TREMORGENIC INDOLE ALKALOIDS. STUDIES DIRECTED TOWARDS THE ASSEMBLY OF THE A, F AND I RINGS OF PENITREM D: OBSERVATION OF AN UNEXPECTED STEREOCHEMICAL OUTCOME

SUPPORTING INFORMATION

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Compound (+)-15. Yellow oil; $[\alpha]_D^{20}$ +2° (c 0.06, $CHCl_3$); IR (neat) 3500 (br), 2920 (s), 1720 (m), 1460 (m), 1370 (m), 1240 (m), 1155 (m), 1100 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.17 (s, 1H), 5.49 (m, 1H), 5.36 (d, J = 5.4 Hz, 1H), 5.11 (m, 1H), 5.05 (brs, 1H), 4.93 (brs, 1H), 4.02 (brd, J = 6.9 Hz, 1H), 3.74 (brt, J = 7.7 Hz, 1H), 3.59 (s, 3H), 3.36 (m, 2H), 3.10 (dd, J = 15.5, 4.9 Hz, 1H), 3.06 (brd, J = 17.2 Hz, 1H), 2.95 (m, 1H), 2.84 (dd, J = 13.9, 9.3 Hz, 1H), 2.61 (dd, J = 13.9, 9.1 Hz, 1H), 2.57 (m, 1H), 2.41 (dd, J = 13.9, 5.9 Hz, 1H), 2.31-2.23 (m, 2H), 2.18-2.00 (m, 6H), 2.13 (s, 3H), 1.93-1.69 (m, 4H), 1.71 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 1.19 (s, 9H), 1.18 (s, 3H), 1.17 (s, 3H), 1.00 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 171.3, 149.7, 144.4, 143.7, 132.6, 131.6, 130.4, 127.5, 126.9, 123.1, 111.4, 107.4, 91.4, 88.2, 74.8, 72.8, 72.7, 71.8, 65.5, 58.2, 53.6, 50.7, 48.2, 42.8, 40.1, 39.0, 34.3, 30.0, 29.8, 29.7, 29.4, 28.8, 27.7, 27.3, 25.9, 25.6, 25.5, 22.3, 22.1, 21.8, 21.5, 19.5, 18.0, 12.0; high resolution mass spectrum (ESI) m/z 902.5966 $[(M+H)^+$; calcd for $C_{54}H_{84}NO_8Si$: 902.5966].

Indole (-)-18. Colorless solid: mp 208-209 °C; $[\alpha]_D^{25}$ +67.1° (c 1.60, $CHCl_3$); IR ($CHCl_3$) 3460 (br, m), 2900 (br, s), 1460 (m), 1440 (w), 1400 (w), 1380 (w), 1360 (m), 1330 (w), 1250 (br, m), 1130 (w), 1100 (s), 1040 (s), 1020 (m), 1005 (m), 900 (w), 840 (br, m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (brs, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.44 (s, 1H), 5.42 (d, J = 2.0 Hz, 1H), 4.72 (ABq, J = 10.7, 7.2 Hz, 2H), 3.80 (app t, J = 7.6 Hz, 1H), 3.56 (app d, J = 11.3, 2H), 3.48 (s, 2H), 3.45 (app d, J = 3.6 Hz, 1H), 3.39 (s, 3H), 3.28 (dd, J = 10.3, 7.6 Hz, 1H), 3.24-3.17 (m, 2H), 3.09 (dd, J = 15.3, 4.7, 1H), 2.81 (dd, J = 15.3, 3.6 Hz, 1H), 2.65 (dd, J = 14.8, 2.5 Hz, 1H), 2.54-2.44 (m, 2H), 2.35 (app d, J = 2.2 Hz, 1H), 2.34-2.27 (m, 1H), 2.22-2.16 (m, 2H), 1.253 (s, 3H), 1.250 (s, 3H), 1.22 (s, 3H), 1.16-1.13 (m, 1H), 1.05 (s, 3H), 1.02 (s, 3H), 0.90 (s, 3H), 0.85 (s, 9H), -0.076 (s, 3H), -0.078 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 138.3, 134.3, 131.1, 126.2, 123.4, 121.0, 107.9, 101.7, 98.0, 91.1, 70.2, 70.0, 66.2, 65.2, 60.4, 55.0, 52.5, 43.6, 42.4, 40.4, 39.9, 39.5, 33.9, 30.2, 30.1, 29.1, 28.3, 27.4, 26.9, 25.9, 25.1, 24.0, 23.4, 22.8, 22.7, 22.6, 18.3, 15.7, 14.2, -5.35, -5.39; high resolution mass spectrum (CI, NH_3) m/z 736.4896 $[(M+H)^+$; calcd for $C_{44}H_{70}NO_6Si$: 736.4971].

Ketone (+)-19. Yellow oil; $[\alpha]_D^{25}$ +1.7° (c 0.90, $CHCl_3$); IR ($CHCl_3$) 2940, 1660, 1420, 1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.22 (s, 1H), 5.92 (d, J = 8.2 Hz, 1H), 5.42 (d, J = 5.4 Hz, 1H), 3.75 (app t, J = 7.8 Hz, 1H), 3.60 (s, 3H), 3.34 (m, 2H), 3.10 (dd, J = 15.4, 4.8 Hz, 1H), 3.00 (ddd, J = 13.2, 5.4, 3.3 Hz, 1H), 2.86 (dd, J = 15.4, 4.6 Hz, 1H), 2.54 (m, 6H), 2.28 (dd, J = 16.8, 7.2 Hz, 1H), 2.06 (m, 4H), 1.89 (m, 2H), 1.43 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 1.00 (m, 22H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 168.1, 148.4, 132.5, 131.8, 130.3, 127.8, 127.0, 123.4, 107.4, 91.7, 87.9, 71.8, 65.4, 58.3, 53.5, 50.6, 47.2, 43.1, 40.0, 34.1, 33.9, 32.2, 30.0, 29.9, 29.3, 27.9, 25.6, 25.5, 22.6, 20.7, 18.9, 18.0, 12.0; high resolution mass spectrum (ESI) m/z 660.4429 $[(M+H)^+$; calcd for $C_{41}H_{62}NO_4Si$: 660.4448].

Octacyclic Ketone (-)-20. To a solution of ketone (+)-**19** (15 mg, 23 μmol) in benzene (1 mL) was added a solution of (+)-camphorsulfonic acid (CSA) (5.3 mg, 23 μmol) in benzene (1 mL) at 0°C and stirred at r.t. for 5 h. The reaction was quenched by addition to excess of i-Pr_2NEt. The mixture was partitioned between EtOAc and saturated aqueous solution of $NaHCO_3$, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexenes/acetone, 3:1, 2:1) to afford 2.3 mg (16% yield, 25% yield based on the recovery) of (-)-**20** as a colorless solid. (-)-**20** was recrystalized from hexanes and small amount of EtOAc; mp 235 °C (dec.); $[\alpha]_D^{20}$ -24.5° (c 0.52, $CHCl_3$); IR ($CHCl_3$) 3360 (s), 2960 (s), 2860 (m), 1660 (s), 1440 (m), 1240 (w), 1120 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (brs, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 5.93 (d, J = 1.5 Hz, 1H), 4.75 (d, J = 7.4 Hz, 1H), 3.82 (dd, J = 9.8, 4.3 Hz, 1H), 3.68 (dd, J = 9.8, 6.6 Hz, 2H), 2.86 (m, 1H), 2.82 (dd, J = 15.4, 3.0 Hz, 1H), 2.70-2.53 (m, 4H), 2.49-2.44 (m, 3H), 2.26 (m, 1H), 2.07 (m, 1H), 2.00-1.89 (m, 5H), 1.48 (s, 3H), 1.41 (s, 3H), 1.14 (s, 3H), 1.08 (m, 21H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 168.9, 147.0, 138.2, 129.5, 129.1, 127.5, 122.5, 122.1, 121.1, 108.6, 75.5, 71.5, 66.3, 56.4, 50.8, 48.2, 43.8, 43.0, 35.9, 33.9, 33.4, 32.0, 31.5, 31.0, 28.3, 27.5, 21.8, 21.1, 20.0, 18.5, 18.1, 12.0; high resolution mass spectrum (ESI) m/z 628.4201 $[(M+H)^+$; calcd for $C_{40}H_{58}NO_3Si$: 628.4186].

Epoxide (-)-21. Pale yellow oil; $[\alpha]_D^{20}$ -165° (c 0.65, $CHCl_3$); IR (neat) 2980 (s), 2900 (s), 1425 (w), 1045 (m), 900 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.02 (m, 1H), 4.76 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 3.88 (d, J = 6.1 Hz, 1H), 3.07 (ddd, J = 6.1, 4.2, 2.7 Hz, 1H), 2.75 (dd, J = 5.0, 4.2 Hz, 1H), 2.59 (dd, J = 5.0, 2.7 Hz, 2H), 2.14 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 114.9, 80.1, 72.4, 53.5, 43.8, 18.6, 13.6; high resolution mass spectrum (CI, CH_4) m/z 175.0791 [$(M+H)^+$; calcd for $C_8H_{15}O_2S$: 175.0793].

Hydrazone (+)-22. Yellow oil; $[\alpha]_D^{20}$ +37° (c 0.45, $CHCl_3$); IR (neat) 3460 (br), 2900 (s), 1725 (m), 1670, (m), 1430 (m), 1370 (m), 1330 (m), 1280 (m), 1150 (s), 1100 (s) 920 (m), 880 (m), 680 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.17 (s, 1H), 5.45 (ddd, J = 10.1, 5.3, 3.0, 1H), 5.38 (d, J = 5.4 Hz, 1H), 5.06 (brs, 1H), 5.03 (brs, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.49 (d, J = 11.4 Hz, 1H), 4.20 (d, J = 5.3 Hz, 1H), 3.73 (brt, J = 7.8 Hz, 1H), 3.59 (s, 3H), 3.37 (m, 2H), 3.20 (m, 1H), 3.09 (dd, J = 15.5 and 4.8 Hz, 1H), 3.06 (dd, J = 13.1 and 10.1 Hz, 1H), 3.00-2.93 (m, 2H), 2.84 (dd, J = 15.5, 4.8 Hz, 1H), 2.65 (brd, J = 13.8, 1H), 2.57 (m, 1H), 2.52 (s, 6H), 2.33 (m, 1H), 2.29 (dd, J = 16.7, 7.8 Hz, 1H), 2.23 (d, J = 9.6 Hz, 1H), 2.20 (s, 3H), 2.13-2.04 (m, 2H), 1.97-1.79 (m, 4H), 1.79 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 1.17 (s, 3H), 1.16 (s, 9H), 1.11 (s, 3H), 1.01 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 163.0, 149.8, 148.3, 140.8, 132.4, 131.5, 130.4, 129.8, 126.8, 123.0, 115.1, 107.4, 91.5, 88.1, 82.1, 73.1, 72.5, 71.7, 65.5, 58.2, 53.6, 50.2, 47.54, 47.45, 42.8, 40.1, 38.8, 34.3, 30.0, 29.6, 29.5, 29.3, 27.7, 27.6, 26.5, 25.9, 25.6, 22.8, 22.3, 20.8, 20.2, 18.9, 18.0, 14.6, 12.0; high resolution mass spectrum (ESI) m/z 960.6313 [$(M+H)^+$; calcd for $C_{56}H_{90}N_3O_6SiS$: 902.5966].

Nonacyclic Pivaloate Ester (-)-23. Yellow oil; $[\alpha]_D^{20}$ -19° (c 0.04, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 7.20 (d, J = 6.6 Hz, 1H), 7.08 (d, J = 6.6 Hz, 1H), 7.02 (brs, 1H), 5.55 (brs, 1H), 5.42 (dt, J = 5.6, 2.9 Hz, 1H), 5.10 (brs, 1H), 4.87 (d, J = 7.5 Hz, 1H), 4.38 (m, 1H), 4.20 (brs, 1H), 3.85 (dd, J = 9.8 and 4.1 Hz, 1H), 3.72 (dd, J = 9.8, 6.1 Hz, 1H), 3.67 (t, J = 9.5 Hz, 1H), 3.15-3.08 (m, 2H), 2.82-2.74 (m, 2H), 2.60 (dd, J = 15.8, 6.1 Hz, 1H), 2.50 (brd, J = 12.0 Hz, 1H), 2.38 (brd, J = 15.8, 1H), 2.30-1.70 (m, 10H), 1.74

(s, 3H), 1.44 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.21 (s, 9H), 1.05 (s, 3H), 1.05 (m, 1H), 1.04 (s, 3H); high resolution mass spectrum (ESI) m/z 810.5497 [$(M+H)^+$; calcd for $C_{51}H_{76}NO_5Si$: 810.5493].

Compound (+)-24. To a solution of **12** (27 mg, 74 μmol) in benzene (4 mL) was added (+)-CSA (8.5 mg, 37 μmol) and stirred at r.t. for 18 h. The reaction mixture was partitioned between EtOAc and saturated aqueous solution of $NaHCO_3$, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexenes/acetone, 7:1) to afford pyrans (+)-**24** and its cis isomer (2:1,13.9 mg, 61% yield). The mixture was separable via flash chromatography (hexanes/EtOAc, 10:1).

(+)-**24.** Colorless oil; $[\alpha]_D^{20}$ +58° (c 0.96, $CHCl_3$); IR (neat) 2910 (s), 1440 (s), 1370 (w), 1210, (w), 1140 (w), 1110 (m), 1040 (m), 920 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (brs, 1H), 4.89 (brm, 1H), 4.69 (d, J = 7.0 , 1H), 4.60 (d, J = 7.0, 1H), 4.21 (m, 1H), 4.15 (m, 1H), 4.06 (dd, J = 9.5, 4.4 Hz, 1H), 3.33 (s, 3H), 2.60 (dd, J = 15.3, 5.4 Hz, 1H), 2.52 (dd, J = 15.3, 4.4 Hz, 1H), 2.39 (brd, J = 13.5 Hz, 1H), 1.91 (brt, J = 13.5 Hz, 1H), 1.84-1.80 (m, 2H), 1.77 (s, 3H), 1.69-1.56 (m, 3H), 1.52-1.40 (m, 3H), 1.35 (m, 1H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 139.3, 125.0, 111.4, 95.9, 78.0, 74.8. 70.16, 55.6, 40.2, 36.2, 35.9, 29.8, 28.1, 25.7, 25.5, 25.3, 22.5, 19.7; high resolution mass spectrum (ESI) m/z 329.2105 [$(M+Na)^+$; calcd for $C_{19}H_{30}O_3Na$: 329.2093].

Cis-pyran (+)-13. To a solution of pyrans (+)-**24** and its cis isomer (37 mg, 0.13 mmol) in MeOH (4 mL) was added HCl (100 μl, 1.2 μmol) and stirred at 65°C for 15 min. The reaction mixture was partitioned between Et_2O and saturated aqueous solution of $NaHCO_3$, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexenes/Et_2O, 1:1) to afford 9 mg (26% yield) of (+)-**13** as the major isomer. White solid; $[\alpha]_D^{20}$ +36° (c 0.87, $CHCl_3$); IR ($CHCl_3$) 3540 (w), 2920 (s), 1440 (m), 1200 (s), 1080 (s), 1050 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.11 (brs, 1H), 4.98 (brs, 1H), 4.02 (brdd, J = 9.1, 6.1 Hz, 1H), 3.98 (brm, 1H), 3.84 (brs, 1H), 3.02 (dd, J = 14.7, 3.4 Hz, 1H), 2.58 (m, 1H), 2.09 (brd, J = 14.8 Hz, 1H), 1.96 (m, 1H), 1.90-1.71 (m, 4H), 1.77 (brs, 3H), 1.62 (tq, J = 3.7, 13.3 Hz, 1H), 1.56-1.45 (m, 3H), 1.34 (dt, J = 2.9, 14.9 Hz, 3H), 1.15

(s, 3H), 1.23-1.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 142.2, 121.9, 111.5, 80.9, 77.1, 66.5. 43.1, 37.2, 36.1, 34.1, 28.0, 25.6, 25.0, 24.0, 22.1, 19.7; high resolution mass spectrum (CI, CH_4) m/z 262.1921 [M^+; calcd for $C_{17}H_{26}O_2$: 262.1932].