SUPPORTING MATERIAL

Annulation of Thioimidates and Vinyl Carbodiimides to Prepare 2-Aminopyrimidines, Competent Nucleophiles for Intramolecular Alkyne Hydroamination. Synthesis of (–)-Crambidine.

Nicholas R. Perl, Nathan D. Ide, Sudeep Prajapati, Hahdi H. Perfect, Sergio G. Durón, and David Y. Gin*

Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065
and the Department of Chemistry, University of Illinois, Urbana, IL 61801

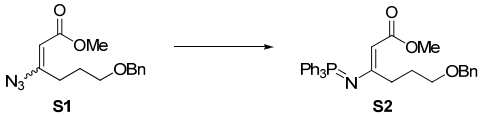
General Procedures. Reactions were performed in flame-dried sealed-tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe. Appropriate substrates and reagents were dried via azeotropic removal of water with benzene or acetonitrile. Molecular sieves were activated at 350 °C and were crushed immediately prior to use, then flame-dried under vacuum. Organic solutions were concentrated by rotary evaporation below 30 °C. Flash column chromatography was performed employing 230-400 mesh silica gel. Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Dichloromethane, tetrahydrofuran, diethyl ether, toluene, and benzene were purified by passage through two packed columns of neutral alumina under an argon atmosphere. Methanol was distilled from magnesium at 760 Torr. Chloroform and 1,2-dichlorethane were distilled from calcium hydride at 760 Torr. Acetone and *N*,*N*-dimethylformamide were purchased as anhydrous reagents and used without further purification. All other chemicals were obtained from commercial vendors and were used without further purification unless noted otherwise.

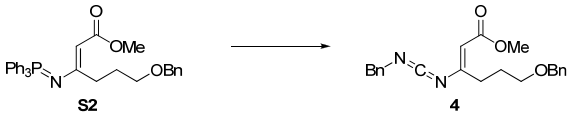
Instrumentation. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum BX spectrophotometer or a Bruker Tensor 27. Data are presented as the frequency of absorption (cm^{-1}). Proton and carbon nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded on a Varian 400, a Varian 500, a Varian Inova 500, or a Bruker Avance III instrument; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual resonance in the NMR solvent ($CDCl_3$: δ 7.26 for ^1H NMR, δ 77.16 for ^{13}C NMR; C_6D_6: δ 7.15 for ^1H NMR, δ 128.06 for ^{13}C NMR; CD_3OD: δ 3.31 for ^1H NMR, δ 49.00 for ^{13}C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, t = triplet, q = quartet, m = multiplet

and/or multiple resonances), coupling constant in hertz (Hz), integration. Optical rotations were measured using a JASCO P-1020 polarimeter. RP-HPLC purification and analyses were carried out on a Waters 2545 binary gradient HPLC system equipped with a Waters 2996 photodiode array detector, and absorbances were monitored at a wavelength of 254 nm.

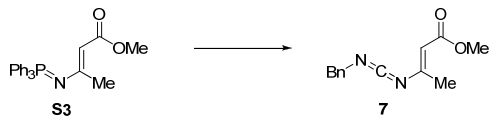
SYNTHESIS OF MODEL [4+2] ANNULATION SUBSTRATES



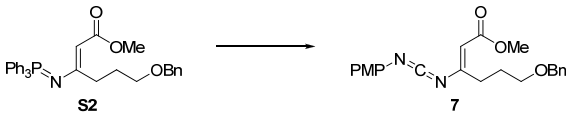
(*E*)-3-Iminotriphenylphosphorane-6-benzyloxy-hex-2-enoic acid methyl ester (S2). To a 23 °C solution of vinyl azide **S1**[1] (1.5:1 *E:Z*) (930 mg, 3.4 mmol, 1.0 equiv) in dichloromethane (10 mL) was added triphenylphosphine as a solution in dichloromethane (11 mL) via an addition funnel. After stirring at 23 °C for 18 h, the solution was concentrated in vacuo to ~ 2 mL. Slow addition of hexanes (~ 50 mL) resulted in the precipitation of crystals, which was isolated by filtration and rinsing with excess hexanes to provide iminophosphorane **S2** (1.42 g, 83% yield) as a tan powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 6H), 7.56 – 7.53 (m, 3H), 7.47 – 7.44 (m, 6H), 7.35 – 7.29 (m, 3H), 4.54 (s, 1H), 4.50 (s, 2H), 3.58 (t, *J* = 7.3 Hz, 2H), 3.47 (s, 3H), 3.04 – 3.00 (m, 2H), 2.13 – 2.07 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.7, 168.9, 139.0, 132.7, 132.6, 132.1, 132.1, 129.4, 128.8, 128.7, 128.6, 128.3, 127.7, 127.3, 95.2, 95.1, 72.8, 71.0, 49.8, 33.7, 33.5, 28.7; FTIR (thin film) 3058, 2942, 2855, 1684, 1542, 1436, 1355, 1133, 1111, 1073, 804, 743, 719, 529 cm^{-1}; HRMS (ESI)$^+$ *m/z* Calcd for $C_{32}H_{33}NO_3P$ $[M+H]^+$ 510.2198, found 510.2187.



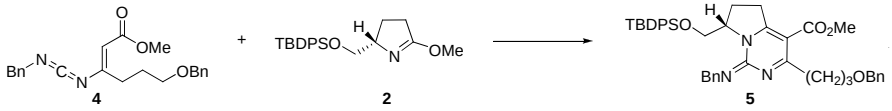
(*E*)-Methyl-3-((benzylimino)methyleneamino)-6-(benzyloxy)hex-2-enoate (4). To a 10 mL sealed-tube containing a 23 °C solution of iminophosphorane **S2** (200 mg, 0.392 mmol, 1.0 equiv) in benzene (4.0 mL) was added benzyl isocyanate (72 μL, 0.58 mmol, 1.5 equiv). The tube was then sealed under argon and heated to 80 °C for 5 h. After cooling the reaction solution to 23 °C, the solvent was removed in vacuo, and the crude material was purified by silica gel column chromatography (hexanes/ethyl acetate 4:1) to yield carbodiimide **4** (65 mg, 42% yield) as a colorless oil. R_f = 0.25 (hexanes/ethyl acetate 9:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.29 – 7.28 (m, 2H), 7.12 – 6.97 (m, 6H), 5.86 (s, 1H), 4.27 (s, 2H), 3.92 (s, 2H), 3.36 – 3.33 (m, 5H), 3.09 – 3.05 (m, 2H), 1.93 – 1.87 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.0, 159.3, 139.5, 137.6, 128.9, 128.5, 127.5, 109.6, 72.9, 69.9, 50.6, 50.0, 30.8, 28.6; FTIR (thin film) 3032, 2948, 2859, 2137, 1710, 1621, 1456, 1435, 1347, 1177, 1126, 1027, 736, 699 cm^{-1}; LRMS (ESI)$^+$ *m/z* Calcd for $C_{22}H_{24}N_2O_3Na$ $[M+Na]^+$ 367.17, found 387.12.



(*E*)-methyl 3-((benzylimino)methyleneamino)but-2-enoate (7, R_1 = Bn, R_2 = Me). To a solution of iminophophorane **S3**[1] (270 mg, 0.719 mmol, 1.0 equiv) in toluene (5 mL) was added benzyl isocyanate (95 μL, 0.76 mmol, 1.1 equiv). After stirring at 85 °C for 5 h, the solution was cooled to 23 °C and purified directly by silica gel column chromatography (hexanes/ethyl acetate 9:1) to provide carbodiimide **7** (114 mg, 87% yield) as a pale yellow oil. R_f = 0.36 (hexanes/ethyl acetate 8.8:1.2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.49 (q, *J* = 0.8 Hz, 1H), 4.55 (s, 2H), 3.66 (s, 3H), 2.26 (d, *J* = 0.8 Hz, 3H); FTIR (thin film) 3058, 2948, 2136, 1708, 1628, 1542, 1437 cm^{-1}.

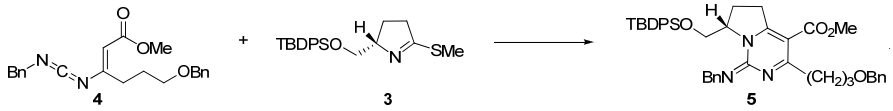


(*E*)-Methyl-6-(benzyloxy)-3-((4-methoxyphenylimino)methyleneamino)hex-2-enoate (7, R_1 = PMP, R_2 = $(CH_2)_3OBn$). To a 10 mL schlenk flask containing a 23 °C solution of iminophosphorane **S2** (300 mg, 0.588 mmol, 1.0 equiv) in benzene (5.8 mL) was added *para*-methoxyphenyl isocyanate (114 μL, 0.879 mmol, 1.5 equiv). The flask was sealed under argon and the reaction was heated to 80 °C for 30 min. After cooling to 23 °C and removing the solvent in vacuo, the crude material was purified by silica gel column chromatography (hexanes/dichloromethane 1:1) to yield carbodiimide **7** (75 mg, 34% yield) as a colorless oil. R_f = 0.39 (hexanes/ethyl acetate 2:1); ^{1}H NMR (500 MHz, C_6D_6) δ 7.25 – 7.23 (m, 2H), 7.09 – 7.07 (m, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 8.7 Hz, 2H), 5.95 (s, 1H), 4.25 (s, 2H), 3.38 – 3.36 (m, 5H), 3.18 – 3.14 (m, 5H), 2.04 – 1.98 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.8, 158.2, 157.9, 139.4, 132.7, 129.7, 127.5, 127.4, 125.7, 115.1, 110.7, 72.8, 69.7, 54.9, 50.7, 31.1, 28.6; FTIR (thin film) 2950, 2137, 1713, 1625, 1515, 1435, 1250, 1171, 1152, 832 cm^{-1}; LRMS (ESI)$^+$ *m/z* Calcd for $C_{22}H_{24}N_2O_4Na$ $[M+Na]^+$ 403.16, observed 403.19.

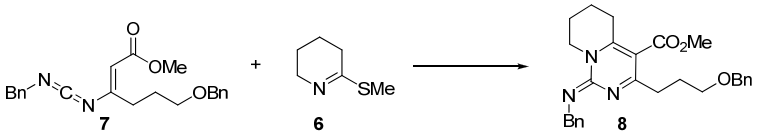


Bicyclic pyrimidine 5. To sealed-tube containing a 23 °C solution of *O*-imidate **2**[2] (12.3 mg, 0.0335 mmol, 1.0 equiv) in benzene (0.5 mL) was added benzyl carbodiimide **4** (24.3 mg, 0.0667 mmol, 2.0 equiv). The reaction tube was sealed under argon and stirred at 80 °C for 24 h. The reaction was cooled to 23 °C and the solvent was removed in vacuo. The crude reaction mixture was purified by silica gel column chromatography (100% ethyl acetate) to afford guanidine **5** (5.5 mg, 24% yield) as a dark yellow oil. R_f = 0.12 (100% ethyl acetate); $[\alpha]_D^{18}$ –178 (c 0.24, $CDCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.64 – 7.62 (m, 2H), 7.62 – 7.52 (m, 4H), 7.35 – 7.32 (m, 2H), 7.24 – 7.09 (m, 12H,), 5.15 (d, *J* = 15.4 Hz, 1H), 5.03 (d, *J* = 15.4 Hz, 1H), 4.53 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.42 (m, 1H), 4.38 (s, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 3.47 (dd, *J* = 10.5, 1.7 Hz, 1H), 3.43 (s, 3H), 3.32 – 3.26 (m, 3H), 2.86 (dd, *J* = 19.3, 9.3 Hz, 1H), 2.35 – 2.22 (m, 2H), 1.70 – 1.65 (m, 1H), 1.43 – 1.34 (m, 1H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.4, 165.7,

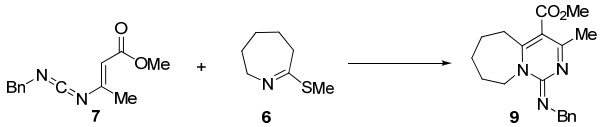
148.0, 139.7, 135.9, 135.9, 133.8, 133.1, 130.2, 130.1, 128.6, 128.5, 127.5, 126.2, 73.0, 70.4, 63.9, 63.1, 51.5, 50.6, 35.3, 35.1, 28.4, 26.9, 23.6, 19.3; FTIR (thin film) 3029, 2951, 2857, 1706, 1628, 1589, 1521, 1497, 1429, 1285, 1112, 738, 700 cm^{-1}; HRMS $(ESI)^+$ m/z Calcd for $C_{43}H_{49}N_3O_4Si$ $[M+H]^+$ 700.3571, observed 700.3586.



Bicyclic pyrimidine 5. To a sealed tube containing a 23 °C solution of thioimidate **3**[3] (15 mg, 0.039, 1.0 equiv) in benzene (0.6 mL) was added benzyl carbodiimide **4** (28.5 mg, 0.0782 mmol, 2.0 equiv). The tube was sealed under argon and stirred at 80 °C for 24 h. The reaction was cooled to 23 °C and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography (100% ethyl acetate) to afford guanidine **5** (16 mg, 59 % yield) as a dark yellow oil. The spectroscopic data of **5** was identical to the product derived from *O*-imidate **2**.

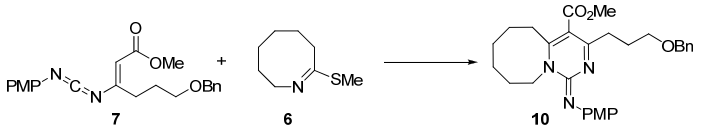


(*E*)-Methyl-1-(benzylimino)-3-(3-(benzyloxy)propyl)-5,6,7,8-tetrahydro-1*H*-pyrido[1,2-c]pyrimidine-4-carboxylate (8). To a sealed-tube containing a 23 °C solution of thioimidate **6** (n = 1)[4] (10 mg, 0.077 mmol, 1.0 equiv) in benzene (0.77 mL) was added silver trifluoromethanesulfonate (35 mg, 0.13 mmol, 1.75 equiv) and carbodiimide **7** (R_1 = PMB, R_2 = $(CH_2)_3OBn$) (42 mg, 0.12 mmol, 1.6 equiv). The reaction vessel was sealed under argon and covered in aluminum foil, at which point the mixture was stirred at 30 °C for 2 h. The temperature was then raised to 40 °C for 4 h, then 50 °C for 13 h. Finally, the temperature was raised to 60 °C for 1.5 h, at which point the reaction mixture was cooled to 23 °C and the solvent was removed in vacuo. The crude residue was purified by silica gel column chromatography (100% ethyl acetate) to afford guanidine **8** (26 mg, 74% yield) as a yellow oil. R_f = 0.59 (ethyl acetate/triethylamine 95:5); ^1H NMR (500 MHz, C_6D_6) δ 7.74 – 7.73 (m, 2H), 7.34 – 7.30 (m, 5H), 7.10 – 7.08 (m, 1H), 5.21 (s, 2H), 4.34 (s, 2H), 3.49 – 3.45 (m, 7H), 2.93 (t, *J* = 7.3 Hz, 2H), 2.36 (t, *J* = 6.6 Hz, 2H), 2.22 – 2.17 (m, 2H), 1.01 – 0.96 (m, 2H), 0.84 – 0.79 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.8, 167.1, 158.9, 150.4, 139.6, 127.5, 126.3, 73.0, 70.1, 51.8, 51.1, 44.9, 34.5, 28.0, 27.3, 21.5, 17.8; FTIR (thin film) 2946, 2860, 1722, 1622, 1495, 1452, 1433, 1103, 737, 698 cm^{-1}; LRMS $(ESI)^+$ m/z Calcd for $C_{27}H_{32}N_3O_3$ $[M+H]^+$ 446.24, observed 446.17.



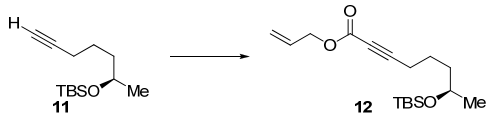
(*E*)-Methyl-1-(benzylimino)-3-methyl-1,5,6,7,8,9-hexahydropyrimido[1,6-a]azepine-4-carboxylate (9). To sealed-tube containing a 23 °C solution of thioimidate **6** (n = 2)[4] (6.4 mg, 0.044 mmol, 1.0 equiv) in 1,2-dichloroethane (0.44 mL) was added silver

trifluoromethanesulfonate (23 mg, 0.088 mmol, 2.0 equiv) and then benzyl carbodiimide **7** (R_1 = Bn, R_2 = Me) (15 mg, 0.065 mmol, 1.5 equiv). The tube was sealed under argon and stirred at 50 °C for 2 h. The solution was cooled to 23 °C and purified by silica gel column chromatography (100% ethyl acetate to 95:5 ethyl acetate/triethylamine) to afford guanidine **9** (11.2 mg, 78% yield) as a yellow oil. R_f = 0.29 (ethyl acetate/triethylamine 95:5); ^{1}H NMR (500 MHz, C_6D_6) δ 7.71 – 7.70 (m, 2H), 7.31 – 7.28 (m, 2H), 7.16 – 7.13 (m, 1H), 5.14 (s, 2H), 4.10 – 4.05 (m, 2H), 3.35 (s, 3H), 2.39 – 2.37 (m, 2H), 2.26 (s, 3H), 1.39 – 1.32 (m, 2H), 1.29 – 1.25 (m, 2H), 1.16 – 1.12 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.5, 167.1, 163.1, 150.7, 142.9, 126.5, 51.3, 50.8, 46.3, 30.2, 28.7, 26.0, 25.1, 24.9; FTIR (thin film) 2933, 2859, 1715, 1625, 1508, 1435, 1344, 1328, 1271, 1217, 1126, 1030 cm^{-1}; HRMS (ESI)$^+$ m/z: Calcd for $C_{19}H_{24}N_3O_2$ $[M+H]^+$ 326.1869, observed 326.1857.



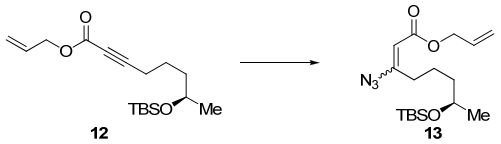
(*E*)-Methyl-3-(3-(benzyloxy)propyl)-1-(4-methoxyphenylimino)-5,6,7,8,9,10-hexahydro-1*H*-pyrimido[1,6-a]azocine-4-carboxylate (10). To a sealed-tube containing a 23 °C solution of thioimidate **6** (n = 3)[4] (6.6 mg, 0.042, 1.0 equiv) in 1,2-dichloroethane (0.38 mL) was added silver trifluoromethanesulfonate (20 mg, 0.078 mmol, 1.8 equiv) and then *para*-methoxyphenyl carbodiimide **7** (R_1 = PMP, R_2 = $(CH_2)_3$OBn) (22 mg, 0.057 mmol, 1.4 equiv). The tube was sealed under argon and stirred at 50 °C for 16 h. The reaction was cooled to 23 °C and the crude mixture was purified by silica gel column chromatography (toluene/ethyl acetate 1:1) to afford guanidine **10** (14.6 mg, 71% yield) as a yellow oil. R_f = 0.23 (toluene/ethyl acetate 1:1); ^{1}H NMR (500 MHz, C_6D_6, 60 °C) δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.25 (m, 2H), 7.09 – 7.08 (m, 1H), 7.00 – 6.97 (m, 2H), 4.29 (s, 2H), 3.95 (br s, 2H), 3.46 (app d, *J* = 6.1 Hz, 6H) 3.37 (t, *J* = 6.1 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.41 (m, 2H), 2.05 – 1.98 (m, 2H), 1.75 (m, 2H), 1.62 (m, 2H), 1.15 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.6, 167.6, 161.7, 155.7, 148.2, 143.4, 139.6, 127.4, 125.1, 114.1, 107.7, 72.8, 69.8, 55.0, 51.4, 44.6, 34.0, 30.8, 30.2, 29.4, 28.0, 27.5, 25.9, 24.7; FTIR (thin film) 2928, 2856, 1714, 1615, 1497, 1475, 1438, 1283, 1262, 1236, 1126, 1102, 1093, 1070, 828, 740, 698 cm^{-1}; HRMS (ESI)$^+$ m/z: Calcd for $C_{29}H_{36}N_3O_4$ $[M+H]^+$ 490.2706, observed 490.2705.

SYNTHESIS OF (–)-CRAMBIDINE AND PRECURSORS

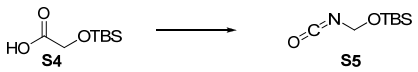


7-(*tert*-Butyl-dimethyl-silanyloxy)-oct-2-ynoic acid allyl ester (12). To a –78 °C solution of alkyne **11**[5] (100 mg, 0.442 mmol, 1.0 equiv) in tetrahydrofuran (4.4 mL) was added *n*-BuLi (1.6 M in hexanes, 414 μL, 0.663 mmol, 1.5 equiv). The resulting solution was stirred at –78 °C for 1 h, at which point allyl chloroformate (94 μL, 0.89 mmol, 2.0 equiv) was added. The solution was immediately warmed to 23 °C and stirred for an additional 1 h. The solution was then diluted with diethyl ether (200 mL) and washed sequentially with saturated aqueous ammonium chloride (200 mL), saturated aqueous sodium bicarbonate (200 mL), and saturated aqueous

sodium chloride (200 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexanes/ethyl acetate 19:1) to provide ynoate **12** (123 mg, 90% yield) as a colorless oil. R_f = 0.47 (hexanes/ethyl acetate 10:1); $[\alpha]_D^{19}$ –5.6 (c 1.11, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 5.61 (ddt, *J* = 17.5, 11.0, 6.0 Hz, 1H), 5.07 – 5.02 (m, 1H), 4.90 – 4.87 (m, 1H), 4.38 – 4.37 (m, 2H), 3.52 – 3.48 (m, 1H), 1.87 – 1.78 (m, 2H), 1.40 – 1.21 (m, 4H), 0.95 – 0.93 (m, 12H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.4, 131.9, 118.4, 89.2, 74.1, 68.1, 65.9, 38.6, 26.0, 23.9, 23.8, 18.5, 18.2, –4.3, –4.7; FTIR (thin film) 2957, 2931, 2858, 2237, 1715, 1472, 1463, 1374, 1361, 1247, 1137, 1093, 1073, 1050, 1022, 1006, 938, 836, 775, 752 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{17}H_{31}O_3Si$ $[M+H]^+$ 311.2042, found 311.2043.

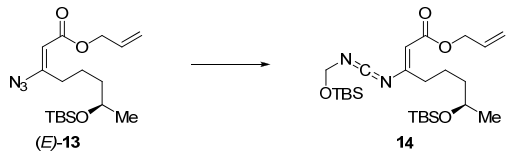


3-Azido-7-(*tert*-butyl-dimethyl-silanyloxy)-oct-2-enoic acid allyl esters (13). To a 23 °C solution of ynoate **12** (577 mg, 1.85 mmol, 1.0 equiv) in $CHCl_3$ (6.2 mL) was added tetramethylguandidinium azide (588 mg, 3.72 mmol, 2.0 equiv) in a single portion. The resulting solution was stirred at 23 °C for 46 h and then, without concentrating the solution, purified by silica gel column chromatography (hexanes/ethyl acetate 99:1 to 96:4) to provide (*E*)-**13** (304 mg, 46% yield) and (*Z*)-**13** (152 mg, 23% yield) as pale yellow oils. *Note: Tetramethylguanidinium azide is capable of reacting with halogenated solvents like chloroform to generate low molecular weight polyazides, which are known to be explosion hazards. Care should be taken in scaling up this reaction and the crude reaction mixture should never be concentrated.* Azide (*E*)-**13**: R_f = 0.33 (hexanes/ethyl acetate 19:1); $[\alpha]_D^{18}$ +0.3 (c 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 5.73 (ddt, *J* = 21.0, 12.5, 6.5 Hz, 1H), 5.52 (s, 1H), 5.13 – 5.07 (m, 1H), 4.98 – 4.94 (m, 1H), 4.48 – 4.46 (m, 2H), 3.68 – 3.64 (m, 1H), 2.76 – 2.71 (m, 2H), 1.75 – 1.67 (m, 1H), 1.60 – 1.35 (m, 3H), 1.04 (d, *J* = 8.0 Hz, 3H), 0.98 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 165.2, 159.9, 132.9, 117.6, 104.8, 68.3, 64.6, 39.1, 30.1, 26.1, 24.2, 23.9, 18.2, –4.2, –4.7; IR (thin film) 2958, 2931, 2859, 2112, 1742, 1715, 1622, 1463, 1379, 1256, 1166, 1138, 1007, 836, 775 cm^{-1}; *Note: Unable to obtain HRMS data by any available method.* Azide (*Z*)-**13**: R_f = 0.24 (hexanes/ethyl acetate 19:1); $[\alpha]_D^{19}$ –4.1 (c 1.64, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) 5.76 (ddt, *J* = 21.0, 12.5, 6.5 Hz, 1H), 5.26 (s, 1H), 5.17 – 5.12 (m, 1H), 4.98 – 4.95 (m, 1H), 4.52 – 4.51 (m, 2H), 3.54 – 3.48 (m, 1H), 1.72 – 1.67 (m, 2H), 1.46 – 1.35 (m, 1H), 1.30 – 1.17 (m, 2H), 1.14 – 1.05 (m, 1H), 0.99 – 0.95 (m, 12H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 163.5, 153.5, 133.0, 117.6, 105.4, 68.1, 64.5, 38.6, 35.1, 26.0, 23.8, 23.4, 18.2, –4.3, –4.7; FTIR (thin film) 2957, 2931, 2858, 2120, 1725, 1714, 1633, 1463, 1374, 1256, 1178, 1128, 1094, 1027, 836, 775 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{17}H_{31}N_3O_3SiNa$ $[M+Na]^+$ 376.2032, found 376.2032.

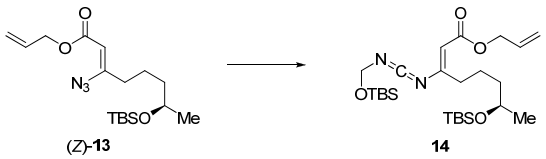


***tert*-Butyl(isocyanatomethoxy)dimethylsilane (S5).** To a 23 °C solution of carboxylic acid **S4**[6] (500 mg, 2.63 mmol, 1.0 equiv) in dichloromethane (6.6 mL) was added oxalyl chloride (343

μL, 3.94 mmol, 1.5 equiv), followed by *N*,*N*-dimethylformamide (~20 μL). The solution was stirred at 23 °C for 45 min (gas evolution) and then concentrated in vacuo. To ensure complete removal of excess oxalyl chloride, benzene (2 mL) was added and removed in vacuo. The resulting residue was dissolved in acetone (3.9 mL) and added to a 23 °C solution of sodium azide (393 mg, 6.05 mmol, 2.3 equiv) in water (3.9 mL). The mixture was stirred at 23 °C for 30 min and then diluted with chloroform (10 mL). The solution was washed sequentially with saturated aqueous sodium bicarbonate (10 mL), water (10 mL) and saturated aqueous sodium chloride (10 mL). The organic layer was dried over sodium sulfate, concentrated to ~5 mL, and heated to reflux for 1 h. The resulting solution was carefully concentrated to give isocyanate **S5** (355 mg, 72% yield) as a volatile colorless oil that was used without further purification. ^{1}H NMR (500 MHz, C_6D_6) δ 4.26 (s, 2H), 0.84 (s, 9H), –0.08 (s, 6H); FTIR (thin film) 2958, 2933, 2860, 2257, 1725, 1473, 1391, 1259, 1119, 1080, 837, 782 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_8H_{18}NO_2Si$ $[M+H]^+$ 188.1107, found 188.1105.

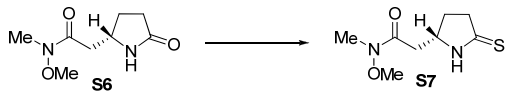


Vinyl carbodiimide 14. To a sealed tube containing a 0 °C solution of azide (*E*)-**13** (90 mg, 0.25 mmol, 1.05 equiv) in dichloromethane (2.5 mL) was added triphenylphosphine (64 mg, 0.24 mmol, 1.0 equiv) in a single portion. After stirring for 10 min at 0 °C, the resulting yellow solution was warmed to 23 °C and stirred for an additional 4 h, during which time the solution became clear. Following concentration in vacuo, a solution of isocyanate **S5** (63 mg, 0.34 mmol, 1.4 equiv) in benzene (2.4 mL) was added and the tube was sealed under argon. After heating the solution at 80 °C for 12 h, the reaction was cooled to 23 °C and purified directly by silica gel column chromatography (hexanes/ethyl acetate 98:2) to provide carbodiimide **14** (59 mg, 49% yield) as a colorless oil. R_f = 0.46 (hexanes/ethyl acetate 9:1); $[\alpha]_D^{22}$ –2.4 (c 0.98, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) δ 5.97 (s, 1H), 5.70 (ddt, *J* = 17.5, 10.5, 5.5 Hz, 1H), 5.11 – 5.06 (m, 1H), 4.95 – 4.92 (m, 1H), 4.55 (s, 2H), 4.70 – 4.45 (m, 2H), 3.8 (sext, *J* = 6.0 Hz, 1H), 3.10 – 3.02 (m, 2H), 1.95 – 1.86 (m, 1H), 1.81 – 1.72 (m, 1H), 1.67 – 1.60 (m, 1H), 1.55 – 1.48 (m, 1H), 1.09 (d, *J* = 6.5 Hz, 3H), 0.99 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), –0.01 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.0, 158.9, 136.3, 133.0, 117.4, 110.6, 71.9, 68.5, 64.4, 39.3, 33.1, 26.1, 25.7, 24.3, 23.9, 18.2, 18.1, –4.3, –4.6, –5.3; FTIR (thin film) 2955, 2931, 2858, 2135, 1715, 1626, 1372, 1257, 1171, 1125, 1020, 836, 777 cm^{-1}; HRMS (ESI)$^+$ *m/z* Calcd for $C_{25}H_{49}N_2O_4Si_2$ $[M+H]^+$ 497.3231, found 497.3218.

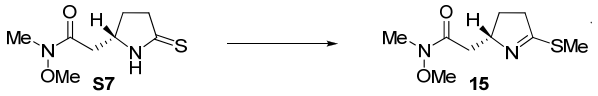


Vinyl carbodiimide 14. To a sealed tube containing a 0 °C solution of azide (*Z*)-**13** (139 mg, 0.369 mmol, 1.04 equiv) in dichloromethane (3.7 mL) was added triphenylphosphine (93 mg, 0.354 mmol, 1.0 equiv) in a single portion. After stirring for 10 min at 0 °C, the resulting yellow

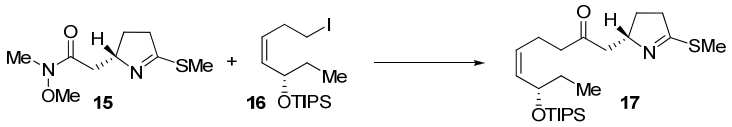
solution was warmed to 23 °C and stirred for an additional 4 h, during which time the solution became clear. Following concentration in vacuo, a solution of isocyanate **S5** (93 mg, 0.50 mmol, 1.4 equiv) in benzene (3.5 mL) was added and the tube was sealed under argon. After heating the solution at 80 °C for 12 h, the reaction was cooled to 23 °C and purified directly by silica gel column chromatography (hexanes/ethyl acetate 98:2) to provide carbodiimide **14** (75 mg, 43% yield) as a colorless oil. The spectral data of the product was identical to the data of the product derived from vinyl azide (*E*)-**13**.



(*S*)-*N*-Methoxy-*N*-methyl-2-(5-thioxopyrrolidin-2-yl)acetamide (S7). To a 0 °C solution of lactam **S6**[7] (105 mg, 0.564 mmol, 1.0 equiv) in tetrahydrofuran (5.6 mL) was added Lawesson's reagent (117 mg, 0.289 mmol, 0.5 equiv) in a single portion. The reaction was stirred at 0 °C for 1 h, warmed to 23 °C over the course of 5 min, and then stirred for an additional 10 min. After removing the solvent in vacuo, the crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes 3:1 to 100% ethyl acetate) to provide thiolactam **S7** (104 mg, 92% yield) as a white solid. R_f = 0.30 (100% ethyl acetate); $[\alpha]_D^{22}$ +21.0 (c 0.86, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) δ 8.76 (br s, 1H), 3.83 (pent, *J* = 7.0 Hz, 1H), 2.96 (s, 3H), 2.81 (s, 3H), 2.68 (ddd, *J* = 17.5, 9.5, 5.0 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.25 – 2.15 (m, 2H), 1.67 – 1.60 (m, 1H), 1.16 – 1.09 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 205.0, 171.4, 60.6, 58.0, 42.8, 37.6, 31.7, 29.0; FTIR (thin film) 3219, 2939, 1644, 1520, 1464, 1408, 1313, 1292, 1269, 1130, 1004 cm^{-1}; HRMS (ESI)$^+$ *m/z* Calcd for $C_8H_{15}N_2O_2S$ $[M+H]^+$ 203.0854, found 203.0855.

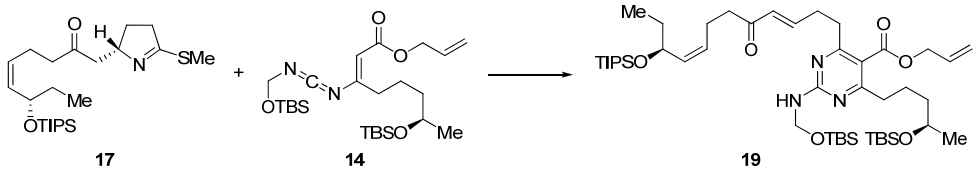


(*S*)-*N*-Methoxy-*N*-methyl-2-(5-(methylthio)-3,4-dihydro-2*H*-pyrrol-2-yl)acetamide (15). To a 23 °C solution of thiolactam **S7** (50 mg, 0.25 mmol, 1.0 equiv) in tetrahydrofuran (2.4 mL) was added potassium bicarbonate (51 mg, 0.37 mmol, 1.5 equiv), followed by iodomethane (23 µL, 0.37 mmol, 1.5 equiv). The solution was stirred for 26 h, and then the solvent was removed in vacuo. The crude material was purified directly by silica gel column chromatography (100% ethyl acetate) to give the thioimidate **15** (49 mg, 92% yield) as a clear oil. R_f = 0.22 (100% ethyl acetate); $[\alpha]_D^{22}$ –8.1 (c 1.87, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) δ 4.66 – 4.59 (m, 1H), 3.14 – 3.07 (m, 1H), 3.00 (s, 3H), 2.84 (s, 3H), 2.42 – 2.28 (m, 5H), 2.25 – 2.06 (m, 2H), 1.48 – 1.39 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.9, 69.3, 60.5, 39.2, 38.5, 31.8, 30.8, 13.5; FTIR (thin film) 3502, 2931, 1660, 1588, 1429, 1386, 1292, 1179, 1093, 996 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_9H_{16}N_2O_2SNa$ $[M+Na]^+$ 239.0830, found 239.0836.

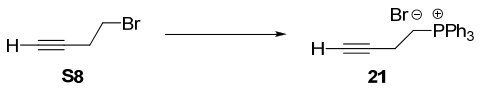


(*S,Z*)-1-((*S*)-5-(Methylthio)-3,4-dihydro-2*H*-pyrrol-2-yl)-7-(triisopropylsilyloxy)non-5-en-2-one (17). A solution of iodide **16**[8] (23 mg, 0.058 mmol, 1.2 equiv) in diethyl ether (100 µL) and

hexanes (100 μL, dried over 4 Å mol. sieves) was degassed (freeze/pump/thaw 3x). The solution was then cooled to –78 °C and *tert*-butyllithium (1.60 M in pentane, 72 μL, 0.12 mmol, 2.4 equiv) was added dropwise over the course of 5 min. After stirring at –78 °C for 30 min, a –78 °C solution of thioimidate **15** (10.5 mg, 0.048 mol, 1.0 equiv) in diethyl ether (200 μL) was added via cannula in three portions over the course of 3 min. The cannula was then rinsed with additional –78 °C diethyl ether (200 μL). The solution was stirred at –78 °C for 30 min, at which point the temperature was raised to 23 °C and stirring continued for an additional 30 min. The reaction mixture was then poured into diethyl ether (100 mL) and washed sequentially with saturated aqueous monobasic potassium phosphate (20 mL), saturated aqueous sodium bicarbonate (20 mL), and saturated aqueous sodium chloride (20 mL). The organic layer was dried over magnesium sulfate, filtered, and the solvent was removed in vacuo. The crude reaction mixture was purified by silica gel column chromatography (hexanes/ethyl acetate 8:1) to give thioimidate **17** (13.6 mg, 67% yield) as a colorless oil. R_f = 0.48 (hexanes/ethyl acetate 1:1); $[\alpha]_D^{23}$ +56.4 (c 0.27, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) δ 5.54 – 5.49 (m, 1H), 5.23 (dt, *J* = 11.1, 7.3 Hz, 1H), 4.61 – 4.57 (m, 1H), 4.28 (quint, *J* = 7.2 Hz, 1H), 2.54 (dd, *J* = 15.6, 6.7 Hz, 1H), 2.40 – 2.23 (m, 6H), 2.22 – 2.11 (m, 3H), 2.08 (dd, *J* = 15.6, 7.4 Hz, 1H), 1.87 – 1.81 (m, 1H), 1.73 – 1.64 (m, 1H), 1.61 – 1.53 (m, 1H), 1.16 – 1.08 (m, 22H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.8, 172.0, 135.1, 128.3, 70.3, 68.9, 49.6, 43.0, 38.4, 22.4, 18.4, 18.3, 13.5, 12.7, 9.4; FTIR (thin film) 2941, 2865, 1716, 1589, 1463, 1084, 882, 681 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{23}H_{44}NO_2SSi$ $[M+H]^+$ 426.2862, found 426.2876.

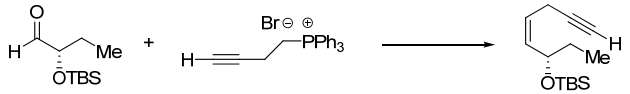


Pyrimidine 19. To a sealed-tube containing thioimidate **17** (3.8 mg, 8.9 μmol, 1.0 equiv) and carbodiimide **14** (9.0 mg, 18 μmol, 2.0 equiv) was added 1,2-dichloroethane (90 μL) The tube was sealed under argon, and the reaction solution was heated to 60 °C for 24 h. After cooling the solution to 23 °C, the solvent was removed in vacuo, and the crude yellow residue was purified by column chromatography (hexanes/acetone/triethylamine 97:1:2 to 96:2:2) to give pyrimidine **19** (5.5 mg, 70% yield) as a yellow oil. R_f = 0.30 (hexanes/diethyl ether/triethylamine 90:5:5); $[\alpha]_D^{19}$ +4.5 (c 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 6.75 (dt, *J* = 14.6, 6.4 Hz, 1H), 6.03 (d, *J* = 15.2 Hz, 1H), 5.80 (ddt, 16.5, 10.3, 6.1 Hz, 1H), 5.60 – 5.51 (m, 2H), 5.26 (ddt, *J* = 11.1, 7.3, 1.0 Hz, 1H), 5.17 – 5.13 (m, 1H), 5.04 – 4.98 (m, 3H), 4.65 – 4.58 (m, 3H), 3.75 (m, 1H), 2.85 (m, 4H), 2.52 (m, 2H), 2.45 – 2.25 (m, 4H), 1.99 (m, 1H), 1.86 (m, 1H), 1.73 – 1.66 (m, 1H), 1.62 – 1.54 (m, 2H), 1.47 (m, 1H), 1.17 – 1.10 (m, 24H), 1.00 (s, 9H), 0.95 – 0.93 (m, 12H), 0.11 (br s, 6H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 170.6, 168.3, 167.9, 160.7, 146.1, 135.2, 131.6, 130.6, 127.0, 119.9, 116.6, 69.9, 68.5, 66.8, 66.2, 39.8, 39.6, 36.3, 34.4, 31.8, 31.1, 26.0, 25.9, 25.1, 23.8, 22.6, 18.3, 18.2, 18.2, 18.1, 12.4, 9.4, –4.3, –4.6, –4.8; FTIR (thin film) 3353, 2865, 1723, 1566, 1530, 1465, 1252, 1094, 1051, 838, 779 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{47}H_{88}N_3O_6Si_3$ $[M+H]^+$ 874.5981, found 874.5991.



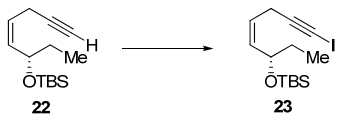
S8 21

But-3-ynyltriphenylphosphonium bromide (21). To a 20 mL sealed-tube containing alkynyl bromide **S8**[9] (1.15 g, 8.65 mmol, 1.11 equiv) in acetonitrile (8 mL) was added triphenylphosphine (2.04 g, 7.78 mmol, 1.0 equiv) which had been recrystallized from 95% ethanol and dried under vacuum over phosphorous pentoxide. The tube was sealed under argon, covered in foil, and heated to 80 °C for 72 h. After cooling to 23 °C, the solvent was removed in vacuo. Benzene (30 mL) was added and the resulting heterogeneous mixture was cooled to –20 °C for 20 min, at which the product (2.58, 84% yield) was filtered off as a white solid. Spectroscopic data of **21** was in agreement with previous reports.[10]



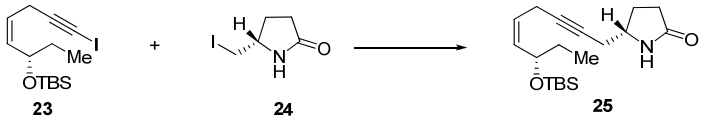
20 21 22

(*S*,*Z*)-*tert*-Butyldimethyl(oct-4-en-7-yn-3-yloxy)silane (22). To a –78 °C solution of phophonium salt **21** (324 mg, 0.820 mmol, 1.1 equiv) in tetrahydrofuran (3.6 mL) was added *n*-butyllithium (1.55 M in hexanes, 530 μL, 0.821 mmol, 1.1 equiv) over the course of 10 minutes. After stirring for 5 min at –78 °C, the reaction solution was warmed to 0 °C for 1 h, and then cooled to –78 °C. The temperature of the mixture was maintained at –78 °C for an additional 40 min, at which point a –78 °C solution of aldehyde **20**[11] (150 mg, 0.741 mmol, 1.0 equiv) in tetrahydrofuran (2.0 mL) was added via cannula over the course of 3 min. The cannula was rinsed with additional –78 °C tetrahydrofuran (1.0 mL), and the reaction mixture was maintined at –78 °C. After 25 min, the temperature of the reaction mixture was raised to –40 °C and maintained at that temperature for 45 min. The temperature was then raised to 0 °C and stirred for 1 h, at which point the reaction mixture was stirred at 23 °C for an additional 45 min. Saturated aqueous ammonium chloride (10 mL) was added and the heterogeneous mixture was stirred for 5 min. After diluting the solution with ethyl acetate (150 mL) and water (100 mL), the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 75 mL). The organic extracts were combined, washed with saturated aqueous sodium chloride (75 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to give the crude product. Purification by silica gel column chromatography (hexanes/dichloromethane 10:1 to 8:1) gave alkene **22** (150 mg, 85% yield) as a slightly-volatile colorless oil. R_f = 0.51 (hexanes/dichloromethane 3:1); $[\alpha]_D^{18}$ +16.6 (c 1.49, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) δ 5.53 – 5.49 (m, 1H), 5.41 (dt, *J* = 10.9, 7.4 Hz, 1H), 4.33 (m, 1H), 2.90 – 2.77 (m, 2H); 1.85 (t, *J* = 2.7 Hz, 1H), 1.68 – 1.59 (m, 1H), 1.54 – 1.45 (m, 1H), 1.08 (s, 9H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.17 (s, 6H); ^{13}C NMR (500 MHz, C_6D_6) δ 135.9, 123.2, 82.0, 70.1, 69.0, 31.4, 26.0, 18.3, 17.6, 9.8, –4.2, –4.7; FTIR (thin film) 3314, 2959, 2931, 2858, 2123, 1464, 1254, 1081, 1046, 1012, 857, 836, 776, 668, 636 cm^{-1}; LRMS (ESI)$^+$ *m/z*: Calcd for $C_{14}H_{26}OSiNa$ $[M+Na]^+$ 261.2, found 261.1.



22 23

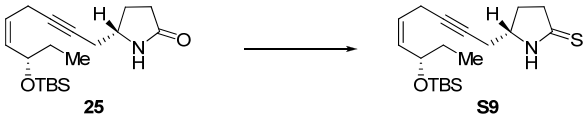
(*S*,*Z*)-*tert*-Butyl(8-iodooct-4-en-7-yn-3-yloxy)dimethylsilane (23). To a 23 °C solution of alkyne **22** (310 mg, 1.30 mmol, 1.0 equiv) in acetone (10 mL) was added *N*-iodosuccinimide (321 mg, 1.43 mmol, 1.1 equiv), followed by silver nitrate (22 mg, 0.13 mmol, 0.1 equiv). After stirring at 23 °C for 2 h, the solution was poured into ice water (75 mL). Hexanes (75 mL) were added, and the layers were separated. The aqueous layer was extracted with hexanes (2 x 50 mL) and the organic extracts were washed with aqueous saturated sodium chloride (50 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting pink oil (429 mg, 91% yield) was used without further purification. R_f = 0.44 (hexanes/dichloromethane 6:1); $[\alpha]_D^{21}$ +13.2 (c 1.40, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) δ 5.39 – 5.35 (m, 1H), 5.17 (dt, *J* = 10.9, 7.5 Hz, 1H), 4.21 – 4.16 (m, 1H), 2.84 (ddd, *J* = 18.2, 7.5, 1.6 Hz, 1H), 2.77 (ddd, *J* = 18.1, 6.9, 1.7 Hz, 1H), 1.54 – 1.45 (m, 1H), 1.39 – 1.31 (m, 1H), 0.96 (s, 9H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 136.1, 122.6, 91.9, 70.0, 31.3, 26.0, 19.8, 18.3, 9.8, –4.2, –4.7, –4.8; FTIR (thin film) 3023, 2957, 2929, 2856, 1463, 1254, 1083, 1046, 1005, 856, 836 cm^{-1}.



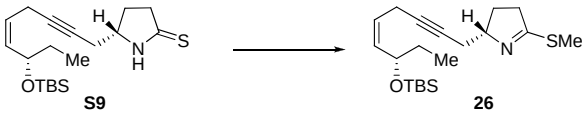
23 24 25

(*S*)-5-((*S*,*Z*)-7-(*tert*-Butyldimethylsilyloxy)non-5-en-2-ynyl)pyrrolidin-2-one (25). A variation of a previously-reported coupling was employed.[12] To a suspension of zinc dust (<10 μm, 243 mg, 3.72 mmol, 6.0 equiv) in *N*,*N*-dimethylformamide (1.0 mL) was added 1,2-dibromoethane (32 μL, 0.37 mmol, 0.60 equiv). The solution was heated to 60 °C for 15 min. After cooling to 23 °C, chlorotrimethylsilane (38 μL, 0.29 mmol, 0.48 equiv) was added and the solution was sonicated for 30 min. The solvent was then decanted via syringe and replaced with fresh *N*,*N*-dimethylformamide (0.6 mL). The reaction solution was cooled to 0 °C, and iodopyrrolidinone **24**[13] (419 mg, 1.86 mmol, 3.0 equiv) was added as a 0 °C solution of *N*,*N*-dimethylformamide (1.0 mL) via cannula over the course of 2 min. The cannula was rinsed with 0 °C *N*,*N*-dimethylformamide (0.5 mL) and the heterogeneous mixture was maintained at 0 °C for 5.5 h. In a separate schlenk flask, copper cyanide (167 mg, 1.86 mmol, 3.0 equiv) and lithium chloride (158 mg, 3.72 mmol, 6.0 equiv) were dried under vacuum at 140 °C for 2 h. After cooling the flask to 23 °C, tetrahydrofuran (14 mL) was added, and the solids became fully soluble after sonicating for ~5 min. The tetrahydrofuran solution was cooled to –40 °C, and the 0 °C *N*,*N*-dimethylformamide solution was added to the copper cyanide/lithium chloride mixture via cannula over the course of 5 min, taking care to minimize the amount of excess solid zinc transferred. The cannula was rinsed with 0 °C *N*,*N*-dimethylformamide (0.3 mL). The solution was immediately warmed to 0 °C for 10 min, and then cooled to –40 °C before adding iodoalkyne **23** (226 mg, 0.621 mmol, 1.0 equiv) as a neat liquid over the course of 10 min. The reaction was warmed slowly to 23 °C over 6 h, and then stirred at 23 °C for an additional 10 h. Saturated aqueous ammonium chloride (30 mL) was added and the reaction solution was stirred for 10 minutes. The crude solution was diluted with ethyl acetate (300 mL), water (150 mL), and saturated aqueous ammonium chloride (150 mL). The layers were separated, and the aqueous

layer was extracted with ethyl acetate (2 x 300 mL). The organic layers were combined and washed sequentially with water (2 x 250 mL) and saturated aqueous sodium chloride (250 mL). The organics were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (ethyl acetate/hexanes 4:1 to 5:1 to 100% ethyl acetate) to provide lactam **25** (112 mg, 54% yield) as a colorless oil. R_f = 0.27 (ethyl acetate/hexanes 4:1); $[\alpha]_D^{18}$ –1.8 (c 0.86, THF); ^{1}H NMR (500 MHz, C_6H_6) δ 7.34 (br s, 1H), 5.47 – 5.38 (m, 2H), 4.31 – 4.27 (m, 1H), 3.21 (quint, *J* = 5.9 Hz, 1H), 2.91 – 2.78 (m, 2H), 2.09 (ddd, *J* = 16.6, 9.9, 6.2 Hz, 1H), 1.98 – 1.88 (m, 3H), 1.62 – 1.53 (m, 2H), 1.48 – 1.39 (m, 1H), 1.33 – 1.26 (m, 1H), 0.99 (s, 9H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.7, 135.4, 124.3, 80.2, 76.8, 70.2, 53.4, 31.6, 30.2, 26.7, 26.2, 26.1, 18.4, 18.1, 9.9, –4.1, –4.6; FTIR (thin film) 3216, 2957, 2929, 2857, 1701, 1463, 1254, 1080, 1044, 1007, 858, 836, 775 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{19}H_{33}NO_2SiNa$ $[M+Na]^+$ 358.2178, found 358.2162.

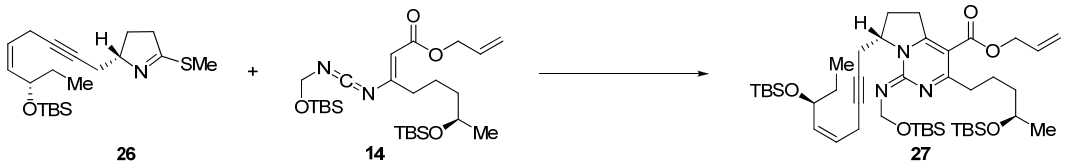


(*S*)-5-((*S,Z*)-7-(*tert*-Butyldimethylsilyloxy)non-5-en-2-ynyl)pyrrolidine-2-thione (S9). To a 0 °C solution of lactam **25** (110 mg, 0.328 mmol, 1.0 equiv) in tetrahydrofuran (6.5 mL) was added Lawesson's reagent (66 mg, 0.16 mmol, 0.5 equiv) in a single portion. After stirring for 1.25 h, the solution was warmed to 23 °C, the solvent was removed in vacuo, and the crude oil purified by silica gel column chromatography (hexanes/ethyl acetate 4:1) to give thiolactam **S9** (108 mg, 94% yield) as a colorless oil. R_f = 0.42 (hexanes/ethyl acetate 2:1); $[\alpha]_D^{18}$ –36.4 (c 2.23, THF); ^{1}H NMR (500 MHz, C_6H_6) δ 8.48 (br s, 1H), 5.48 – 5.43 (m, 1H), 5.38 (dt, *J* = 11.1, 6.7 Hz, 1H), 4.29 (m, 1H), 3.23 – 3.18 (m, 1H), 2.87 (ddq, *J* = 18.1, 7.5, 1.5 Hz, 1H), 2.80 (ddq, *J* = 18.1, 6.7, 1.8 Hz, 1H), 2.67 (ddd, *J* = 18.1, 9.5, 5.8 Hz, 1H), 2.47 (ddd, *J* = 18.0, 9.6, 7.0 Hz, 1H), 1.80 (dt, *J* = 5.8, 2.3 Hz, 2H), 1.62 – 1.54 (m, 1H), 1.49 – 1.40 (m, 2H), 1.20 (dddd, *J* = 12.7, 9.5, 6.9, 5.7 Hz, 1H), 1.00 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 205.5, 135.6, 124.0, 80.9, 76.0, 70.2, 60.8, 43.1, 31.6, 28.3, 26.1, 25.4, 18.4, 18.1, 9.9, –4.0, –4.6; FTIR (thin film) 3163, 2959, 2931, 2858, 1531, 1504, 1296, 1257, 1123, 1082, 1046, 1009, 860, 838, 777 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{19}H_{33}NOSSiNa$ $[M+Na]^+$ 374.1950, found 374.1944.

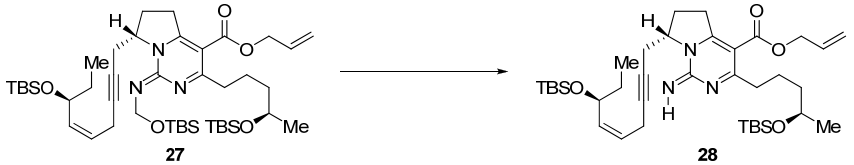


(*S*)-2-((*S,Z*)-7-(*tert*-Butyldimethylsilyloxy)non-5-en-2-ynyl)-5-(methylthio)-3,4-dihydro-2*H*-pyrrole (26). To a 23 °C solution of thiolactam **S9** (132 mg, 0.376 mmol, 1.0 equiv) in tetrahydrofuran (4.5 mL) was added potassium carbonate (103 mg, 0.746 mmol, 2.0 equiv), followed by iodomethane (47 μL, 0.75 mmol, 2.0 equiv). The heterogeneous mixture was stirred at 23 °C for 19 h and then diluted with ethyl acetate (100 mL) and water (75 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The organic extracts were combined, washed with saturated aqueous sodium chloride (75 mL), dried over

magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate/triethylamine 10:1:0.3) to give thioimidate **26** (130 mg, 95% yield) as a colorless oil. R_f = 0.53 (hexanes/ethyl acetate 3:1); $[\alpha]_D^{21}$ –29.6 (c 1.50, C_6H_6); ^{1}H NMR (500 MHz, C_6H_6) δ 5.44 – 5.35 (m, 2H), 4.27 (m, 1H), 4.08 – 4.03 (m, 1H), 2.87 – 2.82 (m, 1H), 2.80 – 2.75 (m, 1H), 2.62 – 2.57 (m, 1H), 2.42 (dddd, *J* = 16.5, 9.9, 5.0, 1.7 Hz, 1H), 2.35 – 2.29 (m, 4H), 2.25 – 2.18 (m, 1H), 1.83 (dddd, *J* = 17.7, 9.9, 7.6, 5.0 Hz, 1H), 1.63 – 1.51 (m, 2H), 1.45 – 1.37 (m, 1H), 0.97 (s, 9H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.2, 135.2, 124.6, 79.1, 78.3, 71.6, 70.2, 38.7, 31.6, 29.3, 26.6, 26.1, 18.4, 18.2, 13.6, 9.9, –4.1, –4.7; FTIR (thin film) 2959, 2930, 2858, 1591, 1291, 1255, 1093, 1047, 1008, 966, 860, 838, 777 cm^{-1}; HRMS (ESI) *m/z*: Calcd for $C_{20}H_{36}NOSSi$ $[M+H]^+$ 366.2287, found 366.2275.

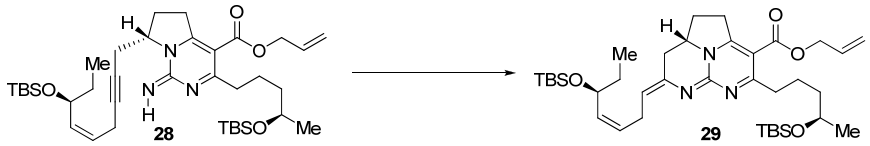


Bicyclic pyrimidine 27. To thioimidate **26** (53 mg, 0.15 mmol, 1.0 equiv) and carbodiimide **14** (145 mg, 0.292 mmol, 2.0 equiv) was added 1,2-dichloroethane (1.5 mL). After the reaction mixture stirred at 23 °C for 110 h, the solvent was removed in vacuo. The crude yellow product was purified by silica gel column chromatography (hexanes/ethyl acetate/triethylamine 45:1:1.4 to 30:1:0.9) to afford guanidine **27** (78 mg, 65% yield) as a yellow oil. R_f = 0.24 (hexanes/ethyl acetate/triethylamine 19:1:1); $[\alpha]_D^{23}$ –177 (c 2.11, C_6H_6); ^{1}H NMR (500 MHz, C_6H_6) δ 5.80 (ddt, *J* = 17.1, 10.6, 5.9 Hz, 1H), 5.74 (s, 2H), 5.44 – 5.40 (m, 1H), 5.28 (dt, *J* = 10.8, 7.3 Hz, 1H), 5.15 – 5.11 (m, 1H), 5.03 – 5.01 (m, 1H), 4.56 (app d, *J* = 5.7 Hz, 2H), 4.37 – 4.33 (m, 1H), 4.23 – 4.19 (m, 1H), 3.78 (app sext, *J* = 6.0 Hz, 1H), 3.17 – 3.09 (m, 2H), 3.03 – 2.97 (m, 2H), 2.85 – 2.73 (m, 2H), 2.71 – 2.66 (m, 1H), 2.53 – 2.49 (m, 1H), 2.08 –1.99 (m, 1H), 1.85 – 1.76 (m, 1H), 1.68 – 1.58 (m, 2H), 1.56 – 1.47 (m, 2H), 1.43 – 1.34 (m, 2H), 1.56 (s, 9H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.01 (s, 9H), 0.98 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.36 (s, 3H), 0.35 (s, 3H), 0.12 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.0, 166.3, 164.8, 145.1, 135.5, 133.0, 123.9, 118.4, 100.7, 80.4, 76.4, 75.7, 70.2, 68.9, 65.1, 61.7, 40.1, 38.5, 34.1, 31.5, 26.5, 26.2, 26.1, 24.9, 24.5, 24.2, 21.6, 18.7, 18.4, 18.4, 18.1, 9.9, –3.8, –3.9, –4.1, –4.1, –4.4, –4.6; FTIR (thin film) 2956, 2929, 2886, 2856, 1707, 1635, 1594, 1501, 1462, 1379, 1360, 1379, 1251, 1099, 1063, 1044, 836, 775 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{44}H_{80}N_3O_5Si_3$ $[M+H]^+$ 814.5406, found 814.5383.

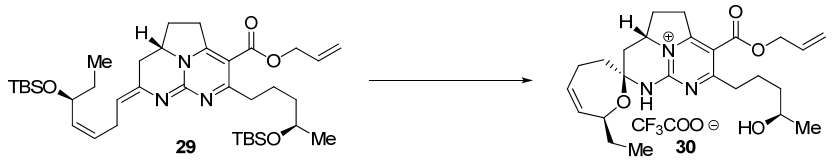


Bicyclic pyrimidine 28. To a plastic 15 mL plastic centrifuge tube containing a 23 °C solution of guanidine **27** (42 mg, 0.052 mmol, 1.0 equiv) in methanol (5.2 mL) was added ammonium fluoride (38 mg, 1.03 mmol, 20 equiv) in a single portion. The heterogeneous mixture was stirred at 23 °C for 6.5 h, at which time the solvent was removed over the course of 30 minutes

under a stream of nitrogen. The crude reaction mixture was purified by silica gel column chromatography (hexanes/ethyl acetate/triethylamine 3:1:0.2 to 1:1:0.1) to afford guanidine **28** (28 mg, 79% yield) as a yellow oil. R_f = 0.24 (hexanes/ethyl acetate/triethylamine 1:1:0.1); $[\alpha]_D^{21}$ –177 (c 0.69, C_6H_6); ^{1}H NMR (500 MHz, C_6H_6) δ 5.80 (ddt, *J* = 17.1, 10.5, 5.9 Hz, 1H), 5.44 – 5.40 (m, 1H), 5.29 (dt, *J* = 10.8, 7.4 Hz, 1H), 5.15 – 5.12 (m, 1H), 5.04 – 5.02 (m, 1H), 4.57 (app d, *J* = 5.6 H, 2H), 4.44 – 4.41 (m, 1H), 4.21 (m, 1H), 3.80 (app sext, *J* = 6.0 Hz, 1H), 3.18 – 3.08 (m, 3H), 3.01 (ddd, *J* = 14.1, 9.5, 5.8 Hz, 1H), 2.85 – 2.64 (m, 3H), 2.55 – 2.51 (m, 1H), 2.08 – 2.01 (m, 1H), 1.90 – 1.81 (m, 1H), 1.71 – 1.48 (m, 4H), 1.43 – 1.34 (m, 2H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.99 (s, 9H), 0.98 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.7, 166.5, 164.8, 154.9, 135.5, 133.0, 123.9, 118.4, 101.4, 80.3, 76.4, 70.2, 68.9, 65.1, 62.0, 40.1, 38.2, 33.9, 31.5, 26.2, 26.1, 24.9, 24.6, 24.1, 21.4, 18.4, 18.4, 18.1, 9.9, –4.1, –4.2, –4.4, –4.7; FTIR (thin film) 2956, 2928, 2855, 1707, 1620, 1506, 1274, 1254, 1091, 835, 775 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{37}H_{64}N_3O_4Si_2$ $[M+H]^+$ 670.4435, found 670.4455.

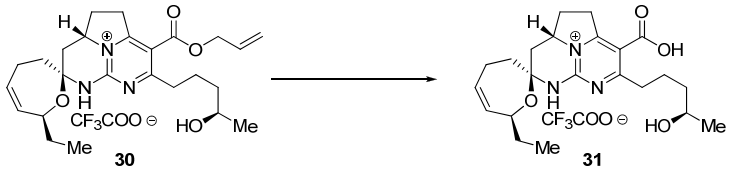


Tricyclic pyrimidine 29. To a sealed-tube containing guanidine **28** (15.3 mg, 0.0229 mmol, 1.0 equiv) was added gold(III) chloride (0.69 mg, 0.0023 mmol, 0.1 equiv) in acetonitrile (0.9 mL). After sealing the tube under an atmosphere of argon, the reaction solution was heated to 40 °C for 4.5 h. The solution was then cooled to 23 °C and the solvent was removed in vacuo. Purification of the crude reaction product by silica gel column chromatography (hexanes/ethyl acetate/triethylamine 8:1:0.45 to 6:1:0.35) gave enamine **29** (12.0 mg, 78%) as a yellow oil. R_f = 0.35 (hexanes/ethyl acetate/triethylamine 5:1:0.3); $[\alpha]_D^{21}$ –131 (c 0.10, C_6H_6); ^{1}H NMR (500 MHz, C_6H_6) δ 5.79 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.68 (dt, *J* = 11.0, 7.3 Hz, 1H), 5.64 – 5.60 (m, 1H), 5.15 – 5.11 (m, 1H), 5.03 – 5.01 (m, 1H), 4.82 – 4.76 (m, 2H), 4.60 – 4.52 (m, 2H), 3.80 (app sext, *J* = 6.1 Hz, 1H), 3.76 – 3.70 (m, 1H), 3.63 – 3.59 (m, 1H), 3.18 (t, *J* = 7.7 Hz, 2H), 3.01 – 2.95 (m, 1H), 2.67 (dd, *J* = 18.7, 8.8 Hz, 1H), 2.17 (ddd, *J* = 18.5, 11.8, 8.4 Hz, 1H), 2.11 – 2.02 (m, 2H), 2.00 – 1.92 (m, 1H), 1.79 – 1.57 (m, 5H), 1.27 – 1.22 (m, 1H), 1.13 (d, *J* = 6.1 Hz, 3H), 1.06 – 1.03 (m, 12H), 1.00 (s, 9H), 0.65 – 0.58 (m, 1H), 0.24 (s, 6H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 174.0, 164.5, 163.8, 145.9, 138.6, 134.5, 132.9, 128.7, 118.5, 117.4, 103.0, 70.6, 69.0, 65.2, 59.5, 40.2, 38.8, 34.1, 32.2, 32.1, 28.6, 26.3, 26.2, 26.1, 24.9, 24.1, 18.5, 18.4, 10.2, –3.8, –4.2, –4.4; FTIR (thin film) 2957, 2929, 2856, 1707, 1603, 1567, 1499, 1362, 1288, 1255, 1091, 1045, 1005, 834, 775 cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{37}H_{64}N_3O_4Si_2$ $[M+H]^+$ 670.4435, found 670.4452.

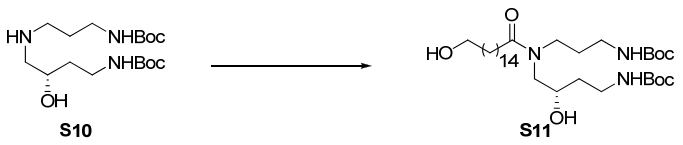


Tetracyclic pyrimidine 30. A solution of *para*-toluenesulfonic acid[14] (31 mg, 0.16 mmol, 10 equiv) in acetonitrile (2.3 mL) was added to pyrimidine **29** (10.9 mg, 0.0163 mmol, 1.0 equiv).

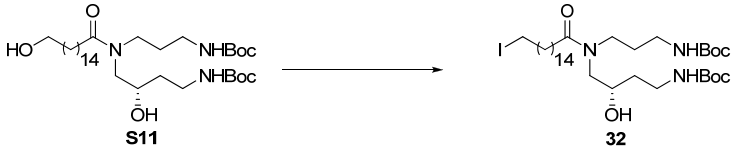
The solution was stirred at 23 °C for 3 h, and triethylamine (100 μL) and ethyl acetate (3 mL) were then added. The resulting orange solution was quickly passed through a plug (2 x 5.7 cm) of silica gel, eluting with an 85:10:5 ratio of ethyl acetate/methanol/triethylamine (~50 mL). The solvent was removed in vacuo to give the crude product as an orange oil. Purification was performed by RP-HPLC on a Sunfire Prep C18 column (5 μm, 10 x 150 mm) using a linear gradient of 20 to 40% acetonitrile in water (0.1% TFA) over 20 min at a flow rate of 5 mL/min. The fraction containing the major peak (t_R = 14.3 min) was collected and lyophilized to dryness to afford the trifluoroacetate salt **30** (7.0 mg, 77% yield) as a colorless film. $[\alpha]_D^{21}$ –33.9 (c 0.65, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 6.09 (ddt, *J* = 17.4, 10.5, 6.1 Hz, 1H), 5.78 – 5.74 (m, 1H), 5.56 – 5.54 (m, 1H), 5.47 – 5.43 (m, 1H), 5.36 – 5.34 (m, 1H), 4.85 (m, 3H), 4.57 – 4.55 (m, 1H), 3.78 – 3.72 (m, 1H), 3.67 – 3.51 (m, 2H), 3.23 – 3.09 (m, 2H), 2.85 (dd, *J* = 13.5, 3.7 Hz, 1H), 2.74 – 2.62 (m, 2H), 2.51 – 2.45 (m, 1H), 2.23 (dt, *J* = 17.7, 6.5 Hz, 1H), 2.14 – 2.01 (m, 2H), 1.92 – 1.78 (m, 2H), 1.69 (t, *J* = 13.0 Hz, 1H), 1.58 – 1.46 (m, 4H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 181.9, 167.5, 164.1, 151.7, 133.7, 132.9, 131.5, 120.2, 114.2, 86.9, 72.6, 68.2, 67.8, 60.9, 39.5, 38.5, 37.5, 35.5, 34.5, 30.2, 30.2, 25.5, 24.9, 23.6, 10.5, FTIR (thin film) 3423, 2967, 2936, 2878, 1685, 1678, 1629, 1580, 1260, 1201, 1178, 1130, 1053, 988, 800, 720, cm^{-1}; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{25}H_{36}N_3O_4$ $[M+H]^+$ 442.2706, found 442.2719.



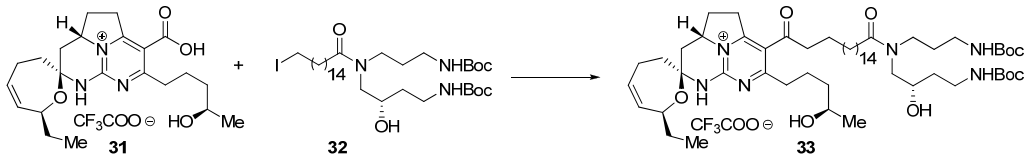
Tetracyclic pyrimidine 31. A solution of pyrimidine **30** (15.1 mg, 0.0272 mmol, 1.0 equiv) in acetonitrile (5.4 mL) was degassed (freeze/pump/thaw 3X). Pyrrolidine (11 μL, 0.14 mmol, 5.0 equiv) was added, followed by tetrakis(triphenylphosphine)palladium(0) (3.1 mg, 0.0027 mmol, 0.1 equiv). The mixture was stirred at 23 °C for 1 h, and the solvent was then removed in vacuo. Purification was performed by RP-HPLC on a Sunfire Prep C18 column (5 μm, 10 x 150 mm) using a linear gradient of 10 to 40% acetonitrile in water (0.1% TFA) over 20 min at a flow rate of 5 mL/min. The fraction containing the major peak (t_R = 12.9 min) was collected and lyophilized to dryness to afford pyrimidine **31** (11.3 mg, 81% yield) as a colorless film. $[\alpha]_D^{21}$ – 37.2 (c 0.69, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.78 – 5.74 (m, 1H), 5.56 – 5.54 (m, 1H), 4.85 (m, 1H), 4.60 – 4.55 (m, 1H), 3.78 – 3.67 (m, 2H), 3.54 (ddd, *J* = 19.2, 11.9, 8.0 Hz, 1H), 3.27 – 3.14 (m, 2H), 2.84 (dd, *J* = 13.4, 3.8 Hz, 1H), 2.74 – 2.62 (m, 2H), 2.52 – 2.45 (m, 1H), 2.23 (dt, *J* = 17.8, 6.4 Hz, 1H), 2.14 – 2.01 (m, 2H), 1.92 – 1.77 (m, 2H), 1.69 (t, *J* = 13.1 Hz, 1H), 1.59 – 1.46 (m, 4H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 182.2, 167.4, 165.8, 151.7, 133.7, 131.5, 115.0, 86.8, 72.6, 68.2, 60.8, 39.5, 38.4, 37.6, 35.6, 34.5, 30.3, 30.2, 25.5, 24.9, 23.6, 10.6; FTIR (thin film) 3423, 2968, 2935, 2876, 1686, 1676, 1628, 1422, 1199, 1131, 1027, 719; HRMS (ESI)$^+$ *m/z*: Calcd for $C_{22}H_{32}N_3O_4$ $[M+H]^+$ 402.2393, found 402.2397.



Amide S11. To a mixture of juniperic acid (15 mg, 0.055 mmol, 1.0 equiv) and amino alcohol **S10**[15] (30 mg, 0.083 mmol, 1.5 equiv) was added dichloromethane (5.5 mL). After addition of triethylamine (280 μL, 1.98 mmol, 36 equiv) and (benzotriazole-yloxy)tris(dimethylamino)phosphonium chloride (37 mg, 0.083 mmol, 1.5 equiv), the solution was stirred at 23 °C for 20 h. The reaction mixture was then diluted with ethyl acetate (150 mL) and saturated aqueous ammonium chloride (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with water (50 mL) and saturated aqueous sodium chloride (50 mL), and dried over magnesium sulfate. After filtration and removal of solvent in vacuo, the crude product was purified by silica gel column chromatography (ethyl acetate/hexanes 4:1 to 100% ethyl acetate) to give amide **S11** (22 mg, 65% yield) as a colorless oil. R_f = 0.38 (100% ethyl acetate); $[\alpha]_D^{21}$ +0.2 (c 2.50, $CHCl_3$). *Note: Amide **S11** exists as a mixture of two rotamers on the NMR timescale at 23 °C. Efforts to resolve the rotamers by raising the temperature (up to 70 °C in C_6D_6) were unsuccessful.* FTIR (thin film) 3370, 2976, 2926, 2854, 1685, 1624, 1421, 1366, 1253, 1161 cm^{-1}; HRMS $(ESI)^+$ *m/z*: Calcd for $C_{33}H_{65}N_3O_7Na$ $[M+Na]^+$ 638.4720, found 638.4718.

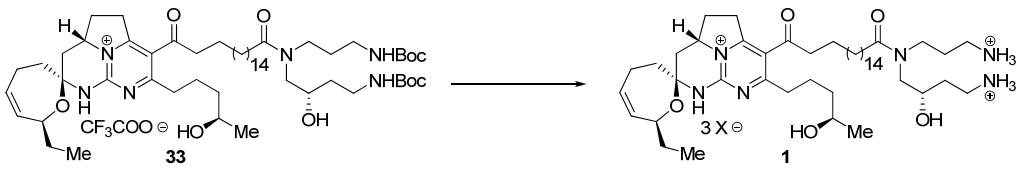


Amide 32. To a 0 °C solution of alcohol **S11** (89 mg, 0.14 mmol, 1.0 equiv) in acetonitrile (0.4 mL) and diethyl ether (1.1 mL) was added triphenylphosphine (41 mg, 0.16 mmol, 1.05 equiv) and imidazole (11 mg, 0.16 mmol, 1.05 equiv). Iodine (40 mg, 0.16 mmol, 1.05 equiv) was then added in a single portion, and the reaction was stirred at 0 °C in the dark for 40 min. The reaction was removed from the ice bath, and the solvent was removed in vacuo as the reaction warmed to 23 °C. Purification of the crude reaction mixture by silica gel column chromatography (100% ethyl acetate) gave iodide **32** (88 mg, 84%) as a colorless oil. R_f = 0.55 (100% ethyl acetate); $[\alpha]_D^{22}$ +5.7 (c 0.27, C_6H_6). *Note: Amide **32** exists as a complex rotameric mixture at room temperature. Efforts to resolve the rotamers by raising the temperature (up to 70 °C in C_6D_6) were unsuccessful.* FTIR (thin film) 3344, 2975, 2924, 2852, 1686, 1624, 1521, 1457, 1365, 1273, 1250, 1171 cm^{-1}; HRMS $(ESI)^+$ *m/z*: Calcd for $C_{33}H_{64}N_3O_6NaI$ $[M+Na]^+$ 748.3734, found 748.3738.



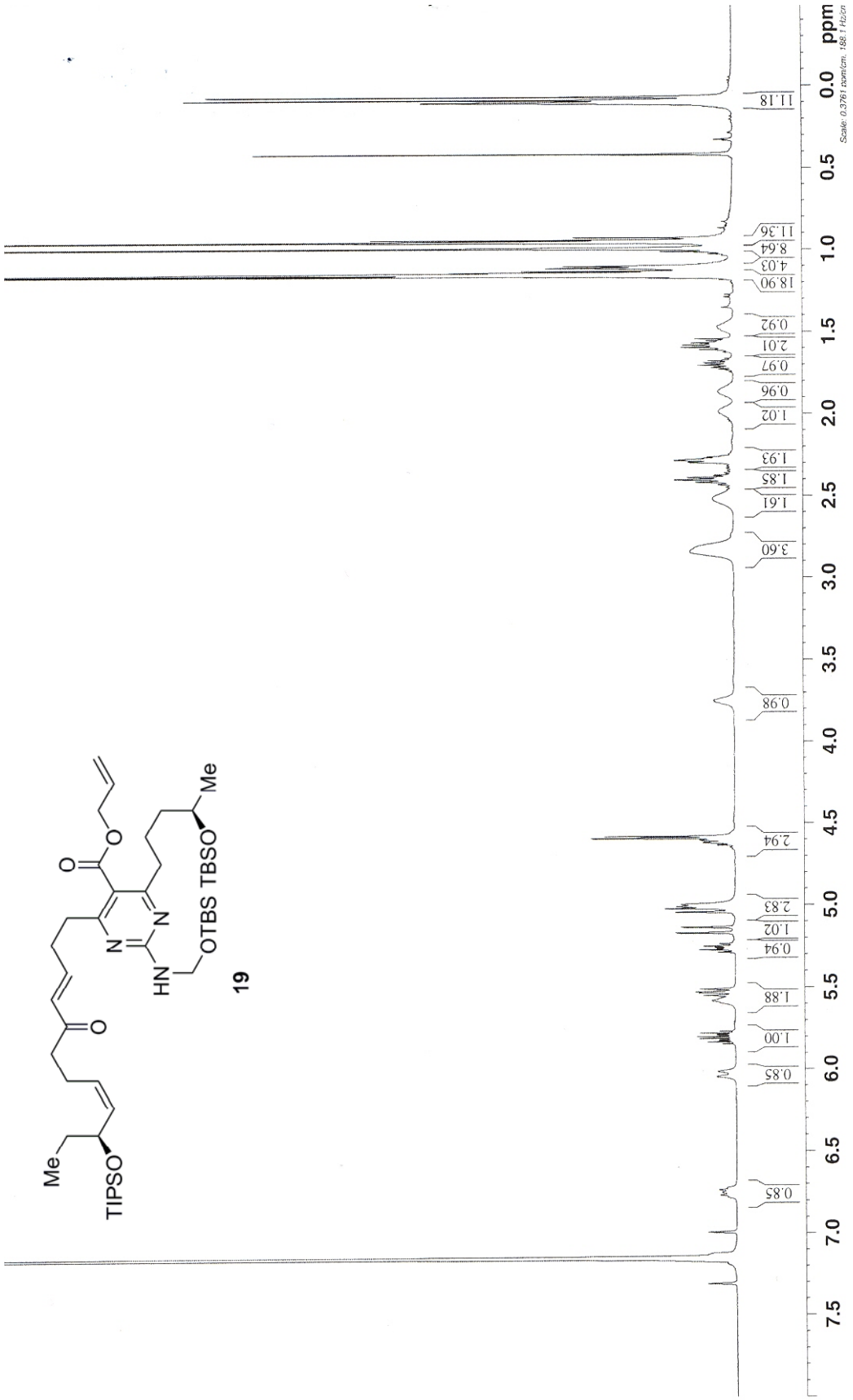
Tetracyclic pyrimidine 33. To a 3 mL sealed-tube containing a 23 °C solution of carboxylic acid **39** (3.1 mg, 6.0 μmol, 1.0 equiv) and iodide **32** (8.9 mg, 12 mmol, 2.0 equiv) in *N*,*N*-

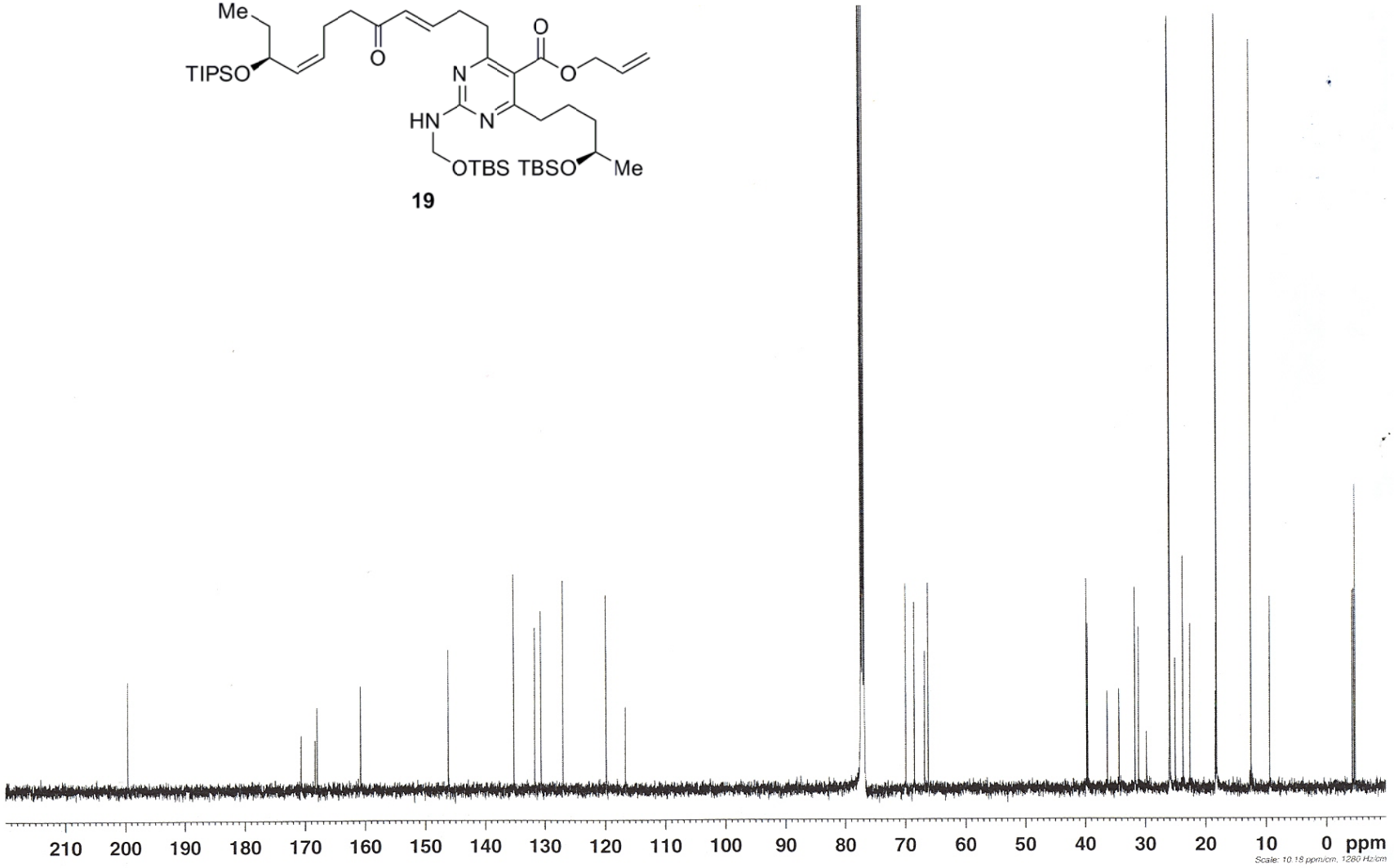
dimethylformamide (370 μL) was added cesium carbonate (7.5 mg, 23 μmol, 3.8 equiv). After sealing the tube under argon and stirring the solution at 23 °C for 14 h in the dark, the solution was diluted with a 30% solution of 2-propanol in chloroform (20 mL) and saturated aqueous ammonium chloride (5 mL). The layers were separated and the aqueous layer was extracted with a 30% solution of 2-propanol in chloroform (2 x 10 mL). The organic extracts were combined, washed with saturated aqueous sodium chloride (5 mL), dried over sodium sulfate, filtered, and the solvent was removed in vacuo. Purification was performed by RP-HPLC on a Sunfire Prep C18 column (5 μm, 10 x 150 mm) using a linear gradient of 50 to 75% acetonitrile in water (0.1% TFA) over 25 min at a flow rate of 5 mL/min. The fraction containing the major peak (t_R = 11.9 min) was collected and lyophilized to dryness to afford trifluoroacetate salt **33** (5.9 mg, 88% yield) as a colorless film. $[\alpha]_D^{21}$ –16.2 (c 0.53, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.78 – 5.74 (m, 1H), 5.56 – 5.54 (m, 1H), 4.85 (m, 1H), 4.57 (m, 1H), 4.37 (t, *J* = 6.6 Hz, 2H), 3.86 – 3.72 (m, 2H), 3.66 – 3.34 (m, 5H), 3.24 – 2.97 (m, 7H), 2.85 (dd, *J* = 13.4, 3.8 Hz, 1H), 2.75 – 2.62 (m, 2H), 2.51 – 2.32 (m, 3H), 2.26 – 2.20 (m, 1H), 2.14 – 2.01 (m, 2H), 1.92 – 1.76 (m, 5H), 1.71 – 1.67 (m, 2H), 1.65 – 1.48 (m, 7H), 1.47 – 1.41 (m, 22H), 1.36 – 1.27 (m, 22H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 181.9, 176.7, 176.3, 167.5, 164.6, 158.7, 151.8, 133.8, 131.6, 114.6, 87.0, 80.1, 80.1, 72.7, 69.2, 68.4, 68.3, 67.5, 61.0, 55.1, 53.6, 45.2, 39.6, 39.0, 38.8, 38.6, 38.2, 37.6, 36.3, 35.6, 34.6, 34.4, 34.2, 30.9, 30.8, 30.8, 30.7, 30.7, 30.7, 30.6, 30.5, 30.4, 30.3, 29.8, 28.9, 27.3, 26.8, 26.7, 25.6, 25.0, 23.8, 10.7; FTIR (thin film) 3331, 2919, 2850, 1685, 1629, 1582, 1457, 1365, 1256, 1201, 1173, 1131 cm^{-1}; HRMS $(ESI)^+$ *m/z*: Calcd for $C_{55}H_{95}N_6O_{10}$ $[M+H]^+$ 999.7110, found 999.7144.

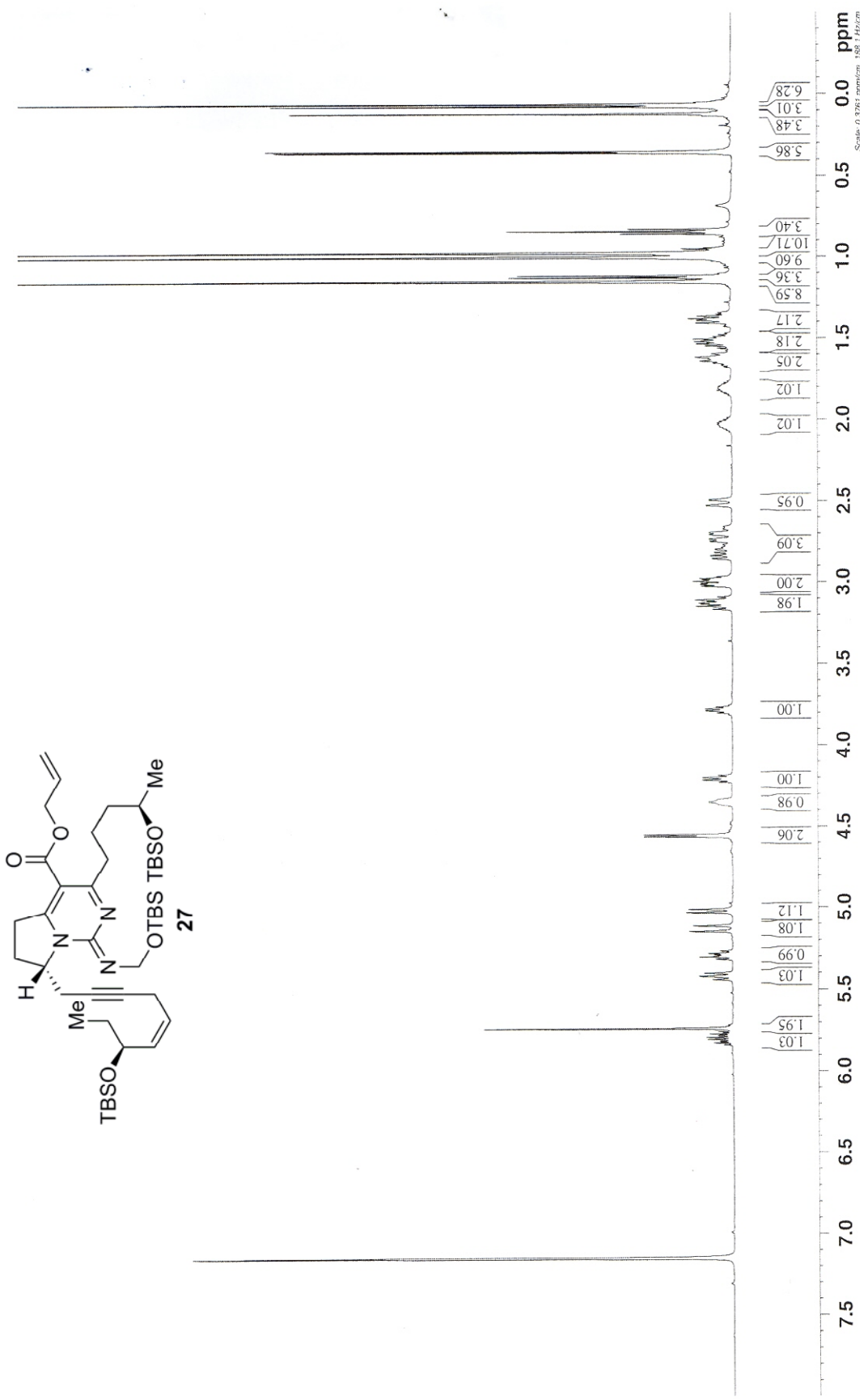


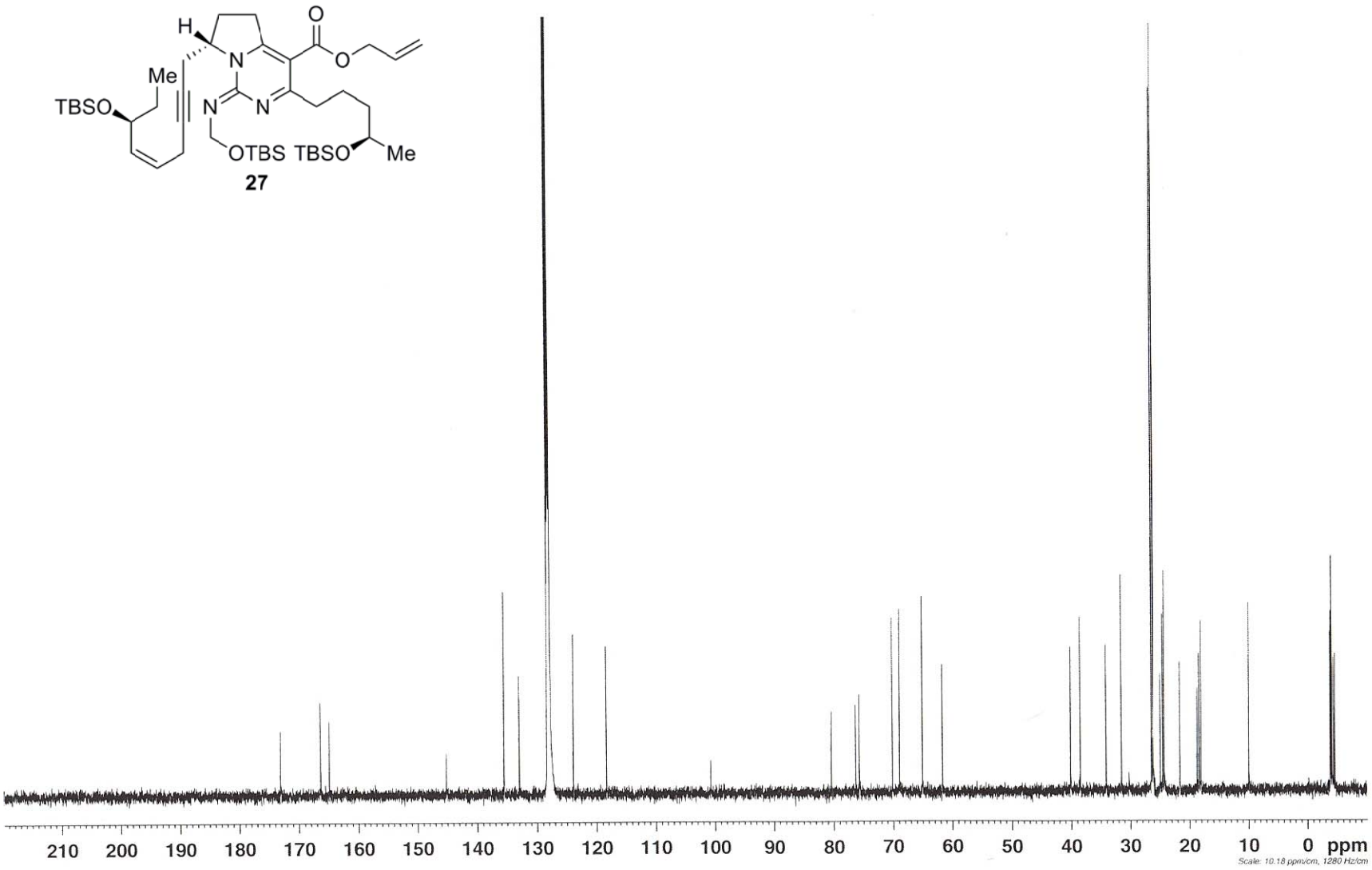
(–)-Crambidine (1). To a 0 °C sealed tube containing guanidine **33** (4.6 mg, 4.1 μmol, 1 equiv) was added a 0 °C solution of 1N HCl in diethyl ether (460 μL, 460 μmol, 112 equiv) via syringe. After stirring at 0 °C for 2 h, the solvent was decanted. The remaining solids adhering to the sides of the sealed tube were rinsed with 0 °C diethyl ether (2 x 500 μL) and decanted. Any remaining solvent was removed under vacuum. Purification of the crude solid was performed by RP-HPLC on a Sunfire Prep C18 column (5 μm, 10 x 150 mm) using a linear gradient of 30 to 40% acetonitrile in water (0.1% TFA) over 30 min at a flow rate of 5 mL/min. The fraction containing the major peak (t_R = 14.2 min) was collected and lyophilized to dryness to afford trifluoroacetate salt TFA-**1** (3.6 mg, 77% yield) as a colorless film. **Chloride counterion switch:** A 2 mg sample of TFA-**1** was resubjected to RP-HPLC conditions on a Sunfire Prep C18 column (5 μm, 10 x 150 mm) using a linear gradient of 35 to 65% acetonitrile in water (0.1% HCl) over 30 min at a flow rate of 5 mL/min. The fraction containing the major peak (t_R = 3.9 min) was collected and lyophilized to dryness to afford chloride salt HCl-**1**. **TFA-1:** $[\alpha]_D^{18}$ – 20.0 (c 0.14, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 5.78 – 5.74 (m, 1H), 5.56 – 5.54 (m, 1H), 4.85 (m, 1H), 4.57 (m, 1H), 4.36 (t, *J* = 6.7 Hz, 2H), 3.98 – 3.92 (m, 1H), 3.78 – 3.72 (m, 1H), 3.70 – 3.37 (m, 5H), 3.23 – 3.06 (m, 5H), 2.99 – 2.84 (m, 3H), 2.75 – 2.70 (m, 1H), 2.67 – 2.62 (m, 1H), 2.53 – 2.39 (m, 3H), 2.26 – 2.20 (m, 1H), 2.15 – 2.01 (m, 2H), 2.00 – 1.76 (m, 7H), 1.71 – 1.66 (m, 2H), 1.61 – 1.42 (m, 8H), 1.40 – 1.27 (m, 22H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 181.8, 177.5, 176.3, 167.4, 164.5, 151.7, 133.7,

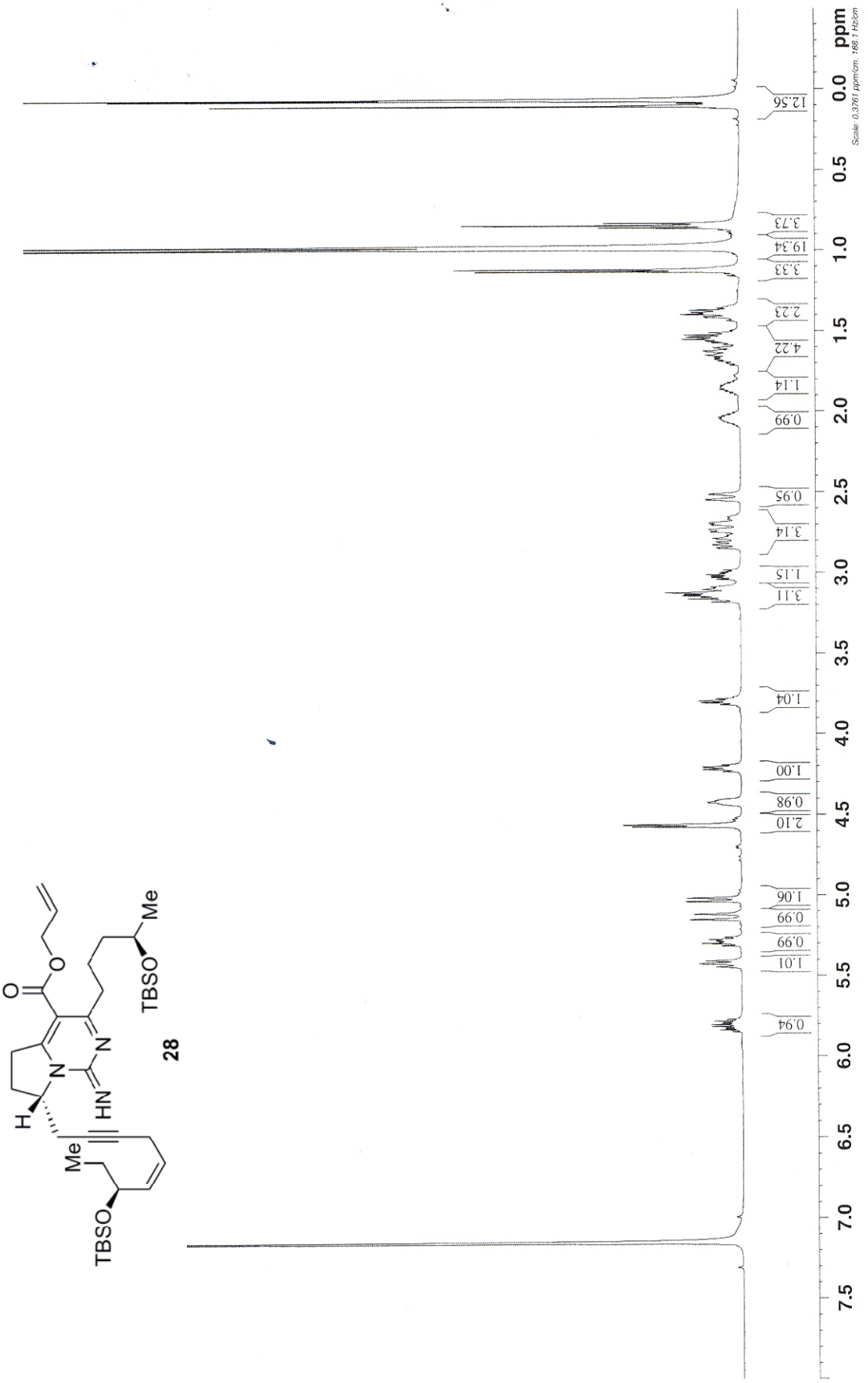
131.5, 114.4, 86.8, 72.6, 69.4, 68.7, 68.2, 67.4, 60.9, 54.7, 53.4, 43.7, 39.5, 38.5, 38.5, 38.2, 38.0, 37.5, 35.5, 34.5, 34.1, 33.9, 33.1, 32.8, 30.9, 30.9, 30.8, 30.8, 30.6, 30.5, 30.3, 30.2, 29.7, 27.9, 27.3, 26.6, 25.5, 24.9, 23.7, 10.6; FTIR (thin film) 3401, 2920, 2851, 1678, 1630, 1585, 1433, 1262, 1204, 1182, 1134, 834, 800, 722, 669 cm^{-1}; HRMS $(ESI)^+$ *m/z*: Calcd for $C_{45}H_{79}N_6O_6$ $[M+H]^+$ 799.6061, found 799.6064. **HCl-1:** ^1H NMR (500 MHz, CD_3OD) δ 5.78 – 5.75 (m, 1H), 5.56 – 5.54 (m, 1H), 4.85 (m, 1H), 4.57 (m, 1H), 4.37 (t, *J* = 6.7 Hz), 3.98 – 3.93 (m, 1H), 3.77 – 3.72 (m, 1H), 3.71 – 3.65 (m, 1H), 3.63 – 3.39 (m, 5H), 3.23 – 3.07 (m, 5H), 3.00 – 2.84 (m, 3H), 2.75 – 2.70 (m, 1H), 2.67 – 2.62 (m, 1H), 2.55 – 2.40 (m, 3H), 2.26 – 2.20 (m, 1H), 2.15 – 2.01 (m, 2H), 2.00 – 1.76 (m, 8H), 1.72 – 1.67 (m, 2H), 1.64 – 1.42 (m, 9H), 1.40 – 1.30 (m, 22H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.83 (t, *J* = 7.3 Hz); ^{13}C NMR (150 MHz, CD_3OD) δ 181.8, 177.5, 176.3, 167.4, 164.6, 151.7, 133.7, 131.5, 114.5, 86.9, 72.6, 69.4, 68.7, 68.2, 67.4, 60.9, 54.7, 53.3, 43.8, 39.6, 38.6, 38.5, 38.2, 38.1, 37.5, 35.5, 34.5, 34.2, 34.0, 33.0, 32.9, 30.9, 30.9, 30.8, 30.8, 30.8, 30.6, 30.5, 30.3, 30.2, 29.7, 27.9, 27.3, 26.6, 26.6, 25.6, 24.9, 23.7, 10.6.

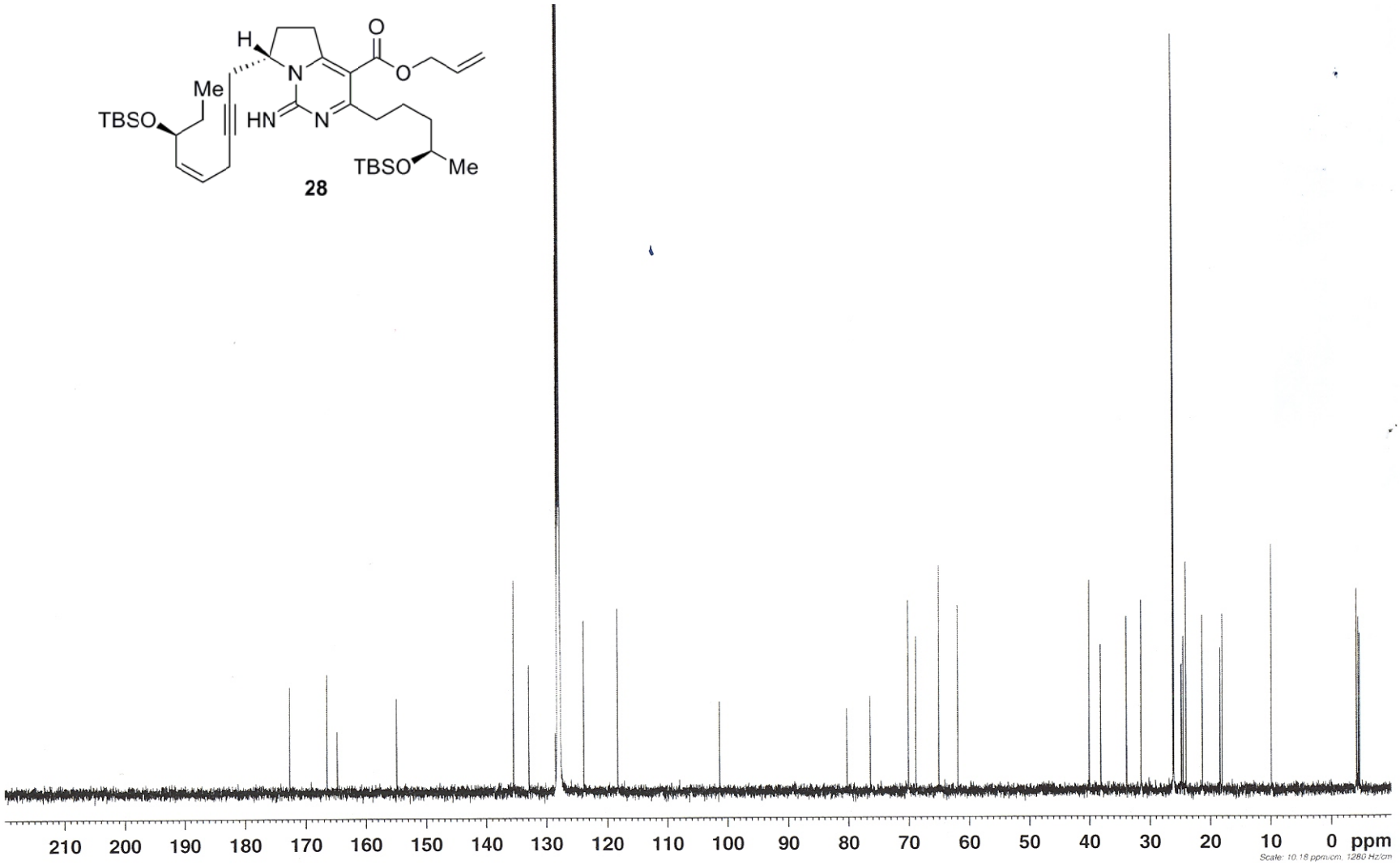

11.18
11.36
8.64
4.03
18.90
0.92
2.01
0.97
0.96
1.02
1.93
1.85
1.61
3.60
0.98
2.94
2.83
1.02
0.94
1.88
1.00
0.85
0.85
ppm
Scale: 0.3761 cm/cm, 188.1 Hz/cm
19

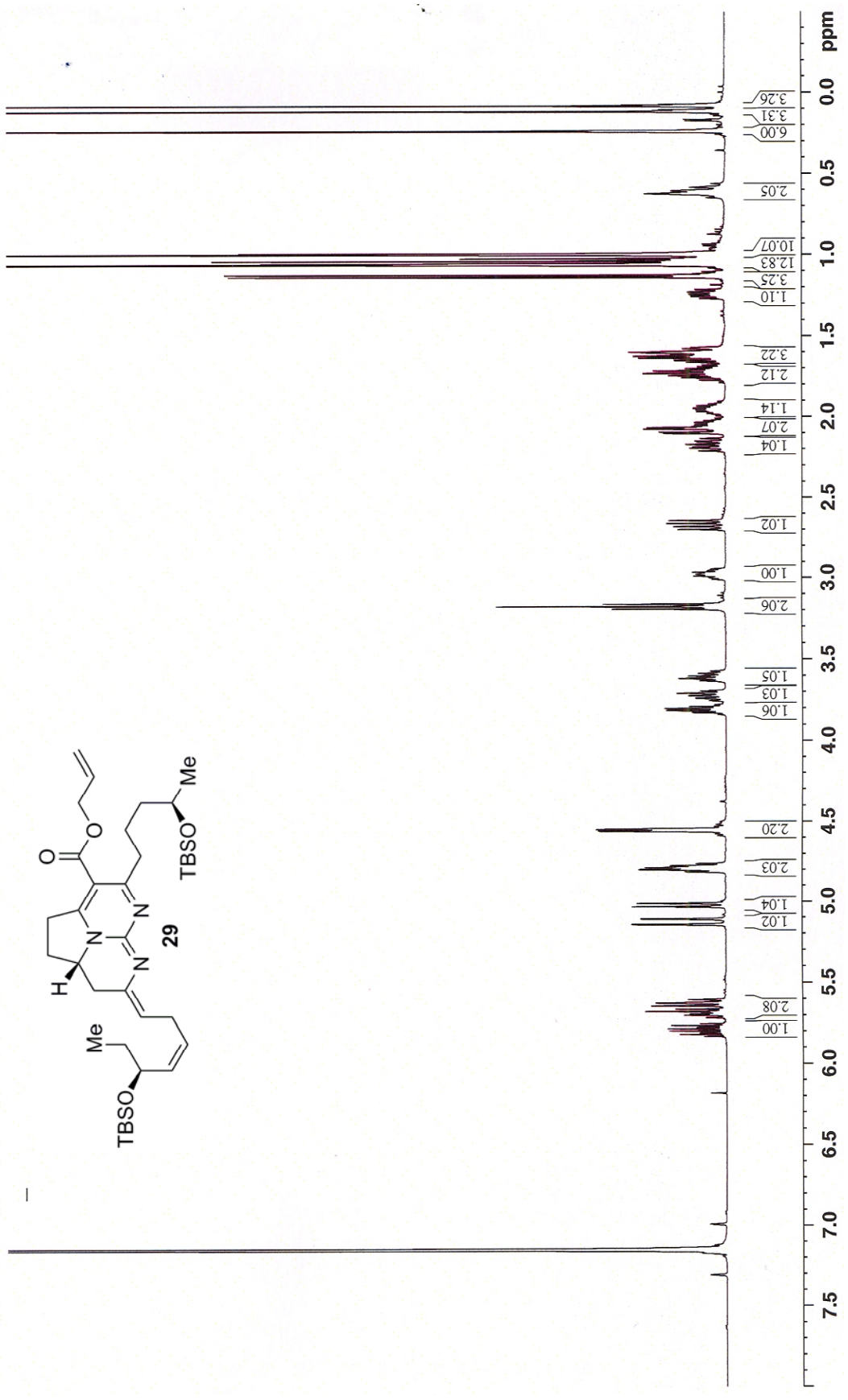

Me
TIPSO
O
O
N
HN
N
O
O
OTBS TBSO
Me
19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

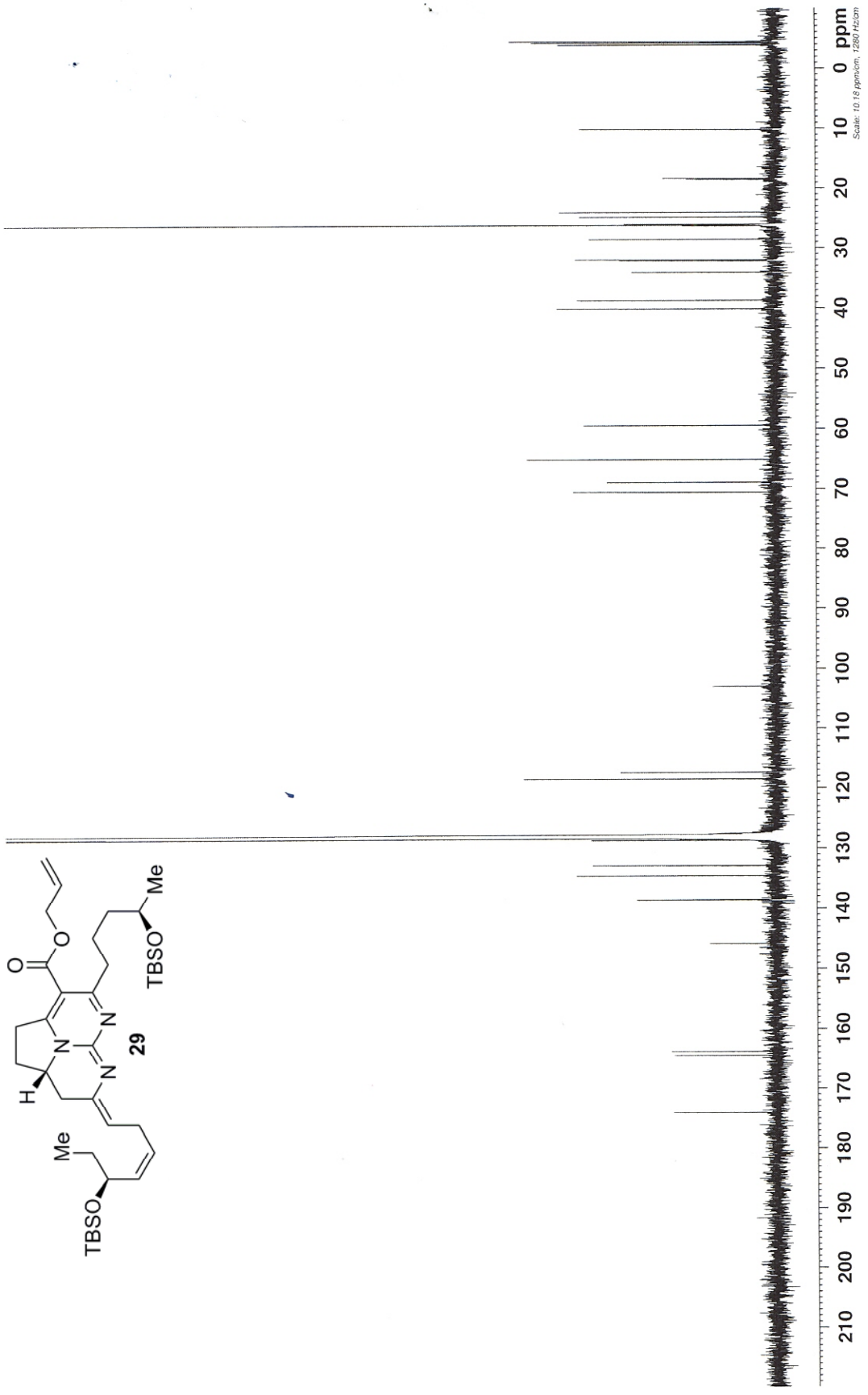

OTBS TBSO Me
27
TBSO
Me
H
O
N
N
N
N
6.28
3.01
3.48
5.86
3.40
10.71
9.60
3.36
8.59
2.17
2.18
2.05
1.02
1.02
0.95
3.09
2.00
1.98
1.00
1.00
0.98
2.06
1.12
1.08
0.99
1.03
1.95
1.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

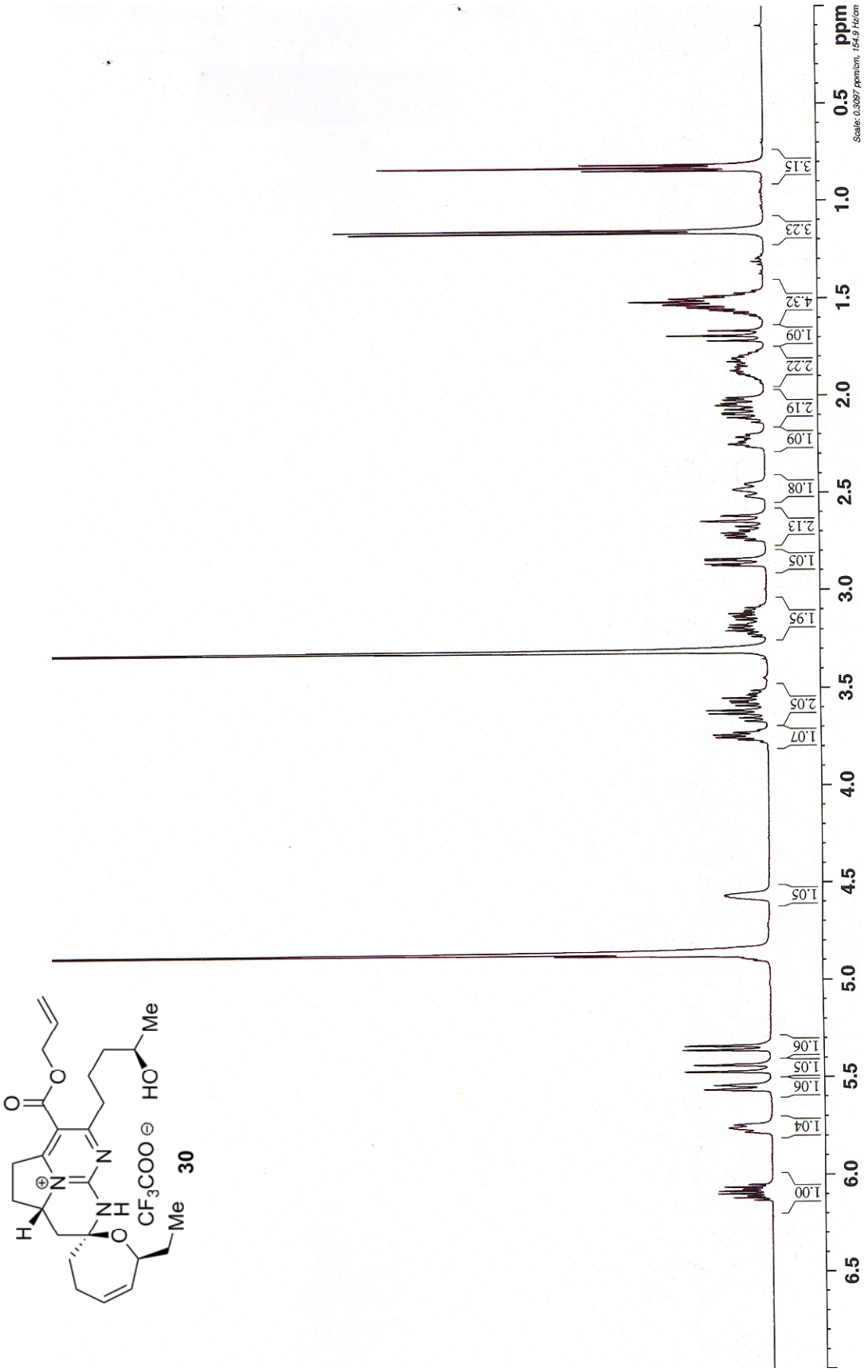

H
N
O
O
Me
TBSO
N
N
OTBS
TBSO
Me
27
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
Scale: 10.18 ppm/cm, 1280 Hz/cm

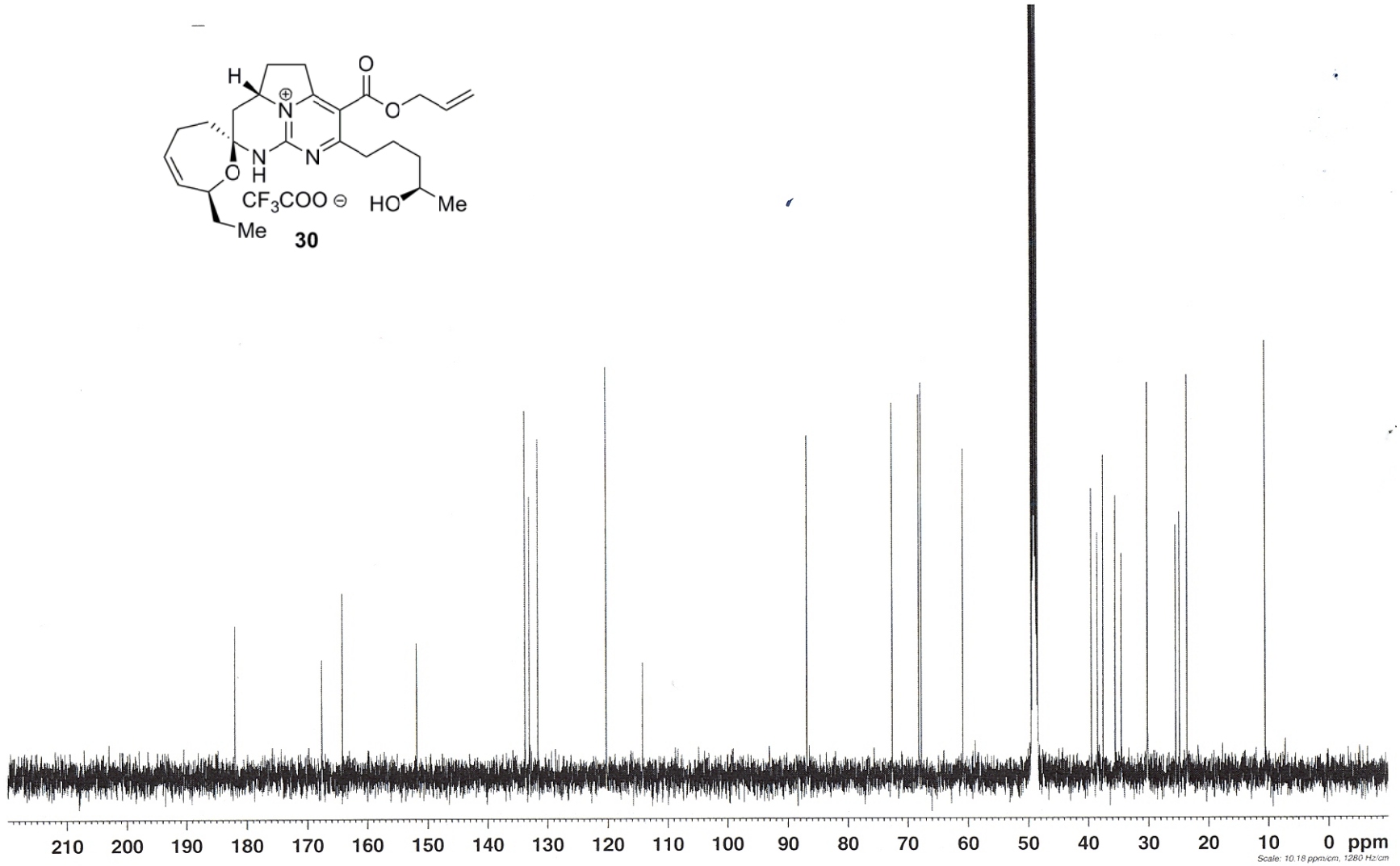

TBSO
Me
Me
TBSO
O
O
N
N
HN
H
28
12.56
3.73
19.34
3.33
2.23
4.22
1.14
0.99
0.95
3.14
1.15
3.11
1.04
1.00
0.98
2.10
1.06
0.99
0.99
1.01
0.94
ppm
Scale: 0.3761 ppm/cm, 188.1 Hz/cm

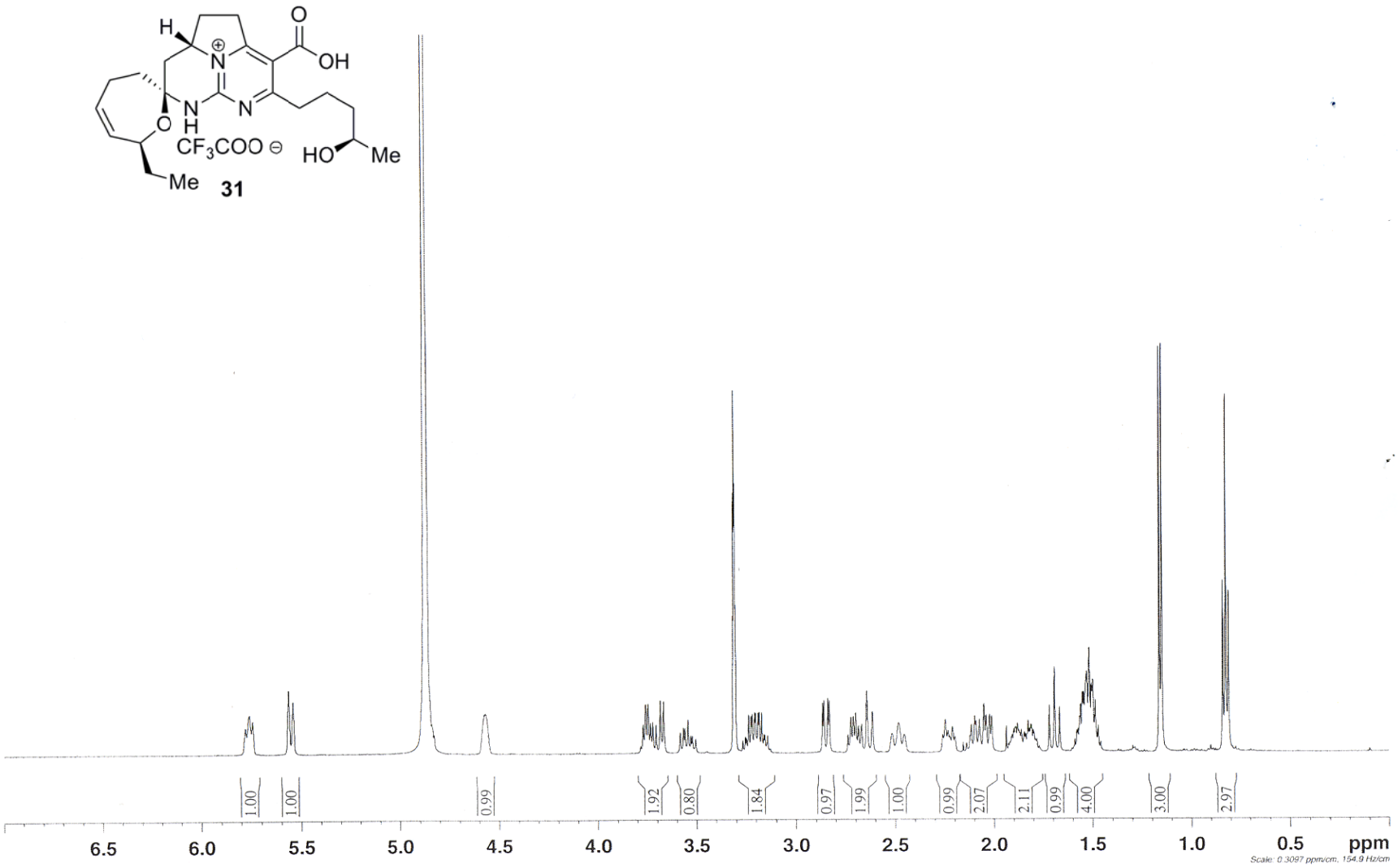

H
O
N
O
Me
TBSO
HN
N
TBSO
Me
28
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Scale: 10.18 ppm/cm, 1280 Hz/cm

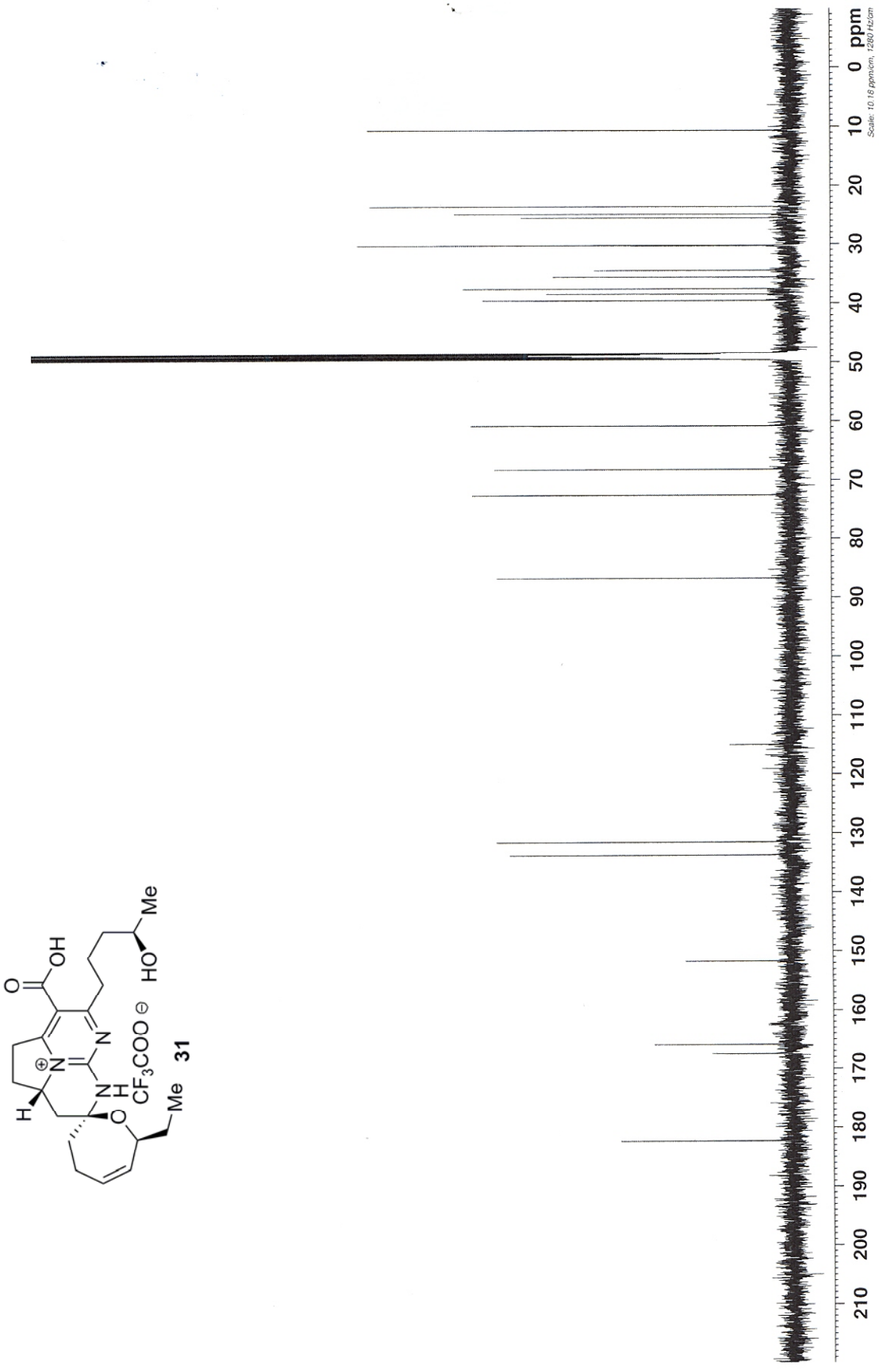

29
TBSO
Me
TBSO
Me
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
2.08
1.02
1.04
2.03
2.20
1.06
1.03
1.05
2.06
1.00
1.02
1.04
2.07
1.14
2.12
3.22
1.10
3.25
12.83
10.07
2.05
6.00
3.31
3.26

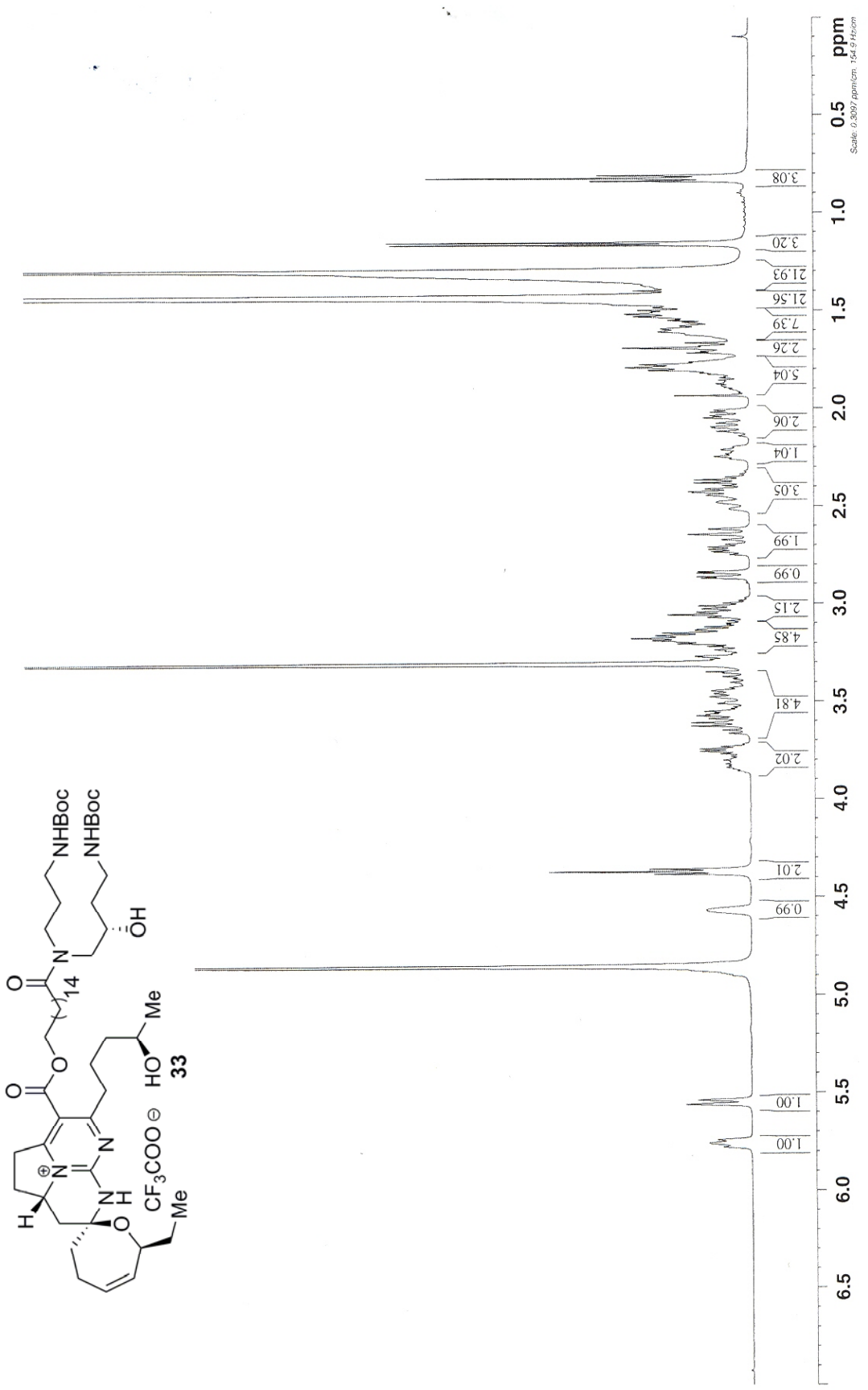

O
O
N
N
N
H
TBSO
Me
Me
TBSO
29
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Scale: 10.18 ppm/cm, 1280 Hz/cm

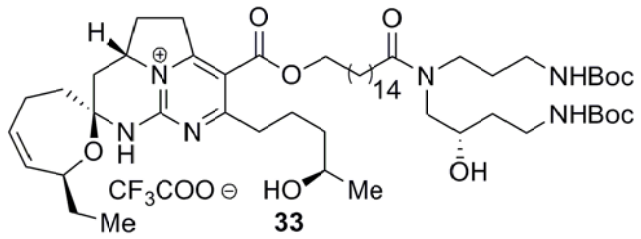

30
$CF_3COO^{\ominus}$
Me
HO
Me
ppm
Scale: 0.3897 ppm/cm, 154.9 Hz/cm
1.00
1.04
1.06
1.05
1.06
1.05
1.07
2.05
1.95
1.05
2.13
1.08
1.09
2.19
2.22
1.09
4.32
3.23
3.15


H
O
N
O
N
N
H
O
CF3COO ⊖
HO
Me
Me
30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Scale: 10.18 ppm/cm, 1280 Hz/cm


H
O
OH
N
N
H
N
O
CF3COO ⊖
HO
Me
Me
31
1.00
1.00
0.99
1.92
0.80
1.84
0.97
1.99
1.00
0.99
2.07
2.11
0.99
4.00
3.00
2.97
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
Scale: 0.3097 ppm/cm, 154.9 Hz/cm

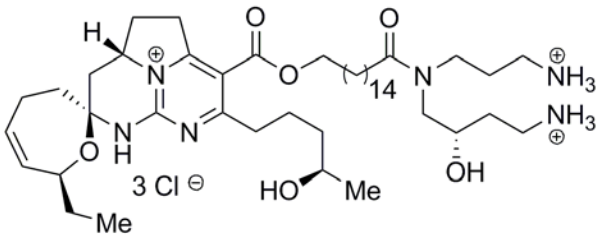

O
OH
HO
Me
N
N
H
H
O
Me
$CF_3COO^{\ominus}$
31
0 ppm
Scale: 10.18 ppm/cm, 1280 Hz/cm


NHBoc
NHBoc
OH
N
O
14
O
O
Me
HO
33
N
N
H
N
H
O
$CF_3COO^{\ominus}$
Me
3.08
3.20
21.93
21.56
7.39
2.26
5.04
2.06
1.04
3.05
1.99
0.99
2.15
4.85
4.81
2.02
2.01
0.99
1.00
1.00
ppm
Scale: 0.3097 ppm/cm, 154.9 Hz/cm

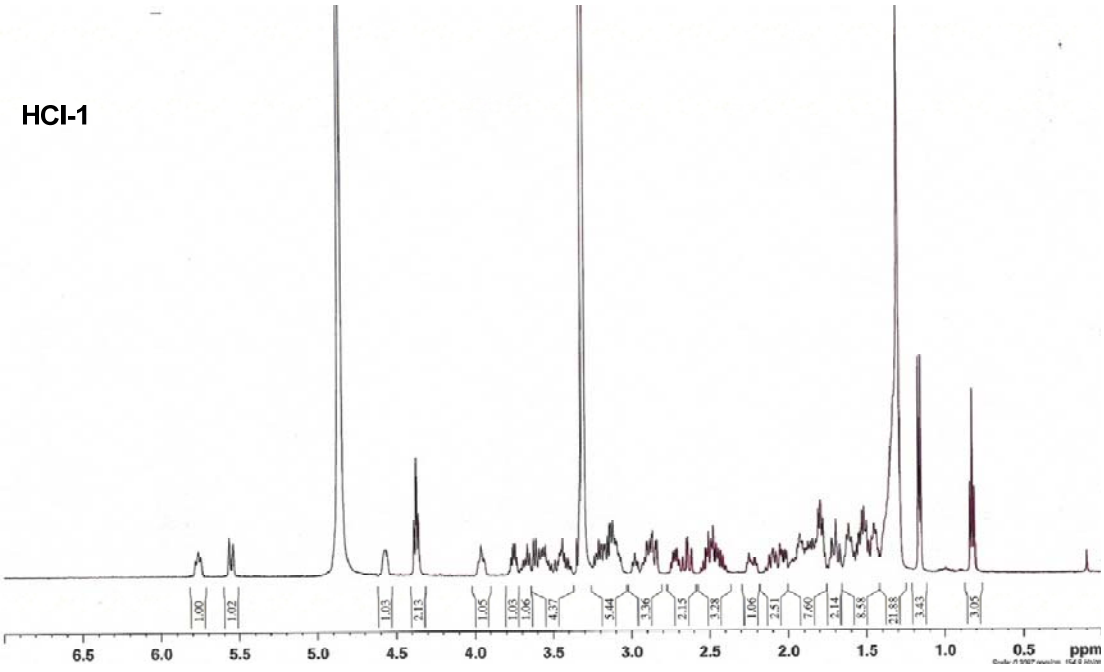

H
N
O
O
O
14
N
NHBoc
NHBoc
N
H
N
O
OH
CF3COO⊖
HO
Me
Me

33

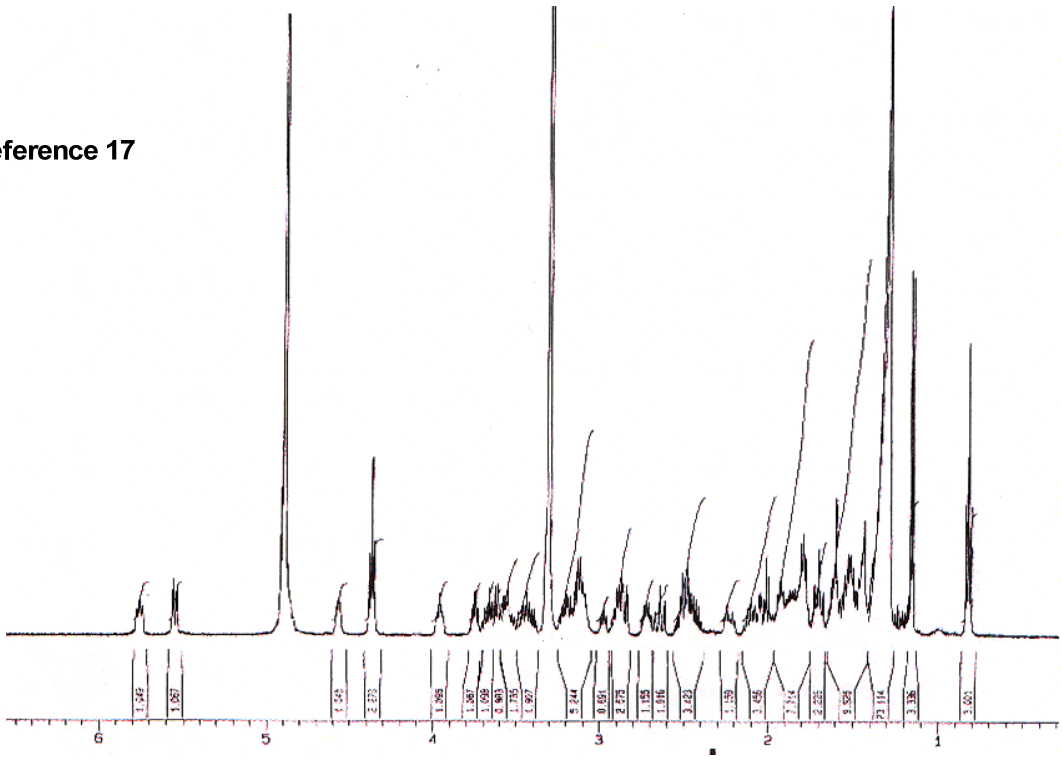
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Scale: 10.62 ppm/cm, 1335 Hz/cm

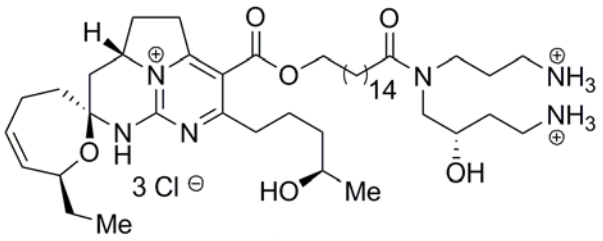


HCl-1

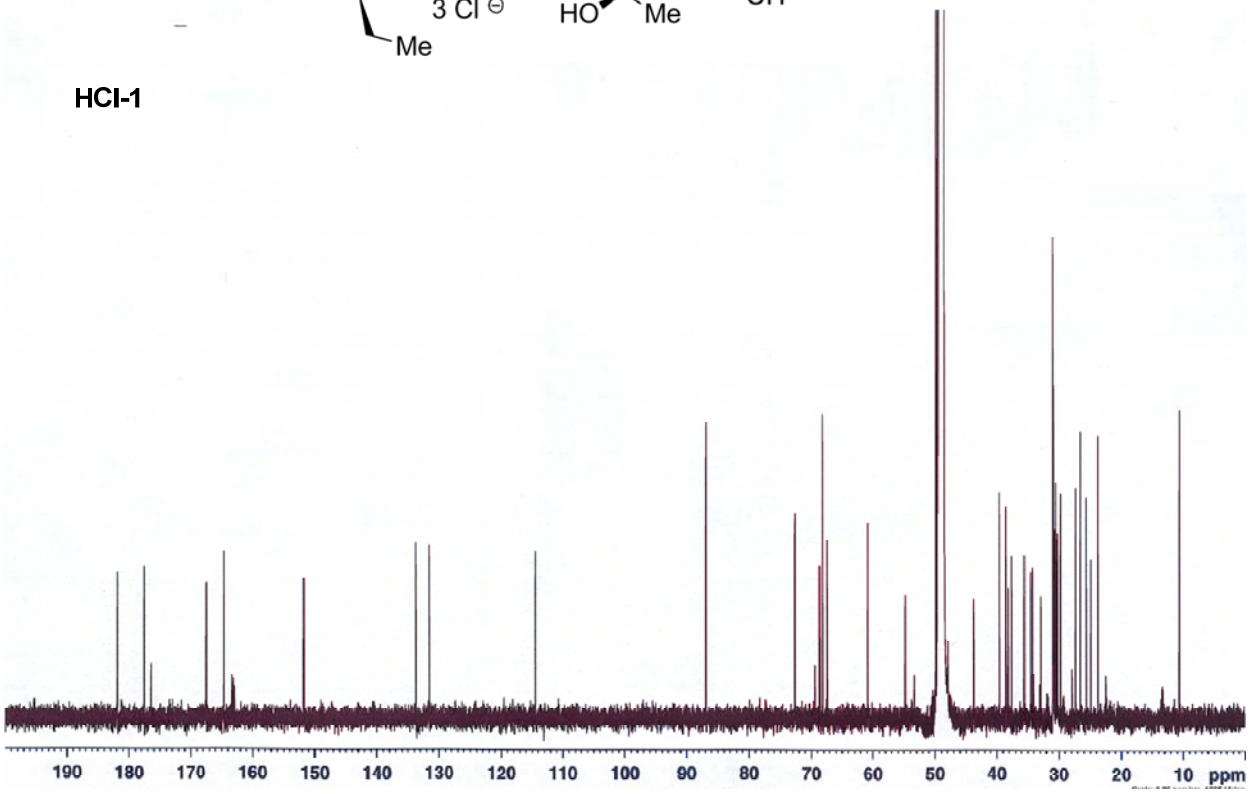


Reference 17

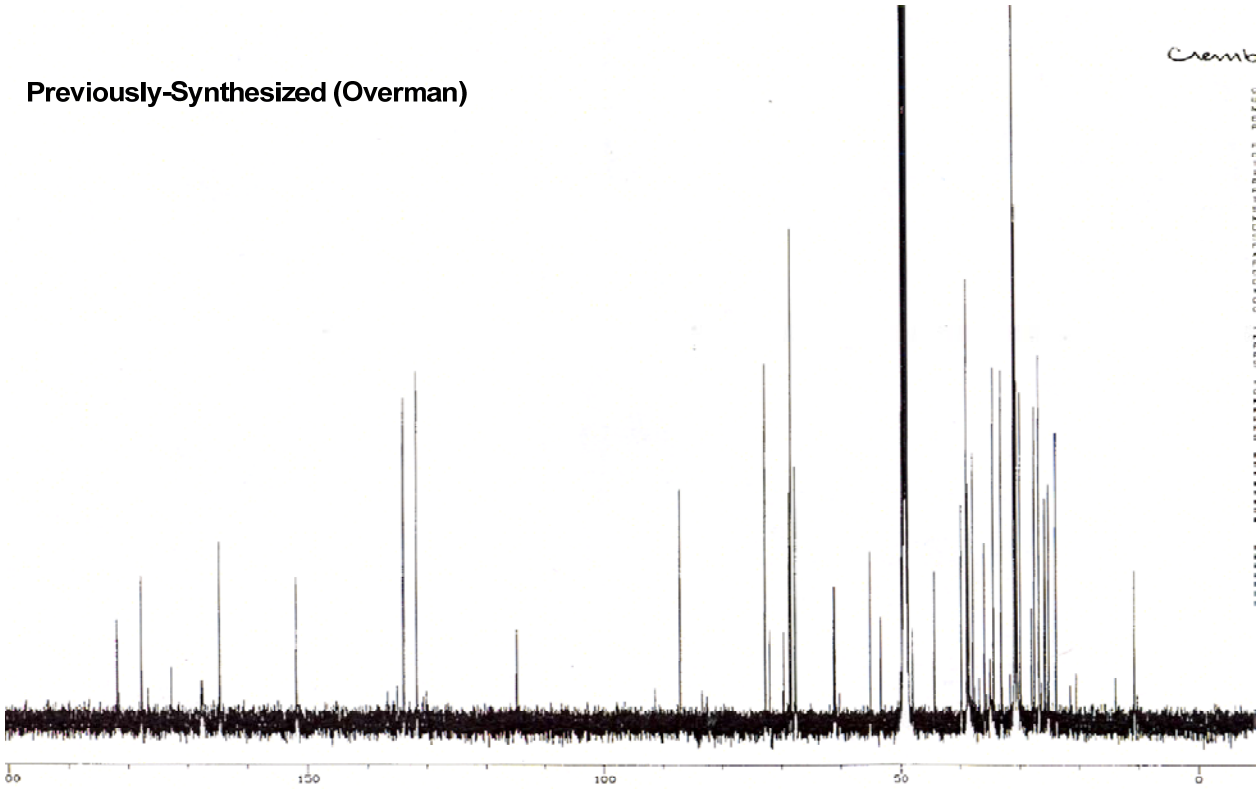




HCl-1



Previously-Synthesized (Overman)



REFERENCES

[1] Arnold, M. A.; Day, K. A.; Durón, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2006,** *128,* 13255.
[2] Hashimoto, M.; Matsumoto, M.; Terashima, S. *Tetrahedron* **2003,** *59,* 3019.
[3] Liu, J.; Swidorski, J. J.; Peters, S. D.; Hsung, R. P. *J. Org. Chem.* **2005,** *70,* 3898.
[4] Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983,** *105, 2831.*
[5] Oliveira, R. A.; Oliveira, J. M.; Rahmeier, L. H. S.; Comasseto, J. V.; Marino, J. P.; Menezes, P. H. *Tetrahedron Lett.* **2008,** *49,* 5759.
[6] Kobayashi, S.; Horibe, M.; Saito, Y. *Tetrahedron* **1994,** *50,* 9629.
[7] Epperson, M. T.; Gin, D. Y. *Angew. Chem. Int. Ed.* **2002,** *41,* 1778.
[8] Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000,** *122,* 4893.
[9] Negishi, E.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, A. T.; Tour, J. M.; Rand, C. L. *J. Am. Chem. Soc.* **1988,** *110,* 5383.
[10] Dharanipragada, R.; Fador, G. *J. Chem. Soc. Perkin Trans. 1* **1986,** 545.
[11] Marshall, J. A.; Yanik, M. M.; Adams, N. D.; Ellis, K. C.; Chobanian, H. R. *Org. Synth.* **2005,** *81,* 157.
[12] Karstens, W. F. J.; Moolenaar, M. J.; Rutjes, F. P. J. T.; Grabowska, U.; Spekamp, W. N.; Hiemstra, H. *Tetrahedron Lett.* **1999,** *40*, 8629.
[13] Provot, O.; Célérier, J. P.; Petit, H.; Lhommet, G. *J. Org. Chem.* **1992,** *57*, 2163.
[14] A standard solution of *p*-TsOH-H_2O (purchased from Aldrich, 98.5%+ ACS reagent, 9.5 – 11.5% H_2O) was prepared by first azeotroping with anhydrous acetonitrile (3x) prior to dissolving in acetonitrile.
[15] Coffey, D. S.; McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999,** *64,* 8741.