Tetrahedron Vol. 44, No. 11, pp. 3195 to 3202, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

A DIRECTED METALATION ROUTE TO THE ZWITTERIONIC INDOLE ALKALOIDS. SYNTHESIS OF SEMPERVIRINE†

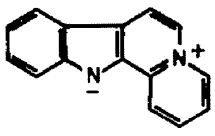
Gordon W. Gribble,* Timothy C. Barden, and David A. Johnson

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755 USA

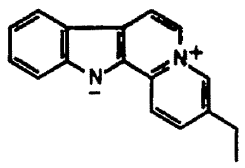
(*Received in USA* 14 *October* 1987)

Abstract: *A synthesis protocol involving beta-lithiation of 2-(2-pyridinyl)indoles (4 → 5) and subsequent reaction with bromoacetaldehyde leads to the indolo[2,3-a]quinolizine (1) ring system. Application of this methodology to 2-(2-pyridinyl)indole 17, which is prepared via Taylor-Boger triazine Diels-Alder annulation chemistry, affords the zwitterionic indole alkaloid sempervirine (3).*

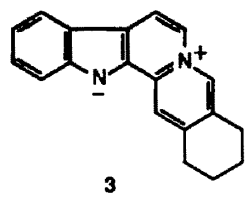
The relatively small assemblage of biogenetically and theoretically fascinating zwitterionic indole alkaloids, such as indolo[2,3-*a*]quinolizine (1), flavopereirine (2), and sempervirine (3), has received only sporadic attention from synthetic chemists[1] since Woodward's synthesis of *N*-methylsempervirine some forty years ago.[2]



1



2

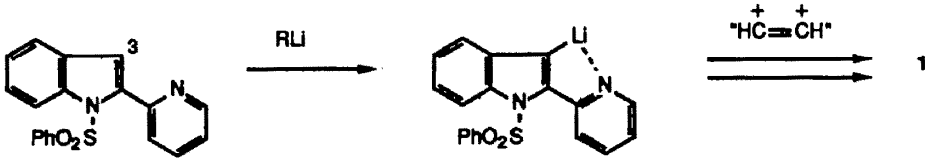


3

Although several strategies have been devised for the construction of the indolo[2,3-*a*]quinolizine ring system, all of the ultimately successful syntheses have necessitated a final ring C and/or ring D oxidation step that can be inefficient and capricious.[1]

Recent reports that flavopereirine (2), sempervirine (3), and some related alkaloids exhibit both strong affinity for DNA and novel antitumor activity[3] have piqued our interest in this area and led us to devise an expedient metalation route to the indolo[2,3-*a*]quinolizine ring system. Thus, in preliminary form,[4,5] we have described a synthetic protocol involving pyridine-nitrogen directed *beta*-lithiation of 1-(phenylsulfonyl)-2-(2-pyridinyl)indole (4) and subsequent reaction of the derived 3-lithio species 5 with an appropriate two-carbon *bis*(1,2)electrophile to furnish the target ring system 1 (Scheme 1).

Scheme I

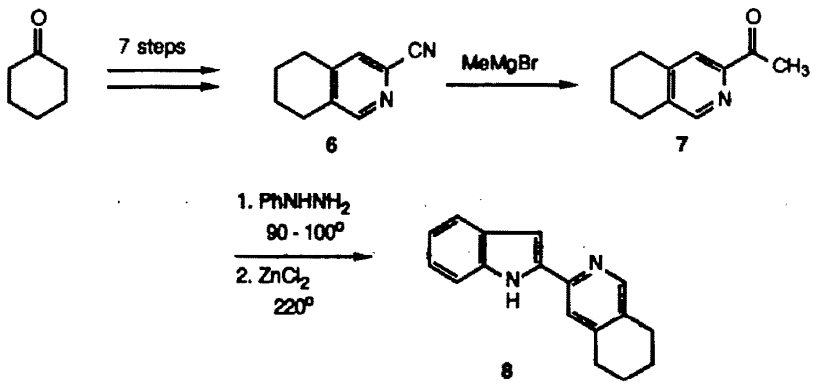


4 5

We now report the full details of this methodology in the context of a new total synthesis of sempervirine (3). Our first synthetic objective was 2-(3-(5,6,7,8-tetrahydroisoquinolinyl))indole (8), which was synthesized by Stevens in an abortive approach to sempervirine.[6] Unfortunately, this synthesis of 8 is extremely lengthy and the overall yield is very low (Scheme 2).

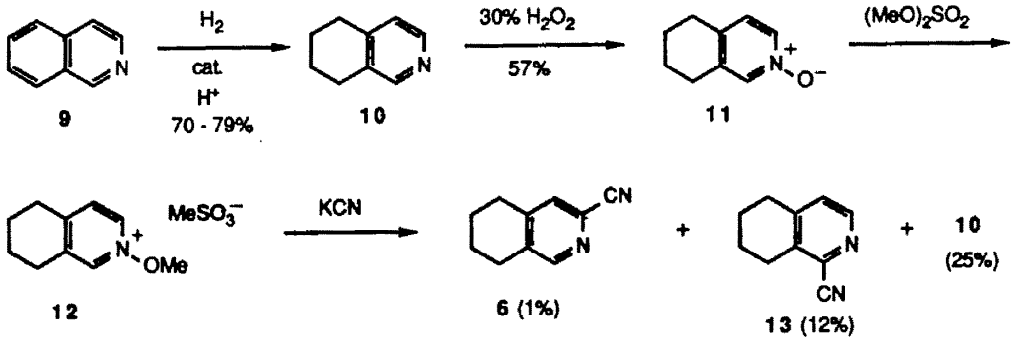
†This paper is dedicated, with affection, to Ted Taylor on the occasion of his 65th birthday.

Scheme 2



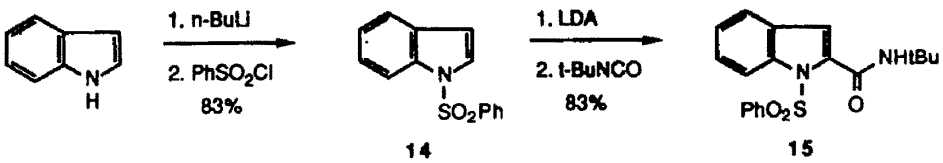
Therefore, we initially investigated a better preparation of nitrile **6**. Selective hydrogenation of isoquinoline (**9**) in 12N hydrochloric acid at 50 psi with platinum oxide[7] or, more economically, in trifluoroacetic acid (TFA) with 10% palladium on carbon[7,8] proceeded very slowly to give a mixture of 5,6,7,8- (**10**) and 1,2,3,4-tetrahydroisoquinoline, in accord with the literature[7] (Scheme 3). Treatment of this mixture with excess acetic anhydride at 100°C facilitated the removal of the secondary amine by-product as the amide and led to the isolation of 5,6,7,8-tetrahydroisoquinoline (**10**) in 72-79% yield. Oxidation with 30% hydrogen peroxide gave *N*-oxide **11** in 57% yield. Treatment of **11** with neat dimethylsulfate afforded the *N*-methoxy methylsulfate salt **12**, which, without being isolated, was stirred at 0°C with aqueous potassium cyanide. Much to our surprise, and in stark contrast to the synthesis of other cyanopyridines,[9] a complex mixture was obtained, consisting of the (separable) isomeric cyanoisoquinolines **6** and **13** in a 1:12 ratio (13% yield), **10** (25% yield), presumably resulting from base-induced elimination of formaldehyde from **12**, and products that appeared to be derived from cleavage of the carbocyclic ring. Furthermore, the reaction of *N*-oxide **11** with trimethylsilyl cyanide in HMPA at 115°C -- alternative conditions that we have found can circumvent the base-induced decomposition of *N*-methoxypyridinium salts[10] -- also gave a complex mixture.

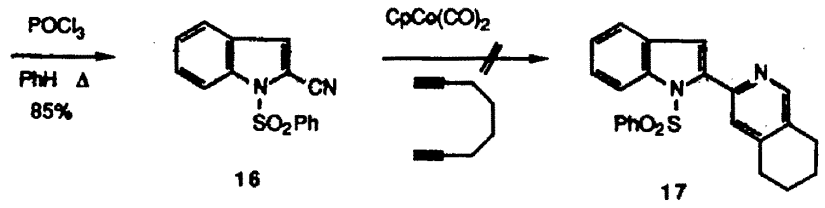
Scheme 3



Known pyridine ring syntheses from nitriles[11,12] prompted us to explore the preparation of **8** (or the *N*-phenylsulfonyl derivative **17**) from the appropriate 2-cyanoindole. Thus, 2-cyano-1-(phenylsulfonyl)indole (**16**) was readily synthesized from indole via *N*-protection,[13] 2-lithiation[13] followed by quenching with *t*-butylisocyanate, and then a von Braun reaction[14] (Scheme 4). Unfortunately, treatment of **16** with 1,7-octadiyne and cyclopentadienylcobalt dicarbonyl[11] in refluxing xylene did not lead to the desired **17** (no reaction). This observation parallels Vollhardt's results with electron-deficient nitriles.

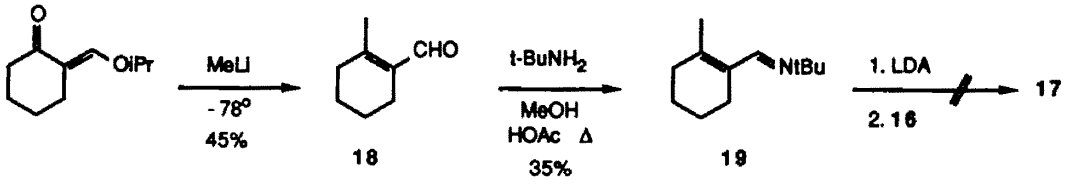
Scheme 4





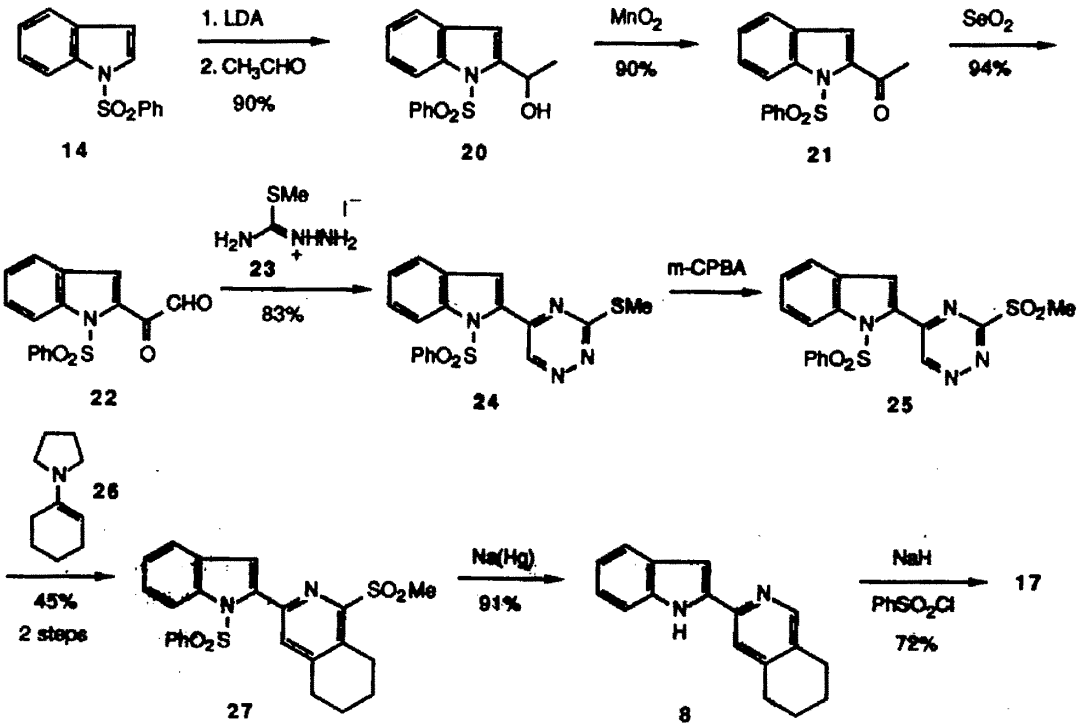
We also examined Takabe's pyridine synthesis[12] as a route to 17 (Scheme 5). Thus, aldehyde 18 was prepared as described[15] and converted to the aldimine 19. However, attempts to condense aldimine 19 with nitrile 16 in the presence of lithium diisopropylamide (LDA) according to Takabe's procedure[12] failed to yield 17.

Scheme 5



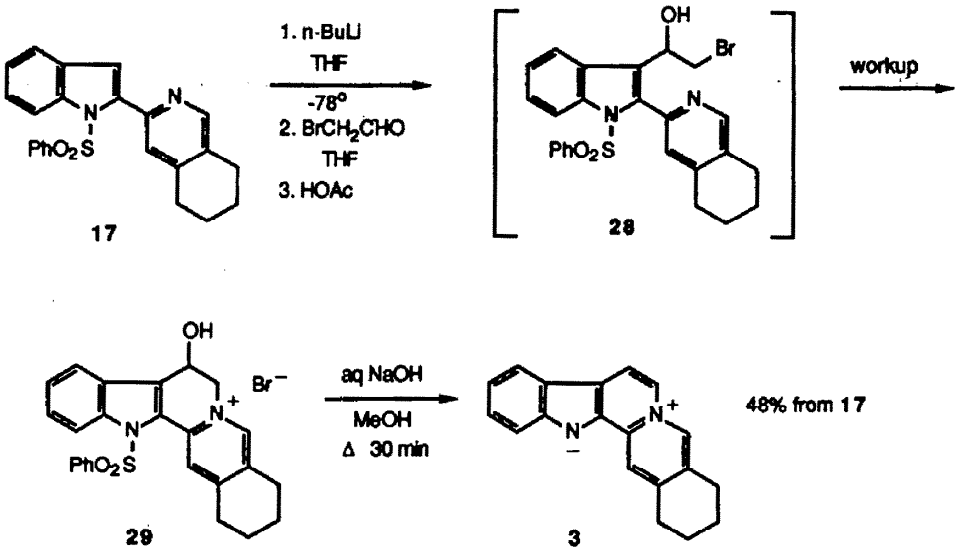
A successful synthesis of 17 was realized using Taylor-Boger triazine Diels-Alder annulation chemistry[16,17] (Scheme 6). Thus, 1-(phenylsulfonyl)indole (14) was converted to ketone 21 in standard fashion.[18] Oxidation of 21 to ketoaldehyde 22 was accomplished with selenium dioxide. Condensation of 22 with methylthiosemicarbazide hydriodide (23) gave the expected triazine 24. Since even forcing conditions failed to induce the Diels-Alder reaction between triazine 24 and enamine 26, 24 was oxidized to sulfone triazine 25 with *m*-chloroperbenzoic acid. Now, as anticipated,[16,17] this electron-deficient triazine 25 reacted rapidly with enamine 26 and gave the expected pyridine sulfone 27. Attempts to desulfonylate 27 selectively to 17 were unsuccessful.[19] However, under carefully controlled conditions, 27 could be efficiently converted to 8 with sodium amalgam. Substantial reduction of the pyridine ring occurred unless this reaction was performed exactly as described. Reprotection of the indole nitrogen of 8 under the usual conditions gave, in good yield, the desired sempervirine precursor 17.

Scheme 6



Finally, the synthesis of sempervirine (3) was completed as follows (Scheme 7). Treatment of 17 with *n*-butyllithium at -78°C followed by quenching with anhydrous bromoacetaldehyde[20] and the usual workup with acetic acid provided the indoloquinolizinium bromide 29. Alkaline hydrolysis of the *N*-phenylsulfonyl protecting group of 29 was accompanied by dehydration to give sempervirine (3). This material was identical to a sample and spectra of the alkaloid.

Scheme 7



In conclusion, the pyridine-nitrogen directed *beta*-lithiation and subsequent annulation of appropriately substituted 2-(2-pyridinyl)indoles provides a convenient entry to the indolo[2,3-*a*]quinolizine ring system, exemplified herein by a total synthesis of the alkaloid sempervirine (3).

Experimental

Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 599 spectrophotometer using $CDCl_3$ solutions unless otherwise noted. ^1H NMR spectra were taken on a Varian EM-360A instrument and ^{13}C NMR spectra were measured with a Varian XL-300 instrument using $CDCl_3$ solutions for all NMR measurements. UV spectra were taken on a HP 8451A Diode Array spectrophotometer. Mass spectral determinations were made at 70eV with a Finnigan 4023 GC/MS system. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Georgia. Tetrahydrofuran (THF), dried over sodium and benzophenone, was distilled immediately before use. Commercial alkyllithium solutions were standardized with diphenylacetic acid.

5,6,7,8-Tetrahydroisoquinoline (10). -

Method A: Compound **10** was prepared in 72-79% yield via catalytic hydrogenation of isoquinoline in TFA with 10% Pd/C according to Eliel's method[7]: bp 113-116°C/26 torr (lit.[21] bp 114-115°C/16 torr). The ^1H NMR and IR data for **10** matched that reported by Ginos[22] for this compound; ^{13}C NMR ($CDCl_3$) δ 150.0, 146.0, 136.4, 132.7, 123.6, 28.5, 26.1, 22.4, 22.2.

Method B: Catalytic hydrogenation of isoquinoline in 12 N aqueous HCl with PtO_2 according to Eliel's procedure[7] provided **10** in 71% yield, identical (TLC, ^1H NMR) to that prepared by Method A.

5,6,7,8-Tetrahydroisoquinoline *N*-oxide (11). - A solution of **10** (14.4 g, 0.108 mol) in glacial HOAc (50 mL) at 65°C was treated dropwise with 30% H_2O_2 (38 mL, 0.44 mol). The solution was stirred for 10 h at 65°C (monitored by TLC). The solution was allowed to cool to room temperature and excess H_2O_2 was destroyed with MnO_2. The resulting dark brown solution, which gave a negative test with starch-iodide paper, was filtered through a pad of diatomaceous earth, concentrated *in vacuo*, and diluted with water. The aqueous solution was then extracted with CH_2Cl_2 (4 × 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give, after vacuum distillation of the crude oil, 9.2 g (57%) of **11** as a colorless oil, bp 140-145°C/0.15 torr (lit.[23] bp 170-175°C/3 torr), which crystallized on standing: mp 102-107°C; IR (KBr) 3010 , 2910, 2850, 1690, 1600, 1480, 1440, 1260, 1220, 1160-1085, 925, 840, 745 cm^{-1}; 300 MHz ^1H NMR

($CDCl_3$) δ 7.99 (s, 1 H), 7.96 (d, J = 7 Hz, 1 H), 6.98 (d, J = 7 Hz, 1 H), 2.71 (m, 4 H), 1.82 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 138.1, 137.3, 135.9, 135.7, 125.7, 27.7, 26.1, 21.9, 21.6.

3-Cyano-5,6,7,8-tetrahydroisoquinoline (6) and 1-Cyano-5,6,7,8-tetrahydroisoquinoline (13). - To *N*-oxide **11** (7.6 g, 0.051 mol) was added dropwise over 35 min dimethylsulfate (6.4 g, 0.051 mol). The resulting mixture was heated at 90-95°C for 2 h, cooled, and dissolved in water (25 mL). This solution of **12** was then added dropwise over 30 min to a solution of KCN (9.9 g, 0.152 mol) in water (25 mL) at -5°C. The reaction mixture was stirred overnight while allowing it to warm to 20°C. Extraction with CH_2Cl_2 (3 x 100 mL), washing the extract with brine, drying ($MgSO_4$), and concentration *in vacuo* gave an oil. Column chromatography over silica gel with hexane-EtOAc-Et_3N (gradient elution, 10:1:0.05) to provide 0.10 g (1%) of **6** as an oily residue followed by 0.92 (12%) of **13** as a colorless solid (mp 59-62°C), and 1.7 g (25%) of by-product **10**. Nitrile **6** slowly crystallized on standing to give colorless plates, mp 66-69°C (lit.[6] mp 65-66°C), and the regioisomer **13** was recrystallized from ether-petroleum ether to furnish colorless needles, mp 62-63°C. Data for **6**: IR (neat) 3025, 2925, 2225, 1590, 1560, 1455, 1435, 1390, 1300, 1265, 1070-1010, 950, 880, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.48 (s, 1 H), 7.48 (s, 1 H), 3.1-2.6 (m, 4 H), 2.1-1.6 (m, 4 H); MS *m/e* (relative intensity) 158 (M^+, 96), 157 (99), 143 (38), 143 (19), 130 (100), 103 (19), 77 (21), 76 (18), 63 (14), 51 (23). Data for **13**: IR (KBr) 2935, 2860, 2220, 1595, 1580, 1460, 1450, 1425, 1400, 1325, 1255, 1185, 845, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (d, J - 5 Hz, 1 H), 7.28 (d, J = 5 Hz, 1 H), 3.23-2.67 (m, 4 H), 2.23-1.63 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.1, 137.7, 133.5, 127.0, 116.0, 28.5, 25.8, 21.7, 21.4; MS *m/e* (relative intensity) 158 (M^+, 100), 157 (98), 143 (33), 130 (79), 118 (18), 103 (20), 77 (19), 51 (21), 41 (21), 39 (25). Anal. of **13** Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.97; H, 6.41; N, 17.62.

Bromoacetaldehyde. - Anhydrous bromoacetaldehyde was prepared in 39% yield from 1,4-dibromo-*trans*-butene according to Kraus' method[20] as a 0.79 M solution in methylene chloride/pentane. This solution, which could be kept at 0°C under argon for several weeks, was used directly in the metalation reaction. ^1H NMR ($CDCl_3$) δ 9.64 (t, J = 2.5 Hz, 1 H), 5.34 (s, CH_2Cl_2), 3.87 (d, J = 2.5 Hz, 2 H).

1-(Phenylsulfonyl)indole (14). - This material was prepared in 89% yield according to our published method[13] from indole with *n*-butyllithium and benzenesulfonyl chloride: mp 76-77.5°C (lit.[24] mp 77.5-79°C).

2-(*t*-Butylaminocarbonyl)-1-(phenylsulfonyl)indole (15). - To a solution of diisopropylamine (0.865 g, 8.55 mmol) in THF (20 mL) under nitrogen at -78°C was added dropwise over 10 min *n*-butyllithium (1.45 M in hexane, 5.63 mL, 8.16 mmol). The resultant solution was stirred at -78°C for 15 min and then treated dropwise over 15 min with a solution of 1-(phenylsulfonyl)indole (**14**) (2.0 g, 7.8 mmol) in THF (20 mL). After stirring at -78°C for 1 h, the resulting milky-white suspension was warmed to -5°C over 20 min and then cooled to -78°C and quenched very rapidly with *t*-butylisocyanate (1.16 g, 11.7 mmol). The mixture was stirred at -78°C for 2 h and then allowed to warm slowly to room temperature over 4 h. The reaction mixture was poured into saturated NH_4Cl (25 mL), stirred 5 min and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a light yellow oil. Crystallization from ether afforded 2.3 g (83%) of **15** as colorless prisms: mp 162.5-165°C; TLC (Et_2O-hexane, 1:1) R_f 0.38; IR (KBr) 3370, 3050, 2960, 1660, 1555, 1510, 1445, 1360, 1315, 1270, 1210, 1170, 1160-1060, 1045, 920, 910, 870, 830, 755, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.4-7.0 (m, 9 H), 6.87 (s, 1 H), 6.1 (br s, 1 H), 1.58 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 161.0, 137.3, 136.7, 136.7, 133.9, 129.0, 128.9, 127.5, 126.0, 124.2, 121.9, 115.2, 113.2, 52.3, 28.5; MS *m/e* (rel int) 356 (M^+, 3), 284 (11), 144 (25), 143 (48), 142 (100), 115 (19), 100 (16), 89 (13), 77 (32), 57 (42), 55 (11), 51 (12), 45 (11). Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found: C, 63.96; H, 5.66; N, 7.80; S, 8.96.

2-Cyano-1-(phenylsulfonyl)indole (16). - A solution of amide **15** (2.06 g, 0.00578 mol) in benzene (50 mL) at room temperature was treated with $POCl_3$ (2.9 mL, 0.031 mol) and refluxed for 6 h. Concentration *in vacuo* gave an oil. This was partitioned between CH_2Cl_2 (50 mL) and 10% aqueous $NaHCO_3$ (50 mL) and stirred until gas evolution had ceased. The layers were separated and the organic layer was washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give 1.6 g of **16** as a pale yellow solid. Crystallization from ether-ethyl acetate gave 1.4 g (86%) of colorless prisms: mp 127.5-129°C; IR (KBr) 3100, 2200, 1610, 1585, 1535, 1445, 1380, 1310, 1250, 1230, 1190-

1070, 1050, 920, 845, 750, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.50-7.98 (m, 3 H), 7.83-7.27 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 136.9, 136.3, 134.6, 129.4, 128.5, 127.2, 126.8, 124.6, 123.1, 122.4, 114.3, 112.0, 108.7.

1-(1-(Phenylsulfonyl)indol-2-yl)ethanol (20). - This was prepared in 90% yield from **14** as described.[13]

1-(Phenylsulfonyl)-2-indolyl Methyl Ketone (21). - A mixture of activated MnO_2 (73 g, 0.84 mol) and alcohol **20** (18.1 g, 0.60 mol) in $CHCl_3$ (200 mL) was heated at reflux for 18 h. The solution was then cooled, filtered, and the solids were extracted with $CHCl_3$ (3 x 100 mL). The combined filtrate and extract was concentrated *in vacuo* to give a crude solid. Recrystallization from ether/hexane (1:1) gave tiny white needles (16.1 g, 90%), mp 89-90°C (lit.[25] mp 90.5-91.0°C); spectral characteristics matched literature reports.[25] Anal.[25] Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68; S, 10.71. Found: C, 64.20; H, 4.39; N, 4.64; S, 10.67.

2-(1-(Phenylsulfonyl)indol-2-yl)-2-oxoethanal (22). - Selenium dioxide (1.69 g, 0.015 mol) and water (0.3 mL, 0.017 mol) in dioxane (20 mL) were heated for 1 h at reflux, at which point ketone **21** (2.38 g, 7.95 mmol) was added. Heating was continued for another 12 h. The yellow solution containing a black precipitate was filtered, the solids were washed with additional dioxane, and the solvent was removed by rotary evaporation. Flash chromatography (ethyl acetate/hexane (1:1)) yielded **22** as a yellow oil (2.33 g, 94%) that slowly solidified. Although this material rapidly oligomerized (trimerized?), the process was reversible as evidenced by the mass spectrum: *m/e* 313 (M^+), 284 (100%), 255, 220, 192, 165, 143, 115, 77.

5-(1-(Phenylsulfonyl)indol-2-yl)-3-thiomethyl-1,2,4-triazine (24). - A mixture of the oligomeric ketoaldehyde **22** (1.98 g, 6.32 mmol), methylthiosemicarbazide hydroiodide (**23**) (1.67 g, 7.16 mmol), $NaHCO_3$ (0.87 g, 10.4 mmol), $CHCl_3$ (30 mL), and water (10 mL) was vigorously stirred at room temperature overnight. The layers were separated, the aqueous portion was extracted with $CHCl_3$ (10 mL), and the combined organic layer was washed with water (2 x 20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a crude solid. Crystallization from ethyl acetate gave dark green prisms (2.01 g, 83%): mp 150-151°C; IR 1610, 1570, 1530, 1495, 1455, 1380, 1260, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (s, 1 H), 7.95 (d, *J* = 6 Hz, 1 H), 6.9-7.5 (m, 8 H), 7.03 (s, 1 H), 2.67 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 150.0, 145.6, 139.4, 136.0, 135.4, 134.1, 129.8, 128.8, 127.4, 126.9, 125.2, 122.4, 121.1, 116.4, 13.9; *MS m/e* 382 (M^+), 318, 281, 242, 156, 149, 140 (100%), 113, 77. Anal. Calcd for $C_{18}H_{14}N_4O_2S_2$: C, 56.53; H, 3.69; N, 14.65; S, 16.77. Found: C, 56.42; H, 3.72; N. 14.64; S, 16.67.

3-(1-(Phenylsulfonyl)indol-2-yl)-1-methanesulfonyl-5,6,7,8-tetrahydroisoquinoline (27). - The triazine **24** (1.14 g, 2.98 mmol) in CH_2Cl_2 (50 mL) was cooled in an ice bath, and technical grade (80-85%) *m*-chloroperbenzoic acid (1.60 g, >7.42 mmol) was added in portions over 3 min. Stirring was continued at 0°C for 1 h followed by 2 h at room temperature. The bright yellow solution was washed with 10% aqueous $NaHCO_3$ (2 x 30 mL) and brine (30 mL). After drying (Na_2SO_4), concentration *in vacuo* gave a somewhat unstable, bright yellow foam which was used directly in the next reaction without further purification (characteristic ^1H NMR resonances: 9.74 (s, 1 H), 3.53 (s, 1 H)). The crude triazine sulfone **25** was dissolved in $CHCl_3$ (50 mL) at room temperature and, to this solution, enamine **26** (0.60 mL, 3.97 mmol) was added dropwise over 2 min, whereupon the solution immediately darkened and gas evolution was observed. After 1 h of stirring at room temperature, the dark red reaction mixture was heated for 10 h at reflux, cooled, and the solution was concentrated *in vacuo*. The residue was passed through a 4 cm pad of silica gel (CH_2Cl_2 as eluent), concentrated to give a crude solid, and recrystallized from ethyl acetate/hexane (1:2) to afford **27** as tiny prisms (0.62 g, 45%): mp 160-161°C; IR 1610, 1550, 1455, 1440, 1380, 1310, 1185, 1160, 1130, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (d, J = 7 Hz, 1 H), 7.0-7.6 (m, 9 H), 6.75 (s, 1 H), 3.23 (s, 3H), 3.0-3.5 (m, 2 H), 2.7-3.0 (m, 2 H), 1.6-2.0 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 155.1, 149.6, 146.1, 139.2, 138.1, 136.9, 133.6, 131.3, 129.9, 129.2, 128.6, 126.6, 125.6, 124.5, 121.3, 116.2, 115.6, 40.3, 29.6, 23.9, 21.6, 21.2; *MS m/e* 466 (M^+), 325 (100%), 261, 245, 218, 77. Anal. Calcd for $C_{24}H_{22}N_2O_4S_2$: C, 61.78; H, 4.75; N, 6.00; S, 13.74. Found: C, 61.76; H, 4.78; N, 5.97; S, 13.68.

3-(Indol-2-yl)-5,6,7,8-tetrahydroisoquinoline (8). - Sulfone **27** (0.405 g, 0.87 mmol) was dissolved in THF (20 mL) at room temperature, dry methanol (20 mL) was added and the rapidly stirred solution was cooled to -30 - -40°C with a dry ice/isopropanol cooling bath. This temperature was maintained as dibasic sodium phosphate (0.31 g, 2.18 mmol) and powdered, 6% sodium amalgam (3.10 g, 7.75 mmol, added in 6 x 0.5-g portions over 3.5 h) were mixed in. After a total of

5 h at -30°C, the pale yellow mixture was decanted from the amalgam and filtered. The filtrate was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic phase was washed with water (2 x 50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (methylene chloride - methylene chloride/ethyl acetate (3:1), gradient elution) gave a gum which solidified after being treated with ether followed by slow evaporation to dryness (0.196 g, 91%). Recrystallization from ethyl acetate/hexane gave flat prisms: mp 159.5-160.5°C (lit.[6] mp 158-158.5°C); ^{1}H NMR ($CDCl_3$) δ 10.08 (br s, 1 H), 8.30 (s, 1 H), 7.0-7.7 (m, 5 H), 6.93 (s, 1 H), 2.5-3.0 (m, 4 H), 1.8-2.0 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 149.5, 147.4, 146.8, 137.2, 136.4, 131.9, 129.2, 122.6, 120.8, 119.9, 119.8, 111.3, 99.4, 28.8, 26.2, 22.6, 22.4; MS *m/e* 248 (M^+, 100%), 220, 117, 85.

3-(1-(Phenylsulfonyl)indol-2-yl)-5,6,7,8-tetrahydroisoquinoline (17). - A 50% dispersion of NaH (19 mg, 0.39 mmol) was stirred in dry pentane (1 mL) for 30 sec and then the solid was allowed to settle. The pentane was decanted and the residue was covered with THF (4 mL). The rapidly stirred suspension was cooled and **8** (16 mg, 0.06 mmol) dissolved in THF (0.5 mL) was added dropwise over 2 min, and stirring was continued at 0°C for 1 h. Phenylsulfonyl chloride (0.07 mL, 0.55 mmol) was then added dropwise over 1 min followed by stirring at 0°C for 1.5 h. Saturated aqueous $NaHCO_3$ (2 mL) was carefully added dropwise and the reaction mixture was vigorously stirred for 30 min at 0°C, and then 30 min at room temperature. The layers were separated and the aqueous phase was extracted with ether (10 mL). The organic layer was washed with brine (2 x 10 mL), dried (K_2CO_3), and concentrated *in vacuo* to give a crude foam. Final purification by flash chromatography (methylene chloride-ethyl acetate, gradient elution) gave **17** as a pale yellow solid (18 mg, 72%) which gave off-white plates after recrystallization from ethyl acetate/hexane: mp 158.5-159.5°C; IR 1605, 1585, 1480, 1450, 1370, 1185, 1170, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1 H), 8.20 (d, J = 8 Hz, 1 H), 7.2-7.7 (m, 9 H), 6.80 (s, 1 H), 2.7-3.0 (m, 4 H), 1.7-2.1 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 149.4, 148.0, 145.7, 141.4, 137.9, 137.2, 133.5, 132.8, 130.5, 128.6, 127.0, 126.3, 125.0, 124.3, 121.2, 116.2, 114.5, 28.7, 26.2, 22.5, 22.3; MS *m/e* 388 (M^+), 324 (100%), 295, 247, 219, 77. Anal. Calcd for $C_{23}H_{20}N_2O_2S$: C, 71.11; H, 5.19; N, 7.21; S, 8.25. Found: C, 71.18; H, 5.25; N, 7.17; S, 8.30.

Sempervirine (3). - The protected indole **17** (18 mg, 0.046 mmol) in THF (5 mL) was immersed in a dry ice/isopropanol cold bath and 1.39 M *n*-butyllithium (0.14 mL, 0.19 mmol) was added dropwise over 1 min. Stirring was continued for 1 h at -75°C, and then a 0.79 M solution of bromoacetaldehyde in pentane (0.35 mL, 0.28 mmol) was added over 2 min, and the reaction mixture was stirred for another 1 h. Acetic acid (0.07 mL, 1.17 mmol) was added dropwise, followed by 1 h of stirring at -75°C. The solution was allowed to warm to 0°C over 30 min and saturated aqueous NH_4Cl (5 mL) was added. The layers were separated, the aqueous phase was extracted with ethyl acetate (5 mL), and the combined organic extracts were washed with 10% aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The yellow solution was dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow gum. The crude reaction mixture was dissolved in $CHCl_3$ (1 mL) and stirred for 30 min to allow for complete cyclization. The solvent was then removed *in vacuo* and the residue was washed with boiling ether (5 x 2 mL) leaving 16 mg of bromide **29** as a pale yellow powder. An additional 4 mg was obtained through chromatography (gradient elution, MeOH - 19:1 MeOH/AcOH) of the ether washings (characteristic ^{1}H NMR signals: 9.09 (s, 1 H), 8.20 (d, J = 9 Hz, 1 H), 8.17 (s, 1 H). This crude salt was dissolved in methanol (5 mL), 10% aqueous NaOH (1 mL) was added, and the resulting yellow solution was heated for 45 min at reflux. The dark yellow reaction mixture was cooled, concentrated *in vacuo*, and partitioned between $CHCl_3$ (10 mL) and 10% aqueous NaOH. The organic phase was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), concentrated *in vacuo*, and subjected to flash chromatography (methanol/acetic acid, 9:1). The appropriate fractions were combined and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (20 mL) and 10% aqueous NaOH (10 mL). The organic layer was washed with water (2 x 20 mL), dried (K_2CO_3), and concentrated *in vacuo* to leave pure sempervirine (**3**) as a red-orange powder (6 mg, 48% from **17**). IR 1645, 1615, 1555, 1480, 1400, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1 H), 7.1-8.1 (m, 7 H), 2.9-3.0 (m, 2 H), 2.7-2.8, (m, 2 H), 1.8-1.9 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 153.7, 143.9, 140.7, 134.3, 130.9, 130.1, 125.9, 123.0, 122.0, 120.6, 120.2, 118.6, 118.0, 117.3, 115.8, 28.8, 26.2, 22.0; UV λ_{max} (MeOH), acidic or neutral conditions, 386, 340, 296, 244 nm; basic, 356, 316, 286, 245 nm (lit.[26] λ_{max} (95% EtOH), pH ≤ 6, 385, 342, 294, 249, 242 nm; pH 12, 435, 360, 320, 288, 242 nm). The nitrate salt of synthetic sempervirine gave an IR spectrum that was superimposable on that of an authentic sample.

Acknowledgements

We are grateful to Professor E. C. Taylor for suggesting the triazine route to **17**, and to Professor Y. Ban for a sample of sempervirine nitrate and spectra. This investigation was supported in part by Merck Sharp & Dohme Research Laboratories.

References and Notes

1. For a review, see: G.W. Gribble in "Studies in Natural Products Chemistry," A. Rahman, Ed., Elsevier, Amsterdam, in press.
2. R.B. Woodward and W.M. McLamore, *J. Am. Chem. Soc.*, **1949**, *71*, 379.
3. a) M. Beljanski and M.S. Beljanski, *Exp. Cell. Biol.*, **1982**, *50*, 79; b) M. Beljanski and M.S. Beljanski, *Oncology*, **1986**, *43*, 198; c) R. Bassleer, D. Clermont, J.M. Marnette, M. Caprasse, M. Tits, and L. Angenot, *Ann. Pharm. Fr.*, **1985**, *43*, 83.
4. D.A. Johnson and G.W. Gribble, *Heterocycles*, **1986**, *24*, 2127.
5. G.W. Gribble and D.A. Johnson, *Tetrahedron Lett.*, **1987**, *28*, 5259.
6. R. Bentley, T.S. Stevens, and M. Thompson, *J. Chem. Soc. (C)*, **1970**, 791.
7. F.W. Vierhapper and E.L. Eliel, *J. Org. Chem.*, **1975**, *40*, 2729.
8. A.I. Meyers and T.R. Bailey, *J. Org. Chem.*, **1986**, *51*, 872.
9. a) W.E. Feely and E.M. Beavers, *J. Am. Chem. Soc.*, **1959**, *81*, 4004; b) T. Okamoto and H. Tani, *Chem. Pharm. Bull. Japan*, **1959**, *7*, 130.
10. a) D.A. Johnson and G.W. Gribble, unpublished observations; b) for an independent discovery of this cyanation reaction, see H. Vorbrüggen and K. Krolikiewicz, *Synthesis*, **1983**, 316.
11. A. Naiman and K.P.C. Vollhardt, *Angew. Chem. Int. Ed. Engl.*, **1977**, *16*, 708.
12. K. Takabe, H. Fujiwara, T. Katagiri, and J. Takanaka, *Tetrahedron Lett.*, **1975**, 4375.
13. M.G. Saulnier and G.W. Gribble, *J. Org. Chem.*, **1982**, *47*, 757.
14. R.B. Perni and G.W. Gribble, *Org. Prep. Proced. Int.*, **1983**, *15*, 297.
15. K.E. Harding and R.C. Ligon, *Syn. Commun.*, **1974**, *4*, 297.
16. a) E.C. Taylor and J.E. Macor, *Tetrahedron Lett.*, **1985**, *26*, 2415, 2419; b) E.C. Taylor, K.F. McDaniel, and J.C. Warner, *Tetrahedron Lett.*, **1987**, *28*, 1977, and earlier papers cited therein.
17. a) D.L. Boger and J.S. Panek, *J. Org. Chem.*, **1981**, *46*, 2179; b) D.L. Boger, J.S. Panek, and M.M. Meier, *J. Org. Chem.*, **1982**, *47*, 895; c) D.L. Boger, *Chem. Rev.*, **1986**, *86*, 781; d) D.L. Boger, *Tetrahedron*, **1983**, *39*, 2869.
18. G.W. Gribble, M.G. Saulnier, M.P. Sibi, J.A. Obaza-Nutaitis, *J. Org. Chem.*, **1984**, *49*, 4518.
19. Aluminum amalgam or Raney nickel only cleaved the phenylsulfonyl group while leaving the other sulfone untouched. The sodium amalgam reduction also proceeded stepwise by initial cleavage of the indole protecting group, although the intermediate could not be seen unless the reaction was carried out at -78°C and stopped short of completion. No trace of **8** was detected under any reaction conditions.
20. G.A. Kraus and P. Guttschalk, *J. Org. Chem.*, **1983**, *48*, 2111.
21. E. Schlittler and R. Merian, *Helv. Chim. Acta*, **1947**, *30*, 1339.
22. J.Z. Ginos, *J. Org. Chem.*, **1975**, *40*, 1191.
23. E. Ochiai and M. Ikehara, *Chem. Pharm. Bull. Japan*, **1954**, *2*, 109.
24. R.J. Sundberg and H.P. Russell, *J. Org. Chem.*, **1973**, *38*, 3724.
25. M.G. Saulnier and G.W. Gribble, unpublished results; M.G. Saulnier, Ph.D. Thesis, Dartmouth College, **1982**.
26. K.T. Potts and G.S. Mattingly, *J. Org. Chem.*, **1968**, *33*, 3985.