Supplementary Material (ESI) for Chemical Communications

Total Synthesis of (+)-Kalkitoxin

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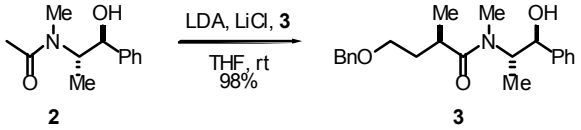
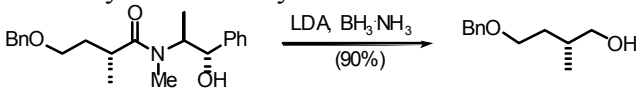
- *Experimental procedure*
- *Characterization data*
- *X-ray crystallographic data for* ***8***



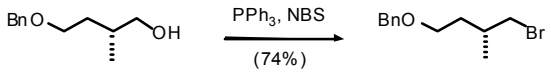
2 **3**

LiCl (2.16 g, 54.8 mmol) was placed in a 100 mL round-bottomed flask which was flame-dried under argon. To the flask were added dry THF (8 mL) at –78 °C, diisopropylamine (2.24 mL, 16 mmol), and *n*-BuLi (7.6 mL, 15.2 mmol, 2.0 M hexane solution). The suspension was stirred for 10 min at –78 °C and for 15 min at 0 °C, and then was cooled to –78 °C. To the suspension was slowly added a THF (8 mL) solution of **2** (1.91 g, 8.64 mmol) by cannula, and the mixture was stirred for 1 h at –78 °C, for 15 min at 0 °C, and for 5 min at ambient temperature. The mixture was cooled to 0 °C, a THF (4 mL) solution of benzyl 2-iodoethyl ether (1.15 g, 4.4 mmol) was added, and the mixture was stirred for 15 h at ambient temperature. The reaction was quenched with sat'd aqueous NH_4Cl, and the solution was extracted with EtOAc (200 mL x 2). The combined extract was washed with aqueous NH_4Cl and brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (40 to 60% EtOAc/hexanes) to give 1.39 g (98%) of **3** as a colorless oil: $[\alpha]_D^{24}$ +52.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (7:3 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$) δ 7.29 (m, 10H), 4.78-4.40 (m, 4H), 4.12* (m, 1H), 3.68* (m, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 3.29 (m, 1H), 3.21* (m, 1H), 2.88 (m, 1H), 2.83 (s, 3H), 2.81* (s, 3H), 2.25* (m, 1H), 1.93 (m, 1H), 1.68* (m, 1H), 1.65 (m, 1H), 1.1 (m, 6H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 176.9*, 142.4, 141.4*, 138.1, 128.3*, 128.1, 128.0*, 127.8, 127.5, 127.4*, 127.3, 127.2*, 126.7, 126.1*, 75.8, 75.0*, 72.6, 68.2*, 67.7, 57.9, 33.8, 32.8, 32.3*, 26.6*, 18.1*, 17.1, 15.5*, 14.1.; IR (neat) 3386, 2968, 2932, 2869, 1618, 1454, 1089 cm^{-1}; MS (CI) *m/z* 356 $(M+H)^+$, 338, 279, 248,191, 148, 121, 91.; HRMS (CI) *m/z* 356.2224 (M+H) (calcd for $C_{22}H_{30}O_3N$: 356.2226)



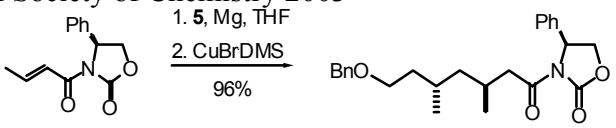
3 4

(2*R*)-4-Benzyloxy-2-methylbutanol. To a solution of diisopropylamine (8.45 mL, 60.3 mmol) in THF (80 mL) was added *n*-BuLi (2.1M, 28.7 mL, 60.3mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 20 min. Borane-ammonia complex (90%, 1.90 g, 61.5 mmol) was added in one portion, the suspension was stirred at 0 °C for 20 min, and was warmed to room temperature. After 15 min, the suspension was cooled to 0 °C and a solution of **3** (4.28 g, 12.06 mmol) in THF (12 mL) was added via cannula. The mixture was warmed to room temperature during 10 min, held at that temperature for 2.5 h, and then cooled to 0 °C. A 3N HCl solution was added slowly to quench the excess hydride, and the biphasic solution was stirred for 30 min at 0 °C and for 15 min at room temperature, and then separated. The aqueous layer was extracted with Et_2O and the extract was washed with brine, dried, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 2:1) gave **4** as a colorless oil (2.11g, 90%): $[\alpha]_D^{20}$ +10.4 (*c* 7.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.38 (m, 5H), 4.51 (s, 2H), 3.38-3.62 (m, 4H), 2.94 (bs, 1H), 1.66-1.83 (m, 2H), 1.49-1.59 (m, 1H), 0.92 (d, 3H, *J* = 6.6 Hz) ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.3, 127.6, 127.5, 72.9, 68.5, 67.8, 33.8, 17.0; IR (neat) 3404, 2926, 2869, 1454, 1097 cm^{-1}; HRMS (CI, M^+) calcd for $C_{12}H_{18}O_2$ *m/z* 194.1307, found *m/z* 194.1303.



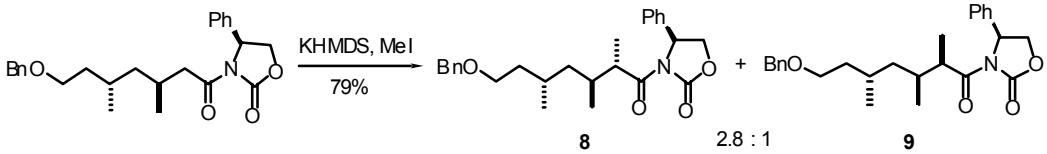
4 5

(2R)-4-Benzyloxy-1-bromo-2-methylbutane. To a solution of **4** (0.25 g, 1.31 mmol) in CH_2Cl_2 (2 mL) was added PPh_3 (0.24g, 1.37 mmol) and NBS (0.36 g, 1.37 mmol) at room temperature. The solution was stirred for 10 min and concentrated under vacuum. The crude product was treated with hexane and filtered, the filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 20:1) to yield **5** as a colorless oil (0.25 g, 74%): $[\alpha]_D^{20}$ -4.7 (*c* 0.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29- 7.42 (m, 5H), 4.54 (s, 2H), 3.57 (dt, *J* = 3.3, 0.1 Hz, 2H), 3.47 (dd, *J* = 9.9, 4.8 Hz, 1H), 3.40 (dd, *J* = 9.9, 5.7 Hz, 1H), 2.03-2.11 (m, 1H), 1.83 (ddd, *J* = 12.9, 12.9, 6.3 Hz, 1H), 1.59 (ddd, *J* = 13.8, 13.8, 6.3 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 128.8, 128.0, 73.4, 68.3, 42.0, 35.1, 32.6, 19.2; IR (film) 2961, 2858, 1454 cm^{-1}; HRMS (FAB, M^++H) calcd for $C_{12}H_{18}OBr$ *m/z* 259.0521, found *m/z* 259.0532.



6

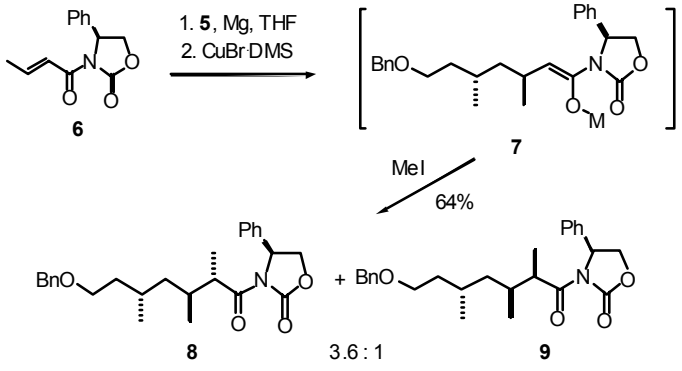
(4*S*,3'*S*,5'*S*)-3-(7'-Benzyloxy-3',5'-dimethylheptanoyl)-4-phenyloxazolidin-2-one. To a suspension of magnesium (0.52 g, 21.4 mmol) in THF (10 mL) was added dibromoethane (0.0384 mL, 0.44 mmol), and the mixture was heated to reflux for 10 min and then cooled to room temperature. A solution of **5** (2.29 g, 8.91 mmol) in THF (2 mL) was added via syringe, and the mixture was heated at reflux for 20 min then cooled and added to a solution of CuBr.DMS (1.83 g, 8.91 mmol) in THF (8 mL) at –78 °C. The resulting suspension was warmed to –20 °C, stirred for 25 min, and cooled to -78°C. 3-(2'-butenoyl)-4-phenyloxazolidin-2-one (0.68 g, 2.94 mmol) in THF (6 mL) was added dropwise, and the dark brown suspension was stirred for 2.5 h at –78 °C, then slowly warmed to –30 °C during 45 min. The reaction was quenched with saturated NH_4Cl, and extracted with Et_2O, and the organic extract was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by flash column chromatography (hexanes/ethyl acetate, 3:1) gave (4*S*,3'*S*,5'*S*)-3-(7'-benzyloxy-3',5'-dimethylheptanoyl)-4-phenyloxazolidin-2-one as a colorless oil (1.16 g, 96%): $[\alpha]_D^{20}$ +20.0 (*c* 2.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.45 (m, 10H), 5.47 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.71 (t, *J* = 8.7 Hz, 1H), 4.52 (s, 2H), 4.30 (dd, *J* = 9.0, 3.9 Hz, 1H), 3.50 (dt, *J* = 7.5, 0.9 Hz, 2H), 2.96 (dd, *J* = 15.9, 5.4 Hz, 1H), 2.76 (dd, *J* = 15.9, 8.1 Hz, 1H), 2.09-2.22 (m, 1H), 1.66-1.75 (m, 1H), 1.58 (ddd, *J* = 12.6, 12.6, 6.6 Hz, 1H), 1.44 (ddd, *J* = 13.2, 13.2, 6.9 Hz, 1H), 1.22 (ddd, *J* = 13.5, 9.6, 4.5 Hz, 1H), 1.09 (ddd, *J* = 13.8, 9.3, 4.8 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 153.6, 139.2, 138.6, 129.1, 128.6, 128.3, 127.6, 127.4, 125.9, 72.8, 69.8, 68.4, 57.5, 44.2, 43.2, 37.4, 27.1, 19.1; IR (film) 2925, 1782, 1705 cm^{-1}; HRMS (FAB, M+H$^+$) calcd for $C_{25}H_{32}O_4N$ *m/z* 410.2331, found *m/z* 410.2339.



8 9

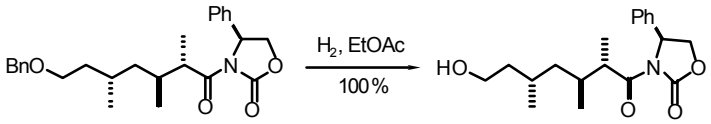
(4*S*,2'*S*,3'*S*,5'*S*)-3-(7'-Benzyloxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (8) and (4*S*,2'*R*,3'*S*,5'*S*)-3-(7'-Benzyloxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (9). To a solution of (4*S*,3'*S*,5'*S*)-3-(7'-Benzyloxy-3',5'-dimethylheptanoyl)-4-phenyloxazolidin-2-one (0.93 g, 2.27 mmol) in THF (8.5 mL) was added HMPA (1.58 mL, 9.08 mmmol) at –78 °C, followed by slow addition of KHMDS (0.5M in toluene, 6.81 mL, 3.40 mmol). The resulting yellow solution was stirred

for 20 min at –78 °C, and MeI (0.56 mL, 9.08 mmol) was added dropwise. After stirring for 2 h at –78 °C, the solution was quenched with MeOH and diluted with Et_2O, and the solution was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 5:1) gave **8** (0.55 g, 58%) and **9** (0.20 g, 21%). **8**: mp 75-76 °C (from hexanes); $[\alpha]_D^{20}$ +49.7 (*c* 1.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.41 (m, 10H), 5.40 (dd, *J* = 8.4, 3.3 Hz, 1H), 4.62 (t, *J* = 8.7 Hz, 1H), 4.50 (s, 2H), 4.22 (dd, *J* = 9.0, 3.3 Hz, 1H), 3.70 (quin, *J* = 7.2 Hz, 1H), 3.51 (t, *J* = 6.6 Hz, 2H), 1.84-1.92 (m, 1H), 1.46-1.71 (m, 3H), 1.15 (ddd, *J* = 10.5, 10.5, 3.6 Hz, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 153.4, 139.3, 138.6, 129.1, 128.5, 128.3, 127.6, 127.4, 125.6, 72.9, 69.6, 68.4, 57.7, 43.1, 39.6, 37.9, 32.7, 27.0, 18.9, 17.8, 13.6; IR (film) 2925, 1780, 1704 cm^{-1}; HRMS (FAB, M+H$^+$) calcd for $C_{26}H_{34}O_4N$ *m/z* 424.2488, found *m/z* 424.2509. **9**: $[\alpha]_D^{20}$ -20.6 (*c* 1.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.41 (m, 10H), 5.46 (dd, *J* = 9.0, 4.5 Hz, 1H), 4.68 (t, *J* = 9.0 Hz, 1H), 4.51 (s, 2H), 4.28 (dd, *J* = 9.0, 4.5 Hz, 1H), 3.68 (quin, *J* = 6.6 Hz, 1H), 3.48 (t, *J* = 6.6 Hz, 2H), 1.89-1.97 (m, 1H), 1.46-1.62 (m, 2H), 1.36-1.42 (m, 1H), 1.16 (ddd, *J* = 13.5, 10.5, 3.6 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.83-0.96 (m, 1H), 0.74 (d, *J* = 6.3 Hz, 3H), 0.62 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 153.8, 139.6, 139.1, 129.4, 129.1, 128.8, 128.0, 127.9, 126.8, 73.3, 69.9, 69.0, 58.1, 43.2, 42.9, 38.1, 33.4, 27.6, 19.3, 14.7, 12.3; IR (film) 2926, 1780, 1704 cm^{-1}; HRMS (FAB, M+H$^+$) calcd for $C_{26}H_{34}O_4N$ *m/z* 424.2488, found *m/z* 424.2490.



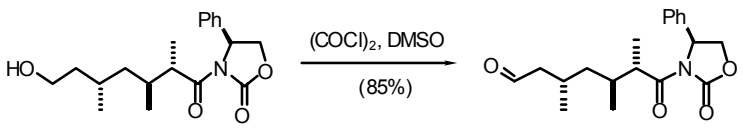
(4*S*,2'*S*,3'*S*,5'*S*)-3-(7'-Benzyloxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (8) and (4*S*,2'*R*,3'*S*,5'*S*)-3-(7'-Benzyloxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (9) from 5. To a suspension of magnesium (0.10 g, 4.14 mmol) in THF (2 mL) was added dibromoethane (0.0074 mL, 0.086 mmol), and the mixture was heated at reflux for 10 min, then cooled to room temperature. A solution of **5** (0.443 g, 1.72 mmol) in THF (0.5 mL) was added via syringe, and the mixture was heated

to reflux for 20 min then cooled and added to a solution of CuBr**.**DMS (0.34 g, 1.72 mmol) in THF (2 mL) at –78 °C. The suspension was warmed to –20 °C, stirred for 25 min, and cooled to –78 °C. A solution of **6** (0.14 g, 0.57 mmol) in THF (1.5 mL) was added dropwise, and the suspension was stirred for 2.5 h at –78 ˚C, then slowly warmed to –30 °C during 45 min. The reaction was cooled again to –78 °C and MeI (0.54 mL, 8.6 mmol) was added. The mixture was allowed to reach room temperature and was stirred overnight. Saturated NH_4Cl was added to quench the reaction, and the aqueous layer was extracted with Et_2O. The Et_2O extract was washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 5:1) afforded **8** (0.117 g, 50%) and **9** (0.038 g, 14%).



8

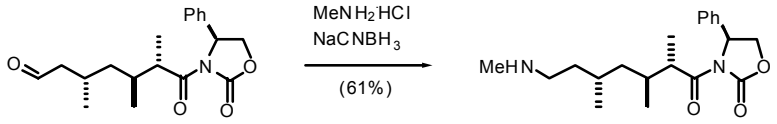
(4*S*,2'*S*,3'*S*,5'*S*)-3-(7'-Hydroxy-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one. To a solution of **8** (0.753 g, 1.78 mmol) in EtOAc (12 mL) at room temperature was added $Pd(OH)_2$-on-carbon (Pearlman's catalyst, 0.116 g), and a balloon containing H_2 was attached to the flask. The mixture was stirred for 2 h, the catalyst was filtered off, and the filtrate was concentrated. Flash column chromatography (hexanes/ethyl acetate, 1:1) of the residue gave a primary alcohol as a pale yellow oil (0.60 g, 100%): $[\alpha]_D^{20}$ +68.6 (*c* 2.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.41 (m, 5H), 5.42 (dd, *J* = 8.4, 3.3 Hz, 1H), 4.66 (t, *J* = 8.7 Hz, 1H), 4.24 (dd, *J* = 9.0, 3.3 Hz, 1H), 3.61-3.73 (m, 3H), 1.83-1.92 (m, 1H), 1.62-1.64 (m, 1H), 1.34-1.55 (m, 3H), 1.09-1.20 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 153.4, 139.2, 129.1, 128.5, 125.6, 69.6, 60.8, 57.7, 43.0, 41.0, 40.0, 32.6, 26.6, 18.8, 17.7, 13.7; IR (film) 3385, 2926, 1779, 1702 cm^{-1}; HRMS (FAB, M+H$^+$) calcd for $C_{19}H_{28}O_4N$ *m/z* 334.2018, found *m/z* 334.2018.



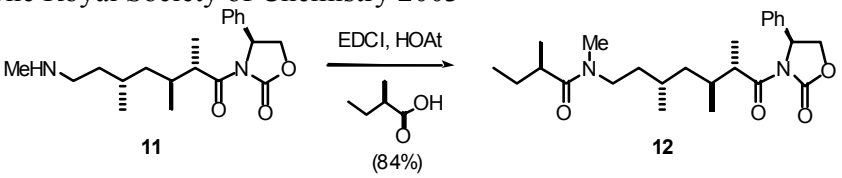
10

(4*S*,2'*S*,3'*S*,5'*S*)-3-(7'-Oxo-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (10). To a solution of $(COCl)_2$ (0.261 mL, 3.0 mmol) in CH_2Cl_2 (3 mL) was added a solution of DMSO (0.284 mL, 4.0 mmol) in CH_2Cl_2 (3 mL) at –78 °C. After stirring for 15 min, a solution of the alcohol prepared above (0.60 g, 1.78 mmol) in CH_2Cl_2 (8 mL) was added dropwise. The solution was stirred for 15 min

followed by addition of NEt_3 (1.09 mL, 8.0 mmol) in CH_2Cl_2 (4 mL) at –78 °C. The mixture was slowly warmed to 0 °C during 30 min, and was quenched with saturated NH_4Cl. The aqueous layer was extracted with Et_2O and the extract was washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 3:1) gave **10** as a pale yellow oil (0.51 g, 85%): $[\alpha]_D^{20}$ +69.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.1 Hz, 1H), 7.26-7.41 (m, 5H), 5.42 (dd, *J* = 8.7, 3.3 Hz, 1H), 4.67 (t, *J* = 9.0 Hz, 1H), 4.25 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.69 (quin, *J* = 6.9 Hz, 1H), 2.29-2.33 (m, 2H), 2.08-2.19 (m, 1H), 1.84-1.93 (m, 1H), 1.28 (ddd, *J* = 13.5, 10.8, 3.0, 1H), 1.10 (ddd, *J* = 14.1, 10.8, 3.6, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 176.6, 153.8, 140.0, 129.6, 129.1, 126.1, 70.1, 58.2, 52.6, 43.5, 40.0, 33.0, 25.8, 19.4, 18.1, 14.2; IR (film) 2964, 2930, 1777, 1721, 1702, 1383 cm^{-1}; HRMS (FAB, M+H$^+$) calcd for $C_{19}H_{26}O_4N$ *m/z* 332.1862, found *m/z* 332.1872.

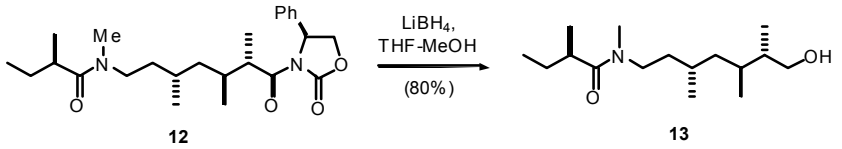


(4*S*,2'*S*,3'*S*,5'*S*)-3-(7'-Methylamino-2',3',5'-trimethylheptanoyl)-4-phenyloxazolidin-2-one (11). To a solution of **10** (0.50 g, 1.51 mmol) in MeOH (10 mL) was added $MeNH_2$.HCl (0.204 g, 3.02 mmol), $MeNH_2$ (2M solution in THF, 2.76 mL, 4.53 mmol) and Na_2SO_4 (0.4 g) at room temperature. The mixture was stirred for 20 min and cooled to 0 °C, and a solution of $NaCNBH_3$ (0.142 g, 2.26 mmol) in MeOH (1.5 mL) was added. The mixture was stirred for 1h, MeOH was removed under vacuum, and the residue was subjected to purification by flash column chromatography (CH_2Cl_2/MeOH, 20:1) to give **11** as a viscous oil (0.314 g, 61%): $[\alpha]_D^{20}$ +52.8 (*c* 1.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.44 (m, 5H), 5.51 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.76 (t, *J* = 8.8 Hz, 1H), 4.26 (dd, *J* = 8.8, 3.6 Hz, 1H), 3.74 (quin, *J* = 6.8 Hz, 1H), 2.98 (dd, *J* = 8.4, 6.0 Hz, 2H), 2.72 (s, 3H), 1.85-1.95 (m, 1H), 1.60-1.80 (m, 3H), 1.22-1.34 (m, 2H), 1.14-1.16 (m, 1H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 154.2, 139.7, 129.6, 129.0, 126.0, 70.4, 58.3, 48.6, 43.4, 39.8, 34.2, 33.9, 33.0, 28.3, 18.8, 17.9, 14.3; IR (film) 2965, 2930, 2333, 2173, 1777, 1703, 1384 cm^{-1}; HRMS (CI, M$^+$) calcd for $C_{20}H_{30}O_3N_2$ *m/z* 346.2256, found *m/z* 346.2249.



11 12

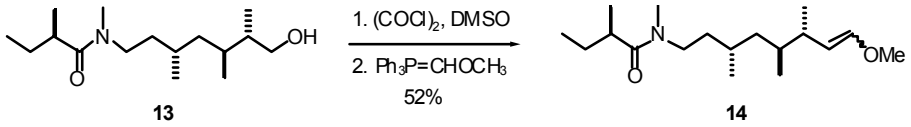
(2*R*,3'*S*,5'*S*,6'*S*,4''*S*)-2,N-Dimethyl-N-[3',5',6'-trimethyl-7'-oxo-7'-(2"-oxo-4''-phenyloxazolidin-3-yl)heptyl]butyramide (12). To a solution of **11** (0.314 g, 0.90 mmol) in DMF (4 mL) at 0 °C were added a solution of (*R*)-2-methylbutyric acid (0.183 g, 1.80 mmol) in DMF (5 mL), followed by 1-hydroxy-7-azabenzotriazole (HOAt, 0.245 g, 1.80 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 0.345 g, 1.80 mmol), and diisopropylethylamine (DIPEA, 0.313 mL, 1.80 mmol). The mixture was kept at room temperature for 12 h, and then diluted with EtOAc. The organic phase was separated and washed with 1N HCl, brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 3:2) gave **12** as pale yellow oil (0.326 g, 84%): $[\alpha]_D^{20}$ +40.0 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 5.43 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.67 (t, *J* = 8.7 Hz, 1H), 4.25 (dd, *J* = 8.4, 4.2 Hz, 1H, one rotamer), 4.24 (dd, *J* = 8.4, 3.3 Hz, 1H, one rotamer), 3.66-3.72 (m, 1H), 3.37 (ddd, *J* = 10.2, 6.0, 3.6 Hz, 1H), 3.28 (ddd, *J* = 10.4, 6.0, 4.0 Hz, 1H), 3.00 (s, 3H, one rotamer), 2.91 (s, 3H, one rotamer), 2.50-2.63 (m, 1H), 1.81-1.90 (m, 1H), 1.64-1.75 (m, 1H), 1.31-1.48 (m, 3H), 1.01-1.11 (m, 9H), 0.84-0.93 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 176.6, 176.5, 153.9, 139.8, 139.6, 129.6, 129.1, 129.0, 126.1, 70.1, 58.2, 48.4, 46.5, 43.5, 40.2, 37.8, 37.7, 37.6, 35.9, 35.6, 34.1, 33.2, 33.0, 28.4, 27.8, 27.5, 19.2, 18.2, 18.0, 17.5, 14.4, 14.1, 12.6, 12.4; IR (film) 2926, 1779, 1704, 1639, 1456 cm^{-1}; HRMS (FAB, $M+H^+$) calcd for $C_{25}H_{39}O_4N_2$ *m/z* 431.2910, found *m/z* 431.2912.



12 13

(2*R*,3'*S*,5'*S*,6'*S*)-2,N-Dimethyl-N-[7'-hydroxy-3',5',6'-trimethylheptyl]butyramide (13). To a solution of **12** (0.084 g, 0.20 mmol) in THF (1.7 mL) was added $LiBH_4$ (2M solution in THF, 0.30 mL, 0.6 mmol) at 0 °C, followed by MeOH (0.042 mL, 1.04 mmol). The solution was stirred for 40 min at 0 °C and for 10 min at room temperature, and quenched with water. The aqueous layer was extracted with EtOAc and the extract was washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 3:2) gave **13** as a pale yellow oil (0.042 g, 80%): $[\alpha]_D^{20}$ -36.2 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58-3.62 (m, 1H), 3.25-3.48 (m, 3H), 3.02 (s, 3H, one rotamer), 2.93 (s, 3H, one rotamer), 2.58 (m, 1H), 1.92 (s, 1H), 1.33-1.73 (m, 6H), 1.11 (d, *J*

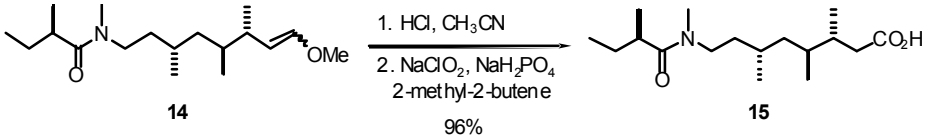
= 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.84-0.91 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 176.7, 66.3, 66.2, 48.5, 46.7, 41.5, 41.3, 40.5, 40.2, 37.8, 37.6, 35.7, 35.6, 34.1, 31.8, 31.7, 28.8, 28.6, 27.8, 27.4, 19.6, 19.4, 18.1, 17.5, 17.4, 17.3, 13.8, 13.6, 12.6, 12.4; IR (film) 3419, 2961, 1624, 1458 cm^{-1}; HRMS (FAB, $M+H^+$) calcd for $C_{16}H_{34}O_2N$ *m/z* 272.2589, found *m/z* 272.2605.



13 **14**

(2R,3'S,5'S,6'S)-2,N-Dimethyl-N-[8'-Methoxy-3',5',6'-trimethyloct-7-enyl]butyramide (14). To a solution of $(COCl)_2$ (0.073 mL, 0.84 mmol) in CH_2Cl_2 (0.8 mL) was added a solution of DMSO (0.079 mL, 1.12 mmol) in CH_2Cl_2 (0.8 mL) at –78 °C. The mixture was stirred for 15 min, and a solution of **13** (0.151 g, 0.56 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The mixture was stirred for 15 min at –78 °C, and a solution of NEt_3 (0.314 mL, 2.24 mmol) in CH_2Cl_2 (0.8 mL) was added. The mixture was warmed to –10 °C during 30 min, and the reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted with Et_2O, and the extract was washed with brine, dried over $MgSO_4$, and concentrated to give the crude, unstable aldehyde which was used without purification..

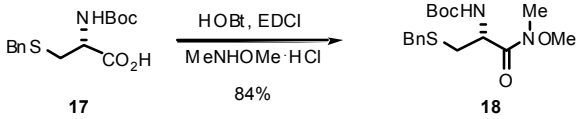
To a suspension of (methoxymethyl)triphenylphosphonium chloride (dried under vacuum at 50 °C, 0.955 g, 2.80 mmol) in THF (4.5 mL) was added *n*-BuLi (1.6 M in hexane, 1.57 mL, 2.52 mmol) at 0 °C, and the resulting deep red solution was stirred for 30 min at room temperature. The solution was cooled to –20 °C and added to a solution of the crude aldehyde prepared above in THF (2 mL). The mixture was kept at –20 °C for 30 min, and then warmed to room temperature. The reaction was quenched with MeOH, diluted with Et_2O, and washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 5:1) gave **4** as a 1:1 *E*/*Z* mixture (0.086 g, 52% from **13**).



14 **15**

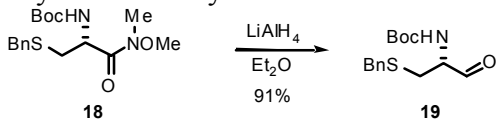
(2'*R*,3*R*,4*S*,6*S*)-3,4,6-Trimethyl-8-[methyl-2'-(methylbutyryl)amino]octanoic acid (15). To a solution of **14** (0.086 g, 0.29 mmol) in CH_3CN (2.1 mL) was added 1N HCl (0.7 mL) at room temperature. After stirring for 1 h, the solution was diluted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated to give the crude aldehyde. To a solution of this aldehyde in MeOH (10 mL) was added 2-methyl-2-butene (1.02 g, 14.5 mmol) followed by a freshly prepared $NaClO_2$ solution (1.25

M in 20% NaH_2PO_4, 1.16 mL, 1.45 mmol). The solution was stirred for 2 h at room temperature, and diluted with Et_2O. The solution was washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate/MeOH, 47.5:47.5:5) gave **15** as a colorless oil (0.083 g, 96%): $[\alpha]_D^{20}$ -35.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24-3.41 (m, 2H), 3.02 (s, 3H, 1 rotamer), 2.93 (s, 3H, one rotamer), 2.53-2.62 (m, 1H), 2.35 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.10 (dd, *J* = 9.6, 7.2 Hz, 1H, one rotamer), 2.06 (dd, *J* = 9.2, 6.8 Hz, 1H, one rotamer), 1.91-2.01 (m, 1H), 1.65-1.74 (m, 1H), 1.30-1.58 (m, 5H), 1.04-1.16 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H, 1 rotamer), 1.08 (d, *J* = 6.8 Hz, 3H, 1 rotamer), 0.80-0.94 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 178.8, 177.3, 177.0, 48.6, 46.7, 40.8, 40.6, 38.6, 38.5, 37.8, 37.6, 37.5, 35.8, 35.7, 35.6, 35.4, 34.7, 34.6, 34.3, 28.6, 27.7, 27.4, 19.5, 18.0, 17.4, 17.0, 16.9, 16.44, 16.39, 13.5, 12.4; IR (film) 2963, 1728, 1611 cm^{-1}; HRMS (CI, M^+) calcd for $C_{17}H_{33}O_3N$ *m/z* 299.2460, found *m/z* 299.2466.

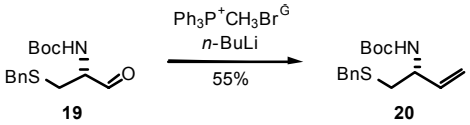


17 **18**

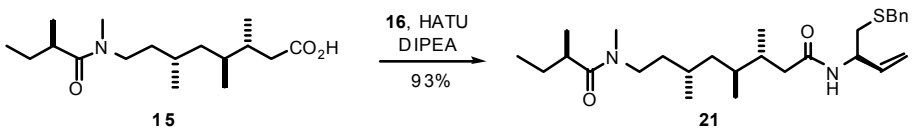
S-Benzyl-N$_\alpha$-(*tert*-butyloxycarbonyl)-cysteine-N-methoxy-N-methylamide (18). To a solution of S-Benzyl-N$_\alpha$-(*tert*-butyloxycarbonyl)-cysteine (**17**, 0.59 g, 1.90 mmol) in THF (38 mL) was added 1-hydroxybenzotriazole (HOBt, 0.282 g, 2.08 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 0.40 g, 2.08 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min, after which MeNHOMe·HCl (0.208 g, 2.09 mmol) and diisopropylethylamine (0.362 mL, 2.08 mmol) were added. The solution was kept at room temperature for 12 h, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 2:1) gave S-benzyl-N$_\alpha$-(*tert*-butyloxycarbonyl)-cysteine-N-methoxy-N-methylamide (0.56 g, 84%): $[\alpha]_D^{20}$ -30.2 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.36 (m, 5H), 5.38 (d, *J* = 8.4 Hz, 1H), 4.92 (bs, 1H), 3.76 (s, 2H), 3.74 (s, 3H), 3.22 (s, 3H), 2.82 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.65 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 155.7, 138.3, 129.4, 128.9, 127.5, 80.2, 62.0, 50.0, 36.7, 33.9, 32.6, 28.8; IR (film) 3321, 2976, 1711, 1662, 1169 cm^{-1}; HRMS (CI, M^+) calcd for $C_{17}H_{26}O_4N_2S$ *m/z* 354.1613, found *m/z* 354.1616.



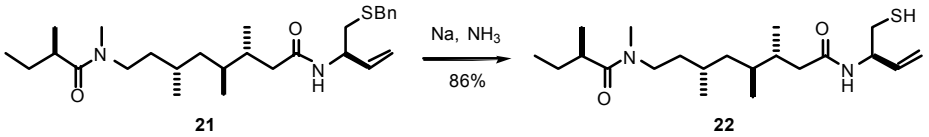
3-Benzylthio-2-(N-*tert*-butyloxycarbonyl)aminopropionaldehyde (19). To a solution of S-benzyl-N_α-(*tert*-butyloxycarbonyl)-cysteine-N-methoxy-N-methylamide (**18**, 0.632 g, 1.78 mmol) in Et_2O (8 mL) was added $LiAlH_4$ (0.085 g, 2.23 mmol) at 0 °C. After stirring for 30 min, the mixture was diluted with Et_2O, washed with 1N HCl, brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 2:1) gave **19** as an oil (0.478 g, 91%): $[\alpha]_D^{20}$ +3.47 (*c* 1.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.21-7.34 (m, 5H), 5.39 (m, 1H), 4.24-4.32 (m, 1H), 3.72 (s, 2H), 2.86 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.80 (dd, *J* = 14.1, 6.0 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 155.8, 138.0, 129.4, 129.1, 127.8, 80.8, 59.5, 37.3, 31.0, 28.7; IR (film) 3354, 2977, 1709, 1495 cm^{-1}.



3-Benzylthio-2-(N-*tert*-butyloxycarbonyl)amino-1-butene (20). To a suspension of methyltriphenylphosphonium bromide (1.27 g, 3.5 mmol) in THF (15 mL) was added KHMDS (0.5 M solution in toluene, 6.48 mL, 3.24 mmol). The resulting yellow suspension was stirred at room temperature for 1 h, and cooled to –78 °C. A solution of **19** (0.478 g, 1.62 mmol) in THF (10 mL) was added, the cooling bath was removed, and the mixture was allowed to reach room temperature. The mixture was diluted with Et_2O, washed with half-saturated Rochelle's salt, dried over $MgSO_4$, and concentrated. Purification of the residu by flash column chromatography (hexanes/ethyl acetate, 8:1) gave **20** (0.263 g, 55%): $[\alpha]_D^{20}$ +12.7 (*c* 2.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.32 (m, 5H), 5.78 (ddd, *J* = 17.1, 10.5, 5.4 Hz, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.13 (d, *J* = 10.2 Hz, 1H), 4.80 (bs, 1H), 4.33 (bs, 1H), 3.73 (s, 2H), 2.58 (d, *J* = 6.0 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 138.4, 137.8, 129.4, 129.0, 127.5, 116.0, 80.0, 52.2, 37.0, 36.8, 28.8; IR (film) 3344, 2977, 1701, 1495 cm^{-1}; HRMS (CI, M^+) calcd. for $C_{16}H_{23}O_2NS$ *m/z* 293.1449, found *m/z* 293.1448.



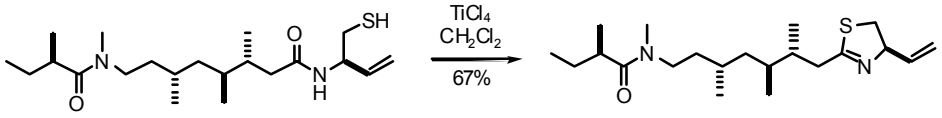
(1''*R*,2'*R*,3*R*,4*S*,6*S*)-3,4,6-Trimethyl-8-[methyl-(2'-methylbutyryl)amino]octanoic acid (1''-benzylsulfanylmethylallyl)amide (21). To a solution of **20** (0.244 g, 0.833 mmol) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (TFA, 3 mL) at 0°C, and the mixture was stirred at 0°C for 30 min. The solvent was removed, and the residue was diluted with CH_2Cl_2. The solution was washed with 5% NaOH aqueous solution, brine, dried over $MgSO_4$, and concentrated to give 3-benzylthio-2-amino-1-butene (**16**) which was used without further purification. To a solution of **15** as an oil (0.083 g, 0.278 mmol) at room temperature was added a solution of **16** prepared above in CH_2Cl_2 (2.5 mL), followed by *O*-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluroniumhexa-fluorophophate (HATU, 0.158 g, 0.417 mmol) and diisopropylethylamine (DIPEA, 0.073 mL, 0.417 mmol). The mixture was kept at room temperature for 12 h, and the solvent was removed under vacuum. Flash column chromatography of the residue (hexanes/ethyl acetate, 1:1) gave **21** (0.122 g, 93%): $[\alpha]_D^{20}$ -15.0 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.31 (m, 5H), 6.03 (d, *J* = 8.4 Hz, 1H, 1 rotamer), 5.97 (d, *J* = 8.4 Hz, 1H, 1 rotamer), 5.79 (ddd, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 4.71 (m, 1H), 3.73 (s, 2H), 3.26-3.41 (m, 2H), 3.00 (s, 3H, 1 rotamer), 2.91 (s, 3H, 1 rotamer), 2.53-2.66 (m, 3H), 2.22 (dt, *J* = 13.6, 3.6 Hz, 1H), 1.92-2.04 (m, 1H), 1.82-1.88 (m, 1H), 1.65-1.74 (m, 1H), 1.31-1.53 (m, 5H), 1.06-1.16 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H, 1 rotamer), 1.07 (d, *J* = 6.8 Hz, 3H, 1 rotamer), 0.80-0.89 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 176.5, 172.8, 172.7, 138.5, 138.4, 137.4, 129.4, 129.0, 127.5, 116.2, 50.3, 48.5, 46.5, 41.1, 41.0, 40.9, 40.6, 37.7, 37.6, 36.9, 36.4, 36.1, 35.8, 35.7, 35.6, 34.8, 34.7, 34.1, 28.6, 28.5, 27.8, 27.5, 19.64, 19.59, 18.2, 17.6, 16.9, 16.7, 16.6, 16.5, 12.6, 12.4; IR (film) 3302, 2917, 1625 cm^{-1}; HRMS (CI, M^+) calcd for $C_{28}H_{46}O_2N_2S$ *m/z* 474.3280, found *m/z* 474.3283.



21 22

(1''*R*,2'*R*,3*R*,4*S*,6*S*)-3,4,6-Trimethyl-8-[methyl-(2'-methylbutyryl)amino]octanoic acid (1''-mercaptomethylallyl)amide (22). To liquid NH_3 (2 mL) at –78 °C was added sodium (0.023 g, 1 mmol). A solution of **22** (0.018 g, 0.042 mmol) in THF (0.5 mL) was added at –78 °C, and the deep blue solution was stirred for 30 min. Solid NH_4Cl was added to quench the reaction, and ammonia was evaporated under argon. The residue was diluted with CH_2Cl_2, and the solution was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate/MeOH, 47.5:47.5:5) gave **22** (0.0125 g, 86%): $[\alpha]_D^{20}$ -4.3 (*c* 0.65, $CHCl_3$); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 5.93 (d, *J* = 8.1 Hz, 1H, 1 rotamer), 5.82 (d, *J* = 8.1 Hz, 1H, 1 rotamer), 5.76 (ddd, *J* = 16.2, 11.1, 5.1 Hz, 1H), 5.20-5.26 (m, 2H), 4.72-4.83 (m, 1H), 3.21-3.45 (m, 2H), 3.01 (s, 3H, 1 rotamer), 2.92 (s, 3H, 1 rotamer), 2.51-2.85 (m, 3H), 2.25-2.30 (m, 1H), 1.88-2.04 (m, 2H), 1.61-1.75 (m, 2H), 1.28-1.57 (m, 6H), 1.12-1.16 (m, 1H), 1.10 (d, *J* = 7.8 Hz, 3H, 1 rotamer), 1.07 (d, *J* = 6.9 Hz, 3H, 1 rotamer), 0.80-0.94 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9,176.6, 172.8, 172.5, 136.32, 136.26, 117.2, 51.9, 51.7, 48.5, 46.5, 41.2, 41.1, 41.0, 40.5, 37.8, 37.6, 36.1, 35.9, 35.7, 34.7, 34.6, 34.1, 30.0, 29.7, 28.6, 27.8, 27.5, 19.7, 19.6, 18.2, 17.5, 16.9, 16.8, 16.6, 12.6, 12.4; IR (film) 3297, 2961, 1640, 1624 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{40}O_2N_2S$ *m/z* 384.2810, found *m/z* 384.2811.



22 **1**

(+)-Kalkitoxin (1). To a solution of **22** (0.012 g, 0.031mmol) in CH_2Cl_2 (1 mL) at room temperature was added freshly distilled $TiCl_4$ (0.034 mL, 0.31 mmol). The orange solution was stirred for 12 h, and the reaction was quenched with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4, and concentrated. Flash column chromatography of the residue (hexanes/ethyl acetate, 1:1) gave (+)-kalkitoxin as a colorless oil (0.0076 g, 67%): $[\alpha]_D^{20}$ +11.5 (*c* 0.34, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 5.85 (ddd, *J* = 16.8, 10.4, 6.0 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.75 (m, 1H), 3.35 (m, 1H), 2.94 (m, 1H), 2.93 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.80 (s, 3H, 1 rotamer), 2.71 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.46-2.55 (m, 1H), 2.42 (s, 3H, 1 rotamer), 2.20-2.37 (m, 2H), 2.06 (m, 1H), 1.84-1.99 (m, 1H), 1.21-1.59 (m, 5H), 1.18 (s, 3H, 1 rotamer), 1.10 (m, 1H), 1.09 (s, 3H, 1 rotamer), 0.69-0.96 (m, 13 H); ^{13}C NMR (100 MHz, C_6D_6) δ 175.5, 175.2, 170.1, 170.0, 138.5, 138.3, 115.5, 115.4, 79.4, 47.9, 46.1, 40.5, 40.4, 39.0, 38.8, 38.6, 38.2, 37.7, 37.6, 37.4, 36.1, 34.7, 34.6, 34.5, 33.6, 28.5, 28.1, 27.7, 19.6, 19.4, 18.4, 17.8, 16.6, 16.5, 12.6, 12.4; IR (film) 2961, 2874, 1643, 1463 cm^{-1}; HRMS (FAB M+H^+) calcd for $C_{21}H_{38}ON_2S$ *m/z* 367.2783, found *m/z* 367.2793.