(±)-1,2-Dialkyl-5-nitro-2,3-dihydro-1*H*-indoles by a Tandem Reductive Amination-S_NAr Reaction

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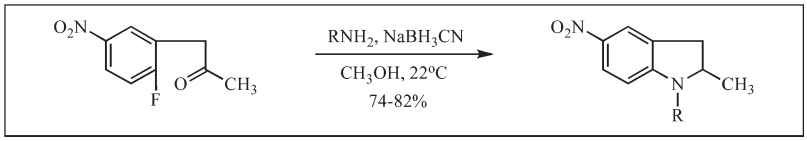

A tandem reductive amination-S_NAr reaction has been applied to the synthesis of (±)-1,2-dialkyl-5-nitro-2,3-dihydro-1*H*-indoles. Treatment of a series of 2-fluoro-5-nitrobenzyl ketones with primary amines and sodium cyanoborohydride in methanol at room temperature provided good yields of the target heterocycles. The reaction is sensitive to steric hindrance and proceeds best with less hindered ketone substrates using primary amines that are unbranched at the α carbon.

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INTRODUCTION

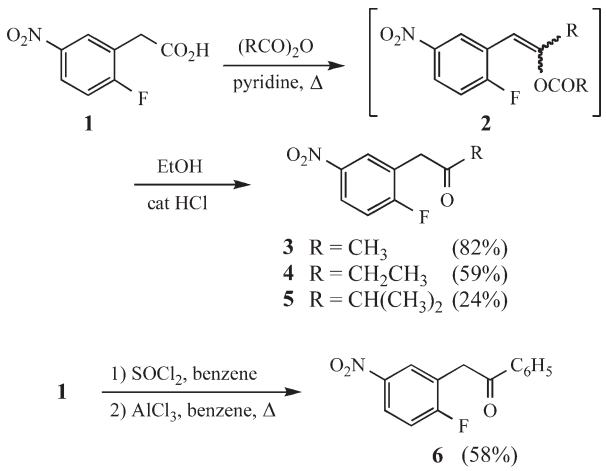
Over the past several years, our work has led to a number of reductive cyclizations that yield 1,2,3,4-tetrahydroquinolines [2]. Recently, we reported a tandem reductive amination-S_NAr reaction for the preparation of substituted 6-nitro-1,2,3,4-tetrahydroquinolines [3]. In the current work, we have extended this sequence to the preparation of (±)-dialkyl-5-nitro-2,3-dihydro-1*H*-indoles. Earlier syntheses of dihydroindoles have involved photolysis of *N*-aryl enamines [4]; reduction of indoles with borane-trimethylamine [5]; base-catalyzed spirocyclization of aromatic imide imines [6]; base-catalyzed tandem hydroamination-aryne addition of chlorostyrenes [7]; and tandem S_N2-S_NAr reaction of 2-(3-bromopropyl)-1-fluoro-4-nitrobenzene [2(b)]. Each of these mechanistically diverse routes provides access to a select group of dihydroindoles but none constitutes a general synthesis.

Dihydroindoles bearing a 1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl group in the C5 position have been shown to exhibit significant biological activity as nonsteroidal liver X receptor-α agonists [8]. Liver X receptors normally bind 24*S*,25-epoxycholesterol and have been found to play an important role in lipid metabolism [8]. These potent modulators of liver X receptor-α are currently being investigated for the treatment of dyslipidemia, atherosclerosis, and diabetes [9]. While the compounds prepared here possess a nitro group at C5, the nitro group could be readily transformed [10,11] to permit installation of the required substituent.

RESULTS AND DISCUSSION

The synthesis of our dihydroindole precursors is shown in Scheme 1. Dakin-West reaction of (2-fluoro-5-nitrophenyl)acetic acid (**1**) [2(b)] with a series of carboxylic acid anhydrides in pyridine followed by refluxing with acidic ethanol gave the 1-(2-fluoro-5-nitrophenyl)-2-propanone derivatives **3**, **4**, and **5** [12,13]. Yields of the ketone products correlated with the steric hindrance of the anhydride with acetic anhydride giving the highest yield (82%) and isobutyric anhydride the lowest (24%). Finally, the desoxybenzoin derivative **6** was prepared in 58% yield by a Friedel-Crafts reaction of (2-fluoro-5-nitrophenyl)acetyl chloride with benzene [14].

Scheme 1



Our cyclization study sought to demonstrate the feasibility of preparing selected dihydroindoles from alkyl 2-fluoro-5-nitrobenzyl ketones and primary amines by a tandem reductive amination-S_NAr sequence. Initially, we believed that the enolizability of the substrates might lead to competitive condensation reactions under the

neutral to basic reaction conditions. Another potential problem was the strain associated with closing a benzo-fused five-membered ring [15]. Neither of these concerns, however, proved to be a significant deterrent to the success of the reaction.

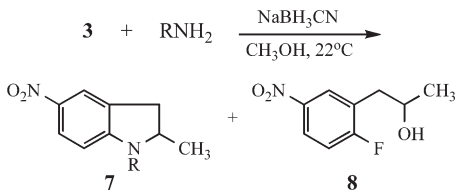
The reaction is run by dissolving 1.00 equivalent of the ketone in methanol, then adding 1.20 equivalents of the amine and 1.25 equivalents of sodium cyanoborohydride, and stirring at room temperature for 48 h. Optimum yields were obtained when two extra portions (0.18 equivalents each) of the amine and the reducing agent were added at 12-h intervals during the first 24 h. The major limitation of the current process is its sensitivity to the steric environment surrounding the ketone and amine functions. For example, the reaction was successful for substrates **3** (R = CH_3) and **4** (R = CH_2CH_3), but proceeded poorly for **5** (R = $CH(CH_3)_2$). The phenyl ketone **6** proved to be inert to the reaction conditions at 22°C, but gave a low yield of the heterocycle, along with three other products, at 65°C. Bulky amines, branched at the α-carbon, also gave lower yields.

The best results were achieved by reacting methyl ketone **3** with unbranched primary amines (see Table 1). These gave the target dihydroindoles **7a–e** in 74–82% yields. In each case, the ketone reduction product, 1-(2-fluoro-5-nitrophenyl)-2-propanol (**8**), was also isolated in 10–15% yield. More hindered amines, such as cyclohexylamine, gave dihydroindole **7f** in much lower yield (22%), with the remainder being alcohol **8** (20%), simple reductive amination product **9** (32%) and recovered **3** (14%). Isolation of **9** in this case suggests that reductive amination initiates the two-step sequence. Finally, *tert*-butylamine gave only alcohol **8** (20%) along with unreacted **3** (75%).

For more sterically congested substrates **4** and **5**, the yield of the dihydroindole decreased and the proportion of ketone reduction product (**11** and **13**, respectively) and unreacted ketone increased (see Tables 2 and 3). Ethyl ketone **4** gave the dihydroindoles in 60–64% yield, which is still synthetically useful. Isopropyl ketone **5**, however, afforded less than 25% yields and the desired products were difficult to separate from unreacted ketone and other minor by-products. Finally,

Table 1

Reductive cyclization of methyl ketone **3**.



7 8

R	Yield of **7** (%)[a]
Unbranched	
a $C_6H_5CH_2$	78
b $C_6H_5CH_2CH_2$	76
c *n*-C_6H_{13}	82
d *i*-$C_3H_7OCH_2CH_2CH_2$	74
e *i*-C_4H_9	82
Branched	
f *c*-C_6H_{11}	22[b]
g *t*-C_4H_9	0[c]

[a] Each reaction also gave **8** in 10–13 % yield.
[b] This reaction also gave reductive amination product **9** in 32% yield, **8** in 20% yield, and unreacted **3** in 14% yield.
[c] This reaction gave **8** in 20% yield and unreacted **3** in 75% yield.

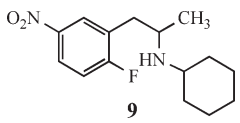


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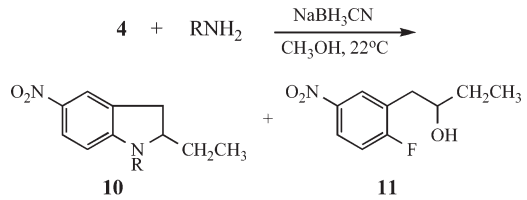
Table 2

Reductive cyclization of ethyl ketone **4**.



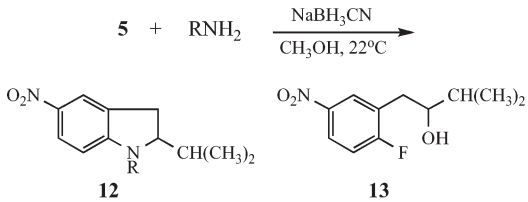
10 11

R	Yield of **10** (%)[a]
a $C_6H_5CH_2$	60
b $C_6H_5CH_2CH_2$	62
c *n*-C_6H_{13}	61
d *i*-$C_3H_7OCH_2CH_2CH_2$	61
e *i*-C_4H_9	64

[a] Each reaction also gave **11** in 18–20% yield and unreacted **4** in 10–12% yield.

Table 3

Reductive cyclization of isopropyl ketone **5**.

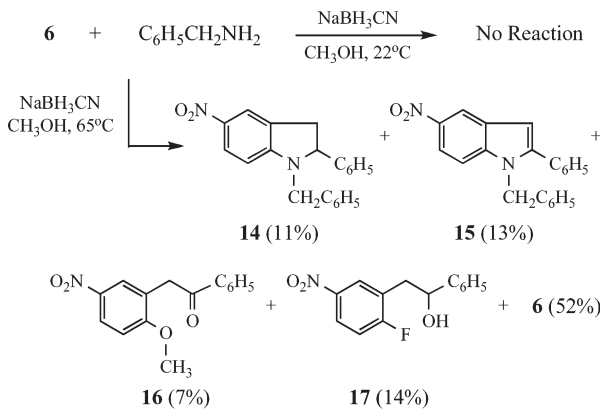


12 13

R	Yield of **12** (%)
a $C_6H_5CH_2$	17[a]
c *n*-C_6H_{13}	22[b]

[a] This reaction also gave **13** in 15% yield and unreacted **5** in 58% yield.
[b] This reaction also gave **13** in 14% yield and unreacted **5** in 55% yield.

Scheme 2



phenyl ketone **6** and benzylamine in methanol reacted only under forcing conditions (65°C, 48 h) to give a low yield of the desired dihydroindole **14** (11%), along with indole **15** (13%) from α deprotonation of the intermediate imine and cyclization by the nitrogen of the delocalized anion, methoxyketone **16** (7%) from solvent addition to the activated ring, alcohol **17** (14%) and unreacted **6** (52%) (see Scheme 2).

CONCLUSION

We have developed an approach to the synthesis of (±)-1,2-dialkyl-5-nitro-2,3-dihydro-1*H*-indoles based on a tandem reductive amination-S_NAr reaction. The reaction gives good yields in many cases but is sensitive to steric hindrance in the ketone and amine reacting partners. Thus, while satisfactory conversions were achieved from substrates **3** and **4**, hindered ketone **5** gave low yields and aromatic ketone **6** was unreactive. Branching at the α-carbon of the amine also proved detrimental to the reaction. We are pursuing further studies of this transformation in systems bearing other electron withdrawing groups at C5 and C7 of the dihydroindole system.

EXPERIMENTAL

All reactions were run under dry nitrogen unless otherwise indicated. Methanol was used from a freshly opened bottle. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521) with ultraviolet detection. Preparative separations were performed by one of the following methods: (1) flash column chromatography [16] on silica gel (grade 62, 60–200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20 cm × 20 cm silica gel GF plates (Analtech 02015). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65–70°C. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (J) are given in Hz. Mass spectra (electron impact/direct probe) were obtained at 70 eV.

1-(2-Fluoro-5-nitrophenyl)-2-propanone (3). This compound was prepared from **1** and acetic anhydride on a 13.2 mmol scale by adapting the method described by Schtacher and Dayagi [12] for the synthesis of 1-(3-nitrophenyl)-2-propanone. The crude product was recrystallized from methanol to give 2.13 g (82%) of **3**, mp 113–114°C. ir: 1725, 1522, 1352, 1246 cm^{-1}; ^{1}H NMR: δ 8.19 (ddd, 1H, J = 8.8, 4.4, 2.7), 8.12 (dd, 1H, J = 6.2, 2.7), 7.22 (t, 1H, J = 8.8), 3.88 (d, 2H, J = 0.9), 2.31 (s, 3H); ^{13}C NMR: δ 202.7, 164.5 (d, J = 257.4), 144.2, 127.4 (d, J = 6.6), 124.9 (d, J = 10.3), 123.4, (d, J = 18.6), 116.2 (d, J = 24.9), 43.3, 29.7; ms: m/z 197 (M^+). Anal. Calcd. for $C_9H_8FNO_3$: C, 54.82; H, 4.06; N, 7.11. Found: C, 54.84; H, 4.07; N, 7.07.

1-(2-Fluoro-5-nitrophenyl)-2-butanone (4). This compound was prepared from **1** and propionic anhydride on a 13.2 mmol scale by adapting the method described by Schtacher and Dayagi [12] for the synthesis of 1-(3-nitrophenyl)-2-propanone. The crude product was flash chromatographed on a 30 cm × 2.5 cm silica gel column eluted with 5% ether in hexanes to give 1.53 g (59%) of **4**, mp 59–61°C. ir: 1721, 1529, 1351, 1248 cm^{-1}; ^{1}H NMR: δ 8.18 (ddd, 1H, J = 8.8, 4.5, 2.9), 8.13 (dd, 1H, J = 6.2, 2.9), 7.21 (t, 1H, J = 8.8), 3.85 (d, 2H, J = 0.8), 2.60 (q, 2H, J = 7.2), 1.12 (t, 3H, J = 7.2); ^{13}C NMR: δ 205.5, 164.5 (d, J = 257.7), 144.1, 127.7 (d, J = 6.6), 124.9 (d, J = 9.6), 123.6 (d, J = 19.1), 116.2 (d, J = 24.3), 42.0 (d, J = 1.5), 35.9, 7.7; ms: m/z 211 (M^+). Anal. Calcd. For $C_{10}H_{10}FNO_3$: C, 56.87; H, 4.74; N, 6.63. Found: C, 56.85; H, 4.73; N, 6.63.

1-(2-Fluoro-5-nitrophenyl)-3-methyl-2-butanone (5). This compound was prepared from **1** and isobutyric anhydride on an 11.5 mmol scale by adapting the method described by Schtacher and Dayagi [11] for the synthesis of 1-(3-nitrophenyl)-2-propanone. The crude product was flash chromatographed on a 30 cm × 2.5 cm silica gel column using 5% ether in hexanes to give 0.62 g (24%) of **5**, mp 46–48°C. ir: 1720, 1530, 1349, 1249 cm^{-1}; ^{1}H NMR: δ 8.18 (ddd, 1H, J = 8.8, 4.5, 2.9), 8.12 (dd, 1H, J = 6.2, 2.9), 7.20 (t, 1H, J = 8.8), 3.90 (s, 2H), 2.79 (septet, 1H, J = 6.8), 1.20 (d, 6H, J = 6.8); ^{13}C NMR: δ 208.8, 164.5 (d, J = 256.9), 144.3, 127.8 (d, J = 6.6), 124.8 (d, J = 10.7), 123.8 (d, J = 18.4), 116.1 (d, J = 24.3), 41.0, 40.1 (d, J = 1.5), 18.2; ms: m/z 182 (M^+-C_3H_7). Anal. Calcd. For $C_{11}H_{12}FNO_3$: C, 58.67; H, 5.33; N, 6.22. Found: C, 58.71; H, 5.34; N, 6.17.

3-(2-Fluoro-5-nitrophenyl)-1-phenyl-1-ethanone (6). [**Caution**! Benzene is a carcinogen. Thionyl chloride is an inhalation hazard and is highly toxic. Both should be handled carefully in a well-ventilated area.] In a round-bottomed flask protected by a drying tube (Drierite®), 2.97 g (1.82 mL, 25.0 mmol) of thionyl chloride was added to a solution of 2.49 g (12.5 mmol) of **1** in 40 mL of benzene and the mixture was stirred and heated under reflux for 3 h. Solvent and excess thionyl chloride were removed by distillation and the resulting acid chloride in 10 mL of benzene was added dropwise to a suspension of 2.00 g (15.0 mmol) of aluminum chloride in 40 mL of benzene [14]. The mixture was heated under reflux for 1

h, then cooled and quenched by addition to 10 mL of concentrated hydrochloric acid and 25 g of crushed ice. The product was extracted with 1:1 benzene:ether (two times) and the combined organic extracts were washed with saturated sodium chloride (one time), dried (magnesium sulfate), and concentrated under vacuum. The crude product was recrystallized from methanol to give 1.88 g (58%) of **6**, mp 89–90°C. ir: 1691, 1527, 1352, 1249 cm^{-1}; ^1H NMR: δ 8.21 (superimposed ddd and dd, 2H), 8.05 (superimposed dd, 2H), 7.64 (tt, 1H, $J = 7.4, 1.2$), 7.52 (t, 2H, $J = 7.4$), 7.24 (t, 1H, $J = 8.2$), 4.44 (d, 2H, $J = 0.8$); ^{13}C NMR: δ 194.5, 164.7 (d, $J = 256.9$), 144.1, 135.9, 133.8, 128.9, 128.3, 127.9 (d, $J = 6.6$), 125.0 (d, $J = 10.3$), 123.8 (d, $J = 18.4$), 116.2 (d, $J = 24.3$), 38.6 (d, $J = 1.5$); ms (30 eV): m/z 259 (M^+). Anal. Calcd. For $C_{14}H_{10}FNO_3$: C, 64.86; H, 3.86; N, 5.41. Found: C, 64.87; H, 3.86; N, 5.42.

Representative procedure for the reductive amination-nucleophilic substitution reaction with 3: (±)-1-Benzyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7a). To a stirred solution of 100 mg (0.51 mmol) of **3** and 64 mg (0.65 mL, 0.60 mmol) of benzylamine at 22°C was added 40 mg (0.64 mmol) of sodium cyanoborohydride. The reaction was stirred at 22°C for 48 h; two additional portions of 10 mg (0.09 mmol) of benzylamine and 6 mg (0.09 mmol) of sodium cyanoborohydride were added at 12-h intervals during the first 24 h. The crude reaction mixture was poured into saturated sodium chloride and extracted with ether (three times). The combined ether extracts were dried (magnesium sulfate), concentrated under vacuum, and purified by preparative thin layer chromatography using 20% ether in hexanes. The bright yellow band contained 106 mg (78%) of **7a** as a yellow solid, mp 94–95°C. ir: 1506, 1315 cm^{-1}; ^1H NMR: δ 8.00 (dd, 1H, $J = 8.8, 2.4$), 7.88 (m, 1H), 7.38–7.22 (complex, 5H), 6.23 (d, 1H, $J = 8.8$), 4.55 (d, 1H, $J = 16.3$), 4.35 (d, 1H, $J = 16.3$), 4.02 (m, 1H), 3.29 (ddd, 1H, $J = 16.1, 9.1, 1.1$), 2.72 (ddd, 1H, $J = 16.1, 7.7, 0.9$), 1.32 (d, 3H, $J = 6.2$); ^{13}C NMR: δ 156.8, 138.1, 136.7, 128.8, 128.5, 127.6, 127.0, 126.6, 120.6, 103.7, 59.7, 48.5, 35.8, 19.8; ms: m/z 268 (M^+). Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.64; H, 5.96; N, 10.42.

This reaction also produced 12 mg (12%) of 1-(2-fluoro-5-nitrophenyl)-2-propanol (**8**), mp 53–54.5°C. ir: 3385, 1527, 1350, 1245 cm^{-1}; ^1H NMR: δ 8.21 (dd, 1H, $J = 6.2, 2.9$), 8.13 (ddd, 1H, $J = 8.8, 4.4, 2.9$), 7.18 (t, 1H, $J = 8.8$), 4.13 (d of sextets, 1H, $J = 6.2, 0.9$), 2.91 (ddd, 1H, $J = 13.8, 4.8, 1.3$), 2.83 (ddd, 1H, $J = 13.8, 7.5, 1.3$), 1.61 (br s, 1H), 1.29 (d, 3H, $J = 6.2$); ^{13}C NMR: δ 164.8 (d, $J = 256.2$), 149.6, 128.3 (d, $J = 18.3$), 127.6 (d, $J = 7.2$), 124.1 (d, $J = 10.3$), 116.2 (d, $J = 25.5$), 67.4, 38.2, 23.3; ms: m/z 199 (M^+). Anal. Calcd. for $C_9H_{10}FNO_3$: C, 54.27; H, 5.03; N, 7.04. Found: C, 54.31; H, 5.05; N, 7.01.

(±)-2-Methyl-5-nitro-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole (7b). This compound (110 mg, 76%) was isolated as a yellow oil. ir: 1508, 1315 cm^{-1}; ^1H NMR: δ 8.00 (dd, 1H, $J = 8.8, 2.2$), 7.83 (m, 1H), 7.34–7.16 (complex, 5H), 6.16 (d, 1H, $J = 8.8$), 3.91 (m, 1H), 3.47 (m, 2H), 3.19 (ddd, 1H, $J = 16.3, 9.3, 0.9$), 2.86 (m, 2H), 2.62 (ddd, 1H, $J = 16.3, 7.5, 0.9$), 1.26 (d, 3H, $J = 6.2$); ^{13}C NMR: δ 156.2, 138.6, 137.6, 128.7, 128.6, 128.4, 126.7, 126.6, 120.5, 103.0, 59.5, 46.2, 35.6, 33.5, 19.7; ms: m/z 282 (M^+). Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38; N, 9.93. Found: C, 72.27; H, 6.40; N, 9.88.

Alcohol **8** (12%) was also isolated.

(±)-1-Hexyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7c). This compound (110 mg, 82%) was isolated as a yellow oil. ir: 1508, 1314 cm^{-1}; ^1H NMR: δ 8.04 (dd, 1H, $J = 8.8, 2.2$), 7.84 (m, 1H), 6.20 (d, 1H, $J = 8.8$), 4.02 (m, 1H), 3.21 (m, 3H), 2.65 (ddd, 1H, $J = 16.3, 7.5, 0.9$), 1.56 (m, 2H), 1.40–1.23 (complex, 6H), 1.31 (d, 3H, $J = 6.2$), 0.90 (t, 3H, $J = 7.0$); ^{13}C NMR: δ 156.6, 137.4, 128.4, 126.8, 120.6, 103.0, 59.2, 44.3, 35.7, 31.5, 27.1, 26.8, 22.6, 19.8, 14.0; ms: m/z 262 (M^+). Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.40; N, 10.69. Found: 68.68; H, 8.45; N, 10.63.

Alcohol **8** (10%) was also isolated.

(±)-1-(3-Isopropoxypropyl)-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7d). This compound (105 mg, 74%) was isolated as a yellow oil that solidified upon standing at 10°C, mp 39–40°C. ir: 1507, 1316 cm^{-1}; ^1H NMR: δ 8.03 (dd, 1H, $J = 8.8, 2.4$), 7.84 (m, 1H), 6.29 (d, 1H, $J = 8.8$), 4.02 (m, 1H), 3.52 (septet, 1H, $J = 6.2$), 3.46–3.30 (complex, 4H), 3.23 (ddd, 1H, $J = 16.1, 9.2, 1.1$), 2.65 (ddd, 1H, $J = 16.1, 7.5, 1.3$), 1.82 (quintet, 2H, $J = 6.8$), 1.32 (d, 3H, $J = 6.2$), 1.16 (d, 6H, $J = 6.1$); ^{13}C NMR: δ 156.8, 137.4, 128.3, 126.7, 120.5, 103.2, 71.6, 64.8, 59.4, 41.2, 35.7, 27.9, 22.1, 22.0, 19.8; ms: m/z 278 (M^+). Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.75; H, 7.91; N, 10.07. Found: C, 64.77; H, 7.94; N, 9.99.

Alcohol **8** (13%) was also isolated.

(±)-1-Isobutyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7e). This compound (96 mg, 82%) was isolated as a yellow oil. ir 1507, 1316 cm^{-1}; ^1H NMR: δ 8.02 (dd, 1H, $J = 8.8, 2.4$), 7.84 (m, 1H), 6.21 (d, 1H, $J = 8.8$), 4.01 (m, 1H), 3.25 (ddd, 1H, $J = 16.2, 8.8, 2.4$), 3.02 (d, 2H, $J = 7.5$), 2.66 (ddd, 1H, $J = 16.2, 7.0, 1.3$), 2.01 (septet, 1H, $J = 7.0$), 1.29 (d, 3H, $J = 6.2$), 0.98 (d, 3H, $J = 6.8$), 0.92 (d, 3H, $J = 6.8$); ^{13}C NMR: δ 157.0, 137.5, 128.1, 126.7, 120.6, 103.2, 59.9, 52.3, 35.6, 27.5, 20.5, 20.3, 19.6; ms: m/z 234 (M^+). Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.67; H, 7.69; N, 11.97. Found: C, 66.63; H, 7.73; N, 11.95.

Alcohol **8** (10%) was also isolated.

(±)-1-Cyclohexyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7f). This compound (29 mg, 22%) was isolated as a yellow oil. ir: 1506, 1313 cm^{-1}; ^1H NMR: δ 8.02 (dd, 1H, $J = 8.8, 2.3$), 7.83 (dt, 1H, $J = 2.3, 1.4$), 6.24 (d, 1H, $J = 8.8$), 4.14 (m, 1H), 3.30 (m, 2H), 2.61 (ddd, 1H, $J = 16.2, 4.5, 0.8$), 1.89 (m, 4H), 1.73 (m, 2H), 1.54 (m, 1H), 1.30 (m, 3H), 1.30 (d, 3H, $J = 6.2$); ^{13}C NMR: δ 155.3, 137.1, 128.5, 126.7, 120.8, 103.6, 57.2, 56.2, 36.0, 31.0, 30.1, 26.1, 26.0, 25.6, 23.2; ms: m/z 245 (M^+-CH_3). Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.69; N, 10.77. Found: C, 69.26; H, 7.71; N, 10.72.

This reaction also produced 45 mg (32%) of *N*-cyclohexyl-α-methyl-2-(2-fluoro-5-nitrophenyl)ethanamine (**9**) as a yellow oil. ir: 3323, 1528, 1350, 1244 cm^{-1}; ^1H NMR: δ 8.16 (dd, 1H, $J = 6.2, 2.7$), 8.11 (ddd, 1H, $J = 9.0, 4.5, 2.7$), 7.16 (t, 1H, $J = 9.0$), 3.11 (sextet, 1H, $J = 6.3$), 2.86 (dd, 1H, $J = 13.5, 6.1$), 2.64 (dd, 1H, $J = 13.5, 7.2$), 2.55 (tt, 1H, $J = 10.3, 3.7$), 1.85 (m, 2H), 1.70 (m, 2H), 1.60 (m, 1H), 1.32–1.15 (complex, 4H), 1.04 (d, 3H, $J = 6.3$), 1.01 (m, 2H); ^{13}C NMR: δ 164.8 (d, $J = 256.2$), 144.3, 128.7 (d, $J = 17.7$), 127.5 (d, $J = 7.4$), 123.8 (d, $J = 10.3$), 116.1 (d, $J = 25.8$), 53.5, 49.7, 36.7, 34.2, 33.9, 26.1, 25.1, 25.0, 20.9; ms: m/z 265 (M^+-CH_3). Anal. Calcd. for $C_{15}H_{21}FN_2O_2$: C, 64.29; H, 7.50; N, 10.00. Found: C, 64.38; H, 7.56; N, 9.95.

Alcohol **8** (20%) and unreacted **3** (14%) were also isolated.

Attempted preparation of (±)-1-*tert*-butyl-2-methyl-5-nitro-2,3-dihydro-1*H*-indole (7g). Treatment of **3** as above gave only alcohol **8** (20%) and unreacted **3** (75%).

Reductive amination-nucleophilic substitution reaction with 4: (±)-1-Benzyl-2-ethyl-5-nitro-2,3-dihydro-1*H*-indole (10a). This reaction was run on a 100 mg (0.47 mmol)-scale using the general procedure given above for the preparation of **7a**. This compound (80 mg, 60%) was obtained as a yellow solid, mp 47–48°C. ir: 1509, 1316 cm^{-1}; ^1H NMR: δ 8.00 (dd, 1H, J = 8.9, 2.3), 7.89 (m, 1H), 7.36–7.22 (complex, 5H), 6.23 (d, 1H, J = 8.9), 4.56 (d, 1H, J = 16.4), 4.36 (d, 1H, J = 16.4), 3.89 (m, 1H), 3.24 (dd, 1H, J = 16.5, 9.6), 2.81 (dd, 1H, J = 16.5, 3.1), 1.81 (sextet d, 1H, J = 7.4, 3.1), 1.58 (m, 1H), 0.90 (t, 3H, J = 7.4); ^{13}C NMR: δ 157.2, 138.0, 136.7, 128.8, 128.6, 127.5, 126.9, 126.7, 120.6, 103.5, 65.1, 48.7, 32.8, 26.2, 8.9; ms: m/z 191 (M^+-C_7H_7). Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38; N, 9.93. Found: C, 72.38; H, 6.41; N, 9.87.

This reaction also produced 19 mg (19%) of 1-(2-fluoro-5-nitrophenyl)-2-butanol (**11**), mp 37–38°C. ir: 3390, 1527, 1350, 1244 cm^{-1}; ^1H NMR: δ 8.23 (dd, 1H, J = 6.2, 2.9), 8.13 (ddd, 1H, J = 8.9, 4.2, 2.9), 7.18 (t, 1H, J = 8.9), 3.84 (m, 1H), 2.95 (ddd, 1H, J = 14.0, 4.1, 1.0), 2.79 (dd, 1H, J = 14.0, 8.4), 1.60 (br s, 1H), 1.58 (m, 2H), 1.02 (t, 3H, J = 7.4); ^{13}C NMR: δ 164.8 (d, J = 256.9), 144.0, 127.8 (d, J = 17.6), 127.6 (d, J = 7.4), 124.0 (d, J = 10.3), 116.1 (d, J = 25.8), 72.6, 36.2, 30.1, 9.8; ms: m/z 184 (M^+-C_2H_5). Anal. Calcd. For $C_{10}H_{12}FNO_3$: C, 56.34; H, 5.63; N, 6.57. Found: C, 56.40; H, 5.66; N, 6.51.

Unreacted **4** (12%) was also recovered.

(±)-2-Ethyl-5-nitro-1-(2-phenylethyl)-2,3-dihydro-1*H*-indole (10b). This compound (87 mg, 62%) was isolated as a yellow oil. ir: 1513, 1322 cm^{-1}; ^1H NMR: δ 8.00 (dd, 1H, J = 8.8, 2.1), 7.83 (m, 1H), 7.32–7.15 (complex, 5H), 6.15 (d, 1H, J = 8.8), 3.76 (m, 1H), 3.51 (ddd, 1H, J = 14.8, 9.0, 6.1), 3.42 (ddd, 1H, J = 14.8, 8.8, 6.8), 3.12 (dd, 1H, J = 16.4, 9.6), 2.89 (ddd, 1H, J = 14.6, 9.0, 6.8), 2.80 (ddd, 1H, J = 14.6, 8.8, 6.1), 2.70 (dd, 1H, J = 16.4, 7.4), 1.78 (sextet d, 1H, J = 7.4, 3.1), 1.50 (m, 1H), 0.88 (t, 3H, J = 7.4); ^{13}C NMR: δ 156.6, 138.6, 137.5, 128.6 (2C), 128.5, 126.7, 126.6, 120.5, 102.8, 64.8, 46.3, 33.4, 32.6, 26.0, 8.8; ms: m/z 205 (M^+-C_7H_7). Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.76; N, 9.46. Found: C, 73.01; H, 6.74; N, 9.47.

Alcohol **11** (19%) and unreacted **4** (10%) were also isolated.

(±)-2-Ethyl-1-hexyl-5-nitro-2,3-dihydro-1*H*-indole (10c). This compound (80 mg, 61%) was isolated as a yellow oil. ir: 1511, 1313 cm^{-1}; ^1H NMR: δ 8.03 (dd, 1H, J = 8.9, 2.3), 7.83 (m, 1H), 6.19 (d, 1H, J = 8.9), 3.89 (m, 1H), 3.31–3.11 (complex, 3H), 2.73 (dd, 1H, J = 17.1, 8.0), 1.80 (m, 1H), 1.57 (m, 3H), 1.31 (m, 6H), 0.91 (t, 3H, J = 7.4), 0.90 (distorted t, 3H, J = 6.2); ^{13}C NMR: δ 157.0, 137.2, 128.4, 126.8, 120.4, 102.7, 64.6, 44.4, 32.6, 31.5, 27.0, 26.8, 26.0, 22.5, 14.0, 8.8; ms: m/z 205 (M^+-C_5H_{11}). Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.57; H, 8.70; N, 10.14. Found: C, 69.63; H, 8.75; N, 10.06.

Alcohol **11** (20%) and unreacted **4** (10%) were also isolated.

(±)-2-Ethyl-1-(3-isopropoxypropyl)-5-nitro-2,3-dihydro-1*H*-indole (10d). This compound (84 mg, 61%) was isolated as a yellow oil. ir: 1515, 1315 cm^{-1}; ^1H NMR: δ 8.03 (dd, 1H, J = 8.8, 2.1), 7.84 (m, 1H), 6.28 (d, 1H, J = 8.8), 3.85 (m, 1H), 3.53 (septet, 1H, J = 6.2), 3.49–3.27 (complex, 4H), 3.18 (dd, 1H, J = 16.4, 9.4), 2.74 (dd, 1H, J = 16.4, 7.4), 1.82 (m, 3H), 1.55 (m, 1H), 1.15 (d, 6H, J = 6.2), 0.91 (t, 3H, J = 7.4); ^{13}C NMR: δ 157.2, 137.4, 128.3, 126.8, 120.4, 102.9, 71.6, 64.8, 64.7, 41.3, 32.6, 27.8, 26.0, 22.1, 22.0, 8.8; ms: m/z 205 (M^+-$C_5H_{11}O$). Anal. Calcd. for $C_{16}H_{24}N_2O_3$: C, 65.75; H, 8.22; N, 9.59. Found: C, 65.79; H, 8.24. N, 9.52.

Alcohol **11** (18%) and unreacted **4** (11%) were also isolated.

(±)-2-Ethyl-1-isobutyl-5-nitro-2,3-dihydro-1*H*-indole (10e). This compound (75 mg, 64%) was isolated as a yellow oil. ir: 1511, 1315 cm^{-1}; ^1H NMR: δ 8.02 (dd, 1H, J = 8.8, 2.3), 7.85 (m, 1H), 6.21 (d, 1H, J = 8.8), 3.88 (m, 1H), 3.20 (ddd, 1H, J = 16.4, 9.6, 1.0), 3.03 (m, 2H), 2.74 (ddd, 1H, J = 16.4, 6.6, 1.0), 2.02 (septet, 1H, J = 6.7), 1.78 (sextet d, 1H, J = 7.4, 3.1), 1.53 (m, 1H), 0.97 (d, 3H, J = 6.7), 0.91 (d, 3H, J = 6.7), 0.90 (t, 3H, J = 7.4); ^{13}C NMR: δ 157.4, 137.1, 128.2, 126.8, 120.5, 102.9, 65.1, 52.3, 32.5, 27.4, 25.9, 20.5, 20.3, 8.8; ms: m/z 205 (M^+-C_3H_7). Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06; N, 11.29. Found: C, 67.69; H, 8.04; N, 11.30.

Alcohol **11** (18%) and unreacted **4** (11%) were also isolated.

Reductive amination-nucleophilic substitution reaction with 5: (±)-1-Benzyl-2-isopropyl-5-nitro-2,3-dihydro-1*H*-indole (12a). This reaction was run on a 100 mg (0.44 mmol)-scale using the general procedure given above for the preparation of **7a**. This compound (22 mg, 17%) was isolated as a yellow oil following preparative thin layer chromatography using 15% ether in hexanes. ir: 1510, 1317 cm^{-1}; ^1H NMR: δ 8.01 (dd, 1H, J = 9.0, 2.3), 7.89 (m, 1H), 7.38–7.20 (complex, 5H), 6.29 (d, 1H, J = 9.0), 4.62 (d, 1H, J = 16.4), 4.33 (d, 1H, J = 16.4), 3.92 (ddd, 1H, J = 10.3, 7.6, 3.9), 3.03 (dd, 1H, J = 16.6, 10.2), 2.89 (dd, 1H J = 16.6, 7.6), 2.17 (sextet d, 1H, J = 6.8, 3.9), 0.91 (d, 3H, J = 6.8), 0.81 (d, 3H, J = 6.8); ^{13}C NMR: δ 157.7, 138.0, 136.4, 128.8, 127.7, 127.6, 127.1, 126.7, 120.6, 103.7, 68.0, 48.4, 28.3, 27.5, 18.6, 14.6; ms: m/z 205 (M^+-C_7H_7). Anal. Calcd. for $C_{18}H_{20}N$ for $C_{18}H_{20}N_2O_2$: C, 72.97; H, 6.76; N, 9.46. Found: C, 72.93; H, 6.72; N, 9.48.

This reaction also produced 15 mg (15%) of 1-(2-fluoro-5-nitrophenyl)-3-methyl-2-butanol (**13**) as a dark yellow oil. ir: 3427, 1526, 1347, 1245 cm^{-1}; ^1H NMR: δ 8.24 (dd, 1H, J = 6.2, 2.9), 8.13 (ddd, 1H, J = 8.8, 4.3, 2.9), 7.17 (t, 1H, J = 8.8), 3.66 (m, 1H), 2.96 (dd, 1H, J = 14.1, 2.0), 2.73 (dd, 1H, J = 14.1, 9.8), 1.77 (septet, 1H, J = 6.8), 1.48 (br s, 1H), 1.03 (d, 3H, J = 6.8), 1.02 (d, 3H, J = 6.8); ^{13}C NMR: δ 164.8 (d, J = 256.2), 144.1, 128.5 (d, J = 18.5), 127.6 (d, J = 7.4), 124.0 (d, J = 10.3), 116.1 (d, J = 25.0), 76.1, 33.9, 33.5, 18.7, 17.1; ms: m/z 184 (M^+-C_3H_7). Anal. Calcd. for $C_{11}H_{14}FNO_3$: C, 58.15; H, 6.17; N, 6.17. Found: C, 58.23; H, 6.19; N, 6.12.

Unreacted **5** (58%) was also recovered.

(±)-1-Hexyl-2-isopropyl-5-nitro-2,3-dihydro-1*H*-indole (12c). This compound (28 mg, 22%) was isolated as a yellow oil. ir: 1516, 1327 cm^{-1}; ^1H NMR: δ 8.03 (dd, 1H, J = 8.8, 2.1), 7.83 (m, 1H), 6.19 (d, 1H, J = 8.8), 4.12 (t, 1H, J = 7.8), 3.93 (ddd, 1H, J = 10.5, 7.3, 3.7), 3.30 (ddd, 1H, J = 14.8, 9.4, 6.3), 3.16 (ddd, 1H, J = 14.8, 9.4, 5.8), 3.06 (septet, 1H, J = 6.8), 2.98 (dd, 1H, J = 16.6, 9.9), 2.82 (dd, 1H, J = 16.6, 7.2), 2.16 (m, 1H), 1.76 (m, 1H), 1.57 (m, 1H), 1.32 (m, 4H), 0.95 (d, 3H, J = 6.8), 0.89 (m, 3H), 0.78 (d, 3H, J = 6.8); ^{13}C NMR: δ 157.3, 139.5, 128.5, 126.9, 120.4, 102.5, 67.9, 44.4, 43.6, 31.5, 28.5, 27.2, 26.8, 26.7, 22.6, 18.6, 14.4; ms: m/z 219 (M^+-C_5H_{11}). Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.34; H, 8.97; N, 9.66. Found: C, 70.40; H, 9.01; N, 9.60.

Alcohol **13** (14%) and unreacted **5** (55%) were also isolated.

Reductive amination-nucleophilic aromatic substitution reactions with 6. Treatment of 100 mg (0.39 mmol) of **6** with 51.8 mg (0.48 mmol) of benzylamine using the general procedure given above for the preparation of **7a** afforded 98% recovery of unreacted **6**.

Repeating this reaction in methanol at 65°C for 48 h yielded four products, in addition to recovered **6**. These products were separated by preparative thin layer chromatography using 10% ether in hexanes to give: band 1: 16 mg (13%) of **15**; band 2: 13 mg (11%) of **14**; band 3: 52 mg (52%) of recovered **6**; band 4: 14 mg (14%) of **17**; and band 5: 7 mg (7%) of **16**. The physical and spectral data for these products were as follows:

1-Benzyl-2-phenyl-5-nitroindole (15). Viscous yellow oil; ir: 1513, 1332 cm^{-1}; ^1H NMR: δ 8.62 (d, 1H, J = 2.2), 8.05 (dd, 1H, J = 9.3, 2.2), 7.43 (apparent s, 5H), 7.30 (m, 1H), 7.28 (apparent t, 2H, J = 6.6), 7.20 (d, 1H, J = 8.8), 6.97 (dd, 2H, J = 8.2, 2.2), 6.80 (s, 1H), 5.41 (s, 2H); ^{13}C NMR: δ 145.0, 142.1, 140.6, 136.9, 131.3, 129.2, 129.0, 128.9, 128.8, 127.7, 127.5, 125.8, 117.6, 117.5, 110.4, 104.3, 48.0; ms: m/z 237 (M^+-C_7H_7). Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.82; H, 4.88; N, 8.54. Found: C, 76.88; H, 4.91; N, 8.50.

(±)-1-Benzyl-2-phenyl-5-nitro-2,3-dihydro-1*H*-indole (14). Yellow solid, mp 137–139°C; ir: 1510, 1313 cm^{-1}; ^1H NMR: δ 8.09 (dd, 1H, J = 8.8, 2.2), 7.93 (s, 1H), 7.41–7.24 (complex, 8H), 7.12 (dd, 2H, J = 7.7, 2.2), 6.39 (d, 1H, J = 8.8), 4.88 (dd, 1H, J = 9.9, 7.7), 4.56 (d, 1H, J = 15.9), 4.01 (d, 1H, J = 15.9), 3.55 (dd, 1H, J = 16.5, 9.9), 3.08 (dd, 1H, J = 16.5, 8.2); ^{13}C NMR: δ 156.8, 141.0, 138.6, 136.0, 129.0, 128.8, 128.4, 128.2, 127.7, 127.5, 127.1, 126.8, 120.8, 103.9, 67.6, 48.4, 37.7; ms: m/z 239 (M^+-C_7H_7). Anal. Calcd. for $C_{21}H_{18}N_2O_2$: C, 76.36; H, 5.45; N, 8.48. Found: C, 76.38; H, 5.46; N, 8.45.

(±)-1-Phenyl-2-(2-fluoro-5-nitrophenyl) ethanol (17). Viscous yellow oil; ir: 3546, 3416, 1526, 1346, 1244 cm^{-1}; ^1H NMR: δ 8.13 (m, 2H), 7.41–7.28 (complex, 5H), 7.16 (t, 1H, J = 8.8), 4.99 (t, 1H, J = 6.6), 3.12 (d, 2H, J = 6.6), 2.00 (br s, 1H); ^{13}C NMR: δ 164.8 (d, J = 256.5), 144.0, 143.1, 128.7, 128.2, 127.8 (d, J = 6.9), 127.2 (d, J = 18.0), 125.7, 124.2 (d, J = 10.0), 116.1 (d, J = 25.5), 73.7, 38.4; ms: m/z 243 (M^+-H_2O). Anal. Calcd. for $C_{14}H_{12}FNO_3$: C, 64.37; H, 4.60; N, 5.36. Found: C, 64.44; H, 4.64; N, 5.29.

3-(2-Methoxy-5-nitrophenyl)-1-phenyl-1-ethanone (16). Light yellow solid, mp 118–120°C; ir: 2848, 1689, 1514, 1330 cm^{-1}; ^1H NMR: δ 8.22 (dd, 1H, J = 9.3, 2.7), 8.11 (d, 1H, J = 2.7), 8.03 (d, 2H, J = 7.7), 7.62 (t, 1H, J = 7.7), 7.51 (t, 2H, J = 7.7), 6.96 (d, 1H, J = 9.3), 4.36 (s, 2H), 3.88 (s, 3H) ^{13}C NMR: δ 196.0, 162.5, 141.3, 136.5, 133.4, 128.7, 128.2, 127.0, 125.1, 124.9, 110.0, 56.2, 39.9; ms: m/z 166 (M^+-C_7H_5O). Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.80; N, 5.17. Found: C, 66.44; H, 4.80; N, 5.19.

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