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Supporting Information

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Synthesis of *cis,cis,cis,cis*-[5.5.5.4]-1-Azafenestrane with Discovery of an Unexpected Dyotropic Rearrangement

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General Experimental

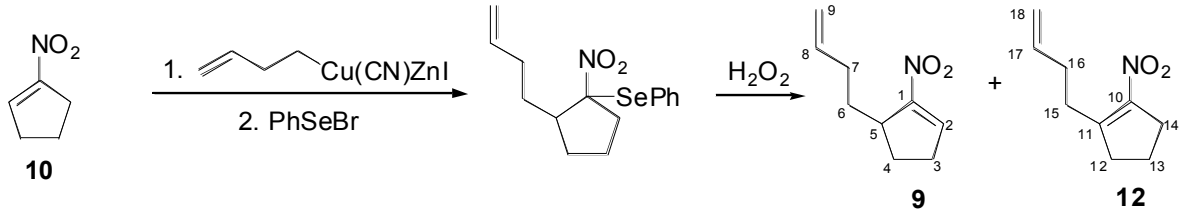
All reactions were performed in oven (140 °C) and/or flame dried glassware under an atmosphere of dry nitrogen. Reaction solvents tetrahydrofuran (Fisher, HPLC grade) and methylene chloride (Fisher, unstabilized HPLC grade) were dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Reaction solvents hexane (Fisher, OPTIMA grade) and toluene (Fisher, ACS grade) were dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Reaction solvents methanol (Mallinckrodt, anhydrous) and ethyl acetate (Acros, spectrophotometric grade) were used without further purification. Solvents for filtration and chromatography were certified ACS grade. "Brine" refers to a saturated solution of sodium chloride. All reaction temperatures correspond to internal temperatures measured with Teflon coated thermocouples.

^{1}H and ^{13}C NMR were recorded on a Varian Unity 500 (500 MHz, ^{1}H; 126 MHz, ^{13}C) spectrometer. Spectra were referenced to residual chloroform (7.26 ppm, ^{1}H; 77.0 ppm, ^{13}C) or benzene (7.15 ppm, ^{1}H; 128.0 ppm ^{13}C). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. COSY, HMQC, and/or HMBC 2D experiments were utilized to make assignments when needed. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Mass Spectrometry

was performed by the University of Illinois Mass Spectrometer Center. Electron Impact (EI) spectra were performed on a Finnagin-MAT C5 spectrometer. Data are reported in the form of m/z (intensity relative to the base peak = 100). Infrared spectra (IR) were recorded on a Perkin Elmer Spectrum BX spectrophotometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 67-100%); m (medium, 34-66%), w (weak, 0-33%). Melting points (mp) were determined on a Thomas Hoover capillary melting point apparatus and are corrected. Kugelrohr distillations were performed on a Büchi GKR-50 Kugelrohr and boiling points correspond to uncorrected air bath temperatures (ABT). Analytical thin-layer chromatography was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV(254) or potassium permanganate ($KMnO_4$). Column chromatography was performed using 230-400 mesh silica gel purchased from EM Science or aluminum oxide (activated, basic, Brockmann I, standard grade, 150 mesh, 58 Å) purchased from Aldrich.

Chlorotrimethylsilane (Aldrich) and *n*-butyl vinyl ether (Aldrich) were purified by distillation prior to use. Zinc dust (Fischer), 1,2-dibromoethane (Aldrich), copper(I) cyanide (ROC/RIC), lithium chloride (Fischer), diphenyl diselenide (Aldrich), bromine (Aldrich), magnesium sulfate (Fischer, anhydrous), hydrogen peroxide (Fischer, 30% aqueous), sodium bicarbonate (Fischer), trimethylaluminum (Aldrich, 2 M toluene), Celite (Fischer), Raney nickel (Activated Metals and Chemicals, A-5000), *t*-butyl vinyl ether (Aldrich), sodium sulfate (Aldrich, anhydrous), triphenylphospine (Aldrich), diisopropyl azodicarbosylate (Aldrich), borane·THF complex (Aldrich, 1 M THF), and boron trifluoride diethyl etherate (Aldrich) were used as received. 4-Iodo-1-butene[1] and 1-nitrocyclopentene[2] were prepared according to literature procedures.

Preparation of 5-(3-Butenyl)-1-nitro-1-cyclopentene (9) and 2-(3-Butenyl)-1-nitro-1-cyclopentene (12)



A suspension of zinc dust (778 mg, 11.9 mmol, 1.67 equiv) in THF (5.0 mL) was sonicated for 15 min at room temperature in a 50-mL, 2-necked round-bottom flask fitted with a N_2 inlet, a rubber septum, and a magnetic stir bar. The sonicator was replaced with a magnetic stirrer and dibromoethane (34.5 μL, 0.4 mmol, 0.06 equiv) was added via syringe with stirring at room temperature. The mixture was heated in a 65 °C oil bath for 3 min then was cooled to room temperature in a H_2O bath. Chlorotrimethylsilane (45.7 μL, 0.36 mmol, 0.05 equiv) was added via syringe and the mixture was stirred for 10 min at room temperature followed by the addition of a solution of 4-iodo-1-butene (2.09 g, 11.5 mmol, 1.61 equiv) in THF (5.0 mL) dropwise via cannula. The suspension was stirred for 12 h in a 38 °C oil bath. A solution of copper(I) cyanide (896 mg, 10.0 mmol, 1.4 equiv) and lithium chloride (848 mg, 20 mmol, 2.8 equiv) in THF (10.0 mL) was prepared by stirring the components together for 12 h in a 25-mL, conical flask equipped with a N_2 inlet and a magnetic stir bar. This solution was added to the cooled (-10 °C, salt-ice) reaction flask rapidly via cannula and the brown mixture was stirred for 15 min. A solution of 1-nitrocyclopentene (808 mg, 7.14 mmol) in THF (15.0 mL) was added at -10 °C dropwise via cannula. After the addition was complete, the reaction mixture was warmed to 0 °C (ice-H_2O bath) and stirred for 1 h then was treated with a solution of phenylselenyl bromide (10 mmol, 1.4 equiv) added via cannula. The phenylselenyl bromide solution was prepared by dissolving diphenyl diselenide (1.56 g, 5.0 mmol, 0.70 equiv) in THF (5.0 mL), adding bromine (256 μL, 5.0 mmol, 0.70 equiv), and stirring for 1 h at room temperature in a 25-mL conical flask equipped with a N_2 inlet and a magnetic stir bar. The reaction mixture was filtered through a short plug of silica gel (40 mm x 2 cm) eluting with hexanes/EtOAc, 1/1 (400 mL). The filtrate was washed with H_2O (400 mL) and brine (400 mL) then the aqueous layers were back extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried

($MgSO_4$) and concentrated to give 2.74 g of crude nitroselenide as a brown oil. The crude product was dissolved in THF (30.0 mL) in a 50-mL, 2-necked round-bottom flask equipped with a N_2 inlet and an internal temperature probe. The mixture was cooled to 0 °C in an ice bath with stirring. Aqueous hydrogen peroxide (30%, 8.1 mL, 71.4 mmol, 10 equiv) was added slowly such that the internal reaction temperature remained below 10 °C. The ice bath was removed and the reaction mixture was allowed to warm. As the internal temperature reached 15-20 °C an exotherm was apparent and the flask was lowered into the ice bath to keep the internal temperature below 25 °C. When the internal temperature dropped below 20 °C, the bath was removed and the reaction stirred at room temperature for 30 min. The mixture was poured into a 1/1 mixture of H_2O and sat. aq. $NaHCO_3$ solution (500 mL) and was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine, then were dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (30 mm x 15 cm silica gel, hexanes/EtOAc, 24/1) provided 937 mg (78%) of **9**:**12** in a 2:1 ratio by ^{1}H NMR integration.

Data for **9** and **12**:

bp: 60 °C (1.4 x 10^{-4} mmHg, ABT)

^{1}H NMR: (500 MHz, $CDCl_3$)

Note: 2:1 ratio **9:12** so integrals for **12** are ½ actual number of protons.

6.98 (t, *J* = 2.5, 1 H, HC(2)), 5.80 (m, 1.5 H, HC(8), HC(17)), 4.99 (m, 3 H, H_2C(9), H_2C(18)), 3.18 (m, 1 H, HC(5)), 2.90 (m, 1 H, H_2C(14)), 2.75 (td, *J* = 8.3, 0.8, 1 H, H_2C(12)), 2.46-2.66 (m, 3 H, H_2C(3), H_2C(13)), 2.25-2.32 (m, 2 H, *H*HC(7), H_2C(16)), 2.00-2.15 (m, 2 H, *H*HC(6), H*H*C(7)), 1.82-1.94 (m, 3 H, *H*HC(4), H*H*C(6), H_2C(15)), 1.46 (dtd, *J* = 14.5, 9.6, 5.1, 1 H, H*H*C(4)).

^{13}C NMR: (126 MHz, $CDCl_3$)

156.0 (C(1)), 154.5 (C(11)), 145.5 (C(10)), 138.7 (C(8)), 137.8 (C(17)), 137.1 (C(2)), 115.6 (C(18)), 115.0 (C(9)), 41.3 (C(5)), 36.9 (C(12)), 31.8, 31.3, 31.2, 31.0, 28.99, 28.97, 28.5, (C(3), C(4), C(6), C(7), C(14), C(15), C(16)), 19.3 (C(13))

IR: (neat)

3079 (m), 2944 (s), 1731 (w), 1640 (s), 1531 (s), 1452 (s), 1352 (s), 995 (m), 916 (m), 786 (w), 731 (m).

MS: (EI, 70 eV)

166 (1), 150 (11), 119 (17), 91 (45), 79 (61), 67 (51), 55 (100).

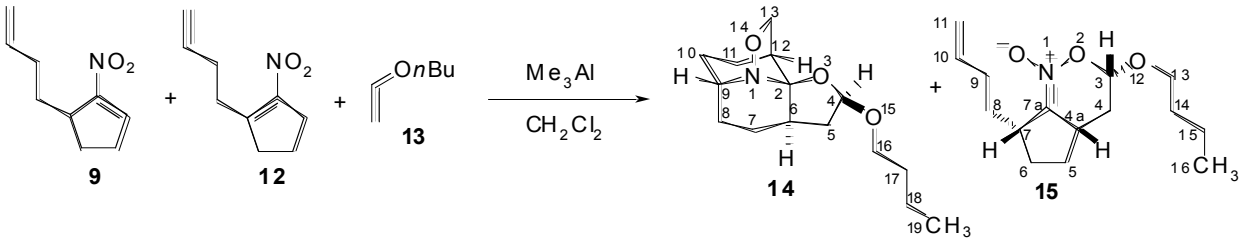
TLC: R_f 0.29 (hexanes/EtOAc, 19/1) [silica gel, UV]

Analysis: $C_9H_{13}NO_2$ (167.21)

Calcd: C, 64.65; H, 7.84; N, 8.38

Found: C, 64.66; H, 7.75; N, 8.10

Preparation of 4-Butoxy-1-aza-3,14-dioxatetracyclo[7.5.0.0^{2,6}.0^{2,12}]tetradecane (14) and 7-(3-Butenyl)-3-butoxy-3,4,4a,5,6,7-hexahydrocyclopent[c][1,2]oxazine 1-oxide (15)



n-Butyl vinyl ether (518 μL, 4.0 mmol, 2.0 equiv) was dissolved in CH_2Cl_2 (3.0 mL) at -78 °C (dry ice/*i*-PrOH bath) in a 50-mL, 2-necked round-bottom flask equipped with a N_2 inlet, a rubber septum, and a magnetic stir bar. A solution of trimethylaluminum (2.0 mL, 2.0 M in toluene, 4.0 mmol, 2.0 equiv) was added via syringe followed by a solution of nitroalkenes **9** and **12** (535 mg, 62.3% **9** by ^{1}H NMR analysis, 2.0 mmol **9**) in CH_2Cl_2 (3.0 mL) dropwise via cannula. The reaction mixture turned deep orange and was stirred at -78 °C for 30 min then was quenched at that temperature by the slow addition of 10 g silica gel suspended in CH_2Cl_2 (25 mL) added through a long stem funnel. Gas evolution was observed and the orange color dissipated. The mixture was filtered through a short silica gel plug (40 mm x 1 cm) eluting with EtOAc (200 mL) and the filtrate was dried ($MgSO_4$) in order to remove any adventitious water trapped in the mixture during the quench and cold filtration. After a second filtration through a short Celite pad (40 mm x 1 cm) to remove the drying agent, the filtrate was concentrated and the crude product was taken up in MeOH (40 mL). Silica gel (2 g) was added to the mixture and the suspension was concentrated at 50 °C (rotovap bath temperature) for 20 min. The crude product was purified by silica gel column chromatography by dry loading a slurry-packed silica

gel column (30 mm x 14 cm) and eluting with hexanes/EtOAc (gradient elution, 9/1 to 4/1 to 1/1) to provide 123 mg of a fraction containing mainly nitroalkene **12**, 257 mg (48%) of aminal **14**, and 193 mg (36%) of nitronate **15** all as heavy oils.

Data for **14**:

^{1}H NMR: (500 MHz, benzene-d_6)

5.13 (t, J = 5.3, 1 H, HC(4)), 4.12 (td, J = 5.8, 2.0, 1 H, *H*HC(13)), 3.94 (dt, J = 9.5, 6.5, 1 H, *H*HC(16)), 3.69 (d, J = 5.8, 1 H, H*H*C(13)), 3.42-3.48 (m, 1 H, HC(9)), 3.44 (dt, J = 9.5, 6.7, 1 H, H*H*C(16)), 2.12-2.19 (m, 1 H, HC(6)), 2.10, (td, J = 11.6, 4.9, 1 H, *H*HC(5)), 2.06 (dt(br), J = 5.8, 3.2, 1 H, HC(12)), 1.91-1.99 (m, 2 H, H*H*C(5), *H*HC(8)), 1.67-1.77 (m, 1 H, *H*HC(10)), 1.52-1.65 (m, 3 H, *H*HC(11), H_2C(17)), 1.31-1.48 (m, 3 H, *H*HC(7), H_2C(18)), 1.17-1.27 (m, 2 H, H*H*C(7), H*H*C(11)), 1.05 (m, 1 H H*H*C(8)), 0.84 (t, J = 7.5, 3 H, H_3C(19)), 0.74 (dd, J = 14.2, 6.9, H*H*C(10)).

^{13}C NMR: (126 MHz, benzene-d_6)

103.1 (C(4)), 99.1 (C(2)), 71.8 (C(13)), 67.8 (C(16)), 60.9 (C(9)), 44.8 (C(12)), 39.4 (C(6)), 38.6 (C(5)), 32.3 (C(17)), 27.6 (C(11)), 27.0 (C(8)), 22.6 (C(7)), 20.5 (C(10)), 19.6 (C(18)), 14.0 (C(19)).

IR: (neat)

2935 (s), 2875 (s), 2658 (w), 1723 (w), 1472 (s), 1453 (s), 1346 (s), 1286 (m), 1121 (s), 1041 (s), 993 (s), 936 (s), 827 (m), 744 (m).

MS: (EI, 70 eV)

267 (M^+, 22), 250 (30), 212 (26), 196 (86), 194 (100), 184 (31), 167 (33), 156 (44), 140 (71), 84 (84).

TLC: R_f 0.28 (hexanes/EtOAc, 2/1) [silica gel, $KMnO_4$]

HRMS: $C_{15}H_{25}NO_3$ (267.36)

Calcd: 267.1834

Found: 267.1837

Data for **15**:

^{1}H NMR: (500 MHz, benzene-d_6)

5.90 (ddt, J = 17.0, 10.1, 6.4, 1 H, HC(10)), 5.19 (dq, J = 17.1, 1.9, 1 H, *H*HC(11)), 5.09 (m, 1 H, H*H*C(11)), 5.01 (m, 1 H, HC(3)), 4.28 (dt, J = 9.4, 6.6, 1 H, *H*HC(13)), 3.41 (dt, J = 9.4, 6.4, 1 H, H*H*C(13)), 2.88 (m, 1 H, HC(7)), 2.28-2.36 (m, 1 H, *H*HC(8)), 2.14-2.24 (m, 1 H, *H*HC(9)), 2.02-2.12 (m, 3 H, *H*HC(4), HC(4a), H*H*C(9)), 1.56-1.68 (m, 2 H, H_2C(14)), 1.32-1.52 (m, 5H, *H*HC(5), H_2C(6), H_2C(15)), 1.24-1.36 (m, 2 H, H*H*C(4), H*H*C(8)), 1.06-1.16 (m, 1 H, H*H*C(5)), 0.96 (t, J = 7.5, 3 H, H_3C(16)).

^{13}C NMR: (126 MHz, benzene-d_6)

138.5 (C(10)), 132.5 (C(7a)), 114.9 (C(11)), 102.6 (C(3)), 68.9 (C(13)), 39.8 (C(7)), 36.7 (C(4)), 35.8 (C(4a)), 32.2 (C(14)), 31.8 (C(5)), 31.0 (C(9)), 28.6 (C(6)), 27.6 (C(8)), 19.5 (C(15)), 13.9 (C(16)).

IR: (neat)

3076 (w), 2958 (s), 2873 (s), 1733 (w), 1652 (s), 1454 (m), 1335 (m), 1223 (s), 1107 (s), 909 (m), 795 (s).

MS: (EI, 70 eV)

267 (M^+, 21), 250 (15), 196 (37), 139 (137), 119 (37), 110 (33), 93 (59), 79 (69), 67 (75), 56 (100).

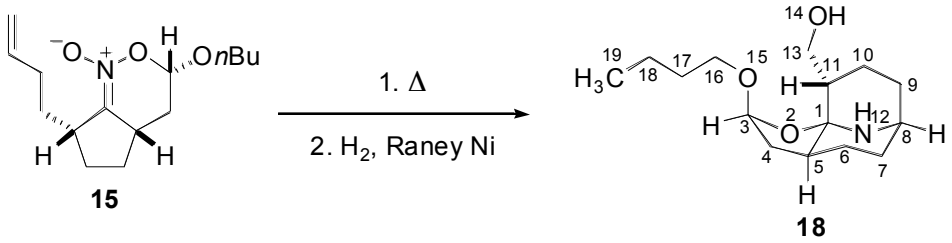
TLC: R_f 0.12 (hexanes/EtOAc, 2/1) [silica gel, UV]

Analysis: $C_{15}H_{25}NO_3$ (267.36)

Calcd: C, 67.38; H, 9.42; N, 5.24

Found: C, 67.44; H, 9.81; N, 5.15

Preparation of (3-Butoxy-2-oxa-12-azatricyclo[6.3.1.0^{1,5}]-11-dodecylmethanol (18)



Nitronate **15** (205 mg, 0.767 mmol) was dissolved in toluene (3.0 mL) in a 15-mL, 1-necked round-bottom flask equipped with a reflux condenser with N_2 inlet and a magnetic stir bar. A spatula tip of potassium carbonate (<10 mg) was added and the mixture was heated to reflux in a 115 °C oil bath for 2 h. The mixture was filtered through a sintered glass funnel eluting with toluene (10 mL), then was concentrated, and the residue was dissolved in EtOAc (20 mL). Silica gel (3 g) was added and the mixture was stirred at room temperature for 3 h. The mixture was filtered through a Celite pad (30 mm x 1 cm) eluting with EtOAc (100 mL) then was concentrated to give the crude product (207 mg). The crude aminal was mixed with a spatula tip of Raney Ni (previously washed with H_2O and MeOH, 2 x 2 mL each) in MeOH (10 mL) in a 25 mm x 15 cm test tube with a magnetic stir bar. The test tube was placed in a steel autoclave which was then pressurized to 380 psi H_2. The autoclave was placed on a magnetic stir plate and the mixture was stirred at room temperature for 14 h. After venting the hydrogen gas, the mixture was filtered through a Celite pad (30 mm x 2 cm) eluting with MeOH (40 mL) and the filtrate was concentrated to give the crude amino alcohol. Purification of the amino alcohol by silica gel column chromatography (20 mm x 12 cm, gradient elution, 9/1 to 4/1 CH_2Cl_2/MeOH) gave 95 mg (46%) of amino alcohol **18** as a white solid. Sublimation of a portion of the purified product at 1.2 mm Hg (80 °C) gave analytically pure material.

Data for **18**:

mp: 77-78 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

5.15-5.18 (m, 1 H, HC(3)), 4.27 (dd, *J* = 9.9, 2.2, 1 H, *H*HC(13)), 3.86 (dt, *J* = 9.5, 6.9, 1 H, *H*HC(16)), 3.66 (dd, *J* = 10.0, 3.0, 1 H, H*H*C(13)), 3.50 (br, 1 H,

HC(8)), 3.43 (dt, *J* = 9.2, 6.7, 1 H, H*H*C(16)), 2.17-2.30 (m, 3 H, *H*HC(4), *H*HC(9), *H*HC(10)), 1.84-2.05 (m, 4 H, $H_2C(6)$, H*H*C(10), HC(11)), 1.73-1.77 (m, 2 H, $H_2C(7)$), 1.60-1.73 (m, 2 H, H*H*C(4), HC(5)), 1.50-1.57 (m, 3 H, H*H*C(9), $H_2C(17)$), 1.34 (sextet, *J* = 7.5, 2 H, $H_2C(18)$), 0.91 (t, *J* = 7.3, 3 H, $H_3C(19)$).

^{13}C NMR: (126 MHz, $CDCl_3$)

103.0 (C(3)), 93.0 (C(1)), 69.5 (C(16)), 68.5 (C(13)), 52.3 (C(8)), 51.3 (C(5)), 37.8 (C(11)), 35.8 (C(4)), 31.7 (C(17)), 31.2 (C(7)), 29.9 (C(9)), 27.1 (C(10)), 25.5 (C(6)), 19.3 (C(18)), 13.9 (C(19)).

IR: (KBr plate)

3413 (m), 3270 (s), 2940 (s), 2863(s), 1477 (m), 1364 (m), 1245 (w), 1146 (m), 1078 (s), 1036 (s), 980 (s), 863 (m).

MS: (EI, 70 eV)

269 (M^+, 11), 252 (83), 212 (34), 196 (100), 168 (84), 154 (47), 141 (33), 98 (56).

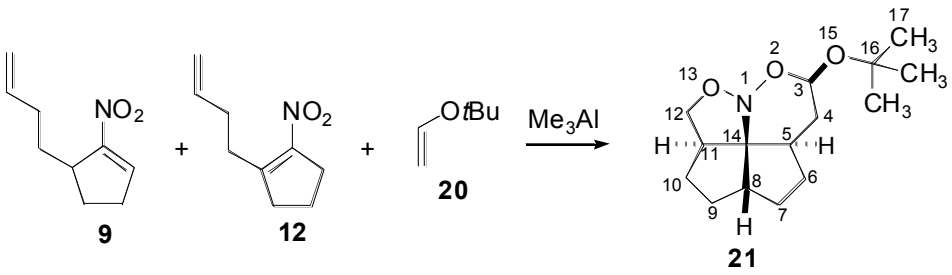
TLC: R_f 0.20 (CH_2Cl_2/MeOH, 4/1) [silica gel, $KMnO_4$]

Analysis: $C_{15}H_{27}NO_3$ (269.38)

Calcd: C, 66.88; H, 10.10; N, 5.20

Found: C, 66.89; H, 10.43; N, 5.25

Preparation of 1-Aza-2,13-dioxa-3-*tert*-butoxytetracyclo[6.5.1.0^{1,14}.0^{8,14}]tetradecane (21)



t-Butyl vinyl ether (350 μL, 2.66 mmol, 2.0 equiv) was dissolved in CH_2Cl_2 (3.0 mL) in a 50-mL, 2-necked round-bottom flask equipped with a N_2 inlet, a rubber septum, and a magnetic stir bar. The mixture was cooled to -78 °C in a dry ice/*i*-PrOH bath. A solution of trimethylaluminum (1.33 mL, 2.0 M in toluene, 2.66 mmol, 2.0 equiv) was added via syringe

followed by a solution of nitroalkenes **9** and **12** (334 mg, 66.7% **9** by ^{1}H NMR analysis, 1.33 mmol **9**) in CH_2Cl_2 (1.5 mL) dropwise via cannula. The solution turned deep orange and was stirred for 1 h at -78 °C. The reaction was quenched at that temperature by the addition of a suspension of 5 g silica gel in CH_2Cl_2 (25 mL) added slowly through a long stem funnel. The mixture was stirred until the color dissipated (1 min) and was immediately filtered through a Celite pad (30 mm x 1 cm) eluting with EtOAc (100 mL). The filtrate was dried ($MgSO_4$) and concentrated at 50 °C (rotovap bath temp) for 20 min. Purification of the product by alumina column chromatography (activated, basic Al_2O_3, Brockmann I, 20 mm x 18 cm, gradient elution, hexanes/EtOAc, 24/1 to 9/1 to 2/1) gave 239 mg (67%) of nitroso acetal **21** as a heavy oil. Bulb-to-bulb distillation of 200 mg of the product provided 190 mg of analytically pure material.

Data for **21**:

bp: 110 °C (1.3 x 10^{-4} mmHg, ABT)

^{1}H NMR: (500 MHz, benzene-d_6)

5.26 (dd, J = 10.0, 2.5, 1 H, HC(3)), 4.48 (t, J = 8.6, 1 H, *H*HC(12)), 3.42 (dd, J = 7.7, 4.1, 1 H, H*H*C(12)), 2.38 (q, J = 9.3, 1 H, HC(8)), 2.33 (pent, J = 4.7, 1 H, HC(11)), 1.78-1.85 (m, 1 H, *H*HC(9)), 1.70-1.77 (m, 1H, *H*HC(4)), 1.50-1.68 (m, 4 H, H*H*C(4), HC(5), *H*HC(6), *H*HC(7)), 1.22-1.44 (3 H, H*H*C(7), H_2C(10)), 1.28 (s, 9 H, H_3C(17)), 1.06 (dd, J = 13.1, 6.9, 1 H, H*H*C(6)), 0.74 (tdd, J = 12.5, 10.5, 6.0, 1 H, H*H*C(9)).

^{13}C NMR: (126 MHz, benzene-d_6)

93.2 (C(3)), 90.9 (C(14)), 76.2 (C(12)), 75.2 (C(16)), 49.1 (C(8)), 46.6 (C(11)), 41.2 (C(5)), 34.2 (C(4)), 32.6 (C(9)), 32.1 (C(7)), 29.9 (C(10)), 28.9 (C(17)), 28.5 C(6)).

IR: (neat)

2946 (s), 2867 (m), 1459 (m), 1396 (m), 1366 (m), 1261 (w), 1196 (m), 1139 (s), 1090 (s), 1005 (m), 918 (m), 890 (m), 825 (s).

MS: (EI, 70 eV)

267 (M^+, 1), 211 (12), 194 (27), 137 (100), 119 (74), 107 (30), 79 (29), 57 (75).

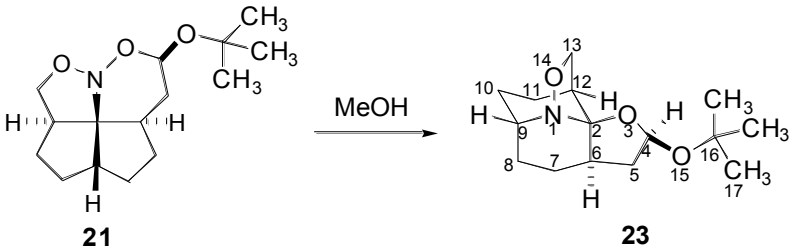
TLC: R_f 0.41 (hexanes/EtOAc, 4/1) [silica gel, $KMnO_4$] – partially rearranges on silica

Analysis: $C_{15}H_{25}NO_3$ (267.36)

Calcd: C, 67.38; H, 9.42; N, 5.24

Found: C, 67.29; H, 9.36; N, 5.33

Preparation of 4-*tert*-Butoxy-1-aza-3,14-dioxatetracyclo[7.5.0.0^{2,6}.0^{2,12}]tetradecane (23)



21 **23**

Nitroso acetal **21** (960 mg, 3.59 mmol) was dissolved in MeOH (12 mL) in a 25-mL, 1-necked round-bottom flask equipped with a N_2 inlet and a magnetic stir bar. The mixture was stirred at room temperature for 3 h. Concentration of the solution gave crude aminal **23** which was purified by silica gel column chromatography (30 mm x 12 cm, gradient elution, hexanes/EtOAc, 2/1 to 1/1) to give 710 mg of aminal **23**. Recrystallization of the residue from ~4 mL of refluxing pentane (hot filtration followed by slow cooling of the filtrate to room temperature then cooling to -20 °C) provided 447 mg of analytically pure **23**. Concentration of the mother liquor followed by cooling provided a second (45 mg) and third (183 mg) crop for a total of 675 mg (70%) of **23** as white hexagonal plates.

Data for **23**:

mp: 74-76 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

5.45 (d, *J* = 5.6, 1 H, HC(4)), 4.05 (td, *J* = 5.8, 1.7, 1 H, *H*HC(13)), 3.91 (d, *J* = 5.8, 1 H, H*H*C(13)), 3.50 (dt, *J* = 6.9, 3.5, 1 H, HC(9)), 2.93 (dt, *J* = 13.9, 7.2, 1 H, HC(6)), 2.49 (dt, *J* = 5.6, 3.0, 1 H, HC(12)), 2.26 (ddd, *J* = 13.3, 12.2, 5.6, 1 H, *H*HC(5)), 1.99-2.10 (m, 2 H, *H*HC(8), *H*HC(11)), 1.79-1.97 (m, 3 H, H*H*C(5), *H*HC(7), *H*HC(10)), 1.61-1.70 (m, 2 H, H*H*C(7), H*H*C(11)), 1.54-1.60 (m, 1 H, H*H*C(8)), 1.21 (s, 9 H, H_3C(17)), 1.16-1.25 (m, 1 H, H*H*C(10)).

^{13}C NMR: (126 MHz, $CDCl_3$)

99.3 (C(2)), 96.3 (C(4)), 74.1 (C(16)), 71.9 (C(13)), 60.7 (C(9)), 45.4 (C(12)), 39.2 (C(5)), 37.1 (C(6)), 29.0 (C(17)), 27.8 (C(11)), 26.9 (C(8)), 21.8 (C(7)), 19.7 (C(10)).

IR: (KBr plate)

2945 (s), 2875 (s), 1470 (m), 1455 (m), 1386 (m), 1360 (s), 1188 (s), 1120 (s), 1066 (s), 970 (s), 920 (s).

MS: (EI, 70 eV)

267 (M^+, 6), 211 (31), 194 (40), 182 (36), 156 (100), 140 (42), 62 (36), 57 (49).

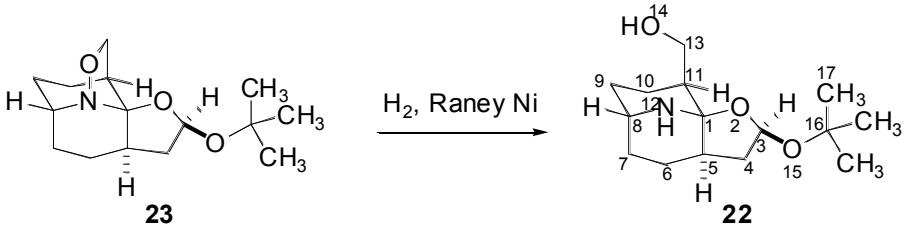
TLC: R_f 0.15 (hexanes/EtOAc, 1/1) [silica gel, $KMnO_4$]

Analysis: $C_{15}H_{25}NO_3$ (267.36)

Calcd: C, 67.38; H, 9.42; N, 5.24

Found: C, 67.38; H, 9.60; N, 5.37

Preparation of (3-*tert*-Butoxy-2-oxa-12-azatricyclo[6.3.1.0^{1,5}]-11-dodecyl)methanol (22)



23 **22**

A solution of aminal **23** (267 mg, 1.0 mmol) in MeOH (4.0 mL) was added to test tube (25 mm x 15 cm) containing a spatula tip of Raney nickel (previously washed with H_2O and MeOH, 2 x 2 mL each) and a magnetic stir bar. The tube was placed in a steel autoclave which was then pressurized to 380 psi H_2. The autoclave was placed on a magnetic stir plate and the mixture was stirred for 15 h at room temperature. After venting the excess H_2, the mixture was filtered through a Celite pad (30 mm x 2 cm) eluting with MeOH (200 mL). Concentration of the filtrate gave crude amino alcohol **22**. Recrystallization of the residue from ~10 mL of refluxing hexane (hot filtration followed by slow cooling to -20 °C) gave 227 mg of analytically

pure **22**. Concentration of the mother liquor followed by slow cooling gave a second crop (36 mg) for a total of 263 mg (98%) of **22** as white needles.

Data for **22**:

mp: 96-98 °C (hexane)

^{1}H NMR: (500 MHz, $CDCl_3$)
5.42 (d, *J* = 5.3, 1 H, HC(3)), 3.95 (dd, *J* = 10.8, 6.4, 1 H, *H*HC(13)), 3.92 (dd, *J* = 10.7, 3.4, 1 H, H*H*C(13)), 3.33 (t (br), *J* = 5.8, 1 H, HC(8)), 2.31 (dtd, *J* = 11.2, 7.3, 3.6, 1 H, HC(5)), 2.05-2.25 (m, 3 H, *H*HC(4), *H*HC(6), *H*HC(10)), 1.88-1.97 (m, 1 H, *H*HC(9)), 1.67-1.87 (m, 4 H, H*H*C(4), *H*HC(7), H*H*C(10), HC(11)), 1.59-1.66 (m, 1 H, *H*HC(6)), 1.38-1.45 (m, 1 H, H*H*C(7)), 1.35 (ddt, *J* = 13.7, 6.1, <1, 1 H, H*H*C(9)), 1.21 (s, 9 H, H_3C(17).

^{13}C NMR: (126 MHz, $CDCl_3$)
97.0 (C(3)), 93.1 (C(1)), 74.2 (C(16)), 65.6 (C(13)), 49.9 (C(8)), 44.0 (C(11)), 39.6 (C(5)), 38.2 (C(4)), 28.8 (C(17)), 26.5 (C(9)), 26.1 (C(7)), 25.3 (C(10)), 23.5 (C(6)).

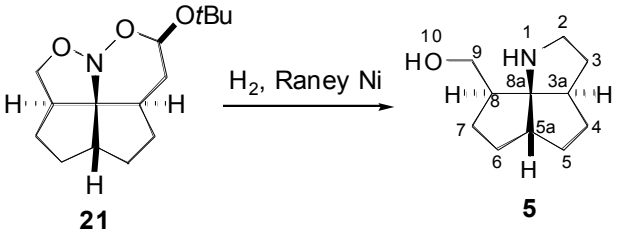
IR: (KBr plate)
3270 (m), 3119 (br, m), 2967 (s), 2934 (s), 2913 (s), 2864 (m), 1475 (m), 1450 (m), 1358 (m), 1140 (m), 1044 (s), 999 (s), 969 (m), 958 (m).

MS: (EI, 70 eV)
269 (M^+, 8), 213 (27), 196 (62), 184 (100), 126 (36).

TLC: R_f 0.16 (CH_2Cl_2/MeOH, 4/1) [silica gel, $KMnO_4$]

Analysis: $C_{15}H_{27}NO_3$ (269.38)
Calcd: C, 66.88; H, 10.10; N, 5.20
Found: C, 66.74; H, 10.32; N, 5.29

Preparation of (Decahydro-1-azacyclopenta[c]-8-pentalenyl)methanol (5)



A solution of nitroso acetal **21** (303 mg, 1.13 mmol) in EtOAc (4.5 mL, 9/1, EtOAc/H_2O saturated EtOAc) was added to a test tube (25 mm x 15 cm) containing a spatula tip of Raney nickey (previously washed with H_2O, MeOH, THF, and EtOAc, 2 x 2 mL each) and a magnetic stir bar. The tube was placed in a steel autoclave which was then pressurized to 380 psi H_2. The autoclave was placed on a magnetic stir plate and the mixture was stirred for 20 h at room temperature. After venting the excess H_2, the mixture was filtered through a Celite pad (30 mm x 2 cm) eluting with EtOAc (200 mL) and the filtrate was dried (Na_2SO_4) and concentrated to give the crude amino alcohol. Purification of the product by silica gel column chromatography (20 mm x 12 cm, CH_2Cl_2/MeOH/NH_4OH, 4/1/0.1) provided 175 mg (85%) of amino alcohol **5** as a heavy oil >95% pure by ^{1}H NMR analysis. Sacrificial bulb-to-bulb distillation at 2 x 10^{-4} mm Hg (90 °C) gave an analytical sample of **5**, but trace solvent trapped in the heavy oil precluded a satisfactory elemental analysis.

Data for **5**:

bp: 90 °C (2 x 10^{-4} mmHg, ABT)

^{1}H NMR: (500 MHz, $CDCl_3$)

3.66 (d, *J* = 10.0, 2 H, $H_2C(9)$), 2.96 (ddd, *J* = 11.1, 6.6, 4.5, 1 H, *H*HC(2)), 2.69 (ddd, *J* = 10.9, 8.4, 5.8, 1 H, H*H*C(2)), 2.14 (qd, *J* = 7.5, 3.6, 1 H, HC(3a)), 2.00-2.06 (m, 1 H, HC(5a)), 1.86-1.95 (m, 1 H, *H*HC(3)), 1.73-1.86 (m, 4 H, *H*HC(4), *H*HC(5), *H*HC(6), HC(8)), 1.50-1.65 (m, 2 H, $H_2C(7)$), 1.40-1.46 (m, 1 H, H*H*C(4)), 1.34-1.39 (m, 1 H, H*H*C(5)), 1.27 (ddt, *J* = 12.2, 8.4, 6.9, 1 H, H*H*C(3)), 1.09-1.17 (m, 1 H, H*H*C(6)).

^{13}C NMR: (126 MHz, $CDCl_3$)

84.6 (C(8a)), 64.1 (C(9)), 52.6 (C(5a)), 51.5 (C(3a)), 49.1 (C(8)), 47.0 (C(2)), 33.7 (C(3)), 30.75, 30.73 (C(4), C(5)), 30.1 (C(6)), 28.8 (C(7)).

IR: (neat)

3000-3400 (w, br), 3267 (m), 2942 (s), 2900 (s), 1450 (m), 1901 (m).

MS: (EI, 70 eV)

181 (M^+, 27), 164 (17), 122 (100), 108 (19), 95 (16).

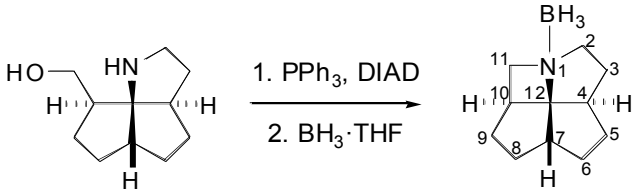
TLC: R_f 0.41 (CH_2Cl_2/MeOH/NH_4OH, 39:10:1) [silica gel, $KMnO_4$]

HRMS: $C_{11}H_{19}NO$ (181.27)

Calcd: 181.1467

Found: 181.1470

Preparation of *cis,cis,cis,cis*-1-Boranyl-1-aza[5.4.1.0^{4,12}.0^{10,12}]tetracyclododecane or *c,c,c,c*-[5.5.5.4]-1-Azfenestrane·Borane Complex (24)



5 **24**

To a solution of amino alcohol **5** (245 mg, 1.35 mmol) in CH_2Cl_2 (6.8 mL) in a 25-mL, 2-necked round-bottom flask equipped with a N_2 inlet, rubber septum, and a magnetic stir bar was added triphenylphosphine (355 mg, 1.35 mmol, 1.0 equiv) followed by diisopropyl azodicarboxylate (262 μL, 1.35 mmol, 1.0 equiv). The pale-yellow solution was stirred for 40 min then was cooled to -78 °C in a dry ice/*i*-PrOH bath. Borane·THF complex (6.76 mL, 1.0 M in THF, 6.76 mmol, 10 equiv) was added slowly via syringe, then the cooling bath was removed and the reaction was allowed to warm to room temperature over 1 h. The mixture was poured slowly into H_2O (100 mL) then was extracted with CH_2Cl_2 (50 mL). Brine (25 mL) was added to the aqueous layer which was then extracted again with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude azafenestrane **24**.

Purification by silica gel column chromatography (15 cm x 20 mm, gradient elution, hexanes/EtOAc, 19/1 to 9/1) gave 208 mg (87%) of azafenestrane·borane complex **24** as a white solid. Recrystallization of a portion of the complex (100 mg) from ~7 mL of refluxing hexane (hot filtration followed by slow cooling to -20 °C) provided 83 mg of analytically pure **24** as fine white needles.

Data for **24**:

mp: 128-129 °C (hexane)

^{1}H NMR: (500 MHz, $CDCl_3$)
3.42-3.50 (m, 2 H, *H*HC(2), *H*HC(11)), 3.23-3.35 (m, 3 H, H*H*C(2), HC(7), H*H*C(11)), 2.64 (m, 1 H, HC(10)), 2.58 (p, J = 7.7, 1 H, HC(4)), 2.11-2.26 (m, 2 H, *H*HC(3), *H*HC(8)), 1.83-2.00 (m, 5 H, H*H*C(3), *H*HC(6), *H*HC(5), H_2C(9)), 1.45-1.53 (m, 1 H, H*H*C(8)), 1.37-1.45 (m, 1 H, H*H*C(5)), 1.26-1.36 (m, 1 H, H*H*C(6)), 1.18-1.80 (br, m, 3 H, H_3B).

^{13}C NMR: (126 MHz, $CDCl_3$)
99.1 (C(12)), 66.9 (C(11)), 62.2 (C(2)), 50.4 (C(4)), 45.4 (C(7)), 39.3 (C(10)), 33.7 (C(6)), 33.3 (C(5)), 31.3 (C(8)), 31.2 (C(3)), 30.8 (C(9)).

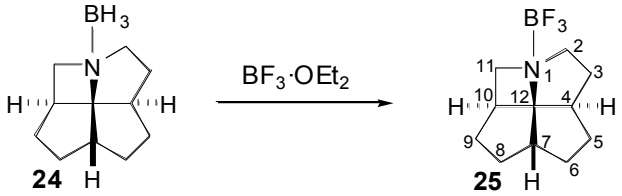
IR: (KBr plate)
3446 (m), 2956 (s), 2863 (m), 2355 (m), 2260 (m), 1450 (m), 1164 (s), 1051 (m), 1037 (m).

MS: (FI, 70 eV)
177 (M^+, 15), 175 (100), 174 (22), 163 (M^+- BH_3, 17).

TLC: R_f 0.26 (hexanes/EtOAc, 4/1) [silica gel, $KMnO_4$]

Analysis: $C_{11}H_{20}BN$ (177.09)
Calcd: C, 74.60; H, 11.38; N, 7.91; B, 6.10
Found: C, 74.69; H, 11.66; N, 8.00; B, 6.09

Preparation of *cis,cis,cis,cis*-1-Trifluoroboranyl-1-aza[5.4.1.0^{4,12}.0^{10,12}]tetracyclododecane or *c,c,c,c*-[5.5.5.4]-1-Azfenestrane Boron Trifluoride Complex (25)



To a solution of azafenestrane·borane complex **24** (64.3 mg, 0.363 mmol) in $CDCl_3$ (2.0 mL) in a 10-mL, 2-necked round-bottom flask equipped with a N_2 inlet, rubber septum, and a magnetic stir bar was added boron trifluoride diethyl etherate (460 μL, 3.63 mmol, 10 equiv) whereupon gas evolution was observed. The mixture was stirred for 1 h then was quenched by the addition of 1 g of silica gel in CH_2Cl_2 (20 mL). The mixture was concentrated and loaded onto a silica column for purification (10 mm x 15 cm, 4/1, hexanes/EtOAc) to give 39 mg of crystalline azafenstrane·trifluoroborane complex **25** (47%). A portion of the complex (10 mg) was dissolved in hot hexane (~2 mL, ~65 °C). Gravity filtration of the solution through a pre-washed (hexane), warmed (heat gun) Pasteur pipette filter (small cotton plug) into a 4-mL glass vial provided a warm solution of **25** in hexane. The vial was capped and the solution was allowed to slowly cool to room temperature (vial covered by an upside-down 50-mL beaker) over 4 h providing flat, white needles that were suitable for X-ray crystallographic analysis.

Data for **25**:

mp: 134-136 °C (hexane)

^{1}H NMR: (500 MHz, $CDCl_3$)

3.78-3.87 (m, 2 H, *H*HC(2), *H*HC(11)), 3.32 (t, *J* = 9.8, 1 H, H*H*C(11)), 3.25 (p, *J* = 7.5, 1 H, HC(7)), 3.15 (br, q, *J* = 9.0, 1 H, H*H*C(2)), 2.72 (tt, *J* = 7.9, 5.8, 1 H, HC(10)), 2.61 (tt, *J* = 9.0, 7.5, 1 H, HC(4)), 2.21-2.32 (m, 2 H, *H*HC(3), *H*HC(8)), 1.86-2.06 (m, 5 H, H*H*C(3), *H*HC(5), *H*HC(6), H_2C(9)), 1.48-1.56 (m, 1 H, H*H*C(5)), 1.42 (dq, *J* = 13.5, 6.6, 1 H, H*H*C(8)), 1.28-1.37 (m, 1 H, H*H*C(6)).

^{13}C NMR: (126 MHz, $CDCl_3$)

100.3 (C(12)), 60.0 (C(2)), 55.9 (C(11)), 50.4 (C(4)), 46.6 (C(7)), 39.4 (C(10)), 33.2 (C(6)), 32.4 (C(5)), 32.0 (C(8)), 31.1 (C(9)), 30.9 (C(3)).

IR: (KBr plate)

3436 (w), 2959 (m), 2873 (w), 1458 (w), 1167 (m), 1114 (s), 979 (m), 931 (s), 921 (s), 906 (m), 893 (m).

MS: (FI, 70 eV)

164 (12), 163 (M^+- BF_3, 100).

TLC: R_f 0.12 (hexanes/EtOAc, 4/1) [silica gel, $KMnO_4$]

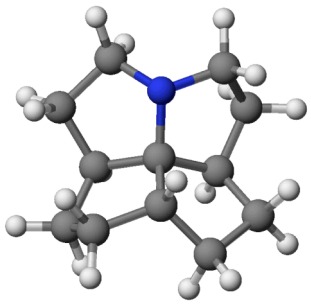
Analysis: $C_{11}H_{17}BF_3N$ (231.07)

Calcd: C, 57.18; H, 7.42; N, 6.06; B, 4.68

Found: C, 57.34; H, 7.58; N, 6.02; B, 4.69

Details on Calculations

All calculations were performed with CAChe WorkSystem Pro Version 6.1.10, Fujitsu Limited. Global minima were found by systematically searching conformers using CONFLEX (MM2 level), further minimizing the lowest energy conformers with a semi-empirical method (PM3), and finally calculating total energy at DFT-B88 LYP level. For *cis,cis,cis,cis*-[5.5.5.5]-1-azafenestrane, 14 structures within 1 kcal/mol of the lowest energy structure were generated. For *cis,cis,cis,cis*-[5.5.5.4]-1-azafenestrane, 2 structures within 4.0 kcal/mol of the lowest energy structure were generated. The global minima for both compounds, as well as the relevant structural data are shown below. Relative strain energy was calculated as footnoted in the main text of the article.



cis,cis,cis,cis-[5.5.5.5]-1-azafenestrane

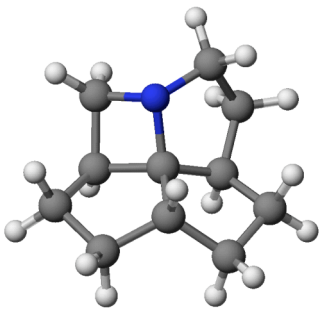
Total E (kcal/mol) = -328353.682

Central Angles:
C-C-C = 117.6
N-C-C = 114.5

cis,cis,cis,cis-[5.5.5.4]-1-azafenestrane

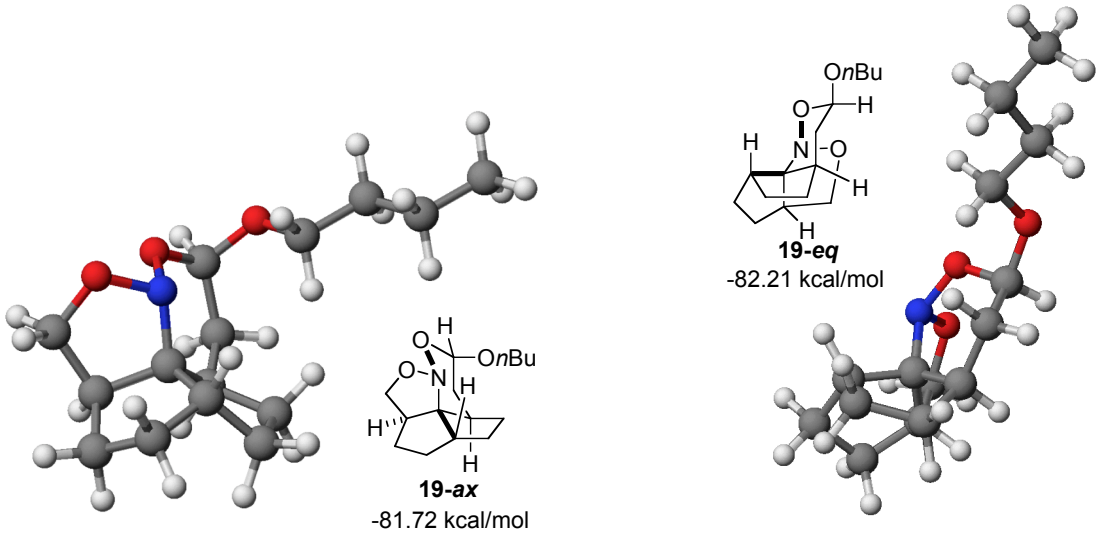
Total E (kcal/mol) = -303678.354

Central Angles:
C-C-C = 123.6
N-C-C = 117.9



Local minima for **19-*ax* and 19-*eq*** were calculated beginning from conformers containing a perfect chair for the six-membered ring with the butyloxy group in the axial or

equatorial position respectively (depending on the "flip" of the chair). An energy minimization was then carried out (PM3) giving the minimized structures below with the butyloxy group in *pseudo*-axial and *pseudo*-equatorial positions respectively.



c,c,c,c-[5.5.5.4]-1-Azfenestrane Boron Trifluoride Complex (25): X-Ray Structure Analysis

The BF_3 adduct of 5.5.5.4-1-azafenestrane (**25**) crystallized in a centrosymmetric, unambiguous space group. Molecule **25** has three unique conformations occupying the same site (forms 1, 2, and 3, Figure 1). Oddly, both enantiomers exist in different proportions at this site. Inversion symmetry generates the enantiomer of each conformation at a separate site.

The assignment of atomic sites belonging to each form was carried out via bond length correspondence. No other assignment maintains a reasonable correlation between chemically

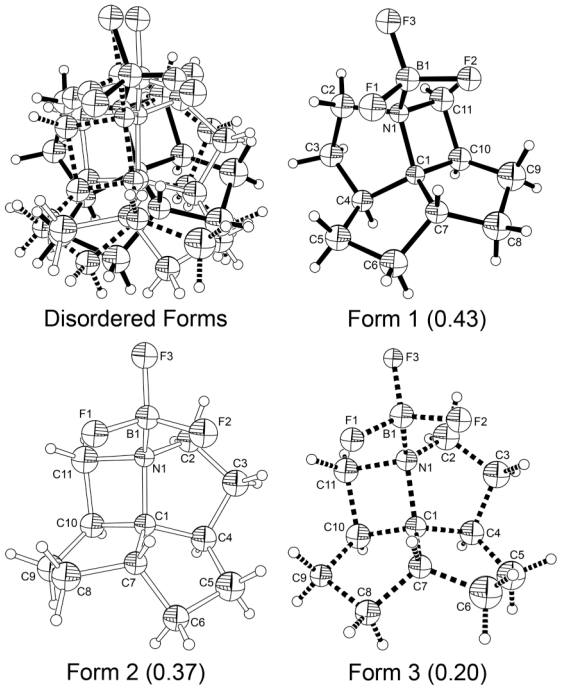


Figure 1. Labeled plots of **25** showing forms 1, 2, and 3 (relative site occupancy) with displacement spheres drawn at 35% probability for non-H atoms.

equivalent C-C and C-N bonds. Of particular interest in fenestrane chemistry are the two distorted angles around the central tetrasubstituted carbon. All of the forms have similar angles around C1 with average values for angles N1-C1-C7 and C4-C1-C10 of 120.3(10)° and 121.3(11)°, respectively. None of the C1 angles differ by more than 1 su from the mean.

	C10–C1–C4	C7–C1–N1
form 1	120.7(8)°	119.8(7)°
form 2	121.2(10)°	119.2(8)°
form 3	121.9(13)°	121.8(12)°

Azafenestrane **25** was primarily synthesized to quantify the deviation of the central carbon from typical tetrahedral geometry. In this case, crystal packing forces failed to isolate a unique geometry, so the question of which form best represents the low-energy conformation of the compound remained unclear.

The relative geometries of the three forms of **25** are depicted as best-fit[3] overlays in Figure 2. From this representation, it is clear that the three forms differ mainly in the conformations of the five-membered rings A, B, and C. These equilibrations are clearly enumerated by changes in dihedral angles terminating at bridgehead atoms N1, C4, C7, and C10. Converting form 1 to form 2 requires opposing flips of rings A and C; torsion N1–C2–C3–C4 rotates 69(2)° and C7–C8–C9–C10 rotates -63(2)°. Converting form 1 to 3 requires flips of rings A and B; N1–C2–C3–C4 rotates 69(3)° and C4–C5–C6–C7 rotates 52(3)°. And, converting form 2 to 3 requires ring B and C flips; C4–C5–C6–C7 rotates

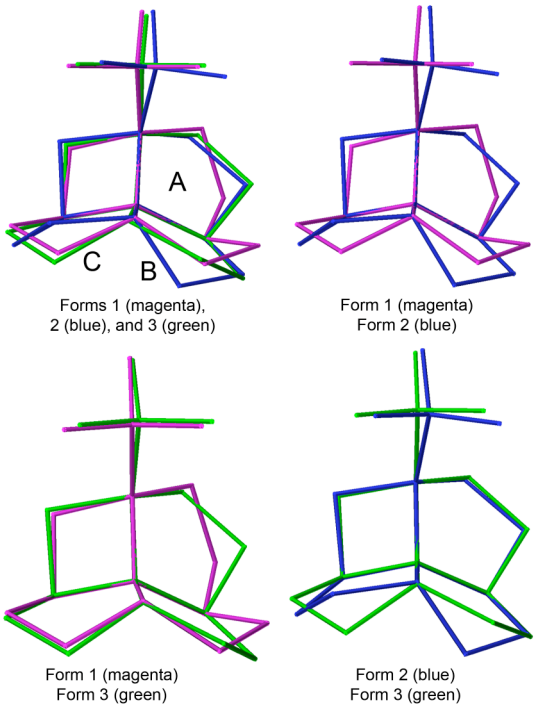


Figure 2. Best-fit overlays of the same enantiomer of the three forms of **25** viewed roughly down the C7–C1 bond.

-52(3)° and C7–C8–C9–C10 rotates -67(3)°. Relative site occupancies suggest form 1 is most stable within this crystal environment.

Calculations[3] suggest very little energy difference between forms 1 and 2 but a slight increase for form 3. With respect to form 1, the relative ΔH_f for forms 2 and 3 are respectively -0.15 and +3.69 kcal/mol (AM1), and +0.65 and +3.79 kcal/mol (PM5). The relative total energy for Forms 2 and 3 are respectively +0.09 and +4.39 kcal/mol (DFT B88-LYP). These energy differences are small with respect to crystal packing forces. Since the two most populated forms are enantiomeric, the unit cell is most likely composed of a static distribution of locally ordered forms. The lattice can readily accommodate either enantiomer of **25** in form 1, 2 or 3 as the crystal grows.

X-Ray Experimental Refinement

Systematic conditions suggested the unambiguous space group. The structure was phased by direct methods.[4] The proposed model includes three unique forms disordered over the same site. Refinement of chemically similar structural models under P1 and the 3 non-isomorphic subgroups failed to resolve this disorder. The three disordered forms were restrained to similar bond lengths and angles with effective standard deviations of 0.01 and 0.03Å, respectively. Owing to the paucity of data observed at the $4\sigma(F_o)$ level, isotropic displacement parameters were refined for each site; parameters for disordered positions separated by less than 1.38 Å were restrained to similar values (esd 0.02). Bridgehead H atom positions surfaced in late difference Fourier maps along with a few methylene H atom positions but given the complexity of the proposed model, no refinement of H atom positions was tested. H atoms were included as riding idealized contributors with U's assigned as 1.2 times adjacent Ueq. The rms deviation for the 153 distance restraints converged without additional dampening to 0.030 (rms sigma 0.025). The rms deviation for 83 displacement restraints converged to 0.013 (rms sigma 0.020). The space group choice was confirmed by successful convergence of the full-matrix least-squares refinement on F^2.[4] Three of the highest four peaks in the final difference Fourier map were located in the vicinity of F atoms suggesting possible additional F atom disorder not accounted for in this proposed model; the final map had no other significant features. A final analysis of variance between observed and calculated structure factors showed dependence on resolution.

All energy calculations were performed with CAChe WorkSystem Pro Version 6.1.10.[3] The best-fit overlays (Figure 2) were generated by selecting the central and bridgehead atoms in the same enantiomer of all forms (mirror transformation) and performing a "superimpose" command. Relative gas phase heats of formation at 298 K (ΔH_f) were calculated with standard semiempirical basis sets (AM1 and PM5) using the "current energy" command and do not involve any optimization of the observed solid-state structure. In addition, total energy of the three forms was calculated using ab initio density functional theory with the B88-LYP exchange-correlation energy functional. ΔH_f and total energy values are reported relative to form 1, which has been assigned an energy of 0 kcal/mol for simplicity.

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