SUPPLEMENTARY MATERIAL

Synthesis and Hetero-Michael Addition Reactions of 2-Alkynyl Oxazoles and Oxazolines

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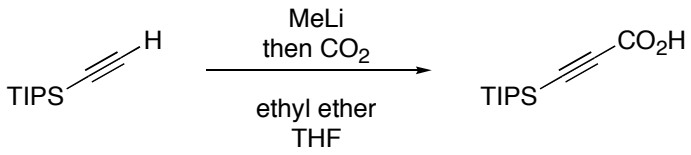
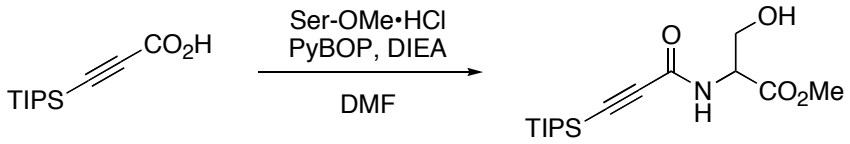
Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra.

General: All moisture sensitive reactions were performed using syringe-septum techniques under an N_2 atmosphere and all glassware was dried in an oven at 140 °C for more than 4 h prior to use. Reactions at -78 °C employed a solid CO_2-acetone bath. THF and ethyl ether were distilled from sodium/benzophenone ketyl. Methylene choride and toluene were filtered through activated alumina prior to use. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualized using UV light (254 nm) or by staining with $KMnO_4$ or phosphomolybdic acid. Flash chromatography on SiO_2 was used to purify compounds unless otherwise stated. Concentration refers to removal of the solvent on a rotary evaporator at water aspirator pressure. Melting Points are uncorrected. Infrared spectra were acquired using KBr pellets or thin films on NaCl plates (i.e. neat). Chemical shifts were reported in parts per million and the residual solvent peak was used as an internal reference. ^{1}H NMR spectra were acquired in $CDCl_3$ at a frequency of 300 MHz unless otherwise stated and are tabulated as follows: chemical shift (multiplicity, number of protons, coupling constants). ^{13}C NMR were acquired in $CDCl_3$ at a frequency of 75 MHz using a proton decoupled pulse sequence unless otherwise stated. For acid sensitive samples, $CDCl_3$ was filtered through activated basic alumina (Brockmann I) immediately prior to sample preparation. For optical rotations, concentration (*c*) is reported in g / 100 mL.



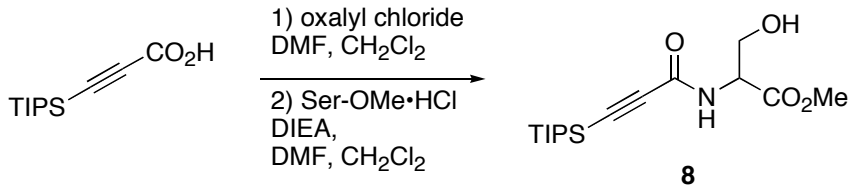
Triisopropylsilanylpropynoic acid. A solution of triisopropylsilanylacetylene (1.00 mL, 4.46 mmol, 1.0 equiv) in THF (40 mL) was cooled under N_2 to 0 °C. A solution of MeLi (0.9 M in ethyl ether, 7.00 mL, 6.30 mmol, 1.4 equiv) was added and the mixture was stirred for 1 h and then cooled to –78 °C and CO_2 gas was bubbled into the solution for 1 h. The reaction mixture was quenched by the slow addition of 2.0 M aqueous $NaHSO_4$ (20 mL), warmed to rt, diluted with water (30 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to a yellow syrup that was diluted with toluene (50

mL), poured onto a pad of SiO_2 (40 mm x 40 mm) and eluted with ethyl acetate (5 X 20 mL). The filtrate was concentrated to afford triisopropylsilanylpropynoic acid (1.01 g, 100%) as yellow syrup that crystallized to a pale yellow solid under vacuum: Mp 60.5-62.5 °C (CH_2Cl_2); ^{1}H NMR α 10.94 (bs, 1 H), 1.21-1.02 (m, 21 H); ^{13}C NMR α 157.7, 96.1, 95.1, 18.6, 11.1; IR (neat) 3068, 2947, 2892, 2868, 2634, 2503, 2185, 2162, 1683, 1460, 1407, 1266 cm^{-1}; MS (EI) *m/z* (rel. intensity) 226 (M^+, 21), 183 ([M-C_3H_7]$^+$, 100), 155 ([M-C_5H_{11}]$^+$, 79), 139 ([M-C_6H_{15}]$^+$, 79), 127 (100), 111 (80), 85 (78), 83 (87), 75 (84), 69 (70); HRMS (EI) *m/z* calcd for $C_{12}H_{22}O_2Si$ 226.1389, found 226.1388.



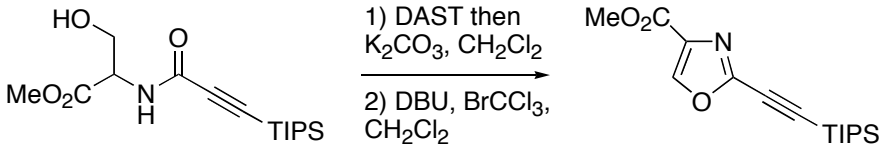
8

3-Hydroxy-2-[3-(triisopropylsilanyl)propynoylamino]propionic acid methyl ester (8). To a suspension of triisopropylsilanylpropynoic acid (1.00 g, 4.45 mmol, 1.0 equiv) and *DL*-serine methyl ester hydrochloride (1.04 g, 6.65 mmol, 1.5 equiv) in DMF (6.0 mL) at 0 °C under argon was added diisopropylethylamine (2.70 mL, 15.5 mmol, 3.5 equiv) and PyBOP (2.54 g, 4.88 mmol, 1.1 equiv) in one portion. The cold bath was removed and the mixture was stirred at rt for 15 h. Saturated, aqueous $NaHCO_3$ (6.0 mL) was added and the mixture was stirred for 1 h at rt, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with 1.0 M aqueous citric acid, water, and 4.0 M aqueous LiCl, dried (Na_2SO_4), filtered and concentrated to a yellow syrup. Purification by chromatography on SiO_2 (40% to 50% ethyl acetate/ hexanes) gave **8** (1.45 g, 100%) as a clear, colorless syrup: ^{1}H NMR α 6.81 (d, 1 H, J = 7.3 Hz), 4.68 (app dt, 1 H, J = 7.2, 3.4 Hz), 4.02, 3.94 (d of AB, 2 H, J = 11.3, 3.4 Hz), 3.80 (s, 3 H), 1.07-1.11 (m, 21 H); ^{13}C NMR α 170.5, 153.0, 99.1, 90.7, 63.1, 55.1, 53.1, 18.7, 11.2; IR (neat) 3421, 3328, 2945, 2892, 2867, 2166, 1747, 1640, 1526, 1463, 1438, 1218 cm^{-1}; MS (EI) *m/z* (rel. intensity) 327 (M^+, 6), 309 ([M-H_2O]$^+$, 10), 297 (16), 284 ([M-C_3H_7]$^+$, 38), 266 ([M-C_3H_7-H_2O]$^+$, 77), 238 (16), 57 (100) ; HRMS (EI) *m/z* calcd for $C_{16}H_{29}NO_4Si$ 327.1866, found 327.1871.



8

3-Hydroxy-2-[3-(triisopropylsilanyl)propynoylamino]propionic acid methyl ester (**8**, scale-up protocol). A solution of triisopropylsilanylpropynoic acid (5.00 g, 22.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was cooled under N_2 to –20 °C and treated with DMF (5 drops). Oxalyl chloride (2.90 mL, 33.24 mmol, 1.5 equiv) was slowly added. The mixture was stirred for 30 min while the bath temperature increased to –10 °C. The cold bath was then removed and the mixture was stirred at rt for 60 min and then concentrated under vacuum, affording an orange-colored oil. The oil was diluted with CH_2Cl_2 (5.0 mL + 5.0 mL rinse) and added via cannula to a stirred mixture of *DL*-serine methyl ester hydrochloride (5.20 g, 33.4 mmol, 1.5 equiv) and diisopropylethylamine (12.0 mL, 69.0 mmol, 3.1 equiv) in DMF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, then at rt for 20 h. Saturated aqueous $NaHCO_3$ (20 mL) was added and after stirring for 1 h at rt, the mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with 1.0 M aqueous citric acid (2 x 100 mL), water (25 mL), and 4.0 M aqueous LiCl (25 mL), dried (Na_2SO_4) and concentrated to an amber syrup. Purification by chromatography on SiO_2 (40% to 60% ethyl acetate/hexanes) gave **8** (5.90 g, 82%) as a pale yellow syrup. The spectral data were identical to material obtained from the PyBOP coupling.

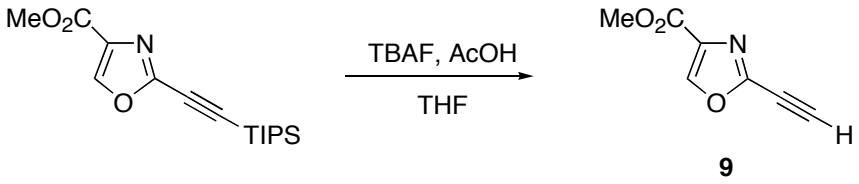


8

2-[(Triisopropylsilanyl)ethynyl]oxazole-4-carboxylic acid methyl ester. A solution of **8** (5.90 g, 18.0 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was cooled to –78 °C under argon. Diethylaminosulfurtrifluoride (DAST) (2.80 mL, 21.2 mmol, 1.2 equiv) was added. After 10 min

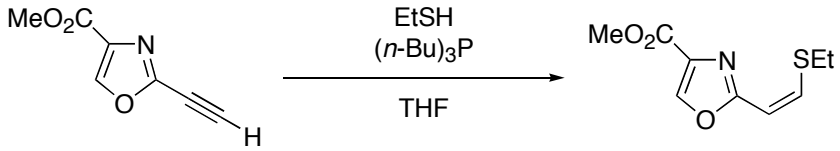
at –78 °C, anhydrous K_2CO_3 (3.74 g, 27.06 mmol, 1.5 equiv) was added and the mixture was stirred at –78 °C for 15 min, then at 0 °C for 1 h. Saturated aqueous $NaHCO_3$ (100 mL) was slowly added (caution: vigorous evolution of gas) and the cold bath was removed. After stirring for 1 h at rt, the mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to an amber oil, which was used without further purification. For analytical purposes, purification by chromatography on SiO_2 (20% to 30% ethyl ether/ hexanes) gave 2-[(triisopropylsilanyl)ethynyl]-4,5-dihydrooxazole-4-carboxylic acid methyl ester as a pale yellow syrup: ^{1}H NMR α 4.84 (dd, 1 H, J = 10.8, 8.4 Hz), 4.57 (app t, 1 H, J = 8.5 Hz), 4.46 (dd, 1 H, J = 10.8, 8.8 Hz), 3.80 (s, 3 H), 1.22-1.09 (m, 21 H); ^{13}C NMR α 170.8, 151.6, 96.4, 93.1, 69.2, 68.5, 53.0, 18.6, 11.1; IR (neat) 2946, 2893, 2867, 2180, 1747, 1619, 1464, 1437, 1349, 1271, 1221 cm^{-1}; MS (EI) *m/z* (rel. intensity) 309 (M^+, 9), 266 ([M-C_3H_7]$^+$, 100), 250 ([M-CO_2CH_3]$^+$, 11), 238 (34); 224 (13), 196 (15); HRMS (EI) *m/z* calcd for $C_{16}H_{27}NO_3Si$ 309.1760, found 309.1760.

The crude oxazoline was azeotropically dried with toluene (2 x 25 mL) at reduced pressure, diluted with CH_2Cl_2 (100 mL) and cooled to –15 °C under N_2. $BrCCl_3$ (2.13 mL, 21.61 mmol, 1.2 equiv) was added. DBU (2.96 mL, 19.79 mmol, 1.1 equiv) was added dropwise and the mixture was stirred for 1 h while the bath temperature increased to –5 °C. Ethyl ether (100 mL) was added and the mixture was filtered through a pad of SiO_2 (80 mm x 40 mm, prewetted with hexanes). The pad was washed with ethyl ether (150 mL) and the combined filtrate was concentrated to an orange-colored oil. Purification by chromatography on SiO_2 (5% to 20% ethyl ether / hexanes) gave 2-[(triisopropylsilanyl)ethynyl]oxazole-4-carboxylic acid methyl ester (4.09 g, 74%) as a pale yellow syrup: R_f 0.45 (20% ethyl ether/ hexanes); ^{1}H NMR α 8.17 (s, 1 H), 3.91 (s, 3 H), 1.18-1.07 (m, 21 H); ^{13}C NMR α 161.1, 146.9, 144.2, 134.0, 98.4, 92.1, 52.5, 18.6, 11.2; IR (neat) 3151, 2946, 2892, 2867, 1753, 1732, 1574, 1536, 1465, 1436 cm^{-1}; MS (EI) *m/z* (rel. intensity) 307 (M^+, 19), 292 ([M-CH_3]$^+$, 5), 264 ([M-C_3H_7]$^+$, 100), 236 (34), 222 ([M-C_6H_{13}]$^+$, 8), 208 (32), 194 (16); HRMS (EI) *m/z* calcd for $C_{16}H_{25}NO_3Si$ 307.1604, found 307.1609.



9

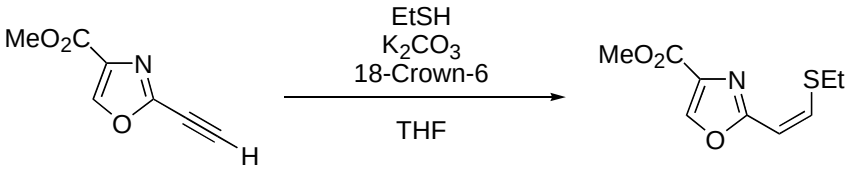
2-Ethynyloxazole-4-carboxylic acid methyl ester (9). A solution of 2-[(triisopropylsilanyl)ethynyl]oxazole-4-carboxylic acid methyl ester (76.0 mg, 247 μmol, 1.0 equiv) in THF (2.5 mL) was cooled to –78 °C under argon. A stock solution of TBAF (0.50 mL of a 1.0 M solution on THF) and glacial acetic acid (50 μL) in THF (2.0 mL) was prepared and 1.25 mL was added dropwise over 5 min. After an additional 10 min, saturated, aqueous NH_4Cl was added (3.0 mL) at –78 °C and the mixture was warmed to rt, diluted with water and extracted with ethyl ether. The combined organic portions were washed with brine, dried (Na_2SO_4), filtered and concentrated to afford **9** (36.9 mg, 99%) as a white, crystalline solid: Mp 92.0-93.0 °C (CH_2Cl_2); ^{1}H NMR α 8.20 (s, 1 H), 3.92 (s, 3 H), 3.29 (s, 1 H); ^{13}C NMR α 160.9, 146.2, 144.7, 134.2, 81.4, 70.5, 52.6; IR (KBr) 3186, 3158, 3116, 2958, 2126, 1729, 1578, 1536, 1437 cm^{-1}; MS (EI) *m/z* (rel. intensity) 151 (M^+, 100), 123 (50), 120 ([M-OCH_3]$^+$, 77), 100 (99), 93 ([M-CO_2CH_3 + H]$^+$,21), 84 (26), 69 (37), 64 (75), 53 (52); HRMS (EI) *m/z* calcd for $C_7H_5NO_3$ 151.0269, found 151.0275.



9 **10a**

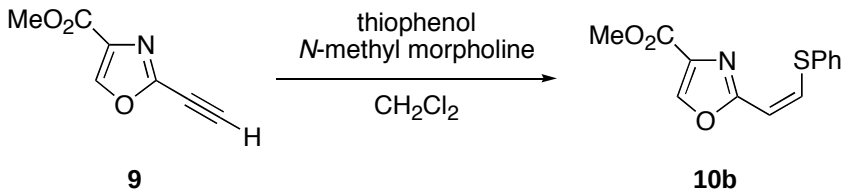
2-(2-Ethylsulfanylvinyl)oxazole-4-carboxylic acid methyl ester (10a). To a solution of **9** (11.0 mg, 73 μmol, 1.0 equiv) in THF (1.0 mL) at rt under N_2, was added ethanethiol (40.0 μl, 540 μmol, 7.4 equiv) and a solution of tri-*n*-butyl phosphine (0.20 mL of a 27 mg/mL solution in THF, 5.4 mg, 26 μmol, 0.4 equiv). After stirring for 36 h at rt under N_2, the mixture was concentrated under vacuum. ^{1}H NMR analysis of the residue indicated a *Z*/*E* ratio of 10.5:1. The residue was purified by chromatography on SiO_2 (30 to 50% ethyl ether/hexanes) to give **10a** (10.9 mg, 70%) as a white solid that contained 7.6% of the (*E*)-isomer. **10a**: Mp 61.9-63.5 °C

(CH_2Cl_2); ^{1}H NMR α 8.20 (s, 1 H), 6.87 (d, 1 H, *J* = 11.0 Hz), 6.34 (dd, 1 H, *J* = 11.0, 0.7 Hz), 3.90 (s, 3 H), 2.85 (dq, 2 H, *J* = 7.4, 0.7 Hz), 1.38 (dt, 3 H, *J* = 7.4, 0.9 Hz); ^{13}C NMR α 162.0, 161.9, 143.0, 140.3, 134.5, 109.0, 52.2, 29.8, 15.6; IR (KBr) 3124, 3076, 2979, 2953, 2929, 2870, 2851, 1737, 1611 cm^{-1}; MS (EI) *m/z* (rel. intensity) 213 (M^+, 41), 184 ([M-CH_2CH_3]$^+$, 6), 153 ([M-CH_2CH_3-OCH_3]$^+$, 7), 86 (6), 84 (87), 66 (100); HRMS (EI) *m/z* calcd for $C_9H_{11}NO_3S$ 213.0460, found 213.0459; Characteristic signals for the (*E*)-isomer: ^{1}H NMR α 8.10 (s, 1 H), 7.49 (d, 1 H, *J* = 15.6 Hz), 6.32 (d, 1 H, *J* = 15.6 Hz).



9 **10a**

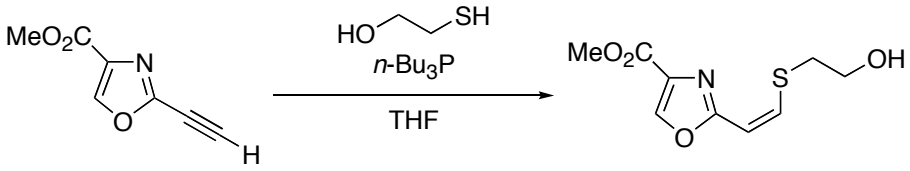
2-(2-Ethylsulfanylvinyl)oxazole-4-carboxylic acid methyl ester (10a). To a solution of **9** (20.0 mg, 132 μmol, 1.0 equiv) in THF (1.20 mL) at rt was added thioethanol (75.0 μL, 1.0 mmol, 7.7 equiv) and anhydrous K_2CO_3 (20.0 mg, 145 μmol, 1.1 equiv). 18-Crown-6 was added and the reaction mixture turned pale yellow. After stirring at rt for 1.5 h, the mixture was diluted with ethyl ether (2.0 mL) and filtered through a plug of Florisil / Celite (1:1, v/v). The plug was washed with ethyl ether (3.0 mL) and the combined filtrate was concentrated to a clear, colorless oil. ^{1}H NMR analysis of the residue indicated a *Z*/*E* ratio of 16.4:1.0. The residue was purified by chromatography on SiO_2 (30 to 50% ethyl ether/hexanes) to give **10a** (25.2 mg, 89%) as a white solid that contained 3.5% of the (*E*)-isomer. The analytical data were identical to material obtained from the tri-*n*-butyl phosphine method.



9 **10b**

2-(2-Phenylsulfanylvinyl)oxazole-4-carboxylic acid methyl ester (10b). To a solution of **9** (6.4 mg, 42 μmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at rt under N_2, was added thiophenol (0.100 mL,

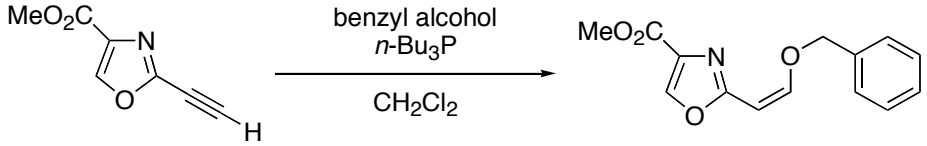
0.974 mmol, 23.2 equiv) and *N*-methyl morpholine (10 μL, 0.091 mmol, 2.1 equiv). After stirring for 48 h at rt, the solvent was removed under vacuum to give a pale yellow solid. Recrystallization from ethyl acetate / hexanes gave **10b** (10.7 mg, 97%) as a white crystalline solid: Mp 119.5-120.5 °C (CH_2Cl_2); ^{1}H NMR α8.22 (s, 1 H), 7.49-7.44 (m, 2 H), 7.37-7.28 (m, 3 H), 7.04 (d, 1 H, *J* = 11.0 Hz), 6.38 (d, 1 H, *J* = 11.0 Hz), 3.90 (s, 3 H); ^{13}C NMR α 161.8, 161.3, 143.1, 140.1, 135.4, 134.5, 131.1, 129.5, 128.3, 109.1, 52.2; IR (KBr) 3124, 3075, 2952, 2848, 1736, 1709, 1614 cm^{-1}; MS (EI) *m/z* (rel. intensity) 261 (M^+, 100), 230 ($[M-OCH_3]^+$, 6), 202 ($[M-OCOCH_3]^+$, 7), 184 ($[M-C_6H_5]^+$, 51), 172 (44), 147 (30), 77 (15); HRMS (EI) *m/z* calcd for $C_{13}H_{11}NO_3S$ 261.0460, found 261.0459.



9 **10c**

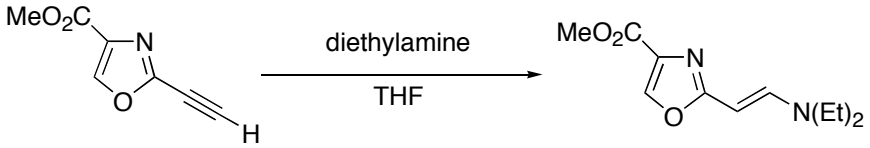
2-[2-(2-Hydroxyethylsulfanyl)vinyl]oxazole-4-carboxylic acid methyl ester (10c). To a solution of **9** (50.0 mg, 331 μmol, 1.0 equiv) in THF (3.0 mL) at rt under N_2 was added 2-mercaptoethanol (28.0 μL, 399 μmol, 1.2 equiv). A solution of tri-*n*-butylphosphine (100 mg / mL, 0.330 mL, 33 mg, 0.5 equiv) was added and the mixture was stirred at rt for 1 h then heated to 60 °C for 6 h. The mixture was then refluxed for 18 h with no additional change occurring as indicated by TLC analysis. Concentration under vacuum and purification by chromatography on SiO_2 (60 % ethyl acetate/ hexanes) gave **10c** (51.6 mg, 68%) in a *Z*/*E* ratio of 6.4:1.0 as an amorphous solid that crystallized on standing: R_f 0.23 (60 % ethyl acetate / hexanes); Mp 95.2-97.2 °C (CH_2Cl_2); ^{1}H NMR α 8.19 (s, 1 H), 6.89 (d, 1 H, *J* = 11.0 Hz), 6.34 (d, 1 H, *J* = 11.0 Hz), 3.90 (s, 3 H), 3.87 (t, 2 H, 6.0), 3.02 (t, 2 H, 6.0), 2.32 (bs, 1 H); ^{13}C NMR α 161.9, 161.6, 143.1, 140.3, 134.3, 109.4, 62.1, 52.4, 38.6; IR (KBr) 3342, 3176, 3017, 2957, 2929, 1752, 1594, 1441 cm^{-1}; MS (EI) *m/z* (rel. intensity) 229 (M^+, 32), 211 ($[M-H_2O]^+$, 37), 198 ($[M-OCH_3]^+$, 25), 184 ($[M-CH_2CH_2OH]^+$, 100), 151 ($[M-HSCH_2CH_2OH]^+$, 52), 139 ($[M-CO_2Me-CH_2OH]^+$, 42), 125 ($[M-CO_2CH_3-CH_2CH_2OH]^+$, 25), 110 (55); HRMS (EI) *m/z* calcd for

$C_9H_{11}NO_4S$ 229.0409, found 229.0411. Characteristic signals for the (*E*)-isomer: ^{1}H NMR α 8.09 (s, 1 H), 7.47 (d, 1 H, 15.7), 6.31 (d, 1 H, 15.7).



9 **10d**

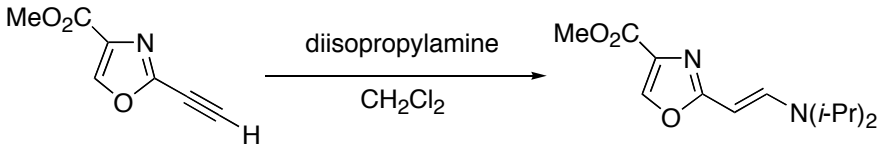
2-(2-Benzyloxyvinyl)oxazole-4-carboxylic acid methyl ester (10d). To a solution of **9** (10.0 mg, 66 μmol, 1.0 equiv)) and benzyl alcohol (20.0 μL, 193 μmol, 2.9 equiv) in CH_2Cl_2 (1.0 mL) was added a solution of tri-*n*-butylphosphine (13.4 mg, 66 μmol, 1.0 equiv) in CH_2Cl_2 (100 μL). The mixture immediately turned yellow then slowly became dark red over 30 min. The mixture was filtered through a plug of SiO_2 (2 cm in a pasteur pipette) and the plug was washed with ethyl ether. The combined filtrate was concentrated under vacuum to a yellow oil. ^{1}H NMR analysis of the oil indicated a *Z*/*E* ratio of 6.4:1.0 Purification by chromatography on SiO_2 (25% ethyl ether / hexanes) gave **10d** (13.0 mg, 76%) as a white, crystalline solid: R_f 0.31 (60 % ethyl ether / hexanes); Mp 79.2-80.5 °C (CH_2Cl_2); ^{1}H NMR α 8.06 (s, 1 H), 7.64 (d, 1 H, J = 12.9 Hz), 7.45-7.31 (m, 5 H), 5.82 (d, 1 H, J = 12.9 Hz), 4.95 (s, 2 H), 3.90 (s, 3 H); ^{13}C NMR α 162.0, 156.3, 142.4, 135.5, 133.8, 128.9, 128.8, 127.9, 93.8, 73.0, 52.3; IR (KBr) 3144, 3082, 3027, 2948, 2917, 1719, 1656, 1576, 1452, 1430 cm^{-1}; MS (EI) *m/z* (rel. intensity) 259 (M^+, 13), 91 (100), 65 (15); HRMS (EI) *m/z* calcd for $C_{14}H_{13}NO_4$ 259.0845, found 259.0855.



9 **10e**

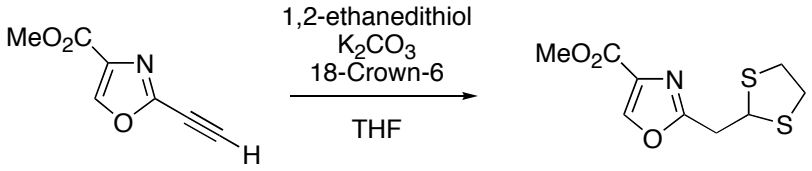
2-(2-Diethylaminovinyl)oxazole-4-carboxylic acid methyl ester (10e). To a solution of **9** (50.0 mg, 331 μmol, 1.0 equiv) in THF (2.0 mL) at rt under N_2 was added diethylamine (50 μL, 480 μmol, 1.5 equiv). After 4 h at rt, additional diethylamine (50 μL, 480 μmol, 1.5 equiv) was added. After 18 h (total reaction time) at rt, TLC analysis indicated that starting alkyne

remained, so additional diethylamine (100 µL, 970 µmol, 3.0 equiv) was added and the mixture was heated to 60 °C for 2 h, then cooled to rt. The volatile components were removed under vacuum and the resulting residue was purified by chromatography on SiO_2 (40% ethyl ether / hexanes) to give **10e** (74.4 mg, 100%) as a clear, colorless oil: R_f 0.23 (60% ethyl ether / hexanes); ^{1}H NMR α 7.90 (s, 1 H), 7.32 (d, 1 H, *J* = 13.6 Hz), 4.93 (d, 1 H, *J* = 13.6 Hz), 3.83 (s, 3 H), 3.15 (q, 4 H, *J* = 7.1 Hz), 1.11 (t, 6 H, *J* = 7.1 Hz); ^{13}C NMR α 166.1, 162.6, 145.4, 140.6, 133.3, 80.1, 51.9, 46.1, 13.2; IR (neat) 3161, 3085, 2975, 2945, 2930, 2868, 1738, 1634, 1573, 1553 cm^{-1}; MS (EI) *m/z* (rel. intensity) 224 (M^+, 83), 209 ($[M\text{-}CH_3]^+$, 21), 195 ($[M\text{-}CH_2CH_3]^+$, 44), 164 ($[M\text{-}HOCOCH_3]^+$, 70), 163 (46), 135 (100), 109 (62), 181 (11); HRMS (EI) *m/z* calcd for $C_{11}H_{16}N_2O_3$ 224.1161, found 224.1158.



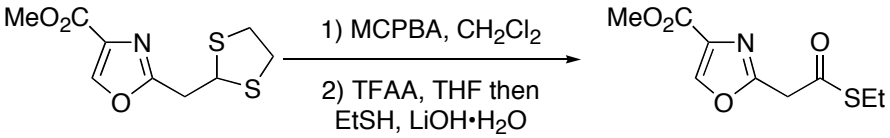
9 **10f**

2-(2-Diisopropylaminovinyl)oxazole-4-carboxylic acid methyl ester (10f). To a solution of **9** (10.0 mg, 66 µmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at rt under N_2 was added diisopropylamine (20 µL, 143 µmol, 2.2 equiv). After 24 h at rt, additional diisopropylamine (100 µL, 714 µmol, 10.8 equiv) was added and the mixture was stirred at rt for an additional 48 h (72 h total). Volatile components were removed under vacuum and the resulting residue was purified by chromatography on SiO_2 (40% ethyl ether / hexanes) to afford **10f** (17.0 mg, 100%) as a clear, colorless oil: ^{1}H NMR α 7.94 (s, 1 H), 7.41 (d, 1 H, *J* = 13.7 Hz), 5.09 (d, 1 H, *J* = 13.7 Hz), 3.87 (s, 3 H), 3.66 (sept, 2 H, *J* = 6.7 Hz), 1.20 (d, 12 H, *J* = 6.7 Hz); ^{13}C NMR α 166.5, 162.8, 141.4, 140.6, 133.4, 80.6, 52.0, 47.8, 21.7; IR (neat) 3160, 3088, 2975, 2934, 2872, 1743, 1720, 1627, 1571, 1552, 1463, 1435 cm^{-1}; MS (EI) *m/z* (rel. intensity) 252 (M^+, 43), 237 ($[M\text{-}CH_3]^+$, 34), 221 ($[M\text{-}OCH_3]^+$, 8), 209 ($[M\text{-}CH(CH_3)_2]^+$, 100), 195 (36), 192 (16), 177 (38), 163 (62), 149 (31), 135 (27); HRMS (EI) *m/z* calcd for $C_{13}H_{20}N_2O_3$ 252.1474, found 252.1473.



9 **11**

2-[1,3]Dithiolan-2-ylmethyloxazole-4-carboxylic acid methyl ester (11). To a solution of **9** (342.5 mg, 2.266 mmol, 1.0 equiv) in THF (11.0 mL) at rt was added anhydrous K_2CO_3 (150.0 mg, 1.085 mmol, 0.5 equiv) and 1,2-ethanedithiol (950 μL, 11.3 mmol, 5.0 equiv). 18-Crown-6 was added and the mixture became turbid and pale yellow within 10 min. The solution was stirred for 12 h at rt and then evaporated onto a blend of Florisil and Celite (1:1 v/v). The resulting solid was directly purified on SiO_2 (30% to 60% ethyl ether/hexanes) and gave **11** (538.0 mg, 97%) as a white, crystalline solid: Mp 84.0-85.0 °C (ethyl acetate/hexanes); ^{1}H NMR α 8.15 (s, 1 H), 4.93 (t, 1 H, J = 7.4 Hz), 3.87 (s, 3 H), 3.27 (d, 2 H, J = 7.4 Hz), 3.23, 3.24 (d of AB, 4 H, J = 6.3, 1.3 Hz); ^{13}C NMR α 162.8, 161.7, 144.1, 133.4, 52.3, 49.9, 39.0, 38.8; IR (KBr) 3165, 3118, 2956, 2919, 1726, 1583, 1437, 1423, 1320, 1159, 1110 cm^{-1}; MS (EI) *m/z* (rel. intensity) 245 (M^+, 25), 217 ([M-C_2H_4]$^+$, 7), 186 ([M-CO_2CH_3]$^+$, 32), 154 ([M-OCH_3-SCH_2CH_2]$^+$, 11), 141 (19), 105 (100), 61 (13), 59 (9); HRMS (EI) *m/z* calcd for $C_9H_{11}NO_3S_2$ 245.0180, found 245.0173.

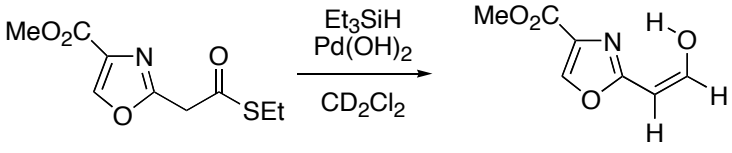


11 **13**

2-Ethylsulfanylcarbonylmethyloxazole-4-carboxylic acid methyl ester (13). A solution of the **11** (620 mg, 2.53 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) was cooled under N_2 to –78 °C. A suspension of MCPBA (920 mg, 5.33 mmol, 2.1 eqiv) in CH_2Cl_2 (5.0 mL + 5.0 mL rinse) was added. After 20 min at –78 °C, Florisil and Celite (1:1 v/v) was added and the mixture was warmed to rt and concentrated under vacuum. The resulting mixture was purified by chromatography on SiO_2 (10% methanol / ethyl acetate) affording the dithiolanedioxide **12** (678

mg, 97%) as a white solid that was used without further purification: R_f 0.25 (10% methanol / ethyl acetate).

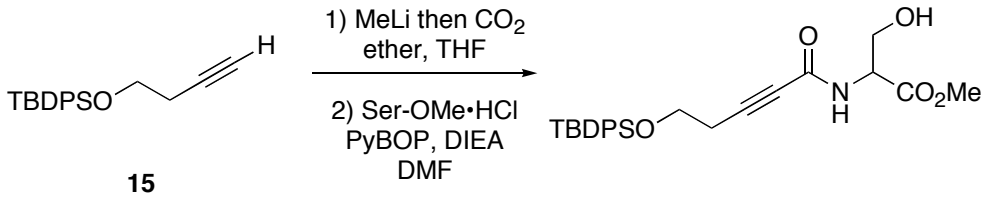
A suspension of **12** (62.0 mg, 224 μmol, 1.0 equiv) in THF (3.0 mL) was cooled to 0 °C under N_2 and pyridine (43.0 μL, 530 μmol, 2.4 equiv) was added. TFAA (44.0 μL, 312 μmol, 1.4 equiv) was added dropwise and the mixture was stirred for 30 min at 0 °C. Additional TFAA (10.0 μL, 71 μmol, 0.3 equiv) was added and after an additional 15 min at 0 °C, ethanethiol (166 μL, 2.24 mmol, 10 equiv), water (100 μL, 5.56 mmol, 25 equiv) and LiOH•H_2O (47.0 mg, 1.12 mmol, 5.0 equiv) were sequentially added. After stirring for 1 h at 0 °C, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were washed with 1.0 M aqueous citric acid, water and brine, dried (Na_2SO_4) and concentrated to a pale yellow oil. Purification by chromatography on SiO_2 (40% ethyl ether / hexanes) gave **13** (41.0 mg, 80%) as a clear, colorless syrup that contained some impurities as indicated by ^{1}H NMR analysis: R_f 0.20 (40% ethyl ether/ hexanes); ^{1}H NMR α 8.21 (s, 1 H), 4.06 (s, 2 H), 3.88 (s, 3H), 2.90 (q, 2 H, *J* = 7.4 Hz), 1.23 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR α 192.0, 161.4, 158.1, 145.0, 133.8, 52.4, 42.9, 24.1, 14.5; IR (neat) 3160, 3124, 2954, 2933, 2868, 2848, 1739, 1688, 1583, 1438, 1323 cm^{-1}; MS (EI) *m/z* (rel. intensity) 229 (M^+, 12), 198 ([M-OCH_3]$^+$, 9), 168 ([M-SCH_2CH_3]$^+$, 27), 141 (100), 109 (72), 89 (37), 57 (43); HRMS (EI) *m/z* calcd for $C_9H_{11}NO_4S$ 229.0409, found 229.0399.



13 **14**

2-(2-Hydroxyvinyl)oxazole-4-carboxylic acid methyl ester (14). To a solution of **13** (11.0 mg, 48 μmol, 1.0 equiv) in CD_2Cl_2 (1.0 mL) was added $Pd(OH)_2$ (wet Degussa type E101 NE/W, 20 % Pd content, 5.5 mg) and the flask was partially evacuated and then flushed with N_2 (2 cycles). Et_3SiH (50 μL, 310 μmol, 6.5 equiv) was added and the mixture was stirred at rt. After 7.5 h, additional Et_3SiH (50 μL, 310 μmol, 6.5 equiv) was added and stirred for 1.5 h (9 h total).

The mixture was filtered rapidly through a plug of Florisil and Celite (1:1 v/v) and the filtrate was carefully concentrated under vacuum to approximately 0.5 mL, then transferred to an NMR tube. ^{1}H NMR analysis indicated a **14**/**13** ratio of 2:1. **14**: R_f 0.46 (60% ethyl ether/ hexanes); ^{1}H NMR (CD_2Cl_2) α 8.13 (s, 1 H), 6.76 (d, 1 H, J = 6.4 Hz), 5.47 (d, 1 H, J = 6.4 Hz), 3.85 (s, 3 H).

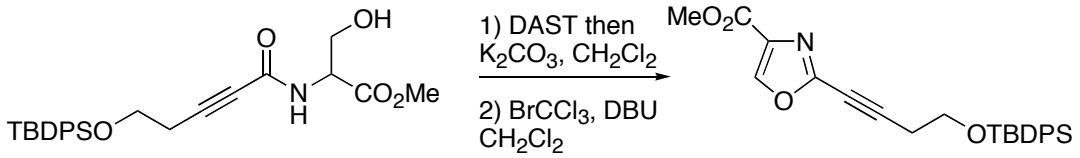


15

2-[5-(*tert*-Butyldiphenylsilanyloxy)pent-2-ynoylamino]-3-hydroxy-propionic acid methyl ester. A solution of **15** (2.00 g, 6.48 mmol, 1.0 equiv) in THF (40 mL) was cooled to –78 °C under N_2. MeLi (1.5 M in diethyl ether, 6.00 mL, 9.00 mmol, 1.4 equiv) was added and the mixture was stirred at –78 °C for 1 h, warmed to 0 °C for 15 min and then cooled to –78 °C. CO_2 (gas from dry ice, passed over anhydrous $CaSO_4$) was bubbled into the reaction mixture. After 10 min, the mixture was warmed to 0 °C, stirred for 20 min and slowly quenched by the addition of 2.0 M aqueous $NaHSO_4$ (20 mL). The mixture was poured into brine (20 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated to afford 5-(*tert*-butyldiphenylsilanyloxy)pent-2-ynoic acid as a pale yellow syrup (2.48 g, quant.) that was used without further purification.

A mixture of the crude 5-(*tert*-butyldiphenylsilanyloxy)pent-2-ynoic acid (2.48 g, 7.04 mmol, 1.0 equiv) and *DL*-serine methyl ester hydrochloride (1.64 g, 10.5 mmol, 1.5 equiv) was dissolved in DMF (10 mL) and cooled to 0 °C under N_2. PyBOP (4.10 g, 7.88 mmol, 1.1 equiv) and diisopropylethylamine (4.30 mL, 24.7 mmol, 3.5 equiv) were added and the cold bath was removed. After stirring at rt for 36 h, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was stirred for 30 min, then poured into water (50 mL) and extracted with ethyl acetate. The combined organic layers were washed with 1.0 M aqueous citric acid (50 mL), water (50 mL) and 4.0 M aqueous LiCl (50 mL), dried (Na_2SO_4) and concentrated. Purification by

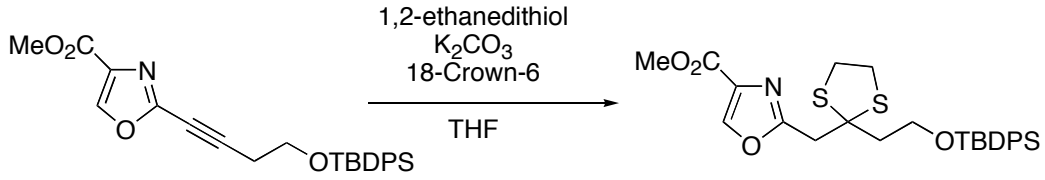
chromatography on SiO_2 (50% ethyl acetate/ hexanes) gave 2-[5-(*tert*-butyldiphenylsilanyloxy)pent-2-ynoylamino]-3-hydroxypropionic acid methyl ester (2.63 g, 90% for 2 steps) as a clear, colorless syrup: R_f 0.40 (60% ethyl acetate/hexanes); ^1H NMR α 7.68-7.66 (m, 4 H), 7.47-7.37 (m, 6 H), 6.67 (d, 1 H, J = 7.4 Hz), 4.67 (ddd, 1 H, J = 7.2, 7.2, 3.4 Hz), 3.99 (ddd, 1 H, J = 11.2, 5.5, 3.9 Hz), 3.90 (ddd, 1 H, J = 11.2, 5.3, 3.5 Hz), 3.81 (t, 2 H, J = 6.9 Hz), 3.78 (s, 3 H), 2.57 (t, 2 H, J = 6.9 Hz), 2.48 (t, 1 H, J = 5.8 Hz), 1.07 (s, 9 H); ^{13}C NMR α 170.4, 153.4, 135.7, 133.4, 130.0, 128.0, 86.2, 76.0, 63.1, 61.6, 54.9, 53.1, 26.9, 22.9, 19.4; IR (neat) 3412, 3071, 3049, 2955, 2930, 2885, 2858, 2243, 1963, 1894, 1829, 1743, 1644, 1516, 1112 cm^{-1}; MS (EI) *m/z* (rel. intensity) 438 ($[M\text{-}OH]^+$, 22), 422 ($[M\text{-}CH_3OH]^+$, 47), 396 ($[M\text{-}C_4H_9]^+$, 100), 378 ($[M\text{-}C_4H_9\text{-}H_2O]^+$, 26), 199 (30), 105 (36); HRMS (EI) *m/z* calcd for $C_{21}H_{22}NO_5Si$ ($M\text{-}C_4H_9$) 396.1267, found 396.1279.



16

2-[4-(*tert*-Butyldiphenylsilanyloxy)but-1-ynyl]oxazole-4-carboxylic acid methyl ester (16). A solution of 2-[5-(*tert*-butyldiphenylsilanyloxy)pent-2-ynoylamino]-3-hydroxypropionic acid methyl ester (2.63 g, 5.81 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was cooled to -78 °C under N_2 and diethylaminosulfurtrifluoride (DAST) (810 µL, 6.13 mmol, 1.1 equiv) was added dropwise over 2 min. The mixture was stirred for 10 min at -78 °C, then anhydrous K_2CO_3 (1.20 g, 8.68 mmol, 1.5 equiv) was added. The -78 °C bath was replaced with a 0 °C bath and, after 10 min, saturated aqueous $NaHCO_3$ (20 mL) was carefully added (caution: vigorous evolution of gas). The cold bath was removed and the mixture was stirred at rt for 1 h, diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The resulting oil was azeotropically dried at reduced pressure from toluene (10 mL), diluted with CH_2Cl_2 (30 mL) and cooled to 0°C under N_2. $BrCCl_3$ (630 µL, 6.39 mmol, 1.1 equiv) and DBU (950 µL, 6.35 mmol, 1.1 equiv) were added and the mixture was stirred at 0 °C for 4 h. Hexanes (50 mL) was added and the mixture was poured onto a pad of SiO_2 (40 mm x 40

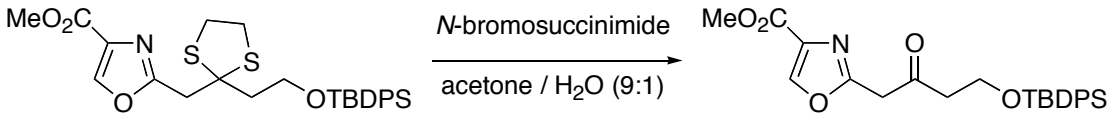
mm) and eluted with 50 % ethyl ether / hexanes. The combined filtrate was concentrated to a yellow syrup which was purified by chromatography on SiO_2 (10% ethyl ether / hexanes) to afford **16** (1.91 g, 76%) as a clear colorless, syrup: R_f 0.37 (40 % ethyl ether / hexanes); ^{1}H NMR α 8.15 (s, 1 H), 7.69-7.66 (m, 4 H), 7.47-7.36 (m, 6 H), 3.91 (s, 3 H), 3.86 (t, 2 H, *J* = 6.8 Hz), 2.69 (t, 2 H, *J* = 6.8 Hz), 1.06 (s, 9 H); ^{13}C NMR α 161.2, 147.3, 144.1, 135.7, 133.9, 133.4, 130.0, 128.0, 92.7, 69.3, 61.6, 52.5, 26.9, 23.5, 19.4; IR (neat) 3158, 3071, 2953, 2932, 2884, 2857, 2249, 1967, 1885, 1829, 1751, 1728, 1574, 1551, 1113 cm^{-1}; MS (EI) *m/z* (rel. intensity) 432 ([M-H]$^+$, 0.3), 418 ([M-CH_3]$^+$, 0.5), 402 ([M-OCH_3]$^+$, 3.3), 376 ([M-C_4H_9]$^+$, 91), 346 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{27}NO_4Si$ (M-H) 432.1631, found 432.1625.



16 **17**

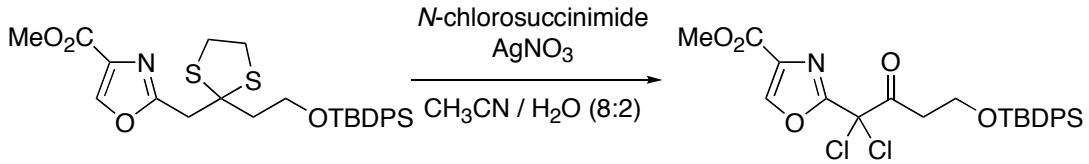
2-{2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-[1,3]dithiolan-2-ylmethyl}oxazole-4-carboxylic acid methyl ester (17). To a solution of **16** (101.5 mg, 234 µmol, 1.0 equiv) in THF (5.0 mL) at rt was added 1,2-ethanedithiol (100 µL, 1.19 mmol, 5.1 equiv) and anhydrous K_2CO_3 (32.0 mg, 232 µmol, 1.0 equiv). 18-Crown-6 (24.0 mg, 91 µmol, 0.4 equiv) was added and the colorless solution immediately became pale yellow. The mixture was stirred for 4 h at rt, slowly becoming turbid and was filtered through a plug of Florisil and Celite (1:1 v/v) and the filtrate was concentrated. Purification by chromatography on SiO_2 (30 % ethyl ether / hexanes) gave **17** (116.4 mg, 94%) as a clear, colorless oil: R_f 0.29 (40% ethyl ether / hexanes); ^{1}H NMR α 8.15 (s, 1 H), 7.70-7.66 (m, 4 H), 7.44-7.34 (m, 6 H), 3.96 (t, 2 H, *J* = 6.7 Hz), 3.90 (s, 3 H), 3.53 (s, 2 H), 3.22 (s, 4 H), 2.42 (t, 2 H, *J* = 6.7 Hz), 1.04 (s, 9 H); ^{13}C NMR α 162.2, 161.8, 144.2, 135.7, 133.6, 133.3, 129.8, 127.8, 66.5, 62.3, 52.2, 44.5, 43.2, 39.9, 26.9, 19.2; IR (neat) 3070, 3048, 2952, 2930, 2890, 2856, 1964, 1897, 1820, 1748, 1729, 1581, 1139 cm^{-1}; MS (EI) *m/z* (rel. intensity) 527 (M$^+$, 0.04), 513 ([M-CH_2]$^+$, 0.16), 499 ([M-C_2H_4]$^+$, 30), 470 ([M-C_4H_9]$^+$, 51),

199(24), 131(32), 91(100); HRMS (EI) *m/z* calcd for $C_{23}H_{24}NO_4S_2Si$ (M-C_4H_9) 470.0916, found 470.0902.



17 **18**

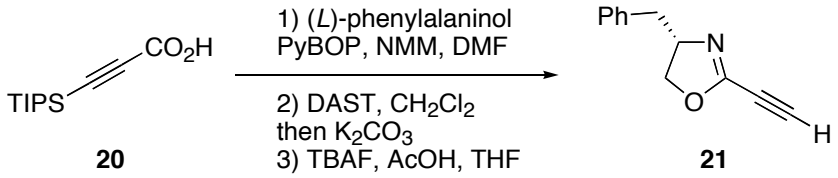
2-[4-(*tert*-Butyldiphenylsilanyloxy)-2-oxobutyl]oxazole-4-carboxylic acid methyl ester (18). A solution of *N*-bromosuccinimide (52.0 mg, 292 μmol, 8.1 equiv) in acetone/ water (9:1 v/v; 1.0 mL) was cooled to 0 °C and a solution of **17** (19.0 mg, 36 μmol, 1.0 equiv) in acetone/water (9:1; 1.0 mL) was added dropwise. The mixture became yellow and after 10 min, saturated, aqueous $NaHCO_3$ (1.0 mL) and saturated, aqueous $Na_2S_2O_3$ (1.0 mL) were added. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the mixture by chromatography on SiO_2 (20% to 30% ethyl acetate/hexanes) gave **18** (12.5 mg, 77%) as a clear, colorless wax: R_f 0.43 (40% ethyl acetate / hexanes); ^{1}H NMR α 8.21 (s, 1 H), 7.66-7.63 (m, 4 H), 7.46-7.36 (m, 6 H), 4.03 (s, 2 H), 3.93 (app q, 2 H, *J* = 6.1 Hz), 3.92 (s, 3 H), 2.73 (app t, 2 H, *J* = 6.1 Hz), 1.03 (s, 9H); ^{13}C NMR α 201.7, 161.6, 159.1, 145.0, 135.7, 133.8, 133.3, 130.0, 128.0, 59.5, 52.4, 45.4, 43.3, 27.0, 19.3 ; IR (neat) 3163, 3071, 3049, 2954, 2931, 2888, 2857, 1964, 1893, 1830, 1729, 1587, 1428, 1112 cm^{-1}; MS (EI) *m/z* (rel. intensity) 420 ([M-OCH_3]$^+$, 1.3), 394 ([M-$C(CH_3)_3$]$^+$, 57), 362 ([M-$C(CH_3)_3$-OCH_3]$^+$, 16), 316 ([M-$C(CH_3)_3$-C_6H_6]$^+$, 29), 199 (100), 105 (44), 77 (32); HRMS (EI) *m/z* calcd for $C_{24}H_{26}NO_4Si$ (M-OCH_3) 420.1631, found 420.1631.



17 **19**

2-[4-(*tert*-Butyldiphenylsilanyloxy)-1,1-dichloro-2-oxobutyl]-oxazole-4-carboxylic acid methyl ester (19). A solution of *N*-chlorosuccinimide (46.5 mg, 348 μmol, 4.0 equiv) and

$AgNO_3$ (66.5 mg, 391 μmol, 4.5 equiv) in 80 % (v/v) aqueous acetonitrile (1.0 mL) was cooled to 0 °C. A solution of **17** (24.2 mg, 87 μmol, 1.0 equiv) in 80 % (v/v) aqueous acetonitrile (0.5 mL+ 0.5 mL rinse) was added via syringe. The cold bath was removed and a white precipitate formed. After 30 min, additional *N*-chlorosuccinimide (26.0 mg, 195 μmol, 2.2 equiv) was added in one portion. After an additional 30 min at rt, the mixture was diluted with ethyl ether (5.0 mL) and filtered through a plug of Florisil and Celite (1:1 v/v). The filtrate was diluted with ethyl acetate (10 mL) and washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated. Purification by chromatography on SiO_2 (20% ethyl ether / hexanes) gave **19** (12.9 mg, 29%) as a clear, colorless oil: R_f 0.43 (40% ethyl ether / hexanes); ^{1}H NMR α 8.30 (s, 1 H), 7.67-7.64 (m, 4 H), 7.46-7.37 (m, 6 H), 4.01 (t, 2 H, *J* = 6.1 Hz), 3.93 (s, 3 H), 3.18 (t, 2 H, *J* = 6.1 Hz), 1.02 (s, 9 H); ^{13}C NMR α 191.6, 160.9, 158.4, 146.3, 135.8, 134.4, 133.3, 130.0, 128.0, 78.8, 59.1, 52.7, 38.7, 26.9, 19.3; IR (neat) 3162, 3071, 3050, 2954, 2931, 2888, 2857, 1959, 1897, 1825, 1752, 1578, 1112 cm^{-1}; MS (EI) *m/z* (rel. intensity) 462 ([M-C_4H_9]$^+$, 11), 426 ([M-$C_2H_5S_2$]$^+$, 32), 384 (64), 350 (23), 217 (32), 199 (100), 135(32); HRMS (EI) *m/z* calcd for $C_{21}H_{18}NO_5SiCl_2$ (M-C_4H_9) 462.0331, found 462.0312.



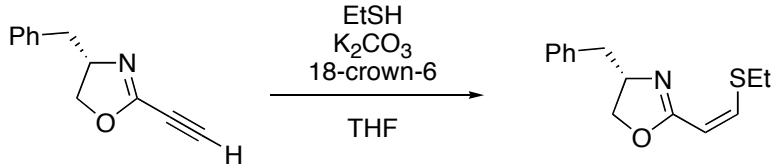
20 **21**

(4*S*)-4-Benzyl-2-ethynyl-4,5-dihydrooxazole (21). A mixture of **20** (354.0 mg, 1.56 mmol, 1.0 equiv), *L*-phenylalaninol (354.0 mg, 2.34 mmol, 1.5 equiv), and PyBOP (900.0, 1.73 mmol, 1.1 equiv) in DMF (3.0 mL) was cooled to 0° C and N-methylmorpholine (400 μL, 3.94 mmol, 2.5 equiv) was added. The mixture was allowed to warm to rt, stirred for 20 h and then poured into saturated aqueous $NaHCO_3$ (10 mL), diluted with water (10 mL) and extracted with ethyl acetate. The combined organic extracts were washed with 1.0 M aqueous citric acid (10 mL), water (10 mL) and 4.0 M aqueous LiCl (10 mL), dried (Na_2SO_4) and concentrated. Purification by chromatography on SiO_2 (30% to 40 % ethyl acetate/ hexanes) gave (1*S*)-3-(triisopropylsilanyl)propynoic acid (1-benzyl-2-hydroxyethyl)amide (580.9 mg, quant.) as a

clear, colorless syrup that was used without further purification. R_f 0.33 (40% ethyl acetate/ hexanes)

A solution of the hydroxyamide (580.0 mg, 1.61 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) was cooled to –78 °C under N_2. Diethylaminosulfurtrifluoride (DAST) (240 μL, 1.82 mmol, 1.1 equiv) was added and, after 10 min, TLC analysis indicated that the hydroxyamide was consumed. Solid anhydrous K_2CO_3 (340.0 mg, 2.46 mmol, 1.5 equiv) was added and the mixture was stirred at –78 °C for 20 min, then at 0 °C for 20 min. Saturated aqueous $NaHCO_3$ (5 mL) was carefully added (caution: vigorous evolution of gas) and the mixture was stirred for 1 h while warming to rt and then extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% ethyl ether / hexanes) gave (4*S*)-4-benzyl-2-[(triisopropylsilanyl)ethynyl]-4,5-dihydrooxazole (338.3 mg, 63%, 2 steps) as a clear, colorless oil that was used without further purification.

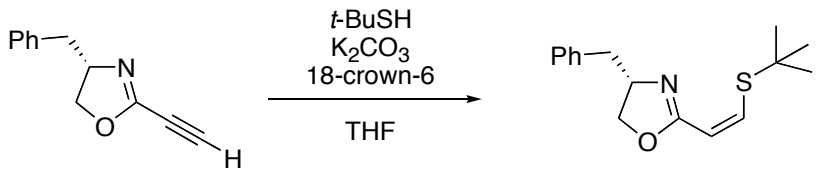
A solution of (4*S*)-4-benzyl-2-[(triisopropylsilanyl)ethynyl]-4,5-dihydrooxazole (338.0 mg, 0.990 mmol, 1.0 equiv) in THF (10.0 mL) was cooled under N_2 to –78 °C. Glacial acetic acid (65 μL, 1.1 mmol, 1.1 equiv) and TBAF (1.0 M in THF, 1.10 mL, 1.1 equiv) were added. After 30 min at –78 °C, saturated aqueous $NaHCO_3$ was added and the mixture was warmed to rt, diluted with water, and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (10% to 20 % ethyl acetate/ hexanes) gave **21** (158.5 mg, 87%) as a clear colorless syrup. The spectral data were in agreement with the literature values.[1] $[\alpha]_D$ = -32.8 (c 0.85, $CHCl_3$, 22 °C), lit. $[\alpha]_D$ = -62.5 (c 1.58, $CHCl_3$, 23 °C).



21 **22**

(4*S*)-4-Benzyl-2-(2-ethylsulfanylvinyl)-4,5-dihydro-oxazole (22). To a solution of **21** (12.2 mg, 66 μmol, 1.0 equiv) in THF (0.5 mL) at rt was added ethanethiol (25 μL, 338 μmol, 5.1

equiv) and anhydrous K_2CO_3 (10.2 mg, 74 μmol, 1.1 equiv). 18-Crown-6 (5.0 mg, 19 μmol, 0.3 equiv) was added and the mixture was vigourously stirred for 4 h at rt, diluted with ethyl ether (1.0 mL) and filtered through a plug of Florisil and Celite (1:1 v/v). The plug was washed with ethyl ether (3.0 mL) and the combined filtrate was concentrated to a pale yellow oil. Purification by chromatography on SiO_2 (20 % ethyl acetate/ hexanes) gave **22** (14.5 mg, 89%) as a clear colorless oil that was a 4:1 (*Z*/*E*) mixture: R_f 0.40 (40% ethyl acetate / hexanes); ^{1}H NMR α 7.32-7.19 (m, 5 H), 6.82 (d, 1 H, *J* = 10.8 Hz), 5.89 (d, 1 H, *J* = 10.8 Hz), 4.51 (dddd, 1 H, *J* = 9.1, 9.1, 7.3, 5.1 Hz), 4.19 (app t, 1 H, *J* = 8.9 Hz), 4.00 (dd, 1 H, *J* = 8.3, 7.3 Hz), 3.21 (dd, 1 H, *J* = 13.7, 5.0 Hz), 2.79 (q, 2 H, *J* = 7.4 Hz), 2.66 (dd, 1 H, *J* = 13.7, 9.0 Hz), 1.36 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR α 163.4, 142.7, 138.4, 129.4, 128.7, 126.6, 110.6, 71.4, 68.0, 42.1, 29.8, 15.6; IR (neat) 3060, 3026, 2967, 2925, 1635, 1585, 1493, 1453, 1183 cm^{-1}; MS (EI) *m/z* (rel. intensity) 247 (M^+, 35), 218 ([M-C_2H_5]$^+$, 25), 156 ([M-C_7H_7]$^+$, 100), 128 (58), 91 (57); HRMS (EI) *m/z* calcd for $C_{14}H_{17}NOS$ 247.1031, found 247.1043; Characteristic signals for the (*E*)-isomer: ^{1}H NMR α 5.94 (d, 1 H, *J* = 15.5 Hz), 4.21 (t, 1 H, *J* = 8.5 Hz), 3.12 (dd, 1 H, *J* = 13.8, 5.4 Hz), 1.35 (t, 3 H, *J* = 7.4 Hz).



21 **23**

(4*S*)-4-Benzyl-2-(2-*tert*-butylsulfanylvinyl)-4,5-dihydrooxazole (23). To a solution of **21** (26.3 mg, 142 μmol, 1.0 equiv) in THF (1.0 mL) at rt was added *t*-butylmercaptane (80 μL, 710 μmol, 5.0 equiv) and anhydrous K_2CO_3 (22.0 mg, 159 μmol, 1.1 equiv). 18-Crown-6 (12.0 mg, 45 μmol, 0.3 equiv) was added and the mixture was stirred for 12 h at rt, diluted with ethyl ether (3.0 mL) and filtered through a plug of Florisil and Celite (1:1 v/v). The plug was washed with ethyl ether (3.0 mL) and the combined filtrate was concentrated to give a pale yellow oil.

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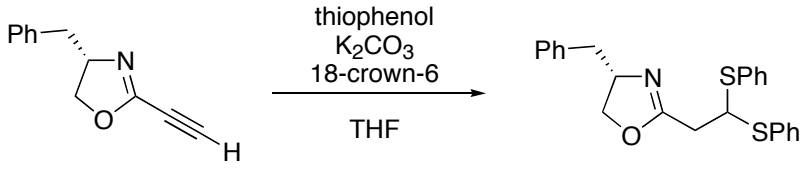
[1] Cevallos, A.; Rios, R.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymm.* **2000**, *11*, 4407.

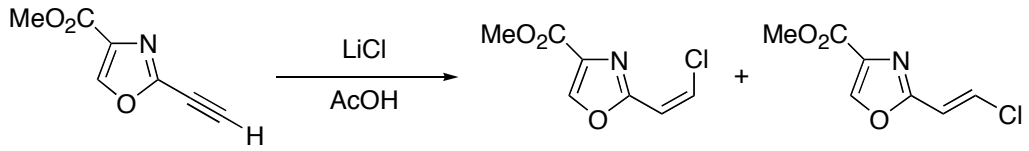
Purification by chromatography on SiO_2 (10% acetone/ hexanes) gave **23** (38.6 mg, 97%) as a clear colorless oil: R_f 0.27 (10 % acetone / hexanes, twofold developed); $[\alpha]_D$ +3.6 (c 1.34, $CHCl_3$, 22 °C); ^1H NMR α 7.31-7.18 (m, 5 H), 6.98 (d, 1 H, *J* = 11.2 Hz), 5.90 (d, 1 H, *J* = 11.2 Hz), 4.56-4.46 (m, 1 H), 4.17 (app t, 1 H, *J* = 8.8 Hz), 3.99 (app t, 1 H, *J* = 7.8 Hz), 3.22 (dd, 1 H, *J* = 13.6, 4.9 Hz), 2.64 (dd, 1 H, *J* = 13.6, 9.2 Hz), 1.42 (s, 9 H); ^{13}C NMR α 163.3, 138.7, 138.4, 129.4, 128.6, 126.5, 110.0, 71.4, 68.1, 44.4, 42.1, 30.9; IR (neat) 3083, 3060, 3026, 2961, 2940, 2926, 2898, 2864, 1950, 1875, 1803, 1637, 1582, 1378, 1366, 1184, 1167 cm^{-1}; MS (EI) *m/z* (rel. intensity) 218 ($[M\text{-}C_4H_9]^+$, 100), 184 ($[M\text{-}C_7H_7]^+$, 22), 128 (81), 117 (53), 100 (22), 91 (53), 57 (37); HRMS (EI) *m/z* calcd for $C_{12}H_{12}NOS$ ($M\text{-}C_4H_9$) 218.0640, found 218.0636.



21 **24**

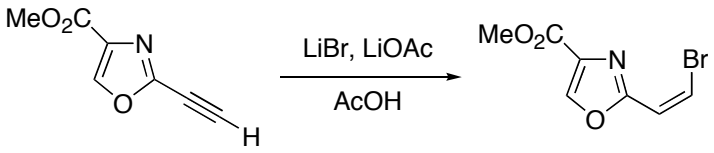
(4*S*)-4-Benzyl-2-(2,2-bisphenylsulfanylethyl)-4,5-dihydrooxazole (24). To a mixture of the oxazoline **21** (29.4 mg, 0.159 mmol, 1.0 equiv) and thiophenol (80 µL, 780 µmol, 4.9 equiv) in THF (1.0 mL) at rt was added anhydrous K_2CO_3 (24.0 mg, 174 µmol, 1.1 equiv) and 18-crown-6 (12.0 mg, 45 µmol, 0.3 equiv). After stirring for 12 h at rt, the mixture was diluted with ethyl ether (3.0 mL) and filtered through a plug of Forisil and Celite (1:1 v/v). The plug was washed with ethyl ether (3.0 mL) and the combined filtrate was concentrated. Purification of the residue by chromatography on SiO_2 (10% acetone / hexanes) gave **24** (53.1 mg, 82%) as a clear colorless oil: R_f 0.27 (10% acetone / hexanes, twofold developed); $[\alpha]_D$ –14.7 (c 1.31, $CHCl_3$, 22 °C); ^1H NMR α 7.54-7.50 (m, 4 H), 7.37-7.19 (m, 11 H), 4.80 (t, 1 H, *J* = 7.5 Hz), 4.43-4.33 (m, 1 H), 4.13 (app t, 1 H, *J* = 8.9 Hz), 3.94 (dd, 1 H, *J* = 8.4, 7.2 Hz), 3.11 (dd, 1 H, *J* = 13.7, 5.6 Hz), 2.81 (dd, 2 H, *J* = 7.6, 0.8 Hz), 2.65 (dd, 1 H, *J* = 13.7, 8.5 Hz); ^{13}C NMR α 164.4, 138.1, 133.6, 133.4, 133.2, 129.4, 129.1, 128.7, 128.3, 128.2, 126.6, 72.0, 67.6, 54.3, 41.9, 35.3; IR (neat) 3058, 3026, 3002, 2960, 2919, 2898, 1951, 1882, 1807, 1669, 1603, 1582 cm^{-1}; MS (EI) *m/z* (rel. intensity) 405 (M^+, 8), 296 ($[M\text{-}C_6H_5S]^+$, 67), 204 ($[M\text{-}C_7H_7\text{-}C_6H_5SH]^+$, 100), 190

(22), 105 (66), 91 (54), 77 (36), 65 (21); HRMS (EI) *m/z* calcd for $C_{24}H_{23}NOS_2$ 405.1221, found 405.1221.



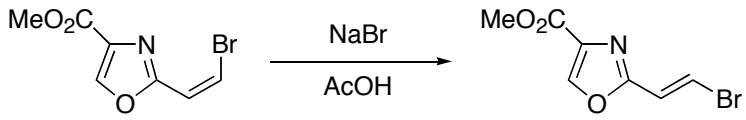
9 (*Z*)-**10g** (*E*)-**10g**

(*Z*)-2-(2-Chlorovinyl)oxazole-4-carboxylic acid methyl ester [(*Z*)-10g] and 2-(*E*)-(2-chlorovinyl)oxazole-4-carboxylic acid methyl ester [(*E*)-10g]. A mixture of **9** (25.0 mg, 165 μmol, 1.0 equiv) and lithium chloride (10.5 mg, 248 μmol, 1.5 equiv) in glacial acetic acid (0.75 mL) was heated under N_2 to 100 °C for 16 h, cooled to rt and diluted with water. The mixture was extracted with ethyl ether and the combined organic layers were washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with brine, dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the residue indicated a *Z*/*E* ratio of 1.3:1.0. The residue was purified by chromatography on SiO_2 (5 to 10% acetone/hexanes) to afford (*Z*)-**10g** (11.2 mg, 36%) and (*E*)-**10g** (8.0 mg, 26%) as white solids. (*Z*)-**10g**: R_f 0.40 (20% acetone/hexanes, twofold developed); Mp 86.3-87.0 °C (CH_2Cl_2); ^{1}H NMR α 8.27 (s, 1 H), 6.72, 6.67 (AB, 2 H, *J* = 8.4 Hz) 3.93 (s, 3 H); ^{13}C NMR α 161.6, 159.0, 143.9, 134.3, 127.0, 116.5, 52.5; IR (KBr) 3165, 3105, 3088, 3038, 2956, 2853, 1744, 1658, 1626, 1564, 1513, 1445 cm^{-1}; MS (EI) *m/z* (rel. intensity) 187 (M^+, 60), 156 ($[M\text{-}OCH_3]^+$, 33), 100 (100), 89 (34), 69 (39); HRMS (EI) *m/z* calcd for $C_7H_6NO_3Cl$ 187.0036, found 187.0036; (*E*)-**10g**: R_f 0.50 (20% acetone/hexanes, twofold developed); Mp 87.5-88.3 °C (CH_2Cl_2); ^{1}H NMR α 8.17 (s, 1 H), 7.28 (d, 1 H, *J* = 13.7 Hz), 6.74 (d, 1 H, *J* = 13.7 Hz), 3.92 (s, 3 H); ^{13}C NMR α 161.5, 159.2, 143.8, 134.5, 130.4, 119.4, 52.5; IR (KBr) 3152, 3113, 3086, 2961, 1731, 1716, 1619, 1573, 1556 cm^{-1}; MS (EI) *m/z* (rel. intensity) 187 (M^+, 63), 156 ($[M\text{-}OCH_3]^+$, 36), 100 (100); HRMS (EI) *m/z* calcd for $C_7H_6NO_3Cl$ 187.0036, found 187.0023.



9 (*Z*)-**10h**

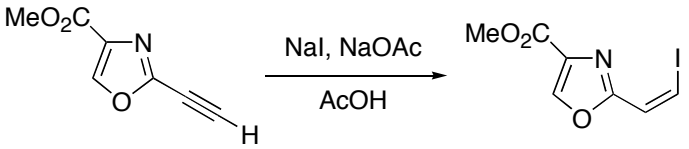
(*Z*)-2-(2-Bromovinyl)oxazole-4-carboxylic acid methyl ester [(*Z*)-10h] . A mixture of **9** (15.0 mg, 99 μmol, 1.0 equiv), lithium bromide (13.0 mg, 150 μmol, 1.5 equiv) and lithium acetate (29.5 mg, 447 mmol, 4.5 equiv) in glacial acetic acid (0.45 mL) was heated under N_2 to 100 °C for 16 h, cooled to rt and diluted with EtOAc (10 ml). The mixture was washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with saturated aqueous $Na_2S_2O_3$ (5 ml) and brine (5 ml) and then dried (Na_2SO_4), filtered and concentrated. ^{1}H NMR analysis of the residue indicated a *Z*/*E*/starting material ratio of 32:1.6:1.0. The residue was purified by chromatography on SiO_2 (5 to 10% acetone/hexanes) to afford (*Z*)-**10h** (19.9 mg, 87%) as a white solid: R_f 0.25 (10% acetone/hexanes, twofold developed); Mp 90.1-91.1 °C (CH_2Cl_2); ^{1}H NMR α 8.27 (s, 1 H), 7.14 (d, 1 H, J = 8.7 Hz), 6.89 (d, 1 H, J = 8.7 Hz), 3.90 (s, 3 H); ^{13}C NMR α 161.5, 159.5, 143.7, 134.3, 119.7, 115.4, 52.5; IR (KBr) 3157, 3100, 3083, 3026, 2939, 1744, 1648 cm^{-1}; MS (EI) *m/z* (rel. intensity) 233 (M^+, 54), 231 (M^+, 53), 202 ([M-OCH_3]$^+$, 20), 200 ([M-OCH_3]$^+$, 19), 174 ([M-$OCOCH_3$]$^+$, 7), 172 ([M-$OCOCH_3$]$^+$, 6), 146 (13), 144 (14), 135 (21), 133 (26), 100 (100), 69 (45), 64 (21), 59 (11); HRMS (EI) *m/z* calcd for $C_7H_6NO_3Br$ 230.9531, found 230.9513.



(*Z*)-**10h** (*E*)-**10h**

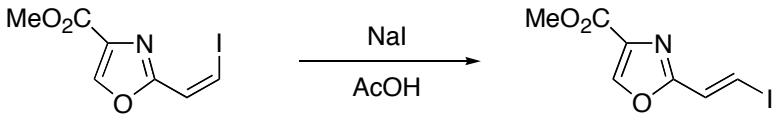
2-(*E*)-(2-bromovinyl)oxazole-4-carboxylic acid methyl ester [(*E*)-10h]. A mixture of **(*Z*)-10h** (20.0 mg, 86 μmol, 1.0 equiv) and sodium bromide (13.3 mg, 129 μmol, 1.5 equiv) in glacial acetic acid (0.37 mL) was heated under N_2 to 100 °C for 16 h, cooled to rt and diluted with EtOAc (10 mL). The mixture was washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with saturated aqueous $Na_2S_2O_3$ (5 ml) and brine (5 ml) and then dried (Na_2SO_4),

filtered and concentrated. ^{1}H NMR analysis of the residue indicated a *Z*/*E* ratio of 1.0:5.9. The residue was purified by chromatography on SiO_2 (5 % acetone/hexanes) affording (*E*)-**10h** (14.8 mg, 74%) as a white solid: R_f 0.34 (10% acetone/hexanes, twofold developed); Mp 118.2-119.2 °C (CH_2Cl_2); ^{1}H NMR α 8.18 (s, 1H), 7.48 (d, 1 H, *J* = 14.2 Hz), 7.02 (d, 1 H, *J* = 14.2 Hz), 3.93 (s, 3 H); ^{13}C NMR α 161.5, 159.9, 143.8, 134.5, 123.1, 118.8, 52.6; IR (KBr) 3152, 3113, 3084, 3012, 2960, 1728, 1710, 1608, 1572, 1556 cm^{-1}; MS (EI) *m/z* (rel. intensity) 233 (M^+, 8), 231 (M^+, 8), 202 ([M-OCH_3]$^+$, 10), 168 (100), 137 ([M-CH_3-Br]$^+$, 34), 110 (84), 109 (37), 67 (57); HRMS (EI) *m/z* calcd for $C_7H_6NO_3Br$ 230.9531, found 230.9531.



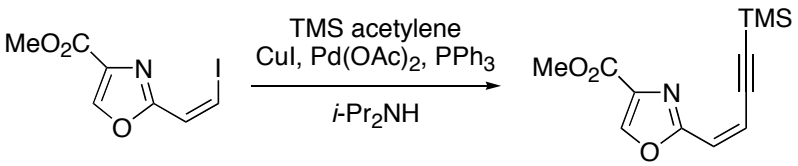
9 (*Z*)-**10i**

(*Z*)-2-(2-Iodovinyl)oxazole-4-carboxylic acid methyl ester [(*Z*)-10i]. A mixture of **9** (25.0 mg, 165 μmol, 1.0 equiv), sodium iodide (24.7 mg, 165 μmol, 1.0 equiv) and sodium acetate (40.7 mg, 496 μmol, 3.0 equiv) in glacial acetic acid (0.75 mL) was heated under N_2 to 100 °C for 12 h, then cooled to rt and diluted with ethyl acetate (10 mL). The organic layer was washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with saturated $Na_2S_2O_3$ (5.0 mL) and brine (5.0 mL). The combined aqueous washings were backwashed with ethyl acetate (3.0 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. ^{1}H NMR analysis of the residue indicated a *Z*/*E* ratio of > 50:1. Purification by chromatography on SiO_2 (5% to 10% acetone / hexanes) (*Z*)-**10i** (42.2 mg, 92%) as a white solid: R_f 0.23 (10% acetone/hexanes, twofold developed); Mp 88.2-89.2 °C (CH_2Cl_2); ^{1}H NMR α 8.30 (s, 1 H), 7.54 (d, 1 H, *J* = 9.5 Hz), 7.24 (d, 1 H, *J* = 9.5 Hz), 3.93 (s, 3 H); ^{13}C NMR α 161.2, 160.2, 143.5, 134.3, 125.9, 87.1, 52.5; IR (KBr) 3161, 3121, 3061, 3008, 2956, 2911, 2845, 1741, 1719, 1629, 1575 cm^{-1}; MS (EI) *m/z* (rel. intensity) 279 (M^+, 100), 248 ([M-OCH_3]$^+$, 14), 220 ([M-$OCOCH_3$]$^+$, 4), 192 (10), 181 (24), 100 (37); HRMS (EI) *m/z* calcd for $C_7H_6NO_3I$ 278.9392, found 278.9392.



(*Z*)-**10i** (*E*)-**10i**

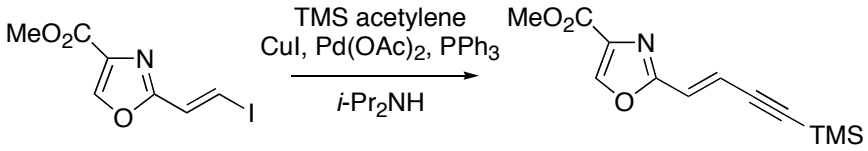
2-(2-(*E*)-iodovinyl)oxazole-4-carboxylic acid methyl ester [(*E*)-10i]. A mixture of (*Z*)-**10i** (41.2 mg, 148 μmol, 1.0 equiv) and sodium iodide (66.6 mg, 444 μmol, 3.0 equiv) in glacial acetic acid (0.75 mL) was heated under N_2 to 100 °C for 12 h, then cooled to rt and diluted with ethyl acetate (10 mL). The organic layer was washed with 2.0 M aqueous NaOH until the washings had a pH>9, washed with saturated $Na_2S_2O_3$ (5.0 mL) and brine (5.0 mL). The combined aqueous washings were backwashed with ethyl acetate (3.0 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. ^{1}H NMR analysis of the residue indicated an *E*/*Z* ratio of 7.8:1.0. Purification by chromatography on SiO_2 (5% acetone / hexanes) afforded (*Z*)-**10i** (2.6 mg, 6%) and (*E*)-**10i** (35.3 mg, 86%) as white solids. (*E*)-**10i**: R_f 0.30 (10% acetone/hexanes, twofold developed); Mp 141.1-142.1 °C (CH_2Cl_2); ^{1}H NMR α 8.18 (s, 1 H), 7.68 (d, 1 H, *J* = 15.2 Hz), 7.33 (d, 1 H, *J* = 15.2 Hz), 3.92 (s, 3 H); ^{13}C NMR α 161.5, 160.9, 143.9, 134.3, 130.3, 89.9, 52.5; IR (KBr) 3149, 3108, 3069, 3007, 2955, 1724, 1705, 1570, 1552 cm^{-1}; MS (EI) *m/z* (rel. intensity) 279 (M^+, 100), 248 ([M-OCH_3]$^+$, 20), 220 ([M-$OCOCH_3$]$^+$, 6), 207 (21), 181 (24), 137 ([M-CH_3I]$^+$, 48), 136 (66), 135 (74), 121 ([M-OCH_3-I]$^+$, 22); HRMS (EI) *m/z* calcd for $C_7H_6NO_3I$ 278.9392, found 278.9393.



(*Z*)-**10i** (*Z*)-**25**

(*Z*)-2-[4-(Trimethylsilanyl)but-1-en-3-ynyl]oxazole-4-carboxylic acid methyl ester [(*Z*)-25]. A mixture of (*Z*)-**10i** (20.0 mg, 72 μmol, 1.0 equiv), CuI (4.0 mg, 22 μmol, 0.3 equiv), $Pd(OAc)_2$ (2.0 mg, 8 μmol, 0.1 equiv) and PPh_3 (8.0 mg, 30 μmol, 0.4 equiv) was dissolved in *i*-Pr_2NH (0.5 mL) and cooled to 0 °C under N_2. Trimethylsilylacetylene (16.0 μL, 0.11 mmol, 1.6 equiv) was added. The reaction mixture was allowed to warm to room temperature and after 30

min, ethyl ether (2.0 mL) and water (2.0 mL) were added. The mixture was poured into water (5.0 mL) and extracted with ethyl ether. The combined organic layers were washed with 1.0 M aqueous citric acid (5.0 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated. Purification of the residue by chromatography on SiO_2 (10% acetone / hexanes) gave (*Z*)-**25** (19.1 mg, 89%) as a white crystalline solid: R_f 0.21 (20% ethyl ether / hexanes); Mp 51.2-51.9 °C (CH_2Cl_2); ^{1}H NMR α 8.23 (s, 1 H), 6.63, 6.06 (AB, 2 H, J = 12.0 Hz), 3.93 (s, 3 H), 9.08 (s, 9 H); ^{13}C NMR α 161.7, 160.8, 143.6, 134.5, 124.0, 116.2, 106.9, 101.4, 52.5, -0.2; IR (KBr) 3178, 3040, 2959, 2900, 2142, 1721, 1616, 1577, 1322 cm^{-1}; MS (EI) *m/z* (rel. intensity) 249 (M^+, 27), 234 ([M-CH_3]$^+$, 56), 204 ([M-C_3H_9]$^+$, 67), 190 ([M-O_2CCH_3]$^+$, 100); HRMS (EI) *m/z* calcd for $C_{12}H_{15}NO_3Si$ 249.0821, found 249.0812.



(*E*)-**10i** (*E*)-**25**

(*E*)-2-[4-(Trimethylsilanyl)but-1-en-3-ynyl]oxazole-4-carboxylic acid methyl ester [(*E*)-25]. A mixture of (*E*)-**10i** (10.0 mg, 36 μmol, 1.0 equiv), CuI (2.0 mg, 11 μmol, 0.3 equiv), $Pd(OAc)_2$ (1.0 mg, 4 μmol, 0.1 equiv) and PPh_3 (4.0 mg, 15 μmol, 0.4 equiv) was dissolved in *i*-Pr_2NH (0.5 mL) and cooled to 0 °C under N_2. Trimethylsilylacetylene (10.0 μL, 70 μmol, 2.0 equiv) was added. The mixture was allowed to warm to rt and after 30 min, ethyl ether (2.0 mL) and water (2.0 mL) were added. The mixture was poured into water (5.0 mL) and extracted with ethyl ether. The combined organic layers were washed with 1.0 M aqueous citric acid (5.0 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated. Purification of the residue by chromatography on SiO_2 (10% to 20% ethyl ether / hexanes) gave (*E*)-**25** (8.1 mg, 90%) as a white crystalline solid: R_f 0.25 (20% ethyl ether / hexanes); Mp 109.1-109.9 °C (CH_2Cl_2); ^{1}H NMR α 8.17 (s, 1 H), 6.75, 6.66 (AB, 2 H, J = 16.3 Hz), 3.92 (s, 3 H), 0.22 (s, 9 H); ^{13}C NMR α 161.6, 161.0, 144.0, 134.9, 125.8, 118.4, 104.0, 102.0, 52.5, -0.1; IR (KBr) 3156, 3110, 3055, 2957, 2177, 2127, 1713, 1567, 1309, 1253 cm^{-1}; MS (EI) *m/z* (rel. intensity) 249 (M^+, 50), 234

([M-CH_3]$^+$, 100), 218 ([M-CH_3O]$^+$, 17), 190 ([M-O_2CCH_3]$^+$, 27), 204 ([M-C_3H_9]$^+$, 20); HRMS (EI) *m/z* calcd for $C_{12}H_{15}NO_3Si$ 249.0821, found 249.0822.