Total Synthesis of Avellanins A and B, New Fungal Metabolites from *Hamigera avellanea* with Pressor Effect[1,2]

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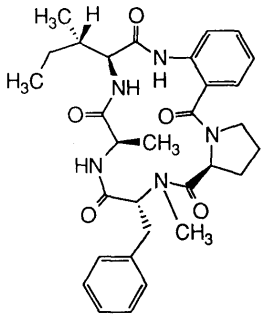
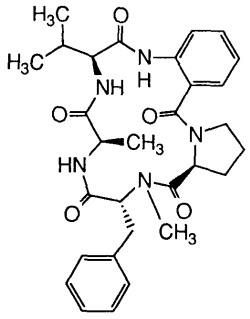
Avellanins A and B (1 and 2), new pressor-active fungal metabolites from *Hamigera avellanea*, have been conveniently synthesized from methyl anthranilate. This synthetic study has established the absolute stereostructure of avellanin B (2). Coupling of methyl anthranilate with *N*-protected amino acid derivatives was best carried out by use of ((9-fluorenylmethyl)oxy)carbonyl (Fmoc)-amino acid chloride. Chain elongation for avellanins was accomplished with diethyl phosphorocyanidate, while cyclization was achieved with diphenyl phosphorazidate.

Keywords avellanin; cyclic peptide; fungal metabolite; Fmoc-amino acid chloride; diethyl phosphorocyanidate; diphenyl phosphorazidate; cyclization; anthranilic acid peptide

Avellanins A and B have recently been isolated by Yamazaki and co-workers[2] from the fungus *Hamigera avellanea* STOLK *et* SAMSON. Avellanins cause a marked increase in blood pressure in rats and mice. The absolute stereostructure of avellanin A has been determined to be cyclo[D-MePhe–D-Ala–L-Ile–Ant–L-Pro][3] (**1**) by X-ray analysis in addition to spectral and chemical studies. Although the primary structure of avellanin B has been assigned as cyclo[MePhe–Ala–Val–Ant–Pro], its absolute configuration remained to be determined. We now report the total synthesis of avellanins A and B, unambiguously determining the absolute stereostructure of avellanin B to be as shown in the structure **2** (Chart 1).



avellanin A (**1**)



avellanin B (**2**)

Chart 1

We had expected that avellanin B would have an analogous absolute stereostructure to that of avellanin A (**1**). Our synthesis of **2** started with the coupling of methyl anthranilate with Boc–L-Val–OH. However, we found that the coupling was sluggish owing to the relatively low nucleophilicity of the amino group of methyl anthranilate. Both DEPC[4] and BopCl[5] were ineffective. The symmetrical anhydride prepared from Boc–L-Val–OH using DCC together with DMAP and diisopropylethylamine in dichloromethane afforded the coupling product in good yield. However, extensive racemization was found to occur by high performance liquid chromatography (HPLC) of the 3,5-dinitrobenzoyl derivative of Val–Ant–OMe using a chiral column. Without DMAP, the coupling proceeded without racemization, but a longer reaction time was required. Finally, we found that Fmoc–L-Val–Cl[6] was easily coupled with methyl anthranilate in good yield without any racemization. After deprotection at the N-terminal with 4-aminomethylpiperidine, Boc–D-Ala–OH, Boc–D-MePhe–OH, and Boc–L-Pro–OH were introduced onto the dipeptide in a stepwise manner, as shown in Chart 2. DEPC was used for the chain elongation while trifluoroacetic acid was used for the deprotection at the N-terminals. The pentapeptide thus obtained was deblocked first at the C-terminal under alkaline conditions, and then at the N-terminal under acidic conditions. The resulting linear precursor was cyclized with DPPA in the presence of sodium hydrogen carbonate[7] in DMF, giving avellanin B (**2**), which was identical with the natural sample on comparison of the thin layer chromatography (TLC) behavior and proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectra. Thus, the absolute stereostructure avellanin B has been clearly established as **2**.

Analogously, avellanin A (**1**) was synthesized by use of Fmoc–L-Ile–Cl in place of Fmoc–L-Val–Cl, as shown in Chart 2 (yields in each step are shown in parenthesis). The synthetic cyclic peptide was identical with natural avellanin A (**1**).

This synthesis, easily carried out on a large scale, will aid investigations of the biological activities in more detail and may afford a convenient route to other cyclic peptides containing anthranilic acid, such as aspercolorin[8] and cycloaspeptides.[9]

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 or IR-810 spectrophotometer using potassium bromide disks or as films. ^{1}H-NMR spectra were recorded on a JEOL PMX-60 or GSX-400 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. Silica gel (BW-820MH or BW-200, purchased from Fuji-Davison) was used for column chromatography.

Coupling of Boc–L-Val–OH with H–Ant–OMe (i) With DCC–DMAP: DCC (4.51 g, 21.9 mmol) was added to a solution of Boc–L-Val–OH (9.64 g, 44.4 mmol) in dichloromethane (100 ml) at room temperature. After vigorous stirring for 30 min, the precipitated urea was removed by filtration, and the solution was concentrated to half the initial volume *in vacuo*. H–Ant–OMe (2.20 g, 14.6 mmol) was added to the solution, followed by the addition of DMAP (0.18 g, 1.5 mmol) and diisopropylethylamine (2.6 ml, 15 mmol) with ice-cooling. The mixture was stirred with ice-cooling for 1 h, then at room temperature for 1 d. The reaction mixture was diluted with ethyl acetate–benzene (2 : 1, 700 ml) and washed with 10% citric acid, water, saturated aqueous sodium hydrogen carbon-

Dedicated to Professor Haruaki Yajima on the occasion of his retirement from Kyoto University in March, 1989.

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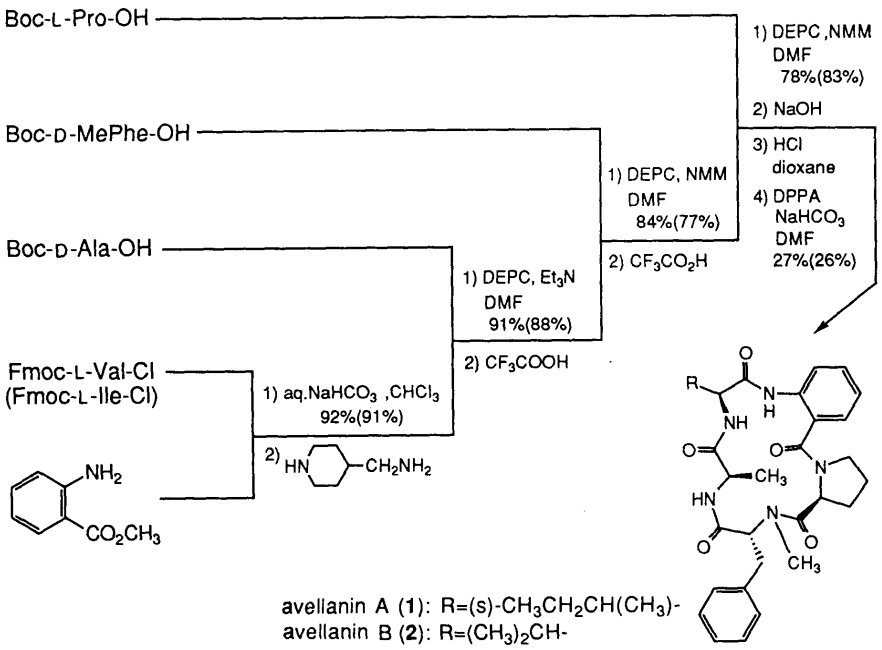

Chart 2

ate, water, and saturated aqueous sodium chloride. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by recrystallization from ether–hexane to give colorless crystals (4.35 g, 83%).

(ii) With DCC: The reaction was carried out as in the case of (i) in the absence of DMAP, using Boc-L-Val-OH (326 mg, 1.50 mmol), DCC (150 mg, 0.728 mmol), H-Ant-OMe (75 mg, 0.497 mmol), and diisopropylethylamine (87 μl, 0.50 mmol). After 2 d, work-up as above and then column chromatographic purification gave colorless crystals (148 mg, 85%).

Fmoc-L-Val-Ant-OMe A solution of Fmoc-L-Val-Cl[6] (7.10 g, 19.7 mmol) in chloroform (100 ml) and 10% aqueous sodium hydrogen carbonate (150 ml) were added to H-Ant-OMe (2.48 g, 16.4 mmol) in chloroform (160 ml). After vigorous stirring for 10 min, the organic layer was separated, and *N*-methylpiperazine (0.5 ml) was added with brisk stirring followed by immediate extraction with 5% aqueous hydrochloric acid. The organic layer was successively washed with water, saturated aqueous sodium hydrogen carbonate, water, and saturated aqueous sodium chloride. After being dried over sodium sulfate, the mixture was concentrated to give the residue, which was purified by recrystallization from dichloromethane–hexane to give colorless needles (7.12 g, 92%), mp 194—196 °C. $[\alpha]_D^{24}$ −13.1° (c=1.05, CH_2Cl_2). IR ν_{max} cm^{-1}: 3400, 1740, 1680, 1550, 1470, 1310, 1280, 760. NMR δ: 0.97 (3H, d, J=6 Hz), 1.08 (3H, d, J=6 Hz), 2.52—2.69 (1H, m), 3.77 (3H, s), 3.97—4.56 (4H, m), 5.26—5.67 (1H, m), 6.83—7.76 (10H, m), 7.93 (1H, d, J=8 Hz), 8.66 (1H, d, J=8 Hz), 11.50 (1H, s). *Anal.* Calcd for $C_{28}H_{28}N_2O_5$: C, 71.17; H, 5.98; N, 5.93. Found: C, 71.03; H, 5.85; N, 5.87.

Fmoc-L-Ile-Ant-OMe The synthesis was carried out as described for the synthesis of Fmoc-L-Val-Ant-OMe using Fmoc-L-Ile-Cl[6] (300 mg, 0.878 mmol), H-Ant-OMe (120 mg, 0.795 mmol), and 10% aqueous sodium hydrogen carbonate (10 ml) in chloroform. Work-up as above gave colorless needles (354 mg, 91%), mp 146—148 °C. $[\alpha]_D^{23}$ −3.7° (c=1.0, CH_2Cl_2). IR ν_{max} cm^{-1}: 3250, 1720, 1660, 1510, 1440, 1090, 740. NMR δ: 0.80—1.77 (5H, m), 1.00 (3H, d, J=6 Hz), 1.80—2.33 (1H, m), 3.80 (3H, s), 4.06—4.64 (4H, m), 5.64 (1H, d, J=8 Hz), 6.88—7.88 (10H, m), 7.97 (1H, dd, J=8, 2 Hz), 8.73 (1H, d, J=8 Hz), 11.50 (1H, br). *Anal.* Calcd for $C_{29}H_{31}N_2O_5$: C, 71.44; H, 6.41; N, 5.75. Found: C, 71.24; H, 6.16; N, 5.71.

General Procedure for the Formation of Peptide Bonds with DEPC (a) Removal of the Fmoc Group from Fmoc-L-Val-Ant-OMe or Fmoc-L-Ile-Ant-OMe: A sample (1 mmol) of Fmoc-L-Val-Ant-OMe or Fmoc-L-Ile-Ant-OMe was dissolved in chloroform (10 ml) and treated with 4-aminomethylpiperidine (3 ml), followed by stirring for 1 h. The reaction mixture was diluted with chloroform (100 ml) and washed with water (2 × 50 ml), phosphate buffer (pH 5.4, 2 × 50 ml), and water. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was directly used for the coupling.

(b) Removal of the Boc Group: A sample (10 mmol) of the Boc-peptide was stirred with trifluoroacetic acid (10 ml) for 40 min. The reaction mixture was concentrated *in vacuo*, and saturated aqueous sodium hydrogen carbonate (10 ml) was added. The mixture was extracted with dichloromethane (3 × 30 ml). The organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was directly used for the coupling.

(c) Coupling with the Amino Acid: DEPC (1.1 eq) was added to an ice-cooled mixture of the amino and carboxyl components in DMF, followed by the addition of TEA (1 eq) or NMM (1 eq). The mixture was stirred with ice-cooling for 2 h, then at room temperature overnight. The mixture was diluted with ethyl acetate–benzene (2 : 1, ten times the quantity of DMF), and washed successively with 10% aqueous citric acid, water, saturated aqueous sodium hydrogen carbonate, water, and saturated aqueous sodium chloride. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography and/or recrystallization.

Boc-D-Ala-L-Val-Ant-OMe The reaction was carried out according to the general procedure using Boc-D-Ala-OH (190 mg, 1.00 mmol), H-L-Val-Ant-OMe (265 mg, 1.05 mmol), DEPC (170 μl, 1.12 mmol), and TEA (140 μl, 1.00 mmol) in DMF (2 ml). Work-up as usual quantitatively gave Boc-D-Ala-L-Val-Ant-OMe, mp 155—156 °C. $[\alpha]_D^{22}$ +11.7° (c=1.02, $CHCl_3$). IR ν_{max} cm^{-1}: 3300, 2900, 1700, 1640, 1510, 1260, 1160, 750. NMR δ: 0.95 (3H, d, J=6 Hz), 1.03 (3H, d, J=6 Hz), 1.39 (9H, s), 1.18—1.64 (3H, m), 2.00—2.66 (1H, m), 3.91 (3H, s), 4.06—4.63 (2H, m), 5.33 (1H, d, J=8 Hz), 6.66—7.66 (3H, m), 8.00 (1H, d, J=8 Hz), 8.73 (1H, d, J=8 Hz), 11.33 (1H, br). *Anal.* Calcd for $C_{21}H_{31}N_3O_6$: C, 59.84; H, 7.41; N, 9.97. Found: C, 59.94; H, 7.28; N, 9.88.

Boc-D-Ala-L-Ile-Ant-OMe The reaction was carried out accoding to the general procedure using Boc-D-Ala-OH (189 mg, 1.00 mmol), H-L-Ile-Ant-OMe (290 mg, 1.01 mmol), DEPC (170 μl, 1.12 mmol), and TEA (140 μl, 1.00 mmol) in DMF (2 ml). Column chromatographic purification with ethyl acetate–hexane (1 : 2) gave a white powder (385 mg, 88%), mp 138—139 °C (ethyl acetate–hexane). $[\alpha]_D^{23}$ +16.6° (c=0.30, $CHCl_3$). IR ν_{max} cm^{-1}: 3300, 2950, 1710, 1640, 1510, 1440, 1270, 1170, 760. NMR δ: 0.74—1.77 (11H, m), 1.40 (9H, s), 1.77—2.44 (1H, m), 3.87 (3H, s), 4.17—4.66 (2H, m), 5.60 (1H, d, J=8 Hz), 6.74—7.64 (3H, m), 7.94 (1H, dd, J=8, 2 Hz,), 8.66 (1H, d, J=8 Hz), 11.40 (1H, br). *Anal.* Calcd for $C_{22}H_{33}N_3O_6$: C, 60.67; H, 7.64; N, 9.65. Found: C, 60.40; H, 7.40; N, 9.61.

Boc-D-MePhe-D-Ala-L-Val-Ant-OMe The reaction was carried out according to the general procedure using Boc-D-MePhe-OH (447 mg, 1.60 mmol), H-D-Ala-L-Val-Ant-OMe (529 mg, 1.65 mmol), DEPC (270 μl, 1.78 mmol), and NMM (180 μl, 1.64 mmol) in DMF (3 ml). Column chromatographic purification with ethyl acetate–hexane (1 : 1) gave a colorless amorphous powder (785 mg, 84%), $[\alpha]_D^{23}$ +30.1° (c=1.00, $CHCl_3$). IR ν_{max} cm^{-1}: 3300, 2950, 1700, 1600, 1500, 1450, 1260, 1100, 760,

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700. NMR δ: 0.94 (3H, d, J=6 Hz), 1.00 (3H, d, J=6 Hz), 1.33 (9H, s), 1.46 (3H, d, J=7 Hz), 2.10—2.60 (1H, m), 2.74 (3H, s), 3.06—3.36 (2H, m), 3.83 (3H, s), 4.26—5.00 (3H, m), 6.66—7.23 (3H, m), 7.10 (5H, s), 7.47 (1H, dt, J=8, 2 Hz), 7.93 (1H, dd, J=8, 2 Hz), 8.63 (1H, d, J=8 Hz), 11.33 (1H, br).

Boc-D-MePhe-D-Ala-L-Ile-Ant-OMe The reaction was carried out according to the general procedure using Boc-D-MePhe-OH (303 mg, 1.09 mmol), H-D-Ala-L-Ile-Ant-OMe (354 mg, 1.09 mmol), DEPC (185 μl, 1.22 mmol), and NMM (120 μl, 1.09 mmol) in DMF (4 ml). Column chromatographic purification with ethyl acetate–hexane (2:3) gave a colorless amorphous powder (506 mg, 77%), $[\alpha]_D^{23}$ +36.7° (c=0.50, $CHCl_3$). IR ν_{max} cm^{-1}: 3300, 2950, 1710, 1520, 1460, 1270, 1100, 760, 720. NMR δ: 0.74—1.87 (1H, m), 1.33 (9H, s), 1.90—2.50 (1H, m), 2.76 (3H, s), 3.10—3.46 (2H, m), 3.87 (3H, s), 4.46—5.10 (3H, m), 6.80—7.33 (3H, m), 7.13 (5H, s), 7.50 (1H, dt, J=8, 2 Hz), 8.00 (1H, dd, J=8, 2 Hz), 8.66 (1H, d, J=8 Hz), 11.33 (1H, br).

Boc-L-Pro-D-MePhe-D-Ala-L-Val-Ant-OMe The reaction was carried out according to the general procedure using Boc-L-Pro-OH (250 mg, 1.27 mmol), H-D-MePhe-D-Ala-L-Val-Ant-OMe (769 mg, 1.27 mmol), DEPC (210 μl, 1.38 mmol), and NMM (140 μl, 1.28 mmol) in DMF (2 ml). Column chromatographic purification with ethyl acetate–hexane (1:1) gave a white powder (766 mg, 89%), mp 82—84 °C (ether–hexane). $[\alpha]_D^{23}$ +39.5° (c=1.00, $CHCl_3$). IR ν_{max} cm^{-1}: 3250, 2950, 1680, 1510, 1440, 1390, 1260, 1160, 750, 700. NMR δ: 1.00 (3H, d, J=6 Hz), 1.07 (3H, d, J=6 Hz), 1.40 (9H, s), 1.20—2.57 (8H, m), 2.97 (3H, s), 3.07—3.66 (4H, m), 3.90 (3H, s), 4.17—4.83 (3H, m), 5.34—5.77 (1H, m), 6.80—7.66 (4H, m), 7.10 (5H, s), 8.10 (1H, dd, J=8, 2 Hz), 8.40 (1H, d, J=8 Hz), 11.33 (1H, br). *Anal.* Calcd for $C_{36}H_{49}N_5O_8$: C, 63.61; H, 7.26; N, 10.30. Found: C, 63.65; H, 7.02; N, 10.25.

Boc-L-Pro-D-MePhe-D-Ala-L-Ile-Ant-OMe The reaction was carried out according to the general procedure using Boc-L-Pro-OH (170 mg, 0.854 mmol), H-D-MePhe-D-Ala-L-Ile-Ant-OMe (437 mg, 0.847 mmol), DEPC (145 μl, 0.956 mmol), and NMM (95 μl, 0.85 mmol) in DMF (2 ml). Recrystallization from ether–hexane gave colorless needles (490 mg, 83%), mp 75—76 °C. $[\alpha]_D^{23}$ +42.4° (c=0.54, $CHCl_3$). IR ν_{max} cm^{-1}: 3300, 2950, 1690, 1510, 1450, 1400, 1270, 1160, 760, 700. NMR δ: 0.66—2.17 (16H, m), 1.30 (9H, s), 2.83 (3H, s), 2.97—3.56 (4H, m), 3.93 (3H, s), 4.07—4.66 (3H, m), 5.17—5.66 (1H, m), 6.65—7.53 (4H, m), 7.00 (5H, s), 7.83 (1H, d, J=8 Hz), 8.57 (1H, d, J=8 Hz), 11.13 (1H, br). *Anal.* Calcd for $C_{37}H_{51}N_5O_8$: C, 64.05; H, 7.41; N, 10.09. Found: C, 63.96; H, 7.33; N, 10.14.

General Procedure for the Cyclization with DPPA (a) Saponification of the Boc-Pentapeptide-OMe (Boc-L-Pro-D-MePhe-D-Ala-L-Val (or L-Ile)-Ant-OMe): A solution of the Boc-pentapeptide-OMe in DMF was cooled in an ice bath. Sodium hydroxide (1 N, 1.2 eq) was added, and the mixture was stirred with ice-cooling for 1 h, then 1 N hydrochloric acid (1.2 eq) was added. The mixture was diluted with ethyl acetate–benzene (2:1, ten times the quantity of DMF), and washed with water and saturated aqueous sodium chloride. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was directly used for the next step.

(b) Removal of the Boc Function: The crude product obtained as above was dissolved in 4 N hydrogen chloride–dioxane (30 eq). The mixture was stirred at room temperature for 1 h, and concentrated *in vacuo*. The residue was washed with dry diethyl ether three times and dried *in vacuo* to give the crystalline pentapeptide hydrochloride.

(c) Cyclization with DPPA: A solution of the pentapeptide hydrochloride in DMF was added to an ice-cooled mixture of sodium hydrogen carbonate (7 eq) and DPPA (2 eq) in DMF under Ar. The mixture was stirred at room temperature for 1 d, filtered, and concentrated *in vacuo*. Ethyl acetate–benzene (2:1) was added to the residue, and the mixture was successively washed with water, saturated aqueous sodium hydrogen carbonate, water, 10% aqueous citric acid, water, and saturated aqueous sodium chloride. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography and recrystallization.

Avellanin B (2) The reaction was carried out according to the general procedure using HCl·H-L-Pro-D-MePhe-D-Ala-L-Val-Ant-OH (468 mg, 0.92 mmol), DPPA (0.4 ml, 2.00 mmol), and sodium hydrogen carbonate (540 mg, 6.43 mmol) in DMF (90 ml). Column chromatographic purification with ethyl acetate–hexane (3:1) afforded a colorless powder (140 mg, 27%). Recrystallization from acetone–hexane gave colorless plates (93 mg), mp 239—241 °C. $[\alpha]_D^{23}$ +203.8° (c=0.17, $CHCl_3$) (lit.[3] $[\alpha]_D^{24}$ +282° (c=0.17, $CHCl_3$)). IR ν_{max} cm^{-1}: 3350, 2950, 1680, 1580, 1520, 1490, 1420, 1300, 750, 700. NMR δ: 0.93 (3H, d, J=7.0 Hz), 0.99 (3H, d, J=7.0 Hz), 1.47—1.55 (1H, m), 1.53 (3H, d, J=7.2 Hz), 1.82—1.91 (1H, m), 1.95—2.19 (2H, m), 2.56—2.68 (1H, m), 2.98 (1H, dd, J=15.9, 12.6 Hz), 3.03 (3H, s), 3.50—3.66 (2H, m), 3.85 (1H, dd, J=16.0, 4.7 Hz), 4.64 (1H, dd, J=9.4, 3.6 Hz), 4.73 (1H, dd, J=8.7, 2.1 Hz), 4.82—4.92 (1H, m), 5.78 (1H, dd, J=12.6, 4.6 Hz), 6.49 (1H, d, J=9.3 Hz), 7.09 (1H, t, J=7.6 Hz), 7.18—7.34 (6H, s), 7.40—7.46 (2H, m), 8.44 (1H, d, J=8.5 Hz), 9.75 (1H, br). *Anal.* Calcd for $C_{30}H_{37}N_5O_5$: C, 65.80; H, 6.81; N, 12.79. Found: C, 65.88; H, 6.85; N, 12.68.

Avellanin A (1) The reaction was carried out according to the general procedure using HCl·H-L-Pro-D-MePhe-D-Ala-L-Ile-Ant-OH (395 mg, 0.60 mmol), DPPA (0.26 ml, 1.20 mmol), and sodium hydrogen carbonate (353 mg, 4.20 mmol) in DMF (60 ml). Column chromatographic purification with ethyl acetate–hexane (3:1) furnished a colorless powder (89 mg, 26%). Recrystallization from acetone–hexane gave colorless plates (70 mg), mp 199—201 °C. $[\alpha]_D^{23}$ +183° (c=0.50, $CHCl_2$) (lit.[2] mp 202—204 °C, $[\alpha]_D^{24}$ +162° (c=0.50, $CHCl_3$)). IR ν_{max} cm^{-1}: 3350, 1680, 1610, 1580, 1520, 1420, 1300, 750, 700. NMR δ: 0.93 (3H, t, J=7.3 Hz), 0.97 (3H, d, J=6.8 Hz), 1.10—1.21 (1H, m), 1.40—1.54 (2H, m), 1.52 (3H, d, J=7.3 Hz), 1.82—1.92 (1H, m), 1.96—2.28 (2H, m), 2.24—2.34 (1H, m), 2.97 (1H, dd, J=15.9, 12.8 Hz), 3.02 (3H, s), 3.50—3.67 (2H, m), 3.83 (1H, dd, J=15.9, 4.7 Hz), 4.67—4.76 (2H, m), 4.84—4.94 (1H, m), 5.78 (1H, dd, J=12.6, 4.8 Hz), 6.47 (1H, d, J=9.5 Hz), 7.08 (1H, t, J=7.5 Hz), 7.18—7.36 (6H, m), 7.40—7.47 (2H, m), 8.45 (1H, d, J=8.4 Hz), 9.79 (1H, br). *Anal.* Calcd for $C_{31}H_{39}N_5O_5$: C, 66.29; H, 7.00; N, 12.47. Found: C, 66.37; H, 6.80; N, 12.49.

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