Supplementary Material

A Concise Synthesis of Turneforcidine via a Metalloiminium Ion Cyclization Terminated by the 2-(Thiomethyl)-3-trimethylsilyl-1-propenyl Moiety.

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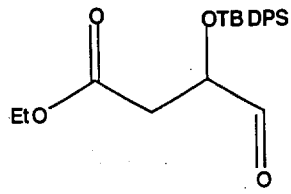
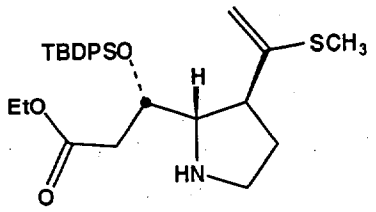
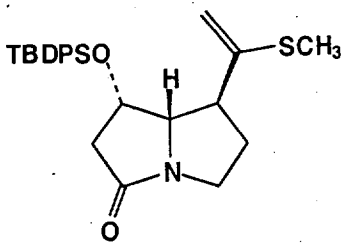


Ethyl 3-(tert-butyldiphenylsilyl)-4-oxobutyrate (3). A 100 mL flame dried round-bottomed flask containing a Teflon coated magnetic stirring bar was charged with 3-(tert-butyldiphenylsilyl)pent-4-eneoic acid ethyl ester (2 g, 5.20 mmol) and CH_2Cl_2 (50 mL). The solution was cooled to –78 °C and slow stream of ozone was bubbled through the reaction mixture until a blue color persisted. The ozone stream was replaced with a stream of N_2 to remove excess ozone from the reaction mixture. The reaction mixture was treated with dimethyldisulfide (1.63 g, 2.60 mmol) and allowed to warm to ambient temperature over a 6 h period and stirred an additional 6 h . The reaction mixture was concentrated under vacuum to give a slightly yellow oil. The crude material was purified by bulb to bulb distillation (110°C @ .25 mmHg) to give a the title compound as a clear, colorless oil (1.81g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (app., s, 1H, -C*H*(O)), 7.63 (m, 4H, Ar*H*), 7.42 (m, 6H, Ar*H*), 4.26 (app. t, 1H, J = 5.3 Hz, -C*H*OSi), 4.10 (q, 2H, J = 7.1Hz, -OCH_2CH$_3$), 2.68 (m, 2H, -C(O)C*H*H-), 1.22 (t, 3H, J = 7.1 Hz, -CH$_2$CH_3), 1.07 (s, 9H, -SiC(CH$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 169.9, 136.2, 130.6, 128.6, 128.4, 128.3, 61.4, 39.6, 27.2, 19.7, 14.6. IR (film): 3070, 3034, 2932, 2858, 1738, 1478, 1428, 1374, 1264, 1188, 1112, 1035, 960, 822, 741 cm^{-1}.

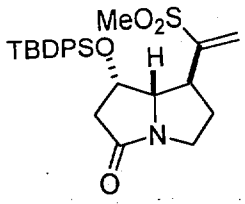


Pyrrolidine (11). A 25 mL flame dried round-bottomed flask containing a Teflon coated magnetic stirring bar and a rubber septum was charged with 4-(methylthio)-5-(trimethylsilyl)pent-3-enylamine (**4**) (203.4 mg, 1.00 mmol), 4Å molecular sieves and CH_2Cl_2 (2 mL). Ethyl-3-(*t*-butyldiphenylsilyloxy)-4-oxobutyrate (**3**) (384.5 mg, 1.00 mmol) was added to the reaction mixture and stirred for 12 h at ambient temperature. The reaction mixture was diluted with hexane and filtered through a plug of celite. The filtrate was concentrated and the residue was dissolved in CH_2Cl_2 (10 mL). The solution was cooled to –78 °C and treated dropwise over a 2 min period with $TiCl_4$ (3.45 mL of mL 0.32 M in toluene, 1.00 mmol) via syringe. The resulting deep orange solution was stirred 3 h at –78 °C followed by an additional 12 h at –20 °C. The reaction mixture was transferred **dropwise** via cannula into a vigorously stirred, saturated aqueous solution of $KHCO_3$ cooled to 0 °C. The biphasic mixture was stirred for 30 min at ambient temperature. The organic phase was removed and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were then dried with Na_2SO_4, filtered and concentrated to give a thick oil which was subjected to flash chromatography (20% ethyl acetate/hexane followed by 100% ethyl acetate for elution) to give the title compound as a colorless oil (298.0 mg, 60%). ^{1}H NMR (300 MHz, C_6D_6): δ 7.94 (m, 2H, Ar*H*), 7.91 (m, 2H, Ar*H*), 7.26 (m, 6H, Ar*H*), 4.90 (app. s, 1H, -C(CH_3S)=C*H*H), 4.58 (m, 1H, -C*H*OSi), 4.40 (app. s, 1H, -C(CH_3S)=CH*H*), 3.85 (q, 2H, J = 7.1 Hz, -

OCH_2CH_3), 3.49 (m, 1H, -C*H*N), 2.83-2.71 (m, 5H, -C*H*C=CH_2, -NC$H_2$$CH_2$-, -C(O)C$H_2$CH-), 1.90 (m, 2H, -NCHC$H_2$-), 1.85 (s, 3H, -SC$H_3$), 1.72 (bs, 1H, -NH), 1.21 (s, 9H, -SiC(CH_3)$_3$), 0.96 (t, 3H, J = 7.1 Hz, -OCH_2CH_3). ^{13}C NMR (75 MHz, C_6D_6): δ 172.1, 150.6, 136.5, 134.9, 134.6, 129.9, 129.8, 128.4, 128.1, 127.9, 103.6, 72.2, 68.0, 60.3, 49.6, 47.0, 40.7, 35.4, 27.5, 20.0, 14.3. IR (film): 3452, 3366, 3078, 3061, 2449, 2940, 2839, 1733, 1694, 1593, 1469, 1430, 1377, 1305, 1181, 1157, 1106, 1080, 1003, 921, 849, 821, 739, 719 cm^{-1}. HRMS (M - C_2H_5OH): 451.1998 (calculated for $C_{26}H_{33}NO_2SSi$, 451.2001), ppm error = 0.6



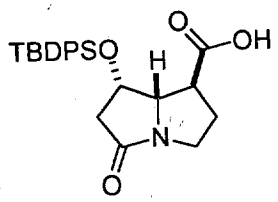
Pyrrolizidone (6). A 25 mL flame dried round-bottomed flask containing a Teflon coated magnetic stirring bar and a rubber septum was charged with pyrrolidine **11** (123 mg, 0.247 mmol) and CH_2Cl_2 (10 mL). The reaction mixture was cooled to 0 °C and treated with trimethylaluminium (0.124 mL of 2 M in hexanes, 0.247 mmol). The solution was stirred for 2 h at 0 °C and transferred by cannula into a vigorously stirred solution of saturated aqueous solution of $KHCO_3$ at 0 °C. The biphasic mixture was stirred for 30 min at ambient temperature and transferred into a separatory funnel. The organic phase was removed and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered and concentrated to give the title compound as a thick oil (110 mg, 99%). ^{1}H NMR (300 MHz, C_6D_6): δ 7.75 (m, 4H, Ar*H*), 7.28 (m, 6H, Ar*H*), 4.97 (app. s, 1H, -C(CH_3S)=C*H*H), 4.50 (app. s, 1H, -C(CH_3S)=CH*H*), 4.30 (app. t, 1H, -C*H*OSi*t*-BuPh_2), 3.81 (dd, 1H, J = 3.9, 8.1 Hz, -NC*H*CHO-), 3.65 (m, 1H, -NC*H*HCH_2-), 3.47 (m, 1H, -C*H*C=CH_2), 3.03 (m, 1H, -NCH*H*CH_2-), 2.24 (m, 1H –NC(O)CH*H*CH-), 2.16 (m, 2H –NCH_2C*H*H-, -NC(O)*CH*HCH-), 1.94 (m, 1H –NCH_2CH*H*-), 1.92 (s, 3H, -S*C*H_3), 1.21 (s, 9H, -C(CH_3)$_3$). ^{13}C NMR (75 MHz, C_6D_6): δ 171.8, 156.6, 136.1, 133.8, 130.1, 129.9, 103.3, 70.4, 69.7, 44.6, 43.5, 41.5, 34.7, 29.9, 27.0, 19.3, 14.0. IR (film): 2916, 1702, 1600, 1560, 1426, 1407, 1111, 1084, 1050, 927, 701, 517 cm^{-1}. HRMS (M^+): 451.1992 (calculated for $C_{26}H_{33}NO_2SSi$, 451.2001), ppm error = 2.2.



2-(2'-Methylsulfonylethylene)-5-aza-8-*t*-butyldiphenylsilyloxybicyclo [3.3.0]octane-6-one.

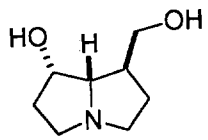
Pyrrolizidone (**6**) (117 mg, 0.26 mmol) was dissolved in methanol (10 mL) and the resulting solution was cooled to 0 °C whereupon a solution of OXONE[1] (369 mg, 0.6 mmol) in water (5 mL) was added. The reaction mixture was stirred for 5 h at room temperature, diluted with water, and extracted with chloroform (3 x 10 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Et_2O for elution) to give 116 mg (92%) of a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.58 (m, 4H, Ar*H*), 7.39 (m, 6H, Ar*H*), 6.27 (app. s, 1H, -C(SO_2CH_3)=C*H*H), 5.73 (app. s, 1H, -C(SO_2CH_3)=CH*H*), 4.58 (app. t, 1H, J = 4.1 Hz, -C*H*OSi-*t*-BuPh_2), 4.05 (app. dd, 1H, J = 3.9, 6.3 Hz, -NC*H*CHO-), 3.83 (m, 1H, -NC*H*HCH_2-), 3.60 (app. q, 1H, J = 6.9 Hz, -C*H*C=CH_2-), 3.15 (m, 1H, -NCH*H*CH_2-), 2.78 (s, 3H, SO_2CH_3), 2.53 (m, 2H, -COCH_2CH-), 2.13 (m, 2H, -NCH_2CH_2CH-), 1.05 (s, 9H, *t-Bu*SiPh_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 151.9, 135.8, 135.7, 132.8, 132.5, 130.2, 130.1, 127.9, 123.7, 70.8, 70.4, 44.4, 41.7, 41.6, 37.1, 33.9, 27.0, 19.2. IR (KBr): 3445, 3134, 2958, 1863, 1429, 1300, 1120, 1082, 1054, 706 cm^{-1}. HRMS (EI^+) *m/z* 484.1967 (calculated for $C_{26}H_{33}NO_4SSi$, 484.1978).

(1) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287-1290.



5-Aza-8-(*t*-butyldiphenylsilyloxy)bicyclo[3.3.0]octane-6-one-2-carboxylic acid (12).

To the vinyl sulfone (114 mg, 0.24 mmol) in CCl_4 (0.8 mL), CH_3CN (0.8 mL), and water (1.2 mL) was added $NaIO_4$ (171 mg, 0.8 mmol) and a catalytic amount (e.g., 2 mg) of $RuCl_3$. The resulting black slurry was stirred for 12 h at room temperature, added to brine, and extracted with chloroform (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Et_2O for elution) to give 89 mg (88%) of **12** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (m, 4H, Ar*H*), 7.37 (m, 6H, Ar*H*), 4.57 (app. t, 1H, J = 4.2 Hz, -C*H*OSi*t*-BuPh$_2$), 4.22 (dd, 1H, J = 4.2, 7.2 Hz -NC*H*CHO-), 3.75 (app. dd, 1H, J = 7.2, 11.1 Hz, -NC*H*HCH$_2$-), 3.47 (app. q, 1H, J = 8.0 Hz, -C*H*CO$_2$H), 3.16 (m, 1H, -NCH*H*CH$_2$-), 2.55-2.14 (m, 4H, -COC*H*$_2$CH- and -NCH$_2$C*H*$_2$CH-), 1.05 (s, 9H, *t-Bu*SiPh$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.2, 173.5, 135.7, 133.0, 132.4, 130.1, 130.0, 127.9, 69.4, 68.9, 44.4, 41.5, 41.0, 31.0, 26.9, 19.2. IR (KBr): 3440, 3125, 2930, 2858, 1726, 1645, 1427, 1400, 1199, 1111, 1092, 705 cm^{-1}. HRMS (EI$^+$) *m/z* 424.1946 (calculated for $C_{24}H_{29}NO_4Si$, 424.1944).



***dl*-Turneforcidine (1).**

Carboxylic acid **12** (88 mg, 0.21 mmol) was dissolved in THF (5 mL) and lithium aluminum hydride (74 mg, 1.95 mmol) was slowly added at room temperature. The resulting mixture was then heated at reflux with stirring for 12 h, after which time THF (5 mL) was added. The stirred mixture was cooled with an ice bath and quenched by the addition of water (0.8 mL), 1 N NaOH (0.8 mL), and water (0.8 mL). The heterogeneous mixture was stirred for an additional 15 min, and then filtered through a pad of Celite. The filter cake was washed with THF (2 mL) and methanol (2 mL). The combined organic phases were concentrated in vacuo, and the residue was purified by column chromatography on silica gel ($CHCl_3$: MeOH : NH_4OH = 5:5:1 for elution) to give 21 mg (65%) of *d,l*-turneforcidine (1) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.79 (app. s, 2H, O*H*), 4.30 (app. dd, 1H, *J* = 5.1, 7.5 Hz, OC*H*), 3.76 (dd, 1H, *J* = 4.8, 10.2 Hz, OCH_2), 3.37 (m, 2H, OCH_2 and N*H*), 3.20 (m, 1H, NCH_2), 3.00 (m, 1H, NCH_2), 2.72-2.42 (m, 3H, NCH_2 and C*H*), 2.07-1.86 (m, 3H, CH_2), 1.59 (m, 1H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.2, 71.2, 64.9, 55.0, 52.1, 40.2, 35.3, 30.8. Spectral properties of synthetic *dl*-turneforcidine were identical with those of authentic *dl*-turneforcidine in all respects.[2,3]

(2) Niwa, H.; Kuroda, A.; Sakata, T.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2541-2543.
(3) Knight, D.; Share, A. C.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. I*, **1997**, 2089-2097.