13 complexed with SO_3; bp ca 80 °C (50 mm). Redistillation at atmospheric pressure gave 13 mixed with the acylketene 14, bp 140–147 °C. For 13: IR 1754 (C=O), 1681 cm^{-1} (C=C); ^{19}F NMR −73.06 (p, 6, J = 3.8 Hz), −75.26 (d, 6, J = 10.0 Hz), −53.08 (d, 1, J = 44.0 Hz, to d, J = 22.0 Hz, to s, J = 3.8 Hz), −55.54 (d, 1, J = 44.0 Hz, to m), −159.26 (m, 1), −181.11 ppm (d, 1, J = 22.0 Hz, to m); mass spectrum, calcd m/e 459.9414, found m/e 459.9452.

Anal. Calcd for $C_9F_{16}SO$: C, 23.49; F, 66.06; S, 6.97. Found: C, 23.70; F, 64.90; S, 7.42.

2-[[1-(Trifluoromethyl)-1,2,2,2-tetrafluoroethyl]thio]-4-(trifluoromethyl)-4,5,5,5-tetrafluoro-1-pentene-1,3-dione (14). From 12. Sulfur trioxide (20 mL) was stirred while 57.9 g of material which was largely compound 12 was added dropwise. The exothermic reaction was kept at about 50 °C by the rate of addition and cooling. When the addition was complete, the mixture separated into two layers. Distillation of the bottom layer gave 35 g (65%) of the acylketene 14. Some codistilled SO_3 was removed by washing with a little dioxane, separating, and distilling: bp 70 °C (40 mm); $n^{25}D$ 1.3472; IR 2179 (C=C=O), 1724 cm^{-1} (C=O); ^{19}F NMR −74.64 (d, 6, J = 6.6 Hz), −75.10 (d, 6, J = 10.0 Hz), −162.0 (s, 1, J = 10.0 Hz), −180.8 ppm (s, 1, J = 6.6 Hz); mass spectrum, calcd m/e 437.9395, found m/e 437.9430.

Anal. Calcd for $C_9F_{14}SO_2$: C, 24.67; F, 60.71; S, 7.32. Found: C, 24.63; F, 60.60; S, 7.77.

From 10. The ether ester 10 (60 g) was added dropwise with stirring to 14 mL of SO_3, and the exothermic reaction was kept below 65 °C. The bottom layer (60 g) was separated from the top layer (26 g) and distilled to give 51 g (94%) of 14.

From 11. The ketal ester 11 (100 g) was added dropwise with stirring to 40 mL of SO_3 with the exothermic reaction kept below 75 °C. The bottom layer (89 g) was separated from the top layer (75 g) and distilled to give 71.7 g (85%) of 14.

The yields, boiling points and/or melting points for compounds prepared in this work are listed in Table I. Details concerning their preparation and characterization, including infrared, NMR, and analytical data, are available as supplementary material.

Registry No. 4, 791-50-4; 7a, 75781-86-1; 7b, 75781-87-2; 8, 756-89-8; 9 (isomer 1), 75781-88-3; 9 (isomer 2), 75782-19-3; 10 (isomer 1), 75781-89-4; 10 (isomer 2), 75782-20-6; 11, 75781-90-7; 12, 75781-91-8; 13, 75781-92-9; 14, 75790-42-0; 16, 75781-93-0; 17, 75781-94-1; 18, 75781-95-2; 19, 75781-96-3; 20, 75781-97-4; 21, 75781-98-5; 22, 75781-99-6; 23, 75782-00-2; 24, 75782-01-3; 25, 75782-02-4; 26, 75782-03-5; 27, 75782-04-6; 28, 75782-05-7; 29, 75782-06-8; 30, 75782-07-9; 31, 75782-08-0; 32, 75782-09-1; 33, 75782-10-4; 34, 75782-11-5; 35, 75782-12-6; 36, 75782-13-7; 37, 75782-14-8; 38, 75782-15-9; 40, 75782-16-0; 43, 75782-17-1; 44, 75782-18-2; 45, 75790-43-1; isobutylene, 115-11-7; styrene, 100-42-5; vinyl acetate, 108-05-4; phenylacetylene, 536-74-3; butylacetylene, 693-02-7; propionaldehyde, 123-38-6; benzaldehyde, 100-52-7; acetone, 67-64-1; dimethylcyanamide, 1467-79-4; benzonitrile, 100-47-0; methyl isocyanate, 624-83-9; phenyl isocyanate, 103-71-9; methyl thiocyanate, 556-61-6; furan, 110-00-9; thiophene, 110-02-1; benzamide, 55-21-0; ketene, 463-51-4; dimethylformamide, 68-12-2; dimethylacetamide, 127-19-5; dimethylpropionamide, 758-96-3; tetramethylurea, 632-22-4; dimethylaniline, 121-69-7; tetraethylurea, 1187-03-7; hydrazoic acid, 7782-79-8; *N,N*-dimethyl-4,4,5,5,5-pentafluoro-2-(trifluoromethyl)-3-oxopentamide, 75782-21-7.

Supplementary Material Available: Details concerning properties and characterization (IR, NMR, analyses) of compounds reported in this work (21 pages). Ordering information is given on any current masthead page.

Synthesis and Reactions of N-Protected 2-Lithiated Pyrroles and Indoles. The *tert*-Butoxycarbonyl Substituent as a Protecting Group

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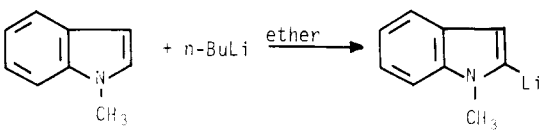
N-(*tert*-Butoxycarbonyl)pyrrole and *N*-(*tert*-butoxycarbonyl)indole have been prepared and lithiated at the 2-position with lithium 2,2,6,6-tetramethylpiperidide and *tert*-butyllithium, respectively. These lithium reagents react with a variety of electrophiles to give the 2-substituted *N*-(*tert*-butoxycarbonyl)pyrroles and *N*-(*tert*-butoxycarbonyl)indoles. The *N*-(*tert*-butoxycarbonyl) substituent may be removed rapidly and in high yield from the pyrrole derivatives under basic conditions. For the indole derivatives, the protecting group may be removed with either acidic or basic conditions.

The directed metalation of aromatic substrates[1] has provided an important synthetic alternative to electrophilic substitution reactions. The rapid expansion of the list of functionalities capable of directing metalations[2] has made this an important strategy for the synthesis of regiospecifically substituted benzenes[3] and heterocycles.[4] The utility of these lithiated derivatives is amply demonstrated by their use as intermediates for the preparation of complex natural products.[5]

Lithioindoles[6] and pyrroles[7] have been useful for the synthesis of regiospecifically substituted derivatives. For example, 2-lithio-*N*-methylindole[6] can be prepared by treatment of *N*-methylindole with *n*-butyllithium in ether (eq 1). Subsequent reaction with electrophiles leads to



(1)

(1) Gilman, H.; Morton, J. W., Jr. *Org. React.* **1954**, *8*, 258.
(2) (a) Gschwend, H. W.; Rodriquez, H. R. *Org. React.* **1980**, *26*, 1. (b) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653. (c) Abicht, H.-P.; Issleib, K. *Z. Chem.* **1977**, *17*, 1.
(3) See for example: (a) Forbes, I.; Pratt, R. A.; Raphael, R. A. *Tetrahedron Lett.* **1978**, 3965; (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4464; (c) Harris, T. D.; Roth, G. P. *Ibid.* **1979**, *44*, 2004.
(4) See for example: (a) Stout, D. M.; Takaya, T.; Meyers, A. I. *J. Org. Chem.* **1975**, *40*, 563; (b) Gjøs, N.; Gronowitz, S. *Acta Chem. Scand.* **1971**, *25*, 2596; (c) Butler, D. E.; Alexander, S. M. *J. Org. Chem.* **1972**, *37*, 215; (d) Florentin, D.; Roques, B. P.; Fournie-Zaluski, M. C. *Bull. Soc. Chim. Fr.* **1976**, 1999; (e) Slocum, D. W.; Grierer, P. L. *J. Org. Chem.* **1976**, *41*, 3668.
(5) (a) Taylor, D. A.; Joule, J. A. *J. Chem. Soc., Chem. Commun.* **1979**, 642. (b) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457.
(6) Shirley, D. A.; Roussel, P. A. *J. Am. Chem. Soc.* **1953**, *75*, 375.
(7) (a) Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887. (b) Gjøs, N.; Gronowitz, S. *Acta Chem. Scand.* **1971**, *25*, 2596. (c) Chadwick, D. J.; Cliff, I. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2845.

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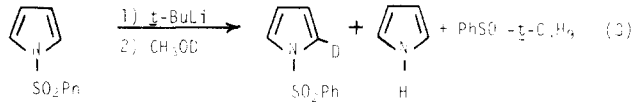
2-substituted indoles which are difficult to prepare by other means. In an analogous manner *N*-methylpyrrole can be lithiated under more vigorous conditions by using *tert*-butyllithium in THF or *n*-butyllithium/TMEDA[7] (eq 2).

(2)

The utility of this sequence for the synthesis of nitrogen heterocycles without *N*-alkyl substituents depends on the use of a nitrogen protecting group. We report on the use of the *tert*-butoxycarbonyl substituent as a protecting group for the pyrrole and indole N–H group and compare it to the previously reported use of the benzenesulfonyl group for indoles.[8]

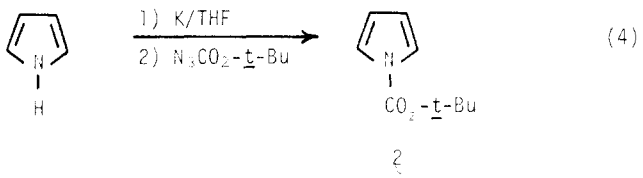
Results and Discussion

***N*-(*tert*-Butoxycarbonyl)pyrroles.** Two constraints are placed upon any proposed protecting group for the pyrryl N–H. First the protecting group must be stable to the strongly basic conditions used to generate the aryllithium, and, second, due to the instability of pyrroles to acid, it must be removable under neutral or basic conditions. Our initial investigation centered around the use of *N*-benzenesulfonylpyrrole (1).[9] Attempts to lithiate 1 with *tert*-butyllithium led to significant amounts of cleavage products (eq 3). In an attempt to overcome this



(3)

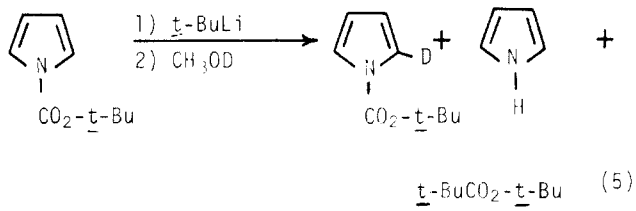
problem we prepared *N*-(*tert*-butoxycarbonyl)pyrrole (2) by the method of Carpino and Barr[10] (eq 4). Treatment



(4)

2

of 2 with *tert*-butyllithium and quenching with CH_3OD led to an unsatisfactory mixture of pyrrole, *tert*-butyl pivalate, and the desired deuterated pyrrole (eq 5). The



(5)

success of Beak[11] at using lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) led us to investigate these bases. To our satisfaction, cleavage could not be detected. Furthermore, under optimum conditions (LTMP/−80 °C) reasonable deuterium incorporation and high recoveries are obtained. Finally, reexamination of the reaction of 1 with LTMP gave only moderate deuterium incorporation. The results are summarized in Table I.

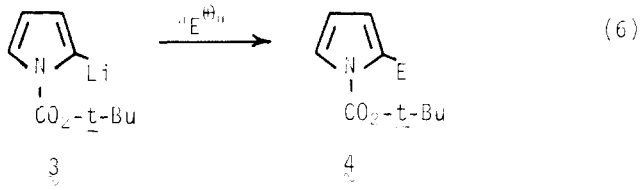
Table I. Lithiation of N-Substituted Pyrroles

entry	R for N-substituted pyrrole	base/temp, °C	reaction time, min	% D incorp	% recov
1	SO_2Ph	*t*-C_4H_9Li[c]/ −18 to room temp	20	100[a]	83[b,e]
2		*t*-C_4H_9Li[c]/ −80	90	80[a]	95[b,e]
3		LTMP[c]/−80	45	70[b]	96
4		LTMP[d]/−80	45	76[b]	90
5	CO_2-*t*-Bu	*t*-C_4H_9Li[c]/ −80	90	50[a]	69[f]
6		LDA[c]/−80	45	51[b]	91
7		LTMP[c]/−80	45	71[b]	93
8		LTMP[d]/−80	45	88[b]	92

[a] Analysis by ^1H NMR. [b] Analysis by mass spectrometry. [c] Quenched by addition of CH_3OD. [d] Inverse quench by addition of lithium reagent to excess CH_3OD. [e] There was 10–11% cleavage product by NMR. [f] There was 50% cleavage product by NMR.

It is clear from a comparison of the results with LTMP upon normal and inverse quenching that deuterium incorporation studies when amide bases are used may not accurately reflect the full extent of lithiation. We believe this is due to rapid proton exchange between the amine and CH_3OD upon quenching rather than to an equilibrium formation of the anion. This interpretation is supported by our quantitative trapping of 3 with trimethylsilyl chloride (vide infra). Furthermore, others have previously noted similar problems with amide bases.[2a]

We have briefly investigated the reaction of 3 generated from LTMP with various electrophiles (eq 6). The results are summarized in Table II.

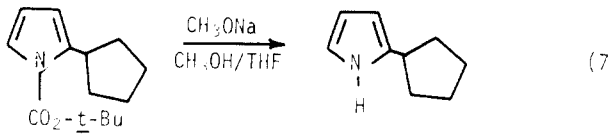


(6)

3 4

The results in Table II suggest 3 has similar reactivity to other lithium reagents. We note, however, that alkylations with simple alkyl halides are not synthetically useful. The problem appears to be a combination of low nucleophilicity, even in the presence of HMPA, and the thermal instability of 3 above ca. −45 °C.

Using 2-cyclopentyl-*N*-(*tert*-butoxycarbonyl)pyrrole[12] (5) as a model, we found that the addition of a solution of sodium methoxide in methanol to a THF solution of 5 removes the protecting group rapidly and in high yield (eq 7). Similar results were obtained for 4a,c,e. However,

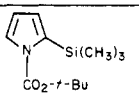
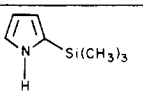
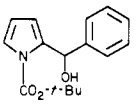
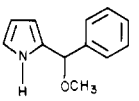
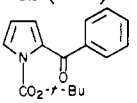
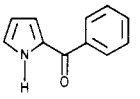
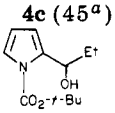
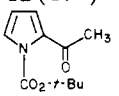
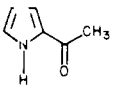


(7)

5 6

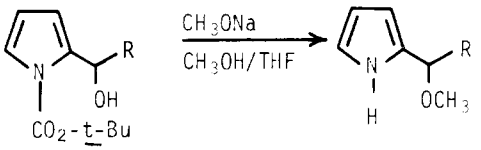
(8) (a) Sundberg, R. J.; Parton, R. L. *J. Org. Chem.* **1976**, *41*, 163. (b) Sundberg, R. J.; Russell, R. J. *Ibid.* **1973**, *38*, 3324.
(9) Papadopoulos, E. P.; Haidar, N. F. *Tetrahedron Lett.* **1968**, 1721.
(10) Carpino, L. A.; Barr, D. E. *J. Org. Chem.* **1966**, *31*, 764.
(11) Upton, C. J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094.
(12) For the preparation of 6 see: Marinelli, E. R.; Kononovich, K.; Brief, D.; Levy, A. B., manuscript in preparation.

Table II. Reaction of 3 with Representative Electrophiles for the Formation of 2-Substituted Pyrroles

entry	electrophile	temp, °C/ time, min	N-(*tert*-butoxycarbonyl)pyrrole (yield, %)	pyrrole (yield, %)
1	$(CH_3)_3SiCl$	−80/60	 **4a** (76,[a] 100[b])	 **7a** (99[a])
2	PhC(O)H	−80/160	 **4b** (75[a])	 **8** (76[a])
3	PhC(O)Cl	−80/15	 **4c** (45[a])	 **7c** (95[a])
4	EtC(O)H	−80/45	 **4d** (47[a])	
5	$CH_3C(O)Cl$	−104/30	 **4e** (35[a])	 **7e** (66[a])

[a] Isolated yield. [b] Yield by GC vs. an internal standard.

the alcohols **4b** and **4d** proved to be labile under these conditions. For example, **4b** gave a high yield of the methyl ethers 8 (eq 8). Unfortunately, under a variety of conditions which remove the protecting group, substitution of the hydroxyl group also occurs.[13]



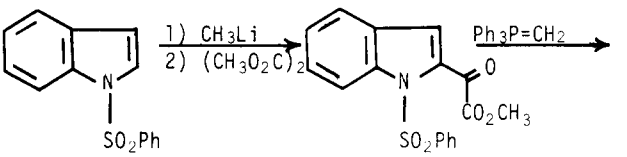
(8)

4b 8

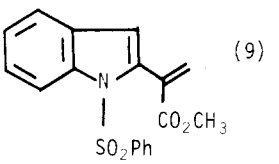
***N*-(*tert*-Butoxycarbonyl)indoles.** The α-indolylacrylates have been postulated to be key intermediates in indole alkaloid biosynthesis.[14] This postulation has led to chemical synthesis of iboga[15] and aspidosperma[16] indole alkaloids via α-indolylacrylates. The 2-lithioindoles have proven to be versatile intermediates for the synthesis of α-indolylacrylates.[15,16a]

The synthesis of indole alkaloids without *N*-alkyl substituents requires the use of a nitrogen protecting group. The benzenesulfonyl group has been suggested as a useful protecting group for the preparation of 2-lithioindoles.[8] In connection with our studies directed toward the synthesis of dehydrosecodine,[17] we prepared acrylate **10** using the *N*-benzenesulfonyl substituent protecting group (eq 9).

Sundberg and Bloom[15] have previously reported a similar intermediate and showed it to be useful for iboga alkaloid synthesis.



9



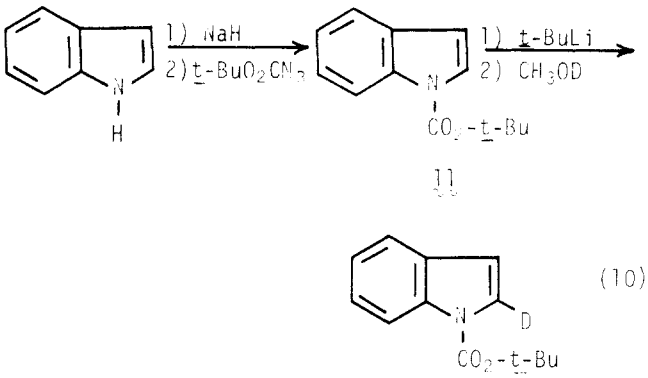
(9)

10

However, because of the sensitivity of the ester and other functional groups to the basic conditions required to remove the benzenesulfonyl substituent, we have investigated other groups for the protection of the indole N–H. The *tert*-butoxycarbonyl substituent appeared to be an attractive possibility, because it is normally removed under mild acidic conditions.[20] Our main concern was whether the *tert*-butoxycarbonyl group would be stable to the strongly basic reagents necessary to generate the anion.[21]

The (*tert*-butoxycarbonyl)indole 11 was prepared from indole by using a standard procedure. Lithiation at −80 °C with *tert*-butyllithium appears to be rapid and complete on the basis of quenching with CH_3OD (eq 10).

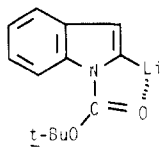
(13) Conditions include heating in aqueous Me_2SO and DMF in the presence of NaOH.
(14) Scott, A. K. *Acc. Chem. Res.* **1970**, *3*, 151; *Bioorg. Chem.* **1974**, *3*, 398.
(15) Sundberg, R. J.; Bloom. J. D. *Tetrahedron Lett.* **1978**, 5157.
(16) (a) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. (b) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705.
(17) Beeken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677.
(18) We have also investigated the MEM group[19] and found it to be unsuitable as a protecting group for the indole N–H. Unfortunately we could not remove this group under a variety of conditions without decomposition.
(19) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(20) Carpino, L. A. *Acc. Chem. Res.* **1973**, *6*, 191.
(21) Elimination of amines with lithium reagents to give alkenes has been reported (see ref 2a, p 53).
(22) The difference in reactivity may be due to the increased availability of the π electrons on the indole nitrogen vs. pyrrole. Thus the *N*-(*tert*-butoxycarbonyl)indole may be more carbamate-like than pyrrole where it costs more resonance energy to donate electron density to the carbonyl.

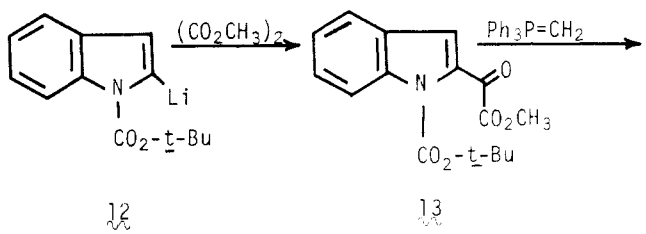


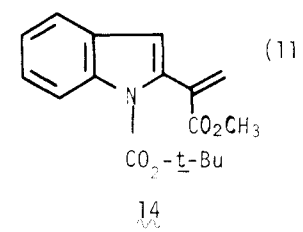
(10)

The *tert*-butoxycarbonyl group probably facilitates the formation of the lithio derivatives in two ways. The greater electronegativity of the *tert*-butoxycarbonyl substituent enhances the acidity of the hydrogen α to the nitrogen atom, and the oxygen of the carbonyl group stabilizes the lithio derivative through coordination.[2]

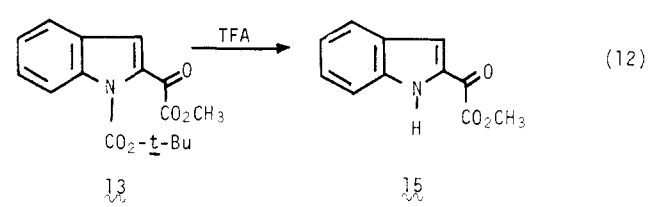
Addition of the lithio derivative **12** to an excess of dimethyl oxalate resulted in **13**. The indolylacrylate **14** could be prepared by treatment of **13** with triphenylmethylenephosphorane at −20 °C (eq 11). The *tert*-butoxycarbonyl group could be rapidly removed at room temperature by treating **13** with trifluoroacetic acid (TFA) (eq 12).[23] The pyruvate **15** was identical with a sample prepared from *N*-benzenesulfonylindole (eq 13).



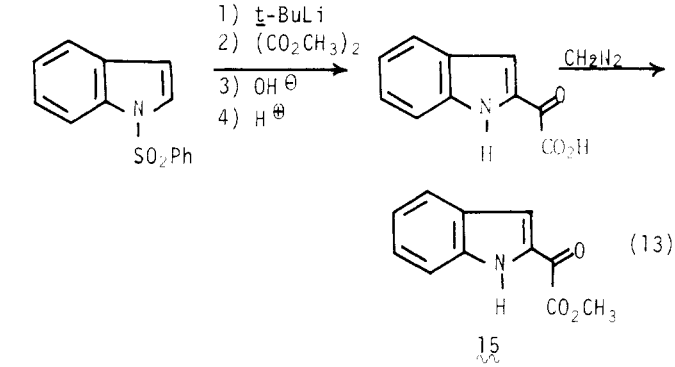




(11)

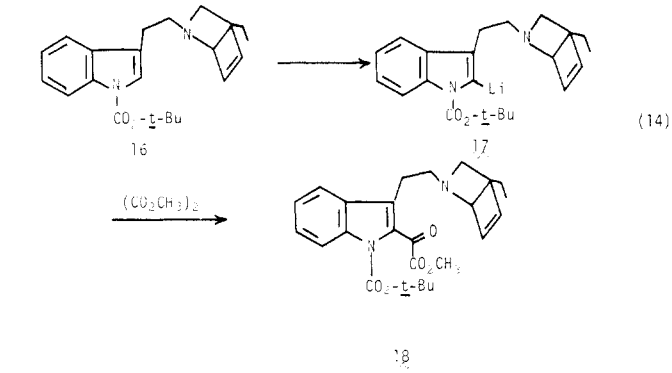


(12)



(13)

We have also succeeded in preparing the 3-substituted indole **18** via the 2-lithioindole **17**. It is of interest to note that the 3-substituent does not interfere in the lithiation or subsequent acylation (eq 14).[21,22] It is anticipated that **18** or related compounds will be of value for the synthesis of indole alkaloids via the elusive dehydrosecodine.[14]



(14)

We have demonstrated the utility of the *N*-(*tert*-butoxycarbonyl) group as a N–H protecting group for the lithiation of pyrroles and indoles. In the indole series, the ability to remove the protecting group *under acidic conditions* as well as basic conditions complements the utility of *N*-benzenesulfonylindoles in natural-products synthesis. This protecting group also provides for the first time the possibility of functionalizing 1-unsubstituted pyrroles at the 2-position via the lithium reagent. The use of the *N*-(*tert*-butoxycarbonyl) substituent as a protecting group should expand the utility of 2-lithiopyrroles and indoles.

Experimental Section

Infrared spectra were recorded on a Pye Unicam SP 1000 instrument or a Perkin-Elmer 727 using a thin film on sodium chloride plates or a potassium bromide solid solution. Where indicated, absorption strengths are described as strong (s), medium (m), or weak (w). ^{1}H NMR spectra were recorded on a Varian EM-360 or a Varian HFT-80 spectrometer using acetone-d_6, CCl_4, or $CDCl_3$ as the solvent and Me_4Si as an internal standard. Low-resolution mass spectra were recorded on a Hewlett-Packard 5980A mass spectrometer. High-resoltuion mass spectra were acquired on an AEI MS-30 instrument. GLC analyses were obtained by using a Hewlett-Packard 5830 gas chromatograph equipped with a flame detector and using 6 ft × 0.125 in. stainless-steel columns filled with 10% loaded Chromasorb W AW-DMCS. SE-30 was used as a liquid phase.

Air-sensitive materials and reactions were handled by employing standard techniques as previously described.[24] All glassware was dried at 150 °C for at least 4 h, assembled hot, and allowed to cool under a nitrogen purge or repeatedly evacuated and refilled

(23) The *tert*-Butoxycarbonyl substituent may be removed from the 2-substituted *N*-(*tert*-butoxycarbonyl)indoles with CH_3ONa/CH_3OH/THF under essentially identical conditions with those described for the 2-substituted pyrroles. For example, the protecting group is removed in less than 20 min at room temperature from *N*-(*tert*-butoxycarbonyl)-indole to give indole in 85% yield (unpublished results with E. R. Marinelli, 1980).

(24) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. "Organic Synthesis via Boranes"; Wiley-Interscience: New York, 1975; Chapter 9.

with nitrogen. The reaction flasks were fitted with a side arm capped with a rubber septum. All reactions were carried out under a static pressure of nitrogen.

Tetrahydrofuran, diethyl ether, and hexane were distilled from benzophenone ketyl under an inert (N_2) atmosphere. All solvent transfers were accomplished by using syringe or double-ended needle techniques. *tert*-Butyllithium and *n*-butyllithium were obtained from Aldrich Chemical Co. and standardized according to the method of Watson and Eastham.[25]

N-Benzene-2-*d*-sulfonylpyrrole (1). A dry 50-mL, round-bottomed flask equipped with magnetic stirrer and a septum-capped inlet was allowed to cool under a nitrogen purge and maintained under a static nitrogen pressure. To this flask was added 2.5 mL of a 1.0 M solution of I_2[9] in THF, and the flask was cooled to −18 °C. The mixture was stirred and 2.75 mmol of *tert*-butyllithium added dropwise. The mixture was allowed to warm to room temperature for 20 min. The mixture was cooled to −30 °C and 0.15 mL of CH_3OD added dropwise, and the mixture was finally allowed to warm to room temperature. The organic phase was diluted with ether and water, separated, and washed sequentially with H_2O, saturated NaCl, and dried ($MgSO_4$). Removal of the solvent on the rotary evaporator gave 0.433 g (83%) of recovered material. This material was directly examined by ^1H NMR with acetone-d_6 as solvent to determine the extent of lithiation.

A similar procedure was used at −80 °C for 80 min. Quenching at −80 °C with CH_3OD followed by the normal workup gave 0.496 g (95%, recovered weight) of **1**. This material was examined by ^1H NMR with acetone-d_6 as solvent to determine the extent of deuterium incorporation and cleavage.

N-Benzene-2-*d*-sulfonylpyrrole (1) with LTMP. To a dry 100-mL, round-bottomed flask was added 4.0 mL of THF and 0.35 mL (2.1 mmol) of 2,2,6,6-tetramethylpiperidine. The mixture was cooled to −80 °C and 2.1 mmol of *n*-butyllithium added dropwise. The mixture was stirred 6 min at −80 °C and then 5 min at −10 °C and cooled to −80 °C. To this mixture was added 2.0 mL of a 1.0 M solution of **1** in THF, and the mixture was allowed to stir 45 min at −80 °C.

To a dry 50-mL, round-bottomed flask was added 3.0 mL of CH_3OD, and the flask was cooled to −80 °C. The preformed lithium reagent was transferred via a short, cooled (CO_2), double-ended needle into the rapidly stirred CH_3OD. The mixture was stirred 15 min at −80 °C, diluted with H_2O at −80 °C, and allowed to warm to room temperature. The organic phase was diluted with ether, separated, and extracted three times with equal volumes of a 1.0 M citrate buffer (pH 3). The organic phase was washed with saturated NaCl and dried over $MgSO_4$. Rotary evaporation yielded 0.372 g (90%) of **1** as a white solid. A small sample was recrystallized and analyzed for deuterium content by mass spectroscopy.

Lithiation of N-(*tert*-Butoxycarbonyl)pyrrole (2) with *tert*-Butyllithium. To a 50-mL, round-bottomed flask was added 1.5 mL of THF and 0.255 mL (1.5 mmol) of *N*-(*tert*-butoxycarbonyl)pyrrole. The mixture was cooled to −80 °C and 1.5 mmol of *tert*-butyllithium added dropwise. The mixture was stirred 1.5 h at −80 °C, and then excess CH_3OD was added. The solution was allowed to warm to room temperature. Normal aqueous workup and drying ($MgSO_4$), followed by removal of the solvent in vacuo, gave 0.174 g (69%, recovered weight) of material. The material was examined directly by ^1H NMR with acetone-d_6 as solvent in order to determine the extent of deuterium incorporation and cleavage.

Lithiation of N-(*tert*-Butoxycarbonyl)pyrrole (2) with LDA. To a dry, 100-mL, round-bottomed flask was added 4.0 mL of THF and 0.294 mL (2.1 mmol) of diisopropylamine. The mixture was cooled to −80 °C and 2.1 mmol of *n*-butyllithium added slowly. The mixture was stirred 5 min at −80 °C and 5 min at −10 °C and then cooled to −80 °C. To this mixture was added 0.34 mL (2.0 mmol) of **2** dropwise. The mixture was stirred 45 min at −80 °C.

To a dry, 100-mL round-bottomed flask was added 3 mL of CH_3OD, and the flask was cooled to −80 °C. The preformed lithium reagent was transferred to the rapidly stirred CH_3OD at −80 °C via a short, cooled (CO_2), double-ended needle. The resultant mixture was stirred 15 min at −80 °C, diluted with H_2O, and allowed to warm to room temperature. Normal aqueous workup, drying ($MgSO_4$), and removal of the solvent on the rotary evaporator yielded 0.304 g (91%) of recovered material. This material was used directly for gas chromatographic–mass spectral analysis to determine the extent of deuterium incorporation.

Lithiation of N-(*tert*-Butoxycarbonyl)pyrrole (2) with LTMP. To a dry, 100-mL, round-bottomed flask was added 4 mL of THF and 0.35 mL (2.1 mmol of 2,2,6,6-tetramethylpiperidine. The mixture was cooled to −80 °C, and 2.1 mmol of *n*-butyllithium was added. The mixture was stirred 5 min at −80 °C and 5 min at −10 °C and then cooled to −80 °C. To this mixture was added 0.34 mL (2.0 mmol) of **2**, and the mixture was stirred 45 min at −80 °C.

To a second dry flask under nitrogen was added 3 mL of CH_3OD, and the solution was cooled to −80 °C. The preformed lithium reagent was added to the rapidly stirred CH_3OD at −80 °C via a short, cooled (CO_2), double-ended needle, and the mixture was stirred 15 min at −80 °C. The mixture was diluted with H_2O at −80 °C and warmed to room temperature. The organic phase was diluted with ether and divided into two equal volumes.

One portion was washed with saturated NaCl solution and dried over $MgSO_4$. The other portion was washed three times with equal volumes of a 1 M citrate buffer solution (pH 3), washed with saturated NaCl solution, and dried over $MgSO_4$. The two samples were analyzed by using gas chromatography–mass spectroscopy to determine the extent of deuterium incorporation in **2** contained in the organic layers. There was no difference in the extent of deuteration, indicating hydrogen exchange during workup is not occurring. The two organic layers were then combined, extracted with 1.0 M citrate buffer solution (pH 3), washed with saturated NaCl solution, and dried ($MgSO_4$), and the solvent was removed in vacuo to give 0.37 g (92%) of recovered material.

N-(*tert*-Butoxycarbonyl)-2-(trimethylsilyl)pyrrole (4a). The reagent **3** was generated on a 2.0-mmol scale as described in the deuteration experiment above and 0.303 mL (2.4 mmol) of chlorotrimethylsilane added dropwise. The mixture was then stirred for 1 h at −80 °C. Finally, 2 mL of 3 N NaOH was added and the solution warmed to room temperature. The mixture was diluted with 10 mL of ether, and the organic layer was separated and extracted three times with 25-mL portions of a 1 M sodium citrate buffer solution (pH 3). The organic layer was then extracted three times with equal volumes of saturated NaCl and dried ($MgSO_4$). Removal of the solvent in vacuo gave 0.464 g (93%) of crude **4a**. The product was distilled in a Kuglerohr oven twice to give 0.366 g (73%) of analytically pure **4a**: bp 65 °C (0.07 mm); IR (liquid film) ν_{max} 3100, 2980, 2960, 2900, 1740, 1547, 1477, 1460, 1390, 1370, 1340, 1292, 1248, 1207, 1165, 1109, 1062, 1000, 882, 850, 777, 767, 735, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.26 (s, 9 H), 1.56 (s, 9 H), 6.23 (m, 1 H), 6.47 (m, 1 H), 7.40 (m, 1 H).

Anal. Calcd for $C_{12}H_{21}NO_2Si$: C, 60.22; H, 8.85. Found: C, 60.19; H, 8.90.

[N-(*tert*-Butoxycarbonyl)pyrrol-2-yl]phenylmethanol (4b). The reagent **3** was generated on a 4.0-mmol scale as described for the deuteration experiment except that 1.0 mL of THF/equiv of **2** was used. Benzaldehyde (0.406 mL, 4.0 mmol) was added dropwise. The mixture was stirred for 2.3 h at −80 °C, and 3 mL of 1 N NaOH was added to the mixture at −80 °C. The solution was immediately allowed to warm to room temperature, the organic layer separated, and 20 mL of ether was added. The organic layer was extracted three times with equal volumes of 1 M citrate buffer (pH 3), washed with a small amount of 1 N NaOH solution, washed three times with saturated aqueous sodium chloride, and dried ($MgSO_4$). Removal of the solvent on the rotary evaporator yielded 1.075 g of a red oil which was chromatographed on 50 g of activity III neutral alumina (5% EtOAc/hexanes). Elution of 60–120 mL of solvent gave 0.814 g (75%) of **4b** as a pale yellow oil: IR (liquid film) ν_{max} 3460, 2980, 2940, 1725, 1490, 1455, 1410, 1395, 1372, 1345, 1290, 1260, 1235, 1165, 1128, 1068, 1035, 1025, 1010, 890, 850, 777, 730, 702, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.60 (s, 9 H), 4.55 (d, 1 H), 5.72

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(27) Carpino, L. A.; Barr, D. E. *J. Org. Chem.* **1966**, *31*, 764.

(m, 1 H), 6.13 (m, 2 H), 7.4 (m, 6 H); high-resolution mass spectrum, m/e 273.1387 ($M^{+\cdot}$) ($C_{16}H_{19}NO_3$ requires 273.1373).

N-(*tert*-Butoxycarbonyl)pyrrol-2-yl Phenyl Ketone (4c). The reagent **3** was generated on a 4.0-mmol scale as described for the deuteration experiment above. To a dry, 100-mL, round-bottomed flask maintained at −80 °C under nitrogen atmosphere was added 4 mL of THF and 0.928 mL (8.0 mmol) of benzoyl chloride. The preformed anion **3** was then added to the rapidly stirred solution of the benzoyl chloride via a short, cooled (CO_2), double-ended needle. The mixture was stirred 15 min at −80 °C, warmed to room temperature, and quenched with 25 mL of 0.04 N NaOH and 20 mL of ether. The organic layer was extracted with saturated NaCl and dried ($MgSO_4$), and the solvent was removed in vacuo to give 1.459 g of a dark brown solid. Chromatography on 37 g of activity III neutral alumina (3% EtOAc/hexane) and elution of 60–110 mL of solution gave 0.533 g of a crude orange solid which was recrystallized to give 0.484 g (45%) of **4c** as a pale brown solid: mp 103–104.5 °C (from hexane); IR (liquid film) ν_{max} 3140, 3120, 2980, 1745, 1642, 1600, 1580, 1452, 1436, 1412, 1396, 1372, 1315, 1280, 1228, 1205, 1182, 1170–1130, 1035, 1026, 940, 918, 900, 880, 852, 841, 800, 778, 762, 728, 700, 682 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.48 (s, 9 H), 6.40 (t, 1 H), 6.80 (m, 1 H), 7.63 (m, 4 H), 8.0 (m, 2 H); high-resolution mass spectrum, m/e 271.1242 ($M^{+\cdot}$) ($C_{16}H_{17}NO_3$ requires 271.1216).

1-[N-(*tert*-Butoxycarbonyl)pyrrole-2-yl]-1-propanol (4d). The reagent **3** was generated on a 4.0-mmol scale as described for the deuteration experiment above and 0.288 mL (4.0 mmol) of propionaldehyde added slowly. The solution was stirred 45 min at −80 °C and quenched by addition of 3 mL of 0.1 N NaOH solution. The solution was immediately allowed to warm to room temperature, and the organic layer was separated. The organic phase was washed three times with equal volumes of a 1.0 M citrate buffer solution (pH 3) and once with a saturated NaCl solution and dried (K_2CO_3). Removal of the solvent on a rotary evaporator gave 0.743 g of a crude red oil which was chromatographed on 50 g of activity III neutral alumina (5% EtOAc/hexanes) to give 0.426 g (47%) of **4d** as a pale yellow oil: IR (liquid film) ν_{max} 3480, 3160, 3110, 2980, 2940, 2880, 1740, 1723, 1478, 1455, 1415, 1395, 1371, 1340, 1260, 1240, 1170, 1138, 1107, 1070, 1020, 970, 900, 850, 815, 778, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.01 (t, 3 H), 1.60 (s, 9 H), 1.80 (m, 2 H), 3.90 (d, 1 H), 4.80 (q, 1 H), 6.20 (m, 2 H), 7.25 (m, 1 H); high-resolution mass spectrum, m/e 225.1388 ($M^{+\cdot}$) ($C_{12}H_{19}NO_3$ requires 225.1367).

N-(*tert*-Butoxycarbonyl)pyrrol-2-yl Methyl Ketone (4e). The reagent **3** was generated on a 4.0-mmol scale as described for the deuteration experiment above. To a dry, 100-mL, round-bottomed flask was added 15 mL of *n*-hexane and 1.422 mL (20 mmol) of acetyl chloride under a nitrogen atmosphere. This solution was cooled to −104 °C and the preformed anion **3** added to the rapidly stirred solution of acetyl chloride via a short, cooled (CO_2), double-ended needle. The mixture was stirred at −104 °C for 30 min, brought to −98 °C, and allowed to warm from −98 to −65 °C over a period of 30 min. The mixture was then quenched by addition of 6 mL of 3 N NaOH at −65 °C and allowed to warm to room temperature. The organic layer was separated and washed three times with equal volumes of a 1.0 M citrate buffer solution (pH 3) and once with a saturated NaCl solution and dried ($MgSO_4$). Removal of the solvent on a rotary evaporator gave a pale brown oil which was chromatographed by using 40 g of activity III neutral alumina (5% EtOAc/hexane). Elution of 20–30 mL of solution gave 0.259 g (39%) of *N*-(*tert*-butoxycarbonyl)pyrrole. Further elution (60–130 mL) gave 0.310 g (37%) of **4e** as a colorless liquid: bp 85–91 °C (0.075 mm); IR (liquid film) ν_{max} 3135, 2990, 2944, 1752, 1680, 1541, 1478, 1445, 1414, 1398, 1372, 1320, 1270, 1213, 1194, 1165, 1090, 1068, 1020, 948, 888, 848, 778, 750, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.60 (s, 9 H), 2.43 (s, 3 H), 6.28 (t, 1 H), 6.95 (m, 1 H), 7.42 (m, 1 H); high-resolution mass spectrum, m/e 209.1069 ($M^{+\cdot}$) ($C_{11}H_{15}NO_3$ requires 209.1058).

General Procedure for the Deprotection of 2-Substituted 1-(*tert*-Butoxycarbonyl)pyrroles. A dry, 10-mL, round-bottomed flask equipped with magnetic stirrer was maintained under a nitrogen atmosphere. The pyrrole was added followed by THF such that the concentration of the solution was between 0.2 and 1.0 M. The mixture was stirred at room temperature and 3 equiv of $NaOCH_3$ in CH_3OH (6.5 N) added. The mixture was allowed to stir 10–30 min and was then diluted with 5 mL each of ether and H_2O. Separation of the organic layer followed by washing with saturated NaCl, drying (K_2CO_3 or $MgSO_4$), and rotary evaporation gave compounds which were pure or were easily purified chromatographically and/or by distillation in a Kugelrohr oven.

2-(Trimethylsilyl)pyrrole (7a). The reaction was carried out on 0.043 g (0.180 mmol) of **4a** in 0.2 mL of THF. Stirring with 0.1 mL of NaOMe/MeOH for 20 min, isolation, and distillation in a Krugelrohr oven gave 0.025 g (0.179 mmol, 99%) of **7a** as a colorless liquid: bp 65–70 °C (2.0 mm) [lit.[28] bp 102–110 °C (45 mm)]; IR (liquid film) ν_{max} 3410, 3100, 2965, 2905, 1532, 1400, 1340, 1254, 1183, 1119, 1109, 1090, 1032, 932, 887, 845, 807, 760, 734, 698, 670, 639 cm^{-1}; ^1H NMR (acetone-d_6, 60 MHz) δ 0.23 (s, 9 H), 6.23 (m, 1 H), 6.42 (m, 1 H), 7.03 (m, 1 H), 9.5–10.5 (br s, 1 H).

1-*H*-Pyrrol-2-yl Phenyl Ketone (7c). The reaction was carried out on 0.025 g (0.09 mmol) of **4c** in 0.5 mL of THF. Stirring with 0.05 mL of CH_3ONa/CH_3OH for 20 min and isolation gave 0.015 g (95%) of **7c** as white crystals which were homogeneous by TLC on silica and alumina: mp 77–78 °C (lit.[29] mp 78–80 °C); IR (liquid film) ν_{max} 3290, 1630, 1573, 1542, 1445, 1427, 1402, 1342, 1205, 1147, 1100, 1077, 1053, 1032, 898, 878, 848, 835, 790, 753, 742, 694, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 6.45 (m, 1 H), 6.98 (m, 1 H), 7.23 (m, 1 H), 7.50 (m, 3 H), 7.95 (m, 2 H), 9.0–10.3 (s, 1 H); high-resolution mass spectrum, m/e 171.687 ($M^{+\cdot}$) ($C_{11}H_9NO$ requires 171.0688).

1-*H*-Pyrrol-2-yl Methyl Ketone (7e). The reaction was carried out on 0.103 g (0.534 mmol) of **4e** in 4 mL of THF. Stirring with 0.20 mL of $NaOCH_3/CH_3OH$ for 5 min and normal isolation gave 45.9 mg of solid **7e**. Recrystallization (ligroin) gave 0.030 g (66%) of **7e** as a pale yellow solid: mp 88–89 °C (lit.[29] mp 90 °C); IR (KBr) ν_{max} 3285, 3110, 2980, 1645, 1548, 1510, 1430, 1405, 1365, 1328, 1265, 1142, 1132, 1080, 1050, 1022, 975, 930, 845, 780, 754, 640 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.40 (s, 3 H), 6.35 (m, 1 H), 7.03 (m, 2 H), 8.0–10.0 (s, 1 H); mass spectrum, m/e (relative intensity) 110.1 (6.8), 109.1 (100), 95.1 (5.4), 94.1 (93.0), 66.1 (29.0).

2-Cyclopentylpyrrole (6). The reaction was carried out on 0.101 g (0.43 mmol) of **5** in 1 mL of THF. Stirring at room temperature with 0.2 mL of $NaOCH_3/CH_3OH$ for 20 min and isolation gave 0.065 g of crude material. Distillation in a Kugelrohr oven gave 0.050 g (87%) of **6** as a colorless liquid: bp 70–80 °C (0.5 mm) [lit.[30] bp 80–81 °C (3 mm)]; IR (liquid film) ν_{max} 3390, 3100, 2955, 2865, 1560, 1465, 1445, 1425, 1345, 1118, 1095, 1028, 883, 790, 715 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.80 (m, 8 H), 3.1 (m, 1 H), 6.00 (m, 1 H), 6.20 (m, 1 H), 6.70 (m, 1 H); high-resolution mass spectrum, m/e 135.1053 ($C_9H_{13}N$ requires 135.1054).

α-Pyrrol-2-yl-α-methoxytoluene (8). The reaction was carried out on 0.110 g (0.40 mmol) of **4b** in 1 mL of THF. Stirring at room temperature with 0.5 mL of $NaOCH_3/CH_3OH$ for 5 min and isolation gave 0.067 g of an oil. Column chromatography on 10 g of activity IV neutral alumina (10% EtOAc/hexane) gave 0.050 g (76%) of **8** as a yellow oil, homogeneous by TLC: IR (liquid film) ν_{max} 3400, 3030, 2990, 2935, 2825, 1482, 1450, 1325, 1190, 1120, 1090, 1075, 1030, 947, 885, 800, 727, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.28 (s, 3 H), 5.33 (s, 1 H), 6.1 (m, 2 H), 6.77 (m, 1 H), 7.41 (s, 6 H), 7.60–9.00 (s, 1 H); high-resolution mass spectrum, m/e 187.0982 ($C_{12}H_{13}NO$ requires 187.1003).

N-(*tert*-Butoxycarbonyl)indole (11). A dry, 250-mL, three-necked flask was charged with N_2, and 5 g of NaH (50% mineral oil dispersion) was added. The mineral oil was removed by washing three times with pentane. The NaH was dried by evacuation, and 50 mL of dry tetrahydrofuran was added. The suspension was stirred and cooled in an ice bath. Indole (10 g) in 20 mL of dry tetrahydrofuran was added. After gas evolution ceased, 12.2 g of *tert*-butoxycarbonyl azide was slowly added. The reaction was stirred for 15 h and worked up by slow addition of H_2O. The reaction mixture was extracted with ether, the ether

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(29) Pesson, M.; Aurousseau, M.; Joannie, M.; Roquet, F. *Chim. Therap.* **1966**, 127.
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extracts were combined and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was passed through Al_2O_3 (activity 1, neutral) with a CH_2Cl_2/pentane gradient (10–30%) to give 16 g (87%) of *N*-(*tert*-butoxycarbonyl)indole as a colorless liquid. An analytical sample was obtained by distillation [bp 110 °C (0.08 mm)]: IR (liquid film) ν_{max} 3060 (w), 2980 (m), 2940 (w), 1740 (s), 1530 (w), 1450 (m), 1380 (s), 1340 (s), 1250 (s), 1210 (m), 1170 (s), 1120 (m), 1040 (m), 1030 (s), 885 (m), 860 (m), 776 (s), 750 (s), 730 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.43 (s, 9 H), 6.48 (dd, J = 4, 1 Hz, 1 H), 7.0–7.65 (m, 3 H), 7.97–8.25 (m, 1 H); mass spectrum (70 eV), m/e (relative intensity) 117 (100), 161 (46), 57 (17), 116 (13); high-resolution mass spectrum, m/e 217.1127 (calcd for $C_{13}H_{15}NO_2$ 217.1152).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.88; H, 6.91. Found: C, 71.75; H, 6.68.

N-Benzenesulfonyl-2-methoxalylindole (9). To 8.6 g (33 mmol) of *N*-benzenesulfonylindole[8] dissolved in 150 mL of dry THF under N_2 and cooled to 0 °C was added 25 mL (36 mmol) of 1.45 M CH_3Li (low halide). The reaction was stirred at 0 °C for 1.5 h, allowed to warm to room temperature, and stirred for another 1.5 h. A dark red color developed immediately after the addition of CH_3Li. Approximately 2.5 h later, salt formation was observed. The resulting α-lithioindole was transferred to an addition funnel. The addition funnel was placed on a 500-mL, three-necked, round-bottomed flask. The reaction flask was evacuated and flushed with N_2 several times, and 16 g (136 mmol) of dimethyl oxalate dissolved in 150 mL of dry THF was placed in the reaction vessel. The α-lithioindole was then added to the cooled solution (0 °C) over a period of 50 min. The reaction was stirred for an additional 5 min, followed by quenching with H_2O. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to high vacuum for approximately 20 min to remove excess dimethyl oxalate. The crude product (7.66 g, 67%) was crystallized by trituration with CH_3OH to give 5.16 g (45%) pure crystalline **9**: IR (KBr) ν_{max} 2870 (w), 1740 (s, C=O), 1685 (s, C=O), 1540 (m), 1443 (m), 1380 (m), 1280 (m), 1235 (s), 1165 (s), 1150 (s), 1000 (m), 722 (m) cm^{-1}; ^1H NMR (C_6D_6, 80 MHz) δ 3.40 (s, 3 H), 6.50–7.25 (m, 8 H), 7.5–7.7 (m, 1 H), 7.95–8.15 (m, 1 H); mass spectrum (70 eV), m/e (relative intensity) 343 (M^+, 11), 285 (17), 284 (100), 143 (36), 115 (22).

Anal. Calcd for $C_{17}H_{13}NO_5S_2$: C, 59.45; H, 3.81. Found: C, 59.35; H, 3.85.

Methyl α-(*N*-Benzenesulfonylindol-2-yl)acrylate (10). To 1.10 g (3.1 mmol) of triphenylmethylphosphonium bromide suspended in 40 mL of dry ether under N_2 was added 1.45 mL (3.17 mmol) of 2.1 M *n*-BuLi. The reaction mixture was refluxed for 2 h. After the mixture cooled to room temperature, 1 g (2.9 mmol) of **9** dissolved in a minimum amount of dry THF (ca. 3 mL) was quickly added to the reaction mixture. The reaction mixture was refluxed for another 10 min and then quenched with water. The organic layer was separated, thoroughly washed with water (three times with 30-mL portions), dried ($MgSO_4$), and concentrated in vacuo to give 0.557 g (56%) of oily product. The acrylate **10** was crystallized by trituration with methanol to give 0.413 g (41%) of crystalline product. It was further purified by recrystallization with methanol and ethyl acetate: mp 160–161 °C; IR (KBr) ν_{max} 2940 (w), 1710 (s, C=O), 1617 (w), 1440 (m), 1430 (m), 1240 (s), 1178 (s), 1110 (m), 1080 (m), 775 (m) cm^{-1}; ^1H NMR (C_6D_6, 80 MHz) δ 3.5 (s, 3 H), 5.53 (d, 1 H, J = 2 Hz), 6.30 (d, 1 H, J = 1 Hz), 6.47 (d, 1 H, J = 2 Hz), 6.65–6.80 (m, 2 H), 6.90–7.2 (m, 2 H), 7.5–7.85 (m, 4 H), 8.15–8.35 (m, 1 H), 8.15–8.35 (m, 1 H); mass spectrum (70 eV), m/e (relative intensity) 341 (M^+, 47), 277 (17), 218 (100), 200 (59), 142 (77), 141 (50), 140 (65), 115 (33), 77 (54).

Anal. Calcd for $C_{18}H_{15}NO_4S$: C, 63.31; H, 4.43. Found: C, 63.45; H, 4.49.

2-Methoxalylindole (15). A solution of 1 g (2.9 mmol) of **9** was stirred with 15 mL of 2.2 N NaOH for 1 h. The solvent was then removed in vacuo, and the residue was dissolved in water. This aqueous solution was extracted with ethyl acetate, neutralized with concentrated HCl at 0 °C, and extracted with ethyl acetate. This extract was dried ($MgSO_4$) and concentrated in vacuo to give 0.463 g (84%) of acid. The product was recrystallized from ether/cyclohexane: mp 163–164 °C; IR (KBr) ν_{max} 3340 (s, N–H), 1717 (s, C=O), 1640 (s), 1620 (s), 1520 (m), 1420 (m), 1280 (m), 1220 (m), 1140 (s), 730 (m) cm^{-1}; ^1H NMR (C_6D_6, 80 MHz) δ 7.1–7.85 (m, 5 H); mass spectrum (70 eV), m/e (relative intensity) 189 (M^+, 47), 144 (100), 116 (28), 89 (51). An ethereal solution of 0.2 g of the above acid was treated with an excess of diazomethane in ether. After the mixture was stirred for 15 min, the excess diazomethane was decomposed with acetic acid. The organic layer was washed with saturated Na_2CO_3 solution dried ($MgSO_4$) and concentrated in vacuo to give 0.207 g (94%) of **15**. The product was recrystallized from ether/cyclohexane: mp 136–136.5 °C; IR (KBr) ν_{max} 3350 (s, N–H), 3050 (w), 1720 (s, C=O), 1645 (s, C=O), 1515 (m), 1440 (m), 1285 (s), 1220 (s), 1150 (s), 1040 (m), 720 (m), cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 4.0 (s, 3 H), 7.1–7.9 (m, 5 H), 9.40 (br s, 1 H); mass spectrum (70 eV), m/e (relative intensity) 203 (M^+, 29), 144 (100), 116 (25), 89 (51).

Anal. Calcd for $C_{11}H_9O_3N$: C, 65.00; H, 4.54. Found: C, 64.89; H, 4.54.

N-(*tert*-Butoxycarbonyl)-2-methoxalylindole (13). A 250-mL flask was charged with nitrogen, and 33 mL of 1.55 M *tert*-butyllithium in *n*-pentane followed by 100 mL of dry tetrahydrofuran was added. The solution was cooled to −78 °C in a dry ice–acetone bath, and 10 g (46 mmol) of *N*-(*tert*-butoxycarbonyl)indole in 5 mL of dry tetrahydrofuran was added. The reaction mixture was stirred for 40 min and transferred by double-ended needle to a stirred solution of 150 mL of dry tetrahydrofuran and 30% of dimethyl oxalate (in order to prevent decomposition of the lithiated indole, the transfer tube should be cooled with dry ice). The reaction mixture was stirred for 1 h and H_2O added. The mixture was then extracted with ether. The organic fraction was dried ($MgSO_4$) and the solvent removed in vacuo. The excess dimethyl oxylate was removed in vacuo with warming, and the product crystallized when triturated with cyclohexane, giving 9.29 g (66%) of **13**: mp 88–89 °C (from cyclohexane); IR (KBr) ν_{max} 2980 (w), 1725 (s), 1700 (s), 1550 (m), 1445 (m), 1385 (s), 1370 (m), 1340 (s), 1230 (s), 1165 (s), 1145 (m), 1125 (s), 1100 (s), 1025 (m), 755 (m), 690 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.63 (s, 9 H), 3.87 (s, 3 H), 7.1–7.8 (m, 4 H), 8.0 (d, J = 7 Hz, 1 H).

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.68. Found: C, 63.45; H, 5.68.

Methyl α-[*N*-(*tert*-Butoxycarbonyl)indol-2-yl]acrylate (14). To 4.5 g of triphenylmethylphosphonium bromide was added 30 mL of dry ether followed by 4.5 mL of 2.2 M *n*-butyllithium in hexane. The reaction mixture was refluxed for 1 h. This Wittig reagent was then added to 3.0 g (10 mmol) of **13** in 300 mL of ether cooled to −15 °C. The reaction mixture was stirred for 7 min and H_2O added. The water layer was separated and extracted with ether. The ethereal extracts were combined and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was passed through activity III Al_2O_3 with hexane to give 1.6 g (53%) of **14** as a yellow oil that crystallized on standing. The analytical sample was obtained by recrystallization from pentane: mp 61–61.5 °C; IR (KBr) ν_{max} 3105 (w), 3055 (w), 2980 (m), 1725 (s), 1620 (m), 1460 (s), 1335 (s), 1165 (s), 1070 (s), 750 (s) cm^{-1}; ^1H NMR (C_6D_6, 80 MHz) δ 1.05 (s, 9 H), 3.05 (s, 3 H), 5.23 (d, J = 3 Hz, 1 H), 5.98 (d, J = 1 Hz, 1 H), 6.03 (d, J = 3 Hz), 6.6–7.2 (m, 3 H), 8.13 (d, J = 7 Hz, 1 H).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.77; H, 6.31. Found: C, 67.95; H, 6.42.

N-(*tert*-Butoxycarbonyl)-3-[β-(2-azabicyclo[2.2.0]hex-5-en-2-yl)ethyl]indole (16). To a 25-mL flask was added 0.20 g of NaH (50% in mineral oil). The mineral oil was removed by three pentane washings, the NaH was dried in vacuo, and the flask was charged with nitrogen and 15 mL of dry tetrahydrofuran. The indole[17] (0.525 g, 2.08 mmol) was added, and the mixture was cooled in an ice bath. *tert*-Butoxycarbonyl azide (0.60 g) was added, and the reaction mixture was allowed to warm to room temperature and stir for 40 h. The excess NaH was decomposed by the slow addition of H_2O. The reaction mixture was extracted with ether and dried ($MgSO_4$). Removal of the ether in vacuo gave 0.708 g (97%) of **16**: IR (film) 3040 (m), 1732 (s), 1455 (m), 1370 (s), 1260 (m), 1160 (s), 1090 (m), 745 (s) cm^{-1}; ^1H NMR (C_6D_6, 80 MHz) δ 0.50 (t, J = 8 Hz, 3 H), 1.1 (s, 9 H), 1.2 (9, J = 8 Hz, 2 H), 2.1–2.7 (m, 5 H), 3.13 (d, J = 8 Hz, 1 H), 3.85–4.00 (m, 1 H), 5.75 (d, J = 3 Hz, 1 H), 6.05 (t, J = 3 Hz, 1 H), 6.6–7.3 (m, 4 H), 8.08–8.25 (m, 1 H); high-resolution mass spectrum, m/e 352.2128 ($C_{22}H_{28}N_2O_2$ requires 252.2150).

***N*-(*tert*-Butoxycarbonyl)-2-methoxalyl-3-[β-(2-azabicyclo[2.2.0]-hex-5-en-2-yl)ethyl]indole (18).** To 10 mL of dry tetrahydrofuran cooled in a dry ice bath (−78 °C) and under N_2 was added 1.0 mL of 1.1 M *tert*-butyllithium in *n*-pentane followed by 120 mg (0.34 mmol) of indole **16** in 1 mL of dry tetrahydrofuran. The reaction mixture was allowed to stir for 1 h and was transferred by a double-ended needle to a flask containing 0.80 mL of dimethyl oxalate and 10 mL of dry tetrahydrofuran at room temperature. In order to minimize decomposition, it is important that the double-ended needle be kept cool (−78 °C) during the transfer of the lithiated indole. The reaction mixture was allowed to stir for 1 h followed by the addition of a saturated NaCl solution. The reaction mixture was extracted with ether. The ether extract was dried ($MgSO_4$), and the solvent was removed in vacuo. The excess dimethyl oxalate was removed in vacuo with slight warming to give 168 mg of the crude product as a yellow oil. This was further purified by silica gel thin-layer chromatography using 1:5:1 benzene–ethyl acetate–methanol containing 1% of diisopropylamine ($R_f \simeq 0.7$): IR (film) ν_{max} 3000 (m), 1705 (br s), 1450 (m), 1370 (s), 1330 (s), 1245 (m), 1140 (s), 1025 (m), 825 (m), 750 (s) cm^{-1}; ^1H NMR (C_6D_6, 80 MHz) δ 0.48 (t, J = 7 Hz, 3 H), 1.04 (s, 9 H), 1.25 (9, J = 7 Hz, 2 H), 2.0–2.6 (m, 5 H), 3.05 (d, J = 8.0 Hz, 1 H), 3.65–3.75 (m, 1 H), 5.76 (d, J = 3 Hz, 1 H), 6.00 (t, J = 3 Hz, 1 H), 6.5–7.2 (m, 3 H), 7.93 (d, J = 7 Hz, 1 H); high-resolution mass spectrum, m/e 438.2160 ($M^{+\cdot}$) ($C_{28}H_{28}N_3O_2$ requires 438.2182).

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Registry No. **1**, 16851-82-4; 1-2-*d*, 75400-55-4; **2**, 5175-27-2; **3**, 75400-56-5; **4a**, 75400-57-6; **4b**, 75400-58-7; **4c**, 75400-59-8; **4d**, 75400-60-1; **4e**, 75400-61-2; **5**, 75400-62-3; **6**, 60443-99-4; **7a**, 18276-13-6; **7b**, 75400-63-4; **7c**, 7697-46-3; **7d**, 75400-64-5; **7e**, 1072-83-9; **8**, 75400-65-6; **9**, 75400-66-7; **10**, 74185-41-4; **11**, 75400-67-8; **13**, 75400-68-9; **14**, 75400-69-0; **15**, 18132-19-9; **16**, 75400-70-3; **18**, 75400-70-3; chlorotrimethylsilane, 75-77-4; benzaldehyde, 100-52-7; benzoyl chloride, 98-88-4; propionaldehyde, 123-38-6; acetyl chloride, 75-36-5; *tert*-butoxycarbonyl azide, 4981-48-0; *N*-benzenesulfonylindole, 40899-71-6; dimethyl oxalate, 553-90-2; *N*-carboxy-2-methoxycarbonylindole, 75400-71-4.

Stereospecific Synthesis of *trans*-1,3-Disubstituted-1,2,3,4-tetrahydro-β-carbolines

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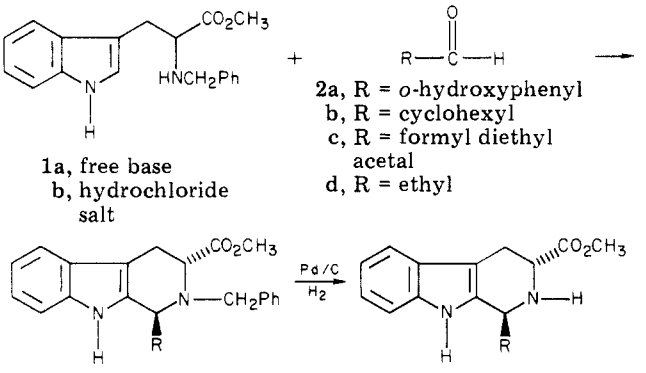
The Pictet–Spengler condensation of N_b-benzyltryptophan methyl ester **1a** with aldehydes **2a–d** has been found to occur in a stereospecific fashion. Stereoelectronic (antiperiplanar) attack of the 2,3-indole double bond on the intermediate benziminium ion **5b**, when combined with conformational analysis, has been employed to explain the complete stereospecificity of this cyclization. The N_b-benzyl derivatives (**3a–d**) were subjected to catalytic hydrogenation to provide the first stereospecific entry into *trans*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines (**4a–d**).

Interest in β-carbolines has been stimulated recently by their demonstrated biological activity[1-3] and the high affinity some of these bases have shown for the benzodiazepine (Valium) receptor.[4-6] Several groups[7-11] have investigated the ratio of cis/trans isomers produced in the Pictet–Spengler reaction of tryptophan derivatives with aldehydes; however, in all of the reactions discussed in 7–10, mixtures of cis and trans diastereomers were reported with the exception of the harman substitution pattern (1-methyl) and, in fact, Brossi[12] has isolated cis and trans isomers (1-methy-3-carboxyl) in this series.

Scheme I[a]



[a] For convenience only one antipode of the intermediate is presented here, although *d,l*-tryptophan was employed for this study.

For some time 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines have been employed in our laboratory as intermediates for the synthesis of oxo-substituted β-carboline

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