The total synthesis of (−)-suaveoline

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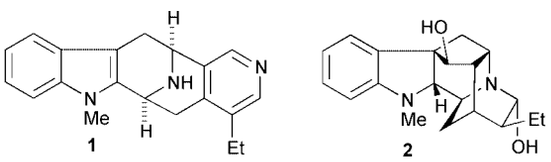
A new synthesis of the indole alkaloid (−)-suaveoline from L-tryptophan is reported (overall yield *ca.* 14%). Key synthetic steps include a high yielding *cis*-specific Pictet–Spengler reaction, a one-pot Horner–Wadsworth–Emmons and alkylation procedure, a vinylogous Thorpe cyclisation and the direct formation of a 3,4,5-trisubstituted pyridine from a 1,5-dinitrile. The direct conversion of ajmaline to semi-synthetic suaveoline is also described.

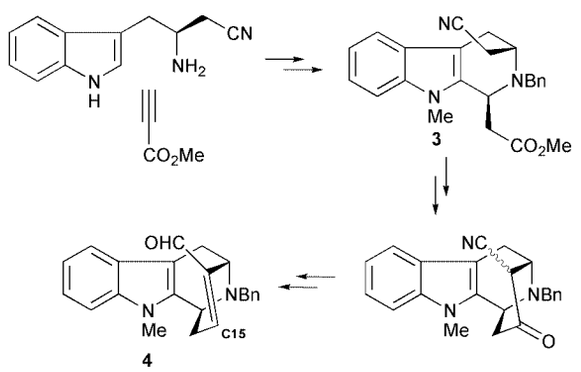
Introduction

Polycyclic indole alkaloids such as suaveoline **1**, ajmaline **2** and



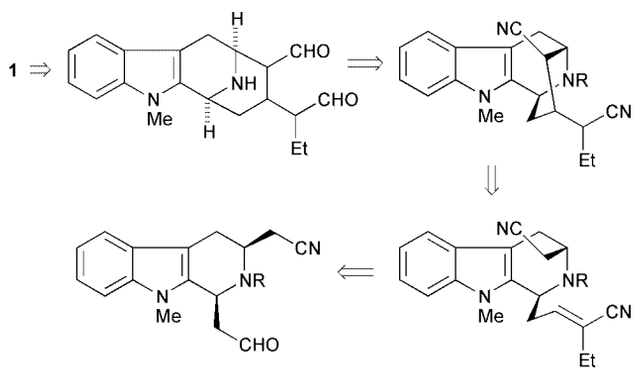
alkaloid G have elicited intense synthetic interest over many years,[1] because of their intriguing structures and interesting biological properties.

Our work in this area has been based on the kinetically controlled Pictet–Spengler reaction to access the *cis*-1,3-disubstituted tetrahydro-β-carboline skeleton **3** required for these bridged structures, and we have achieved formal syntheses of a range of alkaloids including ajmaline and suaveoline through convergence with the tetracyclic aldehyde **4** (Scheme 1).[2]



Scheme 1

We wished to complete our own total synthesis, but in the synthetic routes described in the preceding paper† we encountered great difficulty in introducing a four carbon fragment to C15 (ajmaline numbering) of bridged intermediates such as **4**, and a more efficient route was clearly needed. We chose to investigate the possibility of introducing a suitable four carbon fragment prior to the formation of a tetracyclic bridge, leading to the new route implied by the retro-synthetic analysis outlined in Scheme 2. Thus key objectives included a *cis*-selective Pictet–Spengler reaction,



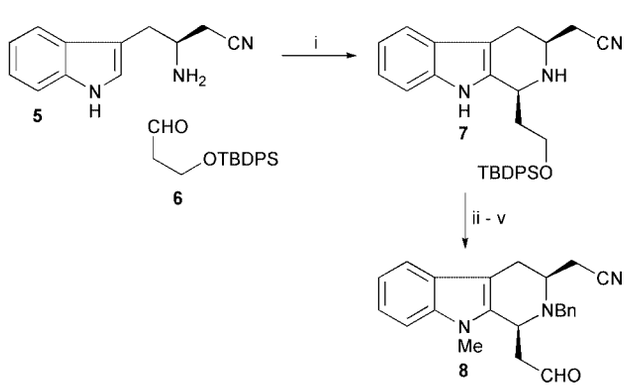
Scheme 2 Proposed retro-synthetic analysis of suaveoline **1**.

a vinylogous Thorpe cyclisation and the eventual formation of a 3,4,5-trisubstituted pyridine.

We describe herein an extremely efficient total synthesis of suaveoline based on this approach, along with an efficient method for obtaining semi-synthetic suaveoline (which is not readily available) from ajmaline.

Results and discussion

Reaction of the readily available homologous nitrile **5**, with the silyl protected aldehyde **6** (itself prepared by silyl protection and PCC oxidation of propane-1,3-diol), under our conditions of kinetic control,[3] afforded the *cis*-1,3-disubstituted tetrahydro-β-carboline **7** in 80% isolated yield, with none of the *trans* isomer apparently generated (Scheme 3). Similarly high



Scheme 3 *Reagents and conditions*: i, DCM, 3 Å molecular sieves, 0 °C, 60 h then TFA, −78 °C to room temp., 6 h (82%); ii, BnBr (neat), $NaHCO_3$, 70 °C, 24 h (79%); iii, MeI, NaH, DMF, 0 °C, 1 h (100%); iv, TBAF, THF, room temp., 2 h (83%); v, $(COCl)_2$, Me_2SO, DCM, −60 °C, 20 min then NEt_3, −60 °C to room temp., 1 h (100%).

† Preceding paper: P. D. Bailey, K. M. Morgan, David I. Smith and J. M. Vernon, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000 (DOI: 10.1039/b005694o).

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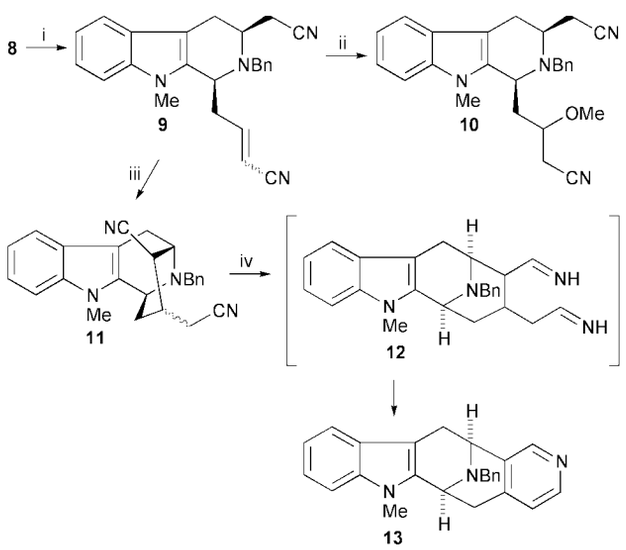
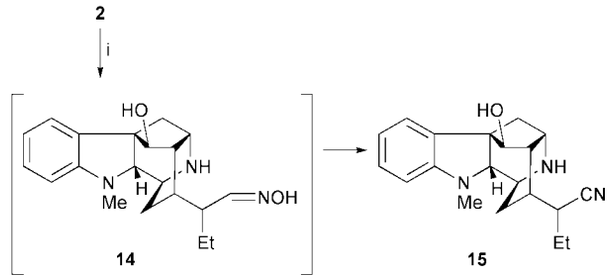
cis-selectivity (>10:1) has been observed in only two other cases,[4] also involving aldehydes of the type RCH_2CHO (where R is bulky and contains one or more remote aromatic rings, perhaps able to π-stack to the indole moiety at a crucial stage of the cyclisation mechanism). Serendipity played a part at this point in the synthesis when a small scale benzylation reaction in DCM boiled dry leaving the carboline **7** in neat benzyl bromide at 70 °C. The carboline **7** turned out to be much more stable than most previously obtained carbolines (which are susceptible to oxidative degradation) and under these conditions was benzylated in good yield. *N*-Methylation of the indole fragment, removal of the silyl protection and Swern oxidation to the aldehyde **8** all proceeded in high overall yield.

To test the viability of our new synthetic route we next attempted the model synthesis of a de-ethyl suaveoline derivative. The required Horner–Wadsworth–Emmons reaction with diethyl cyanomethylphosphonate gave the α,β-unsaturated nitrile **9** as a mixture of *cis* and *trans* isomers. An initial attempt to use potassium methoxide as a base to facilitate the key vinylogous Thorpe cyclisation failed, with the addition product **10** being the only material isolated. However, a subsequent attempt with potassium *tert*-butoxide led to the desired bridged 1,5-dinitrile **11** in good yield. This material effectively represented the first synthetically useful addition of functionality at C15 (ajmaline numbering) in our hands. Crucially, the planned reduction of the dinitrile **11** with DIBAL-H followed by treatment with hydroxylamine hydrochloride in refluxing ethanol actually led directly to the formation of a 3,4-disubstituted pyridine, the de-ethyl suaveoline derivative **13**, presumably *via* oxidative cyclisation of a species such as the diimine **12** (Scheme 4).



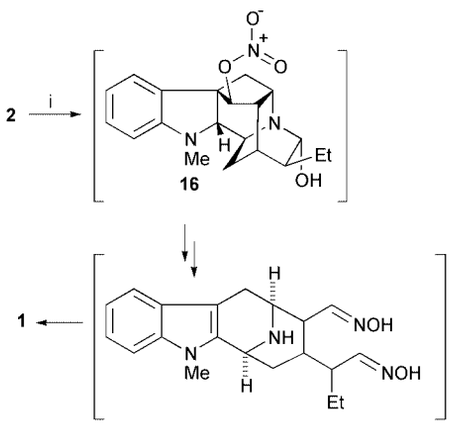
Scheme 4 *Reagents and conditions*: i, $P(O)(OEt)_2CH_2CN$, NaH, DMF, 0 °C, 10 min (97%); ii, KOMe, MeOH, room temp., 24 h (40%); iii, KO-*t*-Bu, THF, 0 °C to room temp., 30 min (43%); iv, DIBAL-H, DCM, −78 °C to room temp., 10 h then $NH_2OH{\cdot}HCl$, EtOH, reflux, 24 h (12%).

Although we were encouraged by this seemingly straightforward route to suaveoline derivatives, the isolated yield of pure pyridine derivative **13** was low, so before embarking on a synthesis of suaveoline itself we wanted to prepare a semi-synthetic sample of suaveoline from ajmaline. As part of our ongoing efforts towards the total synthesis of ajmaline **2** we were also anxious to obtain the cyano-alcohol **15**, because it can be converted into ajmaline,[5] and is very similar to a synthetic intermediate that we had previously made *en route* to (−)-suaveoline. To our surprise, treatment of ajmaline **2** with hydroxylamine hydrochloride in refluxing ethanol yielded the cyano-alcohol **15** directly in 89% yield, presumably *via* the oxime **14** (Scheme 5).



Scheme 5 *Reagents and conditions*: i, $NH_2OH{\cdot}HCl$, EtOH, reflux, 24 h (89%).

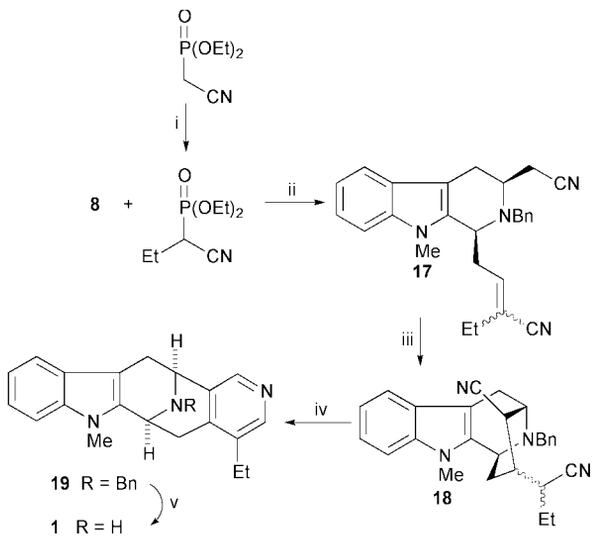
We were further surprised to discover that this reaction was acutely solvent (and temperature) dependent, thus, whilst no reaction was observed in refluxing toluene, replacing ethanol with *n*-butanol led to the direct conversion of ajmaline **2** into suaveoline **1** in 30% overall yield (Scheme 6). This semi-



Scheme 6 *Reagents and conditions*: i, $NH_2OH{\cdot}HCl$, *n*-BuOH, reflux, 24 h (30%).

synthetic suaveoline was identical to our synthetic material. The full mechanism to account for this transformation is discussed in detail elsewhere,[6] but we believe that atmospheric oxygen may be involved in the formation of the nitrate **16**, which then undergoes two ring opening steps to a dialdehyde derivative and ultimately undergoes condensation with hydroxylamine to form the pyridine ring of suaveoline.

The total synthesis of suaveoline itself was next attempted, again from the aldehyde **8**. Rather than attempting an alkylation of the 1,5-dinitrile **11**, the introduction of the four remaining carbons of the suaveoline skeleton was attempted *via* a one-pot Horner–Wadsworth–Emmons and alkylation procedure that could generate the required reagent *in situ*. This procedure proved successful, with the α,β-unsaturated nitrile **17** being isolated in 83% overall yield (Scheme 7). The required bridged skeleton **18** was then constructed by another vinylogous Thorpe cyclisation, again using potassium *tert*-butoxide (67% yield), giving **18** as a mixture of diastereoisomers. Reduction of the dinitrile **18** with DIBAL-H followed by treatment with hydroxylamine hydrochloride produced the required 3,4,5-trisubstituted pyridine directly and so led to the formation of *N*-benzyl-(−)-suaveoline **19** in 53% yield. When attempting to reduce only one of the nitrile groups, we also discovered that pyridine formation was not dependent upon treatment with hydroxylamine hydrochloride, and that an acid work-up from the DIBAL-H reduction was sufficient to generate the pyridine ring directly. Indeed it proved impossible to isolate anything other than *N*-benzylsuaveoline **19** or starting material **18**. Debenzylation of **19** under standard conditions (H_2, Pd–C, MeOH) failed, as expected from our earlier work involving similar bridged skeletons and related results from Cook.[1b] However, debenzylation of **19**·HCl (H_2, Pd–C, EtOH) yielded (−)-suaveoline **1** cleanly. This material was identical in all



Scheme 7 *Reagents and conditions*: i, NaH, DMF, 0 °C then EtBr; ii, NaH, DMF, 0 °C, 1 h (83%); iii, KO*t*-Bu, THF, 0 °C to room temp., 10 min (67%); iv, DIBAL-H, DCM, −78 °C to room temp., 24 h then $NH_2OH{\cdot}HCl$, EtOH, reflux, 24 h (53%); v, HCl, EtOH then evaporate, Pd–C, H_2, EtOH (66%).

respects both to the natural product,[1a] and to the semi-synthetic suaveoline **1** we had earlier synthesized from ajmaline.

Conclusion

We have developed a new route to complex cage-like indole alkaloids which utilises a *cis*-selective Pictet–Spengler reaction and avoids the difficult addition to C15 (ajmaline numbering) of advanced tetracyclic intermediates by virtue of an early construction of the required carbon skeleton prior to a vinylogous Thorpe cyclisation. We utilised this new methodology in a total asymmetric synthesis of (−)-suaveoline **1**, starting from L-tryptophan in *ca.* 14% overall yield. We have also developed an easy method for the direct conversion of ajmaline to the pentacyclic intermediate **15** and semi-synthetic (−)-suaveoline **1**.

Experimental

NMR spectra were recorded on a Bruker AC200 at 200 MHz (^{1}H) and 50 MHz (^{13}C) or a Bruker DPX400 at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts were measured in ppm on the δ scale downfield from tetramethylsilane as internal standard. The solvent employed was $CDCl_3$, unless otherwise stated. When pairs of diastereoisomers were not separated the diastereomeric NMR resonances are bracketed thus {}. All ^{13}C data are quoted with ^{1}H multiplicities (off resonance results) in parentheses thus (), although this multiplicity was inferred from DEPT experiments. Infrared spectra were recorded on a Perkin-Elmer 1420 ratio recording spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter at room temp. Mass spectra were obtained by electron impact on an a VG AUTOSPEC spectrometer. Analytical TLC was carried out on Merck aluminium sheet silica gel 60 F_{254} plates (thickness 0.2 mm). Spots were visualised with a UV hand lamp. Flash chromatography was performed using silica gel 60 (230–400 mesh) as the stationary phase. THF was dried by distillation from sodium or obtained anhydrous from Aldrich. DMF was obtained anhydrous from Aldrich and was stored under dry argon. Chlorinated solvents were distilled from phosphorus pentaoxide. Toluene and ethoxyethane were distilled and stored over sodium. DIBAL-H 1 M solution in DCM was obtained from Aldrich and stored under dry argon. Reactions were routinely run under an argon atmosphere unless otherwise stated.

Preparation of 3-(*tert*-butyldiphenylsilyloxy)propan-1-al 6

The aldehyde was prepared in two steps from propane-1,3-diol.

(a) Propane-1,3-diol (50 ml, 47.5 g, 625 mmol) and imidazole (3.4 g, 50 mmol) were stirred in DCM (200 ml) at room temp. TBDPS-Cl (10 g, 36 mmol) in DCM (30 ml) was added dropwise over 9 h then the reaction stirred overnight. The solution was then washed twice with aqueous citric acid, twice with brine, dried over $MgSO_4$ and evaporated to 13.6 g of colourless oil. This material was subjected to flash chromatography on silica eluted with a solvent gradient of DCM to 1:9 Et_2O–DCM to yield 5.2 g (46%) of 3-(*tert*-butyldiphenylsilyloxy)propan-1-ol as a colourless oil: R_f 0.25 (DCM); ^{1}H NMR δ 1.05 (9H, s, $C(CH_3)_3$), 1.82 (2H, quintet, J 5.7 Hz, $HOCH_2CH_2$), 2.56 (1H, t, J 5.5 Hz, O*H*), 3.80–3.91 (4H, m, $HOCH_2CH_2CH_2$), 7.35–7.72 (10H, m, Ar*H*); ^{13}C NMR δ 19.0 (s), 26.7 (q), 34.2 (t), 61.9 (t), 63.2 (t), 127.7 (d), 129.7 (d), 133.1 (s), 135.5 (d).

(b) The 1-(*tert*-butyldiphenylsilyloxy)propan-1-ol (3.77 g, 12 mmol) was added to 1:1 PCC–Florisil (8.6 g, 20 mmol of PCC) in DCM (25 ml) and stirred at room temp. overnight, then filtered through Florisil, dried over $MgSO_4$, and evaporated to yield the aldehyde **6** (2.4 g, 77%): R_f 0.75 (DCM); ^{1}H NMR δ 1.04 (9H, s, $C(CH_3)_3$), 2.60 (2H, br td, J 5.9, 1.8 Hz, CH_2CHO), 4.02 (2H, t, J 5.9 Hz, CH_2OSi), 7.35–7.71 (10H, m, Ar*H*), 9.81 (1H, br s, C*H*O); IR ν_{max}/cm^{-1} (thin film) 1728.

Preparation of (1*S*,3*S*)-3-cyanomethyl-1-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole 7

The amino nitrile (733 mg, 3.68 mmol) was dissolved in dry DCM (50 ml) and stirred over 3 Å molecular sieves. The aldehyde **6** (1.56 g, 5 mmol) was then added and the reaction stirred at 0 °C for 60 h. After cooling to −78 °C, TFA (855 mg, 578 µl, 7.5 mmol) was added and the reaction stirred at −78 °C for 3 h before being allowed to warm slowly to 0 °C and stirred for a further 1 h, then finally warmed to room temp. and stirred for 2 h. The solvent was then decanted from the sieves which were then washed 5 times with chloroform and aqueous $NaHCO_3$. The combined organic phase was washed with brine, dried over $MgSO_4$ and evaporated to give a yellow oil (2.7 g). This material was subjected to flash chromatography on silica eluted with 1:9 Et_2O–DCM to yield the tetrahydro-β-carboline **7** (1.49 g, 82%). A second reaction run at double this scale afforded the carboline **7** in 75% yield.

R_f 0.46 (1:9 Et_2O–DCM); ^{1}H NMR δ 1.17 (9H, s, $C(CH_3)_3$), 1.76 (1H, br s, N*H*), 1.88 (1H, dq, J 14.5, 3.8 Hz, one of CH_2CH_2OSi), 2.21 (1H, dq, J 14.5, 7.1 Hz, one of CH_2CH_2OSi), 2.59 (1H, ddd, J 15.0, 10.6, 2.5 Hz, one of $ArCH_2CH$), 2.64 (2H, br d, J 6.4 Hz, CH_2CN), 2.97 (1H, ddd, J 15.0, 4.0, 1.8 Hz, one of $ArCH_2CH$), 3.33 (1H, ddt, J 10.6, 6.4, 4.2 Hz, $ArCH_2CH$), 3.98 (2H, dd, J 7.1, 3.7 Hz, CH_2CH_2OSi), 4.28–4.38 (1H, m, $ArCHCH_2$), 7.08–7.75 (14H, m, Ar*H*), 8.96 (1H, br s, indole N*H*); ^{13}C NMR δ 19.2 (s), 24.9 (t), 27.0 (q), 28.3 (t), 37.6 (t), 51.1 (d), 53.6 (d), 62.8 (t), 107.2 (s), 111.0 (d), 117.9 (d), 119.3 (d), 121.5 (d), 126.9 (s), 127.9 (d), 130.0 (d), 132.6 (s), 132.7 (s), 135.5 (d), 135.7 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 3698, 3607, 3476, 3367, 2251 (w), 1605, 1477, 1435; MS *m*/*z* 493 (M^+, 3%), 393 (23), 210 (9), 199 (44), 195 (10), 77 (7), 28 (100); found *m*/*z* 493.2543, calc. for $C_{31}H_{35}N_3OSi$ 493.2549.

Preparation of (1*S*,3*S*)-2-benzyl-3-cyanomethyl-1-[2-(*tert*-butyldiphenylsilyloxyethyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole

The carboline **7** (2.6 g, 5.27 mmol) was dissolved in DCM (10 ml) and stirred over excess $NaHCO_3$ (4.2 g) and benzyl bromide added (4.3 g, 3 ml, 25 mmol). The reaction was heated to 70 °C under a stream of argon and the DCM allowed to evaporate, then the reaction was kept at 70 °C overnight. After cooling to room temp., water and chloroform were added, and the organic layer then washed with brine, dried over $MgSO_4$ and evaporated

to an oil, then subjected to flash chromatography on silica eluted with a solvent gradient of DCM to 1:19 Et_2O–DCM to yield the *N*-benzylcarboline (2.38 g, 77%).

R_f 0.81 (1:9 Et_2O–DCM); ^1H NMR δ 1.14 (9H, s, $C(CH_3)_3$), 1.78–2.24 (2H, m, CH_2CH_2OSi), 2.44 (1H, dd, *J* 16.7, 7.3 Hz, one of CH_2CN), 2.60 (1H, dd, *J* 16.7, 8.4 Hz, one of CH_2CN), 2.74 (1H, br d, *J* 16.0 Hz, one of $ArCH_2CH$), 3.18 (1H, br dd, *J* 16.0, 5.7 Hz, one of $ArCH_2CH$), 3.65–3.77 (1H, m, $ArCH_2CH$), 3.84–3.97 (4H, m, CH_2CH_2OSi and NCH_2Ph), 4.12–4.18 (1H, m, $ArCHCH_2$), 7.01–7.70 (19H, m, Ar*H*), 8.94 (1H, br s, indole N*H*); ^{13}C NMR δ 19.2 (s), 22.0 (t), 23.3 (t), 27.1 (q), 39.1 (t), 54.1 (d), 54.7 (d), 58.8 (t), 63.6 (t), 103.7 (s), 110.7 (d), 117.9 (d), 119.0 (s), 119.2 (d), 121.6 (d), 126.8 (d), 126.9 (d), 127.2 (d), 127.3 (d), 127.7 (d), 127.9 (d), 128.5 (d), 129.9 (d), 130.0 (d), 132.6 (s), 133.0 (s), 133.8 (s), 135.4 (2 × d), 135.9 (s), 139.3 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 3440, 2251, 1589, 1466, 1431; MS *m*/*z* 583 (M^+, 2%), 492 (3), 300 (47), 199 (100), 91 (21), 28 (39); found *m*/*z* 583.3020, calc. for $C_{38}H_{41}N_3OSi$ 583.3019; $[\alpha]_D^{20}$ −11 (*c* 1, $CHCl_3$).

Preparation of (1*S*,3*S*)-2-benzyl-3-cyanomethyl-1-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-2,3,4,9-tetrahydro-9-methyl-1*H*-pyrido-[3,4-*b*]indole

The *N*-benzylcarboline (2.38 g, 4.08 mmol) and MeI (607 mg, 266 ml, 4.28 mmol) were stirred together in dry DMF (25 ml) at 0 °C. NaH (180 mg of 60% dispersion in mineral oil, 4.28 mmol) was then added and the reaction stirred for 30 min at 0 °C, then 1 h at room temp. The DMF was then removed by evaporation and the residue partitioned between EtOAc and brine. The organic layer then twice washed with brine, dried over $MgSO_4$ and evaporated to yield the fully protected carboline as a white foam (2.44 g, 100%).

R_f 0.83 (1:9 Et_2O–DCM); ^1H NMR δ 1.05 (9H, s, $C(CH_3)_3$), 1.68–2.11 (2H, m, CH_2CH_2OSi), 2.43 (2H, dd, *J* 8.0, 4.4 Hz, CH_2CN), 2.59 (1H, br d, *J* 16.2 Hz, one of $ArCH_2CH$), 3.12 (1H, br dd, *J* 16.2, 6.2 Hz, one of $ArCH_2CH$), 3.43–3.50 (1H, m, $ArCH_2CH$), 3.60 (3H, s, indole NCH_3), 3.72–3.88 (2H, AB system, *J* 13.4 Hz, NCH_2Ph), 3.88–4.00 (1H, m, one of CH_2CH_2OSi), 4.10 (1H, dd, *J* 9.2, 4.6 Hz, one of CH_2CH_2OSi), 4.16–4.25 (1H, m, $ArCHCH_2$), 7.06–7.69 (19H, m, Ar*H*); ^{13}C NMR δ 19.1 (s), 20.5 (t), 24.6 (t), 27.0 (q), 30.4 (q), 38.7 (t), 51.4 (d), 52.5 (d), 61.2 (t), 61.6 (t), 103.5 (s), 108.9 (d), 118.0 (d), 118.7 (s), 119.3 (d), 121.6 (d), 126.8 (s), 127.5 (d), 127.8 (d), 128.5 (d), 128.8 (d), 129.7 (d), 129.8 (d), 133.5 (s), 133.7 (s), 134.8 (s), 135.6 (d), 137.8 (s), 139.0 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 2252, 1593, 1476, 1467, 1400; MS *m*/*z* (15 eV) 597 (M^+, 13%), 582 (4), 557 (4), 541 (6), 506 (8), 409 (15), 407 (32), 315 (100), 213 (100), 199 (100), 91 (100); $[\alpha]_D^{20}$ −26 (*c* 1, $CHCl_3$).

Preparation of (1*S*,3*S*)-2-benzyl-3-cyanomethyl-1-(2-hydroxyethyl)-2,3,4,9-tetrahydro-9-methyl-1*H*-pyrido[3,4-*b*]indole

The fully protected carboline (2.5 g, 4.08 mmol) was dissolved in THF (12 ml) and stirred at room temp. TBAF (8.2 ml of 1 M solution in THF, 8.2 mmol) was added dropwise and the reaction stirred for 2 h. The THF was then removed by evaporation and the residue partitioned between chloroform and brine. The organic layer was twice washed with brine, dried over $MgSO_4$ and evaporated to a red oil, then subjected to flash chromatography on silica eluted with a solvent gradient of DCM to 1:9 Et_2O–DCM to yield the deprotected alcohol as a white foam (1.22 g, 83%).

R_f 0.2 (1:9 Et_2O–DCM); ^1H NMR δ 1.67–1.98 (2H, m, CH_2CH_2OH), 2.62 (1H, br s, O*H*), 2.63 (1H, dd, *J* 16.5, 8.8 Hz, one of $ArCH_2CH$), 2.74–2.93 (2H, m, CH_2CN), 3.21 (1H, dd, *J* 16.5, 6.4 Hz, one of $ArCH_2CH$), 3.61 (3H, s, indole NCH_3), 3.58–3.85 (3H, m, $ArCH_2CH$ and CH_2CH_2OH), 3.69–3.90 (2H, AB system, *J* 12.9 Hz, NCH_2Ph), 4.02–4.13 (1H, m, $ArCH-CH_2$), 7.09–7.60 (9H, m, Ar*H*); ^{13}C NMR δ 20.8 (t), 24.8 (t), 30.4 (q), 36.9 (t), 52.6 (d), 53.8 (d), 60.7 (t), 61.3 (t), 103.3 (s), 109.0 (d), 118.1 (d), 118.7 (s), 119.4 (d), 121.8 (d), 126.7 (s), 127.5 (d), 128.5 (2 × d), 129.4 (2 × d), 133.5 (s), 137.8 (s), 138.4 (s); IR ν_{max}/cm^{-1} ($CHCl_3$) 3420, 2247, 1400; MS *m*/*z* 359 (M^+, 6%), 341 (3), 314 (61), 273 (4), 183 (11), 170 (8), 91 (65), 36 (100); found *m*/*z* 359.1967, calc. for $C_{23}H_{25}N_3O$ 359.1998.

Preparation of (1*S*,3*S*)-2-benzyl-3-cyanomethyl-1-formylmethyl-2,3,4,9-tetrahydro-9-methyl-1*H*-pyrido[3,4-*b*]indole 8

Oxalyl chloride (125 mg, 86 ml, 1 mmol) was stirred in dry DCM (3 ml) at −60 °C (using a chloroform–dry ice bath). DMSO (156 mg, 140 ml, 2 mmol) in dry DCM (1 ml) was added slowly and the mixture stirred at −60 °C for 2 min. The alcohol (270 mg, 0.75 mmol) in dry DCM (2 ml) was then added dropwise and the reaction stirred at −60 °C for 20 min. Triethylamine (477 mg, 659 ml, 4.7 mmol) was added and the reaction allowed to warm to room temp., then water (20 ml) was added and then the aqueous layer washed with DCM. The combined organic layers were washed with brine, 1% HCl (aq), saturated $NaHCO_3$ (aq) and brine, then dried over $MgSO_4$ and evaporated to afford the aldehyde **8** in quantitative yield (269 mg) as a pale yellow foam. This material was only partially characterised before being used directly in Horner–Wadsworth–Emmons reactions.

R_f 0.50 (1:9 Et_2O–DCM); ^1H NMR δ 2.55 (1H, dd, *J* 16.7, 8.3 Hz, one of CH_2CHO), 2.66–2.82 (3H, m, one of $ArCH_2CH$ and $CHCH_2CN$), 2.93 (1H, ddd, *J* 16.7, 9.8, 3.0 Hz, one of CH_2CHO), 3.19 (1H, ddd, *J* 16.2, 6.3, 1.5 Hz, one of $ArCH_2-CH$), 3.57–3.65 (4H, m, indole NCH_3 and $ArCH_2CH$), 3.89 (2H, s, NCH_2Ph), 4.62 (1H, ddd, *J* 9.8, 4.6, 1.5 Hz, $ArCHCH_2$), 7.11–7.55 (9H, m, Ar*H*), 9.72 (1H, dd, *J* 2.8, 1.0 Hz, C*H*O).

Model reactions leading to the formation of de-ethyl suaveoline derivative 13

(a) Horner–Wadsworth–Emmons reaction. Diethyl cyanomethylphosphonate (177 mg, 162 μl, 1 mmol) was added to NaH (30 mg of 80% dispersion in mineral oil, 1 mmol) in DMF (2 ml) at 0 °C and stirred for 10 min. This mixture was then added to a solution of the aldehyde **8** (200 mg, 0.55 mmol) in DMF (4 ml), stirred at −20 °C. The reaction was stirred for 1 h, then the DMF removed by evaporation and the residue treated with PhMe and evaporated again to remove the last traces of DMF. The residue was then partitioned between chloroform and brine, the organic layer twice washed with brine, dried over $MgSO_4$ and evaporated. The residue was then subjected to flash chromatography on silica eluted chloroform to yield the *trans* alkene (108 mg), *cis* alkene (70 mg) and some mixed *cis*–*trans* compounds (25 mg, total yield 203 mg, 97%).

^1H NMR (*cis*) δ 2.46–2.92 (5H, m, one of $ArCH_2CH$, $ArCHCH_2$, and CH_2CN), 3.14 (1H, ddd, *J* 16.1, 6.2, 1.5 Hz, one of $ArCH_2CH$), 3.53–3.63 (1H, m, $ArCH_2CH$), 3.66 (3H, s, indole NCH_3), 3.63–3.89 (2H, AB system, *J* 13.4 Hz, NCH_2Ph), 3.96 (1H, dd, *J* 11.0, 2.5 Hz, $ArCHCH_2$), 5.17 (1H, d, *J* 10.9 Hz, CHCHCN), 6.78 (1H, ddd, *J* 10.9, 8.5, 6.3 Hz, CHCHCN), 7.04–7.47 (9H, m, Ar*H*).

^1H NMR (*trans*) δ 2.48 (2H, td, *J* 7.2, 1.4 Hz, $ArCHCH_2$), 2.63–2.75 (3H, m, one of $ArCH_2CH$ and CH_2CN), 3.14 (1H, ddd, *J* 16.1, 6.1, 1.5 Hz, one of $ArCH_2CH$), 3.44–3.65 (1H, m, $ArCH_2CH$), 3.54 (3H, s, indole NCH_3), 3.60–3.87 (2H, AB system, *J* 13.4 Hz, NCH_2Ph), 3.87–3.91 (1H, m, $ArCHCH_2$), 5.29 (1H, dt, *J* 16.4, 1.4 Hz, CHCHCN), 6.51 (1H, dt, *J* 16.4, 7.2 Hz, CHCHCN), 7.05–7.48 (9H, m, Ar*H*).

(b) Small-scale cyclisation attempt with potassium methoxide. The alkene (10 mg of mixed *cis*–*trans*, 0.03 mmol) was dissolved in dry MeOH and successive equivalents of KO*t*-Bu were added until a reaction was observed by TLC, then the reaction was stirred overnight. Water and $CHCl_3$ were added and the organic phase washed with brine, dried over $MgSO_4$ and evaporated.

The residue was then subjected to flash chromatography on silica, eluted with chloroform to yield a small sample (4 mg) of the addition product **10**.

^{1}H NMR (400 MHz) δ 1.74 (1H, ddd, *J* 14.7, 11.5, 1.5 Hz, one ArCHCH_2), 2.02 (1H, ddd, *J* 14.7, 10.5, 2.2 Hz, one ArCHCH_2), 2.43–2.79 (5H, m, one of ArCH_2CH, CH_2CN and CH(OCH$_3$)CH_2CN), 2.99 (3H, s, OCH_3), 3.12 (1H, ddd, *J* 16.2, 6.5, 1.7 Hz, one of ArCH_2CH), 3.44–3.68 (1H, m, C*H*(OCH$_3$)-CH$_2$CN), 3.61 (3H, s, indole NCH_3), 3.70–3.84 (2H, AB system, *J* 13.5 Hz, NCH_2Ph), 3.89–3.95 (1H, m, ArCH$_2$C*H*), 4.12 (1H, d, *J* 11.5 Hz, ArC*H*CH$_2$), 7.14–7.53 (9H, m, Ar*H*); MS *m*/*z* 412 (M$^+$, 29%), 380 (8), 314 (100), 273 (21), 183 (37), 170 (26), 91 (100); found *m*/*z* 412.2257, calc. for $C_{26}H_{28}N_4O$ 412.2263.

(c) Successful cyclisation to tetracycle 11. The alkene **9** (100 mg of *trans* isomer, 0.26 mmol) was dissolved in dry THF (10 ml) and stirred at 0 °C. KO*t*-Bu (30 mg, 0.27 mmol) was added and the reaction allowed to warm to room temp. and stirred 30 min. Saturated citric acid (aq) was added, then the THF was removed by evaporation, the aqueous mixture extracted with $CHCl_3$ and then the organic layer dried over $MgSO_4$ and evaporated. The residue was subjected to flash chromatography on silica, eluted with a solvent gradient of DCM to 1:9 Et_2O–DCM to yield the tetracycle dinitrile **11** as a white foam (43 mg, 43%). The ^{1}H NMR of this material showed a complex mixture of stereoisomers which were not fully resolved, however, mass spectral data at least confirmed the molecular formula prior to the attempted final pyridine formation.

MS *m*/*z* 380 (M$^+$, 69%), 340 (11), 289 (13), 273 (88), 222 (33), 182 (49), 91 (72), 28 (100); found *m*/*z* 380.2005, calc. for $C_{25}H_{24}N_4$ 380.2001.

(d) Formation of de-ethyl suaveoline derivative 13. The dinitrile **11** (43 mg, 0.11 mmol) was dissolved in dry DCM (5 ml) and then cooled to −78 °C. DIBAL-H (440 µl of 1 M solution in DCM, 0.44 mmol) was then added slowly and the reaction stirred at −78 °C for 30 min, then allowed to warm to room temp. and stirred for 10 h. The reaction was then cooled again to −78 °C and quenched with excess saturated NH_4Cl (aq) and 0.1 M H_2SO_4 and stirred at room temp. for 1 h. The aqueous mixture extracted with $CHCl_3$ and then the organic layer dried over $MgSO_4$ and evaporated. The residue was immediately dissolved in EtOH with excess NH_2OH·HCl (40 mg), and the mixture refluxed overnight. The EtOH was then removed by evaporation and the residue partitioned between EtOAc and saturated $NaHCO_3$ (aq) and the organic layer washed with brine, dried over $MgSO_4$ and evaporated. Flash chromatography on silica, eluted with a solvent gradient of DCM to 1:19 Et_2O–DCM afforded the de-ethyl suaveoline derivative **13** (5 mg, 12%) along with a larger quantity of a complex mixture containing more **13** by TLC (34 mg).

^{1}H NMR (400 MHz) δ 2.74 (1H, br d, *J* 15.7 Hz, one of ArCHCH_2), 2.77 (1H, d, *J* 16.5 Hz, one of ArCH_2CH), 3.41–3.59 (2H, m, one of ArCH_2CH and one of ArCHCH_2), 3.62 (3H, s, indole NCH_3), 3.76–3.44 (2H, AB system, *J* 13.5 Hz, NCH_2Ph), 4.24 (1H, d, *J* 5.2 Hz, ArCH$_2$C*H*), 4.40 (1H, d, *J* 5.4 Hz, ArC*H*CH$_2$), 6.91 (1H, d, *J* 5.1 Hz, pyr-H), 7.04–7.45 (9H, m, Ar*H*), 8.24 (1H, d, *J* 5.1 Hz, pyr-H), 8.43 (1H, s, pyr-H); MS *m*/*z* (15 eV) 365 (M$^+$, 18%), 273 (42), 258 (18), 233, (12), 91 (74), 66 (92), 36 (100); found *m*/*z* 365.1915, calc. for $C_{25}H_{23}N_3$ 365.1892.

Conversion of ajmaline to the cyano alcohol 15

Ajmaline (32.6 mg, 0.1 mmol) was dissolved in EtOH (2 ml) and stirred with excess NH_2OH·HCl (35 mg) and stirred at room temp. overnight then refluxed for 24 h. Saturated $NaHCO_3$ (aq) and $CHCl_3$ were added, then the organic layer washed with brine, dried over $MgSO_4$ and evaporated. Flash chromatography on silica eluted with a solvent gradient of $CHCl_3$ to 1:19 MeOH–$CHCl_3$ afforded the cyano alcohol as a white foam (29 mg, 89%). The aliphatic region of the ^{1}H NMR of this material contained many overlapping multiplets and could not be fully assigned. The structure was confirmed by X-ray crystallography, as previously reported.[6]

^{1}H NMR δ 1.15 (3H, t, *J* 7.3 Hz, CH$_2$CH_3), 1.48–1.70 (3H, m), 1.81–2.29 (4H, m), 2.33 (1H, s), 2.65 (1H, br d, *J* 7.5 Hz), 2.70 (3H, s, indole NCH_3), 3.12 (1H, td, *J* 9.5, 3.9 Hz), 3.35–3.53 (4H, m), 4.04 (1H, br d, *J* 1.1 Hz), 6.70 (1H, br d, *J* 7.8 Hz, Ar*H*), 6.82 (1H, td, *J* 7.4, 1.0 Hz, Ar*H*), 7.16 (1H, td, *J* 7.8, 1.4 Hz, Ar*H*), 7.50 (1H, br dd, *J* 7.4, 1.4 Hz, Ar*H*); ^{13}C NMR δ 11.3 (q), 23.2 (t), 29.8 (t), 34.6 (d), 34.9 (q), 39.1 (d), 39.8 (t), 45.0 (d), 48.2 (d), 50.9 (d), 54.3 (s), 76.9 (d), 81.3 (d), 109.7 (d), 119.8 (d), 122.1 (s), 123.3 (d), 127.3 (d), 133.1 (s), 154.1 (s); MS *m*/*z* 323 (M$^+$, 9%), 179 (14), 157 (5), 28 (100); found *m*/*z* 323.2003, calc. for $C_{20}H_{25}N_3O$ 323.1998.

Conversion of ajmaline to suaveoline 1

Ajmaline (163 mg, 0.5 mmol) was suspended in PhMe (10 ml) and stirred with excess NH_2OH·HCl (350 mg) and refluxed for 24 h. When no reaction was observed by TLC the PhMe was removed by evaporation and replaced with a 1:1 mixture of EtOH–$CHCl_3$ and the mixture heated for another 24 h. TLC indicated that the cyano alcohol **15** was the only product, so the solvent was evaporated and replaced with *n*-BuOH and the mixture refluxed for another 24 h (in air, not in an inert atmosphere). TLC indicated that a single major product had been formed, so saturated $NaHCO_3$ (aq) and $CHCl_3$ were added, then the organic layer washed with brine, dried over $MgSO_4$ and evaporated. Flash chromatography on silica, eluted with a 1:19 saturated methanolic ammonia–$CHCl_3$ afforded semi-synthetic suaveoline (59 mg, 30% overall). All data for this material were identical to those reported previously.[1a]

One-pot Horner–Wadsworth–Emmons–alkylation to the alkene 17

Diethyl cyanomethylphosphonate (266 mg, 243 µl, 1.5 mmol) was added to NaH (66 mg of 60% dispersion in mineral oil, 1.65 mmol) in DMF (10 ml) at 0 °C and stirred for 10 min. EtBr (180 mg, 123 µl, 1.65 mmol) was added and the reaction allowed to warm to room temp. and stirred for 1 h. This mixture was then added to another portion of NaH (64 mg of 60% dispersion in mineral oil, 1.60 mmol) in DMF (5 ml) at 0 °C and stirred for 15 min. This mixture was then added dropwise to a stirred solution of the crude aldehyde **8** (270 mg) in DMF (10 ml) at room temp. The reaction was stirred for 1 h, then the DMF removed by evaporation and the residue treated with PhMe and evaporated again to remove the last traces of DMF. The residue was then partitioned between chloroform and brine, the organic layer twice washed with brine, dried over $MgSO_4$ and evaporated. The residue was then subjected to flash chromatography on silica eluted chloroform to yield the *trans* alkene (76 mg), *cis* alkene (53 mg) and some mixed *cis*–*trans* (126 mg, total yield 255 mg, 83%).

Data for *cis* alkene **17**: R_f 0.60 (1:9 Et_2O–DCM); ^{1}H NMR δ 1.08 (3H, t, *J* 7.5 Hz, CH$_2$CH_3), 2.15 (2H, q, *J* 7.5 Hz, CH_2CH$_3$), 2.54–2.91 (5H, m, one of ArCH_2CH, ArCHCH_2, and CH_2CN), 3.21 (1H, dd, *J* 16.1, 6.3 Hz, one of ArCH_2CH), 3.63–3.69 (1H, m, ArCH$_2$C*H*), 3.73 (3H, s, indole NCH_3), 3.64–3.95 (2H, AB system, *J* 13.4 Hz, NCH_2Ph), 3.92–4.01 (1H, m, ArC*H*CH$_2$), 6.32 (1H, t, *J* 7.1 Hz, C*H*C(Et)CN), 7.14–7.57 (9H, m, Ar*H*); ^{13}C NMR δ 12.5 (q), 21.7 (t), 24.9 (t), 27.4 (t), 30.6 (q), 37.3 (t), 54.0 (d), 54.9 (d), 61.3 (t), 104.2 (s), 109.1 (d), 117.3 (s), 117.8 (s), 118.1 (s), 118.7 (s), 119.4 (d), 122.0 (d), 126.4 (s), 127.7 (d), 128.5 (2 × d), 129.1 (2 × d), 132.8 (s), 137.9 (s), 138.4 (s), 144.1 (d); MS *m*/*z* 408 (M$^+$, 1%), 391 (2), 330 (4), 314 (100), 289 (4), 273 (9), 183 (27), 168 (15), 91 (100); found *m*/*z* 408.2281, calc. for $C_{27}H_{28}N_4$ 408.2314.

Data for *trans* alkene **17**: R_f 0.52 (1:9 Et_2O–DCM); ^1H NMR δ 1.04 (3H, t, J 7.5 Hz, CH_2CH_3), 2.07 (2H, br q, J 7.5 Hz, CH_2CH_3), 2.37–3.71 (4H, m, $ArCHCH_2$, and CH_2CN), 2.80 (1H, dd, J 16.1, 3.1 Hz, one of $ArCH_2CH$), 3.23 (1H, dd, J 16.1, 6.3 Hz, one of $ArCH_2CH$), 3.55–3.59 (1H, m, $Ar\,CH_2CH$), 3.61 (3H, s, indole NCH_3), 3.67–3.97 (2H, AB system, J 13.3 Hz, NCH_2Ph), 3.88–3.95 (1H, m, $ArCHCH_2$), 6.32 (1H, br t, J 7.1 Hz, $CHC(Et)CN$), 7.18–7.53 (9H, m, ArH); ^{13}C NMR δ 12.4 (q), 22.1 (2 × t), 24.7 (t), 30.4 (q), 35.0 (t), 53.9 (d), 54.5 (d), 61.2 (t), 104.8 (s), 109.1 (d), 117.5 (s), 118.2 (s), 118.3 (s), 119.3 (s), 119.6 (d), 126.4 (s), 127.9 (d), 128.7 (2 × d), 129.1 (2 × d), 133.4 (s), 137.8 (s), 138.1 (s), 143.9 (d).

Vinylogous Thorpe cyclisation to the tetracycle 18

Each fraction from the one-pot Horner–Wadsworth–Emmons–alkylation reaction was reacted separately using the following general method. The alkene **17** was dissolved in dry THF evaporated to dryness, then redissolved and cooled to 0 °C. KO*t*-Bu (1 eq.) was added in portions and the reaction monitored by TLC. After 10 min, the solvent was removed by evaporation and the residue partitioned between $CHCl_3$ and brine. The organic layer was then dried over $MgSO_4$ and evaporated. The crude ^1H NMR spectra for each reaction were very similar, so the residues were combined to yield 300 mg of crude product which was subjected to flash chromatography on silica eluted with a solvent gradient of $CHCl_3$ to 1:49 Et_2O–DCM to yield the tetracycle dinitrile **18** as a pale yellow foam (170 mg, 67%). The ^1H NMR of this material showed a complex mixture of stereoisomers which were not fully resolved, however, mass spectral data again confirmed the molecular formula prior to the attempted final pyridine formation. R_f 0.60 (ninhydrin −ve, whereas **17** is +ve) (1:9 Et_2O–DCM); MS *m/z* 408 (M^+, 4%), 347 (2), 273 (6), 177 (7), 91 (29), 49 (50), 28 (100); found *m/z* 408.2307, calc. for $C_{27}H_{28}N_4$ 408.2314.

Formation of *N*-benzylsuaveoline 19

The dinitrile **18** (41 mg, 0.10 mmol) was dissolved in dry DCM (6 ml) and then cooled to −78 °C. DIBAL (400 µl of 1 M solution in DCM, 0.4 mmol) was then added slowly and the reaction stirred at −78 °C for 1 h, then allowed to warm to room temp. and stirred for 24 h. The reaction was then cooled again to 0 °C and quenched EtOH (1 ml) then evaporated to dryness. The residue was then dissolved in EtOH with excess $NH_2OH{\cdot}HCl$ (70 mg), and the mixture refluxed overnight. The EtOH was then removed by evaporation and the residue partitioned between $CHCl_3$ and saturated $NaHCO_3$ (aq). The aqueous layer was washed five times with $CHCl_3$ and the combined organic extracts washed with brine, dried over $MgSO_4$ and evaporated to give a crude yield of 69 mg. Flash chromatography on silica eluted with a solvent gradient of DCM to 1:19 Et_2O–DCM afforded *N*-benzylsuaveoline **19** (21 mg, 53%). All data for this material were identical to those reported previously,[1b] except that our optical rotation was found to be slightly higher, following rigorous purification to a white foam {$[a]_D^{17}$ −149 (*c* 0.33, $CHCl_3$); lit.[1b] (from oil) $[a]_D^{24}$ −127 (*c* 0.33, $CHCl_3$)}.

In a second reaction, the dinitrile **18** (20 mg, 0.05 mmol) was dissolved in dry DCM (3 ml) and then cooled to −78 °C. DIBAL-H (50 µl of 1 M solution in DCM, 0.05 mmol) was then added slowly and the reaction stirred at −78 °C for 1 h, then allowed to warm to room temp. and stirred for 100 h. The reaction was then cooled to 0 °C and quenched with excess saturated NH_4Cl (aq) and 0.1 M H_2SO_4 and stirred at room temp. for 1 h. The aqueous mixture was extracted with $CHCl_3$ and the organic layer dried over $MgSO_4$ and evaporated to yield only starting material (by TLC and crude ^1H NMR). Recycling this material under the same reaction conditions, but with increasing quantities of DIBAL-H led solely to the formation of *N*-benzylsuaveoline **19** identical to that we had produced previously.

Formation of suaveoline 1

N-Benzylsuaveoline **19** (9 mg, 0.02 mmol) was dissolved in dry EtOH (1 ml) and methanolic HCl (100 µl of 1 M solution, 0.1 mmol) was added. The solution was evaporated to dryness and redissolved in EtOH (5 ml) and catalytic Pd–C (50% water, Degussa type) added and the mixture stirred under a hydrogen atmosphere for 2 h, then a further quantity of catalyst was added prior to stirring under H_2 for another 1 h. The solution was then filtered through a pad of silica which was washed with methanolic ammonia to give 8 mg of crude product, homogeneous by TLC. Flash chromatography on silica eluted with a slight solvent gradient 1:99 to 3:97 saturated methanolic ammonia–$CHCl_3$ afforded suaveoline as a white foam (4 mg, 66%). This material was identical in all respects to our semi-synthetic material and to the natural product.[1a]

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