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METHODOLOGY FOR THE FACILE AND REGIO-CONTROLLED SYNTHESIS OF INDOLES[1a,b]

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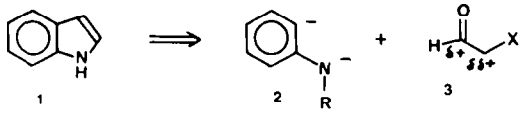
Abstract—A method based on organodimetallic reagents is described for the regiocontrolled synthesis of indoles which proceeds, generally, in one to two operations from commercially or readily available reactants. The method is applied to the synthesis of indole itself, 2-substituted, 3-substituted, 2,3-disubstituted and 6-substituted indoles.

Since the first preparation of indole (**1**) by Baeyer[3] in 1866, this heterocycle and its derivatives have attracted considerable interest understandably arising from the varied and potent biological activity exhibited by indoles, including antineoplastic (vinblastine), tumor promoter (teleocidin), hypotensive (reserpine), psychomimetic (lysergic acid), anti-inflammatory (indomethacin), CNS stimulant (harmaline), antimicrobial (gliotoxin) and plant growth regulatory (indole acetic acid) activities among others.[4] In response to the synthetic needs engendered by these activities, a number of methods[5] have been devised for the synthesis of indole derivatives. The most notable of these methods is that reported by Fischer[6] nearly a century ago involving the condensation of an arylhydrazine with a ketone and subsequent rearrangement of the hydrazone product. Effective refinements of the Fischer procedure[7] and newer methods[8] which complement the Fischer concept and circumvent its limitations have appeared with considerable frequency over the years.

Our own interest[1] in this area arose during studies on a synthesis of reserpine,[9] for which we required access to 6-methoxytryptamine derivatives. While such compounds can be prepared using methodology employed by Woodward *et al.*[10] in their synthesis of reserpine, we sought a method which would be operationally shorter, ideally allowing for a one-operation synthesis. Our approach to this objective, biased in no small way by our previous studies on organodimetallic reagents[1a,c] centered around the expectation that the 1,3-bisnucleophilic character exhibited by such reagents (e.g. **2**) would be manifested in their conjunction with their polarity complements, 1,2-biselectrophiles (e.g. **3**) such as α-halocarbonyls. Where relevant, regulation of the regiochemistry of this 3 + 2-construction of the pyrrole moiety of the indole system was expected to arise from the inherent as well as substituent-dictated differentiation of the relative nucleophilicities and electrophilicities of the conjoining reactant sites. Since both reactants in this process are commercially available or derivable *in situ* from a commercial source, it seemed reasonable that this strategy would allow for the realization of our goal, a one-operation, regiocontrolled synthesis of indoles. Our studies on the development and application of this strategy for indole synthesis are detailed herein.



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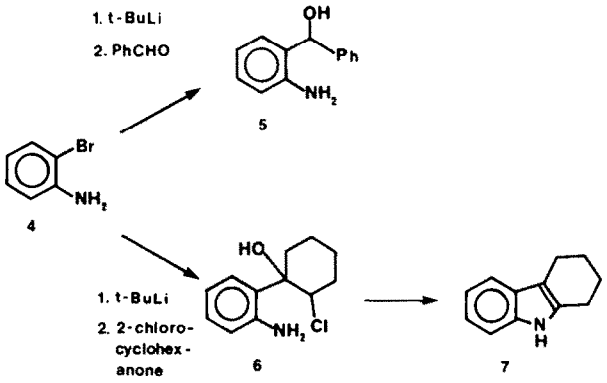
RESULTS AND DISCUSSION

Our first approach to the preparation of the requisite bisnucleophiles was based on the work of Gilman *et al.*,[11] which represents one of the earliest investigations on organodimetallic reagents. These workers reported that treatment of aniline or 2-bromoaniline with n-butyllithium followed by addition of carbon dioxide gave anthranilic acid in 4.2 and 36% yields, respectively, presumably via an organodi- or trimetallic intermediate. While the yield obtained in the former case was low and experimental details for the latter were not given, the potential of such organopolymetallic reagents in the above noted approach to indoles prompted our study on the reaction of 2-bromoaniline with alkyllithiums. Toward this end, 2-bromoaniline (**4**) was treated with t-butyllithium (3 equiv.) and the resulting mixture quenched with deuterium oxide. NMR analysis of the reaction indicated the presence of approx. 90% aniline-d_3, suggesting the intermediacy of an organodimetallic or organotrimetallic in the above reaction. The competence of this intermediate in C–C bond formation was examined next in its reaction with benzaldehyde. In this way, aminoalcohol **5** was obtained, unfortunately in low yield (25%), along with benzyl alcohol and a trace of t-butylphenylmethanol. 2-Chlorocyclohexanone, a possible bis-electrophile, performed more efficiently in its reaction with the above noted intermediate, affording aminoalcohol **6** in 52% yield. While it was encouraging to find that **6**, upon heating with an equivalent of pyridine in DMF, could be converted to indole **7**, the low efficiency of the above C–C bond forming reactions prompted our search for a better bisnucleophilic reagent.

It was subsequently established that the most effective reagents for the desired annelation were those prepared from amide derivatives of 2-bromoaniline. In this connection, Gschwend and Fuhrer[12]



have shown that N-pivaloylaniline (**8**), upon deprotonation using 3 equiv. of n-butyllithium, can be converted over a 20 hr period to dilithium reagent **9a** in, minimally, 88% yield as determined by a trapping reaction with dimethyl disulfide. In our own studies, a halogen–lithium exchange reaction was found to serve as an exceptionally efficient and facile process for the preparation of **9a**. Thus, treatment of **10a** with methyllithium (1 equiv.; to effect amide deprotonation) and t-butyllithium (2 equiv.; to effect Li–Br exchange) gave **9a** in a minimum yield of 89% as determined by its trapping with benzaldehyde. Importantly, reduction of benzaldehyde, a competing reaction observed when the reagent prepared from 2-bromoaniline was used, was not observed in this case.

The efficiency exhibited by organodilithium reagent **9a** in the above C–C bond formation set the stage for the crucial test of its reaction with a biselectrophile. For this purpose, 2-chlorocyclohexanone was added to the reagent **9a** and the reaction quenched with saturated ammonium chloride. Hydroxyamide **11a** was gratifyingly obtained in 92% yield along with amide **8** (7%). The structure of **11a** follows from its spectral data and proposed mechanism of formation involving stereocontrolled addition[13] of the carbanionic site of **9a** to the ketone carbon. The *cis*-chloroalkoxide produced in this fashion would then be expected to undergo S_N2 displacement by the N of the amide ion to provide the observed *cis*-fused product.

Further studies showed that this two bond transformation (C–C and N–C) could also be effected with dilithium reagents **9b**[14] and **9c**, thereby providing greater generality to this method and variability in N protection. The effects of these protecting groups and temperature changes on the above reaction are summarized in Table 1.

The final objective, generation of the indole system from the now readily-available hydroxyamides, was efficiently accomplished in a fashion which allows for isolation of a N protected or unprotected product. Thus, treatment of **11a** with a trace of trifluoroacetic acid in methylene chloride gave the N-protected indole **12a** in 94% yield. Alternatively, the unprotected indole **7** could be obtained in 93% yield by hydrolysis of **11a** according to Gassman's[15] anhydrous hydroxide procedure and standard extractive work-up (5% HCl).[16]

While the individual operations in the above indole synthesis (i.e., amide formation, deprotonation–halogen/metal exchange–condensation, and dehydration) are highly efficient, it was our expectation that they could be combined to establish, ideally, a one operation method. In this connection, it was subsequently found that the hydroxyamide product **11a** need not

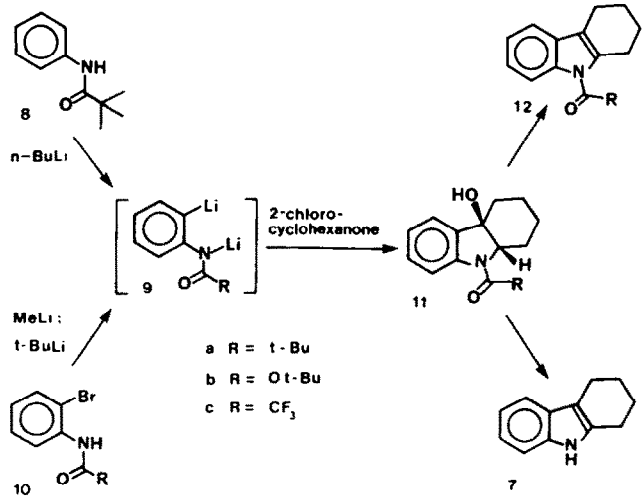
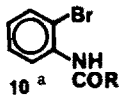
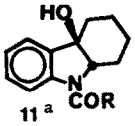
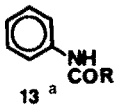
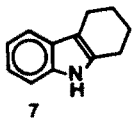


Table 1. The effect of temperature and protecting group variations on the reaction of **10a–c** with 2-chlorocyclohexanone

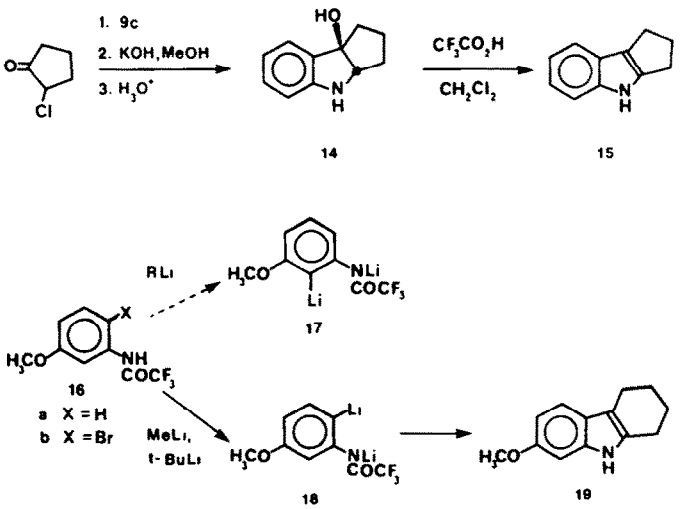
Starting Bromoamide	Reaction Temperature	Product %		
 **10** [a]		 **11** [a]	 **13** [a]	 **7**
10a	-78°	77	13	0
10a	-10°	92	7	0
10b	-10°	67	24	0
10c	-10°	58	15	18

[a] a series, R = tBu; b series, R = OtBu; c series, R = CF_3.

be isolated. Thus, indole **7** can be obtained directly from bromoamide **10a** in 77% yield when the addition of 2-chlorocyclohexanone to reagent **9a** is followed by addition of potassium t-butoxide and water. Furthermore, the formation of the bromoamide **10a** can also be effected *in situ*, thereby allowing for the conversion of commercially available 2-bromoaniline to indole **7** in one operation which proceeds in 74% yield. For this purpose, 2-bromoaniline was treated successively with methyllithium (2 equiv.), pivaloyl chloride (1 equiv.), and t-butyllithium (2 equiv.) to provide reagent **9a**, which was used as previously described to afford indole **7**.

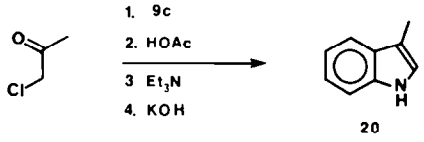
While this method can be readily extended to other substrates, in some cases more than one operation is required. For example, when reagent **9c** (generated *in situ*) was treated with 2-chlorocyclopentanone and the resulting mixture submitted to KOH/MeOH and then aqueous acid, aminoalcohol **14** was obtained rather than the desired indole **15**. However, at the expense of an additional operation, indole **15** could be obtained quantitatively from **14** by exposure of the latter to a trace of trifluoroacetic acid in methylene chloride.

In addition to operational effectiveness, the generality of methodology for indole synthesis is influenced by the degree of regiochemical control offered by the concept. The regiochemical outcome of the present method is determined by the relative nucleophilicities and electrophilicities of the reactants and the regioselectivity realized in their formation. With α-haloketones as biselectrophiles, the annelation process proceeds with complete regiochemical control in that the carbanionic center of the dilithium reagent reacts at the carbonyl carbon of the haloketone reactant. Overall regioselectivity is determined, therefore, by the regioselectivity achieved in reactant preparation, which can usually be accomplished (at times in complementary ways) by using heteroatom directed deprotonation or site-specific halogen–lithium exchange. For example, whereas deprotonation of amide **16a** would be expected to give dilithium reagent **17**,[17] its isomer (**18**) can be readily obtained from bromoamide **16b**[18] through an ex-



change reaction. In accord with this analysis, the use of bromoamide **16b** in the above noted procedure allowed for the formation of tetrahydrocarbazole **19** in 69% yield. No isomeric tetrahydrocarbazole was detected by NMR.

Similar control can be realized in the case of unsymmetrically substituted biselectrophiles. Thus, treatment of dilithium reagent **9c** with chloroacetone at −78 followed by sequential addition of acetic acid, triethylamine, and 10% potassium hydroxide in methanol afforded skatole (**20**) in 52% yield, free of the isomeric α- or 2-methylindole product.



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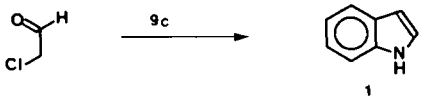
In addition to α-haloketones, other biselectrophiles can be effectively utilized in this method. For example, a modest but important extension was realized in the use of chloroacetaldehyde as a biselectrophile which in conjunction with dilithium reagent **9c** provided the parent system, indole (**1**), in 60% overall



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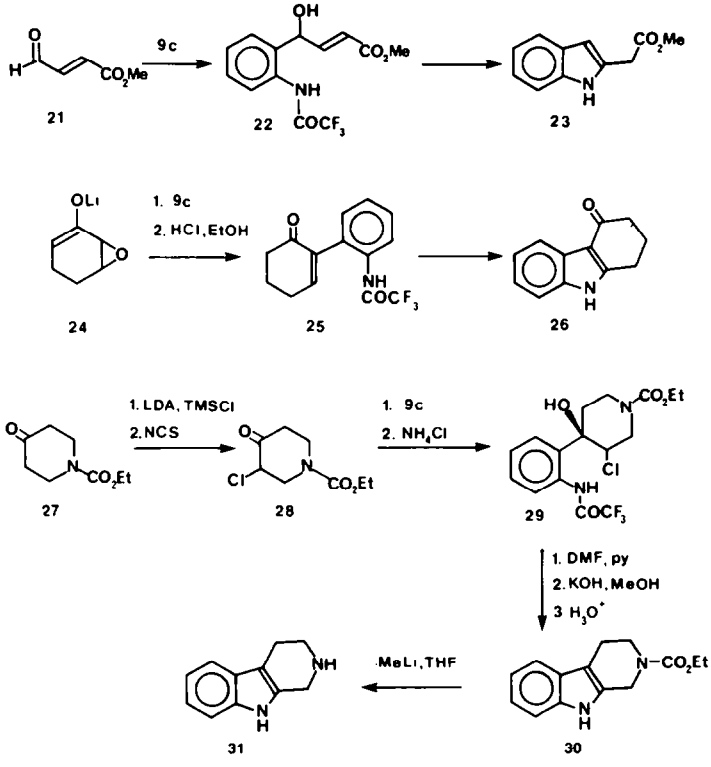
yield. Methyl 4-oxo-2-butenoate (**21**)[19] was also found to function as an effective biselectrophile, differing from the α-halocarbonyls in that C–N bond formation with the former arises through a Michael addition rather than halide displacement. Thus, reaction of dilithium reagent **9c** with **21** gave alcohol **22** in 77% yield. Hydrolysis of **22** with potassium carbonate (MeOH) and dehydration with trifluoroacetic acid (CH_2Cl_2) provided a convenient preparation of the methyl ester of indole 2-acetic acid (**23**; 87% yield).

Recently, in other studies[20] in our laboratories, it was shown that the enolates of cycloalkenone epoxides behave as electrophiles in their reactions with organometallics, providing either 2- or 6-substituted cyclohexenones depending on the choice of organometallic reagent and reaction conditions. In accord with these results and their extension, reaction of enolate **24** with dilithium reagent **9c** gave, after dehydration, enone **25** in 59% yield. Conversion of this compound (**25**) to indole **26** was effected by its reaction with dilute aqueous sodium hydroxide in methanol, which entailed an oxidation arising presumably from the presence of dissolved oxygen.[7b]

The final phase of our study was directed at the synthesis of β-carbolines, due to the general interest in the activity of such compounds and the more complex problems encountered in their synthesis.[22] A design based on the present method would require a 4-piperidone derivative as a biselectrophile, which was expected to be derivable from commercially available carbethoxy-4-piperidone (**27**). In practice, treatment of **27** with sulfuryl chloride or its enolate with trifluoromethanesulfonyl chloride gave the desired α-chloroketone **28** in good yield; however, the product in both cases was contaminated with 15–20% of a dichlorinated compound which could not be separated. Alternatively, a sample of chloroketone **28**, containing less than 5% dichloride, was obtained by conversion of **27** to its trimethylsilyl enolether and reaction of the latter with N-chlorosuccinimide. Re-



action of this material with reagent **9c** gave chlorohydrin **29** in 58% yield. Formation of urethane **30** was achieved by treatment of **29** with pyridine in dimethylformamide at 90° followed by hydrolysis and workup. Treatment of urethane **30** with methyllithium gave tryptoline (**31**) in 77% yield.

In summary, a method has been developed which allows for the synthesis of indoles generally in one to two operations from readily available reactants. Complete regiocontrol is obtained due to the differing site nucleophilicities and electrophilicities of the doubly-functionalized reactants. The method has been used for the synthesis of indole itself, 2-substituted indoles, 3-substituted indoles, 2,3-disubstituted indoles which can also be prepared in an annelative fashion, and 6-substituted indoles.

EXPERIMENTAL

All O_2- or moisture-sensitive reactions were performed in flame- or oven-dried glassware under a positive pressure of prepurified N_2. Sensitive liquids and solns were transferred by syringe or cannula, and were introduced into reaction flasks through rubber septa. Air- or moisture-sensitive solids were transferred in a dry glove bag under N_2 or under a funnel of N_2. All solns were dried by shaking with Na_2SO_4, unless otherwise stated. All temps are given in degrees Centigrade.

For chromatographic separations, commercial grade solvents were used without further purification with the exception of hexanes (used to refer to the fraction of hexanes with a b.p. of 65–69°) and THF which were distilled prior to use.

n-BuLi (~2.4 M in hexanes), MeLi (~1.4 M in ether, low chloride concentration) and t-BuLi (~1.5 M in pentane) were purchased from Aldrich Chemical Co. and Alfa/Ventron. The concentration of alkyllithium and organodilithium reagents was determined by Gilman's method of double titration using dibromoethane,[23] or by titration of a standard alcohol soln using 1,10-phenanthroline or triphenylmethane as indicator.[24]

The terms "chromatography" and "silica gel chromatography" refer to column chromatography with silica gel and the solvent system(s) indicated using a column of the specified inner diameter. Flash column chromatography refers to the method of Still *et al.*[25] and was performed on either Woelm Silica (32–63 m) or Merck Silica Gel 80 (40–63 μm). Dry column chromatography[26] indicates that Woelm Silica (63–200 μm) was employed.

All b.ps are uncorrected. M.ps were taken on a Thomas Hoover capillary m.p. apparatus and are corrected. Those m.ps denoted (vac) were taken in evacuated capillary tubes, and those denoted (d) indicate that the compound decomposed on melting.

UV spectra were measured on either a Perkin–Elmer model 202 or 599a instrument. Absorption maxima are reported in nanometers in the form λ_{max}(log).

IR spectra were measured on either a Perkin–Elmer model 137 or 457a instrument and are reported in wavenumbers (cm^{-1}).

P NMR were measured at 60 MHz on a Varian A-60 instrument, at 80 MHz on a Varian HFT-80 instrument, and at 100 MHz on a Varian HA-100 instrument. C NMR spectra were recorded at 25.2 MHz on a Varian XL-100-15 instrument using broadband proton decoupling. Multiplicity of the C resonances were determined using off-resonance decoupling. Chemical shifts are reported in ppm downfield from TMS, using either TMS or residual $CHCl_3$ as reference. P NMR data are reported in the form: chemical shift (multiplicity, number of protons, coupling in Hz). C NMR data are reported in the form: chemical shift (multiplicity). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, b = broad, dd = doublet of doublets.

Mass spectral data were determined on either an AEI MS-9 instrument or a Kratos MS-50L instrument equipped with a DS-55 data system. Both spectrometers are double focusing instruments and were operated at 70 eV ionization voltage and 8 kV accelerating voltage unless otherwise indicated. Source temps were generally 100–200° above ambient. The metastable scan and high resolution mass spectra were performed on the latter instrument. High resolution mass spectra were determined on both the former (seven significant digits reported) and the latter (eight significant digits reported) instruments. Mass spectral data are presented in the following form: parent ion (relative intensity), *m/e* of significant fragments (relative intensity).

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee, and are reported in per cent.

Aminoalcohol **5**. To a soln of 2-bromoaniline (86 mg, 0.5 mmol) in ether (5 mL) was added (2 min) t-BuLi (1.5 mmol, 2.2 mL of 1.35 M in pentane) at −78°. After the soln had stirred for 1.5 hr at −78°, benzaldehyde (2.1 mmol) was added. The resulting mixture was allowed to warm to ambient temp (15 min) and was then stirred for 30 min. It was then poured into a soln of THF and 2N HCl (1:1, 50 mL) and stirred for 1 hr. Ether was added, and the layers were separated. The organic layer contained mostly benzaldehyde and benzyl alcohol. The aqueous layer was made basic and extracted with ether. The crude material (41 mg) from these organic extracts consisted mainly of the desired **5**. Chromatography (15 mm flash column, 33% ether–hexanes) provided 2-bromoaniline (1 mg), benzyl alcohol (6 mg), and **5** (25 mg, 25% yield). Aminoalcohol **5** was recrystallized from $CHCl_3$ as white prisms. NMR ($CDCl_3$): 7.40–6.55 (m, 9H), 5.82 (s, 1H), 3.85 (bs, NH_2), 2.65 (bs, OH) (reported ($CHCl_3$): 7.32–6.42 (m, 9H), 5.65 (s, 1H), 3.62 (bs, 3H)); IR ($CDCl_3$): 3630, 3475, 3350, 3020, 1620, 1490, 1450, 1010. Mass spectrum: 199 (22), 181 (19), 180 (100), 77 (20). UV: (95% EtOH): 287 (3.2), 233.5 (3.7), 203 (4.4). M.p.: 115–116° (reported:[27] 113–114°).

Aminoalcohol **6**. To a soln of 2-bromoaniline (344 mg, 2.0 mmol) in ether (20 mL) at −78° was added t-BuLi (6.0 mmol, 2.1 mL of 2.9 M in pentane) over 5 min. The resulting soln was stirred for 1.5 hr at −78° before 2-chlorocyclohexanone (0.80 g, 6.0 mmol) was added. After 20 min, the soln was poured directly into 5% HCl and extracted with CH_2Cl_2. The aqueous phase was made basic (pH = 12) and extracted with CH_2Cl_2. These extracts were dried (Na_2SO_4), and the solvent was removed. The crude material was triturated with cold hexanes to provide **6** (228 mg, 51% yield). Recrystallization from ether–hexanes provided **6** as white prisms (m.p. 76.5–77.5°). NMR ($CDCl_3$): 7.15–6.85 (m, 2H), 6.55–6.00 (m, 2H), 4.80–4.55 (m, 1H), 4.10 (bs, NH_2 and OH), 2.80–2.50 (m, 1H), 2.40–1.10 (m, 7H). IR ($CDCl_3$): 3550, 3450, 3350, 1615, 1490, 1440, 1165, 990, 970. Mass spectrum: 227 (17), 225 (43), 190 (27), 172 (18), 171 (15), 149 (18), 148 (48), 143 (18), 135 (37), 130 (18), 120 (100), 92 (15), 65 (17). UV (95% ethanol): 292 (3.3), 239 (3.8), 204 (4.4). Exact mass: Calc. for $C_{12}H_{16}{}^{35}ClNO$: 225.09203; Found: 225.09200. Analysis: (Found: C-64.00, H-7.19, N-6.26, Cl-15.85. Calc. for $C_{12}H_{16}ClNO$: C-63.84, H-7.14, N-6.23, Cl-15.70%.)

Bromoamide **10a**. To a mixture of 10% Na_2CO_3 aq (100 mL) and 2-bromoaniline (8.6 g, 50 mmol) in CH_2Cl_2 (100 mL) was added pivaloyl chloride (6.0 g, 50 mmol) in CH_2Cl_2 (100 mL). After the mixture had been stirred for 3 hr, more pivaloyl chloride (0.2 g) was added. After 30 min, the two phases were separated, and the organic phase was extracted with 10% Na_2CO_3 aq and dried (Na_2SO_4). Bromoamide **10a** (11.5 g, 90% yield) remained after removal of the solvent *in vacuo*. Analytical samples were obtained by low temp recrystallization from hexanes (white needles, m.p. 61.5–62.0°). NMR ($CDCl_3$): 8.39 (dd, 1H, J = 2, 8), 7.39 (bs, 1H, NH), 7.50 (dd, 1H, J = 2, 8), 7.30 (dt, 1H, J = 2, 8), 6.94

(dt, 1H, J = 2, 8), 1.38 (s, 9H). IR (CCl_4): 3400, 2950, 1695, 1590, 1505, 1420, 1290, 1150, 1010, 935. Mass spectrum: 257 (8), 255 (8), 176 (50), 173 (25), 171 (26), 57 (100), 43 (21), 41 (30). UV (95% EtOH): 239 (3.8), 206 (4.3). Exact mass: Found: 257.03377. Calc. for $C_{11}H_{14}{}^{81}BrNO$: 257.03395%.

Bromourethane **10b**. To a soln of 2-bromoaniline (5.16 g, 30 mmol) in THF (50 mL) was added di-t-butyl dicarbonate (7.1 mL, 30 mmol) and 4-dimethylaminopyridine (3 mmol). The resulting soln was heated under reflux for 16 hr. At this point a TLC indicated that no starting material remained and two products had been formed ($R_f = 0.29$ and $R_f \approx 0$, 5% ether–hexanes). Dry column chromatography (30 mm column, 5% ether–hexanes) provided **10b** (2.3 g, $R_f = 0.29$) as a viscous oil which solidified at temps below 0°. NMR ($CDCl_3$): 8.10 (dd, 1H, J = 1.6, 7.8), 7.49 (dd, 1H, J = 1.6, 7.8), 7.26 (dt, 1H, J = 1.6, 7.8), 7.00 (bs, NH), 6.86 (dt, 1H, J = 1.6, 7.8), 1.52 (s, 9H). IR (film): 3400, 2940, 1730, 1590, 1510, 1420, 1240, 1220, 1150, 750. Mass spectrum: 273, 271 (17), 217, 215 (22), 199, 197 (19), 173, 171 (78), 59 (36), 57 (100), 56 (36), 55 (40). UV (95% EtOH): 233 (4.1), 208 (4.5). Exact mass: Calc. for $C_{11}H_{14}{}^{79}BrNO_2$: 271.02084; Found: 271.02074.

Bromoamide **10c**. To a soln of 2-bromoaniline (5.13 g, 30 mmol) in ether (30 mL) at 0° was added solid Na_2CO_3 (5.0 g) and trifluoroacetic anhydride (5.65 mL, 40 mmol). After warming to ambient temp, the mixture was stirred for 24 hr. The resulting suspension was partitioned between CH_2Cl_2 and water. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), and the solvent was removed. Sublimation of the crude material (8.10 g) provided **10c** (7.93 g) as a white crystalline solid in 99% yield (m.p. 60–61°). NMR ($CDCl_3$): 8.30 (bs, 1H, NH), 8.30 (dd, 1H, J = 1.7, 8.0), 7.61 (dd, 1H, J = 1.7, 8.0), 7.38 (dt, 1H, J = 1.7, 8.0), 7.09 (dt, 1H, J = 1.7, 8.0). IR (KBr): 3250, 1700, 1585, 1525, 1430, 1270, 1180, 1030, 915, 770, 760, 740. Mass spectrum: 269 (27), 267 (24), 188 (100), 149 (23), 105 (17), 91 (26). UV (95% EtOH): 203 (4.4). Exact mass: Calc. for $C_8H_5{}^{81}BrF_3NO$: 268.94891; Found: 268.94862.

General procedure (A) for the formation of organodilithium reagents **9**. The above *o*-bromoaniline derivative **10** (1.00 mmol, R = t-Bu, Ot-Bu, or CF_3) was dissolved in THF (20 mL) and cooled to −78°. MeLi (1.00 mmol, low-halide, 1.4 M in ether) was added to the soln, and 10 min later t-BuLi (2.00 mmol, 1.7 M in pentane) was also added (5 min). The resulting soln, which was generally yellow, was stirred for 1 hr at −78° to complete the formation of the dilithium reagent.

Hydroxyamide **11a**. The desired dianion was prepared from **10a** (1.00 mmol) in THF at −78° according to general procedure A. The yellow soln was allowed to warm slowly (20 min) to −10°. After an additional 10 min, the soln was treated with 2-chlorocyclohexanone (1.2 mmol) over 10 min. The resulting colorless soln was stirred for 30 min at −10° and 30 min at ambient temp before it was poured into sat NH_4Cl aq and diluted with ether. After the phases were separated, the aqueous phase was extracted with ether, and the combined organic phases were dried (K_2CO_3). The solvent was then removed. When 25% ether–hexanes was added to the crude material, **11a** (240 mg) precipitated. The remainder of the crude material was chromatographed (dry column, 33% ether–hexanes), resulting in the isolation of **11a** (19 mg, $R_f = 0.64$, 50% ether–hexanes). The hydroxyamide **11a** (92% yield) was recrystallized from hexanes as white needles (m.p. 115.5–116.5 (d)). Because these white needles tended to occlude hexanes, good analytical data had to be obtained from material which had been dissolved in $CHCl_3$ and then had the $CHCl_3$ removed *in vacuo*. The known[28] amide **8** (m.p. 131.5–133°, $CHCl_3$–hexanes) was obtained in 7% yield.

Hydroxyamide **11a**. NMR ($CDCl_3$): 8.30–8.05 (m, 1H), 7.50–7.00 (m, 3H), 4.55–4.30 (m, 1H), 2.65–0.75 (m, 9H), 1.40 (s, 9H). ^{13}C-NMR ($CDCl_3$): 176.78 (s), 144.36 (s), 134.09 (s), 129.61 (s), 124.17 (s), 121.71 (s), 121.06 (s), 78.00 (s), 69.02 (d), 40.70 (s), 31.55 (t), 31.17 (t), 28.31 (s), 22.97 (t), 22.67 (t). IR (KBr): 3350, 2900, 2850, 1620, 1585, 1470, 1450, 1400, 1375, 1280, 1190, 1090, 1060, 925, 765, 744. Mass spectrum: 273 (5), 225 (25), 171 (18), 170 (45), 142 (54), 57 (100). UV (95% EtOH): 252 (4.1), 208 (4.3). Exact mass: Calc. for $C_{17}H_{23}NO_2$: 273.17286; Found: 273.17290. (Found: C-74.56, H-8.30, N-4.99. Calc. for $C_{17}H_{23}NO_2$: C-74.69, H-8.48, N-5.12%.)

Amide **8**. NMR ($CDCl_3$): 7.60–6.90 (m, 6H), 1.31 (s, 9H). IR ($CDCl_3$): 3450, 2900, 1675, 1600, 1510, 1430, 1305, 1220, 1155. Mass spectrum: 187 (14), 93 (40), 57 (100), 41 (28), 39 (15). M.p.: 131.5–133.0° (reported[28]: 132–133°).

Hydroxyurethane **11b**. General procedure A was used for the preparation of the dilithium reagent from **10b** (1.0 mmol). The yellow soln turned orange when it was warmed from −78 to −10° in 15 min. 2-Chlorocyclohexanone (1.2 mmol) was added over 10 min at −10°. The resulting soln was stirred at −10° for 30 min and at ambient temp for 30 min. The work-up was the same as that given for **11a**. Flash column chromatography 25 mm column, 25% ether–hexanes) of the crude material provided the desired **11b** ($R_f = 0.16$, 193 mg, 67% yield), as a colorless viscous oil. NMR ($CDCl_3$): 7.76 (bd, 1H, J = 8), 7.40–6.85 (m, 3H), 4.20–3.95 (m, 1H), 2.60–2.20 (m, 3H), 1.85–0.75 (m, 6H), 1.55 (s, 9H). IR (film): 3350, 2900, 1695, 1600, 1470, 1380, 1170, 1145, 755, 735. Mass spectrum: 289 (2), 271 (18), 215 (86), 171 (37), 170 (23), 143 (63), 57 (100), 41 (38). UV (95% EtOH): 234 (4.1), 205 (4.3). Exact mass: Calc. for $C_{17}H_{23}NO_3$: 289.16778; Found: 289.16744.

Urethane **13b**. NMR ($CDCl_3$): 7.30–6.80 (m, 5H), 6.55 (bs, NH), 1.50 (s, 9H). IR (CCl_4): 3400, 2950, 1730, 1600, 1510, 1430, 1355, 1300, 1215, 1155. Mass spectrum (60 eV): 193 (4), 137 (28), 93 (63), 57 (100), 41 (75), 39 (37). M.p.: 135–136° (reported:[29] 137°).

Hydroxyamide **11c** *and tetrahydrocarbazole* **7**. The dilithium reagent required for this procedure was prepared from **10c** (1.0 mmol) using general procedure A. The light yellow soln was allowed to warm to −10° over 15 min. 2-Chlorocyclohexanone (1.2 mmol) was then added to the soln over 15 min. After stirring for 30 min at −10°, the soln was allowed to warm to ambient temp and to stir for 2 hr. The same workup that was used for **11a** was employed. Over several days the desired product **11c** (106 mg) crystallized from soln (10% $CHCl_3$–hexanes). The remainder of the crude material was chromatographed (20 mm flash column, CH_2Cl_2 then 50% ether–hexanes). An additional amount (59 mg) of **11c** was obtained along with **7** (30 mg, 18% yield) and amide **13c** (20 mg, 15% yield). The total yield of **11c** was 58%, and it was recrystallized from hexanes as a white solid (m.p. 149.5–151.5°(d)).

Hydroxyamide **11c**. NMR ($CDCl_3$): 8.13 (bd, 1H, J = 8), 7.50–7.10 (m, 3H), 4.55–4.25 (m, 1H), 2.15 (s, OH), 2.70–0.75 (m, 8H). IR (mull): 3400, 2900, 1675, 1600, 1260, 1230, 1200, 1160, 1130, 1080, 955, 775, 732, 712. Mass spectrum: 286 (16), 285 (100), 267 (24), 242 (96), 239 (16), 229 (17), 170 (13), 142 (15), 132 (31), 77 (23), 69 (24). UV (95% EtOH): 208 (4.4). Exact mass: Calc. for $C_{14}H_{14}F_3NO_2$: 285.09765; Found: 285.09750.

Amide **13c**. NMR ($CDCl_3$): 8.00 (bs, NH), 7.60–7.10 (m, 5H). IR ($CDCl_3$): 3400, 1730, 1600, 1540, 1490, 1440, 1280, 1240, 1145. Mass spectrum (60 eV): 189 (100), 120 (57), 91 (44), 77 (80), 65 (32). M.p.: 87.0–88.0°.

Tetrahydrocarbazole **7**. Spectral data were the same as that listed in the following experiment.

Tetrahydrocarbazole **7**. t-BuOK (266 mg, 2.7 mmol) was dissolved in THF (5 mL), and the resulting soln was cooled to 0° and stirred rapidly as water (12 μL, 0.67 mmol) was added via syringe. The **11a** was added to the suspension in three portions over 5 min. The mixture was allowed to warm to ambient temp and to stir for 10 min before it was poured into 5% HCl and extracted with CH_2Cl_2. The combined organic phases were washed with sat $NaHCO_3$ aq and dried (Na_2SO_4). Removal of the solvent provided **7** (39.4 mg, 93% yield). The spectral data obtained for **7** were identical with

that obtained for **7** prepared by a known route.[31] NMR ($CDCl_3$): 7.75–7.25 (m, 2H), 7.25–6.90 (m, 3H), 2.70 (m, 4H), 1.88 (m, 4H). IR (CCl_4): 3450, 3350, 3030, 2920, 2840, 1460, 1315, 1295, 1225. Mass spectrum: 171 (52), 170 (20), 144 (13), 143 (100). M.p.: 115–116° (MeOH) (reported:[31] m.p. 117–118°).

Amide **12a**. Hydroxyamide **11a** (57.0 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (1 mL) and treated with trifluoroacetic acid (5 mg). After the soln had stirred at ambient temp for 15 min, sat $NaHCO_3$ aq was added. The resulting mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and the solvent was removed *in vacuo*. Amide **12a** was obtained as a colorless, viscous oil (49.8 mg, 94% yield). NMR ($CDCl_3$): 7.50–7.25 (m, 2H), 7.25–7.00 (m, 2H), 2.69 (m, 4H), 1.86 (m, 4H), 1.42 (s, 9H). IR (film): 2900, 1695, 1445, 1295, 1280, 1175, 1160, 1080, 740. Mass spectrum (60 eV): 255 (24), 171 (31), 170 (11), 143 (58), 57 (100), 41 (24). UV (95% EtOH): 302 (3.5), 263 (4.0), 219 (4.3), 208 (4.4). Exact mass: Calc. for $C_{17}H_{21}NO$. 255.16230; Found: 255.16219. (Found: C, 80.06; H, 8.32; N, 5.66. Calc. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.50%.)

Tetrahydrocarbazole **7** *from* **10a**. General procedure A was used for the preparation of the desired dilithium reagent from **10a** (1.0 mmol). The yellow soln was allowed to warm slowly (20 min) to −15° and was treated with 2-chlorocyclohexanone (1.2 mmol) over 5 min. After the resulting soln had stirred for 30 min at −15° and 30 min at ambient temp, it was cooled to 0°. t-BuOK (5.0 mmol) and water (3.0 mmol) were then added sequentially over 5 min, and the resulting suspension was stirred for 4 hr at ambient temp. The reaction was then poured into 5% HCl and extracted with CH_2Cl_2. The combined organic phases were washed with sat $NaHCO_3$aq and dried (Na_2SO_4). Column chromatography (10 mm flash column, 25% CH_2Cl_2–hexanes) provided pure **7** (132 mg, 77% yield). Spectral data were the same as that provided above.

Tetrahydrocarbazole **7** *from* **10c**. The required dianion was produced from **10c** (1.0 mmol) by general procedure A. To the soln of the dilithium reagent, which was allowed to warm from −78 to −30° over 10 min, was added 2-chlorocyclohexanone (1.2 mmol) over 5 min at −30°. The yellow soln was allowed to warm to ambient temp and stir for 1 hr. Then 10% KOH in MeOH (0.5 mL) was added in one portion, and the suspension was stirred for 10 min before it was poured into 5% HCl. Extraction of the resulting mixture with CH_2Cl_2 was followed by drying (Na_2SO_4) and removal of the solvent. The crude material was triturated with cold hexanes, and the remaining solid was then dissolved in hot hexanes and filtered. Concentration of the filtrate provided **7** (128 mg, 75% yield). Spectral data for **7** were provided in a previous experiment.

Tetrahydrocarbazole **7** *from 2-bromoaniline*. To a soln of 2-bromoaniline (172 mg, 1.0 mmol) in THF (20 mL) at ambient temp was added MeLi (2.0 mmol of 1.40 M in ether). After stirring for 15 min at ambient temp, the soln was cooled to −78° and treated with pivaloyl chloride (123 μL, 1.0 mmol) in one portion. The mixture was then stirred at −78° for 15 min and at ambient temp for 30 min before it was cooled again to −78°. t-BuLi (2.0 mmol of 1.7 M in pentane) was then added, and the soln was stirred for 1 hr at −78°. After warming (20 min) to −10°, the soln was treated with 2-chlorocyclohexanone (1.2 mmol) over 5 min. The soln was then stirred for 30 min at −10° and 30 min at ambient temp. The soln was cooled to 0° and treated with t-BuOK (785 mg, 7 mmol) and water (54 μL, 3 mmol) over 5 min. When the mixture had stirred 3 hr at ambient temp, it was poured into 5% HCl and extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), and the solvent was removed. Column filtration (10 mm flash column, 25% CH_2Cl_2–hexanes) provided pure **7** (126 mg, 74% yield). Spectral data for **7** have been listed previously.

Aminoalcohol **14**. The dilithium reagent needed for this experiment was prepared from **10c** (1.0 mmol) by general procedure A. The yellow soln was allowed to warm from −78 to −30° over 10 min, and 2-chlorocyclopentanone (142 mg, 1.2 mmol) was added over 2 min at −30°. After the soln had warmed to ambient temp and stirred for 2 hr, 10% KOH in MeOH (2 mL) was added, and stirring was continued for 20 min. The crude mixture was poured into 5% HCl and extracted with CH_2Cl_2. Only amide **13c** (45 mg, 24% yield) and a trace of unidentified material were found in the organic extracts. The aqueous layer was basified (15% NaOH) and extracted again with CH_2Cl_2. Drying (Na_2SO_4) of these organic extracts and removal of the solvent provided pure **14** (117 mg, 67% yield). Recrystallization of **14** from ether–hexanes provided white needles (m.p. 130–133° (d)). NMR ($CDCl_3$): 7.30–6.95 (m, 2H), 6.85–6.50 (m, 2H), 3.97 (bd, 1H, J = 6), 3.70 (very broad signal, 2H, NH and OH), 2.60–1.20 (m, 6H). IR ($CDCl_3$): 3600, 3450, 2950, 1615, 1480, 1460, 790. Mass spectrum: 175 (47), 157 (14), 156 (14), 147 (13), 146 (100). A metastable scan indicated that the primary fragmentation of the molecular ion was loss of 29 to *m/e* 146. A high resolution scan showed the following:

$$\begin{aligned} m^+ - 175.1010 &- C_{11}H_{13}NO \\ 157.0883 &- C_{11}H_{11}N\ (-H_2O) \\ 156.0814 &- C_{11}H_{10}N\ (-H_3O) \\ 147.0636 &- C_9H_9NO\ (-C_2H_4) \\ 146.0604 &- C_9H_9NO\ (-C_2H_5). \end{aligned}$$

UV (95% EtOH): 300 (3.4), 244.5 (3.9), 205 (4.4). Exact mass: Calc for $C_{11}H_{13}NO$: 175.09971; Found: 175.09972. (Found: C, 75.27; H, 7.43, N, 7.96. Calc for $C_{11}H_{13}NO$: C, 75.37; H, 7.48; N, 8.02.)

Indole **15**. To a soln of **14** (20.0 mg) in CH_2Cl_2 (40 mL) was added trifluoroacetic acid (20 drops from a Pasteur pipette) in one portion. The soln was stirred for 1.75 hr after which the TLC (50% hexanes–ether) showed a clean conversion to a higher R_f product. The soln was added to sat. $NaHCO_3$aq (5 mL) and extracted with CH_2Cl_2. Drying (Na_2SO_4) and solvent removal provided the desired indole **15** which was contaminated with a trace of water and stopcock grease. Sublimation (50–80°, 0.005 mm) provided pure **15** (18.0 mg) as a white solid in quantitative yield. NMR ($CDCl_3$): 7.65 (bs, NH), 7.50–6.95 (m, 4H), 3.00–2.25 (m, 6H). IR ($CDCl_3$): 3475, 2930, 1460, 1310. Mass spectrum (60 eV): 158 (13), 157 (100), 156 (99), 154 (14), 130 (26), 129 (13), 128 (18). M.p.: 101.5–103.5° (lit. m.p. 103–105°).[32]

Amide **16b**. To a soln of 2-bromo-5-methoxyaniline (0.435 g, 2.15 mmol) in ether (5 mL) was added solid Na_2CO_3 (0.5 g). When the mixture had been cooled to 0°, trifluoroacetic anhydride (0.630 g, 3.0 mmol) was added over 5 min, and the suspension was stirred for 24 hr at ambient temp. The mixture was partitioned between CH_2Cl_2 and water, the layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), and the solvent was removed, leaving **16b** (0.63 g, 98% yield). Analytical samples were prepared by low temp recrystallization from hexanes (m.p. 65–66° (vac) (d)). NMR ($CDCl_3$): 8.35 (bs, NH), 7.88 (d, 1H, J = 2.9), 7.39 (d, 1H, J = 8.9), 6.63 (dd, 1H, J = 2.9, 8.9), 3.78 (s, 3H). IR (CCl_4): 3350, 1740, 1600, 1530, 1460, 1175. Mass spectrum: 299 (16), 297 (16), 219 (23), 218 (100), 198 (20). UV (EtOH): 283 (3.3), 212 (4.5). Exact mass: Calc for $C_9H_7Br^{79}F_3NO_2$: 296.96127; Found: 296.96106.

Indole **19**. Indole **19** was prepared from **16b** by the same procedure as was used in the desmethoxy case for the production of **7**, with the exception that this reaction was done on one-half the scale. The crude material (153 mg) obtained from this reaction was purified by chromatography (10 mm flash column, 50% hexanes–CH_2Cl_2). Indole **19** (69.5 mg, 69% yield, R_f = 0.36) and **16a** (24.3 mg, 11% yield, R_f = 0.22) were obtained as white solids and were recrystallized from hexanes.

Indole **19**. NMR ($CDCl_3$): 7.45 (bs, NH), 7.28 (bd, 1H, J = 8), 6.78 (bs, 1H), 6.70 (dd, 1H, J = 2, 8), 3.82 (s, 3H), 2.67 (m, 4H), 1.86 (m, 4H). IR (CCl_4): 3450, 3350, 2900, 1625, 1455, 1280, 1205, 1155, 1035. Mass spectrum: 202 (15), 201 (100), 200 (23), 186 (62), 173 (92), 130 (30). M.p.: 145.5 147° (vac). (lit. 143–144°).[32]

Amide **16a**. NMR ($CDCl_3$): 7.80 (bs, NH), 7.30–6.15 (m, 4H), 3.80 (s, 3H). IR ($CDCl_3$): 3350, 1725, 1610, 1540, 1485, 1280, 1160, 1050. Mass spectrum (60 eV): 219 (100), 150 (25), 107 (27), 77 (21). M.p.: 72.4–74.0° (lit. 71–72°).[33]

Skatole **20**. The required dilithium reagent was produced from **10c** (1.0 mmol) by general procedure A. To the soln of the dianion at −78° was added chloroacetone (1.2 mmol, 96 μL) over 5 min. After stirring for 15 min at −78°, the reaction was treated with AcOH (3.0 mmol) in one portion. To the resulting suspension was added Et_3N (0.66 mL, 5.0 mmol) after 15 min. When the mixture had warmed to ambient temp (15 min), it was stirred for an additional 3 hr. Then 10% KOH in 10% MeOH (2 mL) was added in one portion, and stirring was continued for 10 min. The thick suspension was poured into 5% HCl and extracted with CH_2Cl_2. After the extracts had been dried (Na_2SO_4) and concentrated *in vacuo*, the remaining crude material was chromatographed (10 mm flash column, 25% CH_2Cl_2–hexanes). Skatole (**20**, 68.1 mg, 52% yield) and amide **13c** (85.6 mg, 45% yield) were obtained as white crystalline solids.

Spectral data for amide **13c** has been given in a previous experiment. Skatole obtained from Eastman Kodak gave spectral data identical with that obtained for the compound produced here. NMR ($CDCl_3$): 7.60–7.45 (m, 1H), 7.35–7.00 (m, 3H), 6.94 (q, 1H, J = 1), 2.33 (d, 3H, J = 1). IR (CCl_4): 3450, 3030, 2900, 1445, 1325, 1245, 1070, 1010. Mass spectrum (66 eV): 131 (62), 130 (100), 77 (21). M.p.: 94–95° (vac) (hexanes) (lit. 95°).[33]

Indole **1**. General procedure A was used for the preparation of the required dilithium reagent from **10c** (1.0 mmol). Chloroacetaldehyde was prepared immediately before use by the pyrolysis of chloroethylene carbonate.[34] To a soln of the dilithium reagent **9c** was added chloroacetaldehyde (94.2 mg, 1.2 mmol) at −78° over 5 min. After 20 min, the soln was treated with glacial AcOH (0.18 mL, 3.0 mmol). 10 min later, Et_3N (0.60 mL, 5.0 mmol) was added in one portion. The resulting suspension was allowed to warm to ambient temp, stirred for 2 hr, and quenched with NH_4Claq. The mixture was extracted with CH_2Cl_2 and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (10 mm flash column, CH_2Cl_2, then 50% ether–hexanes) provided **13c** (66 mg, 35%) and an alcohol intermediate (203 mg, 65%). To a soln of this intermediate (203 mg) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (2 mL). After 10 min, the soln was poured into sat$NaHCO_3$aq and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. To a soln of this crude material in THF (10 mL) was added 10% KOH in MeOH (1 mL). After 2 min, the soln was poured into water and extracted with CH_2Cl_2. The material obtained after drying (Na_2SO_4) and removal of the solvent was filtered through silica gel (1 g) with CH_2Cl_2 as solvent to provide **1**, (m.p. 50–51° (lit. 52°)[33] 70.2 mg, 60% yield overall) as a white solid. The spectral data obtained were identical to that obtained from indole purchased from Fisher Scientific.

Ester **22**. The dilithium reagent, which was prepared by general procedure A from **10c** (1.0 mmol), was added (2 min) via a short cannula to a vigorously stirred soln of **21**[35] (1.5 mmol) in THF (10 mL) at −78°. The mixture was then quenched after 15 min by adding the soln (−78°) to sat NH_4Claq. Extraction with CH_2Cl_2 was followed by drying (Na_2SO_4) and concentration of the extracts. The crude material obtained was chromatographed (25 mm flash column, 50% ether–hexanes). Ester **22** (231 mg, $R_f = 0.31$) was obtained as a white solid in 77% yield and was recrystallized from CH_2Cl_2–hexanes (m.p. 83.5–84.5°). NMR ($CDCl_3$): 9.91 (bs, NH), 8.14 (bd, 1H, J = 7.5), 7.45–7.10 (m, 3H), 6.99 (dd, 1H, J = 4.1, 15.7), 6.11 (dd, 1H, J = 1.9, 15.7), 5.49 (m, 1H, J = 3.8, 4.1, 1.9), 3.71 (s, 3H), 3.11 (d, OH, J = 3.8). IR ($CDCl_3$): 3600, 3400, 1725, 1275, 1195, 1160. Mass spectrum (60 eV): 303 (13), 285 (28), 271 (61), 226 (100), 216 (73), 174 (35), 156 (33), 149 (33), 130 (25), 129 (25), 128 (36), 87 (56), 77 (34), 55 (50). UV (95% EtOH): 245 (4.0), 208 (4.4). (Found: C, 51.35; H, 3.93; N, 4.52; F, 18.69. Calc for $C_{13}H_{12}F_3NO_4$: C, 51.48; H, 3.99; N, 4.64; F, 18.79%.)

Indole **23**. To a suspension of anhyd K_2CO_3 (180 mg) in anhyd MeOH (6 mL) was added ester **22** (51.9 mg). After the reaction had stirred for 1.5 hr it was poured into water and extracted with CH_2Cl_2. The organic phases were dried and concentrated to 6 mL. To this soln was added trifluoroacetic acid (2 drops from a Pasteur pipette). After 1 hr, the soln was poured into sat $NaHCO_3$aq and re-extracted with CH_2Cl_2. Drying (Na_2SO_4) and concentration of the extracts provided the crude material which was subsequently chromatographed (10 mm flash column, 50% ether–hexanes). The results was an 87% yield of **23** (m.p. 72–73° (lit. 71–73°),[36] 28.1 mg, $R_f = 0.4$). Indole **23** was recrystallized from hexanes as white plates. NMR ($CDCl_3$): 8.55 (bs, NH), 7.60–6.90 (m, 4H), 6.34 (m, 1H), 3.81 (bs, 2H), 3.74 (s, 3H), (lit.−8.52 (NH), 7.72–6.89 (m, 4H), 6.28 (m, 1H), 3.81 (s, 2H), 3.70 (s, 3H)).[36] IR ($CDCl_3$): 3450, 1735, 1450, 1430, 1280, 790 (lit. 3405, 1735).[36] Mass spectrum (60 eV): 189 (36), 130 (100), 129 (13), 77 (11).

Enone **25**. The enolate of cyclohexenone epoxide was prepared by the addition (5 min) of cyclohexenone epoxide (112 mg, 1.0 mmol) in THF (1 mL) to a soln of lithium diisopropylamide (prepared from diisopropylamine (1.30 mmol) and n-BuLi (1.25 mmol)) in THF at −78°. After stirring for 20 min at −78°, the soln was treated with n-BuLi (1.1 mmol, 2.4 M) in hexanes to deprotonate the diisopropylamine again. A soln of the dilithium reagent **9c** (prepared from **10c** (1.5 mmol) by general procedure A) was added after 5 min to the enolate via a short cannula at −78°. When the addition had been completed (10 min), the resulting soln was allowed to warm to −23° and stirred at that temp for 2.5 hr. The red soln was poured into sat NH_4Claq and extracted with CH_2Cl_2. Drying (Na_2SO_4) and solvent removal provided the crude hydroxyketone, which was subsequently dissolved in EtOH (5 mL). When 3 M HCl was added to the EtOH soln, the reaction became very dark, but TLC showed no change. The mixture was heated to 70° for 40 min, cooled to ambient temp, and poured into 5% HCl. Extraction with CH_2Cl_2 followed by drying (Na_2SO_4) and concentration of the extracts provided the crude material which was then chromatographed (20 mm dry column, 25% ether–hexanes). The reasonably pure **25** (193 mg, $R_f = 0.37$, 50% ether–hexanes) was rechromatographed (20 mm dry column, CH_2Cl_2) to afford pure **25** (166 mg, 59% yield) as a pale yellow viscous oil. NMR ($CDCl_3$): 8.95 (bs, NH), 7.75–7.00 (m, 5H), 2.75–2.45 (m, 4H), 2.30–2.00 (m, 2H). IR (film): 3250, 1735, 1665, 1525, 1155, 914, 761. Mass spectrum (60 eV): 283 (78), 255 (100), 240 (28), 186 (13), 158 (40), 130 (73), 128 (22), 115 (22), 77 (30), 55 (37). UV (95% EtOH): 207 (4.4). Exact mass: Calc for $C_{14}H_{12}F_3NO_2$: 283.08200; Found: 283.08194.

Indole **26**. To a soln of **25** (60.0 mg) in MeOH (1 mL) was added 0.1 N NaOH (2 mL) at ambient temp. After 1 hr, THF (1 mL) was added to the mixture to aid solubility. When the soln had stirred a total of 12 hr at ambient temp, it was poured into water and extracted with CH_2Cl_2. The organic phases were dried, and the solvent was removed. The crude material obtained (37.5 mg) was mostly the desired indole **26**. Chromatography (10 mm flash column, 25% ether–hexanes) provided pure **26** (m.p. 220–222° (lit. 219–221°),[37] 24.3 mg, 61% yield) as a white solid. The NMR's of **26** prepared by this procedure and by a known route[37] were identical.

Chloroketone **28**. Ketone **27** (5.07 g, 29.6 mmol) in THF (30 mL) was added to a −78° soln of lithium diisopropylamide (38.5 mmol) in THF (35 mL). After 15 min,

chlorotrimethylsilane (4.35 g, 40.0 mmol) was added (2 min) to the soln of the enolate of **27**. When the soln had warmed to 0° (30 min), it was poured into a mixture of sat $NaHCO_3$aq and CH_2Cl_2. The layers were separated, and the aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Distillation provided the enol ether (6.4 g, 89% yield, b.p. 77–78° at 0.06 mm). A soln of the enol ether (2.49 g, 10.2 mmol) in acetone (15 mL) was then added (5 min) to a −5° mixture of N-chlorosuccinimide (1.47 g, 10.7 mmol) and NaOAc (1.5 g) in water (10 mL) and acetone (40 mL). After the mixture had stirred for 1 hr at 0°, more N-chlorosuccinimide (1.5 g) was added, and the mixture was stirred for an additional hr. A 20% $NaHSO_3$aq (20 mL) was then added along with satNaClaq (50 mL) and the mixture was extracted with CH_2Cl_2. The organic extracts were concentrated, dissolved in CH_2Cl_2, and washed with sat $NaHCO_3$aq. The crude material from these extracts was distilled to provide **28** (1.68 g, 80% yield, b.p. 97–98° at 0.012 mm), which was greater than 95% pure.

Enol ether. NMR ($CDCl_3$): 4.79 (m, 1H), 4.14 (q, 2H, J = 6), 3.91 (dd, 2H, J = 6, 2); 3.57 (t, 2H, J = 6), 2.12 (m, 2H), 1.26 (t, 3H, J = 7), 0.19 (s, 9H). IR (neat): 2950, 1705, 1675, 1200, 895, 845.

Chloroketone **28** (95% purity): NMR ($CDCl_3$): 4.50–3.40 (m, 7H), 3.00–2.25 (m, 2H), 1.30 (t, 3H, J = 7). IR ($CDCl_3$): 2950, 1730, 1698, 1425, 1230, 1110. Mass spectrum: 207 (13), 205 (36), 170 (20), 163 (26), 128 (28), 98 (69), 57 (19), 56 (61), 55 (33), 42 (100).

Indole **30**. The required dilithium reagent **9c** was prepared as described in general procedure A from **10c** (1.0 mmol). To this yellow soln of **9c** was added (5 min) **28** (1.2 mmol) in THF (6 mL) at −60°. After the mixture had stirred 1 hr at −60°, it was poured into sat NH_4Claq and extracted with CH_2Cl_2. Chromatography of the crude material (50 mm flash column, 50% ether–hexanes) provided **29** (243 mg, 58% yield) as well as **13** (66 mg, 35% yield). Spectral data obtained for the intermediate **29** were consistent with the proposed structure (IR showed no ketone CO absorption, MS showed $M^+ - 396.08776$; Calc -396.08769). All of **29** obtained was dissolved in DMF (20 mL) and Et_3N (1 mL). The resulting soln was heated to 90° for 1 hr. After the soln had cooled, it was diluted with water (100 mL) and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. The crude material from these extracts was dissolved in THF (2 mL) and 10% KOH in MeOH (1 mL) was added. After 5 min, this soln was poured into 5% HCl and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated. Chromatography of the crude material (10 mm flash column, 33% hexanes–ether) afforded **30** (118 mg, 48% yield overall, $R_f = 0.45$) as a white crystalline solid (m.p. 146–147.5° (hexanes–CH_2Cl_2)).

Indole **30**. NMR ($CDCl_3$): 7.90 (bs, NH), 7.50–6.95 (m, 4H), 4.66 (t, 2H, J = 1.5), 4.22 (q, 2H, J = 7), 3.81 (t, 2H, J = 5.7), 2.79 (tt, 2H, J = 1.5, 5.7), 1.30 (t, 3H, J = 7). IR (CCl_4): 3300, 1680, 1420, 1225, 1105. Mass spectrum (60 eV): 244 (38), 215 (79), 171 (21), 144 (21), 143 (100), 115 (21). UV (95% EtOH): 289 (3.8), 277 (3.9), 223 (4.6), 200 (4.3). Exact mass: Calc for $C_{14}H_{16}O_2$: 244.12117; Found: 244.12125.

Indole **31**. To a soln of **30** (18 mg, 0.074 mmol), in THF (2 mL) was added MeLi (0.3 mmol, 0.5 mL of 1.45 M in ether). When the resulting soln had stirred for 1 hr at room temp, it was poured into 5% HCl. This mixture was extracted with ether and the organic phases were discarded. The aqueous layer was then made basic and extracted with ether. These extracts were dried (Na_2SO_4) and concentrated. Sublimation of the crude material (0.005 mm, 50–80°) provided pure **31** (m.p. 204–205° (lit. m.p. 204–208°)[38] 9.8 mg, 77% yield). NMR ($CDCl_3$): 7.80 (bs, NH), 7.55–6.85 (m, 4H), 4.02 (bs, 2H), 3.20 (t, 2H, J = 6), 2.76 (bt, 2H). IR (mull): 3300–2400, 1450, 1305, 1240, 1160, 1140, 1100, 1010, 950, 890, 740. Mass spectrum: 173 (6), 172 (34), 171 (11), 170 (7), 169 (11), 168 (6), 144 (21), 143 (100), 105 (15).

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