar to intermediates **7** or **8** in Chart 1.^{15–17} The synthetic application of cobalt-catalyzed amidocarbonylation to synthesize functionalized *N*-acyl-α-amino acid derivatives was extended by establishing stereo-selective synthesis of 6-substituted pipecolic acid *via* an anodic oxidation–cobalt-catalyzed carbonylation reaction.^{18,19}

The present study provides a facile stereo-specific route to obtain *trans*-(2*S*,6*S*)-tenuic acid from (*S*)-pipecolic acid by using regioselective anodic oxidation and stereospecific cobalt-catalyzed carbonylation. Furthermore, the details of characterization of *trans*-(2*S*,6*S*)-tenuic acid are presented in the study.

Results and Discussion

Synthesis of Tenuic Acid *via* Cobalt-Catalyzed Hydroformylation–Intramolecular Amidocarbonylation The reaction condition of amidocarbonylation is identical to that of a hydroformylation reaction (*i.e.*, CO–H₂=1 : 1, approximately 13.7 MPa, 100°C). Thus, it is possible to use *N*-alkenyl amides as starting materials to synthesize *N*-acyl-cyclic-imino acids *via* tandem carbonylation (hydroformylation of an olefin followed by an intramolecular amidocarbonylation). First, this method was applied to the synthesis of tenuic acid as shown in Chart 2. This synthesis constitutes a superior process because the desired carbon framework is formed in a single step reaction.

Cobalt-catalyzed amidocarbonylation of (*S*)-*N*-benzoyl-allylglycine (**12**) results in a complex mixture that includes *N*-benzoyl tenuic acid (**18**) as a major product. Specifically, it is considered that the hydrogenation of olefin moiety forms *N*-benzoyl-norvaline (22%). The mixture was treated with ethereal diazomethane (CH₂N₂) and carefully purified by using silica gel column chromatography to obtain *N*-benzoyl-tenuic acid dimethyl ester (**19**) in a 62% isolated yield. The formation of *N*-benzoyl-tenuic acid should initiate the formation of alkyl cobalt intermediate **13**, and this is followed by carbonylation and intramolecular amidocarbonylation *via*

intermediates **14**, **15**, **16**, and **17** as previously discussed. A previous study indicated that hydroformylation of a terminal olefin proceeded regioselectively under these conditions to yield a straight-chain aldehyde, such as intermediate **14**, which subsequently produced an internal *N*- α -hydroxyl amide (**15**) *in situ*.¹⁵ This constitutes the reason for the selective formation of the 6-membered ring selectivity.

Interestingly, normal phase HPLC analysis of obtained *N*-benzoyl-teneraic acid dimethyl ester (**19**) revealed that the *trans*-isomer was obtained predominantly (analytical conditions 2). The mechanism for the significant high *trans*-ste-

Fig. 2. Chiral HPLC Chromatogram of *trans*-(2*S*,6*S*)-*N*-Benzoyl-teneraic Acid Dimethyl Esters (**19a**) and *trans*-(2*R*,6*R*)-*N*-Benzoyl-teneraic Acid Dimethyl Esters (**19b**) Obtained by Hydroformylation–Intramolecular Amidocarbonylation

reoselectivity in the amidocarbonylation step is discussed in detail below. However, the chiral HPLC analysis revealed that the compound **19** approximately corresponds to a 7:3 mixture of *trans*-(2*S*,6*S*)-isomer (**19a**) and *trans*-(2*R*,6*R*)-isomer (**19b**) (analytical conditions 1, Fig. 2). Furthermore, approximately 1:1 ratio of *trans*-(2*S*,6*S*)-isomer (**19a**) and *trans*-(2*R*,6*R*)-isomer (**19b**) were obtained when (*RS*)-*N*-benzoyl-allylglycine was used as a starting material. These results indicate that the reaction using (*S*)-*N*-benzoyl-allylglycine (**12**) proceeded selectively to form *trans*-(2*S*,6*S*)-isomer as a major product although minor *trans*-(2*R*,6*R*)-isomer was produced *via* epimerization at C2 asymmetric center at an early stage of the reaction. The formation of *trans*-(2*R*,6*R*)-isomer (**19b**) can be attributed to the facile migration of cobalt carbonyl moiety from δ -position (**13**) to α -position (**20**) of the amide group and to their equilibrium. This type of isomerization of an alkyl cobalt complex was previously observed in the cobalt-catalyzed isomerization–carbonylation reaction of *N*-acyl unsaturated cyclic amines.¹⁶

Synthesis of Teneraic Acid *via* Anodic Oxidation–Cobalt-Catalyzed Carbonylation An extant study already discussed stereoselective synthesis of methyl *trans*-*N*-benzoyl-6-methylpipercolate.¹⁸ The synthesis consists of regioselective anodic oxidation of *N*-benzoyl-6-methylpiperidine to yield *N*-benzoyl- α -methoxy-6-methylpiperidine, and this is followed by its subsequent stereospecific cobalt-catalyzed carbonylation. This synthesis was applied to methyl *N*-benzoyl-pipecolate (**21**) to obtain *N*-benzoyl-teneraic acid dimethyl ester (**19**) as shown in Chart 3. This synthesis method directly passes through to form a more stable alkyl cobalt complex, namely **23**, and thus it is possible to avoid epimerization as observed in the fore-mentioned synthesis.

The anodic oxidation of methyl (*S*)-*N*-benzoyl-pipecolate (**21**) proceeded regioselectively to result in methyl (*S*)-*N*-benzoyl- α -methoxy-pipecolate (**22**) in good yield.^{20–22} Compound **22** corresponds to the *N*- α -hydroxyalkyl amide intermediate (**7**) in Chart 1 as well as the internal *N*- α -hydroxyalkyl

Reagents: (a) anodic oxidation: Et₄N⁺OTs[−] in CH₃OH; (b) CO/H₂ (13.7 MPa), Co₂(CO)₈ in acetone; (c) CH₂N₂ in CH₃OH; (d) conc. HCl, 110°C; (e) NaOCH₃ in CH₃OH.

Chart 3. Synthesis of Teneraic Acid *via* Anodic Oxidation–Carbonylation

amide intermediate (**15**) in Chart 2.

The cobalt-catalyzed carbonylation ($\text{CO-H}_2=1:1$, approximately 13.7 MPa, 100°C) of compound **22** yielded a mixture of *trans*-(2*S*,6*S*)-*N*-benzoyl-teneraic acid dimethyl ester (**19a**, 36.7%), *i.e.*, a product generated by nucleophilic opening of the complex by MeOH, and its half-ester (**25**, 26.3%), *i.e.*, a product generated by nucleophilic opening of the complex by water, with a combined yield of 63.0%. The configuration of *trans*-(2*S*,6*S*) of compound **25** was confirmed by converting it to compound **19a** by using methyl esterification with CH_2N_2 . It should be noted that cobalt-catalyzed carbonylation of compound **22** resulted in a *trans*-(2*S*,6*S*)-isomer that possesses excellent optical purity (>95% enantiomeric excess (ee)) as determined by a chiral HPLC analysis as shown in Fig. 3. The formation of half-ester (**25**) is thought to be caused by the reaction between the intermediate **24** and water contained in the solvent.

Additionally, *trans*-(2*S*,6*S*)-isomer (**19a**) was easily epimerized to yield a *trans*-(2*R*,6*R*)-isomer (**19b**) and *cis*-*meso*-isomer (**19c**) by treating it with sodium methoxide (CH_3ONa) in methanol (Chart 3). The stereoisomers were used as a mixture of standards for chiral HPLC analysis as well as for normal phase HPLC analysis to differentiate between the isomers and to identify the stereochemistry of reaction products. The *trans*-configuration of compound **19a** was reconfirmed by both HPLC analysis conditions by comparing its retention times with those of *cis*-*meso*-stereoisomer (**19c**) derived from pyridine-2,6-dicarboxylic acid (**26**) as described below (Figs. 3, 4). Finally, the stereochemistry of compound **19a** was established by converting it to *trans*-(2*S*,6*S*)-teneraic acid (**1**) via acidic hydrolysis (Chart 3).

Synthesis of *cis*-*meso*-Teneraic Acid Furthermore, *cis*-*meso*-isomer of teneraic acid (**3**) was prepared according to the reported procedure by PtO_2 catalyzed hydrogenation

of pyridine-2,6-dicarboxylic acid (**26**) as shown in Chart 4.²⁾ Subsequently, compound **3** was converted to *cis*-*meso*-*N*-benzoyl teneraic acid dimethyl ester (**19c**) by methyl esterification that was followed by *N*-benzoylation. The obtained *cis*-*meso*-isomer **19c** was identical to that obtained by the epimerization of compound **19a** with respect to a normal phase HPLC analysis (Fig. 4).

A Potential Mechanism for Stereoselective Carbonylation It is possible to rationalize the cause of high selectivity in the above mentioned two syntheses by a potential mechanism shown in Chart 5.¹⁸⁾ Given that $\text{HCo}(\text{CO})_4$ (which corresponds to the actual catalyst in the carbonylation) is as strongly acidic as hydrochloric acid in a polar solvent, it is reasonable to assume that the reaction proceeds through the *N*-acyl-iminium ion intermediates **23a** and/or **23b**. The severe steric hindrance to 1,2-diequatorial substitution in **23b** requires that the methoxycarbonyl group of the *N*-acyl-iminium intermediate should be axial in a manner similar to **23a**. It is postulated that the stereo-determining step corresponds to the formation of the amidoalkyl cobalt complex **23**. As shown in Chart 5, an attack of $[\text{Co}(\text{CO})_4]^-$ with respect to the *N*-acyl-iminium ion **23a** could occur preferentially from the less hindered equatorial side to exclusively yield the *trans*-*N*-benzoyl-teneraic acid dimethyl ester. This type of a process was favored even though the *cis*-*meso*-isomer could be thermodynamically more stable.

Fig. 3. Chiral HPLC Chromatogram of *trans*-(2*S*,6*S*)-*N*-Benzoyl-teneraic Acid Dimethyl Ester (**19a**) Obtained by Anodic Oxidation–Cobalt-Catalyzed Carbonylation

(a) *trans*-(2*S*,6*S*)-Isomer (**19a**) is initially obtained from the reaction. (b) *trans*-(2*S*,6*S*)-Isomer (**19a**) is obtained by methyl esterification of a half-ester of *trans*-(2*S*,6*S*)-isomer (**25**).

Fig. 4. Normal Phase HPLC Chromatogram of Stereoisomers of *N*-Benzoyl-teneraic Acid Dimethyl Ester (**19**)

(a) Mixture of *cis*-*meso*-isomer (**19c**), *trans*-(2*S*,6*S*)-isomer (**19a**), and *trans*-(2*R*,6*R*)-isomer (**19b**) obtained by epimerization of *trans*-(2*S*,6*S*)-isomer (**19a**). (b) *trans*-(2*S*,6*S*)-Isomer (**19a**).

Reagents: (a) PtO_2 in 50% acetic acid, H_2 (10 MPa); (b) SOCl_2 in CH_3OH ; (c) benzoyl chloride, Et_3N in THF.

Chart 4. Synthesis of *cis*-*meso*-Teneraic Acid

Chart 5. A Possible Mechanism for Stereoselective Carbonylation

Fig. 5. NMR Spectra of *trans*-(2*S*,6*S*)-Teneraic Acid (1) and *cis*-*meso*-Teneraic Acid (3)

(a) ¹H-NMR spectra of *trans*-(2*S*,6*S*)-isomer (1), (b) ¹³C-NMR spectra of *trans*-(2*S*,6*S*)-isomer (1), (c) ¹H-NMR spectra of *cis*-*meso*-isomer (3), (d) ¹³C-NMR spectra of *cis*-*meso*-isomer (3).

Characterization of Teneraic Acid The results indicated that physical property values (NMR spectrum and mass spectrum) of synthesized teneraic acid were in reasonable agreement with those of a natural *trans*-isomer.¹⁾ Additionally, the NMR spectrum of the synthesized teneraic acid were not consistent with those of *cis*-*meso*-isomer that was synthesized independently²⁾ (Fig. 5). The melting point of the synthesized teneraic acid (235–236°C) did not coincide with that of the reported value (217–219°C), and the discrepancy of the melting points of both compounds can be attributed to the low purity of the natural product relative to the synthesized one. Moreover, the circular dichroism (CD) spectra of the synthetic *trans*-(2*S*,6*S*)-teneraic acid (1) and natural product exhibited the same positive Cotton effect, and thus the natural product is considered to possess the same absolute configuration as that of the *trans*-(2*S*,6*S*)-isomer (Fig. 6). It should be noted that the absolute configuration of naturally occurring pyrrolidin-2,5-

dicarboxylic acid, which corresponds to a 5-membered-ring homolog of teneraic acid, is also known as *trans*-(2*S*,5*S*).^{23–25)} Conversely, it has been reported that the configuration of the naturally occurring liner (ring opened) α -iminodicarboxylic acid, alanopine, is of the *meso*-(*RS*)-form.^{26,27)}

Conclusion

In this study, stereoselective synthesis of *trans*-(2*S*,6*S*)-teneraic acid was successfully achieved with high efficiency. The synthesis consists of a regioselective anodic oxidation at the α -position of methyl *N*-benzoyl-pipecolate. This was followed by stereospecific cobalt-catalyzed carbonylation. Additionally, *trans*-(2*S*,6*S*)-stereochemistry of natural teneraic acid was reconfirmed by comparing its physical properties with those of synthetic *trans*-(2*S*,6*S*)-teneraic acid.

Fig. 6. CD Spectra of *trans*-(2*S*,6*S*)-Teneraic Acid (**1**)

(a) Natural authentic.¹⁾ (b) Synthetic compound.

Experimental

General ¹H-NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz) or Varian XL-300 spectrometer (300 MHz), and MS spectra were measured using a Thermo Quest TSQ 700 spectrometer. Melting point (mp) measurements were performed using a Micro Melting Point Apparatus obtained from Yanaco (Japan). Optical rotary power measurements were performed using a DIP-370 Digital Polarimeter that was manufactured by Nippon Bunko (JASCO Corporation, Japan). The CD spectra were measured using a JASCO J-500A spectro polarimeter manufactured by JASCO Corporation (Japan). The chiral column, CHIRALCEL OK, was purchased from DAICEL CHEMICAL INDUSTRIES, Ltd. (Japan). The normal phase column, YMC-Pack A-012 (S-5, 120 Å, SIL), was purchased from YMC Co., Ltd. (Japan).

Analytical Conditions Analytical conditions 1; Chiral HPLC analytical conditions for *N*-benzoyl-teneraic acid dimethyl ester stereoisomers:

Column: CHIRALCEL OK 4.5×250 mm. (10 μm). Detection: UV 254 nm. Eluent: *n*-hexane-*iso*-propanol=8:2 (v/v). Flow rate: 1.0 mL/min. Temperature: 50°C.

Analytical conditions 2; Normal phase HPLC analytical conditions for *N*-benzoyl-teneraic acid dimethyl ester stereoisomers:

Column: YMC-Pack A-012 (S-5, 120 Å, SIL) 4.6×150 mm. (5 μm). Detection: UV 254 nm. Eluent: *n*-hexane-AcOEt=1:1 (v/v), Flow rate: 1.0 mL/min. Temperature: 25°C.

CD spectrum measurement conditions:

Solvent: H₂O (pH 5.9), Sample concentration: 2.0 mg/mL, Cell length: 1.0 mm, Wavelength range: 290–190 nm, Temperature: 25°C.

Synthesis of *trans*-*N*-Benzoyl-teneraic Acid Dimethyl Ester **18 via Cobalt Catalyzed Hydroformylation–Intramolecular Amidocarbonylation of (*S*)-*N*-Benzoyl-Allylglycine (**12**)** Specifically, (*S*)-*N*-benzoyl-allylglycine (**12**) (6.00 g, 27.4 mmol) and Co₂(CO)₈ (600 mg, 1.75 mmol) in acetone (50 mL) were heated in a 100-mL stainless-steel autoclave with a 1:1 mixture of carbon monoxide and hydrogen (total pressure corresponding to 13.7 MPa that was measured at room temperature) at 100°C for 4 h. The autoclave was cooled to ambient temperature, and this was followed by purging out

carbon monoxide and hydrogen. The removal of the solvent under reduced pressure was followed by dissolving the residue in AcOEt (50 mL) and filtering the insoluble material. The filtrate was extracted with 10% aqueous NaHCO₃ (100 mL), and the extract was washed with AcOEt (50 mL). The aqueous phase was acidified at pH 1 with concentrated HCl and then extracted with AcOEt (50 mL, repeated twice). The organic layer was washed with brine (50 mL), dried over MgSO₄, and concentrated to obtain crude *trans*-*N*-benzoyl-teneraic acid (**18**) as a viscous oil (4.2 g). The residue was esterified with ethereal CH₂N₂ and subsequently purified by silica gel column chromatography (eluted with *n*-hexane–AcOEt) to yield a *trans*-*N*-benzoyl-teneraic acid dimethyl ester (**19**) as a viscous oil (5.19 g, 17.0 mmol, 62.0%); ¹H-NMR (400 MHz, CDCl₃) δ: 1.30–2.20 (6H, m), 3.67 (6H, brs), 4.26–4.50 (2H, m), 7.33 (5H, m). ¹³C-NMR (CDCl₃) δ: 18.0, 25.5, 26.3, 52.3, 55.1, 58.1, 127.1, 128.6, 130.3, 135.3, 172.1, 172.5, 174.7. IR (neat): 1740, 1650 (cm⁻¹). Field desorption (FD)-MS *m/z*: 305.0 (M)⁺.

Synthesis of *trans*-(2*S*,6*S*)-Teneraic Acid (**1**) via Anodic Oxidation–Cobalt Catalyzed Carbonylation

Methyl (*S*)-*N*-Benzoyl-α-methoxy-pipecolate (**22**)

In the study, methyl (*S*)-*N*-benzoyl-pipecolate (**21**) (5.50 g, 22.2 mmol), tetraethylammonium tosylate (Et₄N⁺OTs⁻, 1.40 g, 4.64 mmol) as an electrolyte and MeOH (150 mL) as a solvent were placed into a 200-mL electrolysis cell equipped with two graphite-rod anodes and two graphite-rod cathodes. A constant current (1 A, 32 V) was passed through a cell that was externally cooled with ice water for 9 h. The solvent was removed under reduced pressure, and the residue was dissolved in a mixed solvent of ether and AcOEt (200 mL, 1:1, v/v). The organic layer was successively washed with 5% NaHCO₃ (50 mL) and brine (50 mL), dried over MgSO₄, and then concentrated. The residue was purified by silica gel column chromatography (eluted with *n*-hexane–AcOEt) to obtain methyl (*S*)-*N*-benzoyl-α-methoxy-pipecolate (**22**) as a viscous oil (3.57 g, 12.9 mmol, 58.8%); ¹H-NMR (300 MHz, CDCl₃) δ: 1.50–2.15 (5H, m), 2.17–2.28 (0.5H, brd), 2.40–2.50 (0.5H, brd), 3.07 (1.5H, brs), 3.43 (1.5H, brs), 3.75 (3H, brs), 4.30–4.45 (0.5H, m), 4.86 (0.5H, brs), 5.40 (0.5H, brs), 5.87 (0.5H, brs), 7.40 (5H, m). IR (neat): 2950, 1735, 1640, 1440, 1405, 1205 (cm⁻¹). FD-MS *m/z*: 277.0 (M)⁺. Electrospray ionization (ESI)-MS *m/z*: 277.0 (M)⁺.

***trans*-(2*S*,6*S*)-*N*-Benzoyl-teneraic Acid Dimethyl Ester (Dimethyl *trans*-(2*S*,6*S*)-*N*-Benzoyl-piperidine-2,6-dicarboxylate, **19a**)** Specifically, methyl (*S*)-*N*-benzoyl-α-methoxy-2-piperidinecarboxylate (**22**) (3.57 g, 12.9 mmol) and Co₂(CO)₈ (800 mg, 2.34 mmol) in acetone (50 mL) were heated in a 100-mL stainless-steel autoclave with a 1:1 mixture of carbon monoxide and hydrogen (total pressure corresponded to 13.7 MPa and was measured at room temperature) at 100°C for 3.5 h. The autoclave was then cooled to ambient temperature, and carbon monoxide and hydrogen were purged out. The removal of the solvent under reduced pressure was followed by dissolving the residue in AcOEt (50 mL) and filtering off the insoluble material. The filtrate was extracted with 10% aqueous NaHCO₃ (100 mL), and the extract was washed with AcOEt (50 mL). The combined organic phase was washed with brine (50 mL), dried over MgSO₄, and then concentrated. The residue was purified by silica gel column chromatography (eluted with *n*-hexane–AcOEt) to obtain *trans*-(2*S*,6*S*)-*N*-benzoyl-teneraic acid dimethyl ester (**19a**) as a viscous oil (1.45 g,

4.73 mmol, 36.7%).

The aqueous phase was acidified at pH 1 with concentrated HCl and then extracted with AcOEt (50 mL, repeated twice). The organic layer was washed with brine (50 mL), dried over MgSO_4 , and then concentrated to yield a crude half-ester (**25**). The residue was esterified with ethereal CH_2N_2 and purified by silica gel column chromatography (eluted with *n*-hexane–AcOEt) to obtain *trans*-(2*S*,6*S*)-*N*-benzoyl-teneraic acid dimethyl ester (**19a**) as a viscous oil (1.04 g, 3.39 mmol, 26.3%); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.35–2.30 (6H, m), 3.73 (6H, brs), 4.33 (1H, brs), 4.56 (1H, brs), 7.35–7.50 (5H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 18.0, 25.5, 26.3, 52.3, 55.1, 58.1, 127.1, 128.6, 130.3, 135.3, 172.1, 172.5, 174.7. IR (neat): 2950, 1735, 1650, 1440, 1380, 1325, 1200, 1130, 1095, 1070, 980 (cm^{-1}). FD-MS m/z : 305.0 (M) $^+$. ESI-MS m/z : 274.0 ($\text{M}-31$). FAB-MS m/z : 306.1347 ($\text{M}+\text{H}$) (Calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_5$: 306.1342). Specific rotation: $[\alpha]_{\text{D}}^{20}$ –123.8 ($c=1.0$, CH_3OH).

***trans*-(2*S*,6*S*)-Teneraic Acid (*trans*-(2*S*,6*S*)-Piperidine-2,6-dicarboxylic Acid, **1**)** Furthermore, *trans*-(2*S*,6*S*)-*N*-benzoyl-teneraic acid dimethyl ester (**19a**) (1.10 g, 3.60 mmol) was dissolved in 6*N* HCl (50 mL) and heated at 110°C for 9 h. The resulting solution was successively washed with ether (50 mL) and AcOEt (50 mL) and then concentrated under reduced pressure to obtain crude *trans*-(2*S*,6*S*)-piperidine-2,6-dicarboxylic acid (**1**) as a solid (750 mg). A solution of crude **1**·HCl (750 mg) in ion-exchange water (10 mL) was applied to a cation-exchange resin (DOWEXTM 1×8 in the acetate form) column (100 mL) for purification. The column was washed with ion-exchange water (200 mL). Subsequently, compound **1** was eluted with aqueous 2*N* acetic acid (300 mL). The eluates containing **1** were pooled and concentrated *in vacuo*. The residue was dissolved in water (5 mL), and activated carbon (200 mg) was added to the solution. The solution was stirred for 1 h and was then filtered. The filtrate was concentrated *in vacuo* to obtain *trans*-(2*S*,6*S*)-teneraic acid (**1**) as a white solid (465 mg, 2.70 mmol, 74.7%); $^1\text{H-NMR}$ (400 MHz, D_2O) δ : 1.57 (2H, br quint, $J=6.0\text{ Hz}$), 1.85–2.00 (4H, m), 4.11 (2H, dd, $J=4.8, 7.2\text{ Hz}$). $^{13}\text{C-NMR}$ (D_2O) δ : 19.0, 25.0, 55.3, 172.5. IR (KBr): 3460, 3050, 2950, 1660, 1585, 1440, 1380, 1260, 1115, 895, 830, 775 (cm^{-1}). FD-MS m/z : 174.0 ($\text{M}+\text{H}$) $^+$. Elemental analysis: Calcd for $\text{C}_7\text{H}_{11}\text{NO}_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.38; H, 6.41; N, 8.03. Specific rotation: $[\alpha]_{\text{D}}^{20}$ –8.30 ($c=1.0$, H_2O). mp: 235–236°C.

***cis*-meso-Teneraic Acid (*cis*-meso-Piperidine-2,6-dicarboxylic Acid, **3**)** Pyridine-2,6-dicarboxylic acid (**26**) (3.34 g, 20.0 mmol) and PtO_2 (68 mg, 0.30 mmol) in 50% acetic acid (20 mL) were heated in a 100-mL stainless-steel autoclave with hydrogen (10.0 MPa, measured at room temperature) at 80°C for 10 min. The autoclave was then cooled to ambient temperature, and the hydrogen was purged out. The insoluble material (PtO_2) was filtered off, and the filtrate was concentrated to yield crude *cis*-meso-teneraic acid (**3**) as a white solid. The solid was crystallized from aqueous ethanol and dried to obtain pure *cis*-meso-teneraic acid (**3**) as a white solid (2.60 g, 15.0 mmol, 75.0%); $^1\text{H-NMR}$ (400 MHz, D_2O) δ : 1.49–1.62 (3H, m), 1.69 (1H, brs), 2.10–2.25 (2H, m), 3.69–3.73 (2H, m). $^{13}\text{C-NMR}$ (D_2O) δ : 22.2, 25.4, 57.8, 172.6.

***cis*-meso-*N*-Benzoyl-teneraic Acid Dimethyl Ester (Dimethyl *cis*-meso-*N*-Benzoyl-piperidine-2,6-dicarboxylate, **19c**)** Specifically, *cis*-meso-teneraic acid (**3**) (1.0 g, 5.78 mmol) was added to a stirring solution of thionyl chloride

(3.0 mL, 42.0 mmol) in MeOH (30 mL) at 0°C. The mixture was stirred for 30 min at 0°C, then warmed to room temperature, and was stirred overnight. The solvent was evaporated *in vacuo* to yield crude *cis*-meso-teneraic acid dimethyl ester·HCl (692 mg, 2.92 mmol, 51.0%) that is used in the next step without further purification; IR (KBr): 1750 (cm^{-1}).

Additionally, Et_3N (0.44 mL, 3.20 mmol) and benzoyl chloride (0.20 mL, 1.76 mmol) were added to a solution of the forementioned crude *cis*-meso-teneraic acid dimethyl ester·HCl (380 mg, 1.60 mmol) in tetrahydrofuran (8.0 mL) at 0°C. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated *in vacuo*, and the residue was partitioned between water (10 mL) and EtOAc (30 mL). The aqueous phase was further extracted with EtOAc (30 mL). The combined organic layers were washed with water (30 mL), aqueous citric acid (10%, 30 mL), and brine (30 mL) and subsequently dried over anhydrous MgSO_4 and then concentrated. The crude residue was purified by silica gel column chromatography (eluted with *n*-hexane–AcOEt) to obtain *cis*-meso-*N*-benzoyl-teneraic acid dimethyl ester (**19c**) as a viscous oil (250 mg, 8.20 mmol, 51.0%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.60–2.34 (6H, m), 3.72 (6H, s), 4.50–5.40 (2H, m), 7.35–7.45 (5H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 16.9, 25.9, 52.0, 55.0, 52.1, 126.7, 128.6, 129.9, 135.9, 171.3, 172.9. IR (neat): 1730, 1650 (cm^{-1}). FD-MS m/z : 305.0 (M) $^+$. FAB-MS m/z : 306.1347 ($\text{M}+\text{H}$) (Calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_5$: 306.1342).

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Conflict of Interest All authors were employees of Ajinomoto Co., Inc. when the study was conducted and have no further conflicts of interest to declare.

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