

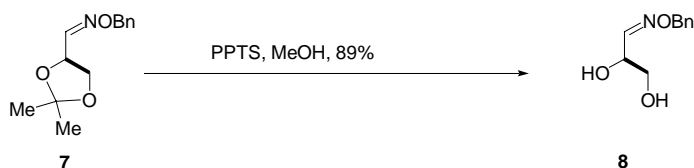
Supporting Information

A New Alternative to the Mannich Reaction: Tandem Radical Addition-Cyclization Reaction for Asymmetric Synthesis of γ -Butyrolactones and β -Amino Acids

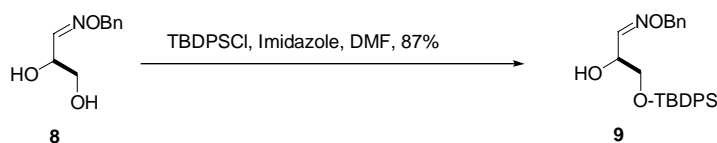
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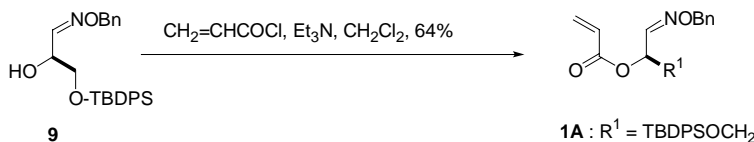
General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 50 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI or CI methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck 60F₂₅₄). Flash column chromatography was performed using E. Merck Kieselgel 60 (230-400 mesh). Medium-pressure column chromatography was performed using Lobar gr \ddot{o} Ùe B (E. Merck 310-25, Lichroprep Si60). Oxime ether **7** was prepared from D-mannitol (See: Miyabe, H.; Shibata, R.; Sangawa, M.; Ushiro, C.; Naito, T. *Tetrahedron* **1998**, *54*, 11431.)



To a solution of **7** (35.3 g, 150 mmol) in MeOH (300 mL) was added pyridinium *p*-toluenesulfonate (37.8 g, 150 mmol) under a nitrogen atmosphere at rt. After being heated at 65 °C for 2 h, the solvent was evaporated at reduced pressure. The reaction mixture was diluted with H₂O and then extracted with AcOEt. The organic phase was washed with brine, dried over MgSO₄, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 1:1) afforded **8** (26.1 g, 89%) as colorless crystals (*E:Z*=3:1): mp 56-58 °C (AcOEt/hexane); $[\alpha]_{\text{D}}^{24} +55.1$ (*c* 1.3, CHCl₃); IR (CHCl₃) 2933, 1604, 1497 cm⁻¹; ^1H NMR (CDCl₃) δ 7.47 (3/4H, d, *J*=4.2 Hz), 7.4-7.3 (5H, m), 6.79 (1/4H, d, *J*=5.1 Hz), 5.10 (2/4H, s), 5.07 (6/4H, s), 4.79 (1/4H, br m), 4.30 (3/4H, br m), 3.8-3.55 (2H, br m); ^{13}C NMR (CDCl₃) δ 151.5, 149.5, 137.1, 136.9, 128.3, 128.2, 128.0, 127.9, 76.3, 76.0, 69.7, 67.4, 64.2, 63.1; HRMS calcd for C₁₀H₁₃NO₃ (*M*⁺) 195.0894, found 195.0916; Anal. calcd C 61.53, H 6.71, N 7.18, found C 61.28, H 6.92, N 6.93.

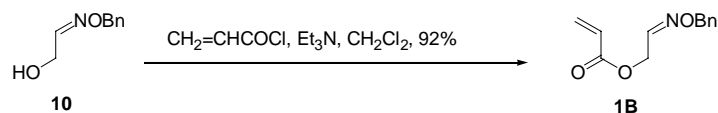


To a solution of **8** (25 g, 128 mmol) and imidazole (21.8 g, 321 mmol) in DMF (80 mL) was added *t*-butyldiphenylsilyl chloride (39.5 mL, 154 mmol) under a nitrogen atmosphere at rt. After the reaction mixture was stirred at the same temperature for 2.5 h, the reaction mixture was diluted with Et₂O. The organic phase was washed with water and brine, dried over MgSO₄, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 20:1 to 10:1) afforded **9** (48.3 g, 87%) as a colorless oil (*E:Z*=3:1): $[\alpha]_{\text{D}}^{24} +7.6$ (*c* 1.6, CHCl₃); IR (CHCl₃) 2932, 1604, 1470 cm⁻¹; ^1H NMR (CDCl₃) δ 7.68-7.61 (4H, m), 7.52 (3/4H, d, *J*=4.8 Hz), 7.47-7.19 (11H, m), 6.83 (1/4H, d, *J*=4.5 Hz), 5.08 (6/4H, s), 5.02 (2/4H, s), 4.86 (1/4H, br m), 4.36 (3/4H, br m), 3.92-3.64 (2H, m), 1.05 (9H, s); ^{13}C NMR (CDCl₃) δ 151.7, 149.5, 137.2, 137.0, 135.4, 134.6, 132.7, 129.8, 128.3, 128.2, 127.9, 127.8, 127.7, 76.3, 76.1, 69.8, 67.4, 65.9, 64.5, 26.7, 19.1; HRMS calcd for C₂₆H₃₁NO₃Si (*M*⁺) 433.2072, found 433.2100.

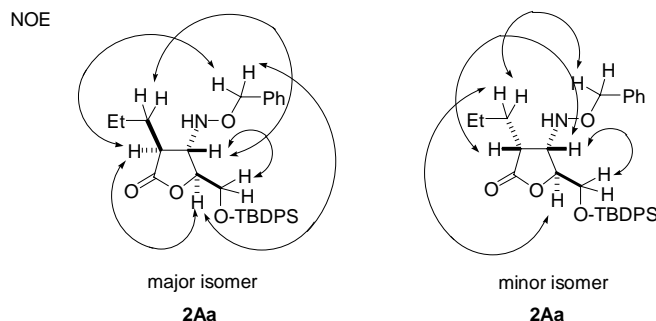
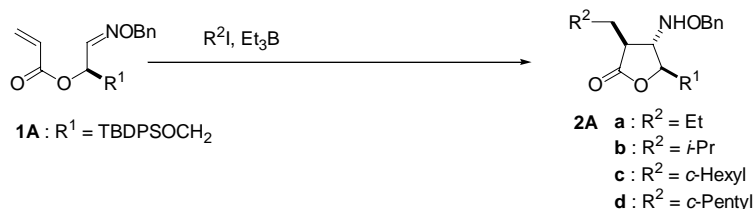


To a solution of **9** (3.0 g, 6.9 mmol) and Et₃N (2.9 mL, 21 mmol) in CH₂Cl₂ (70 mL) was added acryloyl chloride (0.55 mL, 6.9 mmol) under a nitrogen atmosphere at 0 °C. After the reaction mixture was stirred at rt for 6 h, the reaction mixture was diluted with aqueous NaHCO₃ and then extracted with CH₂Cl₂. The organic phase was washed with brine, dried over MgSO₄, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 20:1) afforded **1A** (2.2 g, 64%) as a colorless oil (*E:Z*=3:1): $[\alpha]_{\text{D}}^{24} +29.3$ (*c* 1.5, CHCl₃); IR (CHCl₃)

2932, 1721, 1590, 1472 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.68-7.60 (4H, m), 7.50 (3/4H, d, $J=6.3$ Hz), 7.45-7.23 (11H, m), 6.79 (1/4H, d, $J=5.4$ Hz), 6.45 (1/4H, dd, $J=17.4$, 1.2 Hz), 6.42 (3/4H, dd, $J=18.0$, 1.2 Hz), 6.20-6.06 (1H, m), 6.05 (1/4H, m), 5.88 (1/4H, dd, $J=10.2$, 1.2 Hz), 5.85 (3/4H, dd, $J=10.5$, 1.2 Hz), 5.59 (3/4H, dd, $J=10.8$, 5.1 Hz), 5.09 (2/4H, s), 5.08 (6/4H, s), 4.02-3.87 (2H, m), 1.05 (9H, s); $^{13}\text{C NMR}$ (CDCl_3) δ 165.0, 164.8, 147.9, 146.3, 137.2, 136.9, 133.1, 132.9, 131.3, 129.64, 129.59, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 76.3, 76.2, 71.5, 69.7, 63.8, 62.8, 26.5, 19.1; HRMS calcd for $\text{C}_{29}\text{H}_{33}\text{NO}_4\text{Si}$ (M^+) 487.2179, found 487.2172.



To a solution of **10** (500 mg, 3.0 mmol) and Et_3N (1.27 mL, 9.1 mmol) in CH_2Cl_2 (10 mL) was added acryloyl chloride (0.25 mL, 3.0 mmol) under a nitrogen atmosphere at 0°C . After the reaction mixture was stirred at rt for 10 h, the reaction mixture was diluted with aqueous NaHCO_3 and then extracted with CH_2Cl_2 . The organic phase was washed with brine, dried over MgSO_4 , and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 4:1) afforded **1B** (607 mg, 92%) as a colorless oil (*E:Z*=3:2): IR (CHCl_3) 2939, 1718, 1636, 1619, 1497 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.55 (3/5H, t, $J=6.0$ Hz), 7.4-7.3 (5H, m), 6.84 (2/5H, t, $J=4.0$ Hz), 6.5-6.4 (1H, m), 6.18 (3/5H, dd, $J=10.6$, 3.6 Hz), 6.09 (2/5H, dd, $J=10.2$, 3.2 Hz), 5.9-5.75 (1H, m), 5.14 (4/5H, s), 5.11 (6/5H, s), 4.97 (4/5H, d, $J=4.0$ Hz), 4.74 (6/5H, d, $J=4.0$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 165.5, 165.4, 147.3, 144.9, 137.2, 136.9, 131.64, 131.58, 128.3, 128.2, 127.94, 127.89, 127.6, 127.5, 76.4, 76.2, 61.9, 58.9; HRMS calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3$ (M^+) 219.0894, found 219.0900.



General Procedure. To a solution of **1A** (100 mg, 0.205 mmol) and R^2I (2.46 or 1.23 mmol) in solvent (20 mL) was added Et_3B (1.0 M in hexane, 0.615 or 1.23 mmol) at reflux or 20°C . After the reaction mixture was stirred at the same temperature for 15 min, the reaction mixture was diluted with aqueous NaHCO_3 and then extracted with CH_2Cl_2 . The organic phase was dried over MgSO_4 , and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 6:1) or preparative TLC (hexane/AcOEt 6:1, 2-fold development) afforded **2Aa-d** (see: Table 1).

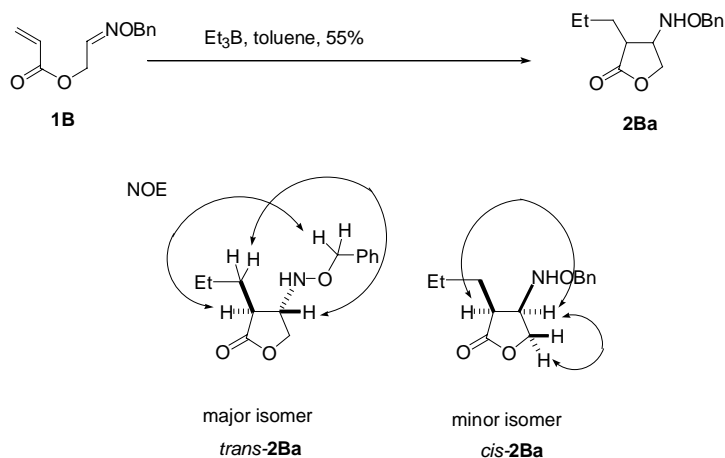
2Aa (major isomer) as a colorless oil: $[\alpha]_D^{25} -38.4$ (*c* 0.5, CHCl_3); IR (CHCl_3) 2932, 1770, 1428 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.68-7.61 (4H, m), 7.46-7.26 (11H, m), 4.64 (2H, s), 4.34 (1H, m), 3.88, 3.76 (each 1H, dd, $J=11.5$, 3.5 Hz), 3.67 (1H, br dd, $J=8.0$, 6.0 Hz), 2.66 (1H, m), 1.81-1.73 (1H, m), 1.64-1.55 (1H, m), 1.51-1.39 (2H, m), 1.04 (9H, s), 0.92 (3H, t, $J=7.0$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 177.3, 137.1, 135.7, 135.6, 132.9, 132.6, 129.92, 129.89, 128.6, 128.5, 128.2, 127.8, 80.6, 76.8, 63.5, 62.8, 42.7, 31.4, 26.8, 20.1, 19.2, 13.9; HRMS calcd for $\text{C}_{31}\text{H}_{39}\text{NO}_4\text{Si}$ (M^+) 517.2647, found 517.2661.

2Aa (minor isomer) as a colorless oil: $[\alpha]_D^{25} +8.92$ (*c* 0.8, CHCl_3); IR (CHCl_3) 2932, 1772, 1472, 1428 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.66-7.60 (4H, m), 7.46-7.27 (11H, m), 4.67 (2H, s), 4.47 (1H, m), 3.89 (1H, dd, $J=11.5$, 3.5 Hz), 3.75 (1H, dd, $J=11.5$, 3.0 Hz), 3.78-3.74 (1H, m), 2.92 (1H, m), 1.84-1.75 (1H, m), 1.55-1.42 (3H, m), 1.03 (9H, s), 0.95 (3H, t, $J=7$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 178.2, 137.0, 135.6, 135.5, 132.7, 132.2, 130.0, 128.52, 128.48, 128.1, 127.9, 81.8, 76.7, 64.7, 60.4, 42.2, 26.8, 26.1, 21.4, 19.2, 14.0; HRMS calcd for $\text{C}_{31}\text{H}_{39}\text{NO}_4\text{Si}$ (M^+) 517.2647, found 517.2636.

2Ab (major isomer) as a colorless oil: $[\alpha]_D^{23} +115.0$ (*c* 1.1, CHCl₃); IR (CHCl₃) 2932, 1771, 1428 cm⁻¹; ¹H NMR (CDCl₃) δ 7.67-7.61 (4H, m), 7.46-7.27 (11H, m), 4.67 (2H, s), 4.37 (1H, m), 3.88, 3.75 (each 1H, dd, *J*=12.0, 3.0 Hz), 3.64 (1H, br dd, *J*=7.5, 7.0 Hz), 2.73 (1H, m), 1.88-1.79 (1H, m), 1.74-1.68 (1H, m), 1.52-1.45 (1H, m), 1.034 (9H, s), 1.030, 0.92 (each 3H, d, *J*=7.0 Hz); ¹³C NMR (CDCl₃) δ 177.5, 137.1, 135.6, 135.5, 132.9, 132.5, 129.89, 129.86, 128.6, 128.5, 128.2, 127.9, 127.81, 127.80, 80.6, 76.8, 63.63, 63.56, 40.7, 39.2, 26.8, 25.5, 22.8, 21.9, 19.2; HRMS calcd for C₃₂H₄₁NO₄Si (M⁺) 531.2803, found 531.2784.

2Ac (major isomer) as a colorless oil: $[\alpha]_D^{23} +89.7$ (*c* 1.5, CHCl₃); IR (CHCl₃) 2930, 1771, 1430 cm⁻¹; ¹H NMR (CDCl₃) δ 7.67-7.61 (4H, m), 7.45-7.26 (11H, m), 4.68 (2H, s), 4.39 (1H, m), 3.89, 3.76 (each 1H, dd, *J*=12.0, 3.0 Hz), 3.64 (1H, m), 2.78 (1H, m), 1.78-0.84 (13H, m), 1.03 (9H, s); ¹³C NMR (CDCl₃) δ 177.5, 136.9, 135.5, 135.4, 132.8, 132.4, 129.7, 128.4, 128.3, 127.9, 127.6, 80.6, 76.3, 63.43, 63.39, 39.9, 37.5, 34.6, 33.3, 32.3, 26.6, 26.3, 26.0, 25.8, 19.0; HRMS calcd for C₃₅H₄₅NO₄Si (M⁺) 571.3115, found 571.3102.

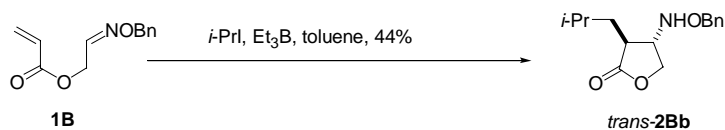
2Ad (major isomer) as a colorless oil: $[\alpha]_D^{23} +143.5$ (*c* 0.9, CHCl₃); IR (CHCl₃) 2933, 1770, 1428 cm⁻¹; ¹H NMR (CDCl₃) δ 7.67-7.64 (4H, m), 7.45-7.27 (11H, m), 4.65 (2H, s), 4.35 (1H, m), 3.88, 3.75 (each 1H, dd, *J*=12.0, 3.5 Hz), 3.67 (1H, br dd, *J*=7.5, 6.0 Hz), 2.66 (1H, m), 2.04-1.96 (1H, m), 1.86-1.01 (10H, m), 1.03 (9H, s); ¹³C NMR (CDCl₃) δ 177.5, 137.1, 135.7, 135.6, 132.9, 132.6, 129.88, 129.86, 128.6, 128.5, 128.1, 127.8, 80.9, 76.7, 63.6, 63.4, 42.1, 37.4, 36.1, 32.9, 32.3, 26.8, 25.1, 25.0, 19.2; HRMS calcd for C₃₄H₄₃NO₄Si (M⁺) 557.2959, found 557.2952.



To a solution of **1B** (200 mg, 0.91 mmol) in toluene (40 mL) was added Et₃B (1.0 M in hexane, 4.6 mL, 4.6 mmol) at reflux. After the reaction mixture was stirred at the same temperature for 15 min, the reaction mixture was diluted with aqueous NaHCO₃ and then extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, and concentrated at reduced pressure. Purification of the residue (a *trans/cis* mixture in 3:1) by preparative TLC (hexane/AcOEt 4:1, 2-fold development) afforded *trans*-**2Ba** (94 mg, 41%) and *cis*-**2Ba** (31 mg, 14%).

trans-**2Ba** (major isomer) as a colorless oil: IR (CHCl₃) 2965, 1773, 1455 cm⁻¹; ¹H NMR (CDCl₃) δ 7.42-7.28 (5H, m), 4.70 (2H, s), 4.32 (1H, dd, *J*=9.6, 6.3 Hz), 4.13 (1H, dd, *J*=9.6, 4.5 Hz), 3.63 (1H, br m), 2.45 (1H, m), 1.75 (1H, m), 1.55 (1H, m), 1.45 (2H, m), 0.94 (3H, t, *J*=7.2 Hz); ¹³C NMR (CDCl₃) δ 178.0, 137.0, 128.7, 128.5, 128.2, 77.1, 69.6, 61.9, 42.7, 31.2, 20.2, 13.8; HRMS calcd for C₁₄H₁₉NO₃ (M⁺) 249.1364, found 249.1377.

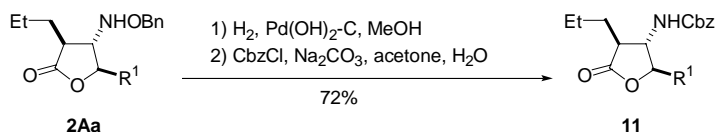
cis-**2Ba** (minor isomer) as a colorless oil: IR (CHCl₃) 2965, 1774, 1455 cm⁻¹; ¹H NMR (CDCl₃) δ 7.4-7.3 (5H, m), 4.71, 4.68 (each 1H, d, *J*=11.5 Hz), 4.37 (1H, d, *J*=10.0 Hz), 4.20 (1H, dd, *J*=10.0, 4.5 Hz), 3.78 (1H, br dd, *J*=6.5, 4.5 Hz), 2.52 (1H, m), 1.80 (1H, m), 1.55-1.4 (3H, m), 0.96 (3H, t, *J*=7.0 Hz); ¹³C NMR (CDCl₃) δ 177.7, 137.0, 128.6, 128.5, 128.2, 76.9, 70.1, 58.5, 42.2, 25.8, 21.1, 14.0; HRMS calcd for C₁₄H₁₉NO₃ (M⁺) 249.1364, found 249.1391.



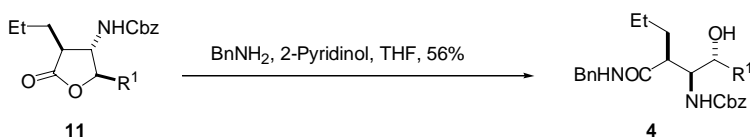
To a solution of **1B** (200 mg, 0.91 mmol) and *i*-PrI (0.45 mL, 4.57 mmol) in toluene (40 mL) was added Et₃B (1.0 M in hexane, 4.6 mL, 4.6 mmol) at reflux. After the reaction mixture was stirred at the same temperature for 15 min, the reaction mixture was diluted with aqueous NaHCO₃ and then extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, and concentrated at reduced pressure. Purification of the residue (a *trans/cis* mixture in 4:1) by preparative TLC (hexane/AcOEt 4:1, 2-fold development) afforded *trans*-**2Bb** (106 mg, 44%).

trans-**2Bb** (major isomer) as a colorless oil: IR (CHCl₃) 2962, 1771, 1455 cm⁻¹; ¹H NMR (CDCl₃) δ 7.41-7.29 (5H, m), 4.70 (2H, s), 4.32 (1H, dd, *J*=9.6, 6.3 Hz), 4.15 (1H, dd, *J*=9.9, 3.9 Hz), 3.59 (1H, br m), 2.51 (1H, m), 1.80 (1H, m),

1.62 (1H, m), 1.40 (1H, m), 0.95, 0.92 (each 3H, d, $J=6.9$ Hz); ^{13}C NMR (CDCl_3) δ 178.3, 136.9, 128.5, 128.3, 128.0, 76.8, 69.3, 62.2, 41.0, 38.1, 25.6, 22.5, 21.7; HRMS calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_3$ (M^+) 263.1520, found 263.1508.



A suspension of 10% $\text{Pd(OH)}_2\text{-C}$ (629 mg) in MeOH (5 mL) was stirred under a hydrogen atmosphere at rt for 30 min. To this suspension a solution of **2Aa** (500 mg, 0.97 mmol) in MeOH (2 mL) was added. After being stirred under a hydrogen atmosphere at rt for 10 h, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure to afford the crude amine. To a solution of the resulting crude amine in acetone (5 mL) was added a solution of Na_2CO_3 (200 mg, 1.9 mmol) in H_2O (3 mL) under a nitrogen atmosphere at rt. After a solution of CbzCl (330 mg, 1.9 mmol) in acetone (2 mL) was added dropwise at rt, the reaction mixture was stirred at rt for 14 h. After the reaction mixture was concentrated at reduced pressure, the resulting residue was diluted with water and then extracted with CH_2Cl_2 . The organic phase was dried over MgSO_4 and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 4:1) afforded **11** (377 mg, 72%) as a colorless oil: $[\alpha]_D^{28} +158.1$ (c 1.1, CHCl_3); IR (CHCl_3) 2962, 1774, 1723, 1456 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.72-7.63 (4H, m), 7.45-7.22 (11H, m), 4.62 (2H, s), 4.4-4.28 (1H, br m), 4.18-4.09 (1H, br m), 3.86, 3.77 (each 1H, br m), 2.64-2.53 (1H, br m), 1.8-1.3 (4H, m), 1.04 (9H, br s), 0.90 (3H, br t, $J=6.9$ Hz); ^{13}C NMR (CDCl_3) δ 176.4, 155.6, 140.6, 135.4, 132.6, 132.4, 129.6, 128.3, 128.2, 127.8, 127.6, 127.2, 126.7, 82.3, 66.7, 64.6, 61.9, 45.6, 30.6, 26.4, 19.4, 18.9, 13.7; HRMS calcd for $\text{C}_{32}\text{H}_{39}\text{N}_{10}\text{O}_5\text{Si}$ (M^+) 545.2596, found 545.2588.



To a solution of **11** (100 mg, 0.18 mmol) in THF (8 mL) were added benzylamine (0.5 mL, 4.6 mmol) and 2-pyridinol (87 mg, 0.92 mmol) under a nitrogen atmosphere at rt. After the reaction mixture was stirred at the same temperature for 20 h, the reaction mixture was concentrated at reduced pressure and then diluted with Et_2O . The organic phase was washed with 5% HCl, water, and brine, dried over MgSO_4 , and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 2:1) afforded **4** (67.4 mg, 56%) as colorless crystals: mp 145-148 $^\circ\text{C}$ (AcOEt/hexane); $[\alpha]_D^{28} -8.65$ (c 0.19, CHCl_3); IR (CHCl_3) 2962, 1721, 1666, 1428 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.65-7.55 (4H, m), 7.45-7.10 (16H, m), 4.66 (2H, s), 4.36, 4.31 (each 1H, d, $J=5.0$ Hz), 4.23 (1H, m), 3.97 (1H, m), 3.80-3.60 (2H, br m), 2.41 (1H, br m), 1.75-1.10 (4H, br m), 1.06 (9H, s), 0.86 (3H, t, $J=7.0$ Hz); ^{13}C NMR (CDCl_3) δ 173.4, 156.5, 140.8, 137.9, 135.5, 132.7, 132.4, 129.8, 128.5, 128.4, 128.3, 127.9, 127.73, 127.65, 127.4, 127.3, 126.8, 71.8, 66.7, 65.5, 65.1, 55.5, 43.4, 31.3, 26.8, 20.7, 19.0, 13.9; HRMS calcd for $\text{C}_{39}\text{H}_{48}\text{N}_2\text{O}_5\text{Si}$ (M^+) 652.3330, found 652.3354.