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6-Nitro-1,2,3,4-tetrahydroquinoline-4-carboxylic Esters and 7-Nitro-3,4-dihydroquinoxaline-1(2*H*)-carboxylic Esters by a Tandem Reductive Amination-S_NAr Reaction

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The tandem reductive amination-S_NAr reaction sequence has recently been reported for the efficient synthesis of 1,2,3,4-tetrahydroquinolines.[1] As part of our effort to develop new routes to biologically active heterocyclic compounds having diverse substitution, we wished to extend this methodology to the synthesis of tetrahydroquinolines and tetrahydroquinoxalines bearing carboxyl groups on the saturated ring, and possibly to dihydrobenzoxazines as well.[2] In the tetrahydroquinoline series, this would provide compounds that have been shown to have useful activities in the treatment of inflammatory diseases such as asthma.[3] Tetrahydroquinoxaline derivatives have been shown to express useful activity as anticancer drugs[4] and cell adhesion agents.[5] Dihydrobenzoxazines have demonstrated activity as antihypertensives[6] and neuroprotective agents.[7]

The substrates for this annulation reaction are trisubstituted aromatic systems bearing a 3-oxo side-chain at C1, a F (or Cl) at C2 and a NO_2 group at C5. We expected that the electronic nature of the atom linking the 3-oxo side chain to the ring would be critical to the success of the final S_NAr ring closure. While the alkyl side-chain of the tetrahydroquinoline precursors should not pose a problem, the alkylamino group in the tetrahydroquinoxaline precursors and the alkoxy side chain required to prepare dihydrobenzoxazines would deactivate the ring toward the final S_NAr cyclization. In the tetrahydroquinoxaline precursors, the electron donating character of the nitrogen could be decreased by protecting it as a carbamate. Derivatization, however, would not be possible in the case of the dihydrobenzoxazine precursors and we anticipated difficulties in the ring closure step using these substrates.

The synthesis of the cyclization substrates is shown in *Scheme 1*. The tetrahydroquinoline precursors were prepared from methyl 2-fluoro-5-nitrophenylacetate obtained by esterification of the corresponding acid;[8] the tetrahydroquinoxaline precursors were

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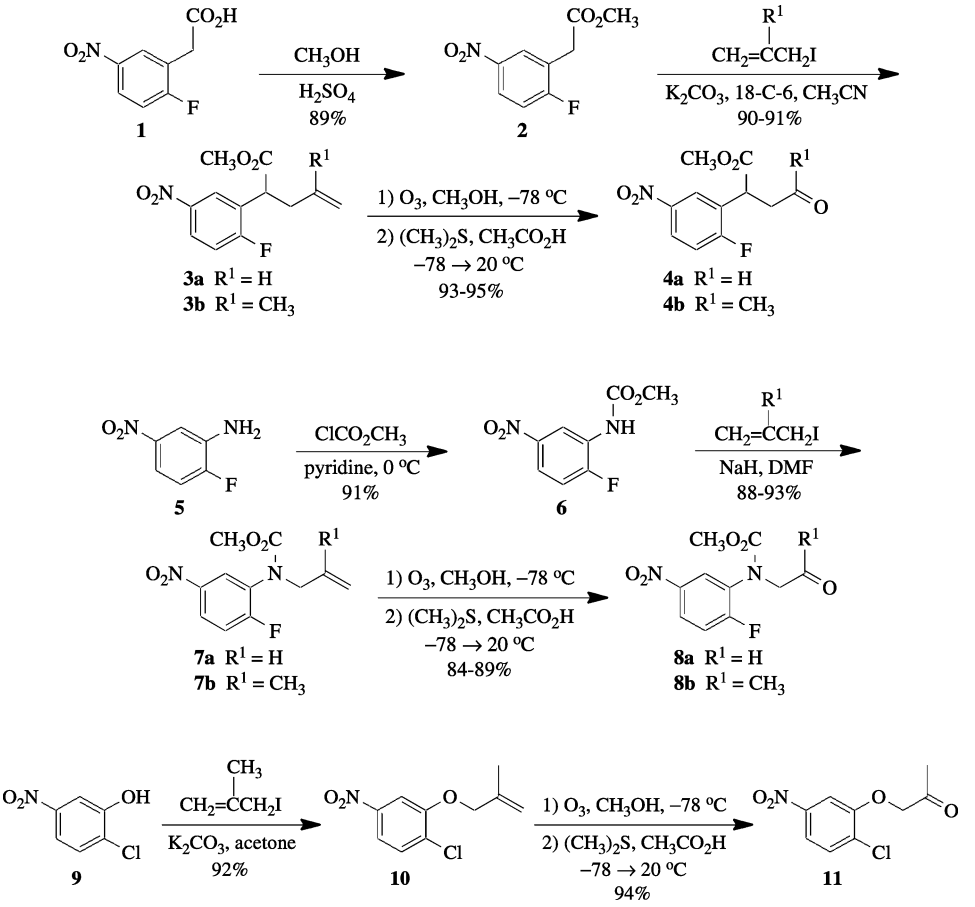
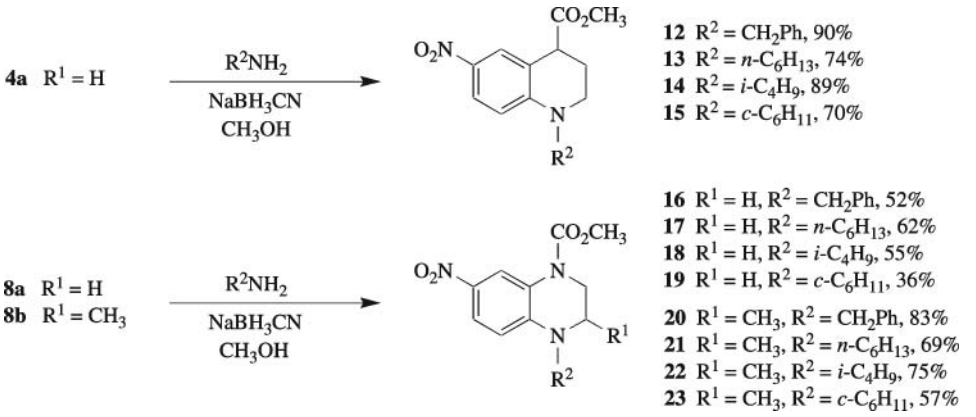


Scheme 1
Synthesis of the cyclization substrates.

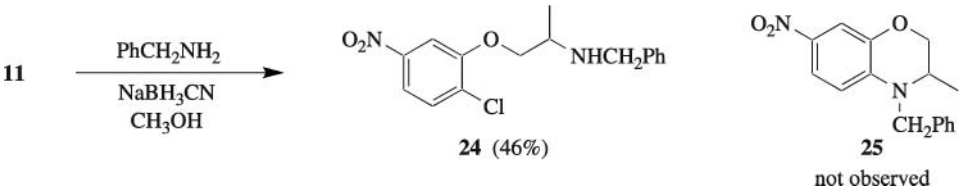
generated from 2-fluoro-5-nitroaniline protected as its methyl carbamate; and finally, a dihydrobenzoxazine precursor was prepared from 2-chloro-5-nitrophenol.[9] The acidity of the benzylic CH, the anilide NH and the phenolic OH in these structures facilitated deprotonation and allylation α to the aromatic ring. Ozonolysis[10] then converted the side-chain double bonds to the necessary carbonyl functions.

The reductive amination-S_NAr sequences were carried out by dissolving 1.00 eq of the carbonyl compound in CH_3OH, adding 1.20 eq of the amine, stirring for 30 min and finally adding (in three portions) 1.40 eq of $NaBH_3CN$. In the preparation of tetrahydroquinolines, the aldehyde precursors gave the best results (70–90% yields of **12–15**). The ketone substrates, however, yielded inseparable mixtures of *cis* and *trans* isomers and were not pursued. In the tetrahydroquinoxaline ring closures, the aldehydes[11] were generally observed to give lower yields (36–62% of **16–19**) than the ketone substrates (57–83% yields of **17–20**). Finally, in our one attempt to close a dihydrobenzoxazine derivative, we observed only the simple reductive amination product **24** (46%) along with recovered starting material (28%); none of the ring-closed product **25** was formed, presumably due to the

unfavorable electronics of the system.[12] In the current reaction, primary amines were more successful than secondary amines while tertiary amines gave complex mixtures containing little if any of the cyclized product. The results of our reductive amination-S_NAr reactions are summarized in *Schemes 2* and *3*.



Scheme 2
Synthesis of tetrahydroquinoline and dihydroquinoxaline carboxylic esters.



Scheme 3
Attempted synthesis of dihydrobenzoxazines.

In conclusion, we have developed a new route to nitro-substituted tetrahydroquinoline-4- and dihydroquinoxaline-1(2*H*)-carboxylic esters based on a tandem reductive amination-S_NAr reaction. In this sequence, an electron deficient aromatic ring is critical to the final S_NAr ring closure. The reaction is also sensitive to steric hindrance in the amine, with primary amines giving the highest yields. Though the current approach to the tetrahydroquinoline systems is not as diastereoselective as our earlier-reported reduction-reductive amination,[10] it does offer a relatively direct route to the title compounds. We are continuing our studies to develop efficient approaches to heterocyclic structures of biological interest.

Experimental Section

All reactions were run in dry glassware under N_2. The saturated NH_4Cl, saturated NaCl, 5% $NaHCO_3$, 5% $Na_2S_2O_3$ and 0.5 M HCl, used in work-up procedures refer to aqueous solutions. Reactions were monitored by TLC on silica gel GF plates (Analtech 21521).

Preparative separations were performed by one of the following methods: (1) flash column chromatography[13] on silica gel (grade 62, 60–200 mesh) containing UV-active phosphor (Sorbent Technologies UV-05) packed into quartz columns or (2) PTLC on 20-cm × 20-cm silica gel GF plates (Analtech 02015). Band elution for all chromatographic separations was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, using $(CH_3)_4Si$ as the internal standard; coupling constants (J) are given in Hz. Mass spectra (EI/DP) were obtained at 70 eV.

Methyl 2-Fluoro-5-nitrophenylacetate (2)

A solution of 5.00 g (25.1 mmol) of 2-fluoro-5-nitrophenylacetic acid (**1**)[8] in 100 mL of CH_3OH containing 2 mL of concentrated H_2SO_4 was refluxed for 24 h, then cooled, concentrated, poured into ice water and extracted with ether (3x). The combined ether extracts were washed with 5% $NaHCO_3$ (2x) and saturated NaCl (1x), then dried ($MgSO_4$) and concentrated under vacuum to give the ester as a light yellow oil that slowly crystallized. The crude solid was triturated with 1% ether in pentane and filtered to give 4.74 g (89%) of **2** as a light yellow solid, mp 52–55°C. IR: 1743, 1529, 1350, 1250 cm^{-1}; ^{1}H NMR: δ 8.22 (m, 2 H), 7.23 (t, J = 8.8 Hz, 1 H), 3.77 (d, J = 1.1 Hz, 2 H), 3.75 (s, 3 H); ^{13}C NMR: δ 169.7, 164.6 (d, J = 257.9 Hz), 144.1, 127.5 (d, J = 6.1 Hz), 125.1 (d, J = 10.7 Hz), 123.1 (d, J = 18.3 Hz), 116.4 (d, J = 24.4 Hz), 52.5 (d, J = 3.8 Hz), 34.0 (d, J = 2.3 Hz); MS: *m/z* 213 (M^+).

Anal. Calcd for $C_9H_8FNO_4$: C, 50.70; H, 3.76; N, 6.57. Found: C, 50.73; H, 3.77; N, 6.53.

Methyl N-(2-Fluoro-5-nitrophenyl)carbamate (6)

To a stirred solution of 5.00 g (32.0 mmol) of 2-fluoro-5-nitroaniline (**5**) in 50 mL of pyridine at 0°C was slowly added 3.35 g (2.74 mL, 35.4 mmol) of methyl chloroformate over 30 min. The reaction was stirred for 2 h with gradual warming to 22°C. The crude reaction mixture was added to water and ether extracted (3x). The combined ether extracts were washed with 0.5 M HCl (4x), water (1x) and NaCl (1x), then dried ($MgSO_4$) and concentrated under vacuum to give a brown powder. Trituration of this solid with ether gave 5.75 g (91%) of **6** as tan crystals, mp 116–118°C (*lit*[14] mp 116–118°C). IR: 3401, 1740, 1533, 1348, 1245 cm^{-1}; ^{1}H NMR: δ 9.08 (br d, J = 4.8 Hz, 1 H), 7.94 (ddd, J = 9.1, 4.2, 2.7 Hz, 1 H), 7.23 (t, J = 9.1 Hz, 1 H), 7.02 (br s, 1 H), 3.86 (s, 3 H); ^{13}C NMR: δ 154.9 (d, J = 254.1 Hz), 153.1, 144.7, 127.5 (d, J = 11.4 Hz), 118.9 (d, J = 9.2 Hz), 115.6 (d, J = 3.4 Hz), 115.4 (d, J = 22.1 Hz); MS: *m/z* 214 (M^+).

Anal. Calcd for $C_8H_7FN_2O_4$: C, 44.86; H, 3.27; N, 13.08. Found: C, 44.77; H, 3.31; H, 13.16.

Alkylation Procedure for the Ester: Methyl 2-(2-Fluoro-5-nitrophenyl)-4-pentenoate (3a)

The general procedure of Makosza and Tyrala was followed.[15] In a 100 mL three-necked round-bottomed flask, a solution of 1.07 g (5.00 mmol) of **2** in 10 mL of dry CH_3CN

was added to a suspension of 5.80 g (42.0 mmol) of anhydrous K_2CO_3 and 10 mg of 18-crown-6 in 40 mL of dry CH_3CN. To the resulting red mixture was added 1.01 g (0.55 mL, 6.00 mmol) of 3-iodo-1-propene. The reaction was stirred under reflux for 6 h, then cooled to 22°C and filtered to remove the solids. The solids were washed with ether and the filtrate was concentrated under vacuum. The remaining oil was purified by flash chromatography on a 30 cm × 2 cm silica gel column eluted with 5–10% ether in hexanes to give 1.15 g (91%) of **3a** as a light yellow oil. IR: 1738, 1646, 1529, 1350, 1245 cm^{-1}; ^1H NMR: δ 8.30 (dd, $J = 6.2$, 2.7 Hz, 1 H), 8.18 (ddd, $J = 9.0$, 4.4, 2.7 Hz, 1 H), 7.21 (t, $J = 9.0$ Hz, 1 H), 5.70 (ddt, $J = 17.0$, 10.2, 7.0 Hz, 1 H), 5.05 (m, 2 H), 4.07 (t, $J = 7.1$ Hz, 1 H), 3.72 (s, 3 H), 2.90 (m, 1 H), 2.59 (m, 1 H); ^{13}C NMR: δ 171.9, 164.0 (d, $J = 257.9$ Hz), 144.4, 133.7, 127.4 (d, $J = 9.0$ Hz), 125.6 (d, $J = 6.1$ Hz), 124.8 (d, $J = 9.9$ Hz), 118.2, 116.5 (d, $J = 25.1$ Hz), 52.5, 43.5, 36.3; MS: *m/z* 253 (M^+).

Anal. Calcd for $C_{12}H_{12}FNO_4$: C, 56.92; H, 4.74; N, 5.53. Found: C, 56.99; H, 4.77; N, 5.49.

Methyl 2-(2-Fluoro-5-nitrophenyl)-4-methyl-4-pentenoate (3b)

This compound (1.20 g, 90%) was prepared as above from 1.07 g (5.00 mmol) of **2** and 1.09 g (6.00 mmol) of 3-iodo-2-methyl-1-propene. IR: 1738, 1651, 1533, 1350, 1248 cm^{-1}; ^1H NMR: δ 8.32 (dd, $J = 6.2$, 2.7 Hz, 1 H), 8.18 (m, 1 H), 7.21 (t, $J = 9.0$ Hz, 1 H), 4.74 (s, 1 H), 4.64 (s, 1 H), 4.23 (t, $J = 7.7$ Hz, 1 H), 3.71 (s, 3 H), 2.88 (dd, $J = 14.4$, 7.3 Hz, 1 H), 2.54 (dd, $J = 14.4$, 8.4 Hz, 1 H), 1.74 (s, 3 H); ^{13}C NMR: δ 172.2, 164.0 (d, $J = 257.1$ Hz), 144.3, 141.1, 127.5 (d, $J = 16.8$ Hz), 125.5 (d, $J = 6.1$ Hz), 124.6 (d, $J = 9.9$ Hz), 116.4 (d, $J = 25.9$ Hz), 113.5, 52.5, 42.0, 40.3, 22.0; MS: *m/z* 267 (M^+).

Anal. Calcd for $C_{13}H_{14}FNO_4$: C, 58.42; H, 5.24; N, 5.24. Found: C, 58.49; H, 5.26; N, 5.18.

*Alkylation Procedure for the Amide: Methyl N-(2-Fluoro-5-nitrophenyl)-*N*-(2-propenyl)carbamate (7a)*

In a 50 mL three-necked round-bottomed flask, 0.24 g of 60% NaH in mineral oil (6.00 mmol) was washed with hexanes (3x) and suspended in 15 mL of dry DMF. To the stirred suspension at 22°C was slowly added a solution of 1.07 g (5.00 mmol) of **6** in 5 mL of dry DMF. Stirring was continued for 30 min and a solution of 1.01 g (0.55 mL, 6.00 mmol) of 3-iodo-1-propene in 1 mL of dry DMF was added. The reaction was stirred for 8 h at 22°C, quenched with saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 5% $Na_2S_2O_3$ (1x) and saturated NaCl (1x), then dried ($MgSO_4$) and concentrated under vacuum. The crude **7a** (1.19 g, 93%) was spectroscopically pure and was used directly in the next reaction. IR: 1718, 1643, 1528, 1348, 1255 cm^{-1}; ^1H NMR: δ 8.20 (m, 2 H), 7.28 (t, $J = 8.9$ Hz, 1 H), 5.86 (ddt, $J = 17.4$, 10.8, 6.0 Hz, 1 H), 5.17 (s, 1 H), 5.13 (dd, $J = 7.3$, 1.3 Hz, 1 H), 4.28 (d, $J = 6.1$ Hz, 2 H), 3.74 (br s, 3 H); ^{13}C NMR: δ 161.2 (d, $J = 261.1$ Hz), 155.0, 144.1, 132.4, 130.2, 125.7 (d, $J = 2.9$ Hz), 124.4 (d, $J = 9.7$ Hz), 118.7, 117.1 (d, $J = 23.2$ Hz), 53.5, 52.7; MS: *m/z* 254 (M^+).

Anal. Calcd for $C_{11}H_{11}FN_2O_4$: C, 51.97; H, 4.36; N, 11.02. Found: C, 51.89; H, 4.39; N, 11.18.

Methyl N-(2-Fluoro-5-nitrophenyl)-N-(2-methyl-2-propenyl)carbamate (7b)

This compound (1.18 g, 88%) was prepared as above from 1.07 g (5.00 mmol) of **6** and 1.09 g (6.00 mmol) of 3-iodo-2-methyl-1-propene. IR: 1723, 1659, 1533, 1348, 1256 cm^{-1}; ^1H NMR: δ 8.18 (m, 2 H), 7.27 (t, $J = 9.0$ Hz, 1 H), 4.85 (s, 1 H), 4.78 (s, 1 H), 4.26 (s, 2 H), 3.74 (br s, 3 H), 1.77 (s, 3 H); ^{13}C NMR: δ 162.0 (d, $J = 261.0$ Hz), 155.2, 144.1, 140.1, 130.1, 125.1 (d, $J = 2.9$ Hz), 124.2 (d, $J = 10.0$ Hz), 117.1 (d, $J = 23.5$ Hz), 114.0, 55.7, 53.5, 19.9; MS: *m/z* 268 (M^+).

Anal. Calcd for $C_{12}H_{13}FN_2O_4$: C, 53.69; H, 4.89; N, 10.44. Found: C, 53.58; H, 4.86; N, 10.52.

1-Chloro-2-(2-methyl-2-propenyloxy)-4-nitrobenzene (10)

In a 100 mL three-necked round-bottomed flask, a solution of 0.87 g (5.00 mmol) of 2-chloro-5-nitrophenol (**9**)[9] in 10 mL of dry acetone was added to a suspension of 5.80 g (42.0 mmol) of anhydrous K_2CO_3 in 25 mL of dry acetone. To the resulting mixture was added 1.09 g (6.00 mmol) of 3-iodo-2-methyl-1-propene. The reaction was stirred under reflux for 6 h, then cooled to 22°C and filtered to remove the solids. The solids were washed with ether and the filtrate was concentrated under vacuum. The remaining oil was purified by flash chromatography on a 30 cm × 2 cm silica gel column eluted with 5–10% ether in hexanes to give 0.98 g (92%) of **10** as a light yellow oil that solidified on standing, mp 59–60°C. IR: 1652, 1528, 1353 cm^{-1}; ^1H NMR: δ 7.80 (dd, $J = 8.5$, 2.4 Hz, 1 H), 7.77 (d, $J = 2.4$ Hz, 1 H), 7.52 (d, $J = 8.5$ Hz, 1 H), 5.19 (dd, $J = 1.3$, 0.9 Hz, 1 H), 5.07 (dd, $J = 2.6$, 1.6 Hz, 1 H), 4.61 (s, 2 H), 1.87 (s, 3 H); ^{13}C NMR: δ 154.4, 147.1, 139.0, 130.4, 116.3, 113.94, 113.93, 108.1, 73.0, 19.2; MS: *m/z* 227, 229 (*ca* 3:1, M^+)

Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.75; H, 4.40; N, 6.15. Found: C, 52.81; H, 4.44; N 6.11.

Representative Ozonolysis Procedure: Methyl 2-(2-Fluoro-5-nitrophenyl)-4-oxobutanoate (4a)

The general procedure of Bunce and co-workers was adapted.[10] In a 250 mL round-bottomed flask, a solution of 1.00 g (3.95 mmol) of **3a** in 100 mL of MeOH was ozonized at –78°C until TLC indicated complete consumption of the starting material. Excess ozone was purged with a stream of dry N_2 and 5.00 g (5.91 mL, 80.6 mmol) of dimethyl sulfide was added. The mixture was warmed to 0°C and 5 mL of acetic acid was added. The solution was stirred at 0°C for 1 h, then warmed to 22°C and stirred for 8 h. The reaction was concentrated, diluted with ether, washed with 5% $NaHCO_3$ (3x) and saturated NaCl (1x) and then dried ($MgSO_4$). Removal of the ether gave 0.94 g (93%) of **4a** as a light yellow oil that solidified on standing, mp 63–64°C. The crude product was spectroscopically pure and was used directly in the next reaction. IR: 2842, 2731, 1738, 1724, 1530, 1350, 1249 cm^{-1}; ^1H NMR: δ 9.08 (s, 1 H), 8.21 (m, 2 H), 7.25 (t, $J = 9.0$ Hz, 1 H), 4.54 (dd, $J = 8.4$, 5.7 Hz, 1 H), 3.73 (s, 3 H), 3.48 (dd, $J = 18.8$, 8.4 Hz, 1 H), 2.91 (dd, $J = 18.8$, 5.7 Hz,

1 H); ^{13}C NMR: δ 198.0, 171.3, 163.8 (d, J = 257.9 Hz), 144.4, 127.0 (d, J = 16.8 Hz), 125.6 (d, J = 6.1 Hz). 125.3 (d, J = 9.9 Hz), 116.9 (d, J = 24.4 Hz), 52.9, 45.3, 38.2; MS: *m/z* 255 (M^+).

Anal. Calcd for $C_{11}H_{10}FNO_5$: C, 51.76; H, 3.92; N, 5.49. Found: C, 51.81; H, 3.93; N, 5.45.

Methyl 2-(2-Fluoro-5-nitrophenyl)-4-oxopentanoate (4b)

This compound (0.96 g, 95%) was prepared as above from 1.00 g (3.75 mmol) of **3b**. IR: 1738, 1717, 1533, 1350, 1250 cm^{-1}; ^{1}H NMR: δ 8.19 (m, 2 H), 7.23 (t, J = 9.0 Hz, 1 H), 4.51 (dd, J = 8.8, 5.3 Hz, 1 H), 3.71 (s, 3 H), 3.45 (dd, J = 18.8, 8.8 Hz, 1 H), 2.80 (dd, J = 18.8, 5.3 Hz, 1 H), 2.22 (s, 3 H); ^{13}C NMR: δ 204.7, 171.7, 163.9 (d, J = 258.6 Hz), 144.6, 127.4 (d, J = 17.5 Hz), 125.6 (d, J = 5.3 Hz), 125.1 (d, J = 9.9 Hz), 116.7 (d, J = 24.4 Hz), 52.8, 45.1, 39.5, 29.8; MS: *m/z* 269 (M^+).

Anal. Calcd for $C_{12}H_{12}FNO_5$: C, 53.53; H, 4.46; N, 5.20. Found: C, 53.61; H, 4.44; N, 5.11.

Methyl N-(2-Fluoro-5-nitrophenyl)-N-(2-oxoethyl)carbamate (8a)

This compound (0.85 g, 84%) was prepared as above from 1.00 g (3.95 mmol) of **7a**. IR: 1713, 1533, 1352, 1256 cm^{-1}; ^{1}H NMR: δ 9.70 (s, 1 H), 8.31 (br s, 1 H), 8.21 (m, 1 H), 7.33 (t, J = 9.1 Hz, 1 H), 4.45 (s, 2 H), 3.76 (br s, 3 H); ^{13}C NMR: δ 196.2, 161.4 (d, J = 260.8 Hz), 155.0, 144.0, 130.1, 125.7, 124.6 (d, J = 8.9 Hz), 117.1 (d, J = 23.2 Hz), 59.1, 53.9; MS: *m/z* 256 (M^+).

Anal. Calcd for $C_{10}H_9FN_2O_5$: C, 46.88; H, 3.54; N, 10.93. Found: C, 47.02; H, 3.59; N, 10.82.

Methyl N-(2-Fluoro-5-nitrophenyl)-*N*-(2-oxopropyl)carbamate (8b)

This compound (0.90 g, 89%) was prepared as above from 1.00 g (3.73 mmol) of **7b**, mp 98–100°C. IR: 1718, 1533, 1348, 1256 cm^{-1}; ^{1}H NMR: δ 8.37 (br s, 1 H), 8.18 (ddd, J = 9.2, 4.1, 3.2 Hz, 1 H), 7.28 (t, J = 9.2 Hz, 1 H), 4.43 (s, 2 H), 3.73 (br s, 3 H), 2.20 (s, 3 H); ^{13}C NMR: δ 202.0, 161.5 (d, J = 260.8 Hz), 155.0, 144.1, 130.3, 126.1, 124.5 (d, J = 9.1 Hz), 117.1 (d, J = 23.2 Hz), 58.9, 53.8, 26.8; MS: *m/z* 270 (M^+).

Anal. Calcd for $C_{11}H_{11}FN_2O_5$: C, 48.89; H, 4.10; N, 10.37. Found: C, 48.92; H, 4.10; N, 10.36.

1-(2-Chloro-5-nitrophenoxy)-2-propanone (11)

This compound (0.95 g, 94%) was prepared as above from 1.00 g (4.38 mmol) of **10**, mp 85–87°C. IR: 1728, 1525, 1348 cm^{-1}; ^{1}H NMR: δ 7.86 (dd, J = 8.8, 2.4 Hz, 1 H), 7.64 (d, J = 2.4 Hz, 1 H), 7.58 (d, J = 8.8 Hz, 1 H), 4.74 (s, 2 H), 2.39 (s, 3 H); ^{13}C NMR: δ 202.7, 153.6, 147.1, 130.8, 130.5, 117.3, 107.9, 73.4, 26.7; MS: *m/z* 229, 231 (*ca* 3:1, M^+)

Anal. Calcd for $C_9H_8ClNO_4$: C, 47.06; H, 3.49; N, 6.10. Found: C, 47.11; H, 3.52; N, 6.07.

Representative Procedure for Reductive Amination-S_NAr Cyclizations: (±)-Methyl 1-Benzyl-6-nitro-1,2,3,4-tetrahydroquinoline-4-carboxylate (12)

The procedure of Bunce and Nago was used.[1] In a 50 mL one-necked round-bottomed flask, a solution of 100 mg (0.39 mmol) of **4a** and 51 mg (0.52 mL, 0.47 mmol) of benzylamine in 4 mL of CH_3OH was stirred for 30 min and 21 mg (0.33 mmol) of $NaBH_3CN$ was added. This was followed by two additional 7 mg (0.11 mmol)-portions of $NaBH_3CN$ at 12 h intervals. Stirring was continued for 48 h and the crude reaction mixture was added to saturated NaCl and extracted with ether (3x). The combined ether extracts were dried ($MgSO_4$), concentrated under vacuum and purified by PTLC using 20% ether in hexanes. Band 1 gave 114 mg (90%) of **12** as a yellow oil. IR: 1734, 1522, 1348 cm^{-1}; ^1H NMR: δ 8.06 (d, $J = 2.7$ Hz, 1 H), 7.93 (dd, $J = 9.3$, 2.7 Hz, 1 H), 7.36 (t, $J = 7.3$ Hz, 2 H), 7.28 (t, $J = 7.3$ Hz, 1 H), 7.18 (d, $J = 7.3$ Hz, 2 H), 6.51 (d, $J = 9.3$ Hz, 1 H), 4.63 (s, 2 H), 3.89 (apparent t, $J = 4.2$ Hz, 1 H), 3.75 (s, 3 H), 3.74 (m, 1 H), 3.44 (dddd, $J = 12.6$, 4.8, 3.7, 1.3 Hz, 1 H), 2.39 (dq, $J = 13.5$, 3.7 Hz, 1 H), 2.09 (ddt, $J = 13.5$, 11.7, 4.8 Hz, 1 H); ^{13}C NMR: δ 173.2, 149.8, 136.7, 136.0, 129.0, 127.5, 126.7, 126.1, 125.5, 117.1, 110.2, 55.0, 52.5, 46.7, 42.1, 23.4; MS: *m/z* 235 ($M^+-C_7H_7$).

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.26; H, 5.52; N, 8.59. Found: C, 66.33; H, 5.56; N, 8.51.

(±)-Methyl 1-Hexyl-6-nitro-1,2,3,4-tetrahydroquinoline-4-carboxylate (13)

This compound (92 mg, 74%) was prepared as above from 100 mg (0.39 mmol) of **4a** and 47 mg (0.062 mL, 0.47 mmol) of hexylamine, mp 60–62°C. IR: 1735, 1522, 1346 cm^{-1}; ^1H NMR: δ 8.02 (m, 2 H), 6.55 (d, $J = 9.9$, Hz, 1 H), 3.80 (apparent t, $J = 4.1$ Hz, 1 H), 3.73 (s, 3 H), 3.61 (td, $J = 12.6$, 3.7 Hz, 1 H), 3.35 (m, 3 H), 2.33 (dq, $J = 13.6$, 3.6 Hz, 1 H), 1.96 (ddt, $J = 13.6$, 11.6, 4.9 Hz, 1 H), 1.63 (m, 2 H), 1.33 (m, 6 H), 0.90 (t, $J = 6.6$ Hz, 3 H); ^{13}C NMR: δ 173.3, 149.5, 135.9, 126.9, 125.5, 116.7, 109.5, 52.4, 51.7, 46.2, 41.9, 31.5, 26.6, 26.2, 23.2, 22.5, 13.9; MS: *m/z* 249 ($M^+-C_5H_{11}$).

Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.75; H, 7.50; N, 8.75. Found: C, 63.74; H, 7.51; N, 8.73.

(±)-Methyl 1-Isobutyl-6-nitro-1,2,3,4-tetrahydroquinoline-4-carboxylate (14)

This compound (101 mg, 89%) was prepared as above from 100 mg (0.39 mmol) of **4a** and 34 mg (0.047 mL, 0.47 mmol) of isobutylamine. IR: 1735, 1522, 1347 cm^{-1}; ^1H NMR: δ 8.02 (d, $J = 2.7$ Hz, 1 H), 7.99 (dd, $J = 9.2$, 2.7 Hz, 1 H), 6.55 (d, $J = 9.2$ Hz, 1 H), 3.81 (apparent t, $J = 4.2$ Hz, 1 H), 3.73 (s, 3 H), 3.65 (td, $J = 11.7$, 3.7 Hz, 1 H), 3.36 (dm, $J = 12.6$ Hz, 1 H), 3.19 (ddd, $J = 23.6$, 14.6, 7.3 Hz, 2 H), 2.32 (dq, $J = 13.6$, 3.7 Hz, 1 H), 2.13 (nonet, $J = 6.7$ Hz, 1 H), 1.98 (ddt, $J = 13.6$, 11.7, 4.9 Hz, 1 H), 0.96 (d, $J = 6.7$ Hz, 3 H), 0.95 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR: δ 173.3, 149.8, 135.9, 126.9, 125.3, 116.7, 109.9, 59.4, 52.4, 47.4, 42.0, 26.7, 23.2, 20.2, 20.1; MS: *m/z* 249 ($M^+-C_3H_7$).

Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.64; H, 6.85; N, 9.59. Found: C, 61.75; H, 6.88; N, 9.53.

(±)-Methyl 1-Cyclohexyl-6-nitro-1,2,3,4-tetrahydroquinoline-4-carboxylate (15)

This compound (87 mg, 70%) was prepared as above from 100 mg (0.39 mmol) of **4a** and 47 mg (0.054 mL, 0.47 mmol) of cyclohexylamine, mp 73–75°C. IR: 1735, 1511, 1326 cm^{-1}; ^1H NMR: δ 8.01 (m, 2 H), 6.64 (d, $J = 10.0$ Hz, 1 H), 3.78 (apparent t, $J = 4.5$ Hz, 1 H), 3.72 (s, 3 H), 3.71 (dm, $J = 12.7$ Hz, 1 H), 3.40 (m, 1 H), 3.36 (td, $J = 12.8$, 3.8 Hz, 1 H), 2.34 (dq, $J = 13.4$, 3.8 Hz, 1 H), 1.95–1.69 (complex, 6 H), 1.62–1.30 (complex, 3 H), 1.26–1.09 (complex, 2 H); ^{13}C NMR: δ 173.2, 149.7, 135.6, 126.9, 125.5, 117.5, 109.6, 57.4, 52.3, 42.3, 38.8, 29.7, 29.4, 25.9, 25.7, 25.5, 23.5; MS: *m/z* 318 (M^+).

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.17; H, 6.99; N, 8.76.

Methyl 4-Benzyl-7-nitro-3,4-dihydroquinoxaline-1(2H)-carboxylate (16)

This compound (66 mg, 52%) was prepared as above from 100 mg (0.39 mmol) of **8a** and 51 mg (0.052 mL, 0.47 mmol) of benzylamine, mp 102–103°C. IR: 1709, 1522, 1330 cm^{-1}; ^1H NMR δ 8.41 (br s, 1 H), 7.86 (dd, $J = 9.3$, 2.6 Hz, 1 H), 7.38–7.25 (complex, 3 H), 7.18 (d, $J = 6.6$ Hz, 2 H), 6.60 (d, $J = 9.3$ Hz, 1 H), 4.65 (s, 2 H), 3.92 (t, $J = 5.3$ Hz, 2 H), 3.85 (s, 3 H), 3.58 (t, $J = 5.3$ Hz, 2 H); ^{13}C NMR: δ 154.3, 143.4, 136.9, 135.7, 129.1, 127.7, 126.2, 123.1, 122.2, 120.7, 110.1, 54.7, 53.5, 49.2, 40.7; MS: *m/z* 236 (M^+-C_7H_7).

Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.39; H, 5.20; N, 12.84. Found: C, 62.42; H, 5.23; N, 12.81.

Methyl 4-Hexyl-7-nitro-3,4-dihydroquinoxaline-1(2H)-carboxylate (17)

This compound (78 mg, 62%) was prepared as above from 100 mg (0.39 mmol) of **8a** and 47 mg (0.062 mL, 0.47 mmol) of hexylamine. IR: 1710, 1522, 1331 cm^{-1}; ^1H NMR δ 8.35 (br s, 1 H), 7.93 (dd, $J = 9.3$, 2.7 Hz, 1 H), 6.60 (d, $J = 9.3$ Hz, 1 H), 3.83 (s, 3 H), 3.83 (t, $J = 5.3$ Hz, 2 H), 3.49 (t, $J = 5.3$ Hz, 2 H), 3.38 (apparent t, $J = 7.7$ Hz, 2 H), 1.63 (quintet, $J = 7.2$ Hz, 2 H), 1.40–1.28 (complex, 6 H), 0.90 (distorted t, $J = 6.8$ Hz, 3 H); ^{13}C NMR: δ 155.1, 143.1, 136.2, 125.5, 122.3, 120.8, 109.3, 53.5, 51.6, 48.8, 40.5, 31.5, 26.6, 26.3, 22.6, 14.0; MS: *m/z* 250 ($M^+-C_5H_{11}$).

Anal. Calcd for $C_{16}H_{23}N_3O_4$: C, 59.81; H, 7.17; N, 13.08. Found: C, 59.90; H, 7.14; N, 12.99.

Methyl 4-Isobutyl-7-nitro-3,4-dihydroquinoxaline-1(2H)-carboxylate (18)

This compound (63 mg, 55%) was prepared as above from 100 mg (0.39 mmol) of **8a** and 34 mg (0.047 mL, 0.47 mmol) of isobutylamine. IR: 1709, 1524, 1328 cm^{-1}; ^1H NMR δ 8.37 (br s, 1 H), 7.92 (dd, $J = 9.3$, 2.4 Hz, 1 H), 6.61 (d, $J = 9.3$ Hz, 1 H), 3.84 (s, 3 H), 3.84 (t, $J = 5.3$ Hz, 2 H), 5.51 (t, $J = 5.3$ Hz, 2 H), 3.21 (d, 2 H, $J = 7.7$ Hz, 2 H), 2.14 (nonet, $J = 6.8$ Hz, 1 H), 0.97 (d, $J = 6.6$ Hz, 6 H); ^{13}C NMR δ 154.4, 143.4, 136.3, 122.6, 122.1, 120.9, 109.8, 59.5, 53.5, 50.1, 40.4, 26.8, 20.3; MS: *m/z* 250 (M^+-C_3H_7).

Anal. Calcd for $C_{14}H_{19}N_3O_4$: C, 57.34; H, 6.48; N, 14.33. Found: C, 57.27; H, 6.44; N, 14.38.

Methyl 4-Cyclohexyl-7-nitro-3,4-dihydroquinoxaline-1(2H)-carboxylate (19)

This compound (45 mg, 36%) was prepared as above from 100 mg (0.39 mmol) of **8a** and 47 mg (0.054 mL, 0.47 mmol) of cyclohexylamine. IR: 1710, 1518, 1329 cm^{-1}; ^1H NMR: δ 8.33 (br s, 1 H), 7.93 (dd, $J = 9.3$, 2.8 Hz, 1 H), 6.68 (d, $J = 9.3$ Hz, 1 H), 3.83 (s, 3 H), 3.78 (t, $J = 5.2$ Hz, 2 H), 3.72 (tt, $J = 11.4$, 3.3 Hz, 1 H), 3.43 (t, $J = 5.2$ Hz, 2 H), 1.98–1.70 (complex, 5 H), 1.58–1.32 (complex, 3 H), 1.20 (m, 2 H); ^{13}C NMR: δ 154.2, 143.4, 135.9, 123.3, 122.4, 120.9, 109.5, 57.1, 53.4, 42.2, 40.7, 29.4, 25.7, 25.5; MS: *m/z* 319 (M^+).

Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.58; N, 13.17. Found: C, 60.31; H, 6.62; N, 13.05.

(±)-Methyl 4-Benzyl-3-methyl-7-nitro-3,4-dihydroquinoxaline-1(2H)-carboxylate (20)

This compound (110 mg, 83%) was prepared as above from 105 mg (0.39 mmol) of **8b** and 51 mg (0.52 mL, 0.47 mmol) of benzylamine, mp 101–103°C. IR: 1710, 1520, 1348 cm^{-1}; ^1H NMR: δ 8.47 (br s, 1 H), 7.81 (dd, $J = 9.3$, 2.7 Hz, 1 H), 7.39–7.24 (complex, 3 H), 7.15 (d, $J = 7.0$ Hz, 2 H), 6.48 (d, $J = 9.3$ Hz, 1 H), 4.70 (d, $J = 17.4$ Hz, 1 H), 4.61 (d, $J = 17.4$ Hz, 1 H), 4.38 (br d, $J = 13.2$ Hz, 1 H), 3.88 (s, 3 H), 3.80 (m, 1 H), 3.37 (dd, $J = 13.2$, 2.9 Hz, 1 H), 1.26 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR: δ 154.8, 142.9, 136.8, 136.1, 129.0, 127.6, 125.9, 122.9, 122.1, 120.1, 110.5, 54.3, 53.6, 52.9, 45.8, 17.6; MS: *m/z* 250 (M^+-C_7H_7).

Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.34; H, 5.57; N, 12.32. Found: C, 63.29; H, 5.58; N, 12.35.

(±)-Methyl 4-Hexyl-3-methyl-7-nitro-3,4-dihydroquinoxaline-1(2H)-carboxylate (21)

This compound (90 mg, 69%) was prepared as above from 105 mg (0.39 mmol) of **8b** and 47 mg (0.062 mL, 0.47 mmol) of hexylamine. IR: 1710, 1522, 1353 cm^{-1}; ^1H NMR: δ 8.41 (br s, 1 H), 7.92 (dd, $J = 9.3$, 2.8 Hz, 1 H), 6.55 (d, $J = 9.3$ Hz, 1 H), 4.34 (dd, $J = 13.1$, 1.8 Hz, 1 H), 3.85 (s, 3 H), 3.69 (m, 1 H), 3.43 (m, 1H), 3.27 (m, 1 H), 3.16 (dd, $J = 13.1$, 3.0 Hz, 1 H), 1.63 (m, 2 H), 1.40–1.28 (complex, 6 H), 1.20 (d, $J = 6.4$ Hz, 3 H), 0.91 (distorted t, $J = 7.0$ Hz, 3 H); ^{13}C NMR: δ 154.7, 142.4, 135.9, 122.4, 122.0, 120.2, 109.3, 53.7, 53.4, 49.7, 45.5, 31.5, 26.7, 26.6, 22.5, 17.6, 13.9; MS: *m/z* 264 ($M^+-C_5H_{11}$).

Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.90; H, 7.46; N, 12.54. Found: C, 61.01; H, 7.49; N, 12.49.

(±)-Methyl 4-Isobutyl-3-methyl-7-nitro-3,4-dihydroquinoxaline-1(2H)-carboxylate (22)

This compound (90 mg, 75%) was prepared as above from 105 mg (0.39 mmol) of **8b** and 34 mg (0.047 mL, 0.47 mmol) of isobutylamine, mp 109–110°C. IR: 1709, 1521, 1354 cm^{-1}; ^1H NMR: δ 8.46 (br s, 1 H), 7.90 (dd, $J = 9.3$, 2.7 Hz, 1 H), 6.56 (d, $J = 9.3$ Hz, 1 H), 4.39 (dd, $J = 13.0$, 1.9 Hz, 1 H), 3.86 (s, 3 H), 3.70 (m, 1 H), 3.46 (dd, $J = 14.5$, 5.3 Hz, 1 H), 3.23 (dd, $J = 13.1$, 2.8 Hz, 1 H), 2.91 (dd, $J = 14.8$, 9.5 Hz, 1 H), 2.15 (m, 1 H), 1.17 (d, $J = 6.4$ Hz, 3 H), 0.964 (d, $J = 6.8$ Hz, 3 H), 0.960 (d, $J = 6.6$ Hz, 3 H); ^{13}C

NMR: δ 154.8, 142.4, 136.0, 122.2, 121.8, 120.2, 109.9, 56.9, 53.9, 53.4, 45.2, 26.6, 20.1, 16.6; MS: *m/z* 264 ($M^+-C_3H_7$).

Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.63; H, 6.84; N, 13.68. Found: C, 58.59; H, 6.82; N, 13.73.

*(±)-Methyl 4-Cyclohexyl-3-methyl-7-nitro-3,4-dihydroquinoxaline-1(2*H*)-carboxylate (23)*

This compound (74 mg, 57%) was prepared as above from 105 mg (0.39 mmol) of **8b** and 47 mg (0.054 mL, 0.47 mmol) of cyclohexylamine. IR: 1709, 1511, 1346 cm^{-1}; ^{1}H NMR: δ 8.50 (br s, 1 H), 7.91 (dd, $J = 9.5$, 2.8 Hz, 1 H), 6.71 (d, $J = 9.5$ Hz, 1 H), 4.43 (d, $J =$ 12.7 Hz, 1 H), 3.93 (m, 1 H), 3.86 (s, 3 H), 3.72 (tt, $J = 11.4$, 3.3 Hz, 1 H), 2.89 (dd, $J =$ 13.0, 2.4 Hz, 1 H), 2.10–1.62 (complex, 5 H), 1.60–1.32 (complex, 3 H), 1.21 (m, 2 H), 1.14 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR: δ 154.7, 141.8, 135.9, 122.6, 121.6, 120.4, 110.3, 58.0, 53.4, 47.3, 45.9, 31.1, 29.6, 26.0, 25.9, 25.5, 19.5; MS: *m/z* 318 (M^+-CH_3).

Anal. Calcd for $C_{17}H_{23}N_3O_4$: C, 61.26; H, 6.91; N, 12.61. Found: C, 61.39; H, 6.94; N, 12.51.

*(±)-*N*-Benzyl-1-(2-chloro-5-nitrophenoxy)-2-propanamine (24)*

This compound (58 mg, 46%) was prepared as above from 90 mg (0.39 mmol) of **11** and 51 mg (0.52 mL, 0.47 mmol) of benzylamine. IR: 3321, 1525, 1345 cm^{-1}; ^{1}H NMR: δ 7.78 (dd, $J = 8.6$, 2.6 Hz, 1 H), 7.74 (d, $J = 2.4$ Hz, 1 H), 7.50 (d, $J = 8.6$ Hz, 1 H), 7.39-7.20 (complex, 5 H), 4.12 (m, 2 H), 3.97 (d, $J = 13.6$ Hz, 1 H), 3.86 (d, $J = 13.6$ Hz, 1 H), 3.25 (m, 1 H), 2.04 (br s, 1 H), 1.25 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR: δ 154.6, 147.2, 140.2, 130.3, 128.4, 128.1, 127.9, 127.0, 116.3, 107.7, 73.7, 51.2, 51.1, 17.2,; MS: *m/z* 320, 322 (ca 3:1, M^+).

Anal. Calcd for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.30; N, 8.74. Found: C, 60.02; H, 5.34; N 8.66.

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References

1. R. A. Bunce and T. Nago, *J. Heterocycl. Chem.*, **45**, 1155 (2008).
2. For a tandem reduction-reductive amination approach to these systems, see R. A. Bunce, D. M. Herron and L. Y. Hale, *J. Heterocycl. Chem.*, **40**, 1031 (2003).

3. J. D. Little, S. Ghosh, S. Harrison, A. E. Elder, C. C. Renou and K. G. Carson, World Patent WO 2006091674 ; *Chem Abstr.*, **145**, 292886 (2006).

4. J. Milne, K. D. Normington and M. Milburn, World Patent WO 2006094210; *Chem. Abstr.* **145**, 306763 (2006).

5. J.-D. Bourzat, A. Commerçon, B. J. C. Filoche, N. V. Harris, T. D. Pallin and K. A. J. Shuttle, World Patent WO0039103; *Chem. Abstr.* **133**, 89546 (2000).

6. T. Kuroita, M. Sakamori and T. Kawakita, *Chem. Pharm. Bull.*, **44**, 756 (1996).

7. M. Largeron, B. Lockhart, B. Pfeiffer and M.-B. Fleury, *J. Med. Chem.*, **42**, 5043 (1999) and M. Largeron, B. Mesples, P. Gressens, R. Cecchelli, M. Spedding, A. Le Ridant and M.-B. Fleury, *Eur. J. Pharmacol.*, **424**, 189 (2001).

8. R. A. Bunce, T. Nago, N. Sonobe and L. M. Slaughter, *J. Heterocycl. Chem.*, **45**, 551 (2008).

9. M. H. Potashman, J. Bready, A. Coxon, T. M. DeMelfi, Jr., L. DiPietro, N. Doerr, D. Elbaum, J. Estrada, P. Gallant, J. Germain, Y. Gu, J.-C. Harmanage, S. A. Kaufman, R. Kendall, J. L. Kim, G. N. Kumar, A. M. Long, S. Neervannan, V. F. Patel, A. Polverino, P. Rose, S. van der Plas, D. Whittington, R. Zanon and H. Zhao, *J. Med. Chem.*, **50**, 4351 (2007).

10. R. A. Bunce, D. M. Herron, L. B. Johnson and S. V. Kotturi, *J. Org. Chem.*, **66**, 2822 (2001).

11. The aldehyde tetrahydroquinoxaline precursors generally yielded 5–20% of the simple reductive amination product in addition to the ring-closed product. Adjustment of the reaction conditions and stoichiometry of reagents had little effect on this outcome.

12. The fluoronitroaromatic substrate was not commercially available and could not be prepared by the Schiemann reaction. The final ring closure of chloride **24** failed at 25°C and at 50°C.

13. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

14. U. Schirmer, R. Becker and B. Wuerzer, German Patent DE 2926049 (1981); *Chem. Abstr.*, **95**, 6871 (1981).

15. M. Makosza and A. Tyrala, *Synth. Commun.*, **16**, 419 (1986).