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Total Synthesis of Tricladins A and B and Identification of Their Absolute Configuration

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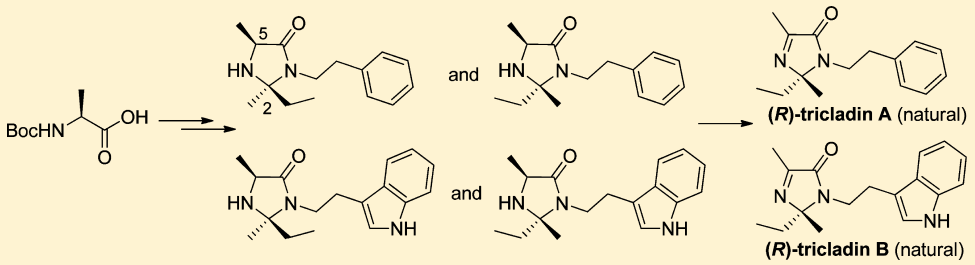
Supporting Information



ABSTRACT: A concise synthesis of both (*S*)- and (*R*)-enantiomers of tricladins A and B from L-Boc alanine was achieved. The diastereomeric intermediates were separated by chiral column chromatography, and the absolute configuration of the 2-position was assigned by observed NOE interactions with the known stereogenic center at the 5-position. By comparison of all synthesized final enantiomers with the corresponding natural products, we concluded that the natural tricladins A and B must have the (*R*)-configuration.

Tricladin A and B (Figure 1) are two natural alkaloids, isolated from the crude extract of the ascomycete fungus

Figure 1. Chemical structures of tricladins.

Tricladium sp. (No. 2520) in 2011 by Li et al.,[1] but their absolute configuration was not elucidated. These two compounds have negative optical rotations. Tricladin B has also demonstrated marginal cytotoxicity (23.1% inhibition) against MDA-MB-231 human breast cancer cells at a concentration of 20 μg/mL. Despite the interesting biological activity and stereochemistry, no total synthesis of tricladin A and B has been reported.

Structurally, tricladins A and B contain a unique core 1*H*-imidazol-5(2*H*)-one with different substitutions on the 3-position: phenylethyl or indolylethyl group. In nature, this skeleton has only been found in kottamides A–D.[2] In medicinal chemistry, this core structure has been used in various drug discovery projects such as glycine transporter type-1 (GlyT1) inhibitors,[3] glucagon receptor antagonists (GRA),[4] and calcitonin gene-related peptide (CGRP) antagonists.[5] These examples are outlined in Figure 2.

From previous research, we have gained considerable experience in imidazolone chemistry by building the cores and studying their reactivities.[4a,d,6] In continuing our work on imidazolone chemistry and exploring new chemicals as potential drugs, we decided to synthesize tricladins A and B and determine their absolute confirmations, which we report herein.

Tricladins A and B have only one stereogenic center connecting two carbon and two nitrogen atoms. In order to determine the absolute configuration for these two natural products, we designed a synthetic route which can provide both the enantiomers represented in Scheme 1. The configuration at the 2-position can be determined by the known stereogenic center at the 5-position on the key intermediate **4**.

The total synthesis started from L-Boc alanine **1**, coupled with 2-phenylethanamine in the presence of propylphosphonic anhydride (T3P) and DIEA at room temperature for 16 h, to obtain amide **2** in 89% yield. The Boc protecting group of amide **2** was removed with 10 equiv of 4 N HCl in dichloromethane to give aminoamide **3** in 84% yield. Cyclization of **3** with 2-butanone in the presence of 4 Å molecular sieves and TEA in ethanol led to a 1:1 mixture of diastereomers **4** in 89%.

The chiral separation was carried out with a ChiralPak AD (5 cm i.d. × 50 cm L) using 2% 2-propanol in hexanes elution. We hypothesized that since the absolute configuration at 5-position was known with the starting material L-Boc-alanine, the absolute configuration of 2-position may also be assigned. The stereochemical configuration at C-2 was determined by NOE correlations observed in the 2D NOESY spectra of **4a** and **4b**. In the NOESY spectrum of **4a** strong NOE correlations were observed between H-5 and protons of the methyl group at

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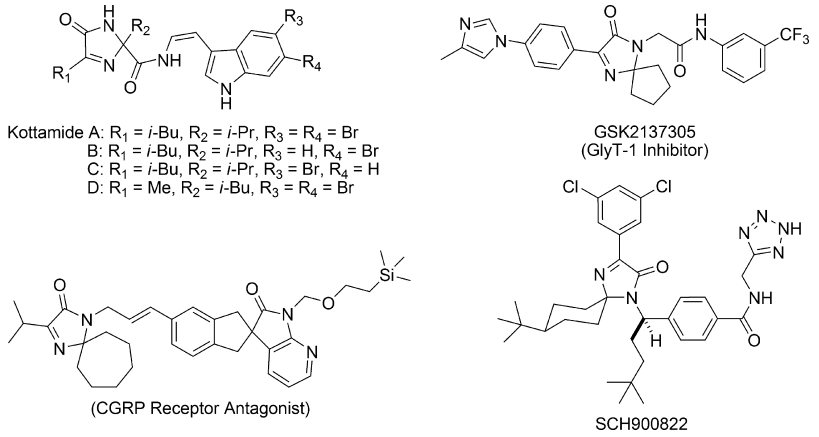
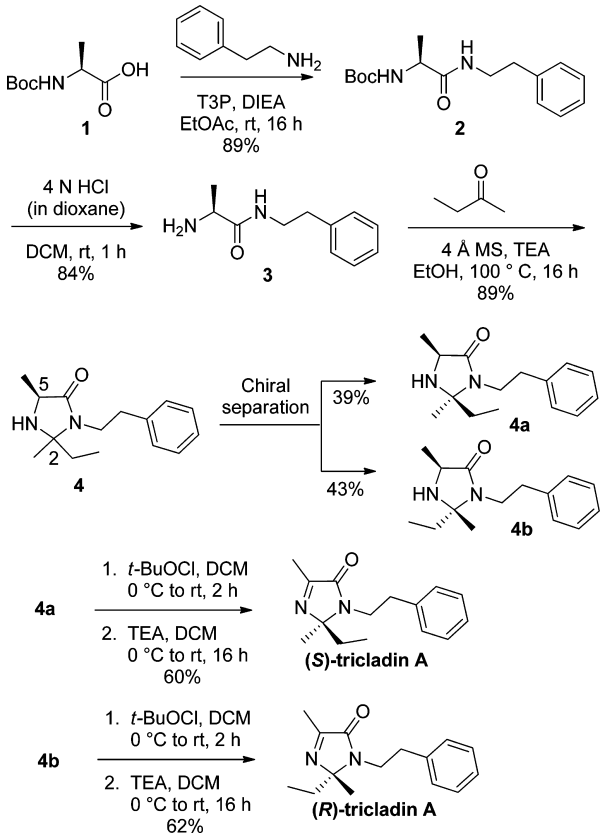


Figure 2. Biologically active imidazolones.

Scheme 1. Total Synthesis of Tricladin A



C-2, while in **4b** strong NOE correlations were observed between H-5 and protons of the ethyl group at C-2 as shown in Figure 3.[7] Therefore, the configurations of **4a** and **4b** are (2*S*,5*S*) and (2*R*,5*S*), respectively.

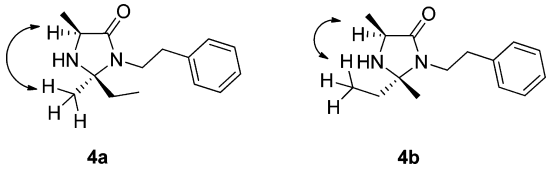


Figure 3. NOE correlations in **4a** and **4b**.

Finally, **4a** and **4b** was treated with *tert*-butyl hypochlorite (*t*-BuOCl, 2 equiv) separately, followed by the treatment with TEA to give the dehydrogenated products (*S*)-tricladin A and (*R*)-tricladin A as colorless oils in 60−70% yields. The ^{1}H and ^{13}C NMR data are identical to those reported in the literature.[1] Chiral HPLC analyses indicated no epimerization about the designated stereogenic centers at the 2-position. Compounds (*S*)-tricladin A and (*R*)-tricladin A showed optical rotation with $[\alpha]^{25}_{D}$ = +6.1 (*c* 0.3, CH_2Cl_2) and $[\alpha]^{25}_{D}$ = −6.0 (*c* 0.3, CH_2Cl_2), respectively. Correspondingly, the literature[1] reported tricladin A as a yellow oil with $[\alpha]^{25}_{D}$ = −12 (*c* 0.06, CH_2Cl_2). In conclusion, natural tricladin A must be the (*R*)-configuration.

Similarly, we synthesized tricladin B as shown in Scheme 2. The diastereomers **7a** and **7b** were separated by a ChiralPak AD (4.6 mm × 250 mm) using 20% ethanol in heptanes. NOE interactions were also observed for these two compounds.[7] However, the final dehydrogenation step toward (*S*)- and (*R*)-tricladin B was found to be challenging. When the same procedure as described in the preparation of tricladin A with 2 equiv of *t*-BuOCl was used, absolutely no desired product was observed. A number of other reagents including DDQ[3a] and NBS[3,5] were also explored, but all failed to give the desired final products. Instead, a complex mixture resulted due to the highly reactive nature of the indolylethyl group toward many halogenating reagents or oxidizers. Thus, we reinvestigated *t*-BuOCl by optimizing the reaction conditions and found the best reaction conditions to be treating diastereomers **7a** and **7b** with 0.7−0.8 equiv of *t*-BuOCl in DCM at 0 °C for 20−30 min followed by the treatment of triethylamine at room temperature for 2 days. Tricladin B was successfully obtained in 40−50% yield. Compounds (*S*)-tricladin B and (*R*)-tricladin B showed optical rotation with $[\alpha]^{25}_{D}$ = +9.9 (*c* 0.36, CH_2Cl_2) and $[\alpha]^{25}_{D}$ = −9.5 (*c* 0.32, CH_2Cl_2), respectively. Since the literature[1] reported tricladin B as a yellow oil with $[\alpha]^{25}_{D}$ = −10 (*c* 0.04, CH_2Cl_2), we have concluded that natural tricladin B must be the (*R*)-configuration as well.

■ CONCLUSION

We have successfully synthesized all four tricladin A and B enantiomers starting from L-alanine and determined their absolute configurations. A known stereogenic center at the 5-position of the key intermediate imidazolidinone **4** and **7** was strategically introduced, and then the relative configurations at the 2-position of **4a**, **4b**, **7a**, and **7b** were determined by means

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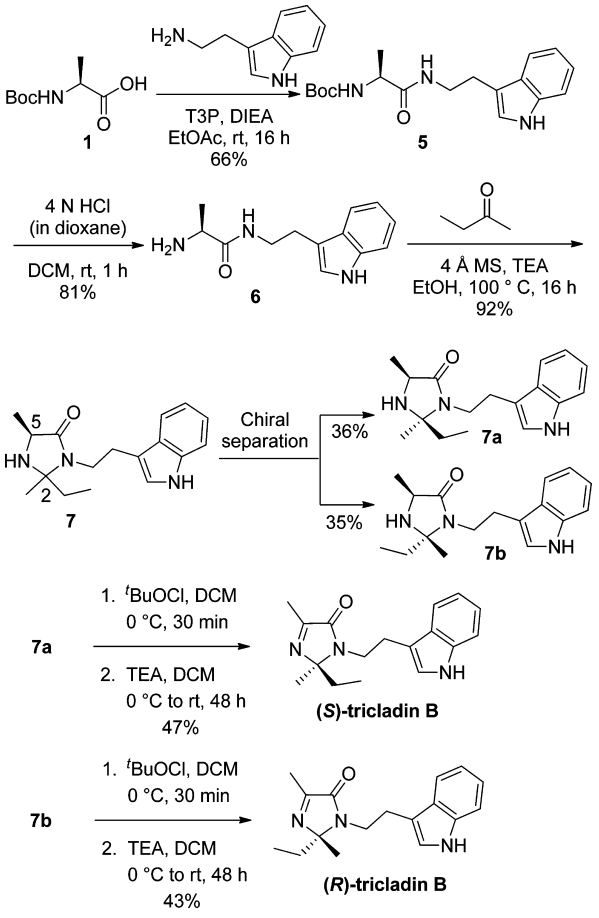
Scheme 2. Total Synthesis of Tricladin B



of NOE interactions. By comparison of the observed optical rotation data of synthesized (*S*)- and (*R*)-tricladin A and B with the literature reports, we assigned the natural products the *R* configuration.

EXPERIMENTAL SECTION

General Experimental Methods. All materials including reagents and solvents were used as received from commercial suppliers. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 500 and 125 MHz, respectively. Chemical shifts are given in ppm (δ), and coupling constants, *J*, are reported in hertz. Tetramethylsilane was used as an internal chemical shift reference for proton spectra, and the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on an electrospray ionization (ESI) mass spectrometer. High-resolution mass spectrometry (HRMS) was performed in an ESI positive or negative mode. Chromatography was performed using a Combi-Flash Companion on a silica gel column. Chiral HPLC analyses were obtained using a ChiralPak AD column (4.6 mm × 250 mm) with PDA detection at 254 nm. Chiral HPLC preparations were performed using a ChiralPak AD column (5 cm i.d. × 50 cm L) with PDA detection at 230 nm. Melting points were determined on a capillary melting point apparatus and are uncorrected.

(*S*)-*tert*-Butyl (1-Oxo-1-(phenethylamino)propan-2-yl)-carbamate (2). 2-(*tert*-Butoxycarbonylamino)acetic acid (**1**) (4.73 g, 25.0 mmol), 2-phenylethanamine (3.03 g, 25.0 mmol), and diisopropylethylamine (DIEA, 7.5 mL, 32.5 mmol) were dissolved in ethyl acetate (250 mL) and cooled to 0 °C. Propylphosphonic anhydride (T3P, 50% in ethyl acetate, 19.0 mL, 60.0 mmol) was added dropwise. The reaction mixture was then stirred for 18 h at room temperature. The solution was quenched with dropwise addition of 2 M aqueous sodium hydroxide solution (50 mL). The organic phase was separated, and the aqueous was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0−10% methanol/methylene chloride) to afford **2** (6.49 g, 89%) as a white solid: $[\alpha]^{25}_D$ = −30.6 (*c* 1.0, $CHCl_3$); mp 76−77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.28 (m, 2H), 7.23−7.18 (m, 3H), 6.24 (br s, 1H), 5.02 (br s, 1H), 4.10 (br s, 1H), 3.56−3.46 (m, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 1.43 (s, 9H), 1.31 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 155.5, 138.7, 128.7, 128.6, 126.5, 80.1, 50.1, 40.7, 35.7, 28.3, 18.6; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}N_2O_3$ 293.1865, found 293.1866.

(*S*)-2-Amino-*N*-phenethylpropanamide (3). HCl solution (4 M in dioxane, 25.0 mL, 100 mmol) was added dropwise at room temperature to a solution of (*S*)-*tert*-butyl (1-oxo-1-(phenethylamino)-propan-2-yl)carbamate (**2**) (2.42 g, 10.0 mmol) in methylene chloride (25 mL). The reaction mixture was stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (100 mL) and 1 N NaOH (25 mL). The organic phase was separated, and the aqueous phase was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0−20% methanol/methylene chloride) to afford **3** (1.62 g, 84%) as a white crystal: $[\alpha]^{25}_D$ = +5.9 (*c* 1.1, $CHCl_3$); mp 37−39 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.24−7.19 (m, 3H), 3.51 (qd, *J* = 7.0, 2.0 Hz, 2H), 3.45 (q, *J* = 7.0 Hz, 1H), 2.82 (t, *J* = 7.0 Hz, 2H), 1.49 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 139.0, 128.8, 128.6, 126.4, 50.8, 40.2, 35.8, 21.8; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{17}N_2O$ 193.1341, found 193.1335.

(2*S*,5*S*)-2-Ethyl-2,5-dimethyl-3-phenethylimidazolidin-4-one (4a) and (2*R*,5*S*)-2-Ethyl-2,5-dimethyl-3-phenethylimidazolidin-4-one (4b). A mixture of (*S*)-2-amino-*N*-phenethylpropanamide (**3**) (1.38 g, 7.2 mmol), 2-butanone (3.22 mL, 36.0 mmol), 4 Å molecular sieves (2.0 g), and triethylamine (3.3 mL, 21.6 mmol) in ethanol (8 mL) under nitrogen in a sealed tube was heated at 100 °C for 16 h. The mixture was cooled to room temperature and filtered through Celite, and the solids were washed with methanol. The filtrate was concentrated and purified by column chromatography (silica, 0−20% methanol/methylene chloride) to afford a mixture of the diastereomers **4** (1.58 g, 89%) as a colorless oil. Subsequently, the diastereomers **4** (290 mg) were separated by a ChiralPak AD (5 cm i.d. × 50 cm L) using 2% 2-propanol in hexanes elution yielding the first fraction **4a** as a light yellow oil (112 mg, 39%) and the second fraction **4b** as a light yellow oil (124 mg, 43%). **4a**: $[\alpha]^{25}_D$ = +19.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.30−7.24, (m, 4H), 7.21−7.18 (m, 1H), 3.58 (q, *J* = 7.0 Hz, 1H), 3.35−3.32 (m, 2H), 2.90 (t, *J* = 8.0 Hz, 2H), 1.76−1.69 (m, 1H), 1.63−1.56 (m, 1H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.29 (s, 3H), 0.90 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 140.3, 130.0, 129.6, 127.6, 80.5, 54.6, 43.7, 35.7, 33.2, 24.1, 17.4, 8.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}N_2O$ 247.1810, found 247.1805. **4b**: $[\alpha]^{25}_D$ = +43.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.30−7.27 (m, 2H), 7.24−7.23 (m, 2H), 7.21−7.18 (m, 1H), 3.53−3.46 (m, 2H), 3.22−3.15 (m, 1H), 2.97−2.86 (m, 2H), 1.67−1.54 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.23 (s, 3H), 0.85 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 140.3, 130.1, 129.6, 127.6, 80.7, 55.7, 43.7, 35.7, 33.3, 26.7, 18.4, 8.5; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}N_2O$ 247.1810, found 247.1804.

(*S*)-Tricladin A [(*S*)-2-Ethyl-2,4-dimethyl-1-phenethyl-1*H*-imidazol-5(2*H*)-one]. (2*S*,5*S*)-2-Ethyl-2,5-dimethyl-3-phenethylimidazolidin-4-one (**4a**) (60 mg, 0.24 mmol) was dissolved in methylene chloride (6 mL) and cooled to 0 °C. *tert*-Butyl hypochlorite (52 mg, 0.48 mmol) was added dropwise. After being stirred at room temperature for 2 h, the reaction mixture was cooled to 0 °C again, and triethylamine (78 mg, 0.72 mmol) was added. The resulting mixture was stirred at room temperature for 16 h, concentrated, and purified by column chromatography (silica, 0−5% methanol/methylene chloride) to afford **(*S*)-tricladin A** (36 mg, 60%) as a colorless oil: $[\alpha]^{25}_D$ = +6.1 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz,

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$CDCl_3$) δ 7.33−7.30 (m, 2H), 7.26−7.22 (m, 3H), 3.64−3.58 (m, 1H), 3.40−3.34 (m, 1H), 3.04−2.94 (m, 2H), 2.25 (s, 3H), 2.03−1.96 (m, 1H), 1.75−1.67 (m, 1H), 1.33 (s, 3H), 0.56 (q, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 164.1, 138.6, 128.8, 128.7, 126.7, 86.9, 42.9, 34.0, 29.9, 24.3, 14.5, 6.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{21}N_2O$ 245.1654, found 245.1649.

(*R*)-Tricladin A [(*R*)-2-Ethyl-2,4-dimethyl-1-phenethyl-1*H*-imidazol-5(2*H*)-one]. Employing the same procedure as described in the preparation of (*S*)-tricladin A, (2*R*,5*S*)-2-ethyl-2,5-dimethyl-3-phenethylimidazolidin-4-one (**4b**) (68 mg, 0.28 mmol) was used to afford **(*R*)-tricladin A** (42 mg, 62%) as a colorless oil: $[\alpha]^{25}_D$ = −6.0 (c 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.30 (m, 2H), 7.27−7.22 (m, 3H), 3.65−3.59 (m, 1H), 3.40−3.34 (m, 1H), 3.04−2.94 (m, 2H), 2.26 (s, 3H), 2.03−1.96 (m, 1H), 1.75−1.67 (m, 1H), 1.33 (s, 3H), 0.56 (q, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 164.1, 138.6, 128.8, 128.7, 126.7, 86.9, 42.9, 34.0, 29.9, 24.3, 14.5, 6.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{21}N_2O$ 245.1654, found 245.1650.

(*S*)-*tert*-Butyl (1-((2-(1*H*-Indol-3-yl)ethyl)amino)-1-oxopropan-2-yl)carbamate (5). Employing the same procedure as described in the preparation of **2**, 2-(*tert*-butoxycarbonylamino)acetic acid (**1**) (4.73 g, 25.0 mmol) and tryptamine (4.0 g, 25.0 mmol) was used to afford **5** (5.48 g, 66%) as a light brown foam: $[\alpha]^{25}_D$ = −25.2 (c 1.0, CH_3OH); mp 63−66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.21 (td, J = 7.5, 1.0 Hz, 1H), 7.13 (td, J = 7.5, 1.0 Hz, 1H), 7.04 (d, J = 1.5 Hz, 1H), 6.10 (s, 1H), 4.93 (br s, 1H), 4.07 (br s, 1H), 3.67−3.58 (m, 2H), 2.98 (t, J = 7.0 Hz, 2H), 1.41 (s, 9H), 1.30 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 155.5, 136.4, 127.3, 122.2, 122.1, 119.4, 118.6, 112.7, 111.3, 80.0, 50.2, 39.7, 28.3, 25.2, 18.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{26}N_3O_3$ 332.1974, found 332.1972.

((*S*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-2-aminopropanamide (6). Employing the same procedure as described in the preparation of **3**, (*S*)-*tert*-butyl (1-((2-(1*H*-indol-3-yl)ethyl)amino)-1-oxopropan-2-yl)-carbamate (**5**) (3.3 g, 25.0 mmol) was used to afford **6** (1.88 g, 81%) as a light yellow oil: $[\alpha]^{25}_D$ = +25.1 (c 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.8 (s, 1H), 7.88 (t, J = 6.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.33 (q, J = 8.0 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 7.06 (td, J = 8.0, 1.0 Hz, 1H), 6.97 (td, J = 8.0, 1.0 Hz, 1H), 3.38−3.34 (m, 2H), 3.22 (q, J = 7.0 Hz, 2H), 2.82 (t, J = 7.0 Hz, 2H), 1.81 (br s, 2H); 1.11 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 136.1, 127.1, 122.5, 120.8, 118.2, 118.1, 111.7, 111.2, 50.2, 25.1, 21.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{18}N_3O$ 232.1450, found 232.1477.

(2*S*,5*S*)-3-(2-(1*H*-Indol-3-yl)ethyl)-2-ethyl-2,5-dimethylimidazolidin-4-one (7a) and (2*R*,5*S*)-3-(2-(1*H*-Indol-3-yl)ethyl)-2-ethyl-2,5-dimethylimidazolidin-4-one (7b). Employing the same procedure as described in the preparation of **4**, ((*S*)-*N*-(2-(1*H*-indol-3-yl)ethyl)-2-aminopropanamide (**6**) (1.58 g, 6.8 mmol) was used to afford **7** as a colorless oil (1.78 g, 92%). Subsequently, the diastereomers **7** (420 mg) were separated by a ChiralPak AD (5 cm i.d. × 50 cm L) using 20% ethanol in heptanes elution yielding the first fraction **7a** as a light oil (152 mg, 36%) and the second fraction **7b** as a white solid (146 mg, 35%). **7a**: $[\alpha]^{25}_D$ = +15.5 (c 0.31, $CHCl_3$); mp 117−118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.19 (td, J = 8.0, 1.0 Hz, 1H), 7.13 (td, J = 8.0, 1.0 Hz, 1H), 7.04 (d, J = 2.0 Hz, 1H), 3.62 (q, J = 7.0 Hz, 1H), 3.46−3.34 (m, 2H), 3.15−3.05 (m, 2H), 1.75−1.68 (m, 1H), 1.67−1.60 (m, 1H), 1.38 (d, J = 7.0 Hz, 3H), 1.30 (s, 3H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 136.3, 127.4, 122.1, 122.0, 119.4, 118.8, 113.2, 111.2, 78.6, 53.5, 41.7, 32.1, 25.2, 24.6, 17.7, 7.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{23}N_3OH$ $C_{17}H_{24}N_3O$ 286.1919, found 286.1908. **7b**: $[\alpha]^{25}_D$ = +29.2 (c 0.33, $CHCl_3$); ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.34 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.18 (td, J = 8.0, 1.0 Hz, 1H), 7.12 (td, J = 8.0, 1.0 Hz, 1H), 7.03 (s, 1H), 3.64−3.59 (m, 1H), 3.56 (q, J = 6.5 Hz, 1H), 3.26−3.21 (m, 1H), 3.10 (t, J = 7.5 Hz, 2H), 1.66−1.52 (m, 2H), 1.38 (d, J = 7.0 Hz, 3H), 1.27 (s, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 136.3, 127.4, 122.1, 122.0, 119.4, 118.8, 113.2, 111.2, 78.7, 54.5, 41.7, 32.3, 27.0, 24.7, 18.6, 8.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{24}N_3O$ 286.1919, found 286.1906.

(*S*)-Tricladin B [(*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-2-ethyl-2,4-dimethyl-1*H*-imidazol-5(2*H*)-one]. (2*S*,5*S*)-3-(2-(1*H*-Indol-3-yl)-ethyl)-2-ethyl-2,5-dimethylimidazolidin-4-one (**7a**) (104 mg, 0.36 mmol) was dissolved in methylene chloride (2 mL) and cooled to 0 °C. *tert*-Butyl hypochlorite (30 mg, 0.28 mmol) was added dropwise. After the mixture was stirred at 0 °C for 30 min, triethylamine (110 mg, 0.72 mmol) was added at this temperature. The resulting mixture was stirred at room temperature for 48 h, concentrated, and purified by column chromatography (silica, 4% methanol/methylene chloride) to afford **(*S*)-tricladin B** (49 mg, 47%) as a white solid: $[\alpha]^{25}_D$ = +9.9 (c 0.36, CH_2Cl_2); mp 146−149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 7.15 (t, J = 7.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 3.73−3.67 (m, 1H), 3.51−3.45 (m, 1H), 3.21−3.10 (m, 2H), 2.27 (s, 3H), 2.05−1.98 (m, 1H), 1.79−1.71 (m, 1H), 1.38 (s, 3H), 0.57 (q, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 164.2, 138.3, 127.2, 122.2, 122.1, 119.6, 118.7, 112.7, 111.3, 86.9, 41.9, 30.0, 24.5, 23.8, 14.5, 6.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{22}N_3O$ 284.1763, found 284.1776.

(*R*)-Tricladin B [(*R*)-1-(2-(1*H*-Indol-3-yl)ethyl)-2-ethyl-2,4-dimethyl-1*H*-imidazol-5(2*H*)-one]. The same procedure as described in the preparation of (*S*)-tricladin B from (2*R*,5*S*)-3-(2-(1*H*-indol-3-yl)ethyl)-2-ethyl-2,5-dimethylimidazolidin-4-one (**7b**) (104 mg, 0.36 mmol) was used to afford **(*R*)-tricladin B** (45 mg, 43%) as a white solid: $[\alpha]^{25}_D$ = −9.5 (c 0.32, CH_2Cl_2); mp 146−150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.20 (td, J = 7.0, 1.0 Hz, 1H), 7.15 (td, J = 7.0, 1.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 3.73−3.67 (m, 1H), 3.51−3.45 (m, 1H), 3.20−3.10 (m, 2H), 2.27 (s, 3H), 2.05−1.98 (m, 1H), 1.79−1.72 (m, 1H), 1.38 (s, 3H), 0.57 (q, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 164.2, 138.3, 127.2, 122.2, 122.1, 119.6, 118.7, 112.7, 111.3, 86.9, 41.9, 30.0, 24.4, 23.8, 14.5, 6.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{22}N_3O$ 284.1763, found 284.1761.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all synthesized compounds; ^{1}H−^{1}H COSY and NOSEY NMR spectra of compounds **4a**, **4b**, **7a**, and **7b**; ^{1}H−^{1}H COSY spectra of tricladins. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Iwao Ojima on the occasion of his 70th birthday, June 5, 2015.

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(7) Please see the Supporting Information for NMR spectra.