filtered off and washed with CH_2Cl_2; the filtrate and washings were evaporated in vacuo to afford the crude product as an orange solid, which was purified by passing it through a short column of silica gel, eluting with dichloromethane, to give (+)-1 (22.7 mg, 95%), $[\alpha]^{20}_D$ +3000° (c = 0.050, CH_2Cl_2).

Similarly, reduction of **7b** gave (-)-1 in 92% yield; $[\alpha]^{20}_D$ -2900° (c = 0.050, CH_2Cl_2). All spectral and TLC data for (+)- and (-)-1 were identical with those obtained for (±)-1 (except for the optical rotations).

Preparation of (±)-8 by Formylation of (±)-1. *N*-Methylformanilide (0.88 mL, 7.13 mmol) and freshly distilled phosphorus oxychloride (0.66 mL, 7.10 mmol) were mixed and left to stand at room temperature for 1 h under argon. Then (±)-1 (208 mg, 0.36 mmol) dissolved in dry dichloromethane (30 mL) was added, via syringe, and the reaction mixture was stirred at room temperature for 2 days. Ice water (10 mL) was added, and the mixture was left to stir for 3 h to ensure complete destruction of the complex. The product was extracted with dichloromethane (2 × 20 mL), and the combined extracts were dried (Na_2SO_4) and evaporated in vacuo, affording the crude product as a red gum. Purification by silica gel chromatography, eluting with dichloromethane, gave pure monoaldehyde (±)-8 (205 mg, 94%) as an orange solid. A sample of analytical purity, mp 280 °C dec, was prepared as orange-red prisms by recrystallization from hexane/CH_2Cl_2. IR (Nujol mull): 3076, 1655, 1330, 1244, 1078, 826, and 712 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.10 (s, 1 H), 5.53 (s, 1 H), 4.97 (d, J = 2.1 Hz, 1 H), 4.83 (d, J = 2.1 Hz, 1 H), 4.65 (d, J = 2.1 Hz, 1 H), 4.43 (d, J = 2.1 Hz, 1 H), 4.33 (d, J = 2.1 Hz, 1 H), 4.24 (d, J = 2.1 Hz, 1 H), 3.60-1.00 (m, 32 H). MS: m/z (relative intensity), 612 ($M^{\bullet+}$, 100), 342 (20), 306 (26), 228 (20). Anal. Calcd for $C_{37}H_{40}Fe_2O$: C, 72.55; H, 6.54. Found: C, 72.02; H, 6.50.

Cyclic Acetals 9a and 9b. Aldehyde (±)-8 (235 mg, 0.38 mmol) was treated with (2*R*,4*R*)-(-)-2,4-pentanediol (80 mg, 0.77 mmol), pyridinium *p*-toluenesulfonate (193 mg, 0.77 mmol), and triethyl orthoformate (0.32 mL, 1.93 mmol) in dry dichloromethane (30 mL) under argon. After stirring at room temperature for 24 h, water (10 mL) was added, the organic phase was collected and dried ($MgSO_4$), and the solvent was removed in vacuo, affording a pale yellow gum. The diastereomeric mixture was then separated by silica gel chromatography on a 6 in. long, 1 in. diameter column [monitored visually and by TLC (silica gel/CH_2Cl_2)], eluting with freshly distilled dichloromethane, to give firstly **9a** (94 mg, 70% of theory) and secondly **9b** (91 mg, 68% of theory) as pale yellow gums. A third fraction containing the aldehyde (±)-8 (70 mg), presumably arising from partial hydrolysis on the column, was also recovered.

9a. IR (neat): 2930, 2850, 1436, 1376, 1237, 1157, 1131, and 812 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.91 (s, 1 H), 5.10 (s, 1 H), 4.94 (d, J = 1 Hz, 1 H), 4.80 (d, J = 1 Hz, 1 H), 4.43 (m, 1 H), 4.20 (m, 3 H), 3.20 (m, 4 H), 2.50-1.00 (m, 38 H). MS: m/z (relative intensity), 698 ($M^{\bullet+}$, 100), 349 (100), 292 (81), 228 (64), 69 (100). Exact mass calcd for $C_{42}H_{50}O_2$ 698.2510, found 698.2553.

9b. IR (neat): 3096, 3070, 2924, 2851, 1436, 1376, 1237, 1157, 1131, and 819 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.75 (s, 1 H), 5.14 (s, 1 H), 4.94 (d, J = 1 Hz, 1 H), 4.88 (d, J = 1 Hz, 1 H), 4.85 (d, J = 1 Hz, 1 H), 4.23 (d, J = Hz, 1 H), 4.21 (d, J = 1 Hz, 1 H), 3.95 (d, J = 1 Hz, 1 H), 3.20 (m, 4 H), 2.60-1.00 (m, 38 H). MS: m/z (relative intensity), 698 ($M^{\bullet+}$, 100), 349 (100), 292 (80), 228 (60), 69 (100). Exact mass calcd for for $C_{42}H_{50}Fe_2O_2$ 698.2510, found 698.2560.

Preparation of (-)- and (+)-8 by Hydrolysis of Acetals 9a and 9b. Acetal **9a** (90 mg, 0.129 mmol) was dissolved in 3 mL of 1:1 MeOH/THF and treated with pyridinium *p*-toluenesulfonate (100 mg, 0.40 mmol), causing the solution to turn immediately from yellow to orange. Water (10 mL) was then added after 3 min, and the product was extracted into dichloromethane (2 × 10 mL). After combining and drying (Na_2SO_4) the extracts, evaporation of the solvent in vacuo gave the crude product as an orange solid. Purification by passing it through a short plug of silica gel eluting with dichloromethane gave (-)-8 (75 mg, 95%) as an orange solid, $[\alpha]^{20}_D$ -3410° (c = 0.100, CH_2Cl_2).

Similarly, hydrolysis of **9b** gave (+)-8 (95% yield), $[\alpha]^{20}_D$ +3400° (c = 0.100, CH_2Cl_2). All spectral data and TLC behavior for (+)- and (-)-8 were identical with those obtained for (±)-8 except the optical rotation.

Preparation of (-)- and (+)-1 by Decarbonylation of (-)- and (+)-(8). The optically pure aldehyde (-)-8 (52 mg, 0.085 mmol) was heated with Wilkinson's catalyst (86 mg, 0.093 mmol, Aldrich) under argon in toluene (2 mL) contained in a sealed tube at 170-180 °C for 6 h. The toluene was evaporated in vacuo, and the crude product was purified by silica gel chromatography, eluting with dichloromethane to give (-)-1 (36 mg, 73%), $[\alpha]^{20}_D$ -2940° (c = 0.100, CH_2Cl_2).

Similarly, decarbonylation of (+)-8 gave (+)-1 (70% yield), $[\alpha]^{20}_D$ +2930° (c = 0.100, CH_2Cl_2). All spectral data and TLC behavior for (+)- and (-)-1 were identical with those obtained for (±)-1 except for optical rotation.

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An Alternative Route to 2-Substituted Indoles via *N*-Aminal-Directed Lithiation

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The directing effect of (dialkylamino)methyl (aminal) groups in carbocyclic metalation chemistry is well known.[1] Recently, we have found that aminal groups can also be successfully employed as protecting groups for the NH of heterocyclic compounds and as directing groups for the subsequent lithiation of heterocyclic compounds. This methodology works well for a variety of NH-containing heterocycles, including carbazole, imidazole, benzimidazole, and pyrazole.[2] In all these cases, the aminal group is easily introduced and directs the lithiation to the appropriate site. The removal of the aminal group is then achieved by gentle warming with aqueous HCl during the workup. Overall, the methodology provides an efficient two-step route to the synthesis of a variety of substituted heterocycles.

Concurrent with our own research into the use of aminal derivatives as NH-protecting and lithiation-directing groups, several other groups have investigated similar *N*-aminal-directed lithiation using other heterocycles. Muchowski and Hess reported the lithiation of 6-(dimethylamino)-1-azofulvene dimer **1**.[3] After reaction with an electrophile and subsequent hydrolysis of the *N*-aminal, the corresponding 5-substituted pyrrole-2-aldehydes **2** were obtained in good yields. More recently, Hlasta and Bell reported the use of (dimethylamino)methyl as a directing group for the lithiation of indole and subsequent reactions with electrophiles, but they were unable to effect the re-

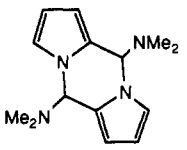
(1) (a) Omae, I. *Chem. Rev.* **1979**, *79*, 287. (b) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (c) Wardell, J. L. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Ed.; John Wiley and Sons, Ltd.: New York, 1987; Vol. 4, p 1. (d) Narashimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63.

(2) (a) Katritzky, A. R.; Rewcastle, G. W.; Vazquez de Miguel, L. M. *J. Org. Chem.* **1988**, *53*, 794. (b) Katritzky, A. R.; Rewcastle, G. W.; Fan, W. Q. *J. Org. Chem.* **1988**, *53*, 5685.

(3) (a) Muchowski, J. M.; Hess, P. *Tetrahedron Lett.* **1988**, *29*, 777. (b) *Ibid.* **1988**, *29*, 3215.

0022-3263/90/1955-3688$02.50/0

moval of the aminal group.[4] We had already encounted the same problem in the synthesis of 3(5)-substituted 1,2,4-triazoles when using *N*-aminal-directed lithiation, but had solved this "removal problem" by subjecting the aminal derivatives to reduction with $NaBH_4$ in refluxing ethanol.[5] Under these conditions, as expected from our work in the benzotriazole series,[6] the aminal group was lost and a variety of 3(5)-substituted 1,2,4-triazoles were obtained in good yields.



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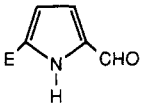
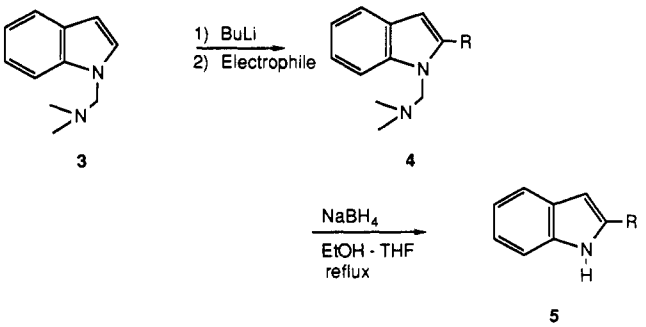


2

Since the lithiation of indole at the 2-position is of considerable importance due to the extensive use of N-protected 2-lithioindoles in natural product synthesis, we attempted to apply $NaBH_4$ reductive elimination to *N*-aminal-substituted indoles.[7] We now report the success of this technique, which enables indole aminals to be applied to the preparation of 2-substituted indoles. This method, together with Sundberg's arylsulfonyl procedure,[8] and the carbamate anion protocol,[9] provides an attractive alternative procedure for the synthesis of 2-substituted indoles.



3 4 5

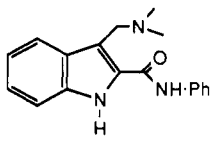
(for designation of R, see Table)

Results and Discussion

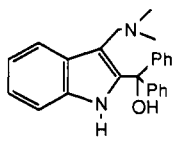
Synthesis of 1-[(*N*,*N*-Dimethylamino)methyl]-indole (3). 1-[(*N*,*N*-Dimethylamino)methyl]indole (3) (isogramine), was readily prepared on a multigram scale (83% yield) by the Mannich reaction of indole, formaldehyde, and dimethylamine at 0–5 °C.[10] The isogramine (3), which was isolated by distillation, contains a trace amount (ca. 2%) of gramine, which does not interfere with the subsequent lithiation.

Lithiation of Isogramine (3). The lithiation of isogramine (3) was accomplished by treatment with 1.0 equiv of butyllithium at low temperature.[4] To avoid any decomposition of the 2-lithio species, caused by the exothermicity of the reaction, the butyllithium was added to the tetrahydrofuran (THF) solution of **3** at −78 °C. The solution was maintained at −78 °C for 10 min and then allowed to warm to ca. 0 °C over 30–45 min. Quenching the lithio species with various electrophiles at low temperature gave the 2-substituted isogramine derivatives **4** in moderate to good yields after normal workup (H_2O at room temperature) (Table I). In comparison with Sundberg's sulfonyl-directed lithiation,[8a] the present aminal-directed lithiation procedure generally affords cleaner reaction products in comparable or somewhat greater yields.

As reported by Hlasta and Bell,[4] the rearrangement of isogramine to gramine was found in some cases. Thus, when the lithiated isogramine was treated with phenyl isocyanate at −78 °C followed by slow warming to room temperature overnight, the gramine derivative **6** was isolated in 93% yield. Attempts to avoid this rearrangement by repeating the reaction at low temperature was unsuccessful (−78 °C for 1 h followed by quenching with methanol at −78 °C). Similar rearrangement was observed using *tert*-butyl isocyanate as the electrophile.



6



7

Deprotection of 2-Substituted Isogramines 4. Our initial investigation utilized alcohol **4a** as a model substrate. Stirring the ethanol–THF solution of **4a** with $NaBH_4$ at room temperature did not cleave the indole *N*-aminal bond. However, reflux of the solution followed by chromatography of the crude product provided **5a** in 67% yield and the gramine derivative **7** in 22% yield. The cleavage of the aminal group of carbinol **4a** with $NaBH_4$ in ethanol represents a general approach to deprotected 2-indolyl carbinols, since 2-indolyl carbinols are too sensitive to survive under strongly acidic conditions (e.g. TFA, acetic anhydride/LiBr, or acetic anhydride/BF_3).[4,8a] Deprotection of the other 2-substituted isogramine derivatives under the same reaction conditions gives the corresponding deprotected indoles **5** in good yield, along with minor amounts of the rearranged products. The results are summarized in Table I. Our reductive elimination method using $NaBH_4$ can be successfully employed for the deprotection of *N*-aminal indoles which possess substituents not reduced under these conditions. Compounds which contain reducible functions, such as ketones or aldehydes, can be deprotected with sodium methoxide in methanol as previously reported.[4]

In comparison with our CO_2 protocol,[9] the CO_2 method is superior to the present method in that the protecting group can be easily introduced and removed, and the whole reaction sequence can be performed in one-pot. However, the aminal method has its own merits: the lithiation,

(4) Hlasta, D. J.; Bell, M. R. *Heterocycles* **1989**, *29*, 849.
(5) Katritzky, A. R.; Lue, P.; Yannakopoulou, K. *Tetrahedron* **1990**, *46*, 641.
(6) (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 805. (b) Katritzky, A. R.; Drewniak, M. *Tetrahedron Lett.* **1988**, *29*, 1755. (c) Katritzky, A. R.; Drewniak, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2339.
(7) The authors in ref 4 reported that the use of reductive condition to remove the aminal group failed. We believe that they probably used Na/NH_3 in an aprotic solvent, which is not effective for the removal of the aminal group.
(8) (a) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324. (b) Sundberg, R. J.; Parton, R. L. *Ibid.* **1976**, *41*, 163. (c) Sundberg, R. J.; Bloom, J. D. *Ibid.* **1980**, *45*, 3382. (d) Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1439. (e) Kano, S.; Sugino, E.; Hibino, S. *J. Chem. Soc., Chem. Commun.* **1980**, 1241. (f) Gribble, G. W.; Barden, T. C.; Johnson, D. A. *Tetrahedron* **1988**, *44*, 3195. (g) Cooper, M. M.; Hignett, G. J.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3008. (h) Gribble, G. W.; Fletcher, G. L.; Ketcha, D. M.; Rajopadhye, M. *J. Org. Chem.* **1989**, *54*, 3264.
(9) (a) Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935. (b) Katritzky, A. R.; Akutagawa, K.; Jones, R. A. *Synth. Commun.* **1988**, *18*, 1151. (c) Bergman, J.; Venemalm, L. *Tetrahedron Lett.* **1988**, *29*, 2993.
(10) Swaminathan, S.; Narasimhan, K. *Chem. Ber.* **1966**, *99*, 889.

Table I. Preparation of 2-Substituted Isogramines 4 and 2-Substituted Indoles 5

		2-substituted isogramines 4[a]			2-substituted indoles 5[a]		
electrophile	R	compd	mp, °C	yield,[b]	compd	mp, °C	yield,[b] %
$(C_6H_5)_2CO$	$(C_6H_5)_2COH$	**4a**	165–167	85	**5a**	136–137	67
C_6H_5CHO	C_6H_5CHOH	**4b**	108–109	75	**5b**	oil	63
4-$CH_3C_6H_4CHO$	4-$CH_3C_6H_4CHOH$	**4c**	95–97	77	**5c**	oil[c]	43
$(C_6H_5S)_2$	C_6H_5S	**4d**	oil	87	**5d**	64–66	71
CH_3I	CH_3	**4e**	oil	77	**5e**	58–60	56
4-$CH_3OC_6H_4CHO$	4-$CH_3OC_6H_4CHOH$	**4f**	108–110	51	**5f**	96–98	51

[a] All new compounds gave satisfactory elemental analyses (C, H, N) and spectral (^1H and ^{13}C NMR) data consistent with their assigned structures, see Experimental Section. [b] The yield refers to isolated and purified (crystallized or column chromatographed) product. [c] Attempted crystallization failed to give a solid.

combined with the subsequent electrophilic substitution, affords cleaner products in good yields, and the removal of protecting group using $NaBH_4$ is gentle and reliable. Furthermore, since the aminal group tolerates a variety of acidic and basic conditions,[4] subsequent synthetic manipulation of the indole is possible.

In summary, we have described a convenient, efficient, and reliable synthesis of 2-substituted indoles. The reductive elimination procedure using $NaBH_4$ is effective for the deprotection of *N*-aminal groups of heterocycles which resist mild acidic hydrolysis.

Experimental Section

Melting points of the products were measured in open capillaries with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian VXR-300 FT mode NMR spectrometer operating at 300 MHz, and chemical shifts are reported in parts per million downfield from tetramethylsilane as the internal reference. ^{13}C NMR spectra were recorded on a Varian VXR-300 FT mode NMR spectrometer operating at 75 MHz using deuterated solvent ($CDCl_3$) as the internal reference. Column chromatography was performed on MCB silica gel (230–400 mesh). Tetrahydrofuran (THF) was distilled from sodium/benzophenone under nitrogen. The electrophiles were purified by standard methods before use. Lithiation reactions were performed in oven-dried (130 °C) Schlenk type reactors under argon or nitrogen.

The purity of all title compounds was judged to be ≥90% by ^{13}C and ^1H NMR spectral determinations.

Preparation of 1-[(*N*,*N*-Dimethylamino)methyl]indole (3). According to the literature procedure,[10] indole (23.4 g, 0.2 mol) was suspended in 60 mL of H_2O, formaldehyde (15 mL, 0.2 mol, 37% aqueous solution), and dimethylamine (0.2 mol, 20% w/w aqueous solution) were added simultaneously over 35 min at 0 °C. The mixture was stirred for 3 h at 0 °C and then warmed to room temperature overnight. The precipitated oil was extracted with diethyl ether (4 × 25 mL), and the combined organic layers were extracted with 2 N HCl (2 × 50 mL). The acid extracts were immediately made alkaline with 45 mL of 40% NaOH, followed by extraction with diethyl ether (4 × 15 mL). Evaporation of the solvents yielded a honey-colored liquid (25 g) which was distilled to give 19 g of product (83% based on the indole consumed; unreacted indole was recovered from acid extracted ether solution): bp 125–127 °C (5 mmHg) (lit.[10] bp 130 °C (6 mmHg)); ^1H NMR ($CDCl_3$, TMS) δ 2.23 (s, 6 H, CH_3), 4.62 (s, 2 H, CH_2), 6.47 (d, *J* = 3 Hz, 1 H), 7.02–7.61 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 42.5 (CH_3), 68.5 (CH_2), 101.4, 109.8, 119.2, 120.5, 121.3, 127.6, 128.2, 136.6.

Preparation of 2-Substituted 1-[(*N*,*N*-Dimethylamino)methyl]indole 4. General Procedure for the *N*-Aminal-Directed Lithiation. 1-[(*N*,*N*-Dimethylamino)methyl]indole (2.0 g, 11.5 mmol) was dissolved in 30 mL of dried THF under nitrogen, and butyllithium (11.5 mmol, 4.6 mL, 2.5 M in hexane) was added dropwise over 5 min at −78 °C. The resultant yellow solution was stirred for another 10 min and then warmed to 0 °C over 35–40 min. The solution was recooled to −78 °C, and the electrophile (11.5 mmol) in 2 mL of THF was added dropwise. The mixture was stirred at −78 °C for 1 h and warmed to room temperature over several hours. After quenching with H_2O and extraction with diethyl ether, the combined organic layers were dried over Na_2SO_4 and concentrated at reduced pressure to give the crude product. Further purification was performed by recrystallization or column chromatography.

[1-[(*N*,*N*-Dimethylamino)methyl]indol-2-yl]diphenylmethanol (4a): granules (from $CHCl_3$–hexane); mp 165–167 °C; ^1H NMR ($CDCl_3$) δ 2.11 (s, 6 H, CH_3), 4.09 (s, 2 H, CH_2), 5.86 (s, 1 H, indole-3H), 7.12–7.50 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 41.4 (CH_3), 65.3 (CH_2), 77.1, 106.9, 108.6, 119.9, 121.1, 122.2, 126.4, 127.1, 127.4, 127.8, 138.6, 145.8, 145.9.

Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.43; H, 6.79; N, 7.72.

[1-[(*N*,*N*-Dimethylamino)methyl]indol-2-yl]phenylmethanol (4b): needles (from diethyl ether and hexane); mp 108–109 °C; ^1H NMR ($CDCl_3$) δ 2.15 (s, 6 H, CH_3), 4.12 (d, *J* = 12.2 Hz, 1 H, CH_2), 4.39 (d, *J* = 12.2 Hz, 1 H, CH_2), 5.97 (s, 1 H, CH), 6.37 (s, 1 H, indole-3H), 7.08–7.56 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 41.5 (CH_3), 65.0 (CH_2), 68.8, 104.3, 108.6, 119.9, 121.0, 122.0, 126.0, 127.0, 127.1, 128.1, 138.1, 142.0, 142.2.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.76; H, 7.21; N, 9.92.

[1-[(*N*,*N*-Dimethylamino)methyl]indol-2-yl]-*p*-tolylmethanol (4c): needles (from hexane and petroleum ether); mp 95–97 °C; ^1H NMR ($CDCl_3$) δ 2.19 (s, 6 H, CH_3), 2.35 (s, 3 H, CH_3), 4.17 (d, *J* = 12.2 Hz, 1 H, CH_2), 4.42 (d, *J* = 12.2 Hz, 1 H, CH_2), 5.95 (s, 1 H, CH), 6.40 (s, 1 H, indole-3H), 7.09–7.36 (m, 7 H), 7.56 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.1, 41.7, 65.2, 68.8, 104.4, 108.7, 119.9, 121.1, 122.1, 125.9, 127.1, 128.8, 136.7, 138.3, 139.1, 142.5.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.63; H, 7.47; N, 9.18.

1-[(*N*,*N*-Dimethylamino)methyl]-2-(phenylthio)indole (4d): oil (purified by column chromatography using $CHCl_3$ as eluate); ^1H NMR ($CDCl_3$) δ 2.22 (s, 6 H, CH_3), 4.70 (s, 2 H, CH_2), 6.89 (s, 1 H, indole-3H), 7.04–7.25 (m, 7 H), 7.49 (d, *J* = 8 Hz, 1 H), 7.60 (d, *J* = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 42.7, 65.8, 111.1, 112.7, 120.2, 120.6, 123.0, 125.8, 126.7, 127.0, 127.7, 129.0, 137.1, 138.8; mass spectrum, *m*/*z* (relative intensity) 282 (M^+, 8), 238 (6), 224 (3), 205 (5), 89 (2), 77 (3), 65 (2), 59 (9), 58 (100); MS (HR) calcd for $C_{17}H_{18}N_2S$ 282.1191, found 282.1192.

1-[(*N*,*N*-Dimethylamino)methyl]-2-methylindole (4e): oil (purified by column chromatography using $CHCl_3$ as eluate); ^1H NMR ($CDCl_3$) δ 2.17 (s, 6 H, CH_3), 2.38 (s, 3 H, CH_3), 4.41 (s, 2 H, CH_2), 6.21 (s, 1 H, indole-3H), 6.98–7.11 (m, 2 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.7, 42.6, 65.6, 100.8, 109.5, 119.4, 120.5, 128.0, 137.0, 137.6; mass spectrum, *m*/*z* (relative intensity) 188 (M^+, 8), 144 (9), 130 (8), 115 (2), 130 (1), 89 (3), 77 (2), 58 (100), 42 (7); MS (HR) calcd for $C_{12}H_{16}N_2$ 188.1313, found 188.1305.

[1-[(*N*,*N*-Dimethylamino)methyl]indol-2-yl](*p*-methoxyphenyl)methanol (4f): purified by column chromatography ($CHCl_3$ as eluate); mp 108–110 °C; ^1H NMR ($CDCl_3$) δ 2.19 (s, 6 H, CH_3), 3.79 (s, 3 H, CH_3), 4.20 (d, *J* = 12.5 Hz, 1 H, CH_2), 4.42 (d, *J* = 12.5 Hz, 1 H, CH_2), 5.93 (s, 1 H, CH), 6.37 (s, 1 H, indole-3H), 6.87–7.57 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 41.7, 55.2, 65.1, 68.5, 104.3, 108.7, 119.5, 119.9, 121.0, 122.1, 127.1, 127.2, 134.1, 138.3, 142.6, 158.7.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15; N, 9.03. Found: C, 73.73; H, 7.30; N, 8.73.

Preparation of 2-Substituted Indoles 5. General Procedure for the Deprotection of *N*-Aminal Indoles. N-Protected indole derivative 4 (5 mmol) was dissolved in ethanol–THF solution (25 mL), and a slight excess of sodium borohydride was added. The mixture was stirred at reflux for several hours. The

solvent was evaporated at reduced pressure, and the residue was treated with H_2O, extracted with ethyl acetate or diethyl ether, and dried (Na_2SO_4). Evaporation of the solvent gave the crude product, which was further purified by column chromatography.

Indol-2-yldiphenylmethanol (5a): separated by column chromatography ($CHCl_3$ as eluate); granule (from hexane); mp 136–137 °C (lit.[11] mp 136–139.5 °C); ^1H NMR ($CDCl_3$) δ 3.20 (s, 1 H, OH), 6.03 (d, J = 2 Hz, indole-3H), 7.01–7.47 (m, 14 H), 8.28 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 77.2, 103.4, 111.0, 119.8, 120.7, 122.2, 127.1, 127.6, 128.0, 128.2, 136.0, 142.6, 145.1.

Indol-2-ylphenylmethanol (5b): separated by column chromatography ($CHCl_3$ as eluate); oil (lit.[8a] oil); ^1H NMR ($CDCl_3$) δ 5.75 (s, 1 H, OH), 5.95 (s, 1 H, CH), 6.17 (s, 1 H, indole-3H), 7.04–7.28 (m, 8 H), 7.49 (d, J = 7.6 Hz, 1 H), 8.21 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 70.6, 100.8, 111.0, 119.8, 120.5, 122.0, 126.5, 127.8, 127.9, 128.5, 136.1, 140.1, 141.5.

Indol-2-yl-*p*-tolylmethanol (5c): separated by column chromatography ($CHCl_3$–CH_3OH, 19.9:0.1); oil; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 3.19 (bs, 1 H, OH), 5.74 (s, 1 H, CH), 6.17 (d, J = 2 Hz, 1 H, indole-3H), 6.97–7.19 (m, 7 H), 7.50 (d, J = 8 Hz, 1 H), 8.29 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3), 70.5, 100.7, 111.0, 119.7, 120.5, 121.9, 126.5, 128.0, 129.2, 136.1, 137.8, 138.6, 140.3; mass spectrum, m/z (relative intensity) 237 (M^+, 64), 220 (70), 204 (100), 130 (24), 120 (38), 119 (60), 91 (82), 79 (20), 65 (31); MS (HR) calcd for $C_{16}H_{15}NO$ 237.1153, found 237.1146.

2-(Phenylthio)indole (5d): separated by column chromatography ($CHCl_3$ as eluate); needles; mp 64–66 °C; ^1H NMR ($CDCl_3$) δ 6.84 (d, J = 2 Hz, 1 H, indole-3H), 7.01–7.75 (m, 9 H), 7.99 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 110.9, 111.5, 120.2, 120.7, 123.2, 126.1, 127.4, 128.4, 129.0, 129.1, 136.6, 137.7; mass spectrum, m/z (relative intensity) 225 (40), 117 (3), 110 (24), 77 (11), 65 (7), 51 (4), 39 (6); MS (HR) calcd for $C_{14}H_{11}NS$ 225.0612, found 225.0615.

2-Methylindole (5e): separated by column chromatography ($CHCl_3$ as eluate); mp 58–60 °C (lit.[9a] mp 58–60 °C); ^1H NMR ($CDCl_3$) δ 2.41 (s, 3 H, CH_3), 6.20 (d, J = 3 Hz, indole-3H), 7.07–7.52 (m, 4 H), 7.85 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 13.7, 100.3, 110.2, 118.9, 119.5, 120.8, 129.0, 135.0, 136.7.

Indol-2-yl(4-methoxyphenyl)methanol (5f): separated by column chromatography ($CHCl_3$–CH_3OH, 19.9:0.1); mp 96–98 °C (lit.[8a] mp 98–100 °C); ^1H NMR ($CDCl_3$) δ 3.01 (bs, 1 H, OH), 3.72 (s, 3 H, CH_3), 5.75 (s, 1 H, CH), 6.18 (d, J = 2 Hz, indole-3H), 6.78 (d, J = 8 Hz, 2 H), 7.05–7.51 (m, 6 H), 8.28 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 55.2, 70.3, 100.6, 111.0, 119.1, 119.8, 120.5, 121.9, 127.9, 128.0, 133.8, 136.1, 140.4, 159.0.

Registry No. 3, 5379-79-3; **4a**, 126594-12-5; **4b**, 126754-44-7; **4c**, 126754-45-8; **4d**, 126754-46-9; **4e**, 126754-47-0; **4f**, 126754-48-1; **5a**, 20538-21-0; **5b**, 40900-00-3; **5c**, 126754-49-2; **5d**, 120517-31-9; **5e**, 95-20-5; **5f**, 40900-01-4; $(C_6H_5)_2CO$, 119-61-9; C_6H_5CHO, 100-52-7; 4-$CH_3C_6H_4CHO$, 104-87-0; $(C_6H_5S)_2$, 882-33-7; 4-$CH_3OC_6H_4CHO$, 123-11-5; indole, 120-72-9; gramine, 87-52-5.

Supplementary Material Available: ^{13}C NMR spectra for compounds **4d**, **4e**, **5c**, **5d**, and **5f** (5 pages). Ordering information is given on any current masthead page.

(11) Dolby, L. J.; Lord, P. D. *J. Org. Chem.* **1969**, *34*, 2988.

Single-Step Removal of the Allyl Ether Protecting Group with $(Ph_3P)_4RhH$ and Trifluoroacetic Acid

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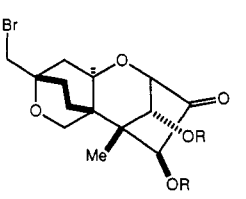
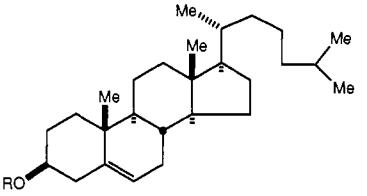
During a study directed toward the synthesis of the highly functionalized trichothecene anguidine and its congeners,[2] we were confronted with the problem of removal of the allyl protecting groups in tetracycle **1a**. A number of procedures for this transformation have been reported,[3] but only the method of Corey and Suggs[3c] was deemed mild enough for our substrate. This procedure effects isomerization of the double bond of the allyl group to the vinyl ether with Wilkinson's catalyst [$(Ph_3P)_3RhCl$] in refluxing ethanol in the presence of diazabicyclooctane (DABCO). The base prevents premature liberation of propionaldehyde, the byproduct of hydrolysis which undergoes decarbonylation in the presence of the catalyst and thereby generates a less active catalyst.[3c] Although isomerization of the double bonds of **1a** proved successful, acidic hydrolysis of the vinyl ethers or ozonolysis followed by deformylation (K_2CO_3/MeOH) gave complex mixtures of products.



1a, R = $CH_2CH{=}CH_2$
b, R = H



2a, R = $CH_2CH{=}CH_2$
b, R = $CH_2C(CH_3){=}CH_2$
c, R = $CH_2CH{=}CHCH_3$ (E + Z)
d, R = $CH_2CH{=}C(CH_3)_2$
e, R = H

A recent report by Sundberg[4] demonstrated that a tertiary allylic amine can be deprotected with 25 mol % of hydridotetrakis(triphenylphosphine)rhodium[5,6] [$(Ph_3P)_4RhH$] in the presence of trifluoroacetic acid in refluxing ethanol. When this procedure was applied to bis allyl ether **1a**, (cat. 25 mol %; 100 equiv of TFA), the diol **1b** was isolated directly in 72% yield.

To explore the reactivity of this catalytic system, we prepared the series of allyl cholesteryl ethers **2a–d** by the Williamson procedure (KH, THF, reflux; allylic halide). Each deprotection was conducted in refluxing ethanol for 30 min using equal amounts of substrate and trifluoroacetic acid and only 3 mol % of catalyst. Table I reveals the relative reactivity of the four allyl ethers under these conditions. Clearly, the allyl ether **2a** is cleaved faster than the mono-methyl-substituted allyl ethers **2b** and **2c**, and

Table I. Isomerization of Cholesteryl Allyl Ethers[a]

ether	isolated yields, % (ether/**2e**)
2a	0/98
2b	66/16
2c[b]	80/9
2d	93/4

[a] Conditions: see Experimental Section. In the absence of catalyst and the presence of TFA, a <4% yield of cholesterol was obtained in 6.5 h. [b] Mixture of E/Z (~5:1) in starting material and recovered **2c**.

(1) Recipient of a Dox Fellowship, 1987–1988. Taken in part from the Ph.D. Thesis of S.B.S., Yale University, 1989.
(2) Ziegler, F. E.; Sobolov, S. B. *J. Am. Chem. Soc.* **1990**, *112*, 2749.
(3) (a) Price, C. C.; Snyder, W. H. *J. Am. Chem. Soc.* **1961**, *83*, 1773. (b) Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558. (c) Corey, E. J.; Suggs, W. J. *J. Org. Chem.* **1973**, *38*, 3224. (d) Kariyone, K.; Yazawa, H. *Tetrahedron Lett.* **1970**, 2885.
(4) Sundberg, R. J.; Hamilton, G. S.; Laurino, J. P. *J. Org. Chem.* **1988**, *53*, 976.
(5) Ahmed, N.; Robinson, S. D.; Uttley, M. F. *J. Chem. Soc., Dalton Trans.* **1972**, 843.
(6) For the isomerization of *N*-acylallylamines with this catalyst, see: Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.

0022-3263/90/1955-3691$02.50/0