TOTAL SYNTHESIS OF THE *AMARYLLIDACEAE* ALKALOID (±)-EPIELWESINE. THE IMPORTANCE OF VINYLSILANE STEREOCHEMISTRY IN IMINIUM ION-VINYLSILANE CYCLIZATIONS [1]**

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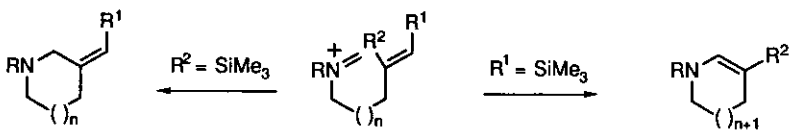
Abstract- (±)-Epielwesine (**9**) was prepared in an efficient and completely stereocontrolled fashion in six steps and 28% overall yield from commercially available 3,4-methylenedioxyphenylacetonitrile (**15a**). The key step is acid promoted cyclization of the (Z)-vinylsilane-iminium cation (**13**) to construct the *cis*-3a-arylhexahydroindole (**12**) in 95% yield. The Z stereochemistry of the vinylsilane is critical to the success of the iminium ion-vinylsilane cyclization, a result that establishes the importance of hyperconjugative electron release from the β-C-Si σ bond in stabilizing the cyclization transition state. A method for the convenient preparation of Δ^1-pyrrolines (3,4-dihydro-2*H*-pyrroles) or Δ^1-piperideines (3,4,5,6-tetrahydropyridines) from nitrile precursors is also provided.

INTRODUCTION

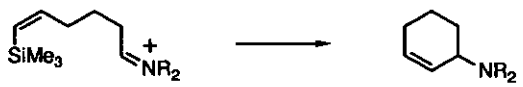
The considerable utility of iminium ion-vinylsilane cyclizations for the synthesis of nitrogen heterocycles has been detailed in recent publications from our laboratories.[3,4] These reports document cyclizations that occur in an endocyclic mode[5] with respect to the iminium ion initiator and occur in either an exocyclic (**1** → **2**) or endocyclic (**1** → **3**) sense with respect to the tethered vinylsilane nucleophile.



2 **1** **3**

** Dedicated with much admiration to Professor Edward C. Taylor on the occasion of his 70th birthday.

During the course of these studies, we became interested in whether these reaction components would also participate in cyclizations that took place in an exocyclic sense with respect to the iminium ion electrophile



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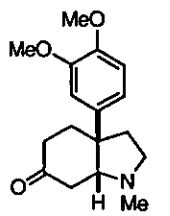
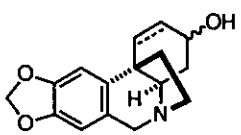
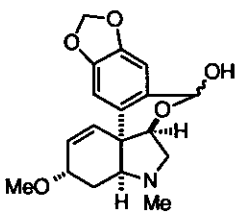
(4 → 5). We chose to investigate this issue in the context of a general approach to the *cis*-3a-aryloctahydroindole nucleus common to many *Amaryllidaceae* alkaloids.[6] These alkaloids constitute one of the most widespread classes of nitrogen containing compounds and their total synthesis has received intense attention over the past two decades.[6] Members of the subgroup possessing the *cis*-3a-aryloctahydroindole unit include mesembrine (**6**), crinine (**7**), elwesine (**8**), epielwesine (**9**), pretazettine (**10**), and tazettine (**11**).



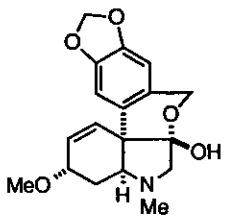
mesembrine (**6**)



crinine (**7**) α - OH, 1,2-dehydro
elwesine (**8**) α - OH, 1,2-dihydro
epielwesine (**9**) β - OH, 1,2-dihydro



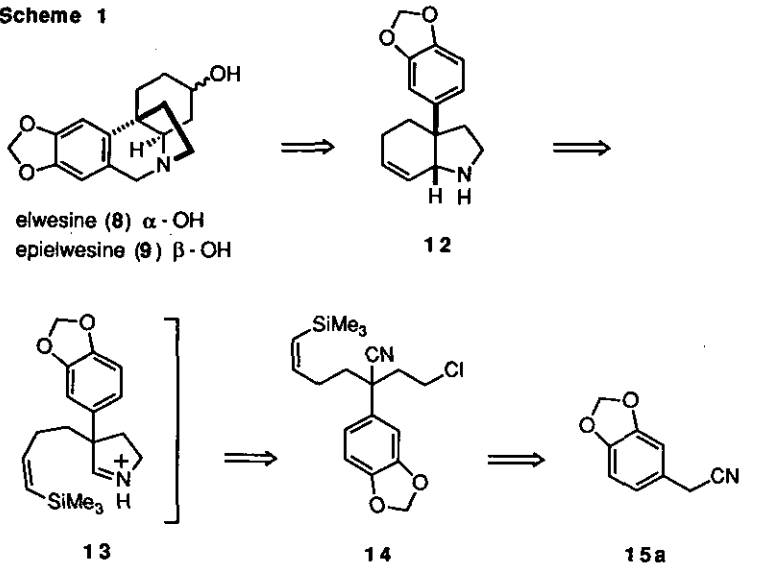
pretazettine (**10**)



tazettine (**11**)

The general approach we opted to pursue is expressed in antithetic format in Scheme 1. Elwesine and epielwesine were chosen as suitable initial targets, which would derive from the *cis*-3a-arylhexahydroindole (**12**). The heart of this plan is the formation of hexahydroindole (**12**) from the cyclization of the iminium ion vinylsilane intermediate (**13**). Envisaged as a potential precursor of (**13**) is the substituted nitrile (**14**), which could reasonably originate from commercially available 3,4-methylenedioxyphenylacetonitrile (**15a**).

Scheme 1



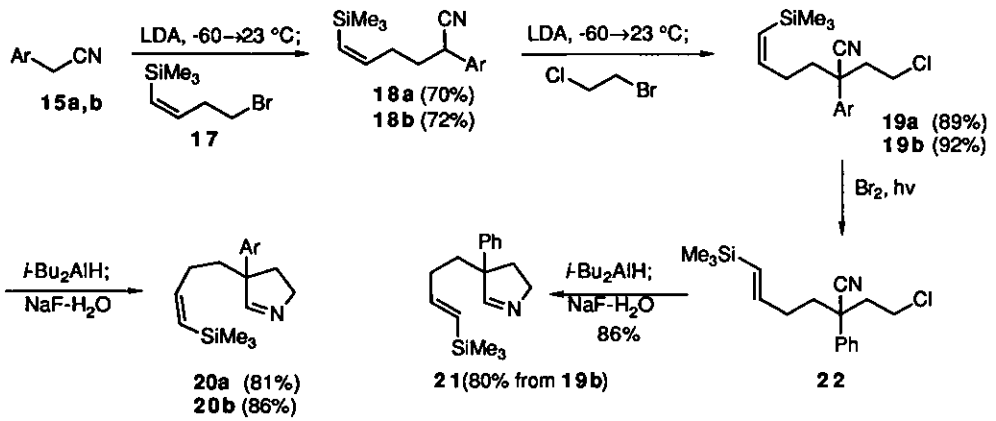
In this paper, we present details of an efficient synthesis of (±)-epielwesine along the lines adumbrated in Scheme 1. The critical importance of the vinylsilane stereochemistry for the success of the key iminium ion-vinylsilane cyclization is demonstrated through kinetic investigations in a model series.[7] We also present experimental details of a convenient preparation of 3,3-disubstituted Δ^1-pyrrolines and Δ^1-piperideines from nitrile precursors.

RESULTS AND DISCUSSION

A General Synthesis of 3,3-Disubstituted Δ^1-Pyrrolines and Δ^1-Piperideines.[8,9] The (Z)-vinylsilane Δ^1-pyrroline cyclization substrates (**20ab**) were prepared from 3,4-methylenedioxyphenylacetonitrile (**15a**) or phenylacetonitrile (**15b**) as summarized in Scheme 2. Specifically, a THF solution of the tertiary carbinyl nitriles (**19a**) or (**19b**) was treated with 1 equiv. of *i*-Bu_2AlH (-78 → 23 °C) followed by workup with NaF and H_2O[10] to provide the 3,3-disubstituted Δ^1-pyrrolines (**20a**) or (**20b**) in excellent (81 - 86%) yield. These pyrrolines showed diagnostic signals for the carbon-nitrogen double bond in their infrared (1610 cm^{-1}) and ^{13}C nmr (171 ppm) spectra. Nitriles (**19ab**) were accessed efficiently by sequential alkylation[11] of arylacetonitriles

(**15a,b**) with (*Z*)-(4-bromo-1-butenyl)trimethylsilane[3c,f] and 1-bromo-2-chloroethane. The corresponding (*E*)-vinylsilane Δ^1-pyrroline (**21**) was prepared in the phenyl series by bromine radical-promoted isomerization[12] of the (*Z*)-vinylsilane nitrile (**19b**), followed by reductive cyclization of (**22**).

Scheme 2



a Ar = 3,4-methylenedioxyphenyl; **b** Ar = Ph

Since Δ^1-pyrrolines and Δ^1-piperideines have been extensively employed in alkaloid construction,[13] we briefly examined the generality of the preparation of these important intermediates from nitrile precursors.[13,14] The results of these investigations are presented in Scheme 3 and Table 1. The reaction of cyclopentanecarbonitrile (**23a**) or cyclohexanecarbonitrile (**23b**) with 1-bromo-2-chloroethane (**24**, m = 1) was realized in yields of 30 - 40%. These low yields contrast markedly with the ~90% yields obtained in the related alkylation of the aryl-substituted nitriles (**19**). Alkylation of (**23a**) or (**23b**) with 1-bromo-3-chloropropane was more efficient and afforded the chloronitriles (**26**) in 67 - 68% yields. Conversion of these intermediates to the unsaturated azaspiranes (**28**) and (**29**) was realized in preparatively useful yields by sequential treatment with *i*-Bu_2AlH and NaF-H_2O. The reduction-cyclization to form the Δ^1-piperideines (**29**) was more efficient when the chloride precursors (**26**) were initially converted to the corresponding iodides (**27**). The cyclic imines (**20**, **21**, **28** and **29**) are labile materials that deteriorate rapidly in the air.[15]

Scheme 3

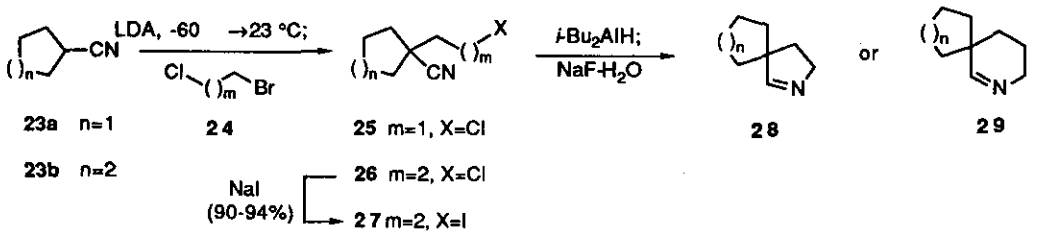
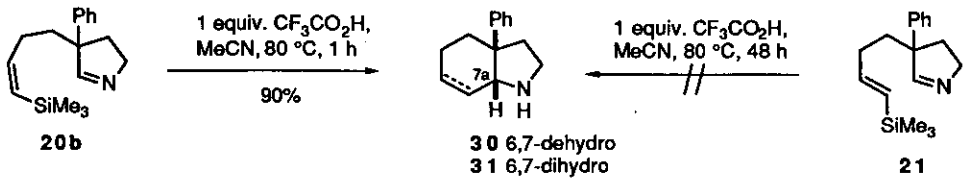


Table 1. Preparation of the Δ^1-Pyrrolines (28) and Δ^1-Piperideines (29) from Nitriles (23)

Alkylation Step		Cyclization Step		
Nitrile	Yield, %	Precursor	Imine	Yield, %
25a	31	**25a**	**28a**	85
25b	40	**25b**	**28b**	81
26a	67	**26a**	**29a**	63
26b	68	**27a**	**29a**	84
		26b	**29b**	54
		27b	**29b**	75

Iminium Ion-Vinylsilane Cyclization to Form Hexahydroindoles. The Importance of Vinylsilane Stereochemistry. The key cyclization step of the synthetic strategy proposed in Scheme 1 was initially examined in a phenyl model series. Attempts to promote the cyclization of pyrroline (**20b**) in acetonitrile by N-alkylation (MeOTs or MeOMs) or treatment with 0.95 equiv. of camphorsulfonic acid (or 1 equiv. of $MeSO_3H$ in CH_2Cl_2) resulted in no reaction, while at 50 °C the latter conditions resulted only in protodesilylation of (**20b**). The desired conversion to the hexahydroindole (**30**) was finally realized in excellent yield by treating (**20b**) with 1.0 equiv. of trifluoroacetic acid in acetonitrile (0.2 M) for 1 h at 80 °C. The *cis*-hexahydroindole (**30**) showed diagnostic signals in the ^1H nmr spectrum at δ 5.9-6.2 (m, CH=CH) and δ 3.66 (broad s, $W_{1/2}$ = 8

Hz, H_{7a}). The structure of this intermediate was further confirmed by catalytic hydrogenation to afford known *cis*-3a-phenyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-indole (**31**, maleate salt, mp 152 °C).[16]



20b

30 6,7-dehydro
31 6,7-dihydro

21

The geometry of the vinylsilane is critical to the success of this cyclization reaction. Thus, while the cyclization of (**20b**) in acetonitrile in the presence of 1 equiv. of CF_3CO_2H proceeded cleanly to give the *cis*-3a-phenylhexahydroindole (**30**), the reaction of the E stereoisomer (**21**) under identical conditions for 48 h provided no trace of (**30**). At higher temperatures (**21**) failed to cyclize but rather underwent protodesilylation. To quantify the difference in cyclization rate between the two stereoisomers, the cyclization of (**20b**) in the presence of 1.0 equiv. of CF_3CO_2H was carried out in C_6D_6 at 115 °C and monitored by ^1H nmr spectroscopy. Under these conditions the cyclization of (**20b**) was complete within 1 h ($t_{1/2}$ = 9 min), while after 72 h (**21**) produced only a trace amount of (**30**). Placing an upper limit of 5% in the amount of (**30**) produced from (**21**) after 48 h leads to the conclusion that the (Z)-vinylsilane stereoisomer cyclizes at least **6850 times faster** than its E counterpart.

This substantial difference in cyclization rate of the stereoisomers (**20b**) and (**21**) provides a striking demonstration of the importance of Si-C hyperconjugation in the cyclization transition state. As illustrated in Figure 1, for a cyclization occurring in a chair topography,[17,18] only a Z alkene substituent can initially participate in $\sigma \rightarrow p$ delocalization with the developing cyclohexyl carbocation center. Current estimates of the magnitude of the β effect of the $SiMe_3$ group for secondary cations range from 19 - 22 kcal/mol,[19,20] thus, nearly one third of the maximal hyperconjugative stabilization is realized in the transition state for the cyclization of (**20b**).

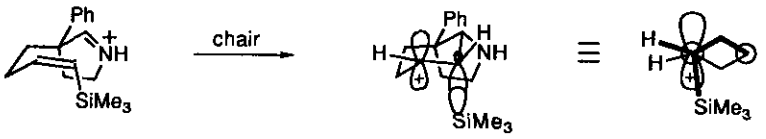


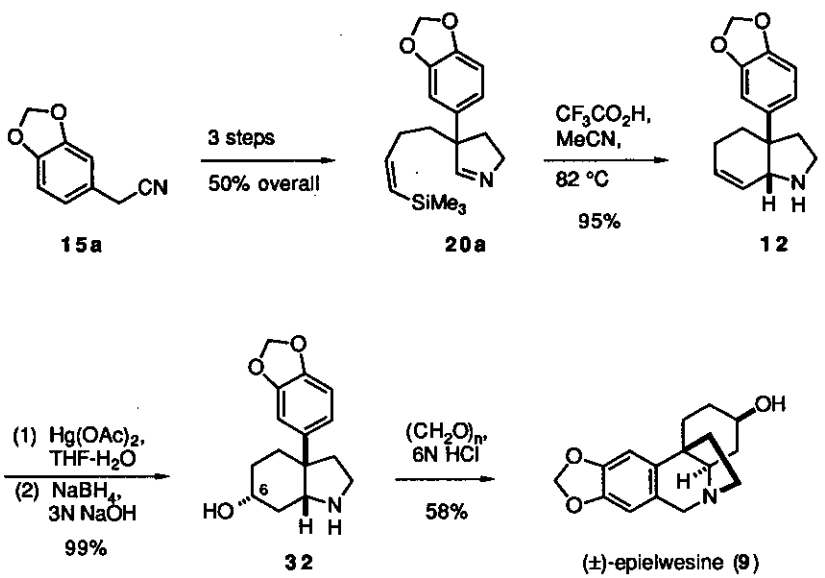
Figure 1. Optimal overlap of the β–C-Si σ-bond and the developing cyclohexyl cation in a chair topography cyclization of a (*Z*)-vinylsilane.

It would be incorrect, however, to conclude from these experiments that a (*Z*)-vinylsilane nucleophile will *always* be required to observe a successful cyclization reaction with a tethered electrophile. Particularly in cases where the electrophile is a powerful one, stabilization of the cyclization transition state by Si-C hyperconjugation may not be required.[21] A number of successful cyclization reactions of (*E*)-vinylsilanes with reactive acylium ion initiators have been reported.[22] Nonetheless, cyclization synthesis strategies that employ vinylsilane nucleophiles should be optimal when the (*Z*)-vinylsilane stereoisomer is employed.

Total Synthesis of (±)-Epielwesine. The three step sequence outlined in Scheme 2 affords the key cyclization substrate (**20a**) on multigram scale in three steps and 50% overall yield from commercially available 3,4-methylenedioxyphenylacetonitrile (**15a**). Cyclization of (**20a**) was accomplished in nearly quantitative yield by exposure of this intermediate to 1.0 equiv. of trifluoroacetic acid in refluxing acetonitrile for 2 h (Scheme 4). The *cis*-3a-arylhexahydroindole (**12**) was isolated in 95% yield and exhibited a diagnostic signal in the ^{1}H nmr spectrum at δ 3.50 (app d, J = 4.1 Hz) for the angular hydrogen H_{7a}. Initial attempts to introduce the C(6) hydroxyl functionality *via* hydroboration (BH_3•THF, BH_3•Me_2S, 9-BBN, or thexylborane) were unsuccessful, a result that was not unexpected.[23] Hydration of (**12**) was finally realized by oxymercuration-demercuration,[24] which proceeded both stereo- and regioselectively[25] to afford the known amino alcohol (**32**) (mp 176-178 °C, lit.,[26] 178-180 °C) as the sole product. Compound (**32**) was obtained in 68% yield (99% based on consumed **12**) and exhibited a diagnostic signal in ^{1}H nmr spectrum at δ 3.98 (broad singlet, $W_{1/2}$ = 8 Hz) for the equatorial C(6) methine hydrogen. The regioselectivity in the hydration of (**12**) is readily attributable to inductive electron withdrawal by the allylic nitrogen. The extremely high face selectivity is more notable.

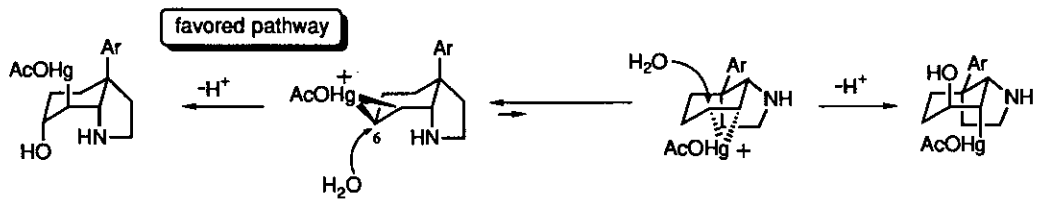
Apparently this conversion is dominated by the thermodynamic preference for *cis*-3a-arylhydroindoles to exist in conformations that place the C(3a) aryl substituent in axial orientations (Scheme 5).[27-30]

Scheme 4. Total Synthesis of (±)-Epielwesine



Completion of the synthesis of (±)-epielwesine (**9**) was accomplished by Pictet-Spengler cyclization[31] of (**32**), which provided (±)-(**9**) as a crystalline solid (mp 182-184 °C, lit.,[26] mp 182-184 °C) in 58% yield.

Scheme 5



CONCLUSION

The first examples of iminium ion-vinylsilane cyclizations that occur in an exocyclic sense with respect to the iminium electrophile are recorded. The cyclization of the (*Z*)-vinylsilane stereoisomer to form hexahydroindole (**30**) has been shown to proceed > **6500** faster than cyclization of the corresponding E stereoisomer. This result provides convincing evidence for hyperconjugative electron-release by the Me_3Si group in the cyclization transition state. This new synthesis of hexahydroindoles is the key step in a notably concise total synthesis of the *Amaryllidaceae* alkaloid (±)-epielwesine (**9**). Starting from commercially available 3,4-methylenedioxyphenylacetonitrile (**15a**), the synthesis of (**9**) proceeds in six steps and 28% overall yield. Details of a convenient two step synthesis of Δ^1-pyrrolines and Δ^1-piperideines from simple nitrile precursors are also provided.

EXPERIMENTAL SECTION

(Z)-2-(3,4-Methylenedioxyphenyl)-6-trimethylsilyl-5-hexenenitrile (18a). According to standard procedures,[11] a solution of diisopropylamine (25.2 ml, 0.180 mol) and THF (150 ml) was cooled to -70 °C and *n*-BuLi (81.8 ml of a 2.2 M solution in hexanes, 0.18 mol) was added dropwise. After stirring for 15 min a solution of 3,4-methylenedioxyphenylacetonitrile (**15a**) (29.0 g, 0.180 mol) in THF (50 ml) was added dropwise, the solution stirred for 5 min and then a solution of (Z)-(4-bromo-1-butenyl)trimethylsilane (**17**, 18.8 g, 0.09 mol prepared from the corresponding tosylate[3c,f] by reaction with LiBr in acetone at room temperature and used directly) in THF (50 ml) was added dropwise. The resulting solution was stirred for 1 h, warmed to room temperature for 15 min and then quenched with 1M HCl (100 ml). The aqueous portion was separated and extracted with diethyl ether (2 x 100 ml). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo* . Purification of the residue by flash column chromatography (silica gel, 20:1 hexane-ethyl acetate) gave 18.1 g (70%) of chromatographically pure **18a** as a clear, colorless oil: ^{1}H Nmr (250 MHz, $CDCl_3$) δ 6.8-6.9 (m, 3 H, ArH), 6.28 (dt, J = 14.0, 7.2 Hz, C*H*=CHSi$(CH_3)_3$), 6.02 (s, OCH_2O), 5.64 (d, J = 14.0 Hz, CH=C*H*Si$(CH_3)_3$), 3.77 (t, J = 7.2 Hz, ArCH_2), 2.28-2.38 (m, CH_2CH=CH), 1.91-2.13 (m, 2 H), 0.15 (s, Si$(CH_3)_3$); ^{13}C nmr (63 MHz, $CDCl_3$) 148.4, 147.6, 145.6, 131.9, 129.4, 120.9, 120.8, 108.7,

107.8, 101.5, 36.6, 36.0, 30.7, 0.2 ppm; ir ($CHCl_3$) 2960, 2895, 2785, 2220, 1610, 1485, 1445, 1240, 1027, 830 cm^{-1}; ms (CI, isobutane) m/z 288 (M^+H); HR-ms (EI) m/z (M^+) 287.1328 (287.1341 calcd for $C_{16}H_{21}NO_2Si$).

(Z)-2-Phenyl-6-trimethylsilyl-5-hexenenitrile (18b) was prepared in a similar fashion from 1.3 g (11.6 mmol) of phenylacetonitrile. Purification of the crude product by flash column chromatography (silica gel, 20:1 hexane-ethyl acetate) gave 1.0 g (72%) of chromatographically pure **18b** as a clear, colorless oil: ^1H nmr (250 MHz, $CDCl_3$) δ 7.33-7.43 (m, PhH), 6.25 (dt, J = 14.0, 7.2 Hz, C*H*=CHSi$(CH_3)_3$), 5.60 (d, J = 7.0 Hz, CH=C*H*Si$(CH_3)_3$), 3.82 (t, J = 8.0 Hz, PhCH_2), 2.26-2.35 (m, CH_2CH=CH), 1.9-2.15 (m, CHCH_2CH_2), 0.09 (s, Si$(CH_3)_3$); ^{13}C nmr (63 MHz, $CDCl_3$) δ 135.8, 131.9, 129.3, 128.6, 128.3, 127.4, 120.8, 37.0, 35.9, 30.8, 0.2 ppm; ir ($CHCl_3$) 3060, 2945, 2885, 2855, 2220, 1605, 1490, 1450, 1240, 840 cm^{-1}; ms (CI, isobutane) m/z 244 (MH^+); HR-ms (EI) m/z (M^+) 243.1430 (243.1443 calcd for $C_{15}H_{21}NSi$).

(Z)-2-(Chloroethyl)-2-(3,4-methylenedioxyphenyl)-6-trimethylsilyl-5-hexenenitrile (19a). A solution of LDA [prepared by addition of *n*-BuLi (20.1 ml of a 2.2M solution in hexanes, 44.2 mmol) to diisopropylamine (6.2 ml, 44.2 mmol) in THF (40 ml) at -70 °C] was added to a solution of nitrile (**18a**) (12.7 g, 44 mmol) in THF (20 ml) at -70 °C while not allowing the internal reaction temperature to exceed -60 °C. After 15 min a solution of 1-bromo-2-chloroethane (6.4 g, 44 mmol) in THF (10 ml) was added while again not allowing the internal reaction temperature to exceed -60 °C. After 1 h, the resulting solution was allowed to warm to temperature, stirred for 1 h and then quenched with H_2O (100 ml). The aqueous layer was separated and extracted with diethyl ether (200 ml). The combined organic portions were washed with 1M HCl (100 ml), saturated aqueous NH_4Cl (100 ml), and dried ($MgSO_4$) and the solvent was concentrated *in vacuo* after filtration. Flash column chromatography (silica gel, 9:1 hexane-ethyl acetate) of the crude product obtained from the reaction gave 13.7 g (89%) of **19a** as a chromatographically pure clear, colorless oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 6.80-6.95 (m, 3 H), 6.15 (dt, J = 13.9, 7.1 Hz, C*H*=CHSi$(CH_3)_3$), 6.00 (d, J = 1.9 Hz, OCH_2O), 5.51 (d, J = 13.9 Hz, CH=C*H*Si$(CH_3)_3$), 3.17-3.63 (m, CH_2Cl), 1.82-2.35 (m, 6 H), 0.02 (s, Si$(CH_3)_3$); ^{13}C nmr (63 MHz, $CDCl_3$) 148.9, 147.9, 145.6, 131.4, 130.4, 121.3, 119.9, 108.8, 106.0, 101.8, 46.8, 43.7, 41.4, 39.6,

29.3, 0.2 ppm; ir ($CHCl_3$) 3050, 2950, 2895, 2760, 2210, 1605, 1480, 1440, 1240, 1025, 825 cm^{-1}; ms (CI, isobutane) m/z 350 (M^+H); HR-ms (EI) m/z (M^+) 349.1236 (349.1264 calcd for $C_{18}H_{24}NO_2ClSi$).

(Z)-2-(Chloroethyl)-2-phenyl-6-trimethylsilyl-5-hexenenitrile (19b) was prepared similarly. Flash column chromatography (silica gel, 9:1 hexane-ethyl acetate) of the crude product obtained from the reaction of **18b** with 1-bromo-2-chloroethane gave **19b** (92% yield) as a chromatographically pure clear, colorless oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 7.3-7.55 (m, PhH), 6.16 (dt, J = 14.0, 7.2 Hz, C*H*=CHSi$(CH_3)_3$), 5.51 (d, J = 13.9 Hz, CH=C*H*Si$(CH_3)_3$), 3.18-3.64 (m, CH_2Cl), 1.8-2.6 (m, 6 H), 0.0 (s, Si$(CH_3)_3$); ^{13}C nmr (63 MHz, $CDCl_3$) 145.6, 136.7, 131.4, 129.5, 128.6, 125.9, 121.2, 47.0, 43.5, 41.3, 39.6, 29.3, 0.14 ppm; ir ($CHCl_3$) 2960, 2890, 2220, 1605, 1490, 1445, 1240, 880, 830 cm^{-1}; ms (CI, isobutane) m/z 306 (M^+H); HR-ms (EI) m/z (M^+) 305.1384 (305.1366 calcd for $C_{17}H_{24}NClSi$).

3-(3,4-Methylenedioxyphenyl)-3-[(Z)-4-(trimethylsilyl)buten-4-yl)]-1-azacylopent-1-ene (20a). To a solution of **19a** (1.01 g, 2.90 mmol) and toluene (10 ml) cooled to -70 °C was added neat diisobutylaluminum hydride (0.52 ml, 2.9 mmol) dropwise. After 1h, the solution was allowed to warm to room temperature, stirred for 12 h, and then recooled to 0 °C before adding NaF[10] (0.49 g, 11.6 mmol). After stirring vigorously for 1h, H_2O (0.16 ml, 8.7 mmol) was added, the mixture was stirred for 45 min. The mixture was allowed to warm to room temperature and then stirred an additional 1 h. The resulting mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 4:1 hexane-ethyl acetate) to afford 0.74g (81%) of chromatographically pure **20a** as a clear, colorless oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 7.64 (t, J = 2.4 Hz, CH=N), 6.65-6.78 (m, ArH), 6.19 (dt, J = 13.9, 7.0 Hz, C*H*=CHSi$(CH_3)_3$), 5.93 (s, OCH_2O), 5.46 (d, J = 13.9 Hz, CH=C*H*Si$(CH_3)_3$), 3.92 (dt, J = 7.4, 2.3 Hz, CH_2N), 1.79-2.08 (m, 6 H), 0.02 (s, Si$(CH_3)_3$); ^{13}C nmr (63 MHz, $CDCl_3$) 171.1, 148.3, 147.6, 146.3, 138.2, 130.1, 119.1, 108.4, 107.0, 101.2, 60.8, 39.0, 36.8, 29.4, 0.3 ppm; ir ($CHCl_3$) 2955, 2890, 2760, 1608, 1480, 1235, 1025, 930, 832 cm^{-1}; ms (CI, isobutane) m/z 316 (M^+H); HR-ms (EI) m/z (M^+) 315.1656 (315.1654 calcd for $C_{18}H_{25}NO_2Si$). This labile material could be stored at 0 °C in a sealed vial under argon; it rapidly decomposed in the air.

3-Phenyl-3-[(Z)-4-(trimethylsilylbuten-4-yl)]-1-azacyclopent-1-ene (20b). This compound was prepared as described for **20a.** Flash column chromatography (silica gel, 4:1 hexane-ethyl acetate) of the crude product obtained from the reaction of **19b** with *i*-Bu_2AlH gave an 86% yield of chromatographically pure **19e** as a clear, colorless oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 7.80 (br s, CH=N), 7.26-7.44 (m, PhH), 6.27 (dt, J = 13.9, 7.0 Hz, C*H*=CHSi$(CH_3)_3$), 5.53 (d, J = 13.9 Hz, CH=C*H*Si$(CH_3)_3$), 3.98-4.04 (m, CH_2N=CHR), 1.9-2.3 (m, 6 H), 0.07 (s, Si$(CH_3)_3$); ^{13}C nmr (63 MHz, $CDCl_3$) 171.3, 147.6, 144.2, 130.0, 128.6, 126.8, 126.2, 60.8, 38.9, 36.5, 29.4, 0.2 ppm; ir ($CHCl_3$) 2950, 2860, 1620, 1605, 1445, 1240, 825 cm^{-1}; ms (CI, isobutane) m/z 272 (M^+H); HR-ms (EI) m/z (M^+) 271.1763 (271.1756 calcd for $C_{17}H_{25}NSi$). This material could be stored at 0 °C in a sealed container under argon; it rapidly decomposed in the air.

3-Phenyl-3-[(E)-4-trimethylsilylbuten-4-yl]-1-azacyclopent-1-ene (21). According to the general procedure of Zwiefel,[12] pyridine (80 mg, 1.0 mmol) was added to a solution of **19b** (0.35 g, 1.0 mmol) and diethyl ether (2 ml). While irradiating with an ultraviolet sunlamp (275 W) at room temperature, the solution was dosed with *N*-bromosuccinimide (5 mol% portions) at 15 min intervals over a period of 1h. The mixture was then poured into a separatory funnel and washed with 10% HCl (5 ml), 20% aqueous cadmium chloride (5 ml), 1N NaOH (5 ml), and saturated aqueous sodium chloride (10 ml). The organic extract was dried ($MgSO_4$), and filtered and the solvent was removed *in vacuo* to give the E vinylsilane isomer (**22**). Reduction of this crude sample of **22** (0.35 g, 1.0 mmol) following the procedure described for the formation of **20a** gave, after purification of the crude product by flash column chromatography (silica gel, 4:1 hexane-ethyl acetate), 0.22 g (80%) of chromatographically pure **21** as a clear, colorless oil: ^1H Nmr 250 MHz, $CDCl_3$) δ 7.79 (br s, CH=N), 7.27-7.45 (m, PhH), 6.05 (dt, J = 18.4, 5.6 Hz, C*H*=CHSi$(CH_3)_3$), 5.69 (d, J = 18.6 Hz, CH=C*H*Si$(CH_3)_3$), 3.98-4.05 (m, CH_2N), 1.98-2.22 (m, 6H), 0.11 (s, Si$(CH_3)_3$); ^{13}C nmr (63 MHz, $CDCl_3$) 171.3, 146.1, 144.4, 130.5, 128.8, 126.6, 126.2, 60.9, 60.8, 37.8, 36.6, 32.2, -1.1 ppm; ir ($CHCl_3$) 2960, 2860, 1615, 1490, 1445, 1240, 850, 830 cm^{-1}; ms (CI, isobutane) m/z 272 (M^+H); HR-ms (EI) m/z (M^+) 271.1743 (271.1756 calcd for $C_{17}H_{25}NSi$).

General procedure for the preparation of nitriles 25 and 26. To a solution of LDA [prepared by addition of *n*-BuLi (20.1 ml of a 2.2 M solution in hexanes, 44.2 mmol) to diisopropylamine (6.2 ml, 44 mmol) in THF (40

ml) at -70 °C] was added a solution of nitrile **23** (44 mmol) in THF (20 ml) at -70 °C while not allowing the internal reaction temperature to exceed -60 °C. After 15 min a solution of the appropriate dihalide **24** (m=1 or 2) (44 mmol) in THF (10 ml) was added while again not allowing the internal reaction temperature to exceed -60 °C. After 1 h, the resulting solution was allowed to warm to temperature, stirred for 1 h and then quenched with water (100 ml). The organic portion was washed with 1M HCl (100 ml), saturated aqueous NH_4Cl (100 ml), and dried ($MgSO_4$) and the solvent was concentrated *in vacuo* after filtration. The residue was purified by fractional distillation or flash column chromatography to give nitriles **25** or **26** as described below.

1-(2-Chloroethyl)cyclopentanecarbonitrile (25a). Fractional distillation under vacuum of the crude product obtained from the reaction of cyclopentanecarbonitrile (**23a**) with **24** (m=1) gave a 31% yield of **25a** as a clear, colorless oil (bp 65-68 °C, 0.4 mm): ^{1}H Nmr (250 MHz, $CDCl_3$) δ 3.68 (dt, J = 7.8, 1.2 Hz, CH_2Cl), 2.05-2.3 (m, 4 H), 1.6-2.0 (m, 6 H); ^{13}C nmr (63 MHz, $CDCl_3$) 124.0, 47.7, 41.0, 40.6, 38.3, 37.7, 29.7, 24.0 ppm; ir (neat) 2975, 2880, 2220, 1444, 750 cm^{-1}; ms (CI, isobutane) m/z 158 (M^+H); HR-ms (EI) m/z (M^+) 157.0640 (157.0658 calcd for $C_8H_{12}NCl$).

1-(2-chloroethyl)cyclohexanecarbonitrile (25b). Fractional distillation under vacuum of the crude product obtained from the reaction of cyclohexanecarbonitrile (**23b**) with **24** (m=1) gave a 40% yield of **25b** as a clear, colorless oil (bp 70-71 °C, 0.4 mm): ^{1}H Nmr (250 MHz, $CDCl_3$) δ 3.68 (t, J = 7.9 Hz, CH_2Cl), 2.11 (t, J = 7.9 Hz, CH_2CH_2Cl), 1.4-2.3 (m, 10 H); ^{13}C nmr (63 MHz, $CDCl_3$) 122.5, 43.0, 39.4, 38.3, 35.6, 25.2, 22.9 ppm; ir (neat) 2915, 2830, 2215, 1502, 745 cm^{-1}; ms (CI, isobutane) m/z 172 (M^+H); HR-ms (EI) m/z (M^+) 171.0796 (171.0814 calcd for $C_9H_{14}ClN$).

1-(3-Chloropropyl)cyclopentanecarbonitrile (26a). Fractional distillation under vacuum of the crude product obtained from the reaction of cyclopentanecarbonitrile (**23a**) with **24** (m=2) gave a 67% yield of **26a** as a clear, colorless oil (bp 75-78 °C, 1 mm): ^{1}H Nmr (250 MHz, $CDCl_3$) δ 3.59 (t, J = 6.2 Hz, CH_2Cl), 1.55-2.25 (m, 12 H); ^{13}C nmr (63 MHz, $CDCl_3$) 122.4, 43.0, 39.5, 38.4, 35.6, 25.2, 22.9 ppm; ir (neat) 2965, 2880, 2238,

1455, 1300, 655 cm^{-1}; ms (CI, isobutane) m/z 172 (M^+H); HR-ms (EI) m/z (M^+) 171.0806 (171.0815 calcd for $C_9H_{14}NCl$).

1-(3-Chloropropyl)cyclohexanecarbonitrile (26b). Fractional distillation under vacuum of the crude product obtained from the reaction of cyclohexanecarbonitrile (**23b**) with **24** (m=2) gave a 68% yield of **26b** as a clear, colorless oil (bp 83-85 °C, 0.5 mm): ^1H Nmr (250 MHz, $CDCl_3$) δ 3.58 (t, J = 6.3 Hz, CH_2Cl), 1.9-2.1 (m, 4 H), 1.5-1.85 (m, 8 H), 1.1-1.3 (m, 2 H); ^{13}C nmr (63 MHz, $CDCl_3$) 123.3, 44.7, 38.6, 37.8, 35.7, 27.7, 25.4, 23.1 ppm; ir (neat) 2940, 2855, 2212, 1450, 1300, 650 cm^{-1}; ms (CI, isobutane) m/z 186 (M^+H); HR-ms (EI) m/z (M^+) 185.0956 (185.0971 calcd for $C_{10}H_{16}NCl$).

General procedure for the preparation of iodides 27. A mixture of chloride **26** (2.1 mmol), NaI (3.1 mmol) and 2-butanone (20 ml) was heated and refluxed for 12 h, cooled and extracted with 5% aqueous sodium thiosulfate (2 x 25 ml). The aqueous portion was extracted with CH_2Cl_2 (2 x 50 ml) and the organic portions were combined, and dried ($MgSO_4$) and the solvent was concentrated *in vacuo* after filtration. The iodides were used directly in crude form due to their instability to fractional distillation or flash column chromatography.

1-(3-Iodopropyl)cyclopentanecarbonitrile (27a). Reaction of **26a** with NaI afforded a 90% yield of crude **27a** as a clear yellow oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 3.22 (t, J = 6.6 Hz, CH_2I), 1.5-2.2 (m, 12 H); ^{13}C nmr (63 MHz, $CDCl_3$) 124.9, 42.5, 39.4, 38.4, 30.3, 24.2, 5.7 ppm; ir (neat) 2960, 2875, 2218, 1735, 1450, 1180 cm^{-1}; ms (CI, isobutane) m/z 264 (M^+H); HR-ms (EI) m/z (M^+) 263.0158 (263.0171 calcd for $C_9H_{14}NCl$).

1-(3-Chloropropyl)cyclohexanecarbonitrile (27b). Reaction of **26b** with NaI afforded a 94% yield of crude **27b** as a clear yellow oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 3.21 (t, J = 6.7 Hz, CH_2I), 1.1-2.1 (m, 14 H); ^{13}C nmr (63 MHz, $CDCl_3$) 123.2, 41.2, 38.4, 35.7, 28.4, 25.3, 23.0, 5.8 ppm; ir (neat) 2930, 2860, 2215, 1450, 900 cm^{-1}; ms (CI, isobutane) m/z 278 (M^+H); HR-ms (EI) m/z (M^+) 277.0321 (277.0328 calcd for $C_{10}H_{16}NI$).

General procedure for the preparation of cyclic imines 28 and 29. To a solution of the nitrile halides(**25** - **27**)(2.9 mmol) in toluene (10 ml) at -70 °C was added neat *i*-Bu_2AlH (2.9 mmol) dropwise. After 1 h, the solution was allowed to warm to room temperature, stirred for 12 h, and then recooled to 0 °C before adding (11.6 mmol) NaF.[10] After stirring vigorously for 1 h, H_2O (8.7 mmol) was added, and the mixture was stirred for 45 min. The mixture was warmed to room temperature and then stirred an additional 1h. The resultant mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography to afford **28** and **29** as described below. Because of rapid decomposition on contact with air these products were stored at 0 °C in sealed containers under argon immediately following removal of the chromatography eluent.

2-Azaspiro[4.4]non-1-ene (28a). Flash column chromatography (silica gel, 2:1 hexane-ethyl acetate) of the crude product obtained from the reaction of **25a** with *i*-Bu_2AlH gave an 85% yield of **28a** as an amorphous solid: ^1H Nmr (250 MHz, $CDCl_3$) δ 7.32 (t, J = 2.3 Hz, CH=N), 3.84 (dt, J = 7.0, 2.3 Hz, CH_2N), 1.1-1.85(m, 10 H); ^{13}C nmr (63 MHz, $CDCl_3$) 174.5, 60.6, 59.9, 37.2, 36.6, 25.4 ppm; ir ($CHCl_3$) 2930, 2558, 1625, 1450, 914, 730 cm^{-1}; ms (CI, isobutane) m/z 124 (M^+H); HR-ms (EI) m/z (M^+) 123.1025 (123.10479 calcd for $C_8H_{13}N$).

2-Azaspiro[4.5]dec-1-ene (28b). Flash column chromatography (silica gel, 2:1 hexane-ethyl acetate) of the crude product obtained from the reaction of **25b** with *i*-Bu_2AlH gave an 81% yield of **28b** as a light-green, crystalline solid (mp 103-105 °C): ^1H Nmr (250 MHz, $CDCl_3$) δ 7.31 (t, J = 2.2 Hz, CH=N), 3.85 (dt, J = 7.2, 2.2 Hz, CH_2N), 1.69 (t, J = 7.3 Hz, CH_2CH_2N), 1.2-1.8 (m, 10 H); ^{13}C nmr (63 MHz, $CDCl_3$) 174.4, 59.9, 54.0, 33.7, 25.7, 23.1 ppm; ir ($CHCl_3$) 2960, 2870, 1640, 1230 cm^{-1}; ms (CI, isobutane) m/z 138 (M^+H); HR-ms (EI) m/z (M^+) 137.1217 (137.1204 calcd for $C_9H_{15}N$).

7-Azaspiro[4.5]dec-6-ene (29a). Flash column chromatography (silica gel, 2:1 hexane-ethyl acetate) of the crude product obtained from the reaction of chloride(**26a**)(or iodide **27a**) with *i*-Bu_2AlH gave a 63% (or 84% yield) of **29a** as a light yellow oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 7.47 (br s, CH=N), 3.49 (m, CH_2N), 1.4-1.8

(m, 12 H); ^{13}C nmr (63 MHz, $CDCl_3$) 169.9, 49.3, 44.7, 37.6, 31.7, 24.4, 20.3 ppm; ir (neat) 2930, 2860, 1630, 1450, 1330, 920 cm^{-1}; ms (CI, isobutane) m/z 138 (M^+H); HR-ms (EI) m/z (M^+) 137.1220 (137.1204 calcd for $C_9H_{15}N$).

2-Azaspiro[5.5]undec-1-ene (29b). Flash column chromatography (silica gel, 2:1 hexane-ethyl acetate) of the crude product obtained from the reaction of chloride(**26b**)(or iodide **27b**) with *i*-Bu_2AlH gave a 54% (or 75% yield) respectively of **29b** as a light yellow oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 7.46 (br s, CH=N), 3.45-3.55 (m, CH_2N), 1.2-1.7 (m, 14 H); ^{13}C nmr (63 MHz, $CDCl_3$) 170.8, 50.1, 36.4, 34.2, 29.0, 25.8, 20.7, 19.1 ppm; ir (neat) 2920, 2860, 1630, 1445, 910 cm^{-1}; ms (CI, isobutane) m/z 152 (M^+H); HR-ms (EI), m/z (M^+) 151.1355 (151.1361 calcd for $C_{10}H_{17}N$).

cis-3a-Phenyl-2,3,3a,4,5,7a-hexahydro-1H-indole (30). Trifluoroacetic acid (0.14 ml, 1.8 mmol) was added to a solution of **20b** (490 mg, 1.8 mmol) and acetonitrile (10 ml) and the resulting solution was heated at reflux for 2 h. The reaction was then quenched with 1*N* NaOH and the aqueous portion was separated and extracted with diethyl ether (2 x 25 ml). The combined organic extracts were dried (Na_2SO_4), and filtered and the solvent was removed *in vacuo* . Purification of the residue by flash column chromatography (silica gel, 9:1:0.2 CH_2Cl_2-MeOH-57% aqueous NH_4OH) followed by bulb-to-bulb distillation (120-125 °C, 0.5 mm) gave 320 mg (90%) of chromatographically pure **30** as a clear colorless oil: ^1H Nmr (250 MHz, $CDCl_3$) δ 7.1-7.4 (m, PhH), 5.9 -6.15 (m, 2 H, CH=CH), 3.66 (br s, $W_{1/2}$ = 7 Hz, H_{7a}), 2.9-3.2 (m, 3 H), 2.19 (t, J = 7.2 Hz, CH_2CH=CH), 1.55-2.2 (m, 4 H); ^{13}C nmr (63 MHz, $CDCl_3$) 146.8, 131.7, 128.1, 126.7, 126.1, 60.1, 47.8, 44.3, 41.4, 32.8, 23.1 ppm; ir ($CHCl_3$) 3030, 1599, 1495, 1455, 840 cm^{-1}; ms (CI, isobutane) m/z 200 (M^+H), HR-ms (EI) m/z (M^+) 199.1352 (199.1361 calcd for $C_{14}H_{17}N$).

cis-3a-Phenyl-2,3,3a,4,5,6,7,7a-octahydro-1H-indole (31). A mixture of **30** (86 mg, 0.43 mmol), a catalytic amount of 10% palladium hydroxide on carbon and absolute ethanol (0.2 ml) was stirred under a hydrogen atmosphere for 4 h. The reaction mixture was filtered and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (silica gel, 9:1:0.2 CH_2Cl_2-MeOH-57% aqueous NH_4OH) gave 78

mg (90%) of chromatographically pure **31** as a clear colorless oil: ^{1}H Nmr (250 MHz, $CDCl_3$) δ 7.15-7.45 (m, PhH), 3.33 (br s, $W_{1/2}$ = 7 Hz, H_{7a}), 3.0-3.3 (m, 2 H), 1.4-2.2 (m, 11 H). Crystallization and recrystallization of the maleate salt from ethanol afforded white, fluffy crystals, mp 152 °C (lit.,[16] mp 152 °C).

***cis*-3a-(3,4-Methylenedioxyphenyl)-2,3,3a,4,5,7a-hexahydro-1H-indole (12).** Trifluoroacetic acid (0.29 ml, 3.8 mmol) was added to a solution of **20a** (1.2 g, 3.8 mmol) and acetonitrile (20 ml) and the resulting solution was heated at reflux for 2 h. After cooling to room temperature, 1*N* NaOH (10 ml) was added. The aqueous portion was separated and extracted with diethyl ether (2 x 25 ml). The combined organic extracts were dried (Na_2SO_4), and filtered and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (silica gel, 9:1:0.2 CH_2Cl_2-MeOH-57% aqueous NH_4OH) followed by bulb-to-bulb distillation (146-150 °C, 0.4 mm) gave 0.88 g (95%) of **12** as a white solid. Recrystallization from benzene-hexane afforded 0.83 g (90%) of a white crystals: mp 101-103 °C: ^{1}H Nmr (250 MHz, $CDCl_3$) δ 6.7-6.75 (m, 3 H, ArH), 5.92 (s, OCH_2O), 5.85-6.05 (m, 2 H, CH=CH), 3.50 (d, J = 4.1 Hz, H_{7a}), 3.17 (dt, J = 11.4, 7.4 Hz, 1H, of CH_2N), 2.94 (dt, J = 11.7, 7.4 Hz, 1H, of CH_2N), 2.11 (t, J = 7.4 Hz, CH_2CH=CH), 1.55-2.0 (m, 4 H); ^{13}C nmr (63 MHz, $CDCl_3$) 147.6, 145.8, 140.5, 132.3, 126.1, 119.6, 107.9, 107.6, 101.0, 60.3, 47.6, 44.1, 41.5, 32.7, 23.1 ppm; ir ($CHCl_3$) 2960, 2880, 1610, 1500, 1485, 1430, 1230, 1030, 925, 845, 795 cm^{-1}; ms (CI, isobutane) m/z 244 (M^+H); HR-ms (EI) m/z (M^+) 243.1268 (243.1259 calcd for $C_{15}H_{17}NO_2$).

***cis*-6-Hydroxy-3a-(3,4-methylenedioxyphenyl)-2,3,3a,4,5,6,7,7a-octahydro-1H-indole (32).** Following the general procedure of Brown,[24] a solution of **12** (0.41 g, 1.7 mmol) and THF (1.7 ml) was added to a mixture of mercuric acetate (1.1 g, 3.4 mmol), H_2O (3.4 ml), and THF (1.7 ml). The resulting mixture was stirred for 24 h at 25 °C before sodium tetrahydridoborate (3.4 ml of a 0.5M solution in 3N NaOH, 1.7 mmol) and 3N NaOH (3.4 ml) were added. After 30 min the mixture was quenched with solid potassium carbonate and extracted with diethyl ether (2 x 25 ml). The combined organic extracts were dried (Na_2SO_4), and filtered and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (silica gel, 9:1:0.2 CH_2Cl_2-MeOH-57% aqueous NH_4OH) gave 0.30 g (68%) of the alcohol (**32**) and 0.13 g (31%) of recovered **12**.

Crystallization and recrystallization of **32** from benzene-cyclohexane afforded 0.27 g (99% yield based on consumed **12**) of **32** as a white powder, mp 174-176 °C (lit.,[26] 176-178 °C).

(±)-Epielwesine (9). According to the general procedure of Whitlock,[31] 37% formalin (1.7 ml, 8.9 mmol) was added to a solution of **32** (140 mg, 0.54 mmol) in MeOH (0.5 ml). The solution was stirred for 15 min and then poured into 6 *M* HCl (25 ml). After stirring for 12 h the reaction solution was basified with concentrated NH_4OH and extracted with $CHCl_3$ (2 x 25 ml). The combined organic extracts were washed with H_2O (10 ml), dried (Na_2SO_4), and filtered and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (silica gel, 9:1:0.2 CH_2Cl_2-MeOH-57% aqueous NH_4OH) gave 100 mg (68%) of chromatographically pure **9**. Recrystallization of the product from benzene-cyclohexane afforded 85 mg (58%) of **9** as colorless needles, mp 182-184 °C (lit.,[26] mp 184-186 °C). This material was indistinguishable by ^1H nmr analysis at 250 MHz from an authentic sample provided by Professor I. Sanchez.

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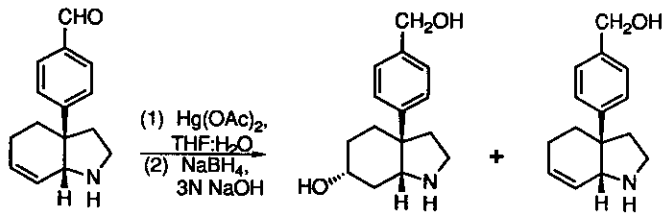

I II III

47% 18%

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