Neighboring Group Participation of the Indole Nucleus: An Unusual DAST-Mediated Rearrangement Reaction

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A rearrangement reaction involving the indole nucleus was investigated using stereochemical markers and low-temperature NMR experiments. Treatment of (3*S*,4*S*)-3-hydroxy-4-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic acid benzyl ester (>90% ee) with diethylaminosulfur trifluoride gave *stereospecifically* (3*S*,4*S*)-4-fluoro-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic acid benzyl ester (>90% ee) with complete regioselectivity. The initial formation of a reactive spirocyclopropyl-3*H*-indole intermediate is believed to be responsible for the stereo- and regiochemical outcome of the reaction.

Introduction

Over 30 years ago, two groups of researchers[1] demonstrated that the indole nucleus could exert a large neighboring-group effect on the rate of solvolysis of derivatives of tryptophol (Scheme 1). They speculated that this process occurred via the reactive 3,3-spirocyclopropyl-3*H*-indole **1** whose structure was more rigorously established some years later.[2]

Spirocyclic and related 3,3-disubstituted intermediates similar to **1** occur throughout indole chemistry and demonstrate the strong preference in indole for electrophilic attack to occur at C-3, even when that position carries a substituent. For example, the Pictet−Spengler type cyclization that gives rise to tetrahydro-β-carbolines is believed to take place via a 3*H*-indolinium ion **2**[3] (Figure 1), while the Plancher rearrangement[4] of 3,3-dialkyl-3*H*-indolinium ions such as **3** is one of the accepted intermediates along the pathway to 2,3-dialkylindoles.[5] We now wish to report a similar pattern of reactivity that was observed unexpectedly during attempts to synthesize fluoropiperidine **4** as part of a medicinal chemistry program.

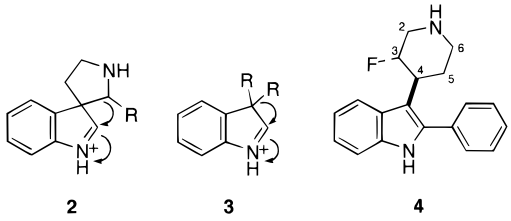
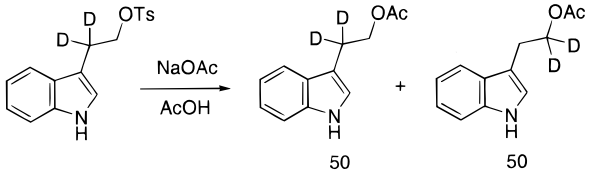
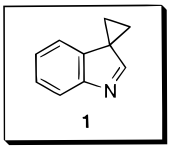


Figure 1.

Scheme 1



k_{318}= 3.4 x 10^6 sec^{-1} [c.f. 2-(1-naphthyl)ethyl tosylate, k_{353}= 1.0 x 10^4 sec^{-1}]



Results and Discussion

It was envisaged that the target fluorinated piperidine **4** might be accessed by reaction of a suitably protected alcohol with diethylaminosulfur trifluoride (DAST).[6] To this end, racemic alcohol **8** was constructed as outlined in Scheme 2. Condensation of 2-phenyl-1*H*-indole **5** with 4-piperidone under acidic conditions[7] gave tetrahydropyridine **6** which was protected as its *N*-benzyl carbamate **7**. Hydroboration[8] with borane-dimethyl sulfide followed by oxidative workup afforded the desired *trans* alcohol

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(2) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.

(3) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1968**, *24*, 403.

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(5) Direct attack at C-2 can and does occur: (a) Casnati, G.; Dossena, A.; Pochini, A. *Tetrahedron Lett.* **1972**, 5277. (b) Iyer, R.; Jackson, A. H.; Shannon, P. V. R.; Naidoo, B. *J. Chem. Soc., Chem. Commun.* **1972**, 461.

(6) Hudlicky, M. *Org. React.* **1988**, *35*, 513.

(7) Freter, K.; Fuchs, V. *J. Heterocycl. Chem.* **1982**, *19*, 377.

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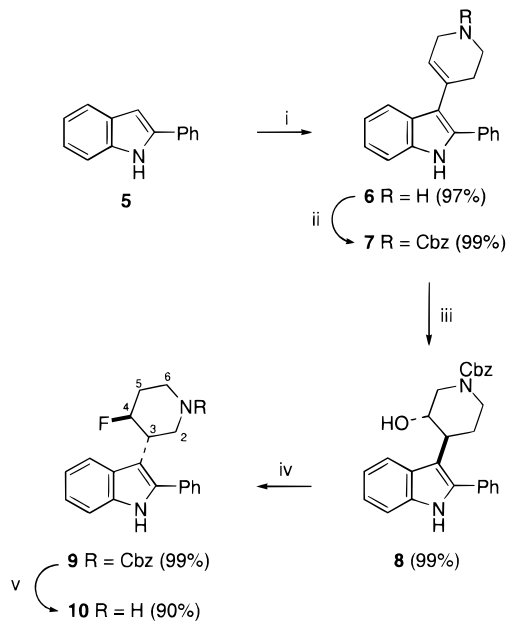
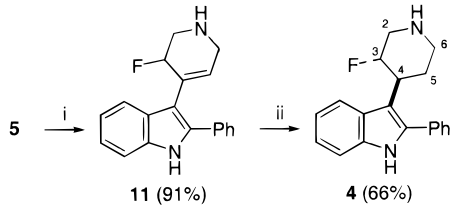
Scheme 2[a]



[a] Key: (i) 4-piperidone monohydrate hydrochloride, HOAc, H_3PO_4, 95 °C; (ii) benzyl chloroformate, $CHCl_3$, K_2CO_3, reflux; (iii) BH_3·DMS, THF then NaOH, H_2O_2; (iv) DAST, EtOAc, −50 °C to ambient temperature; (v) HCO_2H, EtOAc, 10% Pd−C.

Scheme 3[a]



[a] Key: (i) 3-fluoro-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester, HOAc, H_3PO_4, 90 °C; (ii) triethylsilane, TFA.

8, which was anticipated to give a 3-fluoro-4-indolyl substituted piperidine upon treatment with DAST. To our surprise, the low-temperature reaction of DAST with **8** followed by removal of the Cbz group by hydrogen-transfer hydrogenolysis furnished the 4-fluoro-3-indolyl isomer **10** as the exclusive product in excellent yield.

To support the structural assignment of **10** a genuine sample of the 3-fluoro-4-indolyl substituted piperidine was needed for comparison (Scheme 3). Reaction of 2-phenyl-1*H*-indole with 3-fluoro-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester[9] furnished tetrahydropyridine **11** as a single isomer. Initial attempts to reduce the trisubstituted double bond in **11** by catalytic hydrogenation were hampered by concomitant hydrogenolysis of the C−F bond. To circumvent this problem, ionic reduction with trifluoroacetic acid/triethylsilane[10] was utilized and gave the *trans* fluoropiperidine **4** containing only trace amounts of the des-fluoro material.

The structures of **4** and **10** were determined by DQF−COSY experiments (Figure 2). In the 4-fluoro-3-indolyl isomer **10** (Figure 2A) the substitution pattern around the piperidine ring system was apparent from the proton−proton coupling of the proton geminal to the fluorine atom (H3), which is coupled to the ring protons H5 centered at 1.51 and 2.13 ppm, respectively. The chemical shifts of H5 indicate these protons are not attached to a nitrogen-bound carbon. Furthermore, the methylene protons H5 are also coupled to a methylene group (H6) at lower field (2.72 and 2.92 ppm), proving the substitution pattern of piperidine **10**. The relative stereochemistry of this 4-fluoro isomer was determined on the basis of the proton assignment and the coupling pattern of proton H4. This proton showed a large ^2J fluorine coupling (ca. 49 Hz) and two further ^3J axial-axial couplings (ca. 10 Hz), as well as a ^3J axial/equatorial coupling of ca. 2 Hz. This was consistent with the indole residue and the fluorine atom both residing in the equatorial positions of the ring systems.

In contrast, the methylene protons H2 in structure **4** at ca. 2.5 and 3.3 ppm (overlap with residual d_6-DMSO and H_2O signals) are coupled only to proton H3 at 5.03 ppm (Figure 2, **B**). This indicates that the H2 protons are indeed attached to the nitrogen-bound carbon. The entire spin system can be traced around the ring system and is consistent with the 3-fluoro isomer. The relative stereochemistry of the fluoropiperidine ring system present in **4** was again determined on the basis of the coupling pattern of proton H3. This showed one large geminal fluorine coupling (ca. 49 Hz), two ^3J axial-axial couplings (ca. 10 Hz each) and a smaller ^3J axial/equatorial coupling of ca. 5 Hz. When taken with the corresponding coupling constants this coupling pattern is consistent with both the indole residue and the fluorine atom residing in equatorial positions on the ring system.

An enantioenriched sample of alcohol **8** was prepared to investigate the stereochemical course of the DAST reaction. Treatment of tetrahydropyridine **7** at −20 °C with monoisopinocampheylborane ($IpcBH_2$)[11] derived from (−)-α-pinene (Scheme 4), followed by oxidative workup, produced alcohol **12** in good chemical yield but only a modest 56% ee as determined by chiral HPLC. Repeating the reaction with (+)-diisopinocampheylborane (Ipc_2BH)[12] gave a similar result (52% ee) but at the expense of reaction rate (70 h at ambient temperature for complete reaction as compared with 4 h at −20 °C for $IpcBH_2$.) Ultimately the practical ease of synthesizing large quantities of Ipc_2BH made this the reagent of choice.

Two approaches to boost the optical purity of the hydroboration product **12** were performed. On a small scale (<1 g) formation of diastereomeric esters, separation by column chromatography, and hydrolysis seemed most appropriate. After screening several chiral derivatizing reagents, the esters derived from camphanic acid were found to have the largest difference in R_f. When larger quantities of material were required, however, this approach proved time-consuming and so another method was needed. Initial recrystallization of **12** (52% ee) from diethyl ether furnished crystalline material that was shown to be racemic by chiral HPLC but whose mother liquor was enriched with the major enantiomer. With this knowledge it was possible to assay the supernatant as

(9) Van Niel, M. B.; Collins, I.; Beer, M. S.; Broughton, H. B.; Cheng, S. K. F.; Goodacre, S. C.; Heald, A.; Locker, K. L.; MacLeod, A. M.; Morrison, D.; Moyes, C. R.; O'Connor, D.; Pike, A.; Rowley, M.; Russell, M. G. N.; Sohal, B.; Stanton, J. A.; Thomas, S.; Verrier, H.; Watt, A. P.; Castro, J. L. *J. Med. Chem.* **1999**, *42*, 2087.

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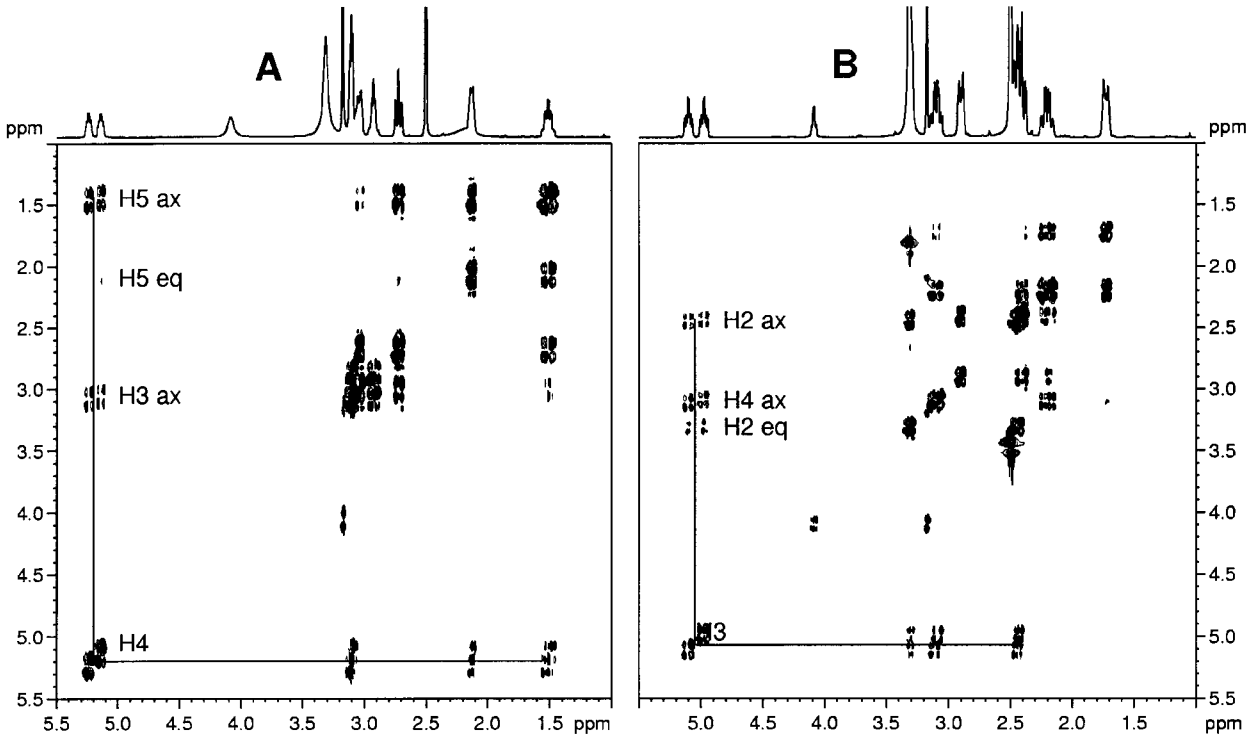
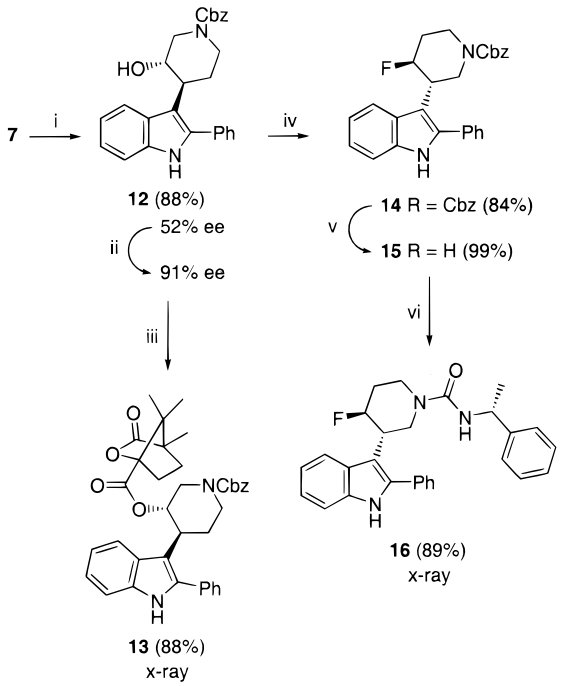


Figure 2. DQF−COSY spectra of 4-fluoro-3-(2-phenyl-1*H*-indol-3-yl)-piperidine **10** (A) and 3-fluoro-4-(2-phenyl-1*H*-indol-3-yl)-piperidine **4** (B).

Scheme 4[a]

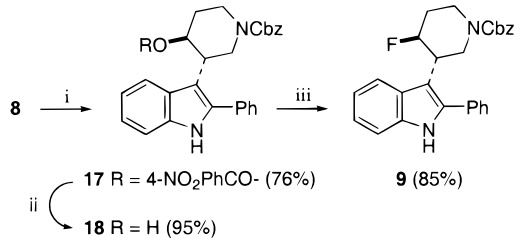


[a] Key: (i) (+)-Ipc$_2$BH, THF, ambient temperature then NaOH, H_2O_2; (ii) recrystallize and retain mother liquors; (iii) (1*S*)-(−)-camphanic chloride, pyridine, DMAP; (iv) DAST, EtOAc, −50 °C to ambient temperature; (v) HCO_2H, EtOAc, 10% Pd−C; (vi) (*R*)-(+)-α-methylbenzylisocyanate, DCE.

the crystallization process progressed and in this way material of 91% ee was obtained from the mother liquors.

Alcohol **12** (91% ee) was then reacted with (1*S*)-(−)-camphanic chloride, and the major diastereoisomer **13** was shown to possess (3*S*,4*S*) absolute stereochemistry

Scheme 5[a]



[a] Key: (i) diethylazodicarboxylate, Ph_3P, 4-nitrobenzoic acid, THF; (ii) K_2CO_3, MeOH; (iii) DAST, EtOAc, −50 °C to ambient temperature.

by X-ray crystallography. Subsequent treatment of **12** (91% ee) with DAST afforded a fluorinated product **14** (ca. 95% ee by HPLC analysis of the crude reaction mixture). Removal of the nitrogen protecting group from **14** and reaction with (*R*)-(+)-α-methylbenzylisocyanate yielded urea **16** as the major diastereoisomer containing (3*S*,4*S*) absolute stereochemistry as determined by X-ray crystallography. The stereochemical information provided by **13** and **16** together with the ee measurements of **12** and **14** indicate that the DAST reaction with alcohol **12** is *completely stereospecific* and that both stereogenic centers in **12** are inverted during the reaction.

Further insight into the DAST reaction was obtained when racemic hydroxypiperidine **8** was subjected to Mitsunobu conditions (Scheme 5) and the *rearranged* nitrobenzoate **17** then hydrolyzed to reveal alcohol **18**, an isomer of **8**. When **18** was treated with DAST, a fluorinated product was obtained, identical in all respects to piperidine **9** from Scheme 2.

This result indicates that alcohols **8** and **18** react with DAST via a common intermediate **19**[13] as shown in Figure 3. Two possible conformations of **19** allow trans-

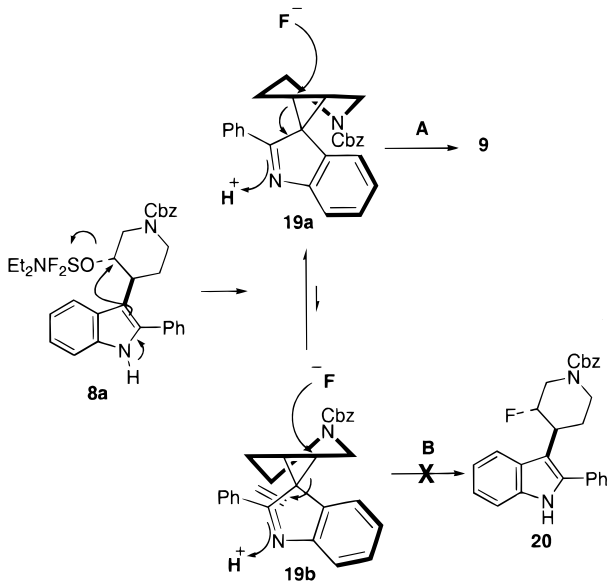


Figure 3. Proposed mechanism for the reaction of hydroxypiperidine **8** with DAST.

diaxial ring-opening; pathway **A** gives rise to the observed fluoropiperidine **9** while pathway **B** (not observed) produces the isomer **20**. A possible reason for the regioselectivity is that conformer **19b** is destabilized relative to **19a** as a result of steric congestion caused by the group *endo* to the piperidine ring.

The reaction of racemic alcohol **8** with DAST was observed by NMR spectroscopy at −50 °C in order to characterize the reaction intermediates further. The assignment of the proton spectrum of hydroxypiperidine **8** at −50 °C (Figure 4A) was complicated by the presence of two stable conformers from the restricted rotation of the benzyloxycarbamate group. On addition of DAST, an equilibration process was observed by proton NMR spectroscopy that appeared to be complete after ca. 15 min. The initially formed derivative **8a** was converted into a major species existing as two stable conformers (Figure 4B). This intermediate remained stable at −50 °C allowing acquisition of DQF−COSY and HMQC experiments (Figure 5) and assignment of the aliphatic proton and carbon resonances. The coupling pattern of the piperidine spin system in the form of a major and a minor conformer was traced around the ring and is consistent with the spirocyclopropyl-3*H*-indole structure **19**.

When comparing the spectra of **8** and **19** the most dramatic changes could be seen in the chemical shift of proton H3 and carbon C3. H3 (major conformer) moved from 4.44 ppm in the starting alcohol **8** to 3.22 ppm in the intermediate. Likewise, C3 in the intermediate moved upfield by ca. 35 ppm (Table 1). This showed C3 was not oxygen bound in **19**. The similarity of the chemical shifts of H3, H4 and C3, C4 in the intermediate **19** is evidence for a similar chemical environment of these atoms. This further supports the spirocyclopropyl-3*H*-indole structure.

(13) For the sake of clarity, only one diastereoisomer at the indole 3-position of **19a** and **19b** are shown. The curly arrows in Figure 3 imply a concerted mechanism to account for the formation of **19**. One of the referees correctly pointed out that since cyclopropanes can only be *cis*-1,2-disubstituted when fused to a second ring **19** may be formed via an S_N1 type process.

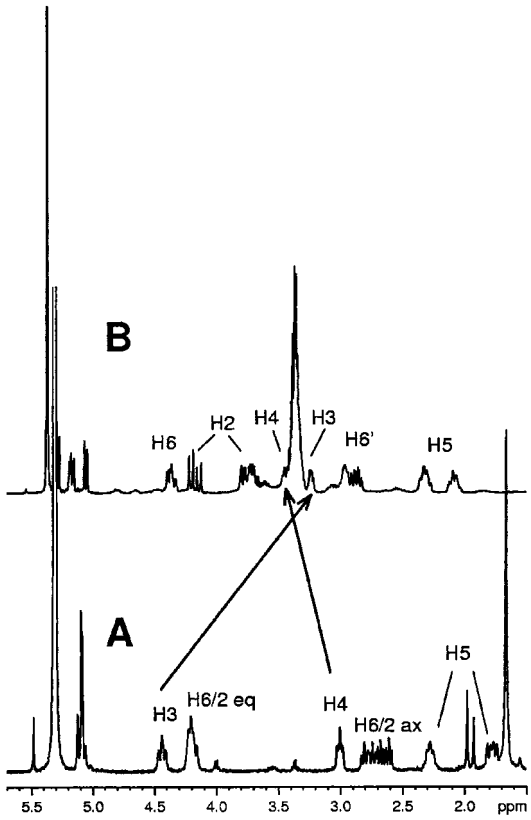


Figure 4. Comparison of the 1-D proton spectra of hydroxypiperidine **8** before DAST addition (A) and the spirocyclopropyl-3*H*-indole **19** (B) at −50 °C.

The mechanistic details presented so far predict that electronic modification of the indole nitrogen should affect its ability to participate in the formation of **19**. With this in mind we attempted to protect the indole nitrogen in **8** as its *N*-alkyl carbamate but failed, presumably as a result of the 2-phenyl substituent. An indole lacking a 2-substituent would overcome this problem, and the synthesis of such a compound **23** is shown in Scheme 6.

The reaction of alcohol **23** with DAST (Scheme 6) gave two major fluorinated products together with several minor alkene-containing materials not isolated in pure form. The fluoropiperidine **24** (the structure of which was assigned from a 2-D ^{1}H NMR spectrum of indole **26**) presumably arises from a S_N1 type reaction with fluoride anion attacking the transient carbocation *anti* to the indole nucleus. The formation of **24**, together with the olefin mixture (produced by an elimination process) is not unusual for reactions involving DAST.[6] The second major component isolated from the reaction mixture was difficult to identify by ^{1}H NMR due to rotamers but was tentatively assigned as fluoropiperidine **25**. To confirm the structural assignment of this unexpected product and examine the role that the indole 2-substituent played in the selectivity of the DAST mediated process, an authentic sample of **25** was prepared as depicted in Scheme 7.

Base-mediated removal of the indole protecting group in **23** revealed alcohol **27** (60% ee by HPLC), whose optical purity could be increased using the same recrystallization protocol developed for **12**. In contrast to Boc-indole **23** the reaction of **27** (88% ee) with DAST afforded fluoropiperidine **28** as the sole product and in good chemical yield. The indole nitrogen in **28** was then reprotected to furnish fluoropiperidine **25** identical in all

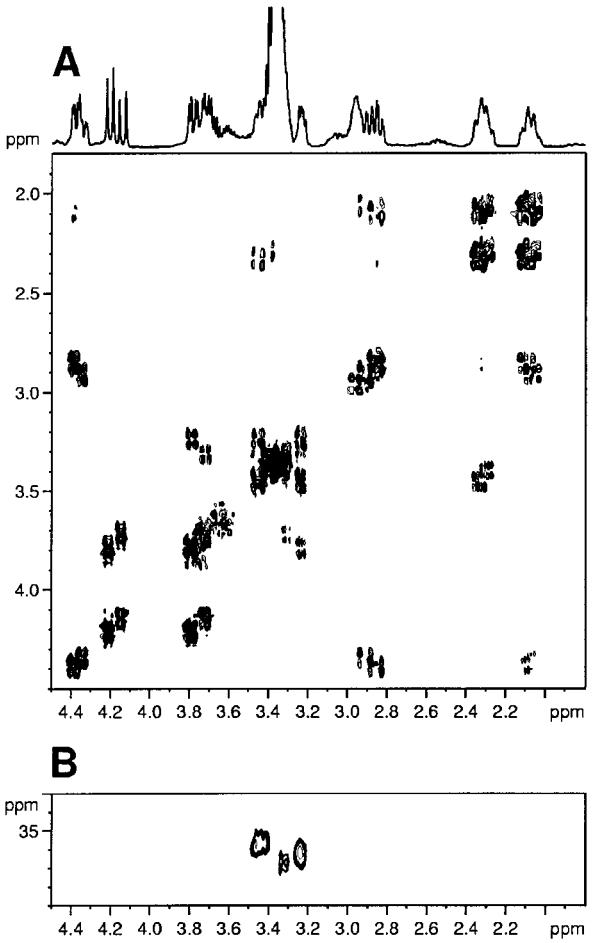


Figure 5. Partial DQF−COSY and HMQC spectra of the spirocyclopropyl-3*H*-indole **19** at −50 °C.

Table 1. Chemical Shifts (ppm) of the Major Conformers of 8 and 19

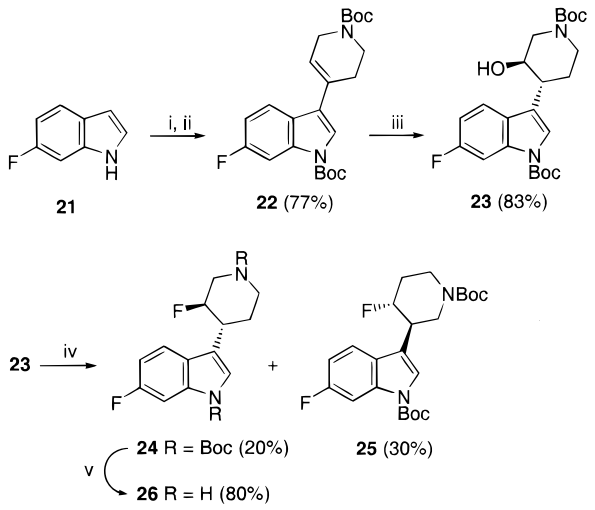
	H3	H4	C3	C4
starting material **8**	4.44	3.00	68.1	42.0
intermediate **19**	3.22	3.45	33.7	34.2

respects (except optical purity) to that obtained in Scheme 6. These results indicate that the indole nitrogen is an important element of the rearrangement mechanism and a hydrogen atom alone at the 2-position of the indole is sufficient to control the regiochemical outcome of the reaction.

The success of the Mitsunobu reaction (Scheme 5) prompted us to examine the possibility of intercepting intermediate **19** with other reagents. This required the development of a general protocol in which **19** could be generated in the absence of a nucleophile. To this end, racemic alcohol **8** was first reacted at low temperature with trifluoromethanesulfonic anhydride before subsequent treatment with a nucleophile (Scheme 8). The results of our brief foray into this area are shown in Table 2.

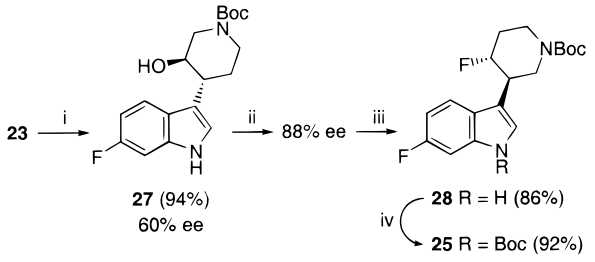
The intermediate **19** was successfully reacted with a number of heteroatom-centered nucleophiles to afford products **29**−**31** in moderate to good yield (not optimized). The structure of **29** was confirmed by removing the acetate group to reveal an alcohol identical in all respects to **18** (Scheme 5). Our attempts to react carbon-centered nucleophiles, e.g. cyanide or the anion of diethyl malonate, were not productive.

Scheme 6[a]



[a] Key: (i) 4-piperidone monohydrate hydrochloride, MeOH, KOH, Δ; (ii) di-*tert*-butyl dicarbonate, DMAP, Et_3N, CH_2Cl_2; (iii) (−)-Ipc_2BH, THF, ambient temperature then NaOH, H_2O_2; (iv) DAST, EtOAc, −50 °C to ambient temperature; (v) TFA, DCM.

Scheme 7[a]



[a] Key: (i) NaOMe, MeOH; (ii) recrystallize and retain mother liquors; (iii) DAST, EtOAc, −50 °C to ambient temperature; (iv) Di-*tert*-butyl dicarbonate, DMAP, Et_3N, CH_2Cl_2.

Scheme 8

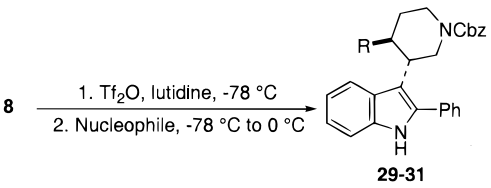


Table 2. Reaction of Intermediate 19 with Other Nucleophiles

nucleophile	product	R	yield (%)
acetic acid	**29**	AcO	74
benzylamine	**30**	BnNH	55
benzyl mercaptan	**31**	BnS	56

Conclusion

Using the combined tools of X-ray crystallography, low-temperature NMR, and chiral HPLC, we have probed the stereo- and regiochemical outcome of an unusual reaction of indoles. We have demonstrated that a spirocyclic indole is the reactive intermediate and that this species reacts with nucleophiles in a completely *stereo*- and *regioselective* manner. We have also shown that this intermediate can be generated using several methods and then trapped with a variety of heteroatom-centered nucleophiles.

Experimental Section

General. All reactions involving air- and/or water-sensitive reagents were carried out under an atmosphere of N_2 using oven-dried glassware. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Unless otherwise indicated, organic extracts were dried over anhydrous sodium sulfate and concentrated at aspirator pressure using a rotary evaporator. Purification by column chromatography was performed according to the method of Still, Kahn, and Mitra[14] using silica gel (particle size 40−63 μm) as the stationary phase. Melting points are uncorrected. Optical rotations were measured at ambient temperature. Enantiomeric excess measurements were determined by analytical HPLC using either a Chiralcel OD-H column (250 mm × 4.6 mm) or a Chiralcel OJ-R column (150 mm × 4.6 mm).

NMR experiments were performed using a 5 mm inverse broadband probe equipped with Z-gradients. Unless otherwise stated, spectra were recorded at 300 K in either d_6-DMSO or CD_2Cl_2; coupling constants are given in hertz.

2-Phenyl-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-indole (6). A 2 L three-necked flask was charged with 2-phenylindole (70 g, 0.36 mol), 4-piperidone monohydrate hydrochloride (100 g, 0.65 mol), glacial acetic acid (700 mL), and 1 M phosphoric acid (150 mL). The resulting suspension was magnetically stirred and heated at 95 °C for 16 h (complete solution is obtained after approximately 1 h at the elevated temperature). The reaction was cooled to ambient temperature and poured into ammonia (5 L of a 15 wt % aqueous solution), the excess 4-piperidone being soluble in aqueous ammonia. After the resulting suspension had cooled to ambient temperature, the cream-colored solid was collected by filtration. The solid was washed with water (2 L) and then dried at 60 °C under vacuum for 16 h. Trituration with diethyl ether afforded the title compound (96 g, 97%) as a pale yellow solid, which was used without further purification: ^{1}H NMR (360 MHz, d_6-DMSO) δ 2.03−2.14 (m, 2 H), 2.89 (t, J = 5, 2 H), 3.36−3.45 (m, 2 H), 5.79 (s, 1 H), 7.00 (t, J = 8, 1 H), 7.08 (t, J = 8, 1 H), 7.31−7.37 (m, 2 H), 7.44−7.52 (m, 3 H), 7.69 (d, J = 7, 2 H), 11.31 (s, 1 H); MS (ES$^+$) m/z 275 (M + H)$^+$, 246 (M − H_2C=NH)$^+$.

4-(2-Phenyl-1*H*-indol-3-yl)-2,3-dihydro-6*H*-pyridine-1-carboxylic Acid Benzyl Ester (7). A solution of indole **6** (10.0 g, 36.5 mmol) in chloroform (175 mL) was treated with solid potassium carbonate (7.5 g, 54.3 mmol) and then with benzyl chloroformate (5.9 mL, 41.3 mmol). The resulting suspension was heated at reflux for 14 h, cooled to ambient temperature, and treated with *N*,*N*-diethylethylenediamine (1.5 mL, 10.7 mmol). After stirring at ambient temperature for 1 h, the majority of the solvent was removed in vacuo and the resulting residue was partitioned between ethyl acetate (500 mL) and water (500 mL). The organic phase was then washed with 0.1 N hydrochloric acid (2 × 500 mL), water (500 mL), and brine (500 mL) to furnish the title compound (14.8 g, 99%) as a pale orange foam: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.20−2.40 (m, 2 H), 3.66 (t, J = 5.5, 2 H), 4.18−4.24 (m, 2 H), 5.19 (s, 2 H), 5.80−5.95 (m, 1 H), 7.16 (t, J = 7, 1 H), 7.21 (dt, J = 7 and 1, 1 H), 7.23−7.41 (m, 9 H), 7.56 (d, J = 7, 2 H), 7.63 (d, J = 8, 1 H), 8.17 (s, 1 H); MS (ES$^+$) m/z 409 (M + H)$^+$.

(3*RS*,4*RS*)-3-Hydroxy-4-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (8). A cooled (−25 °C) solution of carbamate **7** (2.6 g, 6.4 mmol) in anhydrous tetrahydrofuran (50 mL) was treated with borane-methyl sulfide complex (650 μL of a 10 M solution, 6.5 mmol), and this mixture was stirred to ambient temperature over 16 h. The reaction was then cooled to −10 °C and treated with 3 N sodium hydroxide solution (2 mL) followed by hydrogen peroxide (1 mL of a 30 wt % solution in water), and this mixture was stirred to ambient temperature over 24 h. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate (250 mL) and extracted with ethyl acetate (2 × 150 mL). The organics were combined and washed with water (250 mL) and brine (250 mL) to give the title compound (2.69 g, 99%) as a white powder: mp 147−149 °C (Et_2O); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.76−1.86 (m, 2 H), 2.20−2.40 (m, 1 H), 2.62−2.86 (m, 2 H), 3.00−3.10 (m, 1 H), 4.18−4.38 (m, 2 H), 4.50−4.64 (m, 1 H), 5.20 (s, 2 H), 7.11 (dt, J = 8 and 1, 1 H), 7.23 (dt, J = 7 and 1, 1 H), 7.35−7.48 (m, 9 H), 7.60 (d, J = 7, 2 H), 7.68 (d, J = 8, 1 H), 8.15 (s, 1 H); MS (ES$^+$) m/z 427 (M + H)$^+$. Anal. Calcd for $C_{27}H_{26}N_2O_3 \cdot 0.4H_2O$: C, 74.77; H, 6.23; N, 6.46. Found: C, 74.76; H, 5.94; N, 6.31.

(3*RS*,4*RS*)-4-Fluoro-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (9). A cooled (−50 °C) solution of racemic alcohol **8** (1.0 g, 2.3 mmol) in anhydrous ethyl acetate (20 mL) was treated with diethylaminosulfur trifluoride (350 μL, 2.6 mmol). Stirring at −50 °C was continued for 1 h before the solution was allowed to warm to ambient temperature over 3 h. The reaction mixture was then poured into saturated aqueous sodium hydrogencarbonate (100 mL), and the product was extracted into ethyl acetate (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL) and then dried over anhydrous sodium sulfate. This solution was filtered, treated with decolorizing charcoal (0.5 g), and filtered again. The resulting pale yellow filtrate was then treated with Raney nickel (1 mL of a 50% slurry in water). After standing at ambient temperature for 2 h the solution was filtered and evaporated to dryness to afford the title compound (995 mg, 99%) as a white solid: mp 199−201 °C (EtOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.70−1.85 (m, 1 H), 2.20−2.30 (m, 1 H), 2.90−3.10 (m, 1 H), 3.20−3.30 (m, 1 H), 3.40−3.50 (m, 1 H), 4.20−4.50 (m, 2 H), 5.10 (s, 2 H), 5.24 (dtd, J = 54, 11 and 5, 1 H), 7.12 (t, J = 7, 1 H), 7.18 (t, J = 7, 1 H), 7.20−7.43 (m, 9 H), 7.52−7.56 (m, 2 H), 7.67 (d, J = 8, 1 H), 8.15 (s, 1 H); MS (ES$^+$) m/z 429 (M + H)$^+$. Anal. Calcd for $C_{27}H_{25}FN_2O_2$: C, 75.68; H, 5.88; N, 6.54. Found: C, 75.45; H, 5.80; N, 6.34.

(3*RS*,4*RS*)-3-(4-Fluoro-piperidin-3-yl)-2-phenyl-1*H*-indole (10). A solution of racemic fluoropiperidine **9** (975 mg, 2.3 mmol) in ethyl acetate (50 mL) was treated with 99% formic acid (5 mL) and then with 10% palladium on activated carbon (120 mg), and the resulting suspension was stirred at ambient temperature for 4 h. The reaction mixture was filtered and then preadsorbed directly onto silica. Purification by flash chromatography eluting with dichloromethane/methanol/concentrated ammonia (93:7:1) gave the title compound (603 mg, 90%) as white needles: mp 134−136 °C (MeOH); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.42−1.58 (m, 1 H, piperidine H-5_{ax}), 2.08−2.18 (m, 1 H, piperidine H-5_{eq}), 2.72 (dd, J = 12.5 and 12.5, 1 H, piperidine H-6_{ax}), 2.90−2.94 (m, 1 H, piperidine H-2), 2.98−3.15 (m, 3 H, piperidine H-6_{eq}, piperidine H-2′ and piperidine H-3_{ax}), 5.20 (1 H, dddd, J = 49, 10, 10 and 2, piperidine H-4_{ax}), 6.99 (dd, J = 8.0 and 7.5, 1 H, indole H-5), 7.09 (dd, J = 8.0 and 7.5, 1 H, indole H-6), 7.37 (d, J = 8.0, 1 H, indole H-7), 7.41 (dd, J = 7.5 and 7.5, 1 H, phenyl H-4), 7.52 (dd, J = 7.5 and 7.5, 2 H, phenyl H-3), 7.59 (d, J = 7, 2 H, phenyl H-2), 7.77 (d, J = 8.0, 1 H, indole H-4), 11.21 (s, 1 H, indole NH); MS (ES$^+$) m/z 295 (M + H)$^+$. Anal. Calcd for $C_{19}H_{19}FN_2.CH_4O$: C, 73.59; H, 7.10; N, 8.58. Found: C, 73.66; H, 7.05; N, 8.62.

3-(4-Fluoro-1,2,3,6-tetrahydro-pyridin-4-yl)-2-phenyl-1*H*-indole (11). A hot (90 °C) solution of 2-phenylindole (1.5 g, 7.8 mmol) in glacial acetic acid (20 mL) was treated with 3-fluoro-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester[9] (1.7 g, 7.8 mmol) and then with 1 M phosphoric acid (4 mL), and the resulting suspension heated at 90 °C for 14 h. The resulting green solution was poured into ammonia (150 mL of a 15 wt % aqueous solution), and the product was extracted into ethyl acetate (150 mL). The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and then preadsorbed directly onto silica. Purification by flash chromatography eluting with dichloromethane containing 1% concentrated ammonia on a gradient of methanol (1−5%) gave a pale orange solid. This solid was triturated with ether then with methanol to afford the title compound (2.07 g, 91%) as white powder: mp 212−214 °C dec (MeOH); ^{1}H NMR (360

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

MHz, d_6-DMSO) δ 2.35 (br, 1 H), 2.94−3.19 (m, 2 H), 3.24−3.46 (m, 2 H), 4.91 (dm, J = 50, 1 H), 6.08−6.10 (m, 1 H), 7.02 (t, J = 7, 1 H), 7.12 (t, J = 7, 1 H), 7.32−7.40 (m, 2 H), 7.44−7.53 (m, 3 H), 7.70 (d, J = 8, 2 H), 11.41 (s, 1 H); MS (ES^+) m/z 293 $(M + H)^+$, 264 $(M - H_2C{=}NH)^+$. Anal. Calcd for $C_{19}H_{17}FN_2$: C, 78.06; H, 5.86; N, 9.58. Found: C, 78.39; H, 5.80; N, 9.29.

(3*RS*,4*RS*)-3-(3-Fluoro-piperidin-4-yl)-2-phenyl-1*H*-indole (4). A solution of allylic fluoride **11** (500 mg, 1.7 mmol) in trifluoroacetic acid (10 mL) was treated with triethylsilane (500 μL, 3.1 mmol) and then stirred at ambient temperature for 3 h. The reaction mixture was poured carefully into a saturated aqueous solution of sodium hydrogen carbonate (100 mL), and the product was extracted into ethyl acetate (100 mL). The organics were washed with water (75 mL) and then brine (75 mL) to give an oil. This oil was purified by flash chromatography eluting with dichloromethane/methanol/concentrated ammonia (95:4.5:0.5) to furnish the title compound (330 mg, 66%) as a white solid: oxalate salt, colorless needles, mp 206−208 °C (EtOH); ^{1}H NMR (400 MHz, d_6-DMSO, free base) δ 1.67−1.78 (m, 1 H, piperidine H-5_{eq}), 2.12−2.26 (m, 1 H, piperidine H-5_{ax}), 2.34−2.48 (m, 2 H, piperidine H-6_{ax} and piperidine H-2_{ax}), 2.90 (broad d, J = 12, 1 H, piperidine H-6_{eq}), 3.03−3.13 (m, 1 H, piperidine H-4_{ax}), 3.32 (obscured by H_2O, 1 H, piperidine H-2_{eq}), 5.03 (dddd, J = 49, 10, 10 and 5, 1 H, piperidine H-3_{ax}), 7.01 (dd, J = 8.0 and 7.5, 1 H, indole H-5), 7.10 (dd, J = 8.0, 7.5, 1 H, indole H-6), 7.38 (d, J = 8.0, 1 H, indole H-7), 7.40−7.43 (m, 1 H, phenyl H-4), 7.49−7.55 (m, 2 H, phenyl H-3), 7.56−7.60 (m, 2 H, phenyl H-2), 7.80 (d, J = 8.0, 1 H, indole H-4), 11.18 (s, 1 H, indole NH); MS (ES^+) m/z 295 $(M + H)^+$. Anal. Calcd for $C_{19}H_{19}FN_2.C_2H_2O_4$: C, 65.62; H, 5.51; N, 7.29. Found: C, 66.01; H, 5.44; N, 7.20.

(3*S,4*S**)-3-Hydroxy-4-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (12).** A cooled (−10 °C) suspension of (+)-diisopinocampheylborane[12] (9.8 g, 34 mmol) in anhydrous tetrahydrofuran (30 mL) was treated with a solution of 4-(2-phenyl-1*H*-indol-3-yl)-2,3-dihydro-6*H*-pyridine-1-carboxylic acid benzyl ester (7.0 g, 17 mmol) in anhydrous tetrahydrofuran (40 mL), and this mixture was stirred to ambient temperature over 70 h giving a pale yellow solution. The reaction was then cooled to −10 °C and treated with 4 N sodium hydroxide solution (20 mL) followed by hydrogen peroxide (12 mL of a 30 wt % solution in water), and this mixture was stirred to ambient temperature over 16 h. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate (400 mL) and extracted with ethyl acetate (2 × 250 mL). The organics were combined and washed with water (400 mL) and brine (400 mL) to give a yellow oil. Purification by chromatography on silica gel eluting with *iso*-hexane on a gradient of ethyl acetate (0%-40%) gave the title compound (6.4 g, 88%) as a white solid whose spectral data were identical to the racemate **8**: HPLC (OD-H column, 4:1 *iso*-hexane/ethanol with 0.1% diethylamine, 1 mL min^{-1}, UV, 212 nM) 6.4 min (24%), 7.8 min (76%). Recrystallization from diethyl ether over 72 h gave colorless needles (2.8 g, racemic by HPLC) and a mother liquor enriched in the major enantiomer. Concentration of the mother liquor in vacuo gave a pale yellow foam (3.6 g, 91% ee by HPLC).

(3*S*,4*S*)-4-(2-Phenyl-1*H*-indol-3-yl)-3-{(1*S*)-3-oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carbonyloxy}-piperidine-1-carboxylic Acid Benzyl Ester (13). A solution of alcohol **12** (1.0 g, 2.3 mmol, 91% ee) in anhydrous pyridine (10 mL) was treated with (1*S*)-(−)-camphanic chloride (770 mg, 3.6 mmol) then with 4-(dimethylamino)pyridine (10 mg), and this mixture was stirred at ambient temperature for 40 h. The reaction mixture was poured into 1 N hydrochloric acid (200 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with 1 N hydrochloric acid (100 mL), water (100 mL), and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and preadsorbed on to silica. Purification by chromatography on silica gel eluting with *iso*-hexane on a gradient of ethyl acetate (10−40%) gave the title compound (1.25 g, 88%) as a white powder followed by mixed fractions containing the minor diastereoisomer: mp 236−238 °C (EtOAc/heptane); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.01 (s, 3 H), 0.63 (s, 3H), 0.93 (s, 3 H), 1.52−1.58 (m, 1 H), 1.71−1.87 (m, 3 H), 2.18−2.26 (m, 1 H), 2.28−2.40 (m, 1 H), 2.74−2.88 (br m, 2 H), 3.33 (td, J = 11 and 4, 1 H), 4.20−4.36 (br m, 1 H), 4.60−4.70 (br m, 1 H), 5.20 (d, J = 12, 1 H), 5.24 (d, J = 12, 1 H), 5.52−5.64 (br m, 1 H), 7.10 (t, J = 7, 1 H), 7.17 (t, J = 7, 1 H), 7.31−7.45 (m, 7 H), 7.53 (t, J = 8, 2 H), 7.62 (d, J = 7, 2 H), 7.64−7.70 (m, 1 H), 7.98 (s, 1 H).

(3*S,4*S**)-4-Fluoro-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (14).** The title compound was prepared using the same procedure as that described for compound **9** using alcohol **12** (1.3 g, 3.0 mmol, 91% e.e.) and diethylaminosulfur trifluoride (500 μL, 3.8 mmol) to afford a cream-colored solid (1.1 g, 84%). Spectral data as for the racemate **9**: HPLC (OD-H column, 4:1 *iso*-hexane/ethanol, 1 mL min^{-1}, UV, 300 nM) 7.9 min (97.5%), 9.6 min (2.5%).

(3*S*,4*S*)-3-(4-Fluoro-piperidin-3-yl)-2-phenyl-1*H*-indole (15). The title compound was prepared using the same procedure as that described for compound **10** using fluoropiperidine **14** (1.1 g, 2.6 mmol) to give a white solid (748 mg, 99%). A single recrystallization afforded colorless needles. Spectral data as for the racemate **10**: $[\alpha]_D$ −17.5 (*c* 1.2 in DMF); mp 124−126 °C (MeOH); HPLC (OD-H column, 4:1 *iso*-hexane/ethanol, 1 mL min^{-1}, UV, 300 nM) 7.0 min (<0.5%), 8.5 min (>99.5%). Anal. Calcd for $C_{19}H_{19}FN_2{\cdot}CH_4O$: C, 73.59; H, 7.10; N, 8.58. Found: C, 73.82; H, 6.85; N, 8.55.

(3*S*,4*S*)-4-Fluoro-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid [(*R*)-1-phenyl-ethyl]-amide (16). A suspension of fluoropiperidine **15** (100 mg, 0.34 mmol, 95% ee) in 1,2-dichloroethane (5 mL) was treated with (*R*)-(+)-α-methylbenzylisocyanate (1.7 mL of a 0.5 M solution in 1,2-dichloroethane, 0.85 mmol), and this mixture was heated at 50 °C for 90 min. The reaction was cooled to ambient temperature then treated with *N*,*N*-dimethylethylenediamine (500 μL) and stirring continued at ambient temperature for 30 min. The reaction was diluted with ethyl acetate (25 mL) and washed with 0.1 N hydrochloric acid (2 × 20 mL), water (20 mL), and brine (20 mL) to afford the title compound as a white solid (133 mg, 89%). A single recrystallization gave colorless needles: mp 250−252 °C (9:1 EtOAc/MeOH); ^{1}H NMR (360 MHz, d_6-DMSO) δ 1.30 (d, J = 7, 3 H), 1.40−1.56 (m, 1 H), 2.10−2.19 (br m, 1 H), 3.00−3.18 (m, 2 H), 3.39 (t, J = 12, 1 H), 4.08−4.24 (br m, 2 H), 4.81 (quintet, J = 7, 1 H), 5.30 (dddd, J = 54, 10, 10 and 5, 1 H), 6.88 (d, J = 8, 1 H), 7.01 (t, J = 7, 1 H), 7.12 (t, J = 7, 1 H), 7.16−7.24 (m, 5 H), 7.38−7.48 (m, 4 H), 7.61 (d, J = 7, 2 H), 7.85 (d, J = 8, 1 H), 11.31 (s, 1 H).

(3*RS*,4*RS*)-4-(4-Nitro-benzoyloxy)-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (17). To a cooled (0 °C) solution of racemic alcohol **8** (5.0 g, 11.7 mmol) in anhydrous tetrahydrofuran (400 mL) was added triphenylphosphine (9.2 g, 35.1 mmol) followed by 4-nitrobenzoic acid (5.9 g, 35.3 mmol). Diethyl azodicarboxylate (5.5 mL, 34.9 mmol) was then added dropwise over 10 min, and the resulting mixture was stirred to ambient temperature over 16 h. The solvent was removed on a rotary evaporator, and the residue was suspended in water (400 mL) and extracted with diethyl ether (500 mL). The organics were washed with 1 N sodium hydroxide (2 × 500 mL), 1 N hydrochloric acid (500 mL), water (500 mL), and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and preadsorbed onto silica. Purification by chromatography on silica gel eluting with dichloromethane on a gradient of methanol (0−1.5%) gave the title compound (6.21 g, 76%) as a yellow solid: mp 175−176 °C (Et_2O/*iso*-hexane); ^{1}H NMR (360 MHz, d_6-DMSO measured at 340 K) δ 1.61 (qd, J = 13 and 4, 1 H), 2.20−2.28 (m, 1 H), 3.30−3.45 (m, 2 H), 3.66 (t, J = 13, 1 H), 4.19 (dd, J = 14 and 4, 2 H), 5.08 (d, J = 13, 1 H), 5.13 (d, J = 13, 1 H), 5.78 (td, J = 11 and 5, 1 H), 6.99 (*t*, J = 8, 1 H), 7.05 (t, J = 8, 1 H), 7.27−7.56 (m, 10 H), 7.75 (d, J = 9, 2 H), 7.88 (d, J = 8, 1 H), 8.13 (d, J = 8, 2 H), 11.03 (s, 1 H). Anal. Calcd for $C_{34}H_{29}N_3O_6$: C, 70.94; H, 5.08; N, 7.30. Found: C, 70.87; H, 5.04; N, 7.24.

(3*RS*,4*RS*)-4-Hydroxy-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (18). A suspension

of nitrobenzoate **17** (2.0 g, 3.5 mmol) in methanol (75 mL) was treated with potassium carbonate (5.0 g, 36 mmol), and this mixture was stirred at ambient temperature for 3 h. The reaction was filtered, the filtrate was evaporated to dryness, and the residue was suspended in water (150 mL) and extracted with ethyl acetate (150 mL). The organic phase was then washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and preadsorbed on to silica. Purification by chromatography on silica gel eluting with *iso*-hexane on a gradient of ethyl acetate (10−30%) gave the title compound (1.4 g, 95%) as a white foam: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.50−1.63 (m, 1 H), 1.82 (d, J = 2, 1 H), 2.08−2.14 (m, 1 H), 2.94−3.12 (m, 2 H), 3.38−3.51 (m, 1 H), 4.22−4.46 (m, 3 H), 5.11 (s, 2 H), 7.12 (t, J = 8, 1 H), 7.18−7.48 (m, 10 H,), 7.50−7.60 (m, 2 H), 7.73 (d, J = 8, 1 H), 8.23 (s, 1 H). Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57. Found: C, 75.83; H, 6.22; N, 6.30.

A cooled (−50 °C) solution of alcohol **18** (1.3 g, 3.0 mmol) in anhydrous ethyl acetate (25 mL) was treated with diethylaminosulfur trifluoride (500 μL, 3.8 mmol). Stirring at −50 °C was continued for 1 h before the solution was allowed to warm to ambient temperature. The reaction mixture was then poured into saturated aqueous sodium hydrogencarbonate (100 mL) and the product extracted into ethyl acetate (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL) to give a yellow foam. Purification by column chromatography eluting with *iso*-hexane on a gradient of ethyl acetate (0−20%) afforded a white foam (1.1 g, 85%) whose spectral data were identical to fluoropiperidine **9**.

3-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-6-fluoro-indole-1-carboxylic Acid *tert*-Butyl Ester (22). A cooled (0 °C) solution of potassium hydroxide (73 g, 1.3 mol) in methanol (900 mL) was treated with 6-fluoroindole (46 g, 0.34 mol) and then with 4-piperidone monohydrate hydrochloride (138 g, 0.90 mol). The resulting suspension was magnetically stirred and heated under reflux for 60 h. The reaction was cooled to ambient temperature, poured into water (8 L), and the resulting gummy solid was stirred for 16 h to furnish a fine suspension. The solid was collected by filtration, washed with water and dried under vacuum to afford 6-fluoro-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-indole (74 g, 100%) as a pale yellow powder, which was used without further purification: ^{1}H NMR (360 MHz, d_6-DMSO) δ 2.30−2.40 (m, 2 H), 2.92 (t, J = 6, 2 H), 3.38−3.45 (m, 2 H), 6.15−6.20 (m, 1 H), 6.86 (td, J = 9 and 2, 1 H), 7.13 (dd, J = 9 and 2, 1 H), 7.35 (d, J = 2, 1 H), 7.78 (dd, J = 9 and 6, 1 H), 11.13 (s, 1 H); MS (ES$^+$) m/z 217 (M + H)$^+$, 188 (M − H_2C=NH)$^+$.

A suspension of 6-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (74 g, 0.34 mol) in dichloromethane (1 L) was treated with triethylamine (142 mL, 1.02 mol) and then stirred and cooled to 0 °C. Di-*tert*-butyl dicarbonate (163 g, 0.75 mol) was then added portionwise over 15 min followed by 4-(dimethylamino)pyridine (50 g, 0.41 mol), and the resulting solution was stirred at ambient temperature for 90 min. The reaction was treated with *N*,*N*-dimethylethylenediamine (17 mL, 0.16 mol), and stirring was continued at ambient temperature for 30 min. The majority of the solvent was removed on a rotary evaporator, and the residue was dissolved in ethyl acetate (2.5 l). This was washed with 0.01 N hydrochloric acid (2 × 1.5 L), water (1.5 L), and brine (1.5 L). Filtration through a pad of Florisil followed by concentration in vacuo gave the title compound as a viscous yellow oil (109 g, 77% over 2 steps): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 1.67 (s, 9 H), 2.45−2.50 (m, 2 H), 3.67 (t, J = 6, 2 H), 4.15−4.20 (m, 2 H), 6.10−6.15 (m, 1 H), 7.00 (td, J = 9 and 2, 1 H), 7.49 (s, 1 H), 7.70 (dd, J = 9 and 5, 1 H), 7.85−7.90 (m, 1 H).

(3*R,4*R**)-3-(1-*tert*-Butoxycarbonyl-3-hydroxy-piperidin-4-yl)-6-fluoro-indole-1-carboxylic Acid *tert*-Butyl Ester (23).** A cooled (−10 °C) suspension of (−)-diisopinocampheylborane[12] (21.2 g, 74 mmol) in anhydrous tetrahydrofuran (50 mL) was treated with a solution of tetrahydropyridine **22** (19.5 g, 47 mmol) in anhydrous tetrahydrofuran (75 mL) and the resulting suspension was stirred at ambient temperature for 72 h to give a yellow solution. The reaction was then cooled to −10 °C and treated with 4 N sodium hydroxide solution (75 mL) followed by hydrogen peroxide (50 mL of a 30 wt % solution in water), and this mixture was stirred to ambient temperature over 24 h. The majority of the tetrahydrofuran was removed on a rotary evaporator, and the residue was partitioned between ethyl acetate (750 mL) and water (500 mL). The organic phase was then washed with saturated aqueous sodium hydrogen carbonate (2 × 500 mL), water (500 mL), and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and preadsorbed on to silica. Purification by chromatography on silica gel eluting with *iso*-hexane on a gradient of ethyl acetate (0−25%) gave the title compound (16.9 g, 83%) as a colorless, viscous oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 1.67 (s, 9 H), 1.80 (d, J = 3, 1 H), 1.80−1.85 (m, 1 H), 1.90−1.95 (m, 1 H), 2.64−2.74 (m, 1 H), 2.76−2.84 (m, 2 H), 3.75−3.84 (m, 1 H), 4.15−4.26 (m, 1 H), 4.35−4.45 (m, 1 H), 6.99 (td, J = 9 and 2, 1 H), 7.44 (s, 1 H), 7.53 (dd, J = 9 and 5, 1 H), 7.85−7.90 (m, 1 H).

(3*R,4*R**)-3-(1-*tert*-Butoxycarbonyl-3-fluoro-piperidin-4-yl)-6-fluoro-indole-1-carboxylic Acid *tert*-Butyl Ester (24)** and **(3*R**,4*R**)-3-(1-*tert*-Butoxycarbonyl-4-fluoro-piperidin-3-yl)-6-fluoro-indole-1-carboxylic Acid *tert*-Butyl Ester (25).** A cooled (−78 °C) solution of alcohol **23** (1.3 g, 3 mmol) in anhydrous ethyl acetate (25 mL) was treated with diethylaminosulfur trifluoride (400 μL, 3.3 mmol). Stirring at −78 °C was continued for 1 h before the solution was allowed to warm to ambient temperature. The reaction mixture was then poured into saturated aqueous sodium hydrogencarbonate (100 mL), and the product extracted into ethyl acetate (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and preadsorbed on to silica. Purification by chromatography on silica gel eluting with *iso*-hexane on a gradient of ethyl acetate (0−10%) gave 3-fluoropiperidine **24** (260 mg, 20%) as a white foam: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.49 (s, 9 H), 1.67 (s, 9 H), 1.75−1.87 (br m, 1 H), 2.01−2.10 (br m, 1 H), 2.82−2.98 (br m, 2 H), 3.01−3.10 (m, 1 H), 4.08−4.20 (br m, 1 H), 4.40−4.50 (br m, 1 H), 4.55 (dddd, J = 48, 10, 10 and 5, 1 H), 7.00 (td, J = 7 and 2, 1 H), 7.42 (br s, 1 H), 7.50 (dd, J = 9 and 5, 1 H), 7.85−7.87 (br m, 1 H). Anal. Calcd for $C_{23}H_{30}F_2N_2O_4$.0.2-(H_2O): C, 62.77; H, 6.96; N, 6.37. Found: C, 62.76; H, 6.78; N, 6.10.

Further elution gave 4-fluoropiperidine **25** (390 mg, 30%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 1.66 (s, 9 H), 1.74−1.86 (m, 1 H), 2.10−2.22 (m, 1 H), 3.04−3.20 (m, 3 H), 4.00−4.11 (m, 1 H), 4.15−4.31 (m, 1 H), 4.82 (dddd, J = 48, 10, 10 and 4, 1 H), 7.00 (td, J = 9 and 2,1 H), 7.47 (s, 1 H), 7.51 (dd, J = 9 and 5, 1 H), 7.81−7.90 (m, 1 H). Anal. Calcd for $C_{23}H_{30}F_2N_2O_4$: C, 63.29; H, 6.93; N, 6.42. Found: C, 63.68; H, 7.13; N, 6.29.

(3*R,4*R**)-3-(3-Fluoro-piperidin-4-yl)-6-fluoro-1*H*-indole (26).** A solution of fluoro-indole **24** (71 mg, 0.16 mmol) in dichloromethane (2 mL) was treated with trifluoroacetic acid (500 μL), and this mixture was stirred at ambient temperature for 18 h. The reaction mixture was poured carefully into a saturated aqueous solution of sodium hydrogen carbonate (20 mL), and the product was extracted into ethyl acetate (20 mL). The organics were washed with water (20 mL) and then brine (20 mL) to give an oil. This oil was purified by preparative TLC eluting with dichloromethane/methanol/concentrated ammonia (90:10:1) to furnish the title compound (31 mg, 80%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78−1.89 (m, 1 H, piperidine H-5_{ax}), 2.07−2.13 (m, 1 H, piperidine H-5_{eq}), 2.70−2.83 (m, 2 H, piperidine H-2_{ax} and piperidine H-6_{ax}), 3.05−3.15 (m, 2 H, piperidine H-2_{eq} and piperidine H-4_{ax}), 3.42−3.48 (m, 1 H, piperidine H-6_{eq}), 4.58 (dddd, J = 49, 10, 10 and 5, 1 H, piperidine H-3_{ax}), 6.89 (t, J = 9, 1 H, indole), 7.03 (d, J = 9, 1 H, indole), 7.05 (s, 1 H, indole H-2), 7.59 (dd, J = 9 and 5, 1 H, indole), 8.04 (br s, 1 H, indole NH); MS (ES$^+$) m/z 237 (M + H)$^+$. Anal. Calcd for $C_{13}H_{14}F_2N_2$: C, 66.09; H, 5.97; N, 11.06. Found: C, 65.71; H, 6.06; N, 11.70.

(3*R,4*R**)-4-(6-Fluoro-1*H*-indol-3-yl)-3-hydroxy-piperidine-1-carboxylic Acid *tert*-Butyl Ester (27).** A solution of alcohol **23** (16 g, 37 mmol) in methanol (200 mL) was treated with sodium methoxide (12 g, 0.22 mol), and the resulting

yellow solution was heated at 60 °C for 7 h. After cooling to ambient temperature, water (400 mL) was added, the majority of the methanol was removed on a rotary evaporator, and the residue was partitioned between ethyl acetate (500 mL) and water (500 mL). The organic phase was then washed with 0.01 N hydrochloric acid (2 × 500 mL), water (2 × 500 mL), and brine (500 mL) to afford the title compound (11.6 g, 94%) as a white foam: HPLC (OJ-R column, 32% MeCN in 0.1 M perchloric acid, 1 mL min^{-1}, UV, 210 nM) 21.0 min (80%), 22.9 min (20%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 1.86 (d, J = 2, 1 H), 1.82−1.90 (m, 1 H), 1.90−1.98 (m, 1 H), 2.64−2.74 (m, 1 H), 2.78−2.86 (m, 2 H), 3.68−3.78 (m, 1 H), 4.16−4.26 (m, 1 H), 4.38−4.46 (m, 1 H), 6.90 (td, J = 9 and 2, 1 H), 7.02−7.08 (m, 2 H), 7.59 (dd, J = 9 and 5, 1 H), 8.22 (br s, 1 H). Anal. Calcd for $C_{18}H_{23}FN_2O_3$: C, 64.65; H, 6.93; N, 8.38. Found: C, 64.63; H, 6.92; N, 8.32.

This foam was dissolved in ethyl acetate (30 mL) and heated to 65 °C. *iso*-Hexane was slowly added until the solution became turbid, and the heat source was removed. After standing at ambient temperature for 16 h the solid was removed by filtration and shown to be racemic by HPLC. The filtrate was evaporated to dryness, and the above procedure was repeated, giving a second crop of racemic solid (3.6 g, combined mass). Concentration of the filtrate afforded a yellow foam (8.0 g, 88% ee by HPLC).

(3*R,4*R**)-4-Fluoro-3-(6-fluoro-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (28).** A cooled (−78 °C) solution of alcohol **27** (8 g, 24 mmol, 88% ee) in anhydrous ethyl acetate (125 mL) was treated with diethylaminosulfur trifluoride (3.3 mL, 27 mmol). Stirring at −78 °C was continued for 1 h before the solution was allowed to warm to ambient temperature over 90 min. The reaction mixture was then poured into saturated aqueous sodium hydrogen carbonate (300 mL) and then diluted with ethyl acetate (175 mL). The organic phase was then washed with 0.1 N hydrochloric acid (300 mL), water (300 mL), and brine (300 mL) to afford an orange foam. This foam was purified by chromatography on silica gel eluting with *iso*-hexane on a gradient of ethyl acetate (0−20%) to give the title compound (6.9 g, 86%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9 H), 1.75−1.90 (m, 1 H), 2.05−2.20 (m, 1 H), 3.13−3.30 (m, 3 H), 3.90−4.05 (m, 1 H), 4.10−4.24 (m, 1 H), 4.75−4.95 (m,1 H), 6.96 (td, J = 9 and 2, 1 H), 7.00−7.13 (m, 2 H), 7.57 (dd, J = 9 and 5, 1 H), 8.09 (br s, 1 H). Anal. Calcd for $C_{18}H_{22}F_2N_2O_2$: C, 64.27; H, 6.59; N, 8.33. Found: C, 64.13; H, 6.63; N, 8.22.

A solution of indole **28** (6.0 g, 18 mmol) in dichloromethane (100 mL) was treated with triethylamine (5.0 mL, 36 mmol), di-*tert*-butyl dicarbonate (4.9 g, 22 mmol), and 4-(dimethylamino)pyridine (2.5 g, 20 mmol), and the resulting mixture was stirred at ambient temperature for 16 h. The reaction was treated with *N*,*N*-dimethylethylenediamine (2.5 mL), and stirring was continued at ambient temperature for 1 h. The majority of the solvent was removed on a rotary evaporator, and the residue was dissolved in ethyl acetate (300 mL). This was washed with 0.01 N hydrochloric acid (2 × 300 mL), water (300 mL), and brine (300 mL) to give an oil. Purification of this oil by column chromatography eluting with *iso*-hexane on a gradient of ethyl acetate (0−15%) gave a white foam (7.2 g, 92%) whose spectral data were identical to fluoropiperidine **25**.

(3*RS*,4*RS*)-4-Acetoxy-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (29). A cooled (−78 °C) solution of racemic alcohol **8** (853 mg, 2 mmol) in ethyl acetate (20 mL) was treated with 2,6-lutidine (300 μL, 2.6 mmol) and then with trifluoromethanesulfonic anhydride (370 μL, 2.2 mmol), and this mixture was stirred at −78 °C for 1 h before adding acetic acid (500 μL of a 10 M solution in ethyl acetate, 5 mmol). Stirring at −78 °C was continued for 30 min before the reaction mixture was allowed to warm to ambient temperature. The reaction was diluted with ethyl acetate (30 mL) and washed with 0.1 N hydrochloric acid (50 mL), water (50 mL), and brine (50 mL) to give a yellow oil. This oil was purified by chromatography on silica gel eluting with *iso*-hexane on a gradient of ethyl acetate (0−20%) to give the title compound (693 mg, 74%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer) δ 1.52−1.62 (br m, 1 H), 1.76 (s, 3 H), 2.20−2.24 (br m, 1 H), 2.96−3.11 (br m, 1 H), 3.23−3.32 (br m, 1 H), 3.48−3.52 (br m, 1 H), 4.18−4.41 (br m, 2 H), 5.09 (br s, 2 H), 5.47−5.56 (m,1 H), 7.11 (t, J = 8, 1 H), 7.17 (t, J = 8, 1 H), 7.29−7.50 (m, 9 H), 7.52−7.62 (br m, 2 H), 7.23 (d, J = 8, 1 H), 8.07 (s, 1 H). Anal. Calcd for $C_{29}H_{28}N_2O_4.0.2(H_2O)$: C, 73.77; H, 6.06; N, 5.93. Found: C, 73.69; H, 6.13; N, 5.71.

A solution of acetate **29** (275 mg, 0.59 mmol) in methanol (7 mL) was treated with potassium carbonate (810 mg, 5.9 mmol), and this suspension was stirred at ambient temperature for 16 h. The reaction was filtered and the filtrate evaporated in vacuo to give an oil. This oil was purified by chromatography on silica gel eluting with *iso*-hexane on a gradient of ethyl acetate (10−30%) to afford a white foam (223 mg, 89%) whose spectral data were identical to alcohol **18**.

(3*RS*,4*RS*)-4-Benzylamino-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (30). Using the procedure described for **29** with benzylamine (500 μL of a 10 M solution in ethyl acetate, 5 mmol) as the nucleophile afforded the title compound (567 mg, 55%) as a white solid: mp 127−129 °C (EtOAc/*iso*-hexane); ^{1}H NMR (360 MHz, $CDCl_3$, mixture of rotamers) δ 1.30−1.46 (br m, 1 H), 2.04−2.18 (br m, 1 H), 2.86−3.04 (br m, 1 H), 3.08−3.20 (m, 1 H), 3.29−3.45 (br m, 2 H), 3.49 (d, J = 14, 1 H), 3.68 (d, J = 14, 1 H), 4.20−4.42 (br m, 2 H), 5.12 (br s, 2 H), 6.89−6.93 (m, 2 H), 7.04 (t, J = 8, 1 H), 7.10−7.18 (m, 3 H), 7.21 (t, J = 8, 1 H), 7.29−7.40 (m, 9 H), 7.54−7.62 (m, 3 H), 8.11−8.29 (br m, 1 H); MS (ES^+) m/z 516 $(M + H)^+$. Anal. Calcd for $C_{34}H_{33}N_3O_2$: C, 79.19; H, 6.45; N, 8.15. Found: C, 79.03; H, 6.54; N, 7.99.

(3*RS*,4*RS*)-4-Benzylsulfanyl-3-(2-phenyl-1*H*-indol-3-yl)-piperidine-1-carboxylic Acid Benzyl Ester (29). Using the procedure described for **29** with benzylmercaptan (500 μL of a 10 M solution in ethyl acetate, 5 mmol) as the nucleophile afforded the title compound (597 mg, 56%) as a cream-colored solid: mp 135−137 °C (EtOAc/*iso*-hexane); ^{1}H NMR (360 MHz, $CDCl_3$, mixture of rotamers) δ 1.53−1.68 (br m, 1 H), 2.04−2.13 (br m, 1 H), 2.80−2.93 (br m, 1 H), 3.10−3.21 (br m, 1 H), 3.23 (d, J = 13,1 H), 3.34 (d, J = 13, 1 H), 3.40 (td, J = 12 and 4, 2 H), 4.19−4.37 (br m, 2 H), 5.09 (br s, 2 H), 6.90−6.96 (m, 2 H), 7.07 (t, J = 8, 1 H), 7.13−7.16 (m, 3 H), 7.18 (t, J = 8, 1 H), 7.26−7.35 (br m, 6 H), 7.37−7.48 (m, 3 H), 7.52 (d, J = 8, 1 H), 7.54−7.68 (br m, 2 H), 8.11 (br s, 1 H). Anal. Calcd for $C_{34}H_{32}N_2O_2S.0.5(H_2O)$: C, 75.39; H, 6.14; N, 5.17. Found: C, 75.46; H, 6.14; N, 5.03.

Low-Temperature NMR Experiments. The reaction intermediate **19** was generated in an NMR tube by treating a cooled (−78 °C) solution of the racemic alcohol **8** in CD_2Cl_2 with ca. 3 equiv of DAST. The tube was then shaken to effect mixing and transferred immediately into the magnet.

Partial assignment of the proton and carbon spectra of racemic alcohol **8** (where separate assignments for both rotamers were possible, the major isomer is listed first): ^{1}H NMR (500 MHz, CD_2Cl_2, 223 K) δ 1.72−1.84 (m, 1 H, piperidine H-5_{eq}), 1.98 and 1.92 (s, 1 H, OH), 2.20−2.34 (m, 1 H, piperidine H-5_{eq}), 2.57−2.85 (m, 2 H, piperidine H-2_{ax}, piperidine H-6_{ax}), 3.00 (m, 1 H, piperidine H-4_{ax}), 4.11−4.26 (m, 2 H, piperidine H-2_{eq}, piperidine H-6_{eq}), 4.44 (m, 1 H, piperidine H-3_{ax}), 5.04−5.14 (m, 2 H, PhCH_2O), 7.04 (dd, J = 8.0 and 7.5, 1 H, ArH), 7.16 (dd, J = 8.0 and 7.5, 1 H, ArH), 7.27−7.44 (m, 7 H, ArH), 7.48 (dd, J = 7.5 and 7.5, 2 H), 7.60 (dd, J = 8.5 and 9.0, 2 H), 7.68 (d, J = 8.0, 1 H), 8.39 (s, 1 H, indole NH); ^{13}C NMR (100 MHz, d_6-DMSO) δ 30.9 (CH_2), 42.0 (C-4), 44.2 (CH_2), 51.3 (CH_2), 66.4 (CH_2), 68.1 (C-3), 111.7 (CH), 112.4 (C), 118.8 (CH), 120.3 (CH), 121.3 (CH), 126.8 (C), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.6 (2xCH), 129.2 (CH), 133.4 (C), 136.1 (C), 137.3 (C), 154.6 (CO).

Partial assignment of the proton spectrum of 3,3-spirocyclopropyl indolenine **19** at 223 K (where separate assignments for both rotamers were possible, the major isomer is listed first): ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.01−2.14 (m, 1 H, piperidine H-5), 2.25−2.38 (m, 1 H, piperidine H-5′), 2.85 and 2.90 (m, 1 H, piperidine H-6_{ax}), 3.22 and 3.29 (m, 1 H, piperidine H-3), 3.45 and 3.39 (m, 1 H, piperidine H-4), 3.78

and 3.71 (dd, J = 15.5 and 5.5, 1 H, piperidine H-2), 4.14 and 4.20 (d, J = 15.5, 1 H, piperidine H-2′), 4.38 and 4.34 (dd, J = 13.5 and 4.5, 1 H, piperidine H-6_{eq}), 5.05, 5.28, 5.17 and 5.31 (AB systems, J = 12, 2 H, PhCH_2O), 7.05−7.90 (m, 13 H, ArH), 7.97 (dd, J = 8.0 and 7.5, 1 H, ArH).

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Supporting Information Available: Crystal structure data for **13** and **16**. The atomic coordinates have also been deposited with the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K. (deposition numbers 139374 and 139375). This material is available free of charge via the Internet at http://pubs.acs.org.

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