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SUPPORTING INFORMATION

Title: The Intramolecular Aromatic Electrophilic Substitution of Aminocyclopropanes Prepared by the Kulinkovich–de Meijere Reaction

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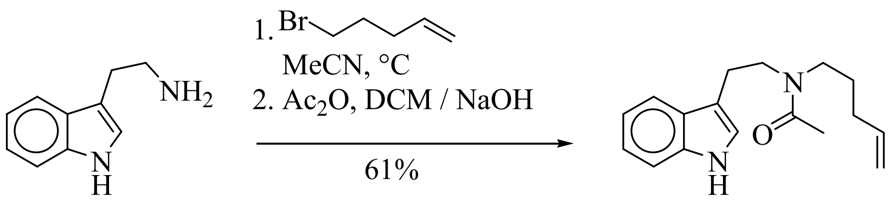
Ref. No.: O200500428

General Remarks: NMR spectra were recorded with AC 250 (^{1}H at 250 MHz, ^{13}C at 62.9 MHz), AM 300, AVANCE 300 (^{1}H at 300 MHz, ^{13}C at 75.5 MHz) and AMX 400 (^{1}H at 400 MHz) Bruker spectrometers. Chemical shifts are given in ppm, referenced to the peak of tetramethylsilane, defined at $\delta = 0.00$ (^{1}H NMR), or the solvent peak of $CDCl_3$, defined at $\delta = 77.1$ (^{13}C NMR). Infrared spectra were recorded with a Perkin-Elmer BX FT-IR spectrometer. Mass spectra were obtained using HP MS 5972 (CI), Thermofinigan Automass (EI), LC/MS Thermoquest Navigator (ES$^+$) and LCT Micromass (low- and high-resolution ES$^+$) spectrometers. Melting points were determined using a Büchi BS540 apparatus and were not corrected. Flash column chromatography was performed on SDS Chromagel silica gel 60 (35-70 µm). All reactions were carried out under argon unless otherwise stated. The temperatures mentioned are the temperatures of the cold baths or the oil baths used. Analytical grade acetonitrile, dichloromethane, diethyl ether, DME, DMF, ethanol and toluene were purchased from SDS and used as such. THF was distilled from sodium/benzophenone under argon. Cyclopentylmagnesium chloride solution in diethyl ether was purchased from Sigma-Aldrich or Fluka and titrated according to a previously reported method.[i] *n*-Butyllithium solution in hexane was also titrated prior to use.[ii]

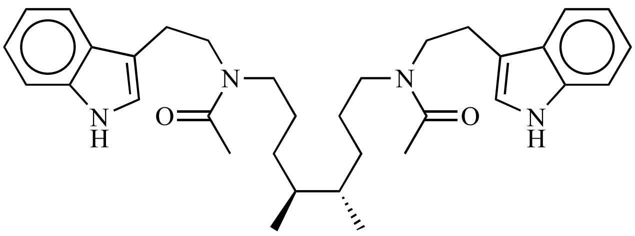
I. Synthesis of *N*-[2-(1*H*-indol-2-yl)-ethyl]-*N*-pent-4-enyl acetamide



***N*-[2-(1*H*-indol-2-yl)-ethyl]-*N*-pent-4-enyl acetamide**: potassium carbonate (1.0 eq., 10 mmol, 1.4 g) and 5-bromopent-1-ene (1.0 eq., 10 mmol, 1.2 mL) were added to a solution of tryptamine (1.0 eq., 10 mmol, 1.6 g) in acetonitrile (50 mL). The mixture was heated at reflux for 2 h 30. After cooling, the solvent and the volatile components were removed under reduced pressure. Dichloromethane (25 mL) and 1N sodium hydroxide aqueous solution (25 mL) were added, followed by acetic anhydride (4.0 eq., 40 mmol, 3.8 mL) dropwise. After 1 h of stirring, the mixture was diluted with dichloromethane (75 mL) and water (25 mL). The aqueous layer was separated. The organic layer was washed with 1N hydrogen chloride aqueous solution (50 mL) and water (2 x 50 mL), then dried over magnesium sulfate, filtered and concentrated. Purification of the crude product (2.9 g) by flash column chromatography (ethyl acetate/heptane, gradient from 40% to 50%) yielded pure ***N*-[2-(1*H*-indol-2-yl)-ethyl]-*N*-pent-4-enyl acetamide** (1.6 g, 6.1 mmol, 61%).

***N*-[2-(1*H*-Indol-2-yl)-ethyl]-*N*-pent-4-enyl acetamide:** Colourless crystals. $C_{17}H_{22}N_2O$ (270.4): calcd. C 75.52, H 8.20; found C 75.26, H 8.14. M.p. 57.9-58.3 °C (heptane/ethanol). R_f 0.55 (ethyl acetate, UV-active, developed with phosphomolybdic acid). MS (CI, NH_3): *m/z* = 144, <u>271</u> [MH^+], 272. IR (mixture of two rotamers): nu(tilde) = 3411, 3266, 2976, 2929, 1626, 1484, 1440, 1426, 1358, 1232, 1009, 913, 742 cm^{-1}. ^1H NMR (mixture of two rotamers): δ = 1.64 and 1.68 (2 x quint, J = 7 Hz, 2 H), 1.92 and 2.11 (2 x s, 3 H), 2.03 and 2. 06 (2 x q, J = 7 Hz, 2 H), 3.00 and 3.03 (2 x t, J = 8 Hz, 2 H), 3.18 and 3.39 (2 x t, J = 8 Hz, 2 H), 3.55 and 3.63 (2 x t, J = 7 Hz, 2H), 4.94-5.07 (m, 2 H), 5.66-5.88 (m, 1 H), 6.98 and 7.02 (2 x bs, 1 H), 7.08-7.25 (m, 2 H), 7.35 and 7.38 (2 x d, J = 8 Hz, 1 H), 7.56 and 7.67 (2 x d, J = 8 Hz, 1 H), 8.25 and 8.38 (2 x bs, 1 H, NH) ppm. ^{13}C NMR (mixture of two rotamers): δ = 21.6 and 21.8, 23.7 and 24.9, 27.0 and 28.1, 30.9 and 31.3, 45.4 and 47.0, 48.9 and 49.5, 111.3 and 111.5, 112.3 and 113.5, 115.0 and 115.7, 118.3 and 118.9, 119.4 and 119.7, 122.0, 122.1, 122.3, 122.4, 127.2, 136.4, 137.3 and 138.1, 170.4 and 170.6 ppm.

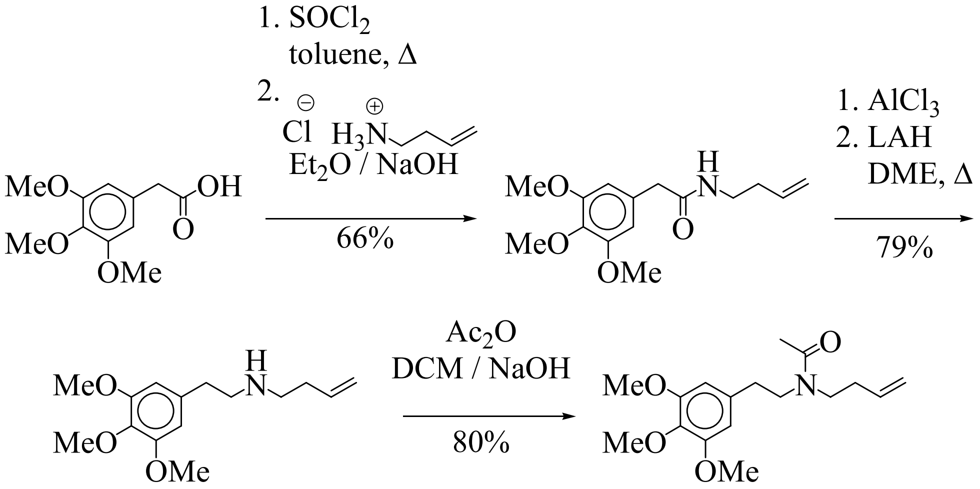
II. Spectroscopic data for *N,N'*-bis[2-(1*H*-indol-2-yl)-ethyl]-*N,N'*-diacyl-4,5-dimethyloctane-1,8-diamine



***N,N'*-Bis[2-(1H-indol-2-yl)-ethyl]-*N,N'*-diacyl-4,5-dimethyloctane-1,8-diamine**: when the crude product of the intramolecular Kulinkovich-de Meijere reaction leading to aminocyclopropane **9** was purified, this by-product was isolated in 21% yield as a 50:27:23 mixture of three rotamers, as determined by integration of the ^{1}H NMR signals.

***N,N'*-Bis[2-(1H-indol-2-yl)-ethyl]-*N,N'*-diacyl-4,5-dimethyloctane-1,8-diamine:** Colourless viscous oil. R_f 0.65 (methanol/dichloromethane 10%, UV-active, developed with phosphomolybdic acid). MS (ES$^+$): *m/z* = 565 [MNa$^+$], 566. HRMS (ES$^+$): calcd. for $C_{34}H_{46}N_4NaO_2$ [MNa$^+$] 565.3518; found 565.3535. IR (mixture of three rotamers): nu(tilde) = 3258, 2927, 1615, 1483, 1454, 1422, 1357, 1264, 1008 cm^{-1}. ^{1}H NMR (mixture of three rotamers): δ = 0.67-0.74 (m, 6 H), 0.95-1.66 (m, 10 H), 1.92 and 2.10 (2 x bs, 6 H), 2.95-3.06 (m, 4 H), 3.06-3.16 and 3.29-3.41 (2 x m, 4 H), 3.54 and 3.61 (2 x t, J = 7 Hz, 4 H), 6.93-6.95 (m, 2 H), 7.05-7.20 (m, 4 H), 7.30-7.36 (m, 2 H), 7.54 and 7.64 (2 x d, J = 7 Hz, 2 H), 8.68 and 8.79 and 8.85 and 8.92 (4 x bs, 2 H, NH) ppm. ^{13}C NMR (mixture of three rotamers): δ = 14.1, 21.4 and 21.6, 23.5, 24.7, 25.8, 26.9, 27.0, 31.8 and 32.0, 36.1 and 36.2 and 36.4, 46.0, 47.0, 47.2, 49.3, 49.6, 49.7, 111.2 and 111.5 and 111.7, 112.9 and 113.0, 118.0, 118.6, 119.0, 119.3, 121.6, 121.7, 121.9, 122.0, 122.3, 122.4, 126.9 and 127.3 and 127.4, 136.3, 170.3 and 170.4 and 170.6 ppm.

III. Synthesis of *N*-(but-3-enyl)-*N*-[2-(3,4,5-trimethoxyphenyl)ethyl] acetamide



a. *N*-(But-3-enyl)-2-(3,4,5-trimethoxyphenyl) acetamide: thionyl chloride (2.3 eq., 3.0 mmol, 0.22 mL) was added to a solution of (3,4,5-trimethoxyphenyl)-acetic acid (1.5 eq., 2.0 mmol, 0.45 g) in toluene (5.0 mL). The mixture was heated at reflux for 3 h, concentrated under reduced pressure, and redissolved in dichloromethane (2.0 mL). A mixture of but-3-enyl ammonium chloride[iii] (1.0 eq, 1.3 mmol, 0.14 g), 1N sodium hydroxide aqueous solution (50 mL), diethyl ether (50 mL), and the acyl chloride solution in dichloromethane just prepared as described above, was shaken vigorously in a separating funnel for 15 minutes. The organic layer was then dried over sodium sulfate, filtered and concentrated. Purification by flash column chromatography (ethyl acetate/heptane, gradient from 30% to 100%) yielded pure ***N*-(but-3-enyl)-2-(3,4,5-trimethoxyphenyl) acetamide** (0.24 g, 0.86 mmol, 66%).

***N*-(But-3-enyl)-2-(3,4,5-trimethoxyphenyl) acetamide:** Yellow solid. R_f 0.45 (ethyl acetate/heptane 20%, UV-active, developed with phosphomolybdic acid). HRMS (ES$^+$): calcd. for $C_{15}H_{21}NO_4Na$ [MNa$^+$] 302.1368; found 302.1326. ^{1}H NMR: $\delta = 2.12$ (q, $J = 7$ Hz, 2 H), 3.29 (q, $J = 7$ Hz, 2 H), 3.48 (s, 2 H), 3.83 (s, 3 H), 3.84 (s, 6 H), 4.94-5.03 (m, 2 H), 5.69 (ddt, $J = 17$, 11, 7 Hz, 1 H), 5.90 (bs, 1 H, NH), 6.47 (s, 2H) ppm. ^{13}C NMR: $\delta = 33.5$, 38.4, 43.9, 56.0, 60.7, 106.3, 116.9, 130.6, 135.1, 137.0, 153.4, 170.8 ppm.

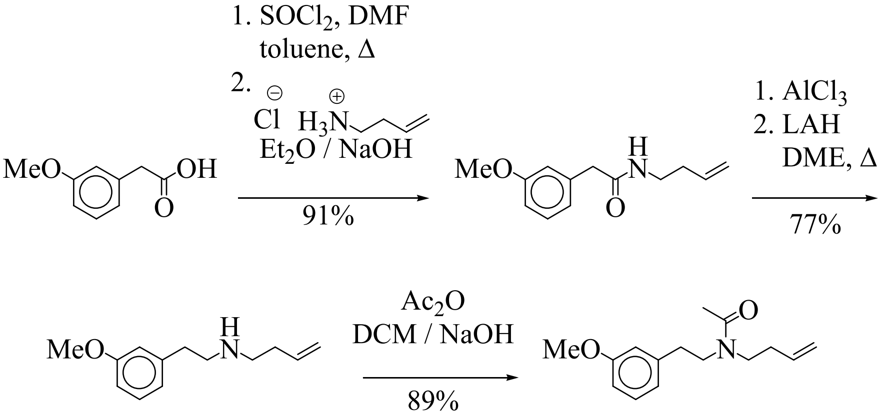
b. But-3-enyl-[2-(3,4,5-trimethoxyphenyl)ethyl] amine: aluminium chloride (1.0 eq., 0.72 mmol, 96 mg) was added at 0°C to a solution of ***N*-(but-3-enyl)-2-(3,4,5-trimethoxyphenyl) acetamide** (1.0 eq., 0.72 mmol, 0.20 g) in ethylene glycol dimethyl ether (10 mL). After 5 minutes of stirring at 0°C, lithium aluminium hydride (5.0 eq, 3.6 mmol, 0.14 g) was added by small portions. The mixture was allowed to warm to 20°C, then heated at reflux for 25 minutes. Water (0.13 mL), 15% w/v NaOH aqueous solution (0.13 mL), then water again (0.42 mL) were added after cooling to 0°C. The mixture was filtered, taken up with diethyl ether (10 mL) and 1N HCl aqueous solution (10 mL). The organic layer was discarded. The aqueous phase was basified with sodium hydroxide (about 0.40 g) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford crude **but-3-enyl-[2-(3,4,5-trimethoxyphenyl)ethyl] amine** (0.15 g, 0.57 mmol, 79%) that was used as such in the next step without further purification.

But-3-enyl-[2-(3,4,5-trimethoxyphenyl)ethyl] amine: Yellow solid. R_f 0.40 (methanol/dichloromethane 10%, UV-active, developed with phosphomolybdic acid). ^{1}H NMR: δ = 1.52 (bs, 1 H, NH), 2.25 (q, J = 7 Hz, 2 H), 2.70 (t, J = 7 Hz, 2 H), 2.75 (t, J = 7 Hz, 2 H), 2.87 (t, J = 7 Hz, 2 H), 3.83 (s, 3 H), 3.85 (s, 6 H), 4.97-5.09 (m, 2 H), 5.75 (m, 1 H), 6.43 (s, 2 H) ppm. ^{13}C NMR: δ = 34.1, 36.6, 48.6, 50.7, 55.7, 60.7, 105.4, 116.2, 135.7, 136.2, 153.0 ppm.

c. *N*-(But-3-enyl)-*N*-[2-(3,4,5-trimethoxyphenyl)ethyl] acetamide: acetic anhydride (20 eq., 20 mmol, 1.9 mL) was added to a solution of **but-3-enyl-[2-(3,4,5-trimethoxyphenyl)ethyl] amine** (1.0 eq., 1.0 mmol, 0.27 g) in dichloromethane (40 mL). 1N sodium hydroxide aqueous solution (60 mL) was then added, and the mixture was shaken vigorously in a separating funnel for 15 minutes. The aqueous phase was separated. The organic layer was washed with 1N HCl aqueous solution (40 mL), dried over sodium sulfate, filtered and concentrated. Purification by flash column chromatography (ethyl acetate/heptane, gradient from 20% to 50%) yielded pure ***N*-(but-3-enyl)-*N*-[2-(3,4,5-trimethoxyphenyl)ethyl] acetamide** (0.25 g, 0.81 mmol, 80%).

***N*-(But-3-enyl)-*N*-[2-(3,4,5-trimethoxyphenyl)ethyl] acetamide:** Yellow oil. R_f 0.4 (methanol/dichloromethane 10%, UV-active, developed with phosphomolybdic acid). HRMS (ES$^+$): calcd. for $C_{17}H_{25}NO_4Na$ [MNa$^+$] 330.1681; found 330.1669. IR (mixture of two rotamers): nu(tilde) = 2939, 1636, 1590, 1508, 1456, 1422, 1239, 1128, 1009 cm^{-1}. ^{1}H NMR (mixture of two rotamers): δ = 1.92 and 2.11 (2 x s, 3 H), 2.20 and 2.33 (2 x q, J = 7 Hz, 2 H), 2.75-2.80 (m, 2 H), 3.25 and 3.41 (2 x t, J = 7 Hz, 2 H), 3.45 and 3.48 (m, 2 H), 3.82 (2 x s, 3 H), 3.85 (s, 6 H), 5.01-5.24 (m, 2 H), 5.77 (m, 1 H), 6.37 and 6.46 (2 x s, 2 H) ppm. ^{13}C NMR (mixture of two rotamers): δ = 21.4 and 21.7, 32.2, 33.3, 34.4, 35.6, 45.3, 48.1, 49.0, 50.6, 56.1 and 56.2, 60.9 and 61.0, 105.7, 116.7 and 117.7, 134.0, 135.6, 134.2, 135.1, 153.2 and 153.5, 170.3 ppm.

IV. Synthesis of *N*-(but-3-enyl)-*N*-[2-(3-methoxyphenyl)ethyl] acetamide



a. *N*-(But-3-enyl)-2-(3-methoxyphenyl) acetamide: DMF (2.5% eq., 0.25 mmol, 20 μL) and thionyl chloride (1.9 eq., 19 mmol, 1.4 mL) was added to a solution of (3-methoxyphenyl)-acetic acid (1.5 eq., 15 mmol, 2.5 g) in toluene (10 mL). The mixture was heated at reflux for 30 min, concentrated under reduced pressure, and redissolved in dichloromethane (5.0 mL). A mixture of but-3-enyl ammonium chloride[iii] (1.0 eq, 10 mmol, 1.1 g), 1N sodium hydroxide aqueous solution (0.15 L), diethyl ether (0.15 L), and the acyl chloride solution in dichloromethane just prepared as described above (and added carefully), was shaken vigorously in a separating funnel for 15 minutes. The organic layer was then washed with 1N hydrogen chloride aqueous solution (0.15 L), dried over sodium sulfate, filtered and concentrated to afford an orange oil (2.1 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 0% to 50%) yielded pure ***N*-(but-3-enyl)-2-(3-methoxyphenyl) acetamide** (2.0 g, 9.1 mmol, 91%).

***N*-(But-3-enyl)-2-(3-methoxyphenyl) acetamide:** Orange oil. R_f 0.2 (ethyl acetate/heptane 40%, UV-active, developed with phosphomolybdic acid). MS (CI, NH_3): *m/z* = 220 [MH^+], 221, 222, 237 (MH^+..NH_3). IR: nu(tilde) = 3288, 2935, 1645, 1600, 1584, 1554, 1490, 1436, 1257, 1151, 1049 cm^{-1}. ^{1}H NMR: δ = 2.18 (qt, *J* = 6, 1 Hz, 2 H), 3.27 (q, *J* = 6 Hz, 2 H), 3.54 (s, 2 H), 3.81 (s, 3 H), 4.90-5.01 (m, 2 H), 5.43 (bs, 1 H, NH), 5.64 (ddt, *J* = 17, 10, 6 Hz, 1 H), 6.76-6.86 (m, 3 H), 7.26 (t, J= 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 33.6, 38.4, 43.9, 55.2, 112.8, 115.0, 117.2, 121.7, 130.0, 135.0, 136.4, 160.0, 170.7 ppm.

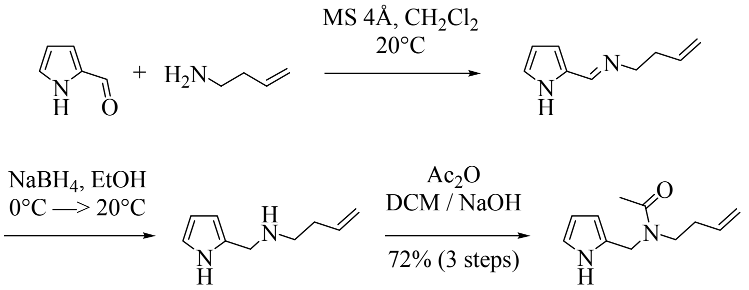
b. But-3-enyl-[2-(3-methoxyphenyl)ethyl] amine: aluminium chloride (1.0 eq., 9.1 mmol, 1.2 g) was added at 0°C to a solution of ***N*-(but-3-enyl)-2-(3-methoxyphenyl) acetamide** (1.0 eq., 9.1 mmol, 2.0 g) in ethylene glycol dimethyl ether (50 mL). After 5 minutes of stirring at 0°C, lithium aluminium hydride (2.0 eq, 18 mmol, 0.70 g) was added by small portions. The mixture was allowed to warm to 20°C, then heated at reflux for 30 minutes. Water (0.71 mL), 15% w/v NaOH aqueous solution (0.71 mL), then water again (0.71 mL) were added after cooling to 0°C. The mixture was filtered, taken up with dichloromethane (50 mL) and 1N HCl aqueous solution (50 mL). The organic layer was separated and washed with 1N NaOH aqueous solution (50 mL). The first aqueous phase was basified with sodium hydroxide (about 2.0 g) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford crude **but-3-enyl-[2-(3-methoxyphenyl)ethyl] amine** (1.43 g, 7.0 mmol, 77%) that was used as such in the next step without further purification.

But-3-enyl-[2-(3-methoxyphenyl)ethyl] amine: Yellow oil. ^{1}H NMR: δ= 1.40 (bs, 1 H, NH), 2.23 (qt, *J* = 7, 1 Hz, 2 H), 2.69 (t, *J* = 7 Hz, 2 H), 2.73-2.92 (m, 4 H), 3.79 (s, 3 H), 4.96-5.10 (m, 2 H), 5.75 (ddt, *J* = 17, 10, 7 Hz, 1 H), 6.70-6.85 (m, 3 H), 7.18 (m, 1 H) ppm. ^{13}C NMR: δ= 34.4, 36.5, 48.8, 51.1, 55.2, 111.5, 114.5, 116.3, 121.2, 129.5, 136.4, 141.8, 159.8 ppm.

c. *N*-(But-3-enyl)-*N*-[2-(3-methoxyphenyl)ethyl] acetamide: acetic anhydride (20 eq., 0.14 mol, 13 mL) was added to a solution of crude **but-3-enyl-[2-(3-methoxyphenyl)ethyl] amine** (1.0 eq., 6.8 mmol, 1.4 g) in dichloromethane (0.20 L). 1N sodium hydroxide aqueous solution (0.45 L) was then added, and the mixture was shaken vigorously in a separating funnel for 15 minutes. The aqueous phase was separated. The organic layer was washed with 1N HCl aqueous solution (0.15 L), dried over sodium sulfate, filtered and concentrated to afford a dark orange oil (1.6 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 0% to 50%) yielded pure ***N*-(but-3-enyl)-*N*-[2-(3-methoxyphenyl)ethyl] acetamide** (1.5 g, 6.1 mmol, 89%).

***N*-(But-3-enyl)-*N*-[2-(3-methoxyphenyl)ethyl] acetamide:** Yellow oil. R_f 0.3 (ethyl acetate/heptane 50%, UV-active, developed with phosphomolybdic acid). MS (CI, NH_3): *m/z* = $\underline{248}$ [MH^+], 249, 250, 251, 265 [$MH^+..NH_3$]. IR (mixture of two rotamers): nu(tilde) = 2935, 1652, 1640, 1611, 1601, 1584, 1490, 1465, 1456, 1453, 1437, 1419, 1259, 1152 cm^{-1}. ^{1}H NMR (mixture of two rotamers): δ= 1.94 and 2.10 (2 x s, 3 H), 2.27 and 2.32 (2 x qt, *J* = 7, 1 Hz, 2 H), 2.77-2.86 (m, 2 H), 3.19 and 3.39 (2 x t, *J* = 7 Hz, 2 H), 3.48 and 3.55 (m, 2 H), 3.77 and 3.78 (2 x s, 3 H), 4.98-5.12 (m, 2 H), 5.65-5.86 (m, 1 H), 6.68-6.83 (m, 3 H), 7.19-7.22 (2 x t, J= 8 Hz, 1 H) ppm. ^{13}C NMR (mixture of two rotamers): δ= 21.2 and 21.5, 32.0, 33.1, 33.9, 35.2, 45.0, 47.8, 48.8, 50.4, 55.0, 111.6 and 111.7, 114.3 and 114.5, 116.4 and 117.4, 120.9 and 121.0, 129.3 and 129.6, 134.1 and 135.4, 139.6 and 140.8, 159.5 and 159.8, 170.1 and 170.2 ppm.

V. Synthesis of *N*-(but-3-enyl)-*N*-(1*H*-pyrrol-2-ylmethyl) acetamide



a. But-3-enyl-(1*H*-pyrrol-2-ylmethylene) amine: 1N NaOH aqueous solution (40 mL) was added to a suspension of but-3-enyl ammonium chloride[iii] (1.1 eq., 7.7 mmol, 0.83 g) in dichloromethane (40 mL) in a separating funnel. After shaking, the organic layer was separated and placed in a round-bottomed flask containing activated powdered 4Å molecular sieves (3.5 g). 1*H*-pyrrol-2-carboxaldehyde (1.0 eq., 7.0 mmol, 0.67 g) was added. The mixture was stirred at 20°C for 17 h, then filtered through celite, dried over sodium sulfate and concentrated to afford crude **but-3-enyl-(1*H*-pyrrol-2-ylmethylene) amine** (0.91 g, 6.1 mmol if pure) that was used as such without purification.

But-3-enyl-(1*H*-pyrrol-2-ylmethylene) amine: Dark orange oil. ^{1}H NMR: δ = 2.38 (qt, J = 7, 1 Hz, 2 H), 3.59 (td, J = 7, 1 Hz, 2 H), 4.18-5.11 (m, 2 H), 5.82 (ddt, J = 17, 10, 7 Hz, 1 H), 6.22 (dd, J = 4, 3 Hz, 1 H), 6.47 (dd, J = 4, 2 Hz, 1 H), 6.86 (m, 1 H), 8.05 (q, J = 1Hz, 1 H), 8.53 (bs, 1 H, NH) ppm. ^{13}C NMR: δ = 35.6, 60.4, 109.7, 114.3, 116.2, 121.9, 130.3, 136.3, 152.2 ppm.

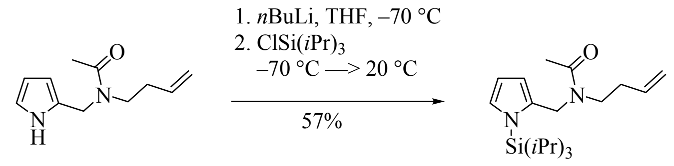
b. But-3-enyl-(1*H*-pyrrol-2-ylmethyl) amine: sodium borohydride (2.0 eq., 12 mmol, 0.47 g) was added by small portions at 0°C to a solution of crude **but-3-enyl-(1*H*-pyrrol-2-ylmethylene) amine** (1.0 eq., assumed 6.1 mmol) in ethanol (50 mL). The mixture was allowed to warm to 20°C for 20 minutes. Saturated $NaHCO_3$ aqueous solution (0.20 L) and diethyl ether (0.20 L) were then added. The organic layer was separated, and the aqueous extracted with diethyl ether (0.20 L, then 0.10 L). The combined organic phases were dried over sodium sulfate, filtered and concentrated to afford crude **but-3-enyl-(1*H*-pyrrol-2-ylmethyl) amine** (0.95 g, 6.3 mmol if pure) that was used as such in the next step without further purification.

But-3-enyl-(1*H*-pyrrol-2-ylmethyl) amine: Yellow oil. ^{1}H NMR: δ = 1.83 (bs, 1 H, NH), 2.26 (q, J = 7 Hz, 2 H), 2.70 (t, J = 7 Hz, 2 H), 3.78 (s, 2 H), 5.01-5.12 (m, 2 H), 5.77 (ddt, J = 17, 10, 7 Hz, 1 H), 6.01 (bs, 1 H), 6.12 (q, J = 3 Hz, 1 H), 6.79 (td, J = 3, 2 Hz, 1 H), 8.60 (bs, 1 H, NH) ppm. ^{13}C NMR: δ = 34.1, 46.5, 48.3, 106.3, 108.0, 116.6, 117.3, 130.5, 136.3 ppm.

c. *N*-(But-3-enyl)-*N*-(1*H*-pyrrol-2-ylmethyl) acetamide: acetic anhydride (5.0 eq., 31 mmol, 2.9 mL) was added to a solution of crude **but-3-enyl-(1*H*-pyrrol-2-ylmethyl) amine** (1.0 eq., assumed 6.3 mmol, 0.95 g) in dichloromethane (0.10 L). 1N sodium hydroxide aqueous solution (0.10 L) was then added, and the mixture was shaken vigorously in a separating funnel for 15 minutes. The aqueous phase was separated. The organic layer was washed with 1N HCl aqueous solution (0.10 L), dried over sodium sulfate, filtered and concentrated to afford a brown oil (1.0 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 20% to 50%) yielded pure ***N*-(but-3-enyl)-*N*-(1*H*-pyrrol-2-ylmethyl) acetamide** (0.97 g, 5.0 mmol, 72% over three steps).

***N*-(But-3-enyl)-*N*-(1*H*-pyrrol-2-ylmethyl) acetamide:** Yellow crystals. M.p. 40.5-42.0 °C. R_f 0.25 (ethyl acetate/heptane 50%, UV-active, developed with phosphomolybdic acid). MS (ES^+): *m/z* = 114, 126, 193 [MH^+], <u>215</u> [MNa^+]. HRMS (ES^+): calcd. for $C_{11}H_{16}N_2ONa$ (MNa^+) 215.1160; found 215.1169. IR: nu(tilde) = 3372, 3141, 2978, 2931, 1626, 1481, 1423, 1364, 1226, 1027 cm^{-1}. ^1H NMR: δ = 2.09 (s, 3 H), 2.32 (qt, *J* = 7, 2 Hz, 2 H), 3.34 (t, *J* = 7 Hz, 2 H), 4.38 (s, 2 H), 4.97-5.10 (m, 2 H), 5.77 (ddt, *J* = 17, 10, 7 Hz, 1 H), 6.02-6.08 (m, 2 H), 6.70 (q, *J* = 2 Hz, 1 H), 9.26 (bs, 1 H, NH) ppm. ^{13}C NMR: δ = 21.5, 33.0, 43.2, 48.8, 107.2, 107.3, 117.8, 118.2, 128.9, 134.1, 171.8 ppm.

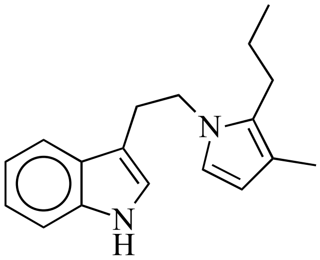
VI. Synthesis of *N*-(but-3-enyl)-*N*-(1-tri*iso*propylsilanyl-pyrrol-2-ylmethyl) acetamide



N-(But-3-enyl)-N-(1-tri*iso*propylsilanyl-pyrrol-2-ylmethyl) acetamide: *n*-butyllithium (1.2 M *in* hexane, 1.0 eq, 0.48 mmol, 0.40 mL) was added dropwise at –70°C to a solution of ***N*-(but-3-enyl)-*N*-(1*H*-pyrrol-2-ylmethyl) acetamide** (1.0 eq., 0.49 mmol, 94 mg) in tetrahydrofurane (20 mL). After 10 minutes of stirring at –70°C, chlorotri*iso*propylsilane (1.0 eq, 0.47 mmol, 0.10 mL) was added dropwise, and then the mixture was allowed to warm to 20°C for 30 minutes. Water (30 mL) was added. The organic layer was separated, and the aqueous extracted with diethyl ether (2 x 30 mL). The combined organic phases were dried over sodium sulfate and concentrated to afford a black mixture of solid and liquid (0.19 g). Purification by flash column chromatography (ethyl acetate/heptane, gradient from 0% to 75%) yielded pure ***N*-(but-3-enyl)-*N*-(1-tri*iso*propylsilanyl-pyrrol-2-ylmethyl) acetamide** (94 mg, 0.27 mmol, 57%).

N-(But-3-enyl)-N-(1-tri*iso*propylsilanyl-pyrrol-2-ylmethyl) acetamide: Colourless oil. R_f 0.6 (ethyl acetate/heptane 50%, UV-active, developed with phosphomolybdic acid). MS (EI): *m/z* = 226, 235, <u>236</u>, 237, 305, 348 $[M^{+\bullet}]$. IR (mixture of two rotamers): nu(tilde) = 2949, 2868, 1640, 1467, 1423, 1143, 1063, 883 cm^{-1}. ^1H NMR (mixture of two rotamers): δ = 1.04 and 1.06 (2 x d, J = 7 Hz, 18 H), 1.42-1.62 (m, 3 H), 1.95 and 2.06 (2 x s, 3 H), 2.15-2.28 (m, 2 H), 3.31 and 3.47 (2 x t, J = 7.5 Hz, 2 H), 4.42 and 4.48 (2 x s, 2 H), 4.93-5.10 (m, 2 H), 5.65-5.82 (m, 1 H), 6.01-6.09 (m, 1 H), 6.16-6.23 (m, 1 H), 6.74-6.86 (m, 1 H) ppm. ^{13}C NMR (mixture of two rotamers): δ = 13.0 and 13.1, 18.2 and 18.3, 21.3 and 21.6, 32.6 and 33.1, 43.0 and 46.1, 47.0 and 48.4, 109.6 and 109.8, 110.0 and 111.6, 116.7 and 117.6, 126.4 and 126.7, 132.6 and 133.0, 134.3 and 135.6, 170.4 and 171.2 ppm.

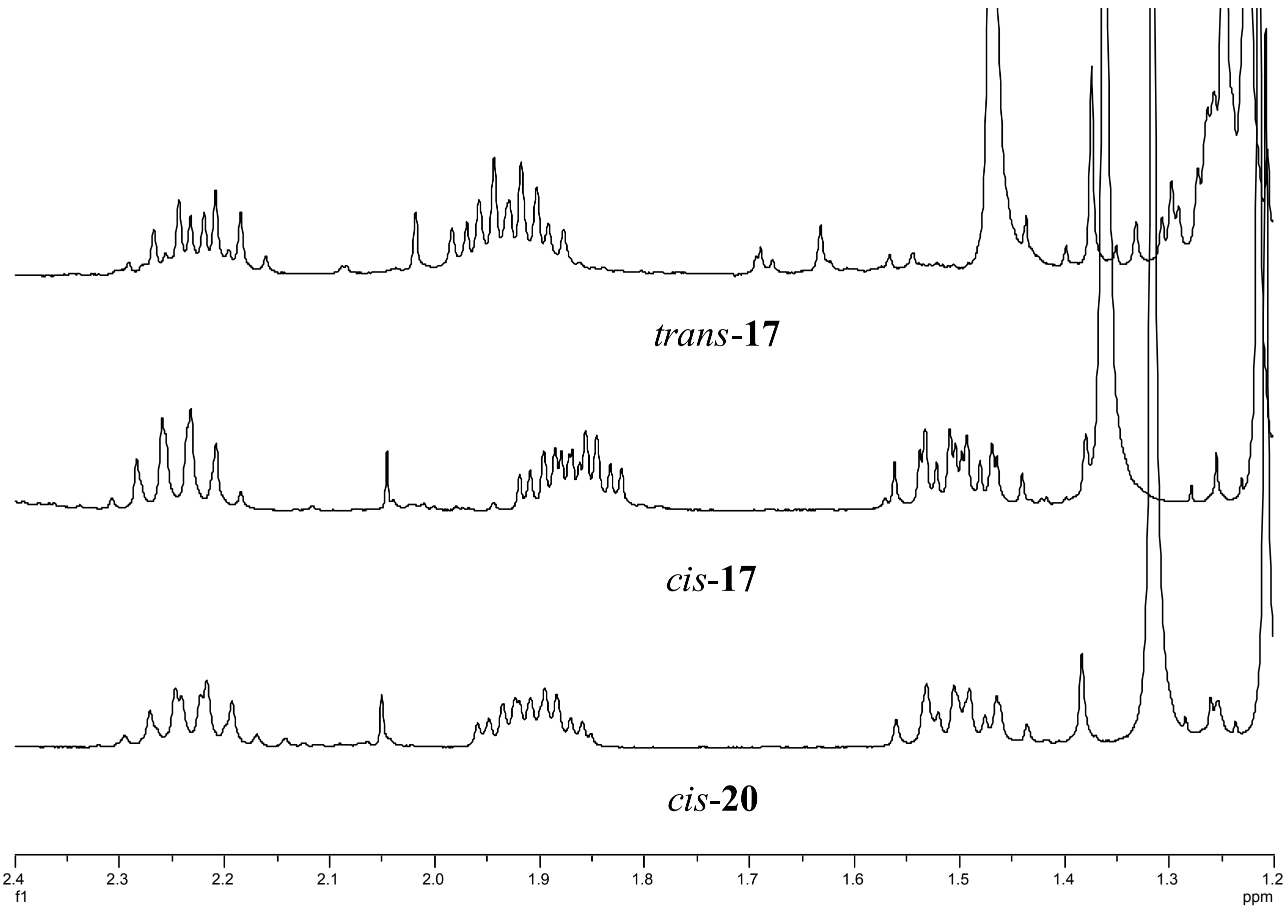
VII. Spectroscopic data for 3-[2-(3-methyl-2-pyrrol-1-yl)]-1*H*-indole



3-[2-(3-methyl-2-pyrrol-1-yl)]-1H-indole: when the crude product of the cyclisation reaction of **8** to **18** was purified, this by-product was isolated in 7% yield.

3-[2-(3-Methyl-2-pyrrol-1-yl)]-1H-indole: Colourless oil. R_f 0.45 (ethyl acetate/heptane 20%, UV-active, developed with phosphomolybdic acid). MS (ES^+): *m/z* = 129, 144, 267 [MH^+], 289 [MNa^+], <u>305</u> [MK^+]. HRMS (ES^+): calcd. for $C_{18}H_{23}N_2$ [MH^+] 267.1861; found 267.1864; calcd. for $C_{18}H_{22}N_2Na$ [MNa^+] 289.1681; found 289.1682; calcd. for $C_{18}H_{22}N_2K$ [MK^+] 305.1420; found 305.1448. IR: nu(tilde) = 3415, 3359, 2957, 2929, 2869, 1489, 1456, 1422, 1333, 1216, 1093 cm^{-1}. ^1H NMR: δ = 0.91 (t, *J* = 7 Hz, 3 H), 1.49 (sext, *J* = 7 Hz, 2 H), 2.05 (s, 3 H), 2.50 (t, *J* = 7 Hz, 2 H), 3.14 (m, 2 H), 4.05 (m, 2 H), 5.96 (d, *J* = 3 Hz, 1 H), 6.53 (d, *J* = 3 Hz, 1 H), 6.86 (d, *J* = 2 Hz, 1 H), 7.11-7.24 (m, 2 H), 7.34 (d, *J* = 8 Hz, 1 H), 7.58 (d, *J* = 8 Hz, 1 H), 7.90 (bs, 1 H, NH) ppm. ^{13}C NMR: δ = 11.7, 14.1, 23.7, 26.4, 28.1, 47.3, 108.5, 111.4, 112.9, 114.7, 118.2, 118.6, 119.6, 122.1, 122.2, 127.3, 129.2, 136.3 ppm.

VIII. Comparison of the ^{1}H NMR spectra of *cis*-20, *cis*-17 and *trans*-17



This picture shows that the ^{1}H NMR signals of the C$\underline{\text{H}}$(Me) and CH(Me)C$\underline{\text{H}}_2$ cyclopentyl protons of *cis*-**20** and *cis*-**17** lie at close chemical shifts and display similar patterns, in contrast to those of *trans*-**17**.

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