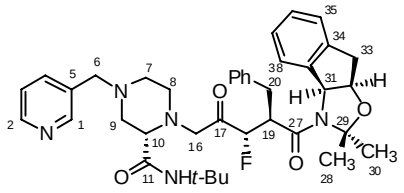
Evidence for an Oxyvinyliminium Ion. On the Inherent Instability of α-Amino α'-Fluoro Ketones.

Andrew G. Myers* and Joseph K. Barbay



anti-4

Ketone anti-4. A solution of dimethyl sulfoxide in dichloromethane (1.25 M, 322 μL, 0.403 mmol, 4.0 equiv) was added to a solution of oxalyl chloride (26.4 μL, 0.302 mmol, 3.0 equiv) in dichloromethane (0.2 mL) at –78 °C. The mixture was stirred at –78 °C for 10 min before addition of a solution of alcohol **anti,anti-3**[4] (67.7 mg, 0.101 mmol, 1 equiv) in dichloromethane (0.6 mL) via cannula. The transfer was quantitated with an additional 0.6-mL portion of dichloromethane. The mixture was stirred at –78 °C for 10 min. Triethylamine (126 μL, 0.907 mmol, 9.0 equiv) was added and the mixture was stirred at –78 °C for 10 min, then was allowed to warm to 0 °C and was stirred at that temperature for an additional 40 min. Water (5 mL) was added, and the resulting mixture was stirred at 0 °C for 5 min. The mixture was extracted with three 5-mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate, were filtered, and were concentrated. The crude product was immediately purified by chromatography (Sephadex LH-20, dichloromethane, gravity). Ketone **anti-4** was obtained as a light yellow oil of mass 46.2 mg (68%): R_f 0.39, 50% dichloromethane–tetrahydrofuran; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, 1H, J = 4.4, 1.2 Hz, C_2**H**), 8.48 (br s, 1H, C_1**H**), 7.59 (dt, 1H, J = 7.9, 1.8 Hz, C_4**H**), 7.11–7.36 (m, 8H, Ar**H**), 6.74 (t, 1H, J = 7.2 Hz, C_{37}**H**), 5.75 (d, 1H, J = 7.6 Hz, C_{38}**H**), 5.33 (d, 1H, J = 4.4 Hz, C_{31}**H**), 4.95 (dd, 1H, J_{HF} = 47.6 Hz, J_{HH} = 9.2 Hz, C**H**F), 4.82 (t, 1H, J = 3.0 Hz, C_{32}**H**), 3.64–3.65 (m, 2H, C_{16}**H**$_2$), 3.54–3.61 (m, 1H, CFC**H**), 3.43 (dd, 1H, J = 12.8, 10.0, Hz, C_{20}**H**), 3.39 (s, 2H, C_6**H**$_2$), 3.11 (dd, 1H, J = 6.6, 3.4 Hz, C_{10}**H**), 3.02–3.04 (m, 2H, C_{33}**H**$_2$), 2.90 (dd, 1H, J = 13.4, 3.4 Hz, C_{20}**H**), 2.83–2.87 (m, 1H, C_7**H**$_2$ or C_8**H**$_2$), 2.74 (dd, 1H, J = 11.8, 3.4 Hz, C_9**H**$_2$), 2.46–2.54 (m, 2H, C_7**H**$_2$ or C_8**H**$_2$), 2.36–2.42 (m, 2H, C_9**H**$_2$, C_7**H**$_2$ or C_8**H**$_2$), 1.65 (s, 3H, C(C**H**$_3$)$_2$), 1.32 (s, 3H, C(C**H**$_3$)$_2$), 1.26 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5 (d, J_{CCF} = 24 Hz), 169.0 (d, J_{CCCF} = 8.4 Hz), 166.3, 150.2, 148.8, 140.0, 139.8, 138.0, 136.5, 132.5, 129.5, 128.8, 128.0, 127.1, 126.9, 125.4, 123.7, 123.3, 97.1, 94.3 (d, J_{CF} = 184 Hz), 79.1, 65.8, 64.7, 62.0, 59.9, 55.3, 52.0, 50.9, 50.5, 49.1 (d, J_{CCF} = 18 Hz), 36.0, 33.7 (d, J_{CCCF} = 6.1 Hz), 28.8, 26.4, 23.9; ^{19}F NMR (11:1 mixture of rotamers, asterisk denotes minor rotamer peaks, 376 MHz, $CDCl_3$) δ -192.5 (d, J_{HF} = 46.7 Hz), -188.0* (d, J_{HF} = 46.1 Hz); FTIR (neat film), cm^{-1} 1734 (m, CFC=O), 1650 (s, 1650, NC=O), 1425 (s), 732 (s); HRMS (TOF MS ES+) *m/z* calcd for $C_{39}H_{49}N_5O_4F$ $(M+H)^+$ 670.3768, found 670.3795.

Ketone syn-4. A solution of dimethyl sulfoxide in dichloromethane (1.25 M, 148 μL, 0.185 mmol, 4.0 equiv) was added to a solution of oxalyl chloride (12.1 μL, 0.138 mmol,

3.0 equiv) in dichloromethane (0.2 mL) at –78 °C. The mixture was stirred at –78 °C for 10 min before addition of a solution of alcohol **anti,syn-3**[4] (31.0 mg, 46.1 μmol, 1 equiv) in dichloromethane (0.3 mL) via cannula. The transfer was quantitated with an additional 0.2-mL portion of dichloromethane. The mixture was stirred at –78 °C for 10 min. Triethylamine (57.9 μL, 0.415 mmol, 9.0 equiv) was added and the mixture was stirred at –78 °C for 10 min, then was allowed to warm to 0 °C and was stirred at that temperature for an additional 20 min. Water (5 mL) was added, and the resulting mixture was stirred at 0 °C for 5 min. The mixture was extracted with three 5-mL portions of ethyl acetate. The combined organic extracts were washed with two 7-mL portions of water, were dried over sodium sulfate, were filtered, and were concentrated, yielding crude ketone **syn-4** as an oil of mass 32.5 mg (quant). A sample of ketone **syn-4** was purified by chromatography (Sephadex LH-20, dichloromethane, gravity): R_f 0.38, 50% dichloromethane–tetrahydrofuran; ^{1}H NMR (400 MHz, $CDCl_3$), numbering scheme as for **anti-4**, δ 8.49–8.53 (m, 2H, C_1**H** and C_2**H**), 7.64 (dt, 1H, J = 7.7, 1.9 Hz, Hz, C_4**H**), 7.17–7.40 (m, 8H, Ar**H**), 6.98 (s, 1H, CON**H**), 6.91 (td, 1H, J = 7.2, 2.0 Hz, C_{37}**H**), 6.18 (d, 1H, J = 8.0 Hz, C_{31}**H**), 5.41 (d, 1H, J = 4.0 Hz, C_{31}**H**), 5.00 (d, 0.5H, J = 5.2 Hz, half of C**H**F dd), 4.87–4.88 (m, 1.5 H, C_{32}**H**, half of C**H**F dd), 3.69–3.79 (m, 1H, CFC**H**), 3.44–3.59 (m, 4H, C_{16}**H**$_2$ and C_6**H**$_2$), 3.35 (dd, 1H, J = 14.0, 8.4 Hz, C_{20}**H**), 3.06–3.13 (m, 4H, both C_{33}**H**, one C_{20}**H**, one C_7**H**$_2$ or C_8**H**$_2$), 3.01 (dd, 1H, J = 9.2, 3.6 Hz, C_{10}**H**), 2.93 (d of m, 1H, J = 10.8 Hz, C_9**H**$_2$), 2.69 (d of m, 1H, J = 8.4 Hz, C_7**H**$_2$ or C_8**H**$_2$), 2.34–2.45 (m, 2H, C_7**H**$_2$ or C_8**H**$_2$), 2.23 (dd, 1H, J = 11.2, 9.2 Hz, C_9**H**$_2$), 1.73 (s, 3H, C(C**H**$_3$)$_2$), 1.31 (s, C(C**H**$_3$)$_2$), 1.29 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8 (d, J_{CCF} = 25 Hz), 170.3 (d, J_{CCCF} = 7.6 Hz), 166.7, 150.2, 148.6, 140.3, 139.8, 138.0, 136.5, 132.8, 129.5, 128.8, 128.2, 127.1,127.0, 125.7, 123.6, 123.3, 97.1, 95.4 (d, J_{CF} = 186 Hz), 79.2, 66.5, 66.0 (d, J_{CCCF} = 2.3 Hz), 62.5, 56.4, 52.3, 51.2, 50.8 (d, J_{CCF} = 19 Hz), 50.7, 50.6, 36.1, 33.9 (d, J_{CCCF} = 8.3 Hz), 28.8, 26.3, 24.9; ^{19}F NMR (18:1 mixture of rotamers, asterisk denotes minor rotamer peaks, 376 MHz, $CDCl_3$) δ -194.6 (dd, J_{HF} = 47.4, 10.5 Hz), –197.4* (m); FTIR (neat film), cm^{-1} 1732 (m, CFC=O), 1658 (s, NC=O), 1643 (s, NC=O), 1426 (s), 731 (s); HRMS (FAB) *m/z* calcd for $C_{39}H_{48}N_5O_4FNa$ $(M+Na)^+$ 692.3588, found 692.3597.

Hydrolytic Fragmentation of Ketone anti-4 (NMR Experiment). *p*-Dioxane-d_8 (0.5 mL), deuterium oxide (0.5 mL), and 1,1,2,2-tetrachloroethane (2 μL, 18.9 μmol) as an internal standard were added in sequence to ketone **anti-4** (10.5 mg, 15.7 μmol) in a round-bottom flask. The progress of the reaction was monitored periodically by ^{1}H-NMR. Ketone **anti-4** was completely consumed within 19 h, with formation of piperazine **7**, aldehyde **8**, and the corresponding keto aldehyde hydrate. Analytical samples of piperazine **7** and aldehyde **8** were obtained from a reaction run in the same manner (without an internal standard) in protio- solvents, after concentration and isolation by flash column chromatography (gradient elution from 25% ethyl acetate–hexanes to 50% ethyl acetate–hexanes, then 30% tetrahydrofuran–dichloromethane to 50% tetrahydrofuran–dichloromethane, then 3% methanol–dichloromethane:ammonium hydroxide 98:2): Piperazine **7**: R_f 0.32, 10% methanol–dichloromethane saturated with ammonia; ^{1}H NMR (400 MHz, $CDCl_3$), numbering scheme as for ketone **anti-4**, δ 8.52 (d, 1H, J = 2.0 Hz, C_1**H**), 8.50 (dd, 1H, J = 4.8, 1.6 Hz, C_2**H**), 7.65 (dt, 1H, J = 7.5, 2.0 Hz, C_4**H**), 7.24 (ddd, 1H, J = 7.6, 4.8, 0.8 Hz, C_3**H**), 6.74 (br s, 1H, CON**H**), 3.50 (s, 2H,

$C_6\mathbf{H}_2$), 3.31 (dd, 1H, J = 8.8, 3.2 Hz, $C_{10}\mathbf{H}_2$), 2.92–2.97 (m, 2H, $C_9\mathbf{H}_2$ and $C_8\mathbf{H}_2$), 2.85 (ddd, 1H, J = 16.4, 9.4, 3.0 Hz, $C_8\mathbf{H}_2$), 2.57 (d of m, 1H, J = 11.2 Hz, $C_7\mathbf{H}_2$), 2.11–2.21 (m, 2H, $C_9\mathbf{H}_2$ and $C_7\mathbf{H}_2$), 1.34 (s, 9H, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 150.3, 148.6, 136.6, 133.1, 123.3, 60.3, 59.0, 56.0, 53.1, 50.6, 44.2, 28.7; FTIR (neat film), cm^{-1} 3295 (br, NH), 1656 (s, C=O); HRMS (FAB) *m/z* calcd for $C_{15}H_{24}N_4ONa$ $(M+Na)^+$ 299.1848, found 299.1858. Aldehyde **8**: R_f 0.52, 50% ethyl acetate–hexanes; ^{1}H NMR (400 MHz, $CDCl_3$), numbering scheme as for ketone **anti-4**, δ 9.19 (s, 1H, C**H**O), 7.19–7.38 (m, 7H, Ar**H**), 6.92 (dt, 1H, J = 6.8, 2.6 Hz, $C_{37}\mathbf{H}$), 6.29 (d, 1H, J = 7.5 Hz, $C_{38}\mathbf{H}$), 6.18 (br s, 1H, O**H**), 5.59 (d, 1H, J = 10.2 Hz, C=C**H**), 5.45 (d, 1H, J = 4.2 Hz, $C_{31}\mathbf{H}$), 4.78 (t, J = 6.5 Hz, $C_{32}\mathbf{H}$), 4.37–4.43 (m, 1H, $C_{19}\mathbf{H}$), 3.63 (dd, 1H, J = 13.6, 8.8 Hz, $C_{20}\mathbf{H}_2$), 3.06 (m, 2H, $C_{33}\mathbf{H}_2$), 2.98 (dd, 1H, J = 13.5, 5.6 Hz, $C_{20}\mathbf{H}_2$), 1.61 (s, 3H, $C\mathbf{H}_3$), 1.25 (s, 3H, $C\mathbf{H}_3$); FTIR (neat film), cm^{-1} 2925 (s), 1683 (s, CHO), 1634 (s, NC=O); HRMS (CI) *m/z* calcd for $C_{24}H_{26}NO_4$ $(M+H)^+$ 392.1862, found 392.1881.

Hydrolytic Fragmentation of Ketone syn-4 (NMR Experiment). Hydrolytic fragmentation of ketone **syn-4** (3.6 mg, 5.4 μmol) in a mixture of *p*-dioxane-d_8 (0.5 mL) and deuterium oxide (0.5 mL) was monitored by ^{1}H-NMR. Nearly complete consumption of **syn-4** occurred within 6 d, with formation of piperazine **7**, aldehyde **8**, and the corresponding keto aldehyde hydrate.

N,O*-acetals 9.** A solution of ketone **anti-4** (7.3 mg, 10.9 μmol, 1 equiv) in methanol (0.2 mL) was treated with triethylamine (3.0 μL, 21.5 μmol, 2.0 equiv). The resulting solution was stirred at 23 °C for 29 h. *N*,*O*-acetals **9** were directly isolated from the reaction mixture by column chromatography (Sephadex LH-20, methanol, gravity), as a colorless oil of mass 5.8 mg (78%). The reaction of ketone **anti-4** (3.5 mg, 5.2 μmol, 1 equiv) with methanol-d_4 in the presence of triethylamine (1.45 μL, 1.04 μmol, 2.0 equiv) and 1,1,2,2-tetrachloroethane (1 μL) as internal standard was also monitored by ^{1}H-NMR. Ketone **anti-4** was completely consumed within 19 h, with formation of *N*,*O*-acetals **9**: R_f 0.31 and 0.19, 30% tetrahydrofuran–dichloromethane; ^{1}H NMR (2:1 mixture of diastereomers, asterisk denotes minor diastereomer signals, 300 MHz, CD_3OD), numbering scheme as for ketone **anti-4**, δ 8.40–8.52 (m, 3H, $C_2\mathbf{H}$, $C_2\mathbf{H}$*, $C_1\mathbf{H}$*), 7.76–7.80 (m, 1H, $C_4\mathbf{H}$*), 7.66 (d of m, 1H, J = 7.8 Hz, $C_4\mathbf{H}$), 7.13–7.44 (m, 16H, Ar**H**, Ar**H), 6.83–6.91 (m, 2H, $C_{38}\mathbf{H}$, $C_{38}\mathbf{H}$*), 6.34 (d, 1H, J = 7.5 Hz, $C_{37}\mathbf{H}$*), 6.11 (d, 1H, J = 4.5 Hz, $C_{31}\mathbf{H}$), 6.04 (d, 1H, J = 7.8 Hz, $C_{37}\mathbf{H}$), 5.75 (d, 1H, J = 4.5 Hz, $C_{31}\mathbf{H}$*), 5.00 (t, 1H, J = 4.1 Hz, $C_{32}\mathbf{H}$), 4.92 (t, 1H, J = 4.4 Hz, $C_{32}\mathbf{H}$*), 4.54 (s, 1H, $C_{16}\mathbf{H}$), 4.35 (s, 1H, $C_{16}\mathbf{H}$*), 1.92–3.59 (m, 41 H), 1.60 (s, 6H, $C(C\mathbf{H}_3)_2$, $C(C\mathbf{H}_3)_2$*), 1.31 (s, 18H, $C(C\mathbf{H}_3)_3$, $C(C\mathbf{H}_3)_3$*), 1.25 (s, 6H, $C(C\mathbf{H}_3)_2$, $C(C\mathbf{H}_3)_2$*); FTIR (neat film), cm^{-1} 1725 (m, C=O), 1667 (s, NC=O), 1644 (s, NC=O), 1425 (s); HRMS (FAB) *m/z* calcd for $C_{40}H_{51}N_5O_5Na$ $(M+Na)^+$ 704.3787, found 704.3766.

Reaction of Ketone syn-4 with Methanol (NMR Experiment). A solution of ketone **syn-4** (3.7 mg, 5.5 μmol, 1 equiv) in methanol-d_4 (1.1 mL) was treated with triethylamine (1.5 μL, 10.8 μmol, 2.0 equiv). The progress of the reaction was monitored by ^{1}H-NMR. Ketone **syn-4** was completely consumed within 3.5 d, with formation of *N*,*O*-acetals **9**.

Independent Synthesis of Piperazine 7. A 50-mL round-bottom flask containing a suspension of 10% palladium on carbon (0.254 g) in ethyl acetate (3 mL) was evacuated and was refilled with hydrogen. The black suspension was stirred at 23 °C for 30 min. A solution of (*S*)-1-*tert*-butoxycarbonyl-2-*tert*-butylcarboxamide-4-benzyloxycarbonyl-piperazine[4] (248 mg, 0.591 mmol, 1 equiv) in ethyl acetate (5 mL) was added via cannula and the transfer was quantitated with an additional 3-mL portion of ethyl acetate. 1,4-Cyclohexadiene (0.559 mL, 5.91 mmol, 10 equiv) was added and the resulting black suspension was stirred at 23 °C for 1 h. The reaction mixture was filtered through a pad of Celite. The collected solids were washed with two 20-mL portions of ethyl acetate. The filtrate was concentrated, yielding a white crystalline solid of mass 160 mg. To the crude product was added sequentially dimethyl formamide (3.6 mL), 3-picolyl chloride hydrochloride (0.232 mg, 1.41 mmol, 2.5 equiv) and triethylamine (0.390 mL, 2.80 mmol, 5.0 equiv). The resulting suspension was stirred at 23 °C for 22 h. The mixture was partitioned between dichloromethane (50 mL) and water (50 mL). The separated aqueous phase was extracted with two 50-mL portions of dichloromethane. The combined organic extracts were washed with water (100 mL) followed by saturated aqueous sodium chloride (100 mL). The organic phase was dried over sodium sulfate and was concentrated. The product was isolated by flash column chromatography (75% ethyl acetate–hexanes initially, grading to 85% ethyl acetate–hexanes), yielding a white crystalline solid of mass 157 mg (71%, two steps). A sample of this material (120 mg, 0.319 mmol, 1 equiv) was treated sequentially with dichloromethane (4.0 mL), triethylsilane (0.127 mL, 0.797 mmol, 2.5 equiv), and trifluoroacetic acid (0.319 mL, 4.14 mmol, 13 equiv). The resulting solution was stirred at 23 °C for 10 h, at which time thin layer chromatographic analysis indicated the presence of remaining starting material. An additional 0.200 mL portion of trifluoroacetic acid was added and the solution was stirred for an additional 10 h. The mixture was partitioned between ether (10 mL) and 0.5 N aqueous hydrochloric acid (10 mL). The separated organic phase was extracted with three 10-mL portions of 0.5 N aqueous hydrochloric acid. The combined aqueous extracts were cooled to 0 °C and were basified to pH 13 by addition of 2 N aqueous sodium hydroxide. The resulting mixture was extracted with three 40-mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate and were concentrated, yielding piperazine **7** as a light yellow oil of mass 85.7 mg (97%). The product was identical (^{1}H-NMR, MS) to that isolated from the hydrolytic fragmentation of ketone **anti-4**.

(±)-1-Fluoro-3-piperidin-1-yl-propan-2-ol (10). Fluorohydrin **10** was prepared by a modification of the reported method.[10] A mixture of piperidine (0.555 mL, 0.561 mmol, 1 equiv) and epifluorohydrin (0.400 mL, 0.561 mmol, 1 equiv) in a sealed tube was heated in a 50 °C oil bath for a period of 4 h. Fluorohydrin **10** was obtained as a colorless liquid of mass 858 mg (95%): R_f 0.23, 25% dichloromethane–tetrahydrofuran; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (ddd, 1H, J_{HF} = 49.2 Hz, J_{HH} = 9.6, 3.6 Hz, C**H**F), 4.35 (ddd, 1H, J_{HF} = 49.0 Hz, J_{HH} = 9.8, 4.6 Hz, C**H**F), 3.84–3.95 (m, 1H, C**H**OH), 2.54–2.65 (br m, 2H, NC**H**$_2$CH$_2$), 2.43 (dd, 1H, J = 12.4, 10.4 Hz, NC**H**$_2$CHOH), 2.33 (dd, 1H, J = 12.4, 4.0 Hz, NC**H**$_2$CHOH), 2.28–2.38 (br m, 2H, NC**H**$_2$CH$_2$), 1.51–1.65 (m, 4H, NCH$_2$C**H**$_2$), 1.40–1.48 (m, 2H, NCH$_2$CH$_2$C**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.9 (d, J_{CF} = 170 Hz), 65.5 (d, J_{CCF} = 19 Hz), 59.5 (d, J_{CCCF} = 7.3 Hz), 54.6, 26.1, 24.2; ^{19}F NMR

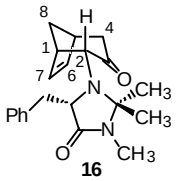
(376 MHz, $CDCl_3$) δ -232.3 (td, J_{HF} = 47.4, 21.8 Hz); FTIR (neat film), cm^{-1} 3402 (br, OH), 2937 (s); HRMS (EI) *m/z* calcd for $C_8H_{17}NOF$ $(M+H)^+$ 161.1216, found 161.1212.

2α-Piperidin-1-yl-bicyclo[3.2.1]oct-6-en-3-one (12). Pyridine (32.7 μL, 0.404 mmol, 2.0 equiv), trifluoroacetic acid (23.3 μL, 0.302 mmol, 1.5 equiv), cyclopentadiene (82.9 μL, 1.01 mmol, 5.0 equiv), and dicyclohexylcarbodiimide (125 mg, 0.606 mmol, 3.0 equiv) were added in sequence to a mixture of (±)-1-fluoro-3-piperidin-1-yl-propan-2-ol (**10**, 32.6 mg, 0.202 mmol, 1 equiv) and flame-dried 4Å molecular sieves in a mixture of dimethyl sulfoxide-d_6 (0.8 mL) and benzene-d_6 (0.8 mL). The resulting suspension was stirred at 23 °C. After 12 h, the reaction mixture was diluted with ether (5 mL) and to the resulting suspension was added a solution of oxalic acid dihydrate (76.3 mg, 0.605 mmol, 3.0 equiv) in methanol (0.5 mL). The resulting suspension was stirred at 23 °C for 30 min. Water (5 mL) was then added and the mixture was filtered through a glass frit. The collected solids were washed with ether (5 mL), followed by water (5 mL). The aqueous phase of the filtrate was separated, was cooled to 0 °C, and was basified to pH 14 by addition of 1 N aqueous sodium hydroxide. The mixture was extracted with three 20-mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate, were filtered, and were concentrated. Analysis of the crude product by ^{1}H-NMR indicated that cycloadduct **12** had been formed as a single diastereomer. Flash column chromatography (10% tetrahydrofuran–dichloromethane initially, grading to 25% tetrahydrofuran–dichloromethane) afforded slightly impure cycloadduct **12** (14.4 mg, 35%): A more pure sample of cycloadduct **12** was obtained by preparative TLC (50% tetrahydrofuran–dichloromethane: ammonium hydroxide, 98:2): R_f 0.33, 15% methanol–dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98–6.03 (m, 2H, C=C**H**), 3.58 (d, 1H, *J* = 2.8 Hz, NC**H**CO), 3.18–3.21 (m, 1H, NCHC**H**), 2.82–2.87 (m, 1H, C=CC**H**CH_2CO), 2.65–2.72 (m, 2H, NC$\mathbf{H}_2$), 2.45 (dd, 1H, *J* = 16.0, 3.2 Hz, COC$\mathbf{H}_2$), 2.39–2.47 (m, 2H, NC$\mathbf{H}_2$), 2.32 (dt, 1H, *J* = 15.7, 2.9 Hz, COC$\mathbf{H}_2$), 2.18–2.24 (m, 1H, NCHCHC$\mathbf{H}_2$), 1.83 (d, 1H, *J* = 10.8 Hz, NCHCHC$\mathbf{H}_2$), 1.52–1.69 (m, 4H, $NCH_2C\mathbf{H}_2$), 1.42–1.48 (m, 2H, $NCH_2CH_2C\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 135.1, 134.7, 79.6, 51.6, 45.9, 44.8, 41.1, 39.5, 26.4, 24.5; FTIR (neat film), cm^{-1} 2935 (s), 1717 (s, C=O); HRMS (CI) *m/z* calcd for $C_{13}H_{20}NO$ $(M+H)^+$ 206.1545, found 206.1544.

(*5S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one (13). (*5S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride[16a] (0.625 g, 2.46 mmol) was partitioned between saturated aqueous sodium bicarbonate (50 mL) and chloroform (50 mL). The separated aqueous phase was extracted with two 50-mL portions of chloroform. The combined organic layers were dried over sodium sulfate and were concentrated, yielding a colorless oil of mass 493.3 mg (92%): R_f 0.22, 100% ethyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.32 (m, 5H, Ar**H**), 3.79 (dd, 1H, *J* = 6.8, 4.4 Hz, C**H**CH_2Ph), 3.15 (dd, 1H, *J* = 14.4, 4.4 Hz, C$\mathbf{H}_2$Ph), 3.01 (dd, 1H, *J* = 14.4, 6.8 Hz, C$\mathbf{H}_2$Ph), 2.76 (s, 3H, NC$\mathbf{H}_3$), 1.26 (s, 3H, CC$\mathbf{H}_3$), 1.16 (s, 3H, CC$\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 137.1, 129.4, 128.5, 126.7, 75.4, 59.2, 37.1, 27.1, 25.2, 25.1; FTIR (neat film), cm^{-1} 3324 (br, NH), 2974 (m), 1693 (s, C=O), 1398 (s); HRMS (TOF MS ES) *m/z* calcd for $C_{13}H_{19}N_2O$ $(M+H)^+$ 219.1497, found 219.1506.

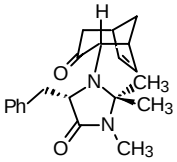
Fluorohydrins 14. A solution of (*5S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (**13**, 949 mg, 4.35 mmol, 1 equiv) and epifluorohydrin (0.310 mL, 4.35 mmol, 1 equiv) in dichloromethane (4.3 mL) was treated with ytterbium(III) trifluoromethanesulfonate (0.539 g, 0.869 mmol, 0.2 equiv). The resulting colorless solution was stirred at 23 °C for 34 h. The solution was diluted with water (50 mL) and the resulting mixture was extracted with three 50-mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate and were concentrated. A 1:1 mixture of fluorohydrins **14** was isolated by flash column chromatography (75% ethyl acetate–hexanes) as a colorless oil (0.895 g, 70%) : R_f 0.33, 100% ethyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.27 (m, 10H, Ar**H**), 4.15–4.44 (m, 4H, C**H**$_2$F), 3.66–3.80 (m, 2H, C**H**OH), 3.61 (t, 1H, J = 4.8 Hz, C**H**CH$_2$Ph), 3.58 (t, 1H, J = 5.4 Hz, C**H**CH$_2$Ph), 3.12–3.21 (m, 2H, C**H**$_2$Ph), 2.94–3.05 (m, 4H, two C**H**$_2$Ph, one NC**H**$_2$, CHO**H**), 2.87 (dd, 1H, J = 13.6, 10.0 Hz, NC**H**$_2$), 2.77 (s, 3H, NC**H**$_3$), 2.76 (s, 3H, NC**H**$_3$), 2.53–2.59 (m, 2H, NC**H**$_2$), 1.22 (s, 3H, CC**H**$_3$), 1.19 (s, 3H, CC**H**$_3$), 1.06 (s, 6H, two CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.2, 137.6, 137.3, 129.5, 129.3, 128.1, 128.0, 126.3 (2 carbons), 84.3 (d, J_{CF} = 170 Hz), 84.2 (d, J_{CF} = 170 Hz), 78.6, 77.9, 67.8 (d, J_{CCF} = 19 Hz), 67.4 (d, J_{CCF} = 20 Hz), 65.7, 65.0, 50.9 (d, J_{CCCF} = 8.0 Hz), 49.1 (d, J_{CCCF} = 8.0 Hz), 37.6, 36.8, 26.9, 26.5, 25.3, 25.0, 20.5, 20.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -233.8 (td, J_{HF} = 47.2, 4.5 Hz), -233.9 (td, J_{HF} = 47.6, 3.5 Hz); FTIR (neat film), cm^{-1} 3402 (br, OH), 1682 (s, C=O); HRMS (FAB) *m/z* calcd for $C_{16}H_{24}FN_2O_2$ $(M+H)^+$ 295.1822, found 295.1834.

α-Fluoro Ketone 15. A solution of dimethyl sulfoxide in dichloromethane (1.25 M, 2.01 mL, 2.51 mmol, 4.0 equiv) was added to a solution of oxalyl chloride (165 μL, 1.89 mmol, 3.0 equiv) in dichloromethane (1.0 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 10 min. A solution of alcohol **14** (0.185 g, 0.629 mmol, 1 equiv) in dichloromethane (1.0 mL) was added via cannula. The transfer was quantitated with an additional two 0.5-mL portions of dichloromethane, and the mixture was stirred at –78 °C for 10 min. Triethylamine (0.788 mL, 5.65 mmol, 9.0 equiv) was added dropwise via syringe. The mixture was stirred at –78 °C for 10 min, then was transferred to an ice–water bath and was stirred for an additional 30 min. Water (20 mL) was added, and the resulting mixture was stirred at 0 °C for 5 min. The mixture was extracted with three 20-mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate and were concentrated. Flash column chromatography (60% ethyl acetate–hexanes, conducted in a column jacketed with an ice–water bath) afforded ketone **15** as a white crystalline solid (mp 120–121 °C, dec) of mass 149 mg (81%): R_f 0.41, 100% ethyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.29 (m, 5H, Ar**H**), 4.52 (dd, J_{HF} = 47.4, J_{HH} = 16.2 Hz, C**H**$_2$F), 4.45 (dd, J_{HF} = 47.4, J_{HH} = 16.2 Hz, C**H**$_2$F), 3.94 (dd, 1H, J = 7.4, 3.4 Hz, C**H**CH$_2$Ph), 3.63 (dd, 1H, J = 18.8, 2.4 Hz, NC**H**$_2$), 3.38 (dd, 1H, J = 18.6, 2.2 Hz, NC**H**$_2$), 3.26 (dd, 1H, J = 14.6, 3.4 Hz, C**H**$_2$Ph), 2.82 (s, 3H, NC**H**$_3$), 2.80 (dd, 1H, J = 14.0, 8.0 Hz, C**H**$_2$Ph), 1.17 (s, 3H, CC**H**$_3$), 1.16 (s, 3H, CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4 (d, J_{CCF} = 17 Hz), 170.1, 138.0, 129.1, 128.1, 126.2, 84.2 (d, J_{CF} = 182 Hz), 78.0, 62.9, 52.3, 38.2, 26.3, 25.1, 20.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -232.3 (t, J_{HF} = 47.4 Hz); FTIR (neat film), cm^{-1} 1745 (s, C=O), 1683 (NC=O); HRMS (FAB) *m/z* calcd for $C_{16}H_{22}FN_2O_2$ $(M+H)^+$ 293.1665, found 293.1676.

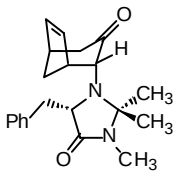


16

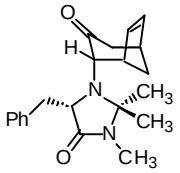
Cycloadduct 16. A solution of ketone **15** (261 mg, 0.893 mmol, 1 equiv) in 1,1,1,3,3,3-hexafluoro-2-propanol (4.5 mL) was treated sequentially with cyclopentadiene (0.367 mL, 4.47 mmol, 5.0 equiv) and triethylamine (0.249 mL, 1.79 mmol, 2.0 equiv). The resulting white suspension was stirred at 23 °C for 24 h. The mixture was partitioned between dichloromethane (25 mL) and water (25 mL). The separated aqueous phase was extracted with two 25-mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate and were concentrated. Crude ^{1}H-NMR spectroscopic analysis indicated a 28.5:4.2:3.6:1.0 mixture of diastereomeric cycloadducts (NOESY experiments established that the two most predominant products are *endo* cycloadducts and that the two minor products are *exo* adducts). Flash column chromatography afforded a total of 285 mg of cycloadduction products (94%), including 197 mg (65%) of the major cycloadduct (**16**) as a single stereoisomer. Cycloadduct **16** was a white crystalline solid (mp 180–182 °C, dec). Crystals of **16** suitable for analysis by X-ray diffraction formed upon allowing a hot solution of this material in 50% ethanol–water to slowly cool to 23 °C. Cycloadduct **16**: R_f 0.10, 50% ethyl acetate–hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 2H, J = 7.2 Hz, Ar**H**), 7.24 (t, 2H, J = 7.6 Hz, Ar**H**), 7.15 (tt, 1H, J = 7.4, 2.2 Hz, Ar**H**), 6.14 (dd, 1H, J = 5.6, 2.8 Hz, C_6**H**), 6.06 (dd, 1H, J = 5.8, 2.6 Hz, C_7**H**), 4.06 (t, 1H, J = 4.8 Hz, C**H**CH_2Ph), 3.79 (d, 1H, J = 2.0 Hz, C_2**H**), 2.96–3.00 (m, 1H, C_1**H**), 2.88–2.92 (m, 1H, C_5**H**), 2.85–2.87 (m, 2H, C**H**$_2$Ph), 2.68 (s, 3H, NC**H**$_3$), 2.51 (dd, 1H, J = 16.0, 3.2 Hz, C_4**H**$_{ax}$), 2.45 (dt, 1H, J = 16.4, 2.7 Hz, C_4**H**$_{eq}$), 2.30–2.36 (m, 1H, C_8**H**$_{eq}$), 1.90 (d, 1H, J = 10.8 Hz, C_8**H**$_{ax}$), 1.26 (s, 3H, CC**H**$_3$), 1.13 (s, 3H, CC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 170.7, 138.1, 137.1, 134.4, 130.3, 127.6, 125.9, 78.9, 70.4, 60.8, 45.8, 45.7, 45.4, 39.0, 37.5, 27.1, 24.8, 23.3; FTIR (neat film), cm^{-1} 1723 (s, C=O), 1694 (s, NC=O); HRMS (TOF MS ES) *m/z* calcd for $C_{21}H_{27}N_2O_2$ $(M+H)^+$ 339.2072, found 339.2059.



R_f 0.11, 2% methanol–dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.26 (m, 5H, Ar**H**), 6.13 (dd, 1H, J = 6.0, 2.4 Hz, C_6**H**), 6.08 (dd, 1H, J = 6.0, 2.8 Hz, C_7**H**), 3.95 (dd, 1H, J = 5.0, 3.4 Hz, C**H**CH_2Ph), 3.85 (d, 1H, J = 2.4 Hz, C_2**H**), 3.11–3.15 (m, 2H, C_1**H**, C**H**$_2$Ph), 2.89–2.93 (m, 1H, C_5**H**), 2.79 (dd, 1H, J = 13.6, 5.6 Hz, C**H**$_2$Ph), 2.65 (s, 3H, NC**H**$_3$), 2.42 (dd, 1H, J = 15.0, 3.4 Hz, C_4**H**$_{ax}$), 2.27–2.34 (m, 2H, C_4**H**$_{eq}$, C_8**H**$_{eq}$), 1.94 (d, 1H, J = 10.8 Hz, C_8**H**$_{ax}$), 1.12 (s, 3H, CC**H**$_3$), 0.57 (s, 3H, CC**H**$_3$); FTIR (neat film), cm^{-1} 1712 (s, C=O), 1685 (s, NC=O); HRMS (TOF MS ES) *m/z* calcd for $C_{21}H_{27}N_2O_2$ $(M+H)^+$ 339.2072, found 339.2084.



The assignment of absolute stereochemistry at C_1, C_2, and C_5 in this product is tentative. R_f 0.24, 2% methanol–dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.30 (m, 5H, Ar**H**), 6.22 (dd, 1H, *J* = 5.6, 2.8 Hz, C_6**H**), 6.06 (dd, 1H, *J* = 5.4, 3.0 Hz, C_7**H**), 4.21 (t, 1H, *J* = 3.8 Hz, C**H**CH_2Ph), 3.13 (br s, 1H, C_2**H**), 3.03 (dd, 1H, *J* = 14.2, 3.4 Hz, C**H**$_2$Ph), 2.88–2.93 (m, 2H, C_1**H**, C_5**H**), 2.78 (dd, 1H, *J* = 14.4, 4.8 Hz, C**H**$_2$Ph), 2.66 (ddd, 1H, *J* = 18.0, 4.4, 0.8 Hz, C_4**H**$_{ax}$), 2.62 (s, 3H, NC**H**$_3$), 2.50 (d, 1H, *J* = 18.0 Hz, C_4**H**$_{eq}$), 2.02–2.09 (m, 2H, C_8**H**$_{ax}$, C_8**H**$_{eq}$), 1.25 (s, 3H, CC**H**$_3$), 1.09 (s, 3H, CC**H**$_3$); FTIR (neat film), cm^{-1} 1698 (s, C=O, NC=O); HRMS (TOF MS ES) *m/z* calcd for $C_{21}H_{27}N_2O_2$ $(M+H)^+$ 339.2072, found 339.2060.



The assignment of absolute stereochemistry at C_1, C_2, and C_5 in this product is tentative. R_f 0.21, 50% ethyl acetate–hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.30 (m, 5H, Ar**H**), 6.21 (dd, 1H, *J* = 5.6, 2.8 Hz, C_6**H**), 5.96 (dd, 1H, *J* = 6.0, 2.8 Hz, C_7**H**), 3.86 (dd, 1H, *J* = 6.0, 2.4 Hz, C**H**CH_2Ph), 3.34 (br s, 1H, C_2**H**), 3.06–3.12 (m, 2H, C_1**H**, C**H**$_2$Ph), 2.88–2.93 (m, 1H, C_5**H**), 2.77 (dd, 1H, *J* = 16.0, 4.0 Hz, C_4**H**$_{ax}$), 2.68 (s, 3H, NC**H**$_3$), 2.63 (dd, 1H, *J* = 14.6, 5.8 Hz, C**H**$_2$Ph), 2.43 (d, 1H, *J* = 16.0 Hz, C_4**H**$_{eq}$), 2.31 (d, 1H, *J* = 10.8 Hz, C_8**H**$_{ax}$), 1.86–1.94 (m, 1H, C_8**H**$_{eq}$), 1.27 (s, 3H, CC**H**$_3$), 1.04 (s, 3H, CC**H**$_3$); FTIR (neat film), cm^{-1} 1701 (s, C=O, NC=O); HRMS (TOF MS ES) *m/z* calcd for $C_{21}H_{27}N_2O_2$ $(M+H)^+$ 339.2072, found 339.2077.

Cycloadduct **16**:

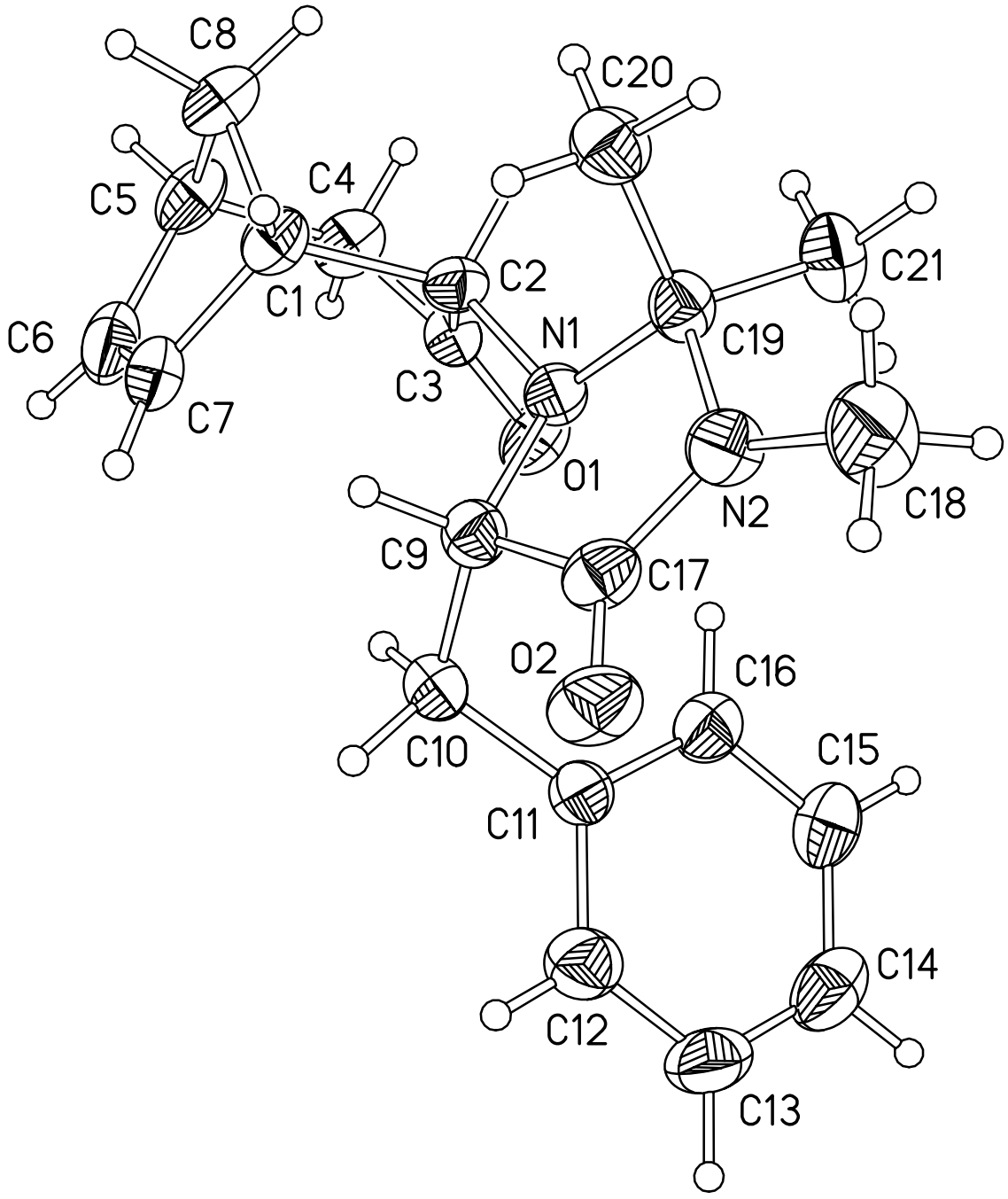


Table 1. Crystal data and structure refinement for cycloadduct **16**.

Identification code	ahkb100t	
Empirical formula	C21 H26 N2 O2	
Formula weight	338.44	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	Hexagonal	
Space group	P6(5)	
Unit cell dimensions	a = 10.0689(13) Å	α= 90°.
	b = 10.0689(13) Å	β= 90°.
	c = 30.962(5) Å	γ = 120°.
Volume	2718.5(7) $Å^3$	
Z	6	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	1092	
Crystal size	0.1 x 0.5 x 1.0 mm^3	
Theta range for data collection	2.34 to 27.84°.	
Index ranges	-12<=h<=13, -12<=k<=10, -40<=l<=20	
Reflections collected	17574	
Independent reflections	3397 [R(int) = 0.0830]	
Completeness to theta = 27.84°	95.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3397 / 1 / 229	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0454, wR2 = 0.1026	
R indices (all data)	R1 = 0.0603, wR2 = 0.1109	
Absolute structure parameter	-1.3(14)	
Largest diff. peak and hole	0.153 and -0.173 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for cycloadduct **16**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4740(2)	11828(2)	-24(1)	38(1)
O(2)	3788(2)	5784(2)	-380(1)	43(1)
N(1)	4360(2)	8974(2)	226(1)	26(1)
N(2)	5315(2)	7374(2)	154(1)	35(1)
C(1)	2070(2)	8764(2)	663(1)	30(1)
C(2)	3749(2)	9741(2)	492(1)	26(1)
C(3)	3970(2)	11242(2)	295(1)	28(1)
C(4)	3240(3)	12022(3)	535(1)	35(1)
C(5)	1659(3)	10864(3)	727(1)	38(1)
C(6)	663(3)	9807(3)	370(1)	42(1)
C(7)	896(3)	8628(3)	332(1)	36(1)
C(8)	1857(3)	9730(3)	1009(1)	37(1)
C(9)	3341(2)	7745(2)	-66(1)	29(1)
C(10)	3006(2)	8275(3)	-498(1)	32(1)
C(11)	4287(2)	8923(3)	-828(1)	30(1)
C(12)	4047(3)	8263(3)	-1236(1)	41(1)
C(13)	5170(3)	8883(4)	-1550(1)	50(1)
C(14)	6558(3)	10179(3)	-1465(1)	47(1)
C(15)	6815(3)	10832(3)	-1061(1)	42(1)
C(16)	5698(3)	10214(3)	-743(1)	36(1)
C(17)	4150(3)	6841(3)	-125(1)	32(1)
C(18)	6252(3)	6667(3)	211(1)	54(1)
C(19)	5337(2)	8502(2)	459(1)	29(1)
C(20)	4679(3)	7693(3)	892(1)	37(1)
C(21)	6935(3)	9867(3)	516(1)	40(1)

Table 3. Bond lengths [Å] and angles [°] for cycloadduct **16**.

		O(1)-C(3)	1.211(2)
O(2)-C(17)	1.225(3)	N(1)-C(2)	1.458(3)
N(1)-C(9)	1.461(3)	N(1)-C(19)	1.476(3)
N(2)-C(17)	1.334(3)	N(2)-C(18)	1.449(3)
N(2)-C(19)	1.467(3)	C(1)-C(7)	1.517(3)
C(1)-C(8)	1.532(3)	C(1)-C(2)	1.564(3)
C(1)-H(1)	0.9900	C(2)-C(3)	1.539(3)
C(2)-H(2)	0.9900	C(3)-C(4)	1.513(3)
C(4)-C(5)	1.546(3)	C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800	C(5)-C(6)	1.514(4)
C(5)-C(8)	1.528(3)	C(5)-H(5)	0.9900
C(6)-C(7)	1.325(4)	C(6)-H(6)	0.9400
C(7)-H(7)	0.9400	C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800	C(9)-C(17)	1.504(3)
C(9)-C(10)	1.538(3)	C(9)-H(9)	0.9900
C(10)-C(11)	1.514(3)	C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800	C(11)-C(12)	1.391(3)
C(11)-C(16)	1.389(3)	C(12)-C(13)	1.382(4)
C(12)-H(12)	0.9400	C(13)-C(14)	1.380(4)
C(13)-H(13)	0.9400	C(14)-C(15)	1.375(4)
C(14)-H(14)	0.9400	C(15)-C(16)	1.386(3)
C(15)-H(15)	0.9400	C(16)-H(16)	0.9400
C(18)-H(18A)	0.9700	C(18)-H(18B)	0.9700
C(18)-H(18C)	0.9700	C(19)-C(21)	1.516(3)
C(19)-C(20)	1.537(3)	C(20)-H(20A)	0.9700
C(20)-H(20B)	0.9700	C(20)-H(20C)	0.9700
C(21)-H(21A)	0.9700	C(21)-H(21B)	0.9700
C(21)-H(21C)	0.9700		
C(2)-N(1)-C(9)	119.67(17)	C(2)-N(1)-C(19)	114.92(17)
C(9)-N(1)-C(19)	109.15(15)	C(17)-N(2)-C(18)	122.6(2)
C(17)-N(2)-C(19)	113.39(17)	C(18)-N(2)-C(19)	122.7(2)
C(7)-C(1)-C(8)	100.33(18)	C(7)-C(1)-C(2)	112.12(17)
C(8)-C(1)-C(2)	106.75(17)	C(7)-C(1)-H(1)	112.3
C(8)-C(1)-H(1)	112.3	C(2)-C(1)-H(1)	112.3
N(1)-C(2)-C(3)	113.94(17)	N(1)-C(2)-C(1)	117.89(17)

C(3)-C(2)-C(1)	109.37(17)	N(1)-C(2)-H(2)	104.7
C(3)-C(2)-H(2)	104.7	C(1)-C(2)-H(2)	104.7
O(1)-C(3)-C(4)	120.50(19)	O(1)-C(3)-C(2)	122.90(19)
C(4)-C(3)-C(2)	116.51(17)	C(3)-C(4)-C(5)	112.42(18)
C(3)-C(4)-H(4A)	109.1	C(5)-C(4)-H(4A)	109.1
C(3)-C(4)-H(4B)	109.1	C(5)-C(4)-H(4B)	109.1
H(4A)-C(4)-H(4B)	107.9	C(6)-C(5)-C(8)	100.37(18)
C(6)-C(5)-C(4)	108.69(19)	C(8)-C(5)-C(4)	108.21(19)
C(6)-C(5)-H(5)	112.9	C(8)-C(5)-H(5)	112.9
C(4)-C(5)-H(5)	112.9	C(7)-C(6)-C(5)	110.0(2)
C(7)-C(6)-H(6)	125.0	C(5)-C(6)-H(6)	125.0
C(6)-C(7)-C(1)	109.8(2)	C(6)-C(7)-H(7)	125.1
C(1)-C(7)-H(7)	125.1	C(5)-C(8)-C(1)	100.77(17)
C(5)-C(8)-H(8A)	111.6	C(1)-C(8)-H(8A)	111.6
C(5)-C(8)-H(8B)	111.6	C(1)-C(8)-H(8B)	111.6
H(8A)-C(8)-H(8B)	109.4	N(1)-C(9)-C(17)	102.95(17)
N(1)-C(9)-C(10)	115.31(17)	C(17)-C(9)-C(10)	112.60(18)
N(1)-C(9)-H(9)	108.6	C(17)-C(9)-H(9)	108.6
C(10)-C(9)-H(9)	108.6	C(11)-C(10)-C(9)	116.68(18)
C(11)-C(10)-H(10A)	108.1	C(9)-C(10)-H(10A)	108.1
C(11)-C(10)-H(10B)	108.1	C(9)-C(10)-H(10B)	108.1
H(10A)-C(10)-H(10B)	107.3	C(12)-C(11)-C(16)	118.1(2)
C(12)-C(11)-C(10)	120.0(2)	C(16)-C(11)-C(10)	121.9(2)
C(13)-C(12)-C(11)	121.1(2)	C(13)-C(12)-H(12)	119.5
C(11)-C(12)-H(12)	119.5	C(14)-C(13)-C(12)	120.4(2)
C(14)-C(13)-H(13)	119.8	C(12)-C(13)-H(13)	119.8
C(15)-C(14)-C(13)	119.1(2)	C(15)-C(14)-H(14)	120.5
C(13)-C(14)-H(14)	120.5	C(14)-C(15)-C(16)	120.9(3)
C(14)-C(15)-H(15)	119.5	C(16)-C(15)-H(15)	119.5
C(15)-C(16)-C(11)	120.5(2)	C(15)-C(16)-H(16)	119.8
C(11)-C(16)-H(16)	119.8	O(2)-C(17)-N(2)	125.9(2)
O(2)-C(17)-C(9)	125.9(2)	N(2)-C(17)-C(9)	108.15(18)
N(2)-C(18)-H(18A)	109.5	N(2)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5	N(2)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5	H(18B)-C(18)-H(18C)	109.5
N(2)-C(19)-N(1)	100.43(16)	N(2)-C(19)-C(21)	112.01(18)

N(1)-C(19)-C(21)	109.90(18)	N(2)-C(19)-C(20)	108.37(17)
N(1)-C(19)-C(20)	114.61(17)	C(21)-C(19)-C(20)	111.10(19)
C(19)-C(20)-H(20A)	109.5	C(19)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5	C(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5	H(20B)-C(20)-H(20C)	109.5
C(19)-C(21)-H(21A)	109.5	C(19)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5	C(19)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5	H(21B)-C(21)-H(21C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for cycloadduct **16**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	41(1)	36(1)	38(1)	9(1)	12(1)	20(1)
O(2)	53(1)	37(1)	42(1)	-11(1)	2(1)	23(1)
N(1)	27(1)	26(1)	27(1)	-4(1)	-1(1)	14(1)
N(2)	41(1)	36(1)	37(1)	-5(1)	-3(1)	27(1)
C(1)	31(1)	27(1)	31(1)	2(1)	6(1)	14(1)
C(2)	30(1)	28(1)	22(1)	-4(1)	0(1)	15(1)
C(3)	25(1)	30(1)	28(1)	-2(1)	-2(1)	13(1)
C(4)	43(1)	31(1)	36(1)	4(1)	6(1)	23(1)
C(5)	44(1)	38(1)	41(1)	6(1)	16(1)	28(1)
C(6)	29(1)	55(2)	46(1)	13(1)	11(1)	24(1)
C(7)	24(1)	41(1)	37(1)	2(1)	6(1)	12(1)
C(8)	44(1)	37(1)	31(1)	6(1)	13(1)	22(1)
C(9)	26(1)	26(1)	30(1)	-1(1)	1(1)	11(1)
C(10)	28(1)	37(1)	31(1)	-5(1)	-4(1)	16(1)
C(11)	31(1)	35(1)	28(1)	0(1)	-2(1)	20(1)
C(12)	45(1)	49(2)	35(1)	-3(1)	-4(1)	29(1)
C(13)	63(2)	76(2)	27(1)	-3(1)	-1(1)	48(2)
C(14)	55(2)	63(2)	39(1)	16(1)	14(1)	42(2)
C(15)	38(1)	40(1)	51(2)	7(1)	8(1)	24(1)
C(16)	36(1)	39(1)	36(1)	-1(1)	3(1)	20(1)
C(17)	37(1)	27(1)	31(1)	-1(1)	5(1)	15(1)
C(18)	59(2)	56(2)	68(2)	-13(1)	-10(2)	44(1)
C(19)	29(1)	29(1)	33(1)	-2(1)	-2(1)	17(1)
C(20)	41(1)	41(1)	35(1)	4(1)	-2(1)	24(1)
C(21)	28(1)	37(1)	54(2)	-4(1)	-3(1)	15(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for cycloadduct **16**.

	x	y	z	U(eq)
H(1)	1851	7753	774	36
H(2)	4396	10064	754	32
H(4A)	3117	12713	338	42
H(4B)	3923	12644	770	42
H(5)	1168	11366	882	45
H(6)	-19	9964	200	50
H(7)	407	7827	131	44
H(8A)	947	9107	1186	44
H(8B)	2760	10253	1196	44
H(9)	2357	7090	84	34
H(10A)	2110	7400	-629	38
H(10B)	2726	9058	-436	38
H(12)	3105	7381	-1299	49
H(13)	4987	8418	-1824	60
H(14)	7318	10611	-1680	56
H(15)	7762	11710	-1000	50
H(16)	5896	10672	-469	43
H(18A)	6176	6326	508	81
H(18B)	7312	7408	145	81
H(18C)	5896	5795	19	81
H(20A)	3668	6812	846	56
H(20B)	4606	8400	1090	56
H(20C)	5349	7356	1013	56
H(21A)	7571	9549	668	60
H(21B)	6877	10656	681	60
H(21C)	7378	10271	234	60

Table 6. Torsion angles [°] for cycloadduct **16**.

C(9)-N(1)-C(2)-C(3)	-95.9(2)
C(19)-N(1)-C(2)-C(3)	131.19(19)
C(9)-N(1)-C(2)-C(1)	34.3(3)
C(19)-N(1)-C(2)-C(1)	-98.6(2)
C(7)-C(1)-C(2)-N(1)	-83.8(2)
C(8)-C(1)-C(2)-N(1)	167.24(18)
C(7)-C(1)-C(2)-C(3)	48.5(2)
C(8)-C(1)-C(2)-C(3)	-60.5(2)
N(1)-C(2)-C(3)-O(1)	-8.5(3)
C(1)-C(2)-C(3)-O(1)	-142.8(2)
N(1)-C(2)-C(3)-C(4)	174.85(18)
C(1)-C(2)-C(3)-C(4)	40.5(2)
O(1)-C(3)-C(4)-C(5)	145.2(2)
C(2)-C(3)-C(4)-C(5)	-38.1(3)
C(3)-C(4)-C(5)-C(6)	-53.3(2)
C(3)-C(4)-C(5)-C(8)	54.9(2)
C(8)-C(5)-C(6)-C(7)	-26.3(2)
C(4)-C(5)-C(6)-C(7)	87.2(2)
C(5)-C(6)-C(7)-C(1)	0.3(2)
C(8)-C(1)-C(7)-C(6)	25.7(2)
C(2)-C(1)-C(7)-C(6)	-87.3(2)
C(6)-C(5)-C(8)-C(1)	40.3(2)
C(4)-C(5)-C(8)-C(1)	-73.5(2)
C(7)-C(1)-C(8)-C(5)	-40.1(2)
C(2)-C(1)-C(8)-C(5)	76.9(2)
C(2)-N(1)-C(9)-C(17)	-156.50(17)
C(19)-N(1)-C(9)-C(17)	-21.2(2)
C(2)-N(1)-C(9)-C(10)	80.5(2)
C(19)-N(1)-C(9)-C(10)	-144.18(18)
N(1)-C(9)-C(10)-C(11)	73.9(2)
C(17)-C(9)-C(10)-C(11)	-43.9(3)
C(9)-C(10)-C(11)-C(12)	122.4(2)
C(9)-C(10)-C(11)-C(16)	-60.3(3)
C(16)-C(11)-C(12)-C(13)	-0.9(3)

C(10)-C(11)-C(12)-C(13)	176.5(2)
C(11)-C(12)-C(13)-C(14)	-0.2(4)
C(12)-C(13)-C(14)-C(15)	0.9(4)
C(13)-C(14)-C(15)-C(16)	-0.6(4)
C(14)-C(15)-C(16)-C(11)	-0.4(4)
C(12)-C(11)-C(16)-C(15)	1.2(3)
C(10)-C(11)-C(16)-C(15)	-176.2(2)
C(18)-N(2)-C(17)-O(2)	-4.7(4)
C(19)-N(2)-C(17)-O(2)	-172.0(2)
C(18)-N(2)-C(17)-C(9)	174.3(2)
C(19)-N(2)-C(17)-C(9)	7.1(2)
N(1)-C(9)-C(17)-O(2)	-172.3(2)
C(10)-C(9)-C(17)-O(2)	-47.4(3)
N(1)-C(9)-C(17)-N(2)	8.7(2)
C(10)-C(9)-C(17)-N(2)	133.54(19)
C(17)-N(2)-C(19)-N(1)	-19.4(2)
C(18)-N(2)-C(19)-N(1)	173.4(2)
C(17)-N(2)-C(19)-C(21)	-136.0(2)
C(18)-N(2)-C(19)-C(21)	56.8(3)
C(17)-N(2)-C(19)-C(20)	101.1(2)
C(18)-N(2)-C(19)-C(20)	-66.1(3)
C(2)-N(1)-C(19)-N(2)	162.12(17)
C(9)-N(1)-C(19)-N(2)	24.5(2)
C(2)-N(1)-C(19)-C(21)	-79.7(2)
C(9)-N(1)-C(19)-C(21)	142.62(19)
C(2)-N(1)-C(19)-C(20)	46.2(2)
C(9)-N(1)-C(19)-C(20)	-91.4(2)

Symmetry transformations used to generate equivalent atoms: