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SYNTHESIS OF THYMINE POLYOXIN C BY USING L-THREONINE ALDOLASE-CATALYZED ALDOL REACTION

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Abstract – Thymine polyoxin C (**2**), a common partial structure of polyoxin H (**3**) and J (**4**) having anti-fungal activity, was formally synthesized from D-ribose in good overall yield by using L-threonine aldolase-catalyzed reaction as a key step, which affords novel β-hydroxy-α-L-amino acids from glycine and aldehydes in an aqueous medium.

INTRODUCTION

Polyoxins, belonging to a class of peptidyl analogs of nucleotides, were isolated from culture broth of *Streptomyces cacaoi* var. *asoensis*[1-5] in the study to investigate antibiotics having a preventive effect against sheath-blight disease of rice plants caused by a pathogenic fungus, *Pellicularia filamentosa f. sasakii*.[6, 7] Polyoxin C (**1**) has the simplest structure among the polyoxins identified to date, being considered to be an artificial component generated during isolation.[2, 3] Moreover, deoxypolyoxin C (**2**) referred to thymine polyoxin C is a common component of polyoxins H (**3**) and J (**4**) that are practical antifungi agents in the clinical treatment of human skin diseases caused by *Candida* sp. (Figure 1).

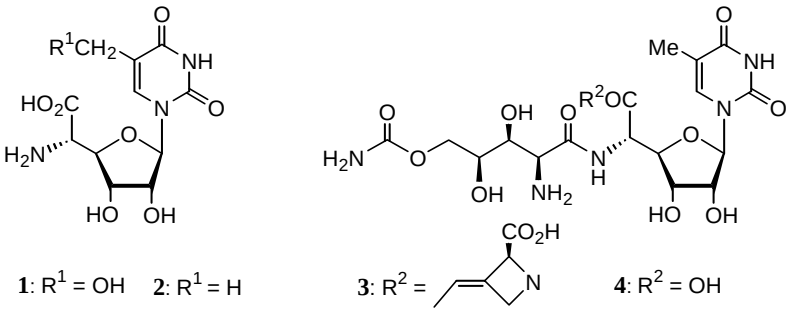


Figure 1 Structure of Deoxypolyoxin C (2) and Its Related Compounds

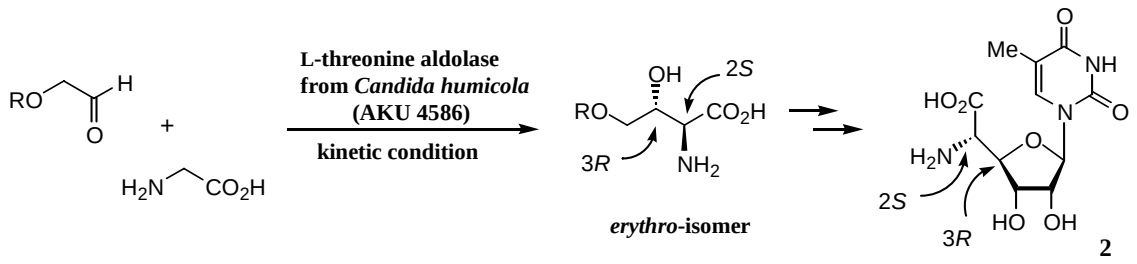
The first synthesis of thymine polyoxin C (**2**) was reported by Kuzuhara and his colleagues starting with a D-allofuranose derivative[7] in advance of a total synthesis of polyoxin J (**4**).[8] In the last decade of the twenty century, many groups reported the synthesis of **2**,[9-25] and some of the groups also achieved the total synthesis of **4** *via* **2**. For example, Ghosh and Wang explored the advantage of [2,3]-Wittig-Still rearrangement to control the stereochemistry of the amino acid moiety on the C-5 of the D-ribofuranose ring.[19, 20] Meanwhile, Garner and Park employed a penaldic acid equivalent, called Garner's aldehyde, as a starting material for the effective synthesis of a key intermediate, glycosyl amino acid. [10, 11] In recent, novel [3+2] cycloaddition of 2-trimethylsilyloxyfuran to a chiral nitrone was developed for targeting polyoxin C.[26] Moreover, Southard and his colleagues established a method where the trimethylsilyloxyfuran was chosen as a four-carbon synthon, and succeeded in the synthesis of **2**.[27]

On the basis of this background, we also embarked on the total synthesis of thymine polyoxin C (**2**) as a part of our synthetic study of bioactive compounds having β-hydroxy-α-L-amino acid moieties, which can be facilely prepared by using L-threonine aldolase-catalyzed reaction.[28, 29] It should be first emphasized that our strategy would offer a most practical method to synthesize all polyoxins as well as **2** because of adapting the enzyme-catalyzed reaction as a key step, which is attainable in an aqueous solution at room temperature.

RESULTS AND DISCUSSION

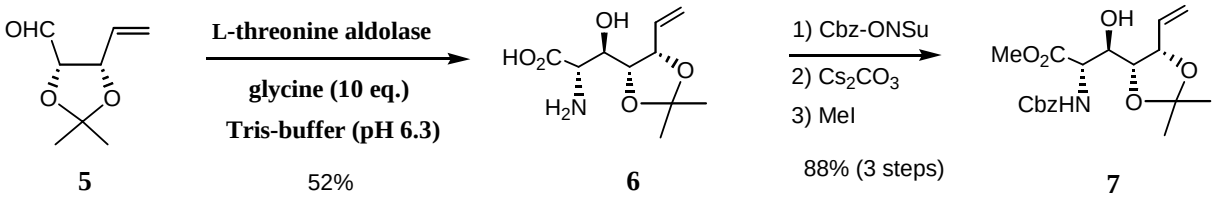
Since thymine polyoxin C (**2**) can be considered as a complex amino acid comprised of nor-thymidine and glycine, it seemed rational to assemble the structure of **2** by aldol condensation where the enolate source is glycine or by carbon-carbon bond forming reaction with amino acid derivatives. Within the synthesis of **2** reported up to date,[9-27] only the Garner route[20] started with an amino acid derivative. Namely, the protocol introduced the β-hydroxy-α-L-amino acid moiety by the nucleophilic attack of a carbanion to the Garner aldehyde prepared from D-serine; however, the reaction afforded a mixture of diastereomers (8 : 1 to 14 : 1) having an epimeric chiral center on the newly generated hydroxyl group.

Meanwhile, the L-threonine aldolase-catalyzed reaction developed by one of the authors can afford a single isomer depending on the structure of aldehyde substrates or by controlling the reaction conditions either kinetically or thermodynamically.[28, 29] In general, under kinetically controlled conditions, the enzyme-catalyzed aldol reaction of glycine and aldehyde carrying an oxygen functional group on the α-carbon has a tendency to afford a single isomer of β-hydroxy-α-L-amino acid with *erythro*-configuration, *i.e.*, (2*S*, 3*R*)-isomer in good yield. Because thymine polyoxin C (**2**) has a (2*S*, 3*R*)-β-hydroxy-α-amino acid moiety in the structure, the L-threonine aldolase-catalyzed reaction would be applicable to establish a facile and short step synthesis of **2** (Scheme 1).



Scheme 1 L-Threonine Aldolase-Catalyzed Reaction and Its Application for the Synthesis of **2**

In addition, thymidine is a nucleoside comprised of thymine and D-ribose as a nucleic base and a sugar moiety, respectively. Therefore, an aldehyde substrate (**5**) of L-threonine aldolase was prepared from a chiral building block having the same set of configurations with D-ribose by the Jeong method.[30] Thus, the aldehyde (**5**) was condensed with glycine in the presence of L-threonine aldolase prepared from *Candida humicola* (AKU 4586)[28] to afford a novel β-hydroxy-α-L-amino acid (**6**) as a single isomer, of which amino group and carboxylic acid were successively protected with carboxybenzyl (Cbz) and methyl groups to yield **7** (Scheme 2). The configuration of the newly generated hydroxyl group of **6** was determined to be *R* by applying modified Moscher's method[31] to the protected amino acid **7** (Figure 2). In this stage, the stereochemistry of **6** was presumed as 2*S*, 3*R*, which would be confirmed later on (*vide infra*).



Scheme 2 L-Threonine Aldolase-Catalyzed Reaction of **5** and Protection of the Aldol Product **6**

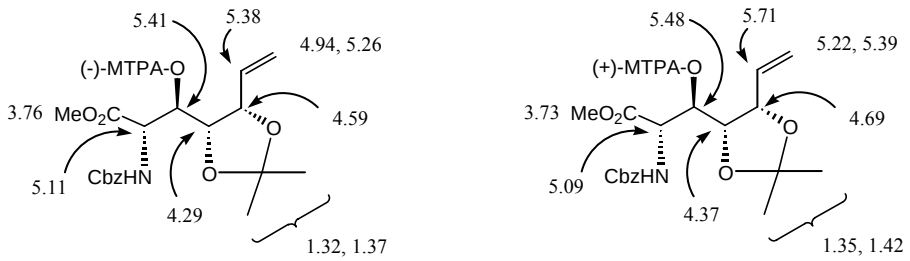
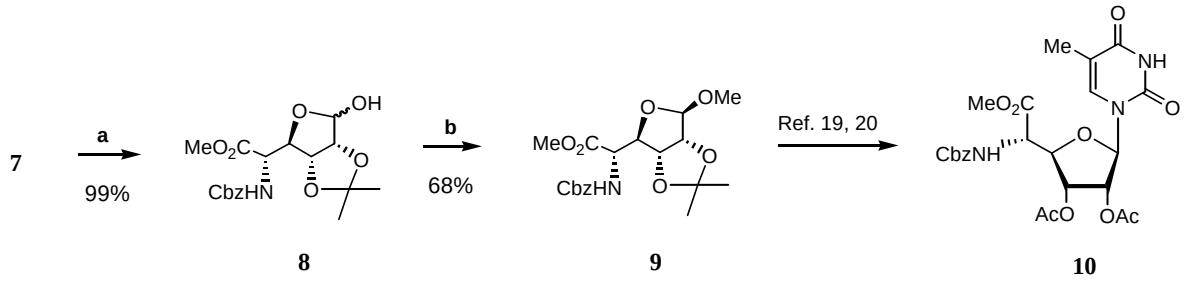


Figure 2 Comparison of the ^{1}H-NMR Signals of MTPA Esters of **7**

Herein, it is worthy emphasizing that aldehyde **5** was the first substrate which was converted to an appropriate amino acid in good yield by the L-threonine aldolase catalyzed reaction in spite of having a

secondary alkoxy group on the α-carbon.

Further ozonolysis of compound **7** followed by reductive treatment of ozonide gave an amino acid bearing a D-ribose unit on the side chain (**8**). Treatment of **8** with methyl orthoformate in the presence of Amberlyst 15 gave methyl acetal (**9**). Conversion of **9** to a fully protected thymine polyoxin (**10**), including the Vorbrügen reaction,[32] was already reported by Ghosh and colleagues.[20] Moreover, transformation of **10** to **2** by the standard method was also reported by Garner and Park.[10, 11]



a: O_3 then PPh_3, b: Amberlyst 15, $HC(OMe)_3$, CCl_4.

Scheme 3 Synthetic Route to Fully Protected Deoxypolyoxin C (10) from 7

In conclusion, we succeeded in the formal synthesis of thymine polyoxin C (**2**) by using L-threonine aldolase-catalyzed reaction. Our method provided an effective and facile conversion of the known aldehyde (**5**) to the key intermediates in the synthetic route of **2**, which was reported by Ghosh and Wang.[19, 20] Presumable application of our method to the Ghosh route improved the overall yield from D-ribose to **2** until higher than 5% within 15 steps. Since the aldolase-catalyzed reaction can be attained in an aqueous medium and at room temperature, application of our method to the synthesis of polyoxins could make the synthetic routes short and make the synthetic protocol attainable on an industrial scale.

EXPERIMENTAL

General. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^{1}H-NMR spectra were obtained on a JEOL JNM-AL400 spectrometer with tetramethylsilane as an internal standard. ^{13}C-NMR spectra were obtained on a JEOL JNM-AL400 spectrometer with $CDCl_3$ as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Kiesel gel Art-7734 (70-230 mesh), Art-9385 (230-400 mesh) (Merck), and ODS gel (100-200 mesh; Chromatorex ODS DM1020T) (Fuji Silysia Chemical Ltd.) were used for open column chromatography. Kieselgel 60 F-254 plate and RP-18 F-254s plate (Merck) were used for thin layer chromatography (TLC). Preparative TLC (PTLC) was conducted with Kieselgel

60 F-254 plate (0.25 mm, Merck) or Silica gel 60 F-254 plate (0.5 mm, Merck). Unless purification with silica gel gave compound being pure enough, the compounds were further treated with a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H).

(2*S*,3*R*,4*S*,5*S*)-2-amino-3-hydroxy-4,5-*O*-isopropyriden-6-hepten-1-oic acid (6)

To a Tris-buffer solution including L-threonine aldolase (265 mL) prepared as in the literature,[28] compound **5** (760 mg, 4.86 mmol) dissolved in DMSO (10 mL), potassium chloride (2.24 g), pyridoxal-5' phosphate (42 mg), and glycine (3.93 g, 52.4 mmol) were added and the pH of the solution was adjusted to 6.3 with 1 M HCl. After incubating the reaction mixture for 22 hours, the mixture was heated at 100°C for 30 min and filtered through Celite®. The filtrate was charged on ODS column chromatography and eluted with distilled water. Fractions containing **6** as a single spot was collected and lyophilized to afford **6** (589 mg, 52%) as an amorphous powder, which was recrystallized from EtOH to yield pure **6** as colorless needles; $[\alpha]_D^{26}$ +27.8 (*c* 0.90, H_2O); ^{1}H-NMR (300MHz, D_2O), δ: 1.28, 1.36 (each s, 3H), 3.80 (d, *J* = 2.7 Hz, 1H, α-H), 3.97 (dd, *J* = 9.9, 2.7 Hz, 1H, β-H), 4.29 (dd, *J* = 9.9, 6.6 Hz, 1H, γ-H), 4.71 (dd, *J* = 7.2, 6.6 Hz, 1H, δ-H), 5.26 (d, *J* = 10.2 Hz, 1H, CH*H*=CH), 5.33 (d, *J* = 17.1, 1H, CH*H*=CH), 5.85 (ddd, *J* = 17.1, 10.2, 7.2 Hz, 1H, CH_2=C*H*); ^{13}C-NMR (75 MHz, D_2O) δ: 25.0, 27.2, 58.1, 68.5, 77.1, 79.2, 110.3, 120.5, 132.5, 171.5; IR (KBr): 3256, 3034, 2990, 2939, 2885, 2569, 2473, 2362, 2343, 1634, 1587, 1419, 1419, 1385, 1342, 1323, 1242, 1218 cm^{-1}; MS (FAB) *m/z*: 232 ($M+H^+$); HRMS (FAB) Found *m/z*: 232.1185 (Calcd for $C_{10}H_{18}NO_5$: 232.1190); *Anal.* Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.96; H, 7.44; N, 6.03.

Methyl (2*S*,3*R*,4*S*,5*S*)-2-*N*-carboxybenzylamido-3-hydroxy-4,5-*O*-isopropyriden-6-hepten-1-oate (7)

Benzylcarboxy-*N*-hydroxysuccinimide (87.6 mg, 0.35 mmol) was added to a solution of **6** (74.2 mg, 0.32 mmol) in acetone and a saturated aqueous Na_2CO_3 (each 5 mL), and the reaction mixture was stirred for 4 h at rt. After the reaction, the pH of the reaction mixture was adjusted to 7.0 with 1 M HCl and the mixture was extracted with AcOEt. The organic layer was washed with a saturated aqueous NaCl, dried over $MgSO_4$, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 1, and then $CHCl_3$: MeOH = 1 : 1) to afford Cbz-protected amino acid. The Cbz-protected amino acid was dissolved in an aqueous MeOH (8.0 mL), to which Cs_2CO_3 (57.3 mg, 0.175 mmol) was added portionwise. After stirring the mixture for 30 min at rt, the pH of the solution was adjusted to 7.0 with 1 M HCl and the mixture was freeze dried. Next, the residual powder was dissolved in DMF (5.0 mL), to which MeI (22 μL, 0.353 mmol) was added. The reaction mixture was stirred for 4 h at rt and partitioned between water and Et_2O. The organic layer was washed with water and a saturated aqueous NaCl, dried over $MgSO_4$, and condensed *in vacuo*. The residue was purified by silica gel column

chromatography (hexane : AcOEt = 3 : 1) to afford **7** (106.7 mg, 88%) as a colorless oil; $[\alpha]_D^{26}$ +59.8 (*c* 0.92, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 1.34, 1.41 (each s, 3H), 3.47 (br d, *J* = 5.2, 1H, -OH), 3.76 (s, 3H, CO_2Me), 4.09-4.15 (m, 2H), 4.69 (d, *J* = 7.6 Hz, 1H), 4.72 (br t, *J* = 6.4 Hz, 1H), 5.14 (s, 2H, -*CH*$_2$Ph), 5.31 (td, *J* = 10.4, 1.4 Hz, 1H, CH*H*=CH), 5.45 (td, *J* = 17.0, 1.4 Hz, 1H, CH*H*=CH), 5.83 (br d, *J* = 6.8 Hz, 1H, -NH), 6.00 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H, CH_2=C*H*), 7.31-7.40 (m, 5H, -Ph); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 25.1, 27.4, 52.6, 57.7, 67.5, 71.6, 77.2, 78.2, 108.9, 118.1, 128.2 (2C), 128.3, 128.6 (2C), 133.1, 135.8, 157.3, 169.7; IR ($CHCl_3$): 3423, 3090, 3066, 3026, 3011, 2991, 2954, 2939, 1748, 1720, 1645, 1602, 1510, 1456, 1439, 1382, 1375, 1348, 1240 cm^{-1}; MS (FAB) *m/z*: 380 ($M+H^+$); HRMS (FAB) Found *m/z*: 380.1702 (Calcd for $C_{19}H_{26}NO_7$: 380.1709).

Methyl 5-*N*-carboxybenzylamido-5-deoxy-2,3-*O*-isopropylidene-D-*allo*-furanosiduronate (8)

Ozone gas was bubbled to a solution of compound **7** (30.8 mg, 0.081 mmol) in CH_2Cl_2 (10 mL) at -78°C until a pale purple color was maintained in the solution. After removing an excess amount of ozone from the reaction mixture by bubbling nitrogen gas, triphenylphosphine (43 mg, 0.16 mmol) was added and the mixture was stirred for 1day at rt. The organic solvent was evaporated off and the residue was purified by silica gel column chromatography (hexane : AcOEt = 3 : 1) to afford **8** (30.8 mg, 99%) as a colorless oil; $[\alpha]_D^{24}$ +21.5 (*c* 0.98, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31, 1.45 (each s, 3H), 3.15 (br s, 1H, -OH), 3.76 (s, 3H, CO_2Me), 4.23 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.62 (m, 2H), 4.94 (br d, *J* = 5.6 Hz, 1H), 5.10 (d, A part of AB, *J* = 12.0 Hz, 1H, -CH*H*Ph), 5.14 (d, B part of AB, *J* =12.0 Hz, 1H, -C*H*HPh), 5.46 (d, *J* = 2.0 Hz, 1H, H-1), 5.59 (d, *J* = 7.6 Hz, 1H, -NH), 7.31-7.39 (m, 5H, Ph); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.4, 52.8, 56.9, 67.4, 81.9, 85.6, 87.7, 103.3 (C-1), 112.7, 128.2, 128.3 (2C), 128.5 (2C), 135.9, 155.6, 170.7; IR ($CHCl_3$): 3676, 3595, 3510, 3429, 3350, 3091, 3068, 3030, 3010, 2993, 2957, 2853, 1724, 1602, 1587, 1510, 1456, 1439, 1375, 1344, 1375, 1298, 1273 cm^{-1}; MS (FAB) *m/z*: 382 ($M+H^+$); HRMS (FAB) Found *m/z*: 382.1495 (Calcd for $C_{18}H_{24}NO_8$: 382.1502).

Methyl (methyl 5-*N*-carboxybenzylamido-5-deoxy-2,3-*O*-isopropylidene-D-*allo*-furanosid)uronate (9)[20]

Amberlyst 15 (H^+ form) (40 mg) and methyl orthoformate (19 μL) were added to a solution of compound **8** (43 mg, 0.11 mmol) in CCl_4 (3.0 ml) at rt, and the mixture was stirred for 1 day at rt. After the reaction, the reaction mixture was filtered and the filtrate was condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 3 : 1) to afford **9** (30.5 mg, 68%) as a colorless oil; $[\alpha]_D^{26}$ -20.4 (*c* 1.36, $CHCl_3$) [lit.[20], $[\alpha]_D^{23}$ -14.0 (*c* 2.81, $CHCl_3$)]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30, 1.46 (each s, 3H), 3.32 (s, 3H, OMe), 3.76 (s, 3H, CO_2Me), 4.34 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.49 (br t, *J* = 8.0 Hz, 1H), 4.56 (br d, *J* = 5.6 Hz, 1H), 4.94 (br d, *J* = 5.6 Hz, 1H), 4.96 (s, 1H), 5.10 (d, A part of AB, *J*

= 12.4 Hz, 1H, -CH*H*Ph), 5.14 (d, B part of AB, *J* = 12.4 Hz, 1H, -C*H*HPh), 5.51 (br d, *J* = 8.0 Hz, 1H, -NH), 7.30-7.39 (m, 5H, Ph); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.5, 52.5, 55.8, 56.5, 67.3, 81.3, 85.2, 87.9, 110.3, 112.6, 128.2, 128.3 (2C), 128.5 (2C), 136.0, 155.7, 170.4; IR ($CHCl_3$): 3533, 3429, 3032, 3020, 2993, 2955, 2937, 2841, 1724, 1510, 1456, 1439, 1385, 1375, 1339, 1263, 1240 cm^{-1}. MS (FAB) *m/z*: 396 ($M+H^+$) HRMS (FAB) Found *m/z*: 396.1661 (Calcd for $C_{19}H_{26}NO_8$: 396.1658).

Preparation of (-)-MTPA Ester of 7

(-)-MTPA chloride (5 μL), triethylamine (4 μL), and DMAP (8.9 mg) were added to a solution of **7** (9.0 mg, 0.024 mmol) in CH_2Cl_2 (1.5 mL), and the mixture was stirred for 3 h at rt. The reaction was quenched by adding a saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The organic layer was washed with a saturated aqueous NaCl, dried over $MgSO_4$, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 3 : 1) to afford (-)-MTPA ester of **7** (12.0 mg, 85%) as a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32, 1.37 (each s, 3H), 3.47 (s, 3H, OMe), 3.76 (s, 3H, CO_2Me), 4.29 (dd, *J* = 10.0, 6.2 Hz, 1H, γ-H), 4.59 (br t, *J* = 6.2 Hz, 1H, δ-H), 4.94 (br d, *J* = 10.0 Hz, 1H, CH*H*=CH), 5.07 (d, A part of AB, *J* = 12.0 Hz, 1H, -CH*H*Ph), 5.11 (dd, *J* = 1.4, 6.2 Hz 1H, α-H), 5.16 (d, B part of AB, *J* = 12.0 Hz, 1H, -C*H*H-Ph), 5.26 (br d, *J* = 16.4 Hz, 1H, CH*H*=CH), 5.38 (ddd, *J* = 16.4, 10.0, 6.2 Hz, 1H, CH_2=C*H*), 5.41 (dd, *J* = 10.0, 1.4 Hz, 1H, β-H), 5.54 (d, *J* = 10.0 Hz, 1H, -NH), 7.33-7.57 (m, 10H, -CH_2*Ph*, -Ph); MS (FAB) *m/z*: 618 ($M+Na^+$) HRMS (FAB) Found *m/z*: 618.1923 (Calcd for $C_{29}H_{32}NO_9F_3Na$: 618.1927).

Preparation of (+)-MTPA Ester of 7

(+)-MTPA chloride (5 μL), triethylamine (4 μL), and DMAP (5.4 mg) were added to a solution of **7** (8.5 mg, 0.024 mmol) in CH_2Cl_2 (1.5 mL), and the mixture was stirred for 3 h at rt. The reaction was quenched by adding a saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The organic layer was washed with a saturated aqueous NaCl, dried over $MgSO_4$, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 3 : 1) to afford (-)-MTPA ester of **7** (11.3 mg, 85%) as a colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.35, 1.42 (each s, 3H), 3.39 (s, 3H, OMe), 3.73 (s, 3H, CO_2Me), 4.37 (dd, *J* = 9.3, 6.3 Hz, 1H, γ-H), 4.69 (br t, *J* = 6.3 Hz, 1H, δ-H), 5.05 (d, A part of AB, *J* = 12.0 Hz, 1H, -CH*H*Ph), 5.09 (dd, *J* = 10.0, 1.8 Hz, 1H, α-H), 5.13 (d, B part of AB, *J* = 12.0 Hz, 1H, -C*H*HPh), 5.22 (d, *J* = 10.0 Hz, 1H, CH*H*=CH), 5.39 (br d, *J* = 17.0 Hz, 1H, CH*H*=CH), 5.48 (dd, *J* = 10.0, 1.8 Hz, 1H, β-H), 5.49 (br d, *J* = 10.0 Hz, 1H, NH), 5.71 (ddd, *J* = 17.0, 10.0, 6.3 Hz, 1H, CH_2=C*H*), 7.28-7.54 (m, 10H, -CH_2*Ph*, -Ph); MS (FAB) *m/z*: 618 ($M+Na^+$) HRMS (FAB) Found *m/z*: 618.1932 (Calcd for $C_{29}H_{32}NO_9F_3Na$: 618.1927).

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