Tetrahedron Vol. 42, No. 11, pp. 2957 to 2969, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00
Pergamon Journals Ltd.

ORGANOMETALLIC REAGENTS IN SYNTHESIS

A NEW PROTOCOL FOR CONSTRUCTION OF THE INDOLE NUCLEUS

AMOS B. SMITH, III,*† MELEAN VISNICK,‡ JOHN N. HASELTINE
and PAUL A. SPRENGELER
Department of Chemistry, Laboratory for Research on the Structure of Matter and the Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, PA 19104, U.S.A.

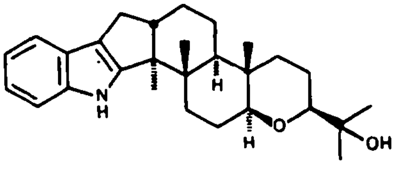
(*Received in U.S.A.* 10 *October* 1985)

Abstract—Organodilithium reagents derived from 2-alkyl-N-trimethylsilyl anilines undergo condensation with esters of carboxylic acids to afford substituted indoles. A total of 16 examples are reported; yields in general were good. In conjunction with this program, a convenient, large-scale procedure for preparation of monosilylated anilines was also developed. To demonstrate the utility of the new indole protocol in natural products synthesis, efficient syntheses of (+)-cinchonamine and (+)-epi-cinchonamine as well as a tetracyclic model system for the architecturally complex penitrem mycotoxins were completed in regio- and stereoselective fashion.

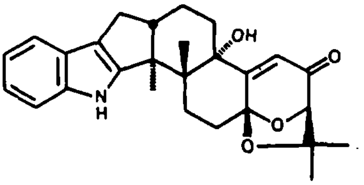
INTRODUCTION AND BACKGROUND

The indole ring system has captured the imagination of organic chemists for over a century. Early work in the area dates to the 1866 isolation of indole from indigo by von Baeyer.[1] For much of the early work commercial interests in synthetic dyestuffs served as the focal point. However since the isolation of the indole alkaloids as the active principles from medicinal plants (i.e. antibiotics, anti-inflammatory, antihypertensive and antitumor agents), the indole nucleus has taken on considerable pharmacological importance. As testament to the activity in this area, no less than ten major syntheses of the indole ring system (i.e. benzo[*b*]pyrrole) have been reported.[2] Nonetheless, with the structural elucidation of increasingly complex indole alkaloids, new more efficient (i.e. convergent) methodology for assembly of the indole nucleus is required.[3]

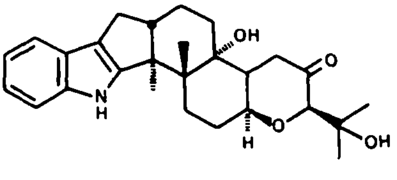
A STRATEGY FOR CONSTRUCTION OF THE PENITREM TREMORGENIC ALKALOIDS



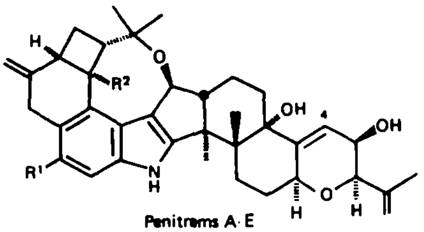
Paspaline (1)



Paspalinine (2)



Paxilline (3)



Penitrems A-E

(4) A $R^1 = Cl$, $R^2 = OH$; 4a, 4aa-epoxide
(5) B $R^1 = R^2 = H$; 4a, 4aa-epoxide
(6) C $R^1 = Cl$, $R^2 = H$
(7) D $R^1 = R^2 = H$
(8) E $R^1 = H$, $R^2 = OH$; 4a, 4aa-epoxide

Our interest in the indole alkaloid field began with the tremorgenic mycotoxins isolated from *Claviceps paspali*.[4] Initial efforts culminated in the first total synthesis of paspaline (1),[5] the simplest member of this rapidly growing family.[6] In a second generation approach, we sought a protocol which would be amenable to a broad spectrum of these compounds, including the architecturally novel penitrems.[7] With

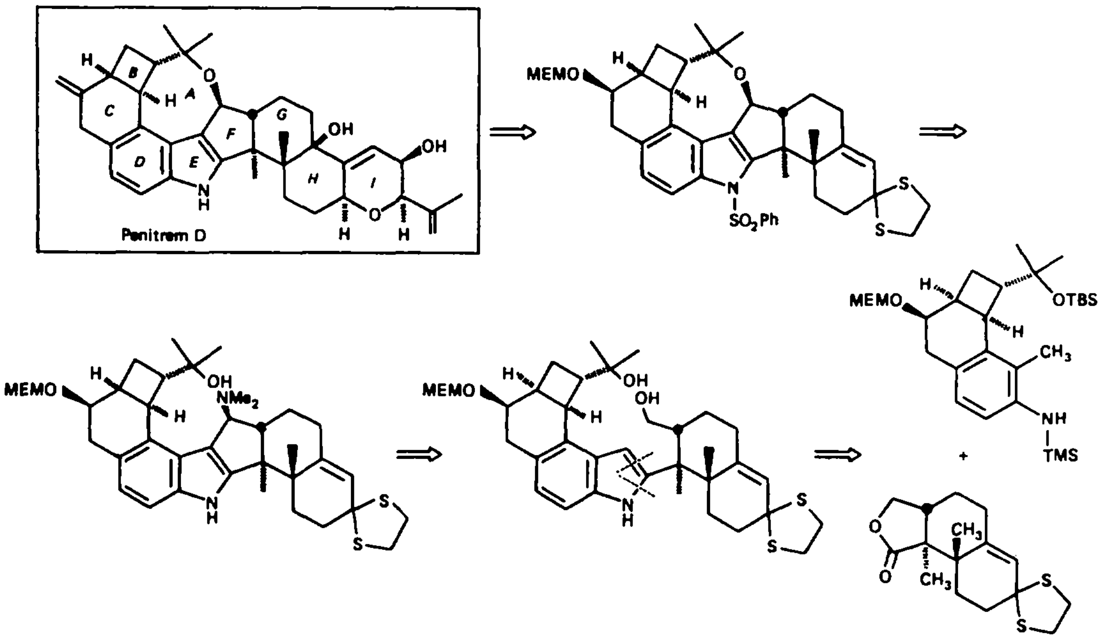
---

† Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980–1985.

‡ American Cancer Society Postdoctoral Fellow, 1983–1985.

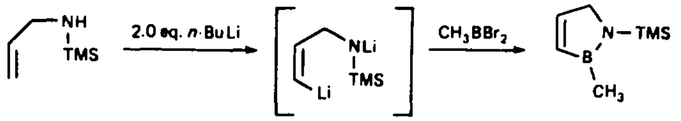
this goal in mind, the focal point of our penitrem antithetic analysis centered on union of two advanced intermediates in an indole forming reaction.

PENITREM D RETROSYNTHETIC ANALYSIS

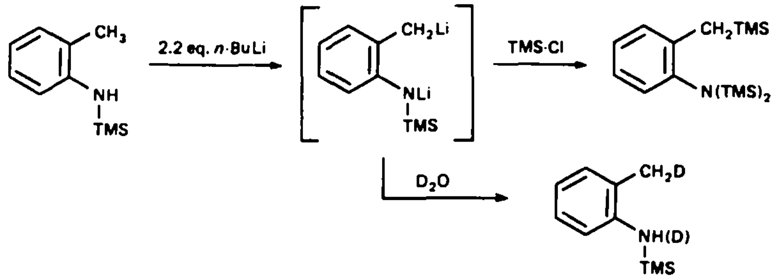


A NEW INDOLE SYNTHETIC PROTOCOL

Well aware of the inherent problems in preparing C(2)-substituted indoles[8] of moderate complexity, we embarked on the development of a new approach. We reasoned that the dianion derived from an appropriately substituted aniline would react with a suitable electrophile (i.e. aldehyde or ester) to provide a C(2)-substituted indole.[9] A search of the literature uncovered a report by Schmid and co-workers in 1981 on the bismetallation of N-trimethylsilyl allylic amines (Eq. 1).[10] Soon thereafter, Corriu and Moreau[11] disclosed that N-trimethylsilyl-*o*-toluidine underwent smooth metallation with n-butyllithium, as evidenced by the isolation of the trisilylated derivative (Eq. 2).[3] In our hands, we found that quenching the reaction mixture obtained upon heating a solution of N-trimethylsilyl-*o*-toluidine and 2.2 equivalents of n-butyllithium in hexanes for 6 h, with deuterium oxide led to N-trimethylsilyl-*o*-toluidine (94% recovery) containing greater than 95% deuterium incorporation at the benzylic position (Eq. 3). Alternatively, interception of the presumed organodilithium intermediate with benzaldehyde gave aminocarbinol **9** in 55% yield. Subsequent Cornforth oxidation[12] led to 2-phenylindole; the overall yield from N-trimethylsilyl-*o*-toluidine was 25%. To avoid the intermediate oxidation step, ethyl benzoate was explored as the electrophile. The result was a substantial increase in the yield of 2-phenylindole (i.e. 65%). Further investigation indicated that order of addition (i.e. normal or inverse had little effect on the overall yield (Table 1, entries 1 and 4).

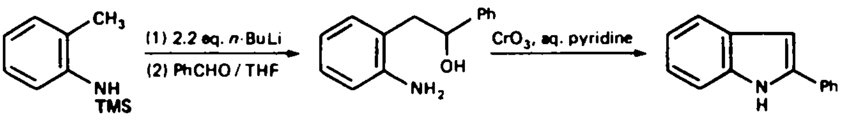


(1)



(2)

(3)



9

We interpret this reaction sequence to involve condensation of the benzylic anion with the ester carbonyl to afford an intermediate N-lithioketoamine. Subsequent intramolecular heteroatom Peterson olefination then affords an indolinine, which in turn undergoes tautomerization to afford the respective indole. Precedent for the heteroatom Peterson olefination can be found in the early work of Wannagat and co-workers,[13] with more recent examples coming from Hart's[14] laboratory.

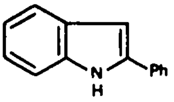
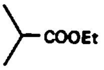
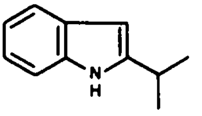
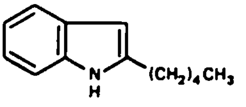
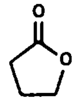
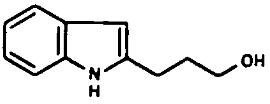
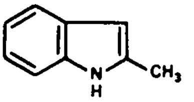
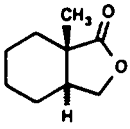
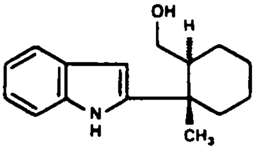
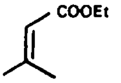
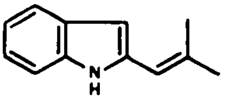
The examples listed in Table 1 document the versatility of this indole synthesis.[3] In general, the method is best for esters which are least likely to undergo facile enolization. Unsaturated esters that show a propensity to undergo polymerization afford only modest yields (Table 1, entry 7). The one exception was ethyl formate which afforded indole in only 11% yield.

A brief examination of other potential electrophiles revealed that N,N-dimethylformamide gave indole in 42% yield, as well as a 20% yield of N-trimethylsilyl indole. In an analogous fashion N,N-diethyl benzamide gave 2-phenylindole in 63% yield. The latter two reactions however appear to involve a different mechanism, given the isolation of N-trimethylsilyl indole products. Simple acid chlorides on the other hand were not effective electrophiles.

PREPARATION OF MONOSILYLATED ANILINES: AN EFFICIENT PROCEDURE

During the course of this investigation it became necessary to develop a general route for the precursor monosilylated anilines. Our initial procedure, which involved generation of the lithioamide (1.2 equiv n-

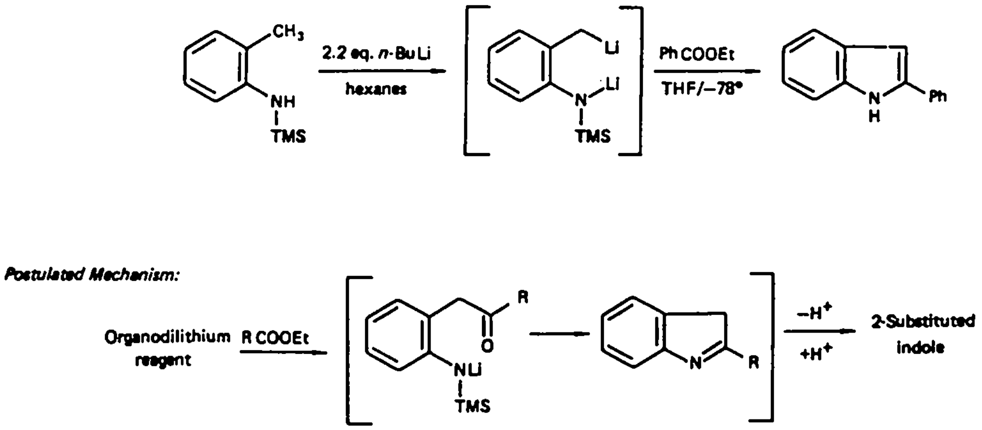
Table 1. Synthesis of indoles

Entry	*Electrophile*	*Indole*[11]	*Method of Addition*[a]	*Yield*	*m.p.*
1.	PhCOOEt		A B	65%	182-184° (lit. 185-187°)[15]
2.			A	62%	72.5-73° (lit. 73-74°)[16]
3.	$CH_3(CH_2)_4COOEt$		A	62%	44-44.5° (lit. 47-48°)[17]
4.			A B	61% 59%	54.5-55.5° (lit. 53-55°)[18]
5.	CH_3COOEt		A	60%	59-59.5° (lit. 56-57°)[19]
6.			A	59%	152.5-154°[20]
7.			B	38%	103-106° (lit. 102-103°)[21]

a) Method A - the preformed organodimetallic reagent in hexanes 0.2 mmol/mL) is cooled to −78°C, and the ester dissolved in THF is added in one operation at this temperature.

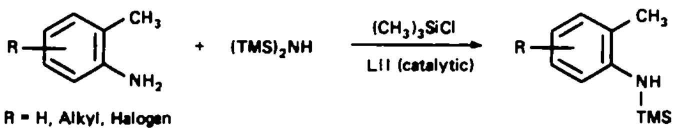
Method B - the preformed organodimetallic reagent is added via cannula to the ester in THF at −78°C.

NEW INDOLE SYNTHESIS



Postulated Mechanism:

butyllithium, −78°) followed by silylation (TMSCl, 0°), although useful for the preparation of 2-methyl- and 2-ethyl-N-trimethylsilylaniline (85 and 82% yield, respectively), was inconvenient on large scale. In addition, it was not widely applicable to systems prone to hydrolyze (*vide infra*). Accordingly, a new method was developed, wherein the aniline is heated at reflux with three equivalents of hexamethyldisilazane and a catalytic amount of trimethylsilyl chloride under argon in the presence of catalytic lithium iodide (Eq. 4). Silylation, which occurs without the added lithium iodide, is much faster in the presence of iodide, presumably due to the *in situ* formation of a catalytic amount of the more reactive trimethylsilyl iodide.



(4)

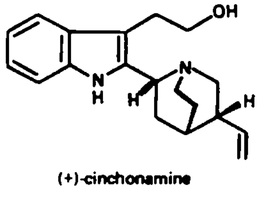
Progress of the reaction is conveniently monitored by capillary GLC. After greater than 95% conversion, the catalyst (TMSI) is effectively quenched with cyclohexene oxide (40 mol%)[22] and the reaction mixture concentrated *in vacuo*. Kugelrohr distillation then gives the silylated aniline contaminated in some cases with a small amount ($\leqslant 3\%$) of the bissilyl derivative. This method, which allows convenient access to a variety of silylated anilines on both large and small scales, precludes a hydrolytic work-up. Significant in the latter regard is the observation that N-trimethylsilyl-2-methyl-4-methoxyaniline hydrolyzes immediately upon exposure to the atmosphere. The non-aqueous procedure however, affords N-trimethylsilyl-2-methyl-4-methoxyaniline (Table 2, entry 3) in 95% yield.

PREPARATION OF SUBSTITUTED INDOLES

The method described above for generation of the organodilithium reagent of N-trimethylsilyl-*o*-toluidine (that is simple dianion formation) was found to be inadequate for preparation of indoles substituted at C(3)—C(7). For example, in the case of 2-ethyl-N-trimethylsilylaniline, TMEDA was required presumably due to the decreased kinetic acidity of the benzylic hydrogens. In other examples where the aromatic ring is substituted, insolubility of the monoanion in hexane was a significant obstacle to further metallation. This problem could be overcome in some cases by the use of polar solvents such as diethyl ether or cyclohexane, while in other cases an additive such as TMEDA was necessary. Several examples of both types of anilines are listed in Table 3. In accord with the inherent difficulties with dianion formation, the yields realized for the substituted indoles were uniformly lower than the simple C(2)-indoles. However, if one considers the difficulty associated with construction of indoles substituted at C(3) through C(7), in conjunction with the potential pharmacological importance of this class, the moderate yields may be inconsequential.

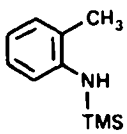
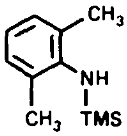
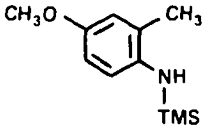
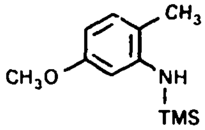
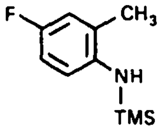
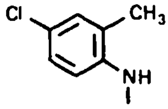
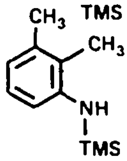
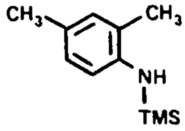
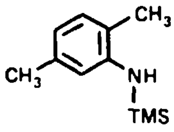
SYNTHESIS OF CINCHONAMINE AND EPI-CINCHONAMINE: A FURTHER APPLICATION OF THE INDOLE PROTOCOL

Cinchonamine, the most prominent member of the 2,2′-indolquinuclidine alkaloids, was isolated from the bark of *Remijia purdiena* in 1881 by Arnaud.[29] The structure however remained unknown until 1950, when Prelog and co-workers,[30] employing classical methods, determined the structure and relative stereochemistry. Some 20 years later Sava and Matsumura[31]



(+)-cinchonamine

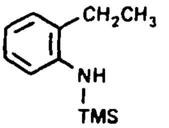
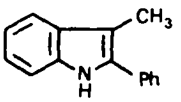
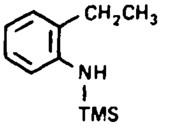
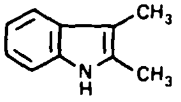
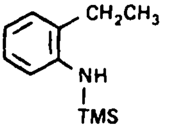
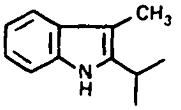
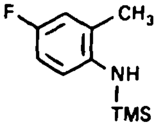
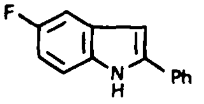
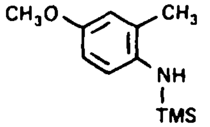
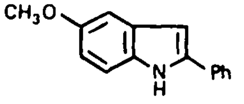
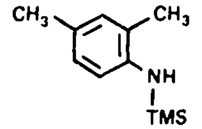
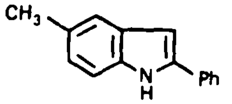
Table 2. Synthesis of N-trimethylsilylanilines

Entry	*Silylated Aniline*	*Quantity of Substrate* [a]	*Reaction Time*	*Isolated Yield* [b]
1.		3.0 g	20 hrs.	92%
2.		4.0 g	22 hrs.	80%
3.		1.3 g	1 hr.	95%
4.		0.7 g	2.5 hrs.	96%
5.		1.0 g	4 hrs.	81%
6.		10.0 g	8 hrs.	86%
7.		9.8 g	3.5 hrs.	80%
8.		3.4 g	3.0 hrs.	88%
9.		10.0 g	5.0 hrs.	97%

[a] The substrate anilines were used as directly obtained from Aldrich.

[b] Yields are of purified material either by short-path or kugelrohr distillation.

Table 3. Synthesis of disubstituted indoles

Entry	*Silylated Aniline*	*Indole*	*Yield*	*m.p.*
1.			50%	91.5-92.5° (lit. 89-90°)[23]
2.			32%	103-105° (lit. 106°)[24]
3.			45%	liquid[25]
4.			36%	179-180° (lit. 178°)[26]
5.			35%	166° (lit. 162-164°)[27]
6.			56%	218-219° (lit. 216-217°)[28]

established the absolute stereochemistry via chemical correlation with dihydrocorynantheol. The first synthetic work in this area, a partial synthesis of cinchonamine, was reported by Preobrazhenskii and co-workers[32] in 1960. To date the only total synthesis of this alkaloid is that of Uskoković and co-workers,[33] which was disclosed in 1976.

To demonstrate the utility of our new indole protocol in natural products synthesis, we completed a formal total synthesis of cinchonamine and its C(2′)-epimer.† To this end, the epimeric quinuclidine esters **10** and **11** were prepared by degradation of quinine according to the procedure of Preobrazhenskii and co-workers.[34] Condensation of each ester in turn with the organodilithium reagent derived from N-trimethylsilyl-*o*-toluidine afforded indoles **12** and **13** in 62 and 32% yield, respectively. Of significance here is the formation of both indoles without epimerization at C(2) of the quinuclidine ring. To complete the synthesis, the C(3)-β-hydroxyethyl substituent was then introduced according to the procedure of Uskoković and co-workers.[33] That is, the indole Grignard reagents of **12** and **13** were prepared at 0° and reacted with 20 equivalents of ethylene oxide.[35] The derived indoles (**14** and **15**) were shown to be identical in all respects to authentic samples of cinchonamine and epi-cinchonamine kindly provided by Uskoković.‡

RETURN TO THE PENITREM PROBLEM: SYNTHESIS OF A MODEL SYSTEM

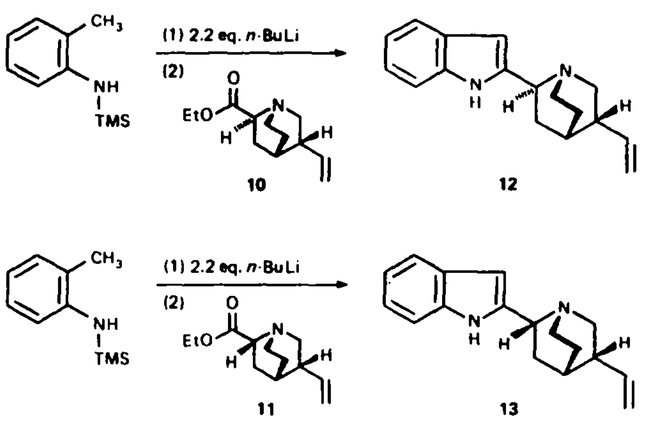
With a viable mild method for the preparation of C(2)-substituted indoles assured, we turned attention to the assembly of the D–G ring system of the penitrem nucleus (see p. 2964).

Preparation of the requisite starting lactone (**16**) begins with anhydride **17**, obtained from mesaconyl chloride according to the procedure of Bloomfield and Lee.[36] Careful methanolysis of **17** gave a mixture of half

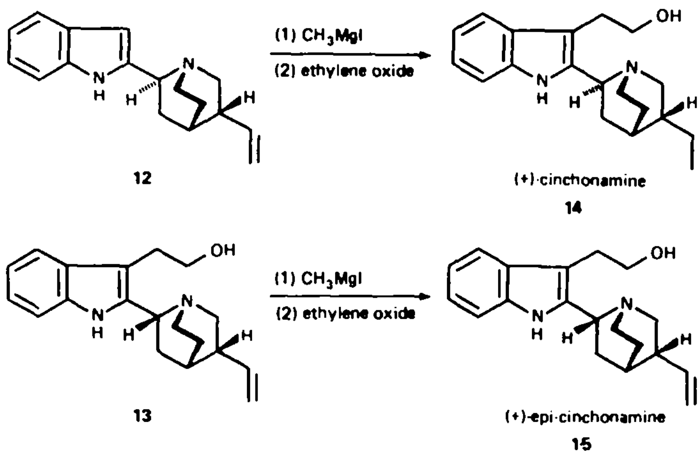
---

† Our approach constitutes a formal total synthesis, since C(2)-indoles **12** and **13** were prepared via total synthesis by Uskoković; see Ref. 33.

‡ We thank Dr Uskoković (Hoffman–LaRoche, Nutley, New Jersey) for the authentic spectra and samples of (+)-cinchonamine and (+)-epi-cinchonamine.

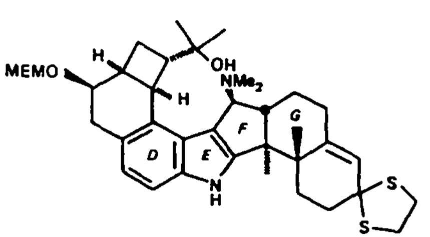


esters, which without purification or separation was hydrogenated to afford a 1 : 1 mixture of **18** and **19** in 96% yield for the two steps. Subsequent reduction with BH$_3$·THF complex gave hydroxy esters **20** and **21**, admixed with 19% of aldehyde **22**. Separation at this point proved convenient by flash chromatography. Individual lactone formation under forcing acidic conditions then gave **16** and **23**, respectively, in 21 and 23% yield from **17**. Lactone **23** was shown by spectral comparison to be identical to that prepared by Bloomfield and Lee,[36] while lactone **16** (—C=O, 1780 cm^{-1}) possessed an 8-line ABX resonance centered at δ 4.28 and 4.00 for each of the doublet of doublets, characteristic for the C(7)-methylene protons.

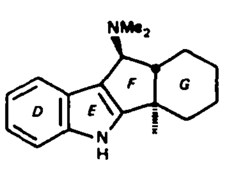


With ample quantities of **16** in hand, inverse addition of the organodilithium reagent derived from N-trimethylsilyl-*o*-toluidine afforded indole **24** in 59% yield. The primary carbinol was next protected as the t-butyldimethylsilyl ether,[37] and the indole nitrogen methylated with methyl iodide employing sodium hydride in DMF. Silyl ether hydrolysis followed by Collins oxidation[38] gave aldehyde **26**, the penultimate intermediate for the formation of ring F. Treatment of the latter with dimethyl amine in hot acetic acid (i.e. Mannich conditions)[39] afforded a single crystalline compound (m.p. 140–142°). The overall yield from indole **24** was 19% for the five steps.

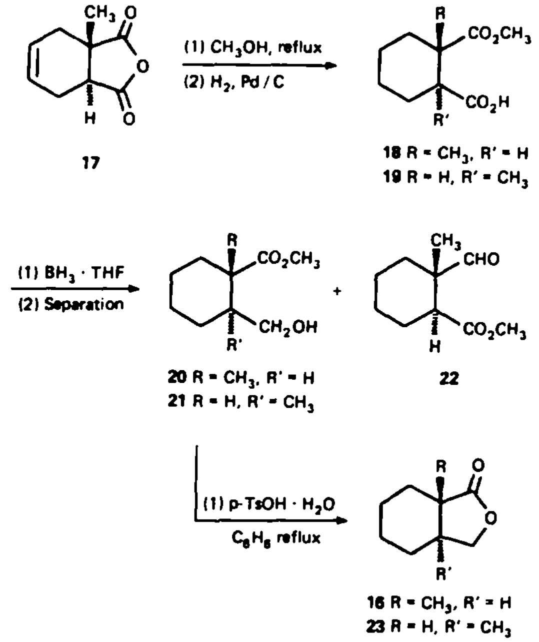
Initial stereochemical assignment for **27** was based on the observed 10 Hz coupling constant for the C(3′)-methine hydrogen indicative of an antiperiplanar relationship with the C(4′)-methine hydrogen.[40] Confirmation of this assignment was obtained through aegis of a single crystal X-ray analysis of **27**, the ORTEP of which is shown on the next page.[41]



Initial Synthetic Target



Model System

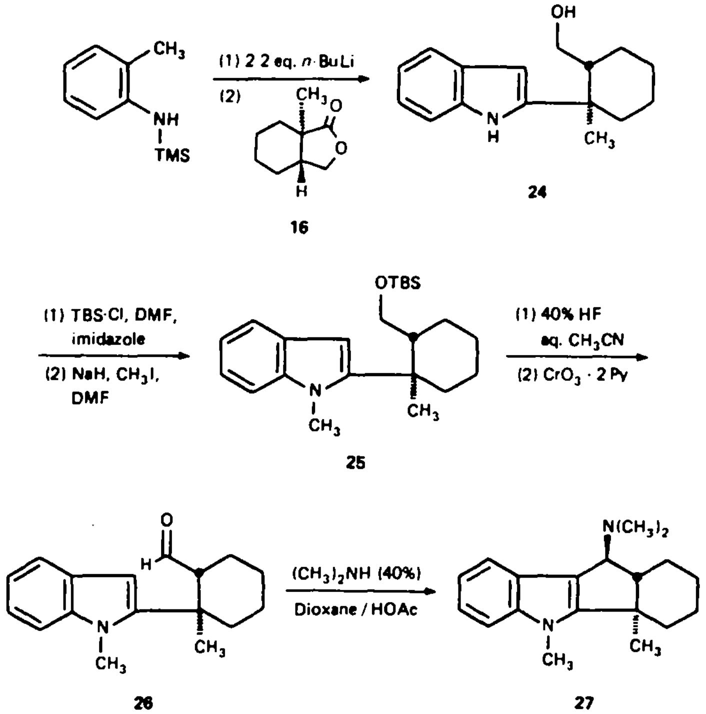


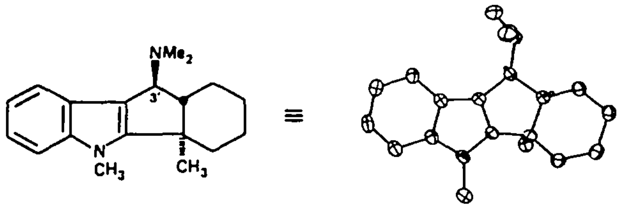
SUMMARY

In this account we report in full detail an effective new indole synthesis which permits functionally diverse subunits to be appended at the C(2)-position of the indole nucleus with complete regio- and stereocontrol. For example, the penultimate intermediates (**12** and **13**, respectively) of (+)-cinchonamine and (+)-epi-cinchonamine were prepared in one synthetic operation from the organodilithium reagent derived from N-trimethylsilyl-*o*-toluidine and the quinuclidine esters **10** and **11**. In connection with the new indole protocol, a convenient, large-scale method for the preparation of monosilylated anilines was developed. This procedure proved applicable to a wide variety of aryl substituted anilines (i.e. OCH_3, F, Cl, and alkyl). Finally, a tetracyclic model system for the penitrem mycotoxins was assembled. Studies to exploit this method in the synthesis of architecturally complex natural products will be reported in due course.

EXPERIMENTAL

Materials and methods. All m.ps were recorded on a Thomas–Hoover apparatus and are corrected. IR spectra were recorded in the solvent indicated on a Perkin–Elmer





m.p. 140-142°C

27

R_1 : 0.067

model 337 spectrophotometer. ^{1}H-NMR spectra were recorded on either an IBM WP-200SY (200 MHz) or a Bruker WM-250 (250 MHz) instrument. Chemical shifts are recorded δ values in ppm relative to TMS or $CHCl_3$. High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center employing either a Hitachi (Perkin–Elmer) RMH-2 or VG 70/70 instrument. All solvents were dried prior to use unless otherwise noted. THF and hexanes were distilled from Na/benzophenone ketyl. n-BuLi was purchased from Alfa Ventron or Aldrich and standardized by titration with diphenylacetic acid. Analytical TLC was carried out with precoated 0.25 mm thick silica gel plates with fluorescent indicator (E. Merck). Flash chromatography[44] was performed with the solvents indicated on Merck silica gel (particle size 0.04–0.633 μm).

Preparation of aminocarbinol (**9**)

A soln of N-trimethylsilyl-*o*-toluidine (220 mg, 1.23 mmol) in 5 ml of dry hexanes was cooled to 0° and treated dropwise over a 5 min period with 1.0 ml of a 2.6 m soln (2.1 equiv) n-BuLi in hexanes. The resultant pale yellow soln was heated at reflux for 6 h, cooled to $-78°$, diluted with 4 ml of dry THF, and freshly distilled benzaldehyde (165 mg, 1.56 mmol) was added all at once. The mixture was warmed to room temp, sat NaCl aq added, and the aqueous phase extracted with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica (10% EtOAc–hexanes) to give 112 mg (55%) of **9** as an *amorphous solid* (m.p. 98–99°): IR ($CHCl_3$) 3590 (m), 3480–3320 (m), 3010 (s), 1640 (m), 1500 (s), 1240 (s), 1050 (m), 800 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.35–8.27 (m, 7H), 6.98–7.09 (m, 2H), 6.66–6.76 (m, 2H), 4.93 (dd, J = 8.6, 4.0 Hz, 1H), 3.00 (dd, J = 14.3, 8.6 Hz, 1H), 2.88 (dd, J = 14.3, 4.0 Hz, 1H).

Preparation of 2-phenylindole by Cornforth oxidation of **9**

To 20 mg (0.094 mmol) of **9** in 1 ml of pyridine and 250 μl of water was added chromium trioxide (20 mg) all at once. The mixture was stirred at room temp for 2 h, diluted with ethyl ether, and filtered through Celite. The filtrate was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (10% EtOAc–hexanes) to give 8 mg (45%) of 2-phenylindole; m.p. 182–184° (lit.[13] 185–187°): IR (CHCl, 3465 (s), 3000 (s), 1600 (m), 1450 (m), 1300 (s), 680 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.30 (br s, 1H), 7.70–7.10 (m, 9H), 6.78 (d, J = 2.5 Hz, 1H).

Preparation of the organodilithium reagent of N-*trimethylsilyl-o-toluidine*

To a mixture of 200 mg (1.12 mmol) of N-trimethylsilyl-*o*-toluidine in 10 ml of dry commercial hexanes was added dropwise 980 μl (2.2 equiv) of a 2.5 M soln of n-BuLi in hexanes. The resultant yellow soln was brought to reflux, maintained at this temp for 6 h and then allowed to cool to room temp. The dianion was then added via cannula to a precooled ($-78°$) soln of the appropriate ester in ~4 ml of dry THF. The mixture was allowed to warm to room temp, quenched with sat NaCl aq, and extracted several times with ether. The organic extracts were concentrated *in vacuo* and the residue chromatographed on silica gel (EtOAc–hexanes) to give the pure product. The following indoles were prepared using this method.

2-*Phenylindole*: 65% yield; m.p. 182–184° (lit.[13] 185–197°); IR ($CHCl_3$) 3465 (s), 3000 (s), 1600 (m), 1450 (m), 1300 (s), 680 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 8.30 (br s, 1H), 7.70–7.10 (m, 9H), 6.78 (d, J = 2.5 Hz, 1H).

2-*Iso-propylindole*: 62% yield; m.p. 72.5–73° (lit.[16] 73–74°); IR (CCl_4) 3480 (s), 2985 (s), 1550 (w), 1470 (s), 1300 (s), 680 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.80 (br s, 1H), 7.52–7.10 (m, 4H), 6.22 (d, J = 1.0 Hz, 1H), 3.05 (heptet, J = 7.0 Hz, 1H), 1.32 (d, J = 7.0 Hz, 6H).

2-n-*Pentylindole*: 62% yield; m.p. 44–44.5° (lit.[17] 47–48°); IR (CCl_4) 3480 (s), 2940 (s), 1460 (s), 1280 (m), 1020 (w) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.85 (br s, 1H), 7.60–7.0 (m, 4H), 6.22 (d, J = 1.0 Hz, 1H), 2.73 (t, J = 7.5 Hz, 2H), 1.74 (m, 2H), 1.40 (m, 4H), 0.90 (m, 3H).

2-(3-*Hydroxypropyl*)*indole*: 61% yield; m.p. 54.5–55.5° (lit.[18] 53–55°); IR ($CHCl_3$) 3470 (s), 3000 (s), 2940 (s), 1560 (w), 1460 (s), 1290 (m), 1050 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 9.30 (br s, 1H), 7.52–7.00 (m, 4H), 6.24 (d, J = 0.8 Hz, 1H), 3.70 (t, J = 6.0 Hz, 2H), 2.84 (t, J = 7.3 Hz, 2H), 1.94 (m, 2H), 1.79 (br s, 1H).

2-*Methylindole*: 60% yield; m.p. 59–59.5° (lit.[19] 56–57°); IR (CCl_4) 3480 (s), 3000 (s), 1465 (s), 1310 (m), 850 (w) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.80 (br s, 1H), 7.50–7.0 (m, 4H), 6.20 (d, J = 1.0 Hz, 1H), 2.43 (s, 3H).

2-(2-*Methyl*-1-*propenyl*)*indole*: 38% yield; m.p. 103–105° (lit.[21] 102–103°); IR ($CHCl_3$) 3490 (s), 3000 (s), 1455 (s), 1340 (m), 1325 (m), 1280 (s), 640 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.90 (br s, 1H), 7.60–7.0 (m, 4H), 6.43 (s, 1H), 6.16 (s, 1H), 2.04 (s, 3H), 1.96 (s, 3H).

A general procedure for the preparation of N-*trimethylsilyl-o-toluidine derivatives*

A stirred mixture of the *o*-toluidine derivative (0.5 g, 5 mmol–10 g, 80 mmol), hexamethyldisilazane (3.1 equiv), and anhyd LiI (catalytic amount, 2 mol%) was treated with chlorotrimethylsilane (~6 mol%) and heated to reflux under Ar for 1–22 h. After this time, cyclohexene oxide (20 mol%) was added and heating continued for 15 min, whereupon another 20 mol% cyclohexene oxide was added. Upon cooling, the flask was fitted with a distillation head and the excess hexamethyldisilazane removed by distillation (atmospheric pressure). The N-trimethylsilyl-*o*-toluidine derivative was then distilled under high vacuum. The following *o*-toluidine derivatives were silylated in this manner.

N-*TMS-o-Toluidine*:[10] 4.63 g (92%) from *o*-toluidine (3.02 g); a colorless oil; IR (CCl_4) 3420 (m), 3020 (m), 2960 (s), 1610 (s), 1585 (s), 1495 (s), 1470 (m), 1445 (m), 1385 (s), 1370 (s), 1290 (s), 1255 (s), 1105 (m), 1050 (m), 980 (w), 905 (s), 845 (s), 710 (m), 680 (m), 610 (w) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.29 (s, 9H), 2.14 (s, 3H), 3.27 (s, 1H), 6.59–5.67 (m, 1H), 6.74 (d, J = 8 Hz, 1H), 7.01–7.10 (m, 2H). Electron impact mass spectrum, *m/e* 179.1129 (M^+ calc for $C_{10}H_{17}NSi$, 179.1125).

N-*TMS*-2,6-*Dimethylaniline*: 5.18 g (80%) from 2,6-dimethylaniline (4.08 g); a colorless oil; IR ($CHCl_3$) 3375 (w), 3000 (m), 2950 (m), 1620 (m), 1590 (m), 1475 (s), 1445 (m), 1430 (m), 1375 (m), 1255 (s), 1220 (m), 1090 (m), 900 (s), 840 (s), 680 (w), 605 (w) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.18 (s, 9H), 2.26 (s, 6H), 2.51 (s, 1H), 6.74–6.83 (m, 1H), 6.93–7.02 (m, 2H). Electron impact mass spectrum, *m/e* 193.1290 (M^+ calc for $C_{11}H_{19}NSi$, 193.1281).

N-*TMS*-4-*Chloro*-2-*methylaniline*: 12.96 g (86%) from 4-chloro-2-methylaniline (10.00 g); a hydroscopic yellow solid; IR ($CHCl_3$) 3420 (m), 2960 (m), 1620 (w), 1600 (m), 1575 (m), 1495 (s), 1385 (s), 1370 (s), 1295 (s), 1255 (s), 1180 (w), 1115 (m), 990 (w), 910 (s), 865 (s), 840 (s), 805 (m), 700 (wA), 680 (w), 645 (m), 610 (w) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.27 (s, 9H), 2.10 (s, 3H), 3.22 (s, 1H), 6.46 (d, J = 8 Hz, 1H), 6.94–7.05 (m, 2H). Electron impact mass spectrum, *m/e* 213.0754 (M^+ calc for $C_{10}H_{16}ClNSi$, 213.0741).

N-*TMS*-2,3-*Dimethylaniline*: 12.44 g (80%) from 2,3-dimethylaniline (9.80 g); a colorless oil; IR ($CHCl_3$) 3430 (w), 3010 (m), 2960 (m), 1585 (s), 1475 (s), 1365 (m), 1300 (s), 1255 (s), 1175 (w), 1095 (m), 1070 (m), 985 (w), 920 (s), 860 (s), 840 (s), 710 (w), 610 (w) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.31 (s, 9H), 2.08 (s, 3H), 2.29 (s, 3H), 3.32 (s, 1H), 6.59 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H), 6.96 (dd, J = 8, 8 Hz, 1H). Electron impact mass spectrum, *m/e* 193.1280 (M^+ calc for $C_{11}H_{19}NSi$, 193.1281).

N-*TMS*-2,4-*Dimethylaniline*: 4.47 g (88%) from 2,4-dimethylaniline (3.43 g); a colorless oil; IR ($CHCl_3$) 3410 (m), 2990 (s), 2950 (s), 1615 (m), 1580 (w), 1500 (s), 1440 (w), 1380 (s), 1370 (s), 1290 (s), 1250 (s), 1155 (w), 1110 (w), 930 (m), 880 (s), 835 (s) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 0.30 (s, 9H), 2.14 (s, 3H), 2.24 (s, 3H), 3.17 (s, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.86–6.95 (m, 2H). Electron impact mass spectrum, *m/e* 193.1289 (M^+ calc for $C_{11}H_{19}$ NSi, 193.1281).

N-*TMS-4-Methoxy-2-methylaniline*: 1.94 g (95%) from 4-methoxy-2-methylaniline (1.28 g, 9.58 mmol); a very hydroscopic colorless solid; IR ($CHCl_3$) 3420 (w), 3005 (m), 2960 (m), 1610 (w), 1505 (s), 1470 (w), 1385 (m), 1375 (m), 1290 (s), 1255 (s), 1160 (m), 1110 (w), 1050 (m), 935 (w), 890 (s), 845 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.25 (s, 9H), 2.11 (s, 3H), 2.96 (s, 1H), 3.72 (s, 3H), 6.58–6.71 (m, 3H). Electron impact mass spectrum, *m/e* 209.1244 (M^+ calc for $C_{11}H_{19}NOSi$, 209.1230).

N-*TMS-5-Methoxy-2-methylaniline*: 1.12 g (96%) from 5-methoxy-2-methylaniline (0.724 g, 5.27 mmol); a colorless oil; IR ($CHCl_3$) 3420 (w), 3005 (m), 2995 (m), 1615 (s), 1585 (m), 1510 (s), 1465 (w), 1445 (w), 1385 (m), 1375 (m), 1310 (m), 1295 (m), 1255 (s), 1200 (m), 1170 (s), 1120 (w), 1030 (w), 995 (w), 875 (s), 845 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.36 (s, 9H), 2.14 (s, 3H), 3.35 (s, 1H), 3.81 (s, 3H), 6.26 (dd, J = 8.2, 2.5 Hz, 1H), 6.41 (d, J = 2.4 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H). Electron impact mass spectrum, *m/e* 209.1236 (M^+ calc for $C_{11}H_{19}NOSi$, 209.1230).

N-*TMS-4-Fluoro-2-methylaniline*: 1.2 g (81%) from 4-fluoro-2-methylaniline (1.0 g); a colorless oil; IR ($CHCl_3$) 3420 (m), 2950 (m), 1630 (s), 1460 (w), 845 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.26 (s, 9H), 2.11 (s, 3H), 3.06 (s, 1H), 6.61–6.69 (m, 1H), 6.71–6.85 (m, 2H). Electron impact mass spectrum, *m/e* 197.1035 (M^+ calc for $C_{10}H_{16}FNSi$, 197.1036).

N-*TMS-2,5-Dimethylaniline*: 13.03 g (81%) from 2,5-dimethylaniline (10.08 g); a colorless oil; IR ($CHCl_3$) 3420 (m), 3000 (s), 2955 (s), 1615 (s), 1580 (s), 1515 (s), 1465 (m), 1445 (m), 1425 (m), 1375 (s), 1300 (s), 1255 (s), 1200 (w), 1160 (w), 1115 (m), 1000 (s), 945 (s), 875 (s), 840 (s), 800 (s), 685 (m), 615 (w), 585 (w) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.41 (s, 9H), 2.21 (s, 3H), 2.38 (s, 3H), 3.33 (s, 1H), 6.60 (d, J = 7 Hz, 1H), 6.68 (s, 1H), 7.05 (d, J = 7 Hz, 1H). Electron impact mass spectrum, *m/e* 193.1289 (M^+ calc for $C_{11}H_{19}NSi$, 193.1281).

Preparation of the organodilithium reagent of N-*trimethylsilyl-2-ethylaniline*

To a soln of 339 μl of tetramethylethylene diamine (2.25 mmol) in 5 ml of dry commercial hexanes was added 900 μl of a 2.5 M soln of n-BuLi (2.25 mmol) in hexanes. After stirring at room temp for 15 min, 200 mg of N-trimethylsilyl-2-ethylaniline (1.04 mmol) was added all at once. The resultant yellow mixture was brought to reflux, maintained at this temp for 6.5 h and then allowed to cool to room temp. The dianion was then added via cannula to a precooled (−78°) soln of the appropriate ester in dry THF (*ca* 4 ml). The mixture was warmed to room temp, sat NaCl aq added, and the aqueous phase extracted with ether. The organic extracts were concentrated *in vacuo*, and the residue chromatographed (EtOAc–hexanes) to give the pure compounds. The following indoles were prepared by this method.

2-Phenyl-3-methylindole: 50% yield; m.p. 91.5–92.5° (lit.[20] 89–90°); IR ($CHCl_3$) 3480 (s), 3000 (m), 1600 (w), 1460 (s), 1300 (w), 700 (s) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 8.0 (br s, 1H), 7.60–7.10 (m, 9H), 2.45 (s, 3H).

2,3-Dimethylindole: 32% yield; m.p. 103–105° (lit.[21] 103–105°); IR (CCl_4) 3480 (s), 2920 (m), 1460 (s), 1380 (m), 1330 (w) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 7.70 (br s, 1H), 7.50–7.05 (m, 4H), 2.34 (s, 3H), 2.22 (s, 3H).

2-Isopropyl-3-methylindole: 45% yield; IR ($CHCl_3$) 3475 (s), 2995 (s), 1470 (m), 1305 (m), 830 (w) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 7.80 (br s, 1H), 7.50–7.10 (m, 4H), 3.25 (heptet, J = 7.0 Hz, 1H), 2.20 (s, 3H), 1.32 (d, J = 7.0 Hz, 6H).

Preparation of 2-phenyl-5-fluoroindole

To a mixture of 197 mg (1.0 mmol) of N-trimethylsilyl-2-methyl-4-fluoroaniline in 10 ml of dry diethyl ether was added 940 μl (2.4 equiv) of a 2.5 M soln of n-BuLi in hexanes. The resultant soln was brought to reflux, maintained at this temp for 5 h, and allowed to cool to room temp. The deep red soln of the dianion thus generated was added via cannula to a precooled (−78°) soln of 175 mg (1.17 mmol) of ethyl benzoate in 4 ml of dry THF. The mixture was allowed to warm to room temp, quenched with sat NaCl aq, and extracted four times with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (10% EtOAc–hexanes) to afford 76 mg (36%) of 2-phenyl-5-fluoroindole as an amorphous solid, m.p. 179–180° (lit.[26] 178°); IR ($CHCl_3$) 3480 (s), 2985 (s), 1465 (m), 1285 (m), 770 (w) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 8.20 (br s, 1H), 7.60–7.20 (m, 7H), 6.92 (m, 1H), 6.77 (d, J = 2.5 Hz, 1H). Electron impact mass spectrum, *m/e* 211.0818 (M^+ calc for $C_{14}H_{10}NF$, 211.0794).

Preparation of 2-phenyl-5-methoxyindole

To a mixture of 140 mg (0.70 mmol) of N-trimethylsilyl-4-methoxy-2-methylaniline in 10 ml of dry commercial hexanes was added dropwise 650 μl (2.3 equiv) of a 2.5 M soln of n-BuLi in hexanes. The resultant clear yellow soln was brought to reflux, maintained at this temp for 7.5 h and then allowed to cool to room temp. The dianion was then added via cannula to a precooled (−78°) soln of 175 mg (1.17 mmol) of ethyl benzoate in 4 ml of dry THF. The mixture was allowed to warm to room temp, quenched with sat NaCl aq, and extracted four times with diethyl ether. The combined organic extracts were washed with sat NaCl aq, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (30% EtOAc–hexanes) to afford 48 mg (35%) of 2-phenyl-5-methoxyindole as an amorphous solid, m.p. 166° (lit.[27] 158–160°); IR ($CHCl_3$) 3460 (m), 3000 (m), 2930 (s), 1605 (m), 1500 (s), 1255 (s), 1035 (s), 840 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.68–6.73 (m, 9H), 3.85 (s, 3H). Electron impact mass spectrum, *m/e* 223.1004 (M^+ calc for $C_{15}H_{13}NO$, 223.0997).

Preparation of 2-phenyl-5-methylindole

To 441 mg (2.28 mmol) of N-trimethylsilyl-2,4-dimethylaniline in 20 ml of dry hexanes was added 2.20 ml (2.2 equiv) of a 2.28 M soln of n-BuLi in hexanes. The resultant pale yellow soln was heated at reflux for 4 h, cooled to −78°, and to this was added via cannula 380 mg (2.5 mmol) of ethyl benzoate in dry THF. The mixture was allowed to warm to room temp, quenched with water, and extracted with diethyl ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resultant thick oil was extracted with hot hexanes, and the supernatant removed on cooling to room temp. The ppt was washed with cold hexanes and dried *in vacuo* to afford 214 mg of a slightly yellow solid. The supernatant was subjected to chromatography (10% EtOAc–hexanes) to give an additional 51 mg of product. The total yield of 2-phenyl-5-methylindole was 255 mg (56%). Recrystallization from benzene gave colorless prisms, m.p. 218–219° (lit.[28] 216–217°); IR ($CHCl_3$) 3480 (s), 3008 (s), 1606 (m), 1479 (s), 1453 (s), 1318 (s), 1301 (m), 1225 (m), 1203 (m), 795–785 (s), 690 (s), 518–475 (s) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 2.46 (s, 3H), 6.76 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 8.0, 1.0 Hz, 1H), 7.27–7.70 (m, 7H), 8.26 (br s, 1H). Electron impact mass spectrum, *m/e* 207.1059 (M^+ calc for $C_{15}H_{13}N$, 207.1044).

Preparation of the quinuclidine esters (**10** *and* **11**)

Quinine was degraded in a four-step procedure according to Preobrazhenskii and co-workers.[32] The resultant esters **10** and **11** obtained by this method were separated by flash chromatography (30% acetone–hexanes).

Ethyl-5-vinyl-2-quinuclidine carboxylate (**10**): $[\alpha]_D^{25}$ = +122° (*c* = 0.026, EtOH); IR ($CHCl_3$) 2950 (s), 1735 (s), 1640 (w), 1230 (m), 1200 (s), 1040 (m), 920 (w) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 5.88 (m, 1H), 5.07 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.45 (m, 1H), 3.15 (dd, J = 13.8, 10.0 Hz, 1H), 2.94 (m, 1H), 2.70 (m, 2H), 2.20 (m, 1H), 1.90–1.45 (m, 5H), 1.25 (t, J = 7.1 Hz, 3H). Electron impact mass spectrum, *m/e* 209.1416 (M^+ calc for $C_{12}H_{19}NO_2$, 209.1410).

Ethyl-5-vinyl-2-quinuclidine carboxylate (**11**): $[\alpha]_D^{25}$ = +23° (*c* = 0.035, EtOH); IR ($CHCl_3$) 2940 (s), 1730 (s), 1630 (w), 1460 (m), 1300 (m), 1200 (s), 1140 (m), 920 (w) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 5.85 (m, 1H), 4.96 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.44 (m, 1H), 3.00–2.65 (m, 4H), 2.20–2.00 (m, 3H), 1.76–1.55 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H). Electron impact mass spectrum, *m/e* 209.1408 (M$^+$ calc for $C_{12}H_{19}NO_2$, 209.1410).

Preparation of indoles **12** *and* **13**

A soln of N-trimethylsilyl-*o*-toluidine (200 mg, 1.12 mmol) in 8 ml of dry hexanes was cooled to 0° and treated dropwise with a 2.5 M soln of n-BuLi in hexanes (1.0 ml, 2.50 mmol). The pale yellow soln was brought to reflux and maintained at this temp for 6.5 h. The resultant orange heterogeneous mixture was cooled to room temp and added via cannula to a precooled (−78) soln of **10** or **11** (180 mg, 0.86 mmol) in 5 ml of THF. The mixture was allowed to warm to room temp, after which it was diluted with diethyl ether (25 ml) and quenched with sat NaCl aq (10 ml). The organic layer was separated, and the aqueous layer extracted five times with diethyl ether (50 ml). The combined organic extracts were washed with sat NaCl aq (10 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (hexanes–acetone (3:2)) to afford **12** and **13** in 63 and 52% yield, respectively from **10** and **11**. No crossover products were observed.

Indole (**12**): m.p. 151° (lit.[33] 148–149°); $[\alpha]_D^{25} = +59°$ (*c* = 0.035, MeOH); IR ($CHCl_3$) 3440 (m), 3000 (s), 2940 (s), 1460 (m), 1220 (m), 780 (s), 500 (s) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 8.90 (br s, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.12 (m, 2H), 6.39 (s, 1H), 5.94 (m, 1H), 5.10 (m, 2H), 4.16 (m, 1H), 3.26 (dd, J = 10.1, 13.7 Hz, 1H), 2.98 (m, 1H), 2.60–2.22 (m, 4H), 1.86 (m, 1H), 1.54 (m, 1H). Electron impact mass spectrum, *m/e* 252.1624 (M$^+$ calc for $C_{17}H_{20}N_2$, 252.1620).

Indole (**13**): m.p. 90–91° (lit.[33] 92–93°); $[\alpha]_D^{25} = +95.5°$ (*c* = 0.045, MeOH); IR ($CHCl_3$) 3440 (m), 3000 (m), 2940 (s), 1455 (m), 1290 (m), 900 (w) cm^{-1}; ^1H-NMR ($CDCl_3$, 250 MHz) δ 8.95 (br s, 1H), 7.60–7.10 (m, 4H), 6.40 (s, 1H), 5.01 (m, 2H), 4.10 (m, 1H), 3.20 (m, 1H), 2.80–1.50 (m, 7H). Electron impact mass spectrum, *m/e* 252.1624 (M$^+$ calc for $C_{17}H_{20}N_2$, 252.1620).

Preparation of (+)-cinchonamine (**14**) *and (+)-epi-cinchonamine* (**15**)

According to the procedure of Uskoković, 350 μl of a 3 M soln of MeMgI (1.05 mmol) was added dropwise to a suspension of 25 mg of **14** or **15** (0.10 mmol) in 1 ml of dry diethyl ether. The mixture was stirred at room temp for 15 min, whereupon 750 μl of a 1.4 M soln of ethylene oxide in diethyl ether (1.05 mmol) was added over a 10 min period. Afterwards the mixture was stirred for 1 h at room temp, brought to reflux for 2 h, and later quenched with NH_4Cl aq. The aqueous phase was extracted five times with diethyl ether, and the combined extracts washed with sat NaCl aq. After drying over $MgSO_4$, the ether soln was concentrated *in vacuo*. The residue was chromatographed on silica (5% MeOH–CH_2Cl_2) to give pure **14** (9.2 mg, 31%) and **15** (10.2 mg, 34%).

(+)-*Cinchonamine* (**14**): m.p. 183° (lit.[33] 185–186°); $[\alpha]_D^{25}$ = +116° (*c* = 0.055, abs EtOH) (lit.[33] +123°); IR ($CHCl_3$) 3500–3100 (m), 3000 (s), 2950 (s), 1240 (s), 915 (m) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 7.50–7.08 (m, 4H), 5.96 (m, 1H), 5.16 (m, 2H), 4.23 (m, 1H), 4.17 (m, 1H), 3.88 (m, 1H), 3.70–1.70 (m, 13H). Electron impact mass spectrum, *m/e* 296.1883 (M$^+$ calc for $C_{19}H_{24}N_2O$, 296.1881).

(+)-*epi-Cinchonamine* (**15**): m.p. 167–169° (lit.[33] 168–169°); $[\alpha]_D^{25} = +43°$ (*c* = 0.040, abs EtOH) (lit.[33] +46.5°); IR ($CHCl_3$) 3400–3100 (m), 2960 (s), 1460 (m), 920 (m) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 7.42–7.02 (m, 4H), 5.92 (m, 1H), 5.16 (m, 2H), 4.22 (t, J = 9.9 Hz), 3.88 (m, 1H), 3.62 (m, 1H), 3.30–1.60 (m, 13H). Electron impact mass spectrum, *m/e* 296.1882 (M$^+$ calc for $C_{19}H_{24}N_2O$, 296.1881).

Preparation of **20**–**22**

According to the method of Bloomfield and Lee,[36] 1.74 g (10.5 mmol) of anhydride **17** in 50 ml of MeOH was heated at reflux for 2 h. Pd–C (360 mg, 10%) was added to the cooled mixture and the resultant mixture hydrogenated with stirring at ambient pressure for 14 h. Filtration and removal of the solvent *in vacuo* afforded 2.00 g (96%) of an approximately 1 : 1 mixture of acid esters **18** and **19**. To 1.16 g (6.37 mmol) of this mixture in THF, cooled to −78° under Ar, was added 15.2 ml of borane THF complex in THF (0.485 M). After 25 min the bath was replaced with an ice–salt bath for 2 h, then stirred at ambient temp for 16 h. The reaction was recooled to 0° and quenched with 6 ml of H_2O. Following extraction with ether the combined extracts were washed with water and then sat NaCl aq, the solvent dried over $MgSO_4$ and removed *in vacuo*. Chromatography on silica gel (hexane–Et_2O, 4:1 (v/v)) afforded 201 mg (19%) of aldehyde **22**, 393 mg (36%) of hydroxy ester **20**, and 166 mg (15%) of hydroxy ester **21**.

Carboxylic acid methyl ester (**20**): IR ($CHCl_3$) 3620–3580 (w), 3520–2480 (w), 2940 (s), 1720 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.84–1.86 (m, 9H), 1.16 (s, 3H), 2.22 (m, 1H), 3.43 (m, 2H), 3.71 (s, 3H). Electron impact mass spectrum, *m/e* 186.1251 (M$^+$ calc for $C_{10}H_{18}O_3$, 186.1256).

Carboxylic acid methyl ester (**21**): IR ($CHCl_3$) 3620–3560 (w), 3500–3490 (w), 2940 (s), 1730 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.05–1.84 (m, 8H), 2.16 (dd, J = 7.5, 5.5 Hz, 1H), 2.53 (dd, J = 11.0, 9.0 Hz, 1H), 3.26 (dd, J = 11.0, 5.5 Hz, 1H), 3.44 (dd, J = 11.0, 7.5 Hz, 1H), 3.71 (s, 3H). Electron impact mass spectrum, *m/e* 186.1260 (M$^+$ calc for $C_{10}H_{18}O_3$, 186.1256).

Carboxaldehyde (**22**): IR ($CHCl_3$) 2940 (m), 1730 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.12–2.00 (m, 8H), 2.77 (dd, J = 10.5, 4.5 Hz, 1H), 3.65 (s, 3H), 9.50 (s, 1H). Electron impact mass spectrum, *m/e* 184.1104 (M$^+$ calc for $C_{10}H_{16}O_3$, 184.1095).

Preparation of hexahydrobenzofuranone (**16**)

Treatment of 538 mg (2.89 mmol) of **20** with a catalytic amount of *p*-TsOH · H_2O in 50 ml of benzene at reflux for 19 h (Dean–Stark trap), followed by removal of solvent *in vacuo* and subsequent recrystallization from hexane afforded 268 mg (60%) of **16** as colorless prisms: m.p. 53.5–55° (hexanes); IR ($CHCl_3$) 2940 (m), 1775 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.17–1.94 (m, 8H), 2.11 (m, 1H), 4.00 (dd, J = 11.5, 8.5 Hz, 1H), 4.28 (dd, J = 8.5, 6.5 Hz, 1H). Electron impact mass spectrum, *m/e* 154.1007 (M$^+$ calc for $C_9H_{14}O_2$, 154.0994).

Preparation of hexahydrobenzofuranone (**23**)

Lactone **23** was obtained from hydroxy ester **21** by the method used in the conversion of **20** to **16**. Kugelrohr distillation provided pure colorless oil in 75% yield: IR ($CHCl_3$) 2940 (m), 1775 (s) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.11–1.99 (m, 8H), 2.09 (dd, J = 11.5, 3.0 Hz, 1H), 3.90 (d, J = 8.5 Hz, 1H), 4.10 (d, J = 1.5 Hz, 1H). Electron impact mass spectrum, *m/e* 154.1001 (M$^+$ calc for $C_9H_{14}O_2$, 154.0994).

Preparation of C(2)-substituted indole **24**

A soln of N-trimethylsilyl-*o*-toluidine (200 mg, 1.12 mmol) in 8 ml of dry hexanes was cooled to 0° and treated dropwise over a 5 min period with 1.0 ml of a 2.5 M soln of n-BuLi in hexanes. The resultant pale yellow soln was brought to reflux and maintained at this temp for 6.5 h. After this time, the orange heterogeneous mixture was cooled to room temp and added via cannula to a precooled (−78°) soln of **16** (142 mg, 1.00 mmol) in 4 ml of dry THF. The mixture was stirred for 15 min at −78°, warmed to room temp, and quenched with sat NaCl aq. The organic layer was separated and the aqueous layer extracted four times with 20 ml of diethyl ether. The combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (15% EtOAc–hexanes) to afford 143 mg (59%) of **24** as an amorphous solid (m.p. 152.5–154°): IR ($CHCl_3$) 3470 (m), 3000 (m), 2935 (s), 1460 (s), 1400 (w), 1280 (m), 1020 (m), 680 (w), 600 (w) cm^{-1}; ^1H-NMR (250 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.26 (m, 1H), 7.10 (m, 2H), 6.30 (d, J = 1.7 Hz, 1H), 3.47 (dd, J = 1.7, 4.4 Hz, 1H), 3.23 (dd, J = 10.7, 7.7 Hz, 1H), 3.10 (br s, 1H), 2.10–1.10 (m, 9H), 1.32 (s, 3H). Electron impact ionization mass spectrum, *m/e* 243.1638 (M$^+$ calc for $C_{16}H_{21}NO$, 243.1614).

Silylation of the 1°-*carbinol in* **24**

Indole **24** (35 mg, 0.14 mmol) was dissolved in 1 ml of N.N-dimethylformamide and treated sequentially with imidazole (26 mg, 0.38 mmol) and t-butyldimethylsilylchloride (28 mg, 0.19 mmol). The mixture was stirred at room temp for 15 min, diluted with n-pentane, and quenched with 10 ml of 5% $NaHCO_3$ aq. The organic layer was separated and the aqueous layer extracted with n-pentane. The combined organic extracts were washed with sat NaCl aq, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (5% EtOAc–hexanes) to afford 42 mg (82%) of **25** as a colorless oil: IR ($CHCl_3$) 3460 (w), 3000 (w), 2920 (s), 2840 (m), 1455 (m), 1250 (m), 1045 (m), 830 (s) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.10 (m, 2H), 6.28 (d, J = 1.3 Hz, 1H), 3.42 (dd, J = 10, 3.3 Hz, 1H), 3.25 (dd, J = 9.4, 8.1 Hz, 1H), 2.0–1.3 (m, 9H), 1.32 (s, 3H), 0.81 (s, 9H), −0.08 (s, 3H), −0.11 (s, 3H). Electron impact mass spectrum, *m/e* 357.2509 (M^+ calc for $C_{22}H_{35}NOSi$, 357.2478).

Preparation of N-*methylindole* (**25**)

Indole **24** (42 mg, 0.12 mmol) was dissolved in 0.5 ml of N,N-dimethylformamide, cooled to 0°, and treated with 80% NaH (5.3 mg, 0.18 mmol) under Ar. The resultant slurry was stirred for 2 min at 0°, warmed to room temp for 15 min, and then cooled to 0°. MeI (79 μl, 0.18 mmol) was added to the slurry, all at once. After stirring for 15 min at 0° the mixture was diluted with diethyl ether and quenched with 5% $NaHCO_3$ aq. The organic layer was separated and the aqueous layer extracted with diethyl ether. The combined organic extracts were washed with sat NaCl aq, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (3% EtOAc–hexanes) to afford 40 mg (91%) of **25** as an amorphous solid: m.p. 58–59°; IR ($CHCl_3$) 3000 (w), 2930 (s), 2850 (m), 1690 (w), 1470 (m), 1255 (m), 1100 (m), 835 (s) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.53 (d, J = 7.65 Hz, 1H), 7.30–7.05 (m, 3H), 6.38 (s, 1H), 3.95 (s, 3H), 3.51 (dd, J = 3.0, 9.7 Hz, 1H), 3.23 (dd, J = 9.7, 8.5 Hz, 1H), 2.38 (m, 1H), 2.08–1.50 (m, 8H), 1.40 (s, 3H), 0.81 (s, 9H), −0.08 (s, 3H), −0.12 (s, 3H). Electron impact mass spectrum, *m/e* 371.2653 (M^+ calc for $C_{23}H_{37}NOSi$, 371.2634).

Hydrolysis of the silyl ether in **25**

t-Butyldimethylsilyl ether **25** (40 mg, 0.11 mmol) was dissolved in 0.5 ml of acetonitrile and added dropwise to a 40% HF soln in acetonitrile (5/95) at room temp. The resultant yellow mixture was stirred for 0.5 h. The mixture was diluted with ether, followed by the dropwise addition of a 5% $NaHCO_3$ aq, separation of the organic layer and extraction of the aqueous phase with ether. The combined organic extracts were washed with a sat NaCl aq, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (30% EtOAc–hexanes) to afford 20 mg (72%) of **26** as an amorphous solid: m.p. 133–134°; IR ($CHCl_3$) 3500 (w), 3000 (s), 2920 (s), 1470 (m), 1220 (s), 1200 (s), 780 (s), 700 (m), 665 (m), 655 (m), 500 (s) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.55 (dd, J = 0.7, 7.7 Hz, 1H), 7.30–7.05 (m, 3H), 6.40 (d, J = 0.5 Hz, 1H), 3.96 (s, 3H), 3.57 (dd, J = 10.8, 5.7 Hz, 1H), 3.22 (dd, J = 10.8, 7.4 Hz, 1H), 2.49 (m, 1H), 2.10 (m, 2H), 1.88–1.11 (m, 7H), 1.43 (s, 3H). Electron impact mass spectrum, *m/e* 257.1794 (M^+ calc for $C_{17}H_{23}NO$, 257.1781).

Preparation of aldehyde **27**

Chromium trioxide (100 mg) was added portionwise to a stirred soln of anhyd pyridine (160 μl) in 10 ml of CH_2Cl_2. The resultant deep red soln of Collins reagent was stirred for 15 min at room temp, whereupon alcohol **26** (20 mg, 0.08 mmol) was added all at once. After 0.5 h, the mixture was diluted with ether (10 ml) and filtered through a short plug of florisil. The ether layer was washed with 5% NaOH aq, sat NaCl aq, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica (10% EtOAc–hexanes) to give 15 mg (76%) of aldehyde **27** as a slightly yellow oil: IR ($CHCl_3$) 3000 (s), 2920 (s), 1715 (s), 1470 (m), 1320 (m), 790 (s), 500 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 9.60 (d, J = 1.3 Hz, 1H), 7.52 (dd, J = 7.7, 0.77 Hz, 1H), 7.31–7.05 (m, 3H), 6.35 (d, J = 0.5 Hz, 1H), 3.95 (s, 3H), 3.04 (dd, J = 2.8, 10.4 Hz, 1H), 2.00–1.20 (m, 8H), 1.56 (s, 3H). Electron impact mass spectrum, *m/e* 255.1629 (M^+ calc for $C_{17}H_{21}NO$, 255.1617).

Preparation of tetracyclic model system (**27**)

Aldehyde **26** (15 mg, 0.059 mmol) was dissolved in 250 μl of 1,4-dioxane and treated with 250 μl of glacial AcOH and 10 μl of a 40% aqueous soln of dimethyl amine. The mixture was allowed to stand at room temp for 2 h, after which time a much lower R_f material (0.02 in 30% EtOAc–hexanes vs 0.67 for **26** in the same solvent mixture) was observed by TLC. After 18 h at room temp, the mixture was diluted with ether, washed with 5% $NaHCO_3$ aq, sat NaCl aq, and dried over $MgSO_4$. Chromatography (EtOAc–hexanes–acetone (4:1:1)) afforded 8 mg (47%) of **27** as a crystalline solid: m.p. 140–142°; IR ($CHCl_3$) 3000 (s), 2920 (s), 1450 (m), 1220 (m), 1200 (m), 790 (m), 500 (s) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.54 (dd, J = 2.3, 7.2 Hz, 1H), 7.26–7.04 (m, 3H), 3.83 (d, J = 10.0 Hz, 1H), 3.71 (s, 3H), 2.53 (s, 6H), 2.32–1.51 (m, 9H), 1.03 (s, 3H). Electron impact mass spectrum, *m/e* 282.2100 (M^+ calc for $C_{19}H_{26}N_2$, 282.2088).

Acknowledgement—It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (Institute of Neurology, Communication Disorders and Stroke) through Grant 18254. In addition we thank Drs G. Furst, J. Dykins and P. Carroll of the University of Pennsylvania Spectroscopic Facilities for aid in obtaining the highfield NMR, high resolution mass spectral and X-ray crystallographic data.

REFERENCES

[1] A. von Baeyer, *Ann. Chem.* **140**, 295 (1866).

[2] R. K. Brown, *Indoles, Part One* (Edited by W. J. Houlihan), Vol. 25, Chap. II. Wiley-Interscience, New York (1972); P. A. Gassman and W. N. Shenk, *J. Org. Chem.* **42**, 3240 (1977); T. Sugasawa, M. Adachi, K. Susakura and A. Kitagawa, *Ibid.* **42**, 3240 (1977); T. Sugasawa, M. Adachi, K. Susakura and A. Kitagawa, *Ibid.* **44**, 578 (1979); P. A. Wender and A. W. White, *Tetrahedron Lett.* **22**, 1475 (1981).

[3] For a preliminary account of this work see: A. B. Smith, III and M. Visnick, *Tetrahedron Lett.* **26**, 3757 (1985).

[4] C. M. Cristensen, *Molds, Mushrooms, and Mycotoxins*, p.35. University of Minnesota Press, Minneapolis, Minnesota (1975); J. P. Springer and J. Clardy, *Tetrahedron Lett.* 231 (1980).

[5] A. B. Smith, III and R. Mewshaw, *J. Am. Chem. Soc.* **107**, 1769 (1985).

[6] B. J. Wilson, C. H. Wilson and A. W. Hayes, *Nature* **220**, 77 (1968).

[7] C. T. Hou, A. Ciegler and C. W. Hesseltine, *Can. J. Microbiol.* **17**, 599 (1971); A. E. de Jesus, P. S. Steyn, F. F. Van Heerden, R. Vleggaar, P. L. Wessels and W. E. Hill, *J. Chem. Soc. Chem. Commun.* 289 (1981).

[8] R. L. Augustine, A. J. Gustavsen, S. F. Wanat, I. C. Pattison, K. S. Houghton and G. Koletar, *J. Org. Chem.* **38**, 3004 (1973).

[9] For a related indole synthesis, see the modified Madelung indole synthesis developed by the Sandoz group: W. J. Houlihan, V. A. Parrino and Y. Uike, *J. Org. Chem.* **46**, 4511 (1981). In this two-step procedure the order of bond formation is reversed. That is, nitrogen bond formation proceeds carbon bond formation.

[10] J. Schulze, R. Boese and G. Schmid, *Chem. Ber.* **114**, 1297 (1981).

[11] R. J. P. Corriu and J. J. E. Moreau, Some uses of silicon–nitrogen bonds in organic synthesis, *Selectivity—A Goal for Synthetic Efficiency* (Edited by W. Bartmann and B. M.

Trost), p. 21. Verlag Chemie, Deerfield Beach, Florida (1984).

[12] R. H. Cornforth, J. W. Cornforth and G. Popjak, *Tetrahedron* **18**, 135 (1962).

[13] C. Kruger, E. G. Rochow and V. Wannagat, *Chem. Ber.* **109**, 1491 (1963).

[14] D. J. Hart, K. Kanai, D. G. Thomas and T.-K. Yang, *J. Org. Chem.* **48**, (1983).

[15] W. E. Noland, K. R. Rush and L. R. Smith, *Ibid.* **31**, 65 (1966).

[16] H. Illy and L. Funderburk, *Ibid.* **33**, 4283 (1968).

[17] F. Piozzi and M. R. Langella, *Gazz. Chim. Ital.* **93**(11), 1382 (1963).

[18] Y. Ito, K. Kobayashi, N. Seko and T. Saegusa, *Bull. Chem. Soc. Japan* **57**, 73 (1984).

[19] C. F. H. Allen and J. VanAllan, *Org. Synth. Coll. Vol.* 3, 597 (1967).

[20] This indole, an unknown compound, was an intermediate in our model study for the D–G ring system of the penitrems (*vide infra*).

[21] N. N. Komzolova, N. F. Kucherova and V. A. Zagorevski, *Zh. Org. Khim.* **1**(6), 1139 (1965).

[22] J. N. Denis and A. Krief, *Tetrahedron Lett.* **22**, 1429 (1981).

[23] M. Nakazaki, *Bull. Chem. Soc. Japan* **33**, 461 (1960).

[24] A. H. Jackson and P. Smith, *Tetrahedron* **24**, 2227 (1968).

[25] H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.* **65**, 2452 (1943).

[26] H. Junjappa, *Synthesis* 798 (1975).

[27] W. J. Houlihan, V. A. Parrino and Y. Vike, *J. Org. Chem.* **46**, 4511 (1981).

[28] Y. Ito, K. Kobayashi and T. Saegusa, *Ibid.* **44**, 2030 (1979).

[29] M. Arnaud, *C.r. hebd. Séanc. Acad. Sci.* **93**, 593 (1881).

[30] R. Goutarel, M.-M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim Acta* **33**, 150 (1950).

[31] Y. K. Sava and H. Matsumura, *Tetrahedron* **26**, 2923 (1970).

[32] C. Ch'ang-pai, R. P. Evstigneeva and N. Preobrazhenskii, *Dokl. Akad. Nauk SSSR* 927 (1958).

[33] G. Grethe, H. L. Lee and M. R. Uskoković, *Helv. Chim. Acta* **59**, 2268 (1976).

[34] C. Ch'ang-pai, R. P. Evstigneeva and N. Preobrazhenskii, *J. Gen. Chem. U.S.S.R.* **30**, 495 (1960).

[35] B. Oddo and L. Sessa, *Gazz. Chim. Ital.* **41**, 234 (1911).

[36] J. J. Bloomfield and S. L. Lee, *J. Org. Chem.* **32**, 3919 (1967).

[37] E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.* **94**, 6190 (1972).

[38] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.* **35**, 4000 (1970).

[39] A. Ek and B. Withkap, *J. Am. Chem. Soc.* **76**, 5579 (1954).

[40] L. M. Jackman and S. Sternhell, *Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon Press, New York (1969).

[41] Unpublished results of Dr Patrick J. Carroll, Spectroscopic Service Center, Department of Chemistry, University of Pennsylvania.

[42] W. C. Still, M. Kahn and A. J. Mitra, *J. Org. Chem.* **43**, 2923 (1978).