

Supporting Information

SYNTHESIS OF ORTHOGONALLY PROTECTED ACTINOIDIC ACID TRIMETHYL ETHER

Yusuke Amino^{c*} and Robert M. Williams^{a,b*}

^aDepartment of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA. ^bUniversity of Colorado Cancer Center, Aurora, CO 80045, United States. ^cPresent address: Institute for Innovation, Ajinomoto Co., Inc., 1-1 Suzuki-cho, Kawasaki-ku, Kawasaki, Kanagawa 210-8681, Japan.

e-mail: yusuke_amino@ajinomoto.com; robert.williams@colostate.edu

EXPERIMENTAL

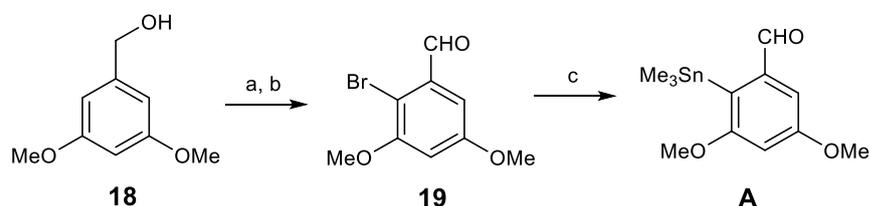
General Information

¹H-NMR spectra were recorded on a Bruker AC 300 MHz spectrometer or a Bruker WP200SY 200 MHz spectrometer. Infrared spectra were recorded on a PerkinElmer 1600 Series Fourier-transform infrared spectroscope and are reported as λ_{max} in cm^{-1} . Melting points were determined in open-ended capillary tubes on a MeI-Temp apparatus and are uncorrected. Optical rotations were obtained on a Rudolph Research Autopol III automatic polarimeter at a wavelength of 589 nm (sodium “D” line) using a 0.1 dm cell with a total volume of 1.0 mL. Specific rotations, $[\alpha]_{\text{D}}$, are reported in degrees per decimeter at the specified temperature and concentration (c) given in grams per 100 mL in the specific solvent. Fast atom bombardment (FAB) mass spectra, field desorption (FD) mass spectra, and high-resolution mass spectra were assessed at the Analytical Department, Institute for Innovation, Ajinomoto Co., Inc., using a ThermoQuest TSQ 700 spectrometer, and the Midwest Center for Mass Spectrometry, Department of Chemistry,

University of Nebraska–Lincoln, Lincoln, NE, USA. Thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed on 0.25 mm or 1.0 mm Merck precoated silica gel glass plates. Column chromatography was performed with Merck silica gel grade 60, 230–400 mesh, 60 Å. Reagents and solvents were of commercial grade and were used as supplied with the following exceptions. Dioxane was obtained by distillation over Na. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dry CH₂Cl₂ was obtained by distillation over CaH₂. DMF was dried over activated 4 Å molecular sieves. Pd(PPh₃)₄ was prepared in the usual manner and stored under Ar. All moisture-sensitive reactions were carried out under Ar.

Synthesis of Starting Materials

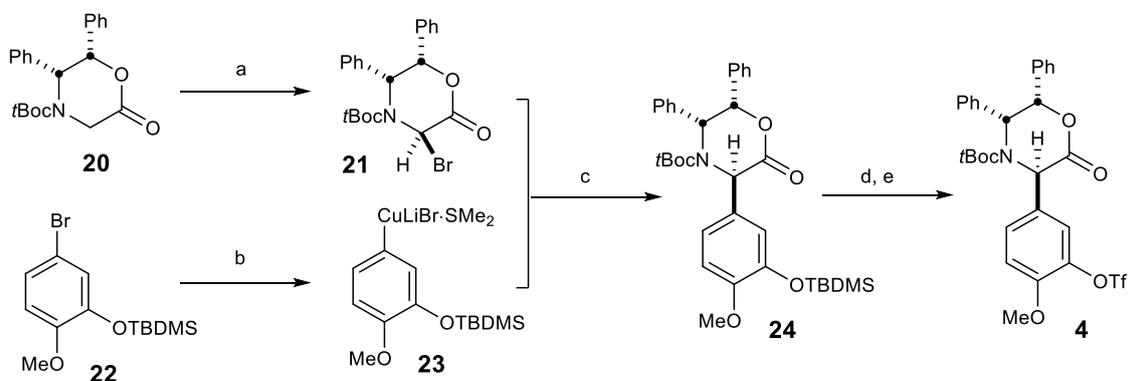
Scheme S1: Synthesis of (3,5-dimethoxy-2-trimethylstannyl)benzaldehyde (**A**).



Reagents and conditions: (a) NBS (1.1 eq.), CCl₄, reflux, 2.5 h (97%); (b) MnO₂ (3.0 eq.), dioxane, reflux, 2.5 h (92%); (c) Me₃SnSnMe₃ (1.2 eq.), Pd(PPh₃)₄ (0.02 eq.), toluene, reflux, 16 h (82%).

Compound **A**: ¹H-NMR (CDCl₃) δ: 0.30 (9H, s), 3.78 (3H, s), 3.87 (3H, s), 6.62 (1H, d, *J* = 2.2 Hz), 7.07 (1H, d, *J* = 2.2 Hz), 9.95 (1H, s); IR (neat): 2965, 2938, 2912, 2838, 1694, 1587, 1459, 1438, 1324, 1281, 1213, 1156, 1071, 952, 847, 774 cm⁻¹.

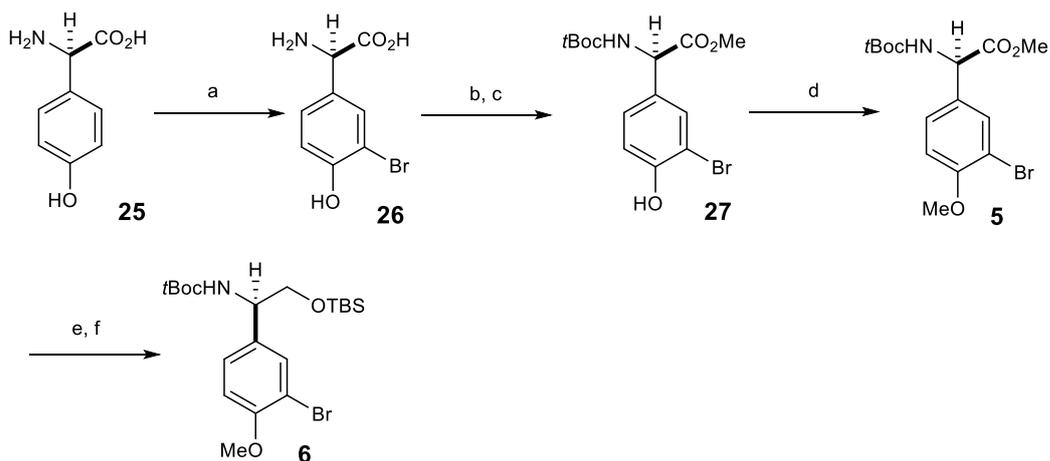
Scheme S2: Synthesis of (3*R*,5*R*,6*S*)-3-(3-trifluoromethanesulfonyl-4-methoxyphenyl)-2-oxo-5,6-diphenyl-4-morpholinecarboxylic acid 1,1-dimethylethyl ester (**4**).



Reagents and conditions: (a) NBS (1.1 eq.), CCl₄, reflux, 1 h; (b) *n*-BuLi (1.05 eq.), CuBr·SMe₂ (0.5 eq.), Et₂O, -78 °C to -15 °C, 2 h; (c) cuprate (**23**) (2.0 eq.), THF, -78 °C, 2 h (61.6%, three steps); (d) F⁻ buffer, THF, rt, two days (97.4%); (e) Tf₂O (1.15 eq.), *N,N*-diisopropylamine (3.0 eq.), CH₂Cl₂, -78 °C, 30 min (81.0%, >90% ee).

Compound **4**: ¹H-NMR (CDCl₃) δ: 1.14 (6H, s), 1.29 (3H, s), 3.92 (s) and 3.94 (s) (3H), 5.17 (d, *J* = 3.0 Hz) and 5.44 (d, *J* = 2.8 Hz) (1H), 5.71 (d, *J* = 3.1 Hz) and 5.80 (d, *J* = 2.9 Hz) (1H), 6.12 (s) and 6.34 (s) (1H), 6.70 (2H, m), 6.90 (2H, m), 7.10–7.26 (7H, m), 7.43 (1H, m), 7.56 (1H, m); IR (KBr): 3031, 2981, 2937, 1746, 1704, 1516, 1423, 1380, 1349, 1301, 1271, 1221, 1166, 1141, 1098, 1058, 1027, 968, 947, 881, 851, 768, 720, 699 cm⁻¹; [α]_D²⁵ +47.8 (C 1.0, CH₂Cl₂); m.p. 198-199°C; FABMS *m/z*: 607.0 (M)⁺; exact mass (FABMS): 607.1472 (M)⁺ (Calcd. for C₂₉H₂₈NO₈SF₃: 607.1487).

Scheme S3: Synthesis of (αR)-3-bromo-4-methoxy- α -[[1,1-dimethoxy)carbonyl]amino]benzeneacetic acid methyl ester (**5**) and *N*-[(R) -2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-1-(3-bromo-4-methoxyphenyl)ethyl]carbamic acid 1,1-dimethylethyl ester (**6**).



Reagents and conditions: (a) (*R*)-phenylglycine (**25**), Br₂ (1.0 eq.), HBr, AcOH, rt, 16 h (62%); (b) SOCl₂ (3.5 eq.), MeOH, rt, 16 h; (c) (Boc)₂O (1.0 eq.), NaHCO₃ (2.5 eq.), NaCl, CHCl₃-H₂O, reflux, 4 h (88%, two steps); (d) Me₂SO₄ (1.0 eq.), K₂CO₃ (1.0 eq.), DMF, rt, 3.5 h (79%); (e) NaBH₄ (2.0 eq.), LiCl (2.0 eq.), THF-EtOH, rt, 3 h (93%, 90%ee); (f) TBDMSCl (1.2 eq.), imidazole (2.4 eq.), DMAP (cat.), DMF, 60 °C, 16 h (100%, 90%ee).

Compound **5**: ¹H-NMR (CDCl₃) δ: 1.93 (9H, s), 3.73 (3H, s), 3.89 (3H, s), 5.23 (1H, d, *J* = 6.8 Hz), 5.55 (1H, brs), 6.87 (1H, d, *J* = 8.5 Hz), 7.28 (1H, dd, *J* = 2.2 and 8.5 Hz), 7.55 (1H, d, *J* = 2.2 Hz); IR (KBr): 3366, 2973, 2952, 2839, 1737, 1710, 1681, 1605, 1524, 1506, 1438, 1367, 1325, 1258, 1165, 1060, 1018, 917, 879, 812, 760, 728, 682, 648, 616, 590 cm⁻¹; [α]_D²⁵ -117.6 (C 1.0, CHCl₃); m.p. 66-67°C; FABMS *m/z*: 374.0 (M+H)⁺; exact mass (FABMS): 374.0595 (M+H)⁺ (Calcd. for C₁₅H₂₁NO₅: 374.0603).

Compound **6**: $^1\text{H-NMR}$ (CDCl_3) δ : -0.10–0.23 (6H, m), 0.83 (9H, s), 3.60–3.68 (1H, m), 3.77–3.84 (1H, m), 3.86 (3H, s), 4.67 (1H, brs), 5.21 (1H, brd, $J = 6.1$ Hz), 6.82 (1H, d, $J = 8.5$ Hz), 7.18 (1H, dd, $J = 2.1$ and 8.5 Hz), 7.47 (1H, d, $J = 2.1$ Hz); IR (neat): 3450, 3344, 2955, 2930, 2857, 1704, 1605, 1497, 1366, 1256, 1170, 1108, 1056, 1023, 837, 778, 668 cm^{-1} ; $[\alpha]_{\text{D}}^{25}$ -23.9 (C 1.0, CHCl_3); FABMS m/z : 460.0 ($\text{M}+\text{H}$) $^+$; exact mass (FABMS): 460.1519 ($\text{M}+\text{H}$) $^+$ (Calcd. for $\text{C}_{20}\text{H}_{35}\text{NO}_4\text{SiBr}$: 460.1519).

The General Procedure for Palladium-Catalyzed Stille Biaryl Coupling

Dry dioxane (2.5 mL) was added to a flask containing aryl triflate (**4**) or aryl bromide (**5**, **6**) (0.4 mmol), stannane (**A**) (135 mg, 0.41 mmol), $\text{Pd}(\text{PPh}_3)_4$ (185 mg, 0.16 mmol), and CuBr (23 mg, 0.16 mmol). The resulting mixture was stirred at reflux under Ar for 16 h. The mixture was concentrated, dissolved in AcOEt, and filtered through a plug of celite. The filtrate was concentrated and purified by PTLC (eluted with hexane/AcOEt = 2 : 1) to give the desired biphenyls.

Compound **7**: (3*R*,5*R*,6*S*)-3-[2-formyl-4,6,6'-trimethoxy-1,1'-biphenyl]-4'-yl-2-oxo-5,6-diphenyl-4-morpholinecarboxylic acid 1,1-dimethylethyl ester

$^1\text{H-NMR}$ (CDCl_3) δ : 1.09–1.30 (9H, main signals; 1.09 (s), 1.10 (s), 1.24 (s), 1.30 (s)), 3.65–3.80 (3H, m), 3.91 (3H, s), 3.92 (3H, s), 5.13–5.34 (1H, main signals: 5.13 (d, $J = 3.1$ Hz), 5.17 (d, $J = 3.1$ Hz), 5.37 (d, $J = 2.9$ Hz), 5.34 (d, $J = 2.9$ Hz)), 5.82–6.01 (1H, main signals: 5.82 (d, $J = 3.1$ Hz), 5.85 (d, $J = 3.0$ Hz), 5.92 (d, $J = 3.0$ Hz), 6.01 (d, $J = 2.9$ Hz), 6.17 (1/2H, s), 6.40 (1/2H, s), 6.65–7.65 (15H, m), 9.64–9.72 (1H, main signals: 9.64 (s), 9.69 (s), 9.72 S)); IR (KBr): 2973, 2843, 2754, 1756, 1694, 1601, 1504, 1455, 1436, 1391, 1319, 1287, 1264, 1220, 1157, 1118, 1062, 1030, 954, 927, 848, 753, 699

cm⁻¹; [α]_D²⁵ +24.8 (C 1.0, CHCl₃); FABMS *m/z*: 623.0 (M)⁺; exact mass (FABMS): 623.2530 (M)⁺ (Calcd. for C₃₇H₃₇NO₈: 623.2519).

Compound **8**: (α'*R*)-α'-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-formyl-4,6,6'-trimethoxy-1,1'-biphenyl-3'-acetic acid methyl ester

¹H-NMR (CDCl₃) δ: 1.43 (9H, s), 3.72 (3H, s), 3.73 (3H, s), 3.89 (3H, s), 5.30 (1H, brd, *J* = 6.5 Hz), 5.47 (1H, brs), 6.77 (1H, d, *J* = 2.3 Hz), 6.95 (1H, d, *J* = 8.5 Hz), 7.10 (1H, d, *J* = 2.4 Hz), 7.21 (1H, d, *J* = 2.6 Hz), 7.38 (1H, dd, *J* = 2.0 and 8.5 Hz), 9.59 (1/2H, s), 9.60 (1/2H, s); IR (neat): 3370, 2975, 2842, 2757, 1747, 1715, 1694, 1602, 1505, 1464, 1438, 1392, 1367, 1335, 1264, 1158, 1058, 1031, 756 cm⁻¹; [α]_D²⁵ -60.8 (C 1.0, CHCl₃); FABMS *m/z*: 459.0 (M)⁺; exact mass (FABMS): 460.1977 (M)⁺ (Calcd. for C₂₄H₃₀NO₈: 460.1971).

Compound **9**: *N*-[(α'*R*)-1-(2-formyl-4,6,6'-trimethoxy-1,1'-biphenyl-3'-yl)-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]carbamic acid 1,1-dimethylethyl ester

¹H-NMR (CDCl₃) δ: -0.07–0.00 (6H, m), 0.80 (9H, s), 1.39 (9H, s), 3.60–3.85 (2H, m), 3.68 (3H, s), 3.70 (3H, s), 3.87 (3H, s), 4.65 (1H, brs), 5.20 (1H, brd, *J* = 7.3 Hz), 6.74 (1H, d, *J* = 2.5 Hz), 6.89 (1/2H, d, *J* = 8.5 Hz), 6.90 (1/2H, d, *J* = 8.6 Hz), 7.08 (1H, d, *J* = 2.6 Hz), 7.10–7.40 (2H, m), 9.57 (1/2H, s), 9.59 (1/2H, s); IR (neat): 3449, 3362, 2955, 2931, 2856, 2754, 1715, 1694, 1602, 1486, 1464, 1391, 1334, 1286, 1256, 1157, 1121, 1031, 838, 778, 754 cm⁻¹; [α]_D²⁵ -16.8 (C 1.0, CHCl₃); FABMS *m/z*: 545.0 (M)⁺; exact mass (FABMS): 546.2874 (M)⁺ (Calcd. for C₂₉H₄₅NO₇Si: 546.2887).

Construction of A-Ring Glycine Side Chain

Compound **11a**: ($\alpha S, \alpha' R$)- α -[(*R*)-2-hydroxy-1-phenylethyl]amino]- α' -[(1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl]amino]-4,6,6'-trimethoxy-1,1'-biphenyl-2,3'-diacetic acid dimethyl ester

To a suspension of **7** (595 mg, 0.954 mmol) in MeOH (5 mL), (*R*)-2-phenylglycinol (151 mg, 1.10 mmol) was added. The solution was stirred for 2 h at r.t. and then cooled down to 0 °C. Trimethylsilyl cyanide (0.26 mL, 1.91 mmol) was added to the mixture, which was allowed to warm up to r.t. and stirred for 4 h. Aqueous NaHCO₃ was added to the solution, followed by extraction with CHCl₃ three times. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give compound **10** (780 mg, quantitatively) as a pale-brown foam; FABMS *m/z*: 770.0 (M+H)⁺; exact mass (FABMS): 770.3470 (M+H)⁺ (Calcd. for C₄₆H₄₇N₃O₈: 770.3442). To a flask containing the above compound **10** (760 mg), dioxane (7 mL) and conc. HCl (4 mL) were added. After being stirred for 16 h at rt, the mixture was concentrated and the residue was treated with aqueous NH₃. The separated oil was extracted three times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give *bis*-carboxylic acid (611 mg, 91%) as a brown solid; FABMS *m/z*: 707.0 (M+H)⁺; exact mass (FABMS): 707.2954 (M+H)⁺ (Calcd. for C₄₁H₄₃N₂O₉: 707.2969).

To a flask containing the above *bis*-carboxylic acid (590 mg, 0.84 mmol) in MeOH (20 mL), excess ethereal CH₂N₂ was added. The resulting mixture was allowed to stand at rt for 1 h and was then concentrated. The residue was purified by PTLC (hexane/AcOEt = 1:2) to give **11** [336 mg, 58%, **11a** (4:1 diastereoisomer mixture, 68%), **11b** (2:1 diastereoisomer mixture, 32%)].

11a: ¹H-NMR (CDCl₃) δ: 3.40–3.90 (4H, m), 3.49 (3H, s), 3.51 (3H, s), 3.62 (3H, s), 3.72 (3H, s), 3.80 (3H, s), 4.06 (1/2H, s), 4.08 (1/2H, s), 4.15 (1/2H, s), 4.21 (1/2H, s), 4.70 (1/2H, d, *J* = 6.5 Hz), 4.79 (1/2H, d, *J* = 6.3 Hz), 6.50 (1H, d, *J* = 2.3 Hz), 6.55 (1H, d, *J* = 2.4 Hz), 6.74–7.72 (18H, m); IR (neat): 3342, 3061, 3005, 2951, 2838, 1734, 1684, 1652, 1604, 1558, 1540, 1506, 1488, 1455, 1437, 1320, 1266, 1201, 1173, 1158, 1120, 1164, 1030, 936, 819, 755, 722, 701, 668 cm⁻¹; [α]_D²⁵ +74.8 (C 1.0, CHCl₃); FABMS *m/z*: 735.0 (M+H)⁺; exact mass (FABMS): 735.3294 (M+H)⁺ (Calcd. for C₄₃H₄₇N₂O₉: 735.3282).

Compound **3a** (from **7**): actinoidic acid trimethyl ether ((*αS,α'R*)-*α,α'*-diamino-4,6,6'-trimethoxy-1,1'-biphenyl-2,3'-diacetic acid)

To a solution of compound **11a** (190 mg, 0.26 mmol) in a mixed solution of CH₂Cl₂ (6 mL) and MeOH (3 mL), Pb(OAc)₄ (275 mg, 0.26 mmol) was added under ice cooling. After being stirred at this temperature for 5 min, the reaction was quenched by the addition of aqueous NaHCO₃. The resulting insoluble material was removed by filtration and washed with CH₂Cl₂. The combined filtrate was extracted three times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated to give *bis*-benzaldehyde imine (129 mg, 83%) as a pale-brown foam.

To a flask containing the above residue (129 mg), 2 N HCl (3 mL) and dioxane (1 mL) were added. The resulting mixture was stirred at reflux for 16 h and then concentrated under reduced pressure to give a brown solid. The residue was purified with Dowex 50W (H⁺) (eluted with 3% aqueous NH₃) and a Sep-Pak C18 cartridge (eluted with H₂O). The resulting solution was lyophilized to give **3a** (61 mg, 72%) as a pale-brown solid.

3a: ¹H-NMR (D₂O) δ: 3.58 (3H, s), 3.63 (3H, s), 3.74 (3H, s), 4.27 (1H, s), 4.67 (1H, s), 6.53 (1H, d, *J* = 2.2 Hz), 6.63 (1H, d, *J* = 2.2 Hz), 7.08 (1H, d, *J* = 8.6 Hz), 7.16 (1H, d, *J* = 2.3 Hz), 7.37 (1H, dd, *J* = 2.3 and 8.6 Hz); [α]_D²⁵ +29.7 (C 1.0, H₂O); FABMS *m/z*: 391.0 (M+H)⁺; exact mass (FABMS): 391.1505 (M+H)⁺ (Calcd. for C₁₉H₂₃N₂O₇: 391.1518).

Compound **13a**: (α*S*,α'*R*)-α-[(*R*)-(2-hydroxy-1-phenylethyl)amino]-α'-[2-hydroxyethyl]-1-(phenylmethoxy)carbonylamino-4,6,6'-trimethoxy-1,1'-biphenyl-2-acetic acid methyl ester

To a suspension of compound **9** (1.80 g, 3.30 mmol) in MeOH (18 mL), (*R*)-2-phenylglycinol (498 mg, 3.63 mmol) was added. The mixture was stirred for 3 h at rt and then cooled down to 0 °C. Trimethylsilyl cyanide (0.88 mL, 6.60 mmol) was added before the mixture was allowed to warm up to rt and stirred for 16 h. Aqueous NaHCO₃ was added to the mixture, followed by extraction with CHCl₃ three times. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was quickly separated by PTLC (eluted with hexane/AcOEt = 1:1) to give **12** [1.34 g, 59%, **12a** (725 mg, 54%), **12b** (148 mg, 11%), and **12c** (470 mg, 35%)] as a pale-yellow foam; FABMS *m/z*: 692.0 (M+H)⁺; exact mass (FABMS): 692.3734 (M+H)⁺ (Calcd. for C₃₈H₅₄N₃O₇Si: 692.3730).

To a solution of **12a** (643 mg, 0.93 mmol) in dioxane (5 mL), conc. HCl (4 mL) was added under ice cooling. The mixture was allowed to warm up to rt and stirred for 16 h, and then it was concentrated under reduced pressure to give a pale-yellow solid. To a flask containing the above residue, a solution of SOCl₂ (0.32 mL, 3.72 mmol) in MeOH (5 mL) was added under ice cooling. The mixture was allowed to warm up to rt and stirred for

16 h, and then it was concentrated and the residue was washed with Et₂O to give a methyl ester compound as a pale-yellow solid; FABMS *m/z*: 511.0 (M+H)⁺.

To a flask containing the above residue in CH₂Cl₂ (5 mL) and H₂O (5 mL), CbzCl (174 mg, 1.02 mmol) and NaHCO₃ (273 mg, 3.25 mmol) were added. The resulting mixture was stirred at rt for 6 h and extracted three times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was separated by PTLC (eluted with hexane/AcOEt = 1:5) to give **13** (482 mg, 80%; **13a**: 331 mg, 69%; **13b**: 151 mg, 31%) as a pale-yellow foam.

13a: ¹H-NMR (CDCl₃) δ: 2.50 (3H, brs), 3.44 (3H, s), 3.66 (3H, s), 3.68 (3H, s), 3.77 (3H, s), 3.45–3.85 (5H, m), 4.14 (1H, s), 4.89 (1H, brs), 5.09 (2H, s), 5.95 (1H, d, *J* = 8.6 Hz), 6.37 (1H, d, *J* = 2.1 Hz), 6.47 (1H, d, *J* = 2.2 Hz), 6.86 (1H, d, *J* = 8.3 Hz), 7.17–7.31 (12H, m); IR (neat): 3396, 3007, 2951, 2838, 1716, 1605, 1582, 1506, 1456, 1323, 1237, 1202, 1157, 1058, 1035, 944, 912, 837, 817, 755, 701, 668 cm⁻¹; [α]_D²⁵ –32.0 (C 1.0, CHCl₃); FABMS *m/z*: 645.0 (M+H)⁺; exact mass (FABMS): 645.2821 (M+H)⁺ (Calcd. for C₃₆H₄₁N₂O₉: 645.2812).

Compound **14a**: (α*S*,3'*R*)-α-[[1,1-dimethylethoxy)carbonyl]amino]-3'-[[1-(phenylmethoxy)carbonyl]amino-2-hydroxyethyl]-4,6,6'-trimethoxy-1,1'-biphenyl-2-acetic acid methyl ester

To a solution of **13a** (331 mg, 0.51 mmol) in a mixed solution of CH₂Cl₂ (5 mL) and MeOH (3 mL), Pb(OAc)₄ (455 mg, 1.03 mmol) was added under ice cooling. After being stirred at this temperature for 5 min, the reaction was quenched by the addition of aqueous NaHCO₃. The resulting insoluble material was removed by filtration and washed with CH₂Cl₂. The filtrate was extracted three times with CH₂Cl₂. The combined organic layers

were dried over MgSO₄, filtered, and concentrated to give a pale-yellow foam. To a flask containing the above residue, 2 N HCl (2 mL) and MeOH (5 mL) were added under ice cooling. The mixture was allowed to warm up to r.t., stirred for 16 h, and then concentrated under reduced pressure to give a pale-yellow solid. To a flask containing the above residue, a solution of SOCl₂ (0.13 mL, 1.54 mmol) in MeOH (5 mL) was added under ice cooling. The mixture was allowed to warm up to r.t., stirred for 16 h, and then concentrated to give a pale-yellow solid. To a flask containing the above residue in CHCl₃ (8 mL) and H₂O (4 mL), (Boc)₂O (224 mg, 1.03 mmol), NaCl (100 mg), and NaHCO₃ (108 mg, 1.28 mmol) were added. The resulting mixture was heated to reflux for 4 h, followed by extraction three times with CHCl₃. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by PTLC (eluted with hexane/AcOEt = 1:4) to afford **14a** (219 mg, 68%) as a pale-yellow foam.

14a: ¹H-NMR (CDCl₃) δ: 1.30 (9H, s), 1.61 (1H, brs), 3.62 (3H, s), 3.65 (1/2H, s), 3.67 (1/2H, s), 3.69 (3H, s), 3.81 (3H, s), 3.75–3.90 (2H, m), 4.81 (1H, brs), 5.03–5.22 (4H, m), 5.60 (1H, brs), 6.41 (1H, brs), 6.50 (1H, d, *J* = 2.2 Hz), 6.89 (1H, d, *J* = 8.5 Hz), 7.10 (1H, brs), 7.23–7.31 (6H, m); IR (neat): 3366, 3006, 2952, 2838, 1700, 1606, 1583, 1506, 1456, 1340, 1239, 1203, 1160, 1054, 1030, 940, 913, 839, 815, 755, 698, 668 cm⁻¹; [α]_D²⁵ +53.1 (C 1.0, CHCl₃); FABMS *m/z*: 625.0 (M+H)⁺; exact mass (FABMS): 625.2747 (M+H)⁺ (Calcd. for C₃₃H₄₁N₂O₁₀: 625.2761).

Compound **15a**: (α*S*,α'*R*)-α-[(1,1-dimethylethoxy)carbonyl]amino]-α'-[[[(phenylmethoxy)carbonyl]amino-4,6,6'-trimethoxy-1,1'-biphenyl-2,3'-diacetic acid 2-methyl 3'-(1-trimethylsilyl)ethyl diester

To a solution of **14a** (157 mg, 0.25 mmol) in a mixed solution of MeCN (0.3 mL) and H₂O (4.5 mL), RuCl₃·3H₂O (4 mg) and NaIO₄ (215 mg, 1.00 mmol) were added under ice cooling. After being stirred at this temperature for 1 h, the mixture was extracted three times with AcOEt. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated to give a carboxylic acid compound as a pale-yellow foam; FABMS *m/z*: 661.0 (M+Na)⁺, FDMS *m/z* 638.0 (M)⁺.

To a flask containing the above residue in dry CH₂Cl₂ (3.5 mL), trimethylsilylethanol (45 mg, 0.38 mmol), EDCI·HCl (72 mg, 0.38 mmol), and DMAP (15 mg, 0.12 mmol) were added. The mixture was stirred for 16 h at rt and concentrated. The residue was dissolved in AcOEt and the organic layer was washed successively with aqueous citric acid, brine, aqueous NaHCO₃, and then brine again, before being dried over MgSO₄, filtered, and concentrated. The residue was separated by PTLC (eluted with hexane/AcOEt = 1:1) to give **15a** (53 mg, 29%) as a pale-yellow foam.

15a: ¹H-NMR (CDCl₃) δ: -0.20 (9/2H, s), 0.14 (9/2H, s), 0.97 (2H, brt, *J* = 8.3 Hz), 1.36 (9H, s), 3.63 (3H, s), 3.68 (3H, s), 3.80 (6H, s), 4.11–4.30 (2H, m), 4.92 (1H, brd, *J* = 7.1 Hz), 5.09 (2H, s), 5.17 (1H, brs), 5.27 (1H, brt, *J* = 8.6 Hz), 5.70 (1H, brd, *J* = 7.2 Hz), 6.46 (1H, d, *J* = 2.3 Hz), 6.48 (1H, d, *J* = 2.2 Hz), 6.89 (1H, d, *J* = 8.6 Hz), 7.14 (1H, d, *J* = 2.1 Hz), 7.23–7.36 (6H, m); IR (neat): 3364, 2954, 2839, 1718, 1606, 1584, 1506, 1465, 1367, 1329, 1251, 1203, 1161, 1152, 990, 938, 860, 838, 755, 698 cm⁻¹; [α]_D²⁵ +52.1 (C 1.0, CHCl₃); FABMS *m/z*: 739.0 (M+H)⁺; exact mass (FABMS): 739.3226 (M+H)⁺ (Calcd. for C₃₈H₅₁N₂O₁₁Si: 739.3262).

Compound **3a** (from **9**): actinoidic acid trimethyl ether

To a solution of **15a** (53 mg, 0.072 mmol) in THF (2 mL), 5% Pd/C (20 mg) and 2 N HCl (0.1 mL) were added. The mixture was stirred under a H₂ atmosphere at r.t. for 4 h. The mixture was filtered through a plug of celite with THF and concentrated. A solution of the above residue in 2 N HCl (1.5 mL) was heated to reflux for 16 h. The mixture was concentrated and the residue was purified with Dowex 50W (H⁺) (eluted with 3% aqueous NH₃) and a Sep-Pak C18 cartridge (eluted with H₂O). The resulting solution was lyophilized to give **3a** (18 mg, 64%) as a colorless solid.

3a: ¹H-NMR (D₂O) δ: 3.58 (3H, s), 3.63 (3H, s), 3.74 (3H, s), 4.27 (1H, s), 4.67 (1H, s), 6.53 (1H, d, *J* = 2.2 Hz), 6.63 (1H, d, *J* = 2.2 Hz), 7.08 (1H, d, *J* = 8.6 Hz), 7.16 (1H, d, *J* = 2.3 Hz), 7.37 (1H, dd, *J* = 2.3 and 8.6 Hz); [α]_D²⁵ +58.6 (C 1.0, H₂O); FABMS *m/z*: 391.0 (M+H)⁺; exact mass (FABMS): 391.1505 (M+H)⁺ (Calcd. for C₁₉H₂₃N₂O₇: 391.1518).

Isolation of actinoidic acid trimethyl ether (**3**) from vancomycin

Compound **16**: (α*S*,α'*R*)-[α,α'-di-[(1,1-dimethylethoxy)carbonyl]amino]-4,6,6'-trimethoxy-1,1'-biphenyl-2,3'-diacetic acid dimethyl ester

A suspension of vancomycin (3.0 g) in 6 N HCl (20 mL) was heated to reflux for 8 h. The mixture was concentrated under reduced pressure and the residue was purified with a Dowex 50W (H⁺) ion exchange resin (eluted with 3% aqueous NH₃) to give a mixture of amino acids (450 mg) as a brown solid. To a suspension of the above residue (270 mg) in dioxane (4.5 mL), (Boc)₂O (590 mg, 2.7 mmol) and 1 N NaOH (1.8 mL) were added. The resulting mixture was stirred at rt for 4 h and then concentrated under reduced pressure. To a solution of the above residue in acetone (10 mL), K₂CO₃ (1.24 g, 9.0 mmol), *n*-

Bu₄Ni (665 mg, 1.8 mmol), and MeI (1.12 mL, 18.0 mmol) were added. The mixture was heated to reflux for 15 h. Insoluble material was separated by filtration and the filtrate was concentrated to give an oily material. The residue was purified with PTLC (eluted with hexane/AcOEt = 1:1) to give compound **16** as a pale-yellow foam (72 mg).

16: ¹H-NMR (CDCl₃) δ: 1.38–1.58 (18H, main signals; 1.38 (s), 1.43 (s), 1.45 (s), 1.58 (s)), 3.59–3.83 (15H, main singlets; 3.59 (s), 3.62 (s), 3.66 (s), 3.68 (s), 3.70 (s), 3.73 (s), 3.75 (s), 3.76 (s), 3.83 (s)), 4.92–5.47 (2H, main signals: 4.92 (brd, *J* = 6.3 Hz), 5.17 (brd, *J* = 8.8 Hz), 5.29 (brd, *J* = 7.9 Hz), 5.47 (brd, *J* = 8.9 Hz)), 6.20–6.50 (2H, main signals: 6.20 (brd, *J* = 7.8 Hz), 6.44–6.50 (m)), 6.92–6.95 (1H, main signals 6.92 (d, *J* = 8.4 Hz), 6.95 (d, *J* = 8.5 Hz)), 7.04–7.14 (1H, main signals: 7.04 (brs), 7.14 (d, *J* = 2.2 Hz)), 7.32–7.41 (1H, main signals: 7.32 (d, *J* = 2.2 Hz), 7.37 (brs), 7.41 (d, *J* = 2.0 Hz)); IR (neat): 3365, 2977, 2935, 2841, 1747, 1714, 1698, 1606, 1505, 1463, 1456, 1437, 1392, 1368, 1338, 1255, 1204, 1162, 1054, 1029, 756 cm⁻¹; FABMS *m/z*: 619.0 (M+H)⁺; exact mass (FABMS): 618.2764 (M+H)⁺ (Calcd. for C₃₁H₄₃N₂O₁₁: 374.0603).

Compound **3**: actinoidic acid trimethyl ether

A solution of compound **16** (36 mg) in 2 N HCl (1.0 mL) was heated to reflux for 13 h. The mixture was concentrated under reduced pressure and the residue was purified with Dowex 50W (H⁺) (eluted with 3% aqueous NH₃) followed by a Sep-Pak C18 cartridge (eluted with H₂O). The resulting eluate was lyophilized to give actinoidic acid trimethyl ether (**3**) (18 mg) as a white solid.

3: ¹H-NMR (D₂O) δ: major isomer: 3.57 (3H, s), 3.62 (3H, s), 3.73 (3H, s), 4.34 (1H, s), (4.60, (3H, s)), 6.55 (1H, d, *J* = 2.3 Hz), 6.64 (1H, d, *J* = 2.2 Hz), 7.03 (1H, d, *J* = 2.3 Hz), 7.07 (1H, d, *J* = 8.6 Hz), 7.36 (1H, dd, *J* = 2.5 and 8.7 Hz); main isomer: 3.58 (3H, s),

3.64 (3H, s), 3.73 (3H, s), 4.28 (1H, s), 4.71 (1H, s), 6.53 (1H, d, $J = 2.3$ Hz), 6.64 (1H, d, $J = 2.2$ Hz), 7.08 (1H, d, $J = 8.7$ Hz), 7.16 (1H, d, $J = 2.3$ Hz), 7.35 (1H, dd, $J = 2.3$ and 8.6 Hz); IR (KBr): 3433, 2944, 1609, 1508, 1491, 1466, 1388, 1347, 1326, 1273, 1204, 1160, 1062, 1023, 946, 809, 554 cm^{-1} ; $[\alpha]_{\text{D}}^{25} +5.0$ (C 1.0, H_2O); m.p. 187-188 °C; FABMS m/z : 391.0 (M+H)⁺.

Compound **17**: ($\alpha S, \alpha' R$)-[α, α' -di-[1-(+)-methoxytrifluoromethylphenylacetyl-amino]-4,6,6'-trimethoxy-1,1'-biphenyl-2,3'-diacetic acid dimethyl ester

To a stirred suspension of compound **3** (5 mg, 0.013 mmol) in THF (0.5 mL), (*S*)-(+)-Mosher's acid chloride (6.8 mg, 0.030 mmol) and propylene oxide (5.9 mg, 0.102 mmol) were added. The resulting mixture was heated to reflux for 0.5 h and concentrated to provide a crude oil. To a solution of the above residue in MeOH (1 mL), excess CH_2N_2 in Et₂O (5 mL) was added. After being stirred for 1 h at rt, the solution was concentrated and the residue was purified by PTLC (eluted with hexane/AcOEt = 2 : 1) to give *bis*-amide *bis*-ester (**17**) (9 mg, 84%) as a viscous oil.

17: ¹H-NMR (CDCl_3) δ : 3.20–3.82 (21H, main signals; 3.48 (s), 3.58 (s), 3.63 (s), 3.68 (s), 3.82 (s)), 5.12 (1/3H, d, $J = 6.6$ Hz), 5.37 (2/3H, d, $J = 7.6$ Hz), 5.52 (2/3H, d, $J = 7.6$ Hz), 5.53 (1/3H, d, $J = 7.4$ Hz), 6.37–7.65 (15H, m).