Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

New Entry to Heterocycles Based on Indium-Catalyzed Conia-Ene Reactions: Asymmetric Synthesis of (–)-Salinosporamide A

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Supporting Information

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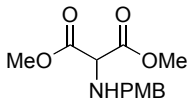
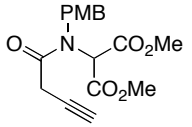
General. Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. *N*,*N*-Dimethyformamide (DMF), dichloromethane (CH_2Cl_2), acetonitrile (MeCN), and pyridine were distilled from CaH_2. Ethanol (EtOH) was distilled from sodium. Thin-layer chromatography (TLC) was performed using glass-packed silica gel plates (0.2 or 0.5 mm thickness). Column chromatography was performed using silica gel (particle size 100-210 mm (regular), 40-50 mm (flush)). Optical rotations were recorded on a digital polarimeter at ambient temperature. IR spectra were measured on a Fourier transform infrared spectrometer. ^{1}H NMR (400 and 500 MHz) and ^{13}C NMR (100 MHz) spectra were measured using $CDCl_3$, DMSO-d_6, or C_5D_5N as solvent, and chemical shifts are reported as δ values in ppm based on internal TMS (0.00 ppm, ^{1}H), $CHCl_3$ (7.26 ppm, ^{1}H; 77.0 ppm, ^{13}C), or C_5H_5N (135.4 ppm, ^{13}C). HRMS spectra were taken in EI or FAB mode.

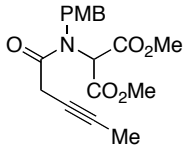


Dimethyl 2-(4-Methoxybenzylamino)malonate: To a solution of 2,5-dichlorothiophenium-1-bis(methoxycarbonyl)methylide[1] (5.80 g, 20.6 mmol) in toluene (75 mL) were added 4-methoxybenzylamine (2.7 mL, 20.6 mmol) and $Cu(acac)_2$ (53 mg, 0.206 mmol), and mixture was heated at 100 ˚C for 30 min. Most of the toluene was evaporated and the residue was with Et_2O, washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 100 g, hexane/AcOEt = 4/1) to give dimethyl 2-(4-methoxybenzylamino)malonate (2.60 g, 47 %) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7Hz, 2H), 6.86 (d, *J* = 8.7Hz, 2H), 4.08 (s, 1H), 3.77 (s, 3H), 3.76 (s, 6H), 3.74 (s, 2H), 2.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 158.9, 130.6, 129.6, 113.8, 63.7, 55.2, 52.7, 51.3; FTIR (neat) 3341, 1731, 1612, 1511, 1434, 1242, 1031, 819 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{17}NO_5$ (M^+) 267.1107, found 267.1087.

Preparation of Amide 1a-d, 6a, and 6b. To an ice-cooled solution of the carboxylic acid (1.0 mmol) and DMF (0.02 mL) in CH_2Cl_2 (2 mL) was added $(COCl)_2$ (0.1 mL, 1.2 mmol), and the mixture was stirred at rt for 1 h. The mixture was concentrated at 40 °C under atmospheric pressure to give the corresponding acid chloride. To a solution of crude acid chloride were added saturated $NaHCO_3$ (2 mL) and 2-(4-methoxybenzylamino)malonate (727 mg, 2.54 mmol) (or methyl 2-(4-methoxybenzylamino)acetate (418 mg, 2.0 mmol)). After being stirred at rt for 30 min, the reaction mixture was diluted with Et_2O, washed with 5 M HCl, saturated $NaHCO_3$, and brine, dried, concentrated, and chromatographed on silica gel.

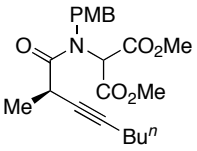


Dimethyl 2-(*N*-(4-Methoxybenzyl)but-3-ynamido)malonate (1a). Purification conditions (hexane/AcOEt = 4/1), a colorless oil, 65% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.28 (s, 1H), 4.70 (s, 2H), 3.80 (s, 3H), 3.68 (s, 6H), 3.35 (d, *J* = 2.44 Hz, 2H), 2.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168,1. 166.2, 159.3, 128.0, 127.2, 114.2, 75.6, 72.7, 61.0, 55.3, 52.9, 51.1, 26.1; FTIR (neat) 3282, 1748, 1671, 1612, 1513, 1436, 1279. 1029 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{19}NO_6$ (M^+) 333.1212, found 333.1212. Note that commercial available but-3-ynoic acid was used.

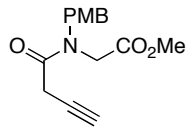


Dimethyl 2-(*N*-(4-Methoxybenzyl)pent-3-ynamido)malonate (1b). Purification conditions (hexane/AcOEt = 3/1), a colorless oil, 62% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.28 (s, 1H), 4.70 (s, 2H), 3.79 (s, 3H), 3.66 (s, 6H), 3.30 (q, *J* = 2.4 Hz, 2H),

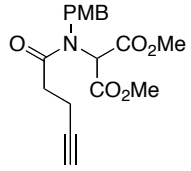
1.78 (t, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 166.3, 159.2, 128.1, 127.4, 114.1, 80.3, 70.5, 61.0, 55.3, 52.8, 51.1, 26.4, 3.6; FTIR (neat) 1763, 1675, 1515, 1438, 1254, 1178, 1031 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{21}NO_6$ (M^+) 347.1369, found 347.1361. Note that commercial available pent-3-ynoic acid was used.



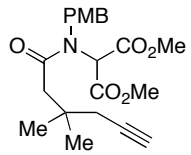
Dimethyl 2-((*R*)-*N*-(4-Methoxybenzyl)-2-methyloct-3-ynamido)-malonate (1c). Purification conditions (toluene/AcOEt = 7/1 then hexane/AcOE = 4/1), a colorless oil, 54% yield from (*R*)-2-methyloct-3-yn-1-ol (3 steps): $[\alpha]_D^{26}$ –0.82° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 1H), 4.88 (d, *J* = 17.1 Hz, 1H), 4.72 (d, *J*= 17.1 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.55 (s, 3H), 3.54-3.48 (m, 1H), 2.13 (td, *J* = 2.4, 6.8 Hz, 2H), 1.44-1.35 (m, 4H), 1.38 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 166.4, 166.3, 159.2, 128.2, 127.8, 114.0, 83.8, 77.2, 61.1, 55.3, 52.8, 52.7, 50.8, 30.7, 30.1, 21.9, 18.4, 17.9, 13.6; FTIR (neat) 1760, 1674, 1513, 1250, 1033 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{29}NO_6$ (M^+) 403.1994, found 403.2010; HPLC conditions, DAICEL CHIRALCEL OJ-H, hexane/*i*-PrOH = 10/1 (1.0 mL/min), t_R = 13.03 min (*R*). Note that the required carboxylic acid was prepared by Jones oxidation of (*R*)-2-methyloct-3-yn-1-ol[2] and used without purification.



Methyl 2-(*N*-(4-Methoxybenzyl)but-3-ynamido)acetate (1d). Purification conditions (hexane/Et_2O = 2/3), a colorless oil, 98% yield: ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 1.4H), 6.83 (d, *J* = 8.8 Hz, 0.6H), 4.03 (s, 0.3H), 3.98 (s, 0.7H), 3.78 (s, 0.9H), 3.76 (s, 2.1H), 3.68 (s, 3H), 3.41 (d, *J* = 3.2 Hz, 1.4H), 3.30 (d, *J* = 3.2 Hz, 0.6H), 2.43-2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.32, 169.30, 166.3, 167.4, 167.0, 159.4, 159.2, 129.8, 128.4, 128.0, 127.1, 114.3, 114.0, 76.2, 76.1, 72.7, 72.6, 55.21, 55.17, 52.3, 52.01, 51.97, 49.3, 48.3, 46.6, 26.2, 25.9; FTIR (neat) 3284, 1742, 1650, 1511, 1438, 1254, 1204, 1173, 1029 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1158, found 275.1149. Note that commercial available but-3-ynoic acid was used.

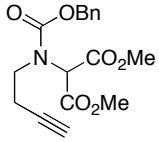


Dimethyl 2-(*N*-(4-Methoxybenzyl)pent-4-ynamido)malonate (6a). Purification conditions (hexane/AcOEt = 4/1), a colorless oil, 93% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.38 (s, 1H), 4.64 (s, 2H), 3.79 (s, 3H), 3.64 (s, 6H), 2.65-2.63 (m, 2H), 2.56-2.54 (m, 2H), 1.95 (t, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 160.5, 159.1, 127.7, 127.5, 114.1, 83.0, 68.9, 60.7, 55.3, 52.8, 50.3, 32.4, 14.3; FTIR (neat) 3287, 1757, 1666, 1613, 1514, 1436, 1279, 1029 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{21}NO_6$ (M^+) 347.1369, found 347.1368. Note that commercial available pent-4-ynoic acid was used.

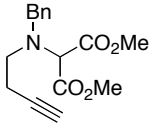


Dimethyl 2-(*N*-(4-Methoxybenzyl)-3,3-dimethylhex-5-ynamido)-malonate (6b). Purification conditions (hexane/AcOEt = 5/1), a colorless oil, 29% from 3,3-dimethylhex-5-yn-1-ol (3 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.24 (s, 1H), 4.67 (s, 2H), 3.80 (s, 3H), 3.64 (s, 6H), 2.45 (s, 2H), 2.33 (d, *J* = 2.5 Hz, 2H), 1.97 (t, *J* = 2.5 Hz, 1H), 1.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 166.7, 159.1, 128.0, 127.9, 114.1, 82.4, 70.4, 60.7, 55.3, 52.3, 51.1, 41.5, 34.3, 31.5, 27.2; FTIR (neat) 3287, 2113, 1761,1660, 1514, 1440, 1256, 1030 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{27}NO_6$ (M^+) 389.1838, found 389.1830. Note that the required carboxylic acid was prepared by Jones oxidation of 3,3-dimethylhex-5-yn-1-ol[3] and used without purification.

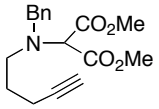
Preparation of Carbamate 6c and Amine 6d-f. To a solution of 2,5-dichlorothiophenium-1-bismethoxycarbonylmethylide[1] (5.3 g, 18.85 mmol) and the amine (18.85 mmol) in toluene (70 mL) was added $Cu(acac)_2$ (49 mg, 0.19 mmol). After heating at 100 °C for 2 h, saturated $NaHCO_3$ was added and the reaction mixture was extracted with Et_2O. The extract was washed with brine, dried, concentrated, and chromatographed on silica gel. Note that **6c** was obtained by benzyloxycarbonylation of dimethyl 2-(but-3-ynylamino)malonate prepared from but-3-yn-1-amine as mentioned above.



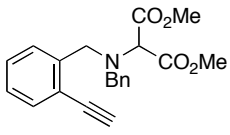
Benzyl Di(methoxycarbonyl)methylbut-3-ynylcarbamate (6c). Purification conditions (hexane/AcOEt = 5/1), a colorless oil, 50% yield from but-3-yn-1-amine via dimethyl 2-(but-3-ynylamino)malonate (2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 7.36 -7.31 (m, 5H), 5.34 (s, 0.6H), 5.20 (s, 1.2H), 5.10 (s, 0.8H), 5.04 (s, 0.4H), 3.81 (s, 3.7H), 3.68 (s, 2.3H), 3.58-3.53 (m, 2H), 2.55-2.50 (m, 2H), 1.96 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 166.5, 156.1, 135.8, 128.6, 128.4, 128.2, 128.1, 127.9 81.4, 81.1, 69.9, 69.8, 68.2, 68.0, 63.6, 62.9, 53.0, 52.9, 47.9, 46.5, 19.1, 18.4; FTIR (neat) 3291, 2118, 1772, 1470, 1039 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{19}NO_6$ (M^+) 333.1212, found 333.1205.



Dimethyl 2-(*N*-Benzyl-*N*-(but-3-ynyl)amino)malonate (6d). Purification conditions (hexane/AcOEt = 5/1), a colorless oil, 56% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 4.25 (s, 1H), 3.92 (s, 2H), 3.77 (s, 6H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.36 (dt, *J* = 2.4, 7.2 Hz, 2H), 1.95 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 138.7, 128.6, 128.4, 127.3, 82.5, 69.2, 66.6, 56.3, 52.3, 51.0, 19.0; FTIR (neat) 3292, 1741, 1438, 1234, 1152 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}NO_4$ (M^+) 289.1314, found 289.1309.

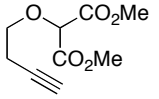


Dimethyl 2-(*N*-Benzyl-*N*-(pent-4-ynyl)amino)malonate (6e). Purification conditions (hexane/AcOEt = 5/1), a colorless oil, 55% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 4.22 (s, 1H), 3.85 (s, 2H), 3.77 (s, 6H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.22 (dt, *J* = 2.7, 7.2 Hz, 2H), 1.89 (t, *J* = 2.7 Hz, 1H) 1.69 (quin *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 139.0, 128.7, 128.3, 127.2, 84.4, 68.2, 66.3, 56.0, 52.2, 50.6, 27.3, 15.9; FTIR (neat) 3293, 1754, 1438, 1156, 1023 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1471, found 303.1456.



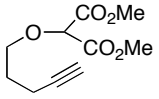
Dimethyl 2-(*N*-(2-Ethynylbenzyl)-*N*-benzylamino)malonate (6f). Purification conditions (hexane/AcOEt = 4/1 containing 1% Et_2O), a colorless oil, 45% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 9.6 Hz, 1H), 7.72-7.19 (m, 8H), 4.23 (s, 1 H), 4.10 (s, 2H), 3.89 (s, 2H), 3.78 (s, 6H), 3.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 141.2, 138.7, 132.7, 129.1, 128.9, 128.8, 128.3, 127.3, 126.8, 121.8, 81.64, 81.59, 65.4, 55.7, 52.8, 52.2; FTIR (neat) 3277, 1734, 1434, 1227, 1147 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{21}NO_4$ (M^+) 351.1471, found 351.1469.

Preparation of Ether 6g and 6h. To a stirred solution of dimethyl diazomalonate (1.0 g, 6.32 mmol) and the alcohol (6.0 mmol) in benzen (20 mL) was added $Rh_2(OAc)_4$ (15 mg, 0.034 mmol). After being heated at 60 °C for 2 h, the reaction mixture concentrated and chromatographed on silica gel.



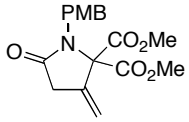
Dimethyl 2-(But-3-ynyloxy)malonate (6g). Purification conditions (hexane/AcOEt = 3/1), a colorless oil, 97% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 1H), 3.81 (s, 6H), 3.74 (t, *J* = 7.3 Hz, 2H), 2.57 (tt, *J* = 7.3, 2.4 Hz, 2H),

1.98 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 80.1, 79.0, 69.9, 69.2, 52.9, 19.7; FTIR (neat) 3285, 2140, 1748, 1438, 1241 cm^{-1}; HRMS (EI) calcd for $C_9H_{12}O_5(M)^+$ 200.0685, found 200.0655.

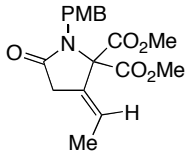


Dimethyl 2-(Pent-4-ynyloxy)malonate (6h). Pureification conditions (hexane/AcOEt = 3/1), a colorless oil, 71% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (s, 1H), 3.77 (s, 6H), 3.66 (t, J = 6.3 Hz, 2H), 3.23 (dt, J = 2.4, 6.8 Hz, 2H) 1.91 (t, J = 2.4 Hz, 1H)1.83 (quin, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 83.3, 79.0, 69.6, 68.6, 52.8, 28.2, 14.9; FTIR (neat) 3284, 2116, 1738, 1435, 1131 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{14}O_5(M\text{-}H)^+$ 213.0763, found 213.0734.

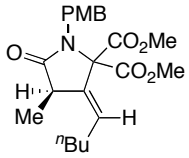
General Procedure for In(OTf)$_3$-catalyzed cyclizations (Table 1 and Table 2). The substrate (0.2 mmol) was azeotropically dried with toluene and dissolved in toluene (4 mL). To this solution at rt were added In(OTf)$_3$ (5-15 mol%) and DBU (0-15 mol%), and the mixture was refluxed for the indicated time. Most of the toluene was evaporated and the residue was purified by preparative TLC. The isolated yields of the cyclization products were given in Table 1 and Table 2.



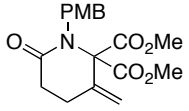
Dimethyl 1-(4-Methoxybenzyl)-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate (3a). Preparative TLC (MeOH/$CHCl_3$ = 1/50), a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 5.52 (t, J = 2.9 Hz, 1H), 5.38 (t, J = 2.9 Hz, 1H), 4.65 (s, 2H), 3.76 (s, 3H), 3.50 (s, 6H), 3.29 (t, J = 2.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 167.2, 158.7, 135.6, 129.1, 128.4, 114.5, 113.5, 75.4, 55.2, 53.2, 45.1, 35.5; FTIR (neat) 1740, 1710, 1611, 1515, 1434, 1389, 1246, 1170, 1045 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{19}NO_6$ (M^+) 333.1212, found 333.1212.



Dimethyl 1-(4-Methoxybenzyl)-3-ethylidene-5-oxopyrrolidine-2,2-dicarboxylate (3b). Preparative TLC (MeOH/$CHCl_3$ = 1/30), a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 5.92- 5.90 (m, 1H), 4.62 (s, 2H), 3.76 (s, 3H), 3.47 (s, 6H), 3.18 (t, J = 2.4 Hz, 2H), 1.71-1.69 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 167.7, 158.7, 129.0, 127.4, 128.6, 125.0, 113.5, 75.2, 55.2, 53.0, 45.1, 32.9, 15.1; FTIR (neat) 1745, 1713, 1514, 1226 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{21}NO_6$ (M^+) 347.1369, found 347.1371.

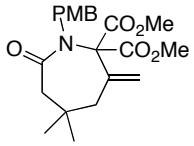


(*R*,*E*)-Dimethyl 1-(4-Methoxybenzyl)-4-methyl-5-oxo-3-pentylidene-pyrrolidine-2,2-dicarboxylate (3c). Preparative TLC (toluene/AcOEt = 4/1), a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 5.82-5.79 (m, 1H), 4.67 (d, J = 15.0 Hz, 1H), 4.54 (d, J = 15.0 Hz, 1H), 3.76 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H), 3.27-3.24 (m, 1H), 2.18-2.05 (m, 2H), 1.39 (d, J = 7.5 Hz, 3H), 1.39-1.30 (m, 4H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 168.3, 167.8, 158.7, 132.3, 131.3, 129.0, 128.8, 113.6, 74.6, 55.2, 52.9, 52.8, 45.1, 38.3, 31.1, 28.7, 22.2, 17.7, 13.9; FTIR (neat) 1740, 1707, 1513, 1244 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{29}NO_6$ (M^+) 403.1994, found 403.2010; HPLC conditions, DAICEL CHIRALCEL OD-H, hexane/*i*-PrOH = 10/1 (0.12 mL/min), t_R = 58.3 min (*R*) and 62.9 min (*S*).

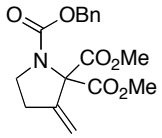


Dimethyl 1-(4-Methoxybenzyl)-3-methylene-6-oxopiperidine-2,2-dicarboxylate (7a). Preparative TLC (MeOH/$CHCl_3$ = 1/50), a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H),

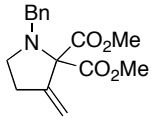
5.20-5.21 (m, 2H), 4.52 (s, 2H), 3.76 (s, 3H), 3.50 (s, 6H), 2.63-2.60 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 167.4, 158.5, 139.2, 129.1, 128.7, 114.9, 113.4, 75.1, 55.2, 53.1, 49.2, 32.6, 29.3; FTIR (neat) 1744, 1671, 1514, 1255, 1054 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{18}NO_6$ (M^+) 347.1369, found 347.1363.



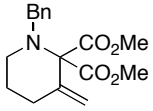
Dimethyl 1-(4-Methoxybenzyl)-5,5-dimethyl-3-methylene-7-oxo-azepane-2,2-dicarboxylate (7b). Preparative TLC (hexane/Et_2O = 1/1), a colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 7.13 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 7.8 Hz, 2H), 5.52 (s, 1H), 5.22 (s, 1H), 4.39 (s, 2H), 3.73 (s, 3H), 3.55 (s, 6H), 2.38 (s, 2H), 2.07 (s, 2H), 0.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.17, 167.74, 158.30, 140.84, 130.62, 128.08, 117.64, 113.45, 77.2, 55.23, 53.12, 50.93, 46.83, 45.93, 32.24, 28.02; FTIR (neat) 1745, 1667, 1513, 1444, 1248 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{27}NO_6$ (M^+) 389.1838, found 389.1847.



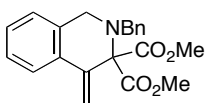
1-Benzyl 2,2-Dimethyl 3-methylenepyrrolidine-1,2,2-tricarboxylate (7c). Preparative TLC (hexane/AcOEt = 3/1), a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 7.38-7.26 (m, 5H), 5.49 (s, 0.5H), 5.45 (s, 0.5H), 5.12 (s, 0.5H), 5.18 (s, 1.5H), 5.11 (s, 1H), 3.77 (s, 3H), 3.77-3.70 (m, 2H), 3.56 (s, 3H), 2.73-2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 145.8, 136.1, 128.42, 128.40, 128.2, 128.0, 127.8, 111.9, 111.8, 86.8, 53.2, 53.0, 46.3, 45.9, 31.4, 30.4; FTIR (neat) 1706, 1404, 1350, 1232, 1044 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{19}NO_4$ (M^+) 333.1212, found 333.1208.



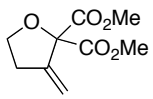
Dimethyl 1-Benzyl-3-methylenepyrrolidine-2,2-dicarboxylate (7d). Preparative TLC (hexane/AcOEt = 3/1), a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.24 (m, 5H), 5.38 (t, J = 2.2 Hz, 1H), 5.21 (t, J = 2.2 Hz, 1H), 3.86 (s, 2H), 3.82 (s, 6H), 2.84 (t, J = 6.6 Hz, 2H), 2.56-2.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 147.0, 139.3, 128.5, 128.2, 127.0, 111.1, 77.7, 54.7, 52.4, 49.5, 31.1; FTIR (neat) 1744, 1659, 1438, 1368, 1235, 1141, 1054 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}NO_4$ (M^+) 289.1314, found 289.1301.



Dimethyl 1-Benzyl-3-methylenepiperidine-2,2-dicarboxylate (7e). Preparative TLC (hexane/AcOEt = 3/1), a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.3 Hz, 2H), 7.32-7.23 (m, 3H), 5.08 (s, 1H), 4.71 (s, 1H), 3.87 (s, 2H), 3.83 (s, 6H), 2.59 (t, J = 5.4 Hz, 2H), 2.34 (t, J = 6.4 Hz, 2H), 1.60-1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 143.3, 140.1, 128.3, 128.1, 126.8, 112.2, 58.3, 52.4, 46.6, 32.2, 25.9; FTIR (neat) 1738, 1448, 1251, 1148, 1023 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1471, found 303.1474.

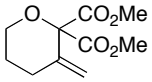


Dimethyl 2-Benzyl-1,2-dihydro-4-methyleneisoquinoline-3,3(4*H*)-di-carboxylate (7f). Preparative TLC (tolune/AcOEt = 0/1), a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 6.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 2H), 7.33-7.16 (m, 5H), 6.91 (d, J = 7.3 Hz, 1H), 5.92 (s, 1H), 5.15 (s, 1H), 3.99 (s, 2H), 3.81 (s, 6H), 3.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 139.1, 139.0, 133.3, 130.7, 128.5, 128.3, 127.9, 127.1, 126.8, 126.1, 124.1, 112.0, 78.0, 58.3, 52.6, 49.8; FTIR (neat) 1732, 1450, 1233, 1151, 1118 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{21}NO_4$ (M^+) 351.1471, found 351.1481.



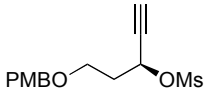
Dimethyl Dihydro-3-methylenefuran-2,2(3*H*)-dicarboxylate (7g). Preparative TLC (toluene/AcOEt = 5/1), a colorless oil: ^{1}H NMR (400 MHz,

$CDCl_3$) δ 5.51 (t, *J* = 2.0 Hz, 1H), 5.38 (t, *J* = 1.9 Hz, 1H), 4.12 (t, *J* = 6.84, 2H), 3.79 (s, 6H), 2.72-2.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 144.0, 112.3, 86.7, 68.8, 53.1, 32.8; FTIR (neat) 1770, 1442 cm^{-1}; HRMS (EI) calcd for $C_9H_{12}O_5$ (M^+) 200.0685, found 200.0660.

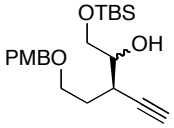


Dimethyl Tetrahydro-3-methylenepyran-2,2-dicarboxylate (7h). Preparative TLC (toluene/AcOEt = 4/1), a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 1H), 4.81 (s, 1H), 3.89 (s, 8H), 2.43 (s, 2H), 1.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 140.5, 113.3, 85.9, 65.1, 53.1, 30.5, 26.6; FTIR (neat) 1758, 1651, 1438, 1115 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{15}O_5$ [$(M+H)^+$] 215.0919, found 215.0890.

Asymmetric Synthesis of (–)-Salinosporamide A



(*S*)-5-(4-Methoxybenzyloxy)pent-1-yn-3-yl Methanesulfonate. Propargyl alcohol **8**[4] (98% ee) (1.21 g, 5.51 mmol) was dissolved into CH_2Cl_2 (18 mL), and Et_3N (1.15 mL, 8.25 mmol), MsCl (0.51 mL, 6.60 mmol), and DMAP (34 mg, 0.275 mmol) were added to the solution at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with Et_2O, washed with water and brine, dried and concentrated. Purification of the residue by column chromatography (SiO_2 50 g, hexane AcOEt = 5/1) gave the mesylate (1.56 g, 95%) as a colorless oil: $[\alpha]_D^{23}$ –49.9° (*c* 0.98, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.43-5.39 (m, 1H), 4.46 (d, *J* = 9.2 Hz, 1H), 4.43 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 3.62-3.55 (m, 2H), 3.11 (s, 3H), 2.70 (d, *J* = 2.0 Hz, 1H), 2.24-2.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.0, 129.4, 113.8, 79.2, 76.9, 72.9, 68.6, 64.6, 55.2, 39.0, 35.9; FTIR (neat) 3276, 1612, 1514, 1362, 1248, 1176, 1094, 1033 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}O_5S$ (M^+) 298.0875, found 298.0865.

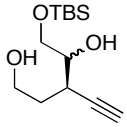


(2*RS*,3*R*)-3-(2-(4-Methoxybenzyloxy)ethyl)-1-(*tert*-butyldimethylsilyloxy)pent-4-yn-2-ol (9). To a degassed solution of $Pd(OAc)_2$ (900 mg, 4 mmol) in THF (200 mL) at –70 °C were added triphenylphosphine (1.05 g, 4 mmol), a solution of the mesylate (12.2 g, 40.9 mmol) in THF (200 mL), a solution of (*tert*-butyldimethylsilyloxy)acetaldehyde[4] (12.9 g, 74 mmol) in THF (200 mL), and Et_2Zn (1 M in hexane, 444 μL, 444 mmol). After being stirred at –40 °C for 5 min, the mixture was allowed to warm to –20 °C over 50 min, and stirred for additional 20 min. 2 M HCl (500 mL) was added and the reaction mixture was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine, dried, concentrated, chromatographed (SiO_2 500 g, hexane/AcOEt = 10/1) to give **9** (9.73 g, 63 %), a colorless oil, as a 90:10 epimeric mixture, a part of which was separated by preparative TLC (hexane/AcOEt-3/1) for data-collection.

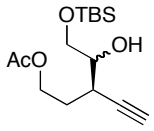
More Polar Epimer (major): $[\alpha]_D^{22}$ –10.9° (*c* 1.34, $CHCl_3$) (93 % ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.73-3.59 (m, 5H), 2.93-2.87 (m, 1H), 2.84 (d, *J* = 4.4 Hz, 1H), 2.12 (d, *J* = 2.4 Hz, 1H), 1.98-1.83 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.2, 129.3, 113.8, 82.8, 72.80, 72.77, 71.9, 67.3, 65.1, 55.2, 31.9, 31.8, 25.9, 18.3, –5.4; FTIR (neat) 3438, 3300, 1617, 1514, 1466, 1256, 1120 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{34}O_4Si$ (M^+) 378.2227, found 378.2226; HPLC conditions: DAICEL CHIRALCEL OD-H, hexane/*i*-PrOH = 20/1 (0.7 mL/min), t_R = 10.4 min (enantiomer: 15.1 min).

Less Polar Epimer (minor): $[\alpha]_D^{23}$ –9.2° (*c* 0.38, $CHCl_3$) (93 % ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.46 (s, 2 H), 3.86-3.76 (m, 1H), 3.80 (s, 3H), 3.75-3.56 (m, 4H), 2.75 (d, *J* = 5.4 Hz, 1H), 2.76-2.68 (m, 1H), 2.14-2.05 (m,

1H), 2.09 (d, *J* = 2.4 Hz, 1H), 1.78-1.69 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.5, 129.2, 113.7, 83.9, 73.3, 72.7, 71.4, 67.5, 64.9, 55.3, 32.0, 30.6, 25.9, 18.3, –5.4; FTIR (neat) 3466, 3305, 1611, 1514, 1250, 1098, 1039 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{34}O_4Si$ (M^+) 378.2226, found 378.2240; HPLC conditions: DAICEL CHIRALPAK AS, hexane/*i*-PrOH = 20/1 (0.7 mL/min), t_R = 7.4 min (enantiomer: 9.0 min).



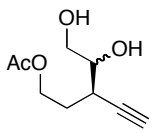
(3*R*,4*RS*)-3-Ethynyl-5-(*tert*-buthyldimethylsilyloxy)pentane-1,4-diol. To an ice-cooled solution of **9** (9.73 g, 25.7 mmol) in CH_2Cl_2 (235 mL) and water (24 mL) was added DDQ (7.59 g, 33.4 mmol), and the mixture was stirred at 0 °C for 2 h. Water (12 mL) was added and stirring was continued at 0 °C for additional 2 h. The reaction mixture was filtered through Celite, washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 350 g, hexane/AcOEt = 3/1) gave the corresponding alcohol (5.77 g, 87 %), a colorless oil, as a 90:10 epimeric mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85-3.75 (m, 1H), 3.74-3.67 (m, 1H), 3.66-3.55 (m, 3H), 2.82-2.76 (m, 1H), 2.09 (d, *J* = 2.4 Hz, 0.9H), 2.07 (d, *J* = 2.4 Hz, 0.1H), 1.83-1.75 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.7, 82.5, 73.2, 72.8, 72.2, 71.7, 65.0, 60.3, 59.8, 34.3, 33.7, 32.0, 31.8, 25.8, 18.2; FTIR (neat) 3389, 3309, 1468, 1391, 1255, 1127 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{26}O_3Si$ (M^+) 258.1651, found 258.1636.



(3*R*)-3-((1*R*,*S*)-(2-*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl)pent-4-ynyl Acetate. To a stirred solution of the diol (5.77 g, 22.4 mmol) in CH_2Cl_2 (220 mL) were added 2,4,6-trimethylpyridine (5.9 mL, 44.6 mmol) and acetyl chloride (1.9 mL, 26.8 mmol) at -78 °C. After stirring at –40 °C for 3.5 h, additional 2,4,6-trimethylpyridine (3 mL, 22.7 mmol) and acetyl chloride (1 mL, 14 mmol) were added. After being stirred at –40 °C for 3.5 h, the reaction mixture was diluted with water and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$, brine, dried, concentrated, and chromatographed (SiO_2 250 g, hexane/AcOEt = 5/1) to give the acetate (6.73 g, 100%), a colorless oil, as a 90:10 epimeric mixture, a part of which was separated by preparative TLC (hexane/AcOEt = 3/1, three times) for data-collection.

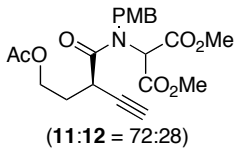
More Polar Epimer (major isomer): $[\alpha]_D^{22}$ –19.7° (*c* 0.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33-3.27 (m, 1H), 4.25-4.19 (m, 1H), 3.72-3.61 (m, 3H), 2.84-2.76 (m, 1H), 2.33 (d, *J* = 5.4 Hz, 1H), 2.16 (d, *J* = 2.4 Hz, 1H), 2.05 (s, 3H), 1.97-1.90 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 82.2, 72.6, 72.4, 64.9, 62.3, 31.6, 30.4, 25.8, 20.9, 18.2, –5.4; FTIR (neat) 3472, 3305, 1739, 1467, 1366, 1247, 1113 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{28}O_4Si$ (M^+) 300.1757, found 300.1730.

Less Polar Epimer (minor isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36-4.27 (m, 1H), 4.26-4.19 (m, 1H), 3.88-3.82 (m, 1H), 3.76-3.71 (m, 1H), 3.62-3.54 (m, 1H), 2.66-2.58 (m, 1H), 2.57 (d, *J* = 5.4 Hz, 1H), 2.21-2.11 (m, 1H), 2.13 (d, *J* = 2.0 Hz, 1H), 2.05 (s, 3H), 1.81-1.70 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H).



(3*R*)-3-((1*R*,*S*)-1,2-Dihydroxyethyl)pent-4-ynyl Acetate (10). To an ice-cooled solution of the acetate (6.73 g, 22.4 mmol) in THF (224 mL) was added TBAF (1M in THF, 24.6 mL, 24.6 mmol), and stirring was continued at the same temperature for 2 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried, concentrated, and chromatographed (SiO_2 150 g, Hexane/AcOEt = 1/1) to give **10** (3.82 g, 92 %), a colorless oil, as a 90:10 epimeric mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36-4.27 (m, 1H), 4.26-4.18 (m, 1H), 3.76-3.66 (m, 3H), 2.78-2.72 (m, 1H), 2.22 (d, *J* = 2.4 Hz, 0.9H), 2.19 (d, *J* = 3.0 Hz, 0.1H), 2.06 (s, 3H), 1.95-1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 100.5, 82.0, 73.4, 73.1, 72.8, 64.8,

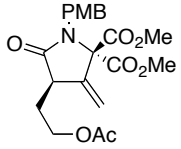
64.6, 62.2, 32.2, 30.3, 29.6, 20.9; FTIR (neat) 3428, 3291, 1732, 1391, 1369, 1247, 1041 cm^{-1}; HRMS (EI) calcd for $C_9H_{14}O_4$ (M^+) 186.0892, found 186.0875.



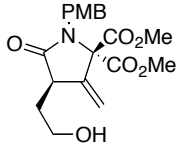
(**11**:**12** = 72:28)

Amide 11. To an ice-cooled solution of **10** (1.06 g, 5.69 mmol) in acetone (63 mL) were added $HIO_4 \cdot H_2O$ (5.16 g, 22.8 mmol) and CrO_3 (1.70 g, 17.1 mol) and water (63 mL), and the mixture was stirred at 0 °C for 1.5 h. $NaHSO_3$ (2.1 g) was added and the reaction mixture was acidified with 1 M HCl and extracted with AcOEt. The extract was washed with saturated $Na_2S_2O_3$ and brine, dried, and concentrated to give the corresponding carboxylic acid (1.00 g).

To an ice-cooled solution of crude carboxylic acid (1.00 g) in CH_2Cl_2 (57 mL) were added DMF (0.6 mL) and oxalyl chloride (1.5 mL, 17.1 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated and the residue was dissolved into toluene (28 mL) and cooled to 0 °C. To this mixture was added a solution of 2-(4-methoxybenzylamino)malonate (2.28 g, 3.79 mmol) in toluene (28 mL), and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with Et_2O, washed with water, saturated $NaHCO_3$, and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 90 g, hexane/AcOEt = 3/1 to 1/1) to give a 72:28 inseparable mixture of **11** and **12** (1.78 g, 75 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.8 Hz, 1.4H), 7.12 (d, *J* = 8.8 Hz, 0.6H), 6.88 (d, *J* = 8.8 Hz, 1.4H), 6.80 (d, *J* = 8.8 Hz, 0.6H), 5.63 (s, 0.3H), 5.41 (s, 0.3H), 5.19 (s, 0.7H), 4.92 (d, *J* = 16.7 Hz, 0.7H), 4.69 (d, *J* = 15.6 Hz, 0.3H), 4.66 (d, *J* = 16.7 Hz, 0.7H), 4.61 (d, *J* = 15.6 Hz, 0.3H), 4.30-4.09 (m, 2H), 3.80 (s, 2.1H), 3.76 (s, 0.9H), 3.73 (s, 2.1H), 3.65 (s, 2.1H), 3.69-3.54 (m, 1H), 3.53 (s, 0.9H), 3.46 (s, 0.9H), 3.35-3.30 (m, 0.3H), 2.31 (d, *J* = 2.4 Hz, 0.3H), 2.31 (d, *J* = 2.4 Hz, 0.3H) 2.33-2.22 (m, 1H), 2.21-2.04 (m, 1H), 2.04 (s, 0.9H), 1.94 (s, 2.1H); ^{13}C NMR (100 MHz, $CDCl_3$, ca 2.5 : 1 mixture of amide and lactam) δ 176.2, 171.8, 171.6, 170.7, 168.2, 168.1, 167.0, 166.9, 160.1, 159.6, 140.5, 129.8, 129.5, 129.1, 128.6, 128.3, 128.0, 115.5, 114.7, 114.2, 79.6, 77.6, 73.1, 61.9, 61.6, 61.1, 55.5, 53.4, 53.3, 53.1, 51.1, 45.4, 41.7, 32.1, 31.1, 30.0, 21.0, 20.0; FTIR (neat) 3275, 1763, 1674, 1613, 1514, 1438, 1263, 1039 cm^{-1};); HRMS (EI) calcd for $C_{21}H_{25}NO_8$ (M^+) 419.1581, found 419.1572.

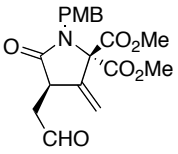


(*R*)-Dimethyl 1-(4-Methoxybenzyl)-4-(2-acetoxyethyl)-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate (12). To a solution of **11** (containing **12**) (1.70 g, 4.06 mmol) in toluene (40 mL) was added $In(OTf)_3$ (114 mg, 0.203 mmol), and the mixture was refluxed for 20 min. Most of the toluene was evaporated and the residue was chromatographed (SiO_2 40 g, hexane/AcOEt = 1/1) to give the lactam (1.63 g, 96 %) as a colorless oil: $[\alpha]_D^{24}$ +23.7° (*c* 1.00, $CHCl_3$) (90 % ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.63 (s, 1H), 5.40 (s, 1H), 4.69 (d, *J* = 15.6 Hz, 1H), 4.61 (d, *J* = 15.6 Hz, 1H), 4.30-4.18 (m, 2H), 3.76 (s, 3H), 3.53 (s, 3H), 3.46 (s, 3H), 3.35-3.30 (m, 1H), 2.20-2.14 (m, 2H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 170.6, 167.1, 158.6, 139.7, 129.0, 128.6, 128.3, 114.7, 113.4, 74.4, 60.7, 55.0, 52.9, 45.0, 41.4, 29.8, 20.7, 14.0; FTIR (neat) 2956, 1750, 1612, 1514, 1437, 1391, 1261, 1040 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{25}NO_8$ (M^+) 419.1580, found 419.1568; HPLC conditions: DAICEL CHIRALCEL OJ-H, hexane/*i*-Pr-OH = 3/1 (0.5 mL/min), t_R = 58.1 min (enantiomer: 42.0 min).

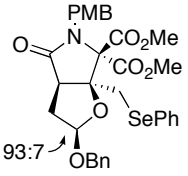


(*R*)-Dimethyl 1-(4-Methoxybenzyl)-4-(2-hydroxyethyl)-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate (13). To an ice-cooled solution of **12** (1.63 g, 3.89 mmol) in phosphate buffer (pH 6.4) (2.2 mL) and acetone (2.2 mL) was added lipase PS (1.63 g), and the mixture was stirred at 35 °C for 24 h.

The reaction mixture was filtered through Celite, concentrated, and chromatographed (SiO_2 50 g, hexane/AcOEt = 1/1) to give **13** (1.30 g, 89 %) as a colorless oil: $[\alpha]_D^{26}$ +26.9° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.61 (s, 1H), 5.41 (s, 1H), 4.72 (d, *J* = 15.6 Hz, 1H), 4.61 (d, *J* = 15.6 Hz, 1H), 3.91-3.84 (m, 2H), 3.77 (s, 3H), 3.53 (s, 3H), 3.48 (s, 3H), 3.50-3.44 (m, 1H), 3.36 (m, 1H), 2.12-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 167.22, 167.17, 158.8, 140.4, 129.0, 128.2, 114.6, 113.6, 77.2, 75.0 60.6, 55.2, 53.2, 45.3, 43.7, 34.6; FTIR (neat) 3420, 1745, 1514, 1438, 1253, 1176, 1057 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{23}NO_7$ (M^+) 377.1475, found 377.1461.

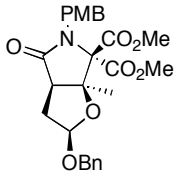


(*R*)-Dimethyl 1-(4-Methoxybenzyl)-4-(formylmethyl)-3-methylene-5-oxo-pyrrolidine-2,2-dicarboxylate (14). To an ice-cooled solution of **13** (509 mg, 1.35 mmol) in CH_2Cl_2 (17 mL) was added Dess-Matin periodinane (861 mg, 2.03 mmol), and the mixture was stirred at 0 °C for 4 h. The reaction was quenched with *i*-PrOH (3 mL), and the mixture was filtered through Celite which was washed with Et_2O. The combined filtrate and washings were concentrated and chromatographed (SiO_2 30 g, hexnane/Et_2O = 1/3) to give **14** (445 mg, 88 %) as a colorless oil: $[\alpha]_D^{25}$ +13.6° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.57 (s, 1H), 5.33 (s, 1H), 4.68 (s, 2H), 3.77 (s, 3H), 3.75-3.71 (m, 1H), 3.512 (s, 3H), 3.509 (s, 3H), 3.14 (dd, *J* = 18.3, 4.4 Hz, 1H), 2.91 (dd, *J* = 18.3, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 174.8, 167.2, 167.0, 158.8, 140.0, 129.1, 128.3, 114.9, 113.6, 77.2, 74.6, 55.2, 53.2, 45.4, 45.2, 39.1; FTIR (neat) 1749, 1709, 1613, 1513, 1436, 1395, 1247, 1175, 1054 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{21}NO_7$ (M^+) 375.1318, found 375.1313.

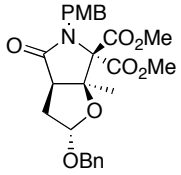


Cyclic Acetl 15. BnOH (0.46 mL, 4.48 mmol) and $AgBF_4$ (872 mg, 4.48 mmol) were added to an ice-cooled solution of **14** (420 mg, 1.12 mmol) in CH_2Cl_2 (56 mL) and then PhSeBr (924 mg, 3.92 mmol) was added at –20 °C. After being stirred at –20 °C for 30 min, the mixture was allowed to warm up to 0 °C and stirring was continued for 3 h. The reaction mixture was poured into a mixture of saturated $NaHCO_3$ (16 mL), brine (16 mL), and saturated Na_2SO_3 (16mL), and filtered through Celite. The filtrate was concentrated and chromatographed (SiO_2 50 g, hexnane/Et_2O = 4/1) to give **15** (608 mg, 85 %), a colorless oil, as an inseparable 93:7 epimeric mixture: (major *S*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2H), 7.34-7.19 (m, 10H), 6.70 (d, *J* = 8.8 Hz, 2H), 5.20 (d, *J* = 5.4 Hz, 1H), 5.03 (d, *J* = 15.2 Hz, 1H) 4.58 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 15.2 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 3.87 (s, 3H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.73 (s, 3H), 3.20 (d, *J* = 13.2 Hz, 1H), 3.16 (s, 3H), 3.00 (d, *J* = 8.8 Hz, 1H), 2.80 (ddd, *J* = 13.2, 8.8, 5.4 Hz, 1H), 2.50 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 168.0, 166.2, 158.8, 137.6, 131.9, 130.7, 129.1, 128.3, 128.2, 127.8, 127.4, 127.2, 113.4, 104.0, 91.1, 78.9, 77.2, 69.2, 55.2, 52.8, 52.5, 49.5, 45.5, 37.8, 32.9; FTIR (neat) 1754, 1708, 1513, 1438, 1392, 1247, 1017 cm^{-1}; HRMS (EI) calcd for $C_{32}H_{33}NO_8Se$ (M^+) 639.1371, found 639.1374.

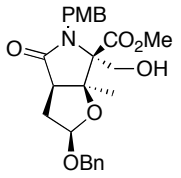
Deselenylation of 15. To a solution of **15**, a 93:7 epimeric mixture, (1.09 g, 1.71 mmol) in toluene (21 mL) were added AIBN (28 mg, 0.17 mmol) and *n*-Bu_3SnH (1.1 mL, 4.27 mmol). The mixture was heated at 100 °C for 1 h and most of the toluene was evaporated. Purification of the residue by column chromatography (SiO_2 70 g, hexane/AcOEt = 5/1-1/1) gave **16** (686 mg, 83 %) and its epimer (57.0 mg, 7 %) each as a colorless oil.



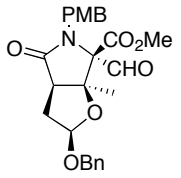
Compound 16 (major): $[\alpha]_D^{23}$ –48.1° (*c* 0.82, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 7H), 6.72 (d, *J* = 8.3 Hz, 2H), 5.16 (d, *J* = 5.2 Hz, 1H), 5.07 (d, *J* = 15.1 Hz, 1H) 4.60 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 15.1 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 1H), 3.90 (s, 3H), 3.74 (s, 3H), 3.16 (s, 3H), 2.97 (d, *J* = 8.3 Hz, 1H), 2.63 (d, *J* = 13.2 Hz, 1H), 2.25 (ddd, *J* = 13.2, 8.3, 5.2 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 168.0, 166.0, 158.8, 137.7, 130.8, 128.3, 128.2, 127.6, 127.3, 113.3, 102.3, 88.5, 78.3, 68.7, 55.2, 52.5, 52.4, 49.9, 45.3, 35.0, 21.3; FTIR (neat) 1753, 1710, 1513, 1440, 1392, 1247, 1176, 1028 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{29}NO_8$ (M^+) 483.1894, found 483.1891.



Epimer of 16 (minor): $[\alpha]_D^{23}$ +34.9° (*c* 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.24 (dd, *J* = 5.4, 4.4 Hz, 1H), 5.15 (d, *J* = 15.1 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 15.1 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 3.12 (s, 3H), 3.08 (d, *J* = 9.2 Hz, 1H), 2.77 (dd, *J* = 14.0, 5.4 Hz, 1H), 2.29 (ddd, *J* = 14.0, 9.2, 4.4 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 167.4, 166.3, 159.0, 137.6, 130.9, 128.4, 128.0, 127.9, 127.7, 113.5, 104.1, 87.6, 77.7, 70.4, 55.2, 52.5, 52.4, 50.9, 45.2, 35.1, 20.5; FTIR (neat) 2952, 1751, 1705, 1513, 1441, 1393, 1248, 1177, 1033 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{29}NO_8$ (M^+) 483.1893, found 483.1892.

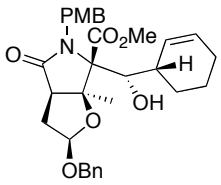


$NaBH_4$ Reduction of 16. To an ice-cooled solution of **16** (100 mg, 0.207 mmol) in EtOH (2.8 mL) and THF (1.3 mL) was added $NaBH_4$ (47.0 mg, 1.24 mmol), and the mixture was stirred at rt for 14 h. The reaction mixture was diluted with AcOEt, washed with 1 M citric acid (3 mL), saturated $NaHCO_3$, and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 3 g, hexane/AcOEt = 1/4) gave the corresponding alcohol (82.9 mg, 88 %) as a colorless amorphous: $[\alpha]_D^{20}$ = -87.7° (*c* 1.42, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.33-7.23 (m, 5H), 6.78 (d, *J* = 8.3 Hz, 2H), 5.18 (d, *J* = 15.4 Hz, 2H), 5.13 (d, *J* = 5.4 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 15.4 Hz, 1H), 4.26 (d, *J* = 12.0 Hz, 1H), 3.89 (dd, *J* = 12.9, 10.2 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.43 (dd, *J* = 12.9, 4.9 Hz, 1H), 2.79 (d, *J* = 8.3 Hz, 1H), 2.58 (d, *J* = 13.3 Hz, 1H), 2.23 (ddd, *J* = 13.3, 8.3, 5.4 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 168.7, 158.9, 138.0, 130.5, 129.3, 128.2, 127.5, 127.2, 114.1, 102.1, 88.7, 78.4, 68.8, 61.2, 55.2, 52.0, 50.5, 44.9, 34.9, 20.9; FT-IR (neat) 3377, 2925, 1755, 1681, 1514, 1449, 1247, 1179, 1036, 735 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{29}NO_7$ (M^+) 455.1944, found 455.1944.

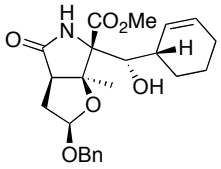


Aldehyde 17. To an ice-cooled solution of the alcohol (300 mg, 0.659 mmol) in CH_2Cl_2 (6.5 mL) was added Dess-Martin periodinane (560 mg, 1.318 mmol). After stirring at rt for 2 h, additional Dess-Martin periodinane (560 mg, 1.318 mmol) was added, and the mixture was stirred at rt for 1 h. The reaction was quenched with *i*-PrOH (4.6 mL), and the mixture was stirred for 5 min. The reaction mixture was diluted with AcOEt, washed with saturated $Na_2S_2O_3$, water, saturated $NaHCO_3$, and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 40 g, hexane/AcOEt = 1/1-1/4) gave **17** (281 mg, 94 %) as a colorless amorphous: $[\alpha]_D^{24}$ –65.5° (*c* 1.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.36-7.27 (m, 5H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 5.18 (d, *J* = 5.4 Hz, 1H), 4.66 (d, *J* = 14.9 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.48 (d, *J* = 14.9 Hz, 1H), 4.30 (d, *J* = 12.2 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 2.82 (d, *J* = 7.9 Hz, 1H), 2.64 (d, *J* = 13.3 Hz, 1H), 2.24 (ddd, *J* = 13.3, 7.9, 5.4 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 175.0, 166.7, 158.9, 137.6, 130.4, 128.4, 128.3, 127.3, 113.7, 102.8, 88.8, 82.1, 68.9, 55.1, 52.6, 49.5, 46.0, 34.9, 21.7; FTIR (neat) 1761, 1727, 1685, 1513, 1453, 1292, 1247, 1179,

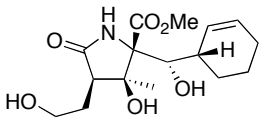
1037 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{27}NO_7$ (M^+) 453.1788, found 453.1785.



Alcohol 18. To a stirred solution of tri-*n*-butyl(cyclohex-2-enyl)stannane (1.27 g, 3.41 mmol) in THF (6 mL) at –78 °C were added *n*-BuLi (1.65 M in hexane, 2.07 mL, 3.41 mmol). After stirring at –78 °C for 1 h, $ZnCl_2$ (1.0 M in THF, 3.40 mL, 3.40 mmol) was added and the mixture was stirred at –78 °C for 30 min. To the resulting solution of the cyclohexenylzinc chloride at –78 °C was added a solution of **17** (258 mg, 0.569 mmol) in THF (3.5 mL), and stirring was continued at the same temperature for 2h. The reaction was quenched with saturated NH_4Cl and the reaction mixture was extracted with AcOEt. The extract was washed with water and brine, dried, concentrated, and chromatographed (SiO_2 10 g, Hexane/AcOEt = 2/1-1/1) to give **18** (267 mg, 88 %) as a colorless amorphous: $[\alpha]_D^{24}$ –41.4° (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 7H), 6.58 (d, *J* = 8.8 Hz, 2H), 5.81 (d, *J* = 10.2 Hz, 1H), 5.68 (d, *J* = 10.2 Hz, 1H), 5.11 (d, *J* = 5.4 Hz, 1H), 4.81 (d, *J* = 15.1 Hz, 1H), 4.57 (d, *J* = 15.1 Hz, 1H), 4.52 (d, *J* = 12.2 Hz, 1H), 4.27 (d, *J* = 12.2 Hz, 1H), 4.00 (t, *J* = 8.8 Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 2.91 (d, *J* = 8.3 Hz, 1H), 2.53 (d, *J* = 13.8 Hz, 1H), 2.29 (ddd, *J* = 13.8, 8.3, 5.4 Hz, 1H), 2.13 (br, 1H), 1.97 (br, 2H), 1.73-1.67 (m, 3H), 1.57 (s, 3H), 1.41-1.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 169.6, 158.0, 138.0, 130.5, 129.9, 128.6, 128.2, 127.6, 127.2, 127.1, 113.3, 102.1, 91.3, 79.7, 76.6, 68.9, 55.1, 51.6, 50.2, 47.8, 39.5, 35.1, 26.3, 25.0, 21.3, 20.9; FTIR (neat) 3317, 1750, 1680, 1511, 1450, 1248, 1177, 1089, 1034 cm^{-1}; HRMS (EI) calcd for $C_{31}H_{37}NO_7$ (M^+) 535.2571, found 535.2567.



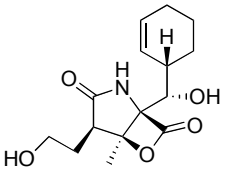
Lactam 19. To an ice-cooled solution of **18** (79.0 mg, 0.147 mmol) in MeCN were added CAN (194 mg, 0.355 mmol) and water (5 mL), and the mixture was stirred at 0 °C for 3 h. The reaction was quenched with saturated Na_2SO_3 and the reaction mixture was extracted with AcOEt. The extract was washed with water, saturated $NaHCO_3$, and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 2.5 g, hexane/AcOEt = 1/2-1/4) gave **19** (50.6 mg, 83 %) as a colorless amorphous: $[\alpha]_D^{23}$ –101.1° (*c* 1.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.24 (m, 5H), 6.30 (brs, 1H), 5.99-5,97 (m, 1H), 5.64-5.62 (m, 1H), 5.10 (d, *J* = 4.4 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.23 (m, 1H), 4.02 (m, 1H), 3.81 (brs, 3H), 2.83 (d, *J* = 7.8 Hz, 1H), 2.51 (d, *J* = 13.2 Hz, 1H), 2.32 (d, *J* = 9.8 Hz, 1H), 2.19 (m, 2H), 1.97 (m, 2H), 1.89 (brs, 1H), 1.77-1.68 (m, 1H), 1.60 (s, 3H), 1.54-1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 170.2, 137.9, 134.2, 128.1, 127.8, 127.2, 124.3, 101.6, 92.2, 77.2, 76.0, 68.4, 52.2, 50.3, 38.0, 34.6, 27.8, 24.7, 20.8, 20.6; FTIR (neat) 3357, 1712, 1439, 1376, 1264, 1091, 1026 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{29}NO_6$ (M^+) 415.1995, found 415.1992.



Triol 20. Na (80 mg, 3.5 mmol) was dissolved into liquid NH_3 (8 mL) at –78 °C. To this mixture was added a solution of **19** (78.0 mg, 0.188 mmol) in THF (2 mL). After stirring at –78 °C for 40 min, NH_4Cl was added and the mixture was allowed to warm up to rt, and stirring was continued until most of the NH_3 was evaporated. The reaction mixture was diluted with AcOEt, washed with water and brine, dried, and concentrated to give the corresponding lactol (65 mg) which was used for the next reaction without purification.

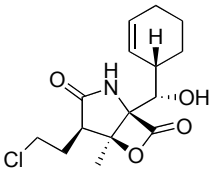
To an ice-cooled solution of crude lactol (65 mg) in THF (1.2 mL) and water (0.6 mL) was added $NaBH_4$ (42.0 mg, 1.13 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated NH_4Cl and the reaction mixture was extracted with AcOEt. The extract was washed with brine, dried, concentrated, and chromatographed (SiO_2 4

g, hexane/AcOEt = 1/4 then MeOH/AcOEt = 1/20) to give the **20** (44.0 mg, 71 %) as a colorless solid: $[\alpha]_D^{26}$ –50.0° (*c* 1.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 6.12-6.03 (m, 1H), 5.82-5.72 (m, 1H), 5.26 (br s, 1H), 4.14 (d, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 3.84-3.67 (m, 3H), 2.85 (d, *J* = 7.8 Hz, 1H), 2.21-2.16 (m, 2H), 2.02-1.96 (m, 3H), 1.80-1.70 (m, 2H), 1.67-1.56 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 172.7, 135.0, 123.5, 81.8, 79.8, 75.3, 62.1, 52.9, 51.5, 38.7, 28.5, 26.2, 24.8, 20.4, 19.7; FTIR (neat) 3317, 1726, 1690, 1436, 1381, 1278, 1045 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{25}NO_6$ (M^+) 327.1682, found 327.1669.



β-Lactone. To a suspension of Te (1.45 g, 11.4 mmol) in toluene (5 mL) was added Me_3Al (2.0 M in toluene, 5 mL, 10 mmol), and the mixture was refluxed for 6 h and cooled to rt. The resulting $[Me_2AlTeMe]_2$ (ca 0.8 M in toluene, 2.1 mL, 10.4 mmol) was added to **20** (52.0 mg, 0.159 mmol). After stirring at rt for 8 h, 1 M HCl (3 mL) and AcOEt (3 mL) were added, and the mixture was stirred at rt for 1h. The aqueous layer was washed with AcOEt, acidified (pH 1) with 1 M HCl, and extracted with AcOEt. The extract was washed with water, dried, and concentrated to give the corresponding carboxylic acid (41 mg).

To a solution of the carboxylic acid (41 mg) in CH_2Cl_2 (2.7 mL) were added pyridine (323 μl) and BOPCl (121 mg, 0.476 mmol) and the mixture was stirred at rt for 3 h. The reaction mixture was diluted with AcOEt, washed with saturated NH_4Cl and brine, dried, concentrated, and chromatographed (SiO_2 2 g, hexane/AcOEt = 1/1–1/4) to give the β-lactone (25.3 mg, 54 %) as a colorless solid: $[\alpha]_D^{24}$ –76.7° (*c* 0.63, MeOH); ^{1}H NMR (400 MHz, C_5D_5N) δ 10.57 (s,1H), 6.43 (d, *J* = 9.3 Hz, 1H), 5.87 (d, *J* = 9.3 Hz, 1H), 5.01 (br, 2H), 4.31-4.23 (m, 2H), 4.22-4.13 (m, 1H), 3.37 (t, *J* = 6.8 Hz, 1H), 2.92-2.81 (m, 1H), 2.58-2.49 (m, 1H), 2.35-2.27 (m, 2H), 2.16 (s, 3H), 1.95-1.87 (m, 2H), 1.75-1.64 (m, 2H), 1.43-1.29 (m, 1H); ^{13}C NMR (100 MHz, C_5D_5N) δ 178.3, 170.0, 129.1, 128.9, 87.1, 80.3, 71.1, 59.9, 46.4, 39.4, 29.2, 26.6, 25.4, 21.8, 20.4; FTIR (neat) 3443, 1815, 1672, 1428, 1348, 1079, 1028 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{21}NO_5$ (M^+) 295.1420, found 295.1408.



Salinosporamide A. To a stirred solution of the β-lactone (31.0 mg, 0.105 mmol) in MeCN (1.4 mL) and pyridine (1.4 mL) at rt was added Ph_3PCl_2 (199 mg, 0.597 mmol), and stirring was continued for 3.5 h. The reaction was quenched with water (3 mL) and the reaction mixture was extracted with AcOEt. The extract was washed with brine, dried, concentrated, and chromatographed (SiO_2 6 g, hexane/AcOEt = 4/1-2/1) to give salinosporamide A (25.3 mg, 77 %) as a colorless solid, which was recrystallized from toluene to give colorless needles: $[\alpha]_D^{24}$ –76.0° (*c* 0.48, MeOH) [lit.[5] $[\alpha]_D^{24}$ –72.9° (*c* 0.55, MeOH)]; mp 167-168 °C (lit.[5] mp 169-171 °C); ^{1}H NMR (500 MHz, C_5D_5N) δ 10.66 (s,1H), 6.44 (d, *J* = 10.5 Hz, 1H), 5.92-5.90 (m, 1H), 5.07 (brs, 1H), 4.27 (t, *J* = 11.5 Hz, 1H), 4.19-4.13 (m, 1H), 4.07-4.01 (m, 1H), 3.20 (t, *J* = 7.0 Hz, 1H), 2.92-2.83 (m, 1H), 2.53-2.48 (m, 1H), 2.37-2.32 (m, 2H), 2.09 (s, 3H), 1.93 (m, 2H), 1.74-1.66 (m, 2H), 1.38 (m, 1H); ^{13}C NMR (125 MHz, C_5D_5N) δ 176.82, 169.31, 128.94, 128.56, 86.19, 80.23, 70.85, 46.18, 43.17, 39.19, 28.88, 26.33, 25.23, 21.61, 19.87; FTIR (neat) 3393, 1826, 1696, 1433, 1383, 1227, 1145, 1022 cm^{-1}; MS (FAB) m/z 154 (100), 314 [(M+H)$^+$]; HRMS (FAB) calcd for $C_{15}H_{21}ClNO_4$ [(M+H)$^+$] 314.1159, found 314.1178.

References and Note

[1] S. Husinec, I. Juranic, A. Llobera, A. E. A. Porter, *Synthesis* **1988**, 721-723.

[2] Prepared from enantiomerically pure (*R*)-4-(*tert*-butyldimethylsilyl)oxy-3-methylbut-1-

yne in two steps in 97% yield (i. *n*-BuLi, BuI, THF-HMPA, –78 °C; ii. TBAF, THF).
[3] S. Bogen, L. Fensterbank, M. Malacria, *J. Org. Chem.* **1999**, *64*, 819-825.
[4] Y. Kiyotsuka, J. Igarashi, Y. Kobayashi, *Tetrahedron Lett.* **2002**, *43*, 2725-2729.
[5] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *43*, 355.