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Enantioselective Total Synthesis of (-)-Indolizidines 209B and 209D via a Highly Efficient Aza-[2,3]-Wittig Rearrangement of Vinylaziridines

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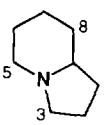
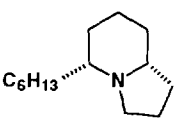
Abstract: A novel protocol for the enantioselective synthesis of (-)-indolizidines 209B (**2**) and 209D (**1**) is described, in which the key step is the highly efficient aza-[2,3]-Wittig rearrangement of vinylaziridines **11a,b** into tetrahydropyridines **12a,b**. Functional group manipulation and chain elongation then gave esters **16a,b** which were converted to the target alkaloids via lactams **17a,b**.

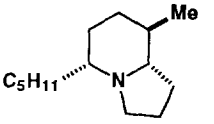
The systematic investigation of extracts from the skin of neotropical amphibians, most notably from frogs belonging to the Dendrobatidae family, has resulted in the isolation of a number of alkaloids.[1] The potent biological activity of several of these compounds, their ability to function as non-competitive blockers of neuromuscular transmission,[1a,2] together with their intriguing molecular architecture and often minute natural abundance has aroused interest among organic chemists. Consequently, an impressive effort has been devoted to the total synthesis of these alkaloids in order to provide material for biological testing, but also in order to verify the often tentative structural assignments. It is noteworthy that these studies have resulted in the development of several new methodologies.[3] Within the Dendrobatidae alkaloids the indolizidines, previously referred to as "bicyclic gephyrotoxins", constitute a class with some 20 members (Figure 1).[1] In this group the simplest members have a single substituent at C5, e. g. indolizidine 209D (**1**),[4] while in the more complex ones the indolizidine nuclei are substituted at C3/C5 or C5/C8, e. g. indolizidine 209B (**2**).[5] As noted above, several of the indolizidine alkaloids have been isolated in only minute quantities, and sometimes only from a single population of frogs, with the result that their structures have only been tentatively assigned. For example, the optical rotation of synthetic **2**, prepared by Holmes and co-workers,[5a,b] could not be compared with that of a natural sample due to insufficient material being isolated, while the structural assignment of **1** is based solely on mass



The indolizidine nuclei



Indolizidine 209D (**1**)

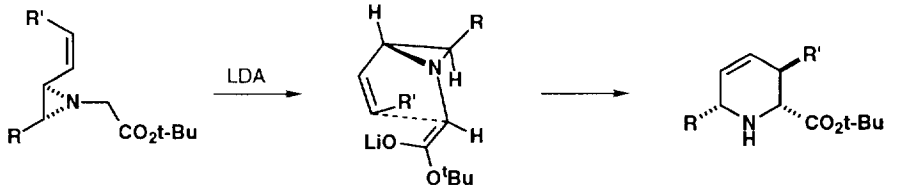


Indolizidine 209B (**2**)

Figure 1.

spectral evidence, i. e. a molecular ion peak at *m/z* 209 and a base peak at *m/z* 124, typical for 5-substituted indolizidines. The absolute stereochemistry was inferred by analogy with a related and fully characterised alkaloid.[1a]

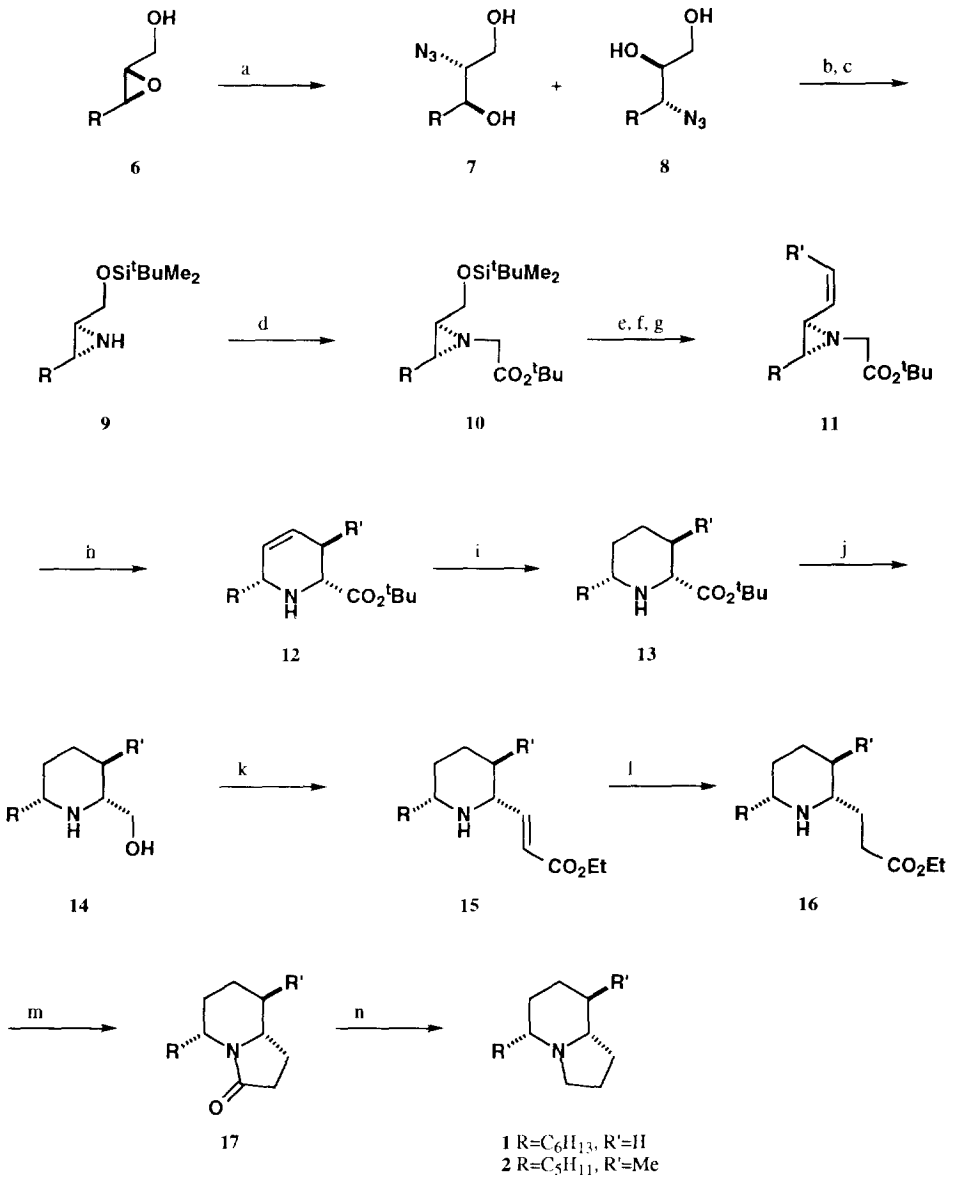
We recently communicated the preliminary results from an ongoing investigation of the aza-[2,3]-Wittig rearrangement.[6] Thus, it was shown that when vinylaziridines **3** are treated with base a smooth and rapid (<5 min) reaction ensues furnishing tetrahydropyridines **4** in high yield (>90% yield) and as a single detectable diastereomer (Scheme 1).[7,8] The stereochemical outcome of this rearrangement was rationalized by invoking transition state geometry **5** in which (i) the enolate and vinyl moieties are *cis* so as to facilitate bond formation (ii) the vinyl group adopts an *endo* conformation, projecting over the three-membered ring (iii) for steric or electronic reasons, or perhaps both, the enolate is oriented *exo*. It should be noted that structure **5** bears a strong resemblance to analogous structures suggested for the "normal" pericyclic [2,3]-Wittig rearrangement.[9] The products from the above rearrangement, compounds **4**, have the same substitution pattern and relative stereochemistry as the C5 and C5/C8 substituted indolizidines and should therefore have potential as precursors toward these types of alkaloids. Herein we detail the realization of such a strategy by the enantioselective synthesis of (-)-indolizidines 209B (**2**) and 209D (**1**) with the key step in each case being a highly selective aza-[2,3]-Wittig rearrangement of a vinylaziridine.



3 **5** **4**

Scheme 1.

In order to test the viability of the above strategy we selected the structurally simpler indolizidine 209D (**1**) as our primary target.[10] The vinylaziridine **11a** required for the projected key aza-[2,3]-Wittig rearrangement was prepared from the known epoxy alcohol **6a** (Scheme2),[11a,b] the enantiomeric excess of which was determined to be >95% (^{1}H NMR) by conversion to the corresponding Mosher ester and comparison with a sample prepared from racemic material.[12] Exposure of **6a** to sodium azide resulted in nucleophilic opening of the epoxide to yield the regioisomeric azido diols **7a** and **8a** (96%).[13] Since the isomeric composition of this mixture is of no consequence for the subsequent aziridination, no attempts were made to separate these compounds. Selective silylation of the above mixture at the primary hydroxyls[14] (94%) and subjecting the resultant silyl ethers to triphenylphosphine in refluxing toluene yielded aziridine **9a** (96%) with its absolute stereochemistry being inverted compared to the parent epoxide.[15] Next the nitrogen substituent, an anion-stabilizing group required for the subsequent rearrangement, which is to become the C9 substituent (indolizidine numbering), was introduced by subjecting **9a** to *tert*-butyl bromoacetate and K_2CO_3/18-crown-6 in THF for 40 h to afford aziridine **10a** as a mixture of nitrogen invertomers.[16] Compound **10a** was then converted into **11a** by a three-step sequence involving removal of the hydroxyl protecting group (89%), Swern oxidation[17] of the resultant primary alcohol and Wittig olefination (82%, two steps).[18] Inspection of the ^{1}H NMR spectrum of **11a** clearly shows the presence of two equilibrating nitrogen invertomers at room temperature in a ratio of 2.6/1. Previously it was shown that the inversion barrier for a structurally similar vinylaziridine was 16.5 kcal/mol, which is typical for an *N*-alkyl substituted aziridine, and it is reasonable to assume the barrier to be of the same magnitude in **11a**.[19a] However, the composition of this mixture is apparently of no importance for the projected aza-[2,3]-Wittig rearrangement.



Scheme 2. **a** R=C_6H_{13}, R'=H, **b** R=C_5H_{11}, R'=Me (a) NaN_3, NH_4Cl, $MeOCH_2CH_2OH/H_2O$, **a** 96%, **b** 89% (b) $^tBuMe_2SiCl$, CH_2Cl_2, Et_3N, DMAP, **a** 94%, **b** 90% (c) Ph_3P, toluene, Δ, **a** 96%, **b** 90% (d) *tert*-butyl bromoacetate, K_2CO_3, 18-crown-6, THF, **a** 67%, **b** 60% (e) Bu_4NF, THF, **a** 89%, **b** 81% (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 -78 °C (g) **a** Ph_3PCH_2, THF, 82% (two steps), **b** Ph_3PCH_2Me, THF, 80% (two steps) (h) LDA, THF, -78 °C, **a** 98%, **b** 97% (i) 5% Pd/C, H_2, EtOH, **a** 83%, **b** 55% (two steps) (j) $LiAlH_4$, THF, 0 °C→RT, **a** 94%, **b** 90% (k) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 -78 °C, then Ph_3PCHCO_2Et, **a** 50%, **b** 75% (l) 5% Pd/C, H_2, 4 kg/cm^2, EtOH, **a** 90%, **b** 84% (m) Me_3Al, benzene, **a** 69%, **b** 88% (n) $LiAlH_4$, THF, Δ, **a** 88%, **b** 70%.

When compound **11a** was subjected to LDA in THF at -78 °C a fast (<5 min) reaction ensued, furnishing the *cis*-2,6-disubstituted tetrahydropyridine derivative **12a** in 98% yield and, judging from its ^{1}H NMR spectrum, as a single diastereomer.[6] The relative stereochemistry of **12a** was originally assigned in analogy with the results obtained from the rearrangemnt of aziridines structurally similar to **11a**. Additional proof for this stereochemistry was obtained from a NOE experiment on the piperidine derivative **13a**, obtained from **12a** (*vide infra*), the relevant signal enhancements being indicated in Figure 2. It should be noted that the formation of **12a** is in complete agreement with the transition state geometry **5** discussed above (Scheme 1). One final point concerning this aza-[2,3]-Wittig rearrangement that needs to be commented upon is the observed ratio of invertomers in **11a** (2.6/1) compared to the obtained yields of **12a** (98%). According to our suggested structure **5** the vinyl group and enolate moiety should be *cis* in order to allow for efficient orbital overlap and resultant bond formation. However, with an inversion barrier of the order of 16 kcal/mol and considering the rapidity of the rearrangement (<5 min, -78 °C) there needs to be a mechanism for lowering the nitrogen inversion barrier upon going from **11a** to the corresponding enolate. It was previously suggested that formation of the lithium enolate (cf **5**) from the corresponding vinylaziridine was accompanied by a substantial reduction of this barrier. This is reasonable since amines, including aziridines, in which the nitrogen can interact with a substituent by (p-p)π-conjugation, as is the case for **5**, exhibit a lower inversion barrier than would be expected from purely steric considerations. For example, for *N*-phenyl substituted aziridines the barrier is about 7 kcal/mol lower compared to the *N*-alkyl substituted ones, and the nitrogen atom is somewhat less pyramidal.[19]

13a **13b**

Figure 2. The results of NOE experiments on **13a** and **13b** (% signal enhancement).

Attempts to purify **12a** by flash chromatography on silica gel generally resulted in some loss of material, probably due to the known sensitivity of this type of compound.[20] As judged from the ^{1}H NMR spectrum of the crude reaction mixture this material is pure (>98%) and was generally, without further purification, hydrogenated to yield the pipecolinic acid derivative **13a** (81% from **11a**). Initially we had some concerns as to whether the unprotected secondary amine moiety in **13a** would interfere with our projected synthetic plan but fortunately this was not the case. Reduction of **13a** with $LiAlH_4$ gave amino alcohol **14a** in 94% yield. The required two-carbon homologation was then efficiently accomplished by subjecting **14a** to the one-pot Swern-Wittig protocol developed by Ireland to give the α,β-unsaturated ester **15a** (50%),[21] hydrogenation of which afforded **16a** (90%). Attempts to convert this material into indolizidine 209D (**1**) by adopting the cyclization procedure of Kibayashi met with limited success.[5e] Thus, reduction of **16a** ($LiAlH_4$) to the corresponding alcohol and subjecting it to $CBr_4/Ph_3P/Et_3N$ gave a complicated mixture of products from which **1** could be extracted in only minor amounts. Instead a more reliable and direct method was desired and thus ester **16a** was treated with $AlMe_3$ in benzene to afford lactam **17a** (69%).[22] Finally, reduction of **17a** with $LiAlH_4$ gave indolizidine 209D (**1**) in 88% yield, its spectroscopic and analytical data being in excellent agreement with literature values.[4b,c]

With the completion of the above synthesis an efficient route from vinylaziridine **11a** to the indolizidine nuclei had been established. In an effort to expand the scope of this methodology we next turned our attention to the enantioselective preparation of the more highly substituted (-)-indolizidine

209B (**2**). The synthesis commences with the readily available epoxy alcohol **6b** (>95% ee, Scheme 2).[11b,c] This material was uneventfully converted into silyl ether **10b** which was then deprotected, oxidized and treated with Ph_3PEtBr and KHMDS in THF to yield vinylaziridine **11b** (80%) as a mixture of nitrogen invertomers but as a single detectable olefinic isomer (*Z*/*E*>20/1), as evident from its ^1H NMR spectrum. Rearrangement of **11b** gave **12b** as a single diastereomer (97%) which was immediately hydrogenated to afford **13b** in excellent overall yield (55% from **11b**). The stereochemical assignment of **13b** was verified by a NOE experiment (Figure 2) and is that predicted from transition state geometry **5**. It is noteworthy that the aza-[2,3]-Wittig rearrangement of **11b** correctly establishes the three stereogenic centers present in alkaloid **2** in a single step. Conversion of **13b** to the target compound was then accomplished by using the synthetic sequence discussed above, ultimately affording 209B (**2**), the physical data of which closely match those previously reported.[5b,e]

In conclusion, a novel entry to the C5 and C5/C8 substituted indolizidine alkaloids has been developed and its potential demonstrated by the successful total synthesis of (-)-indolizidines 209B (**2**) and 209B (**1**), the key step being a highly selective aza-[2,3]-Wittig rearrangement of vinylaziridines **11a,b** to afford tetrahydropyridines **12a,b** in excellent yield and as a single diastereomer in each case. The remarkable diastereoselectivity observed in this reaction, together with its predictable stereochemical outcome, should make it a useful tool for the construction of a variety of alkaloids containing the piperidine nuclei and further studies will be reported in due course.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ ($CHCl_3$, δ 7.26) as solvent. IR spectra were run on a Perkin-Elmer 298 spectrophotometer and only the strongest/structurally most important peaks (ν, cm^{-1}) are listed. Optical rotations, $[\alpha]_D$, were measured on a Perkin-Elmer 141 polarimeter at the sodium D line and at ambient temperatures. Flash chromatography employed Grace Amicon silica gel 60 (0.035-0.070 mm). Dichloromethane was distilled from calcium hydride immediately before use; tetrahydrofuran (THF) and toluene were distilled from sodium-benzophenone ketyl; benzene was dried over 4Å molecular sieves. All reactions were run in septum-capped, oven-dried flasks under atmospheric pressure of nitrogen, solvents, reactant solutions and liquid reagents being transferred *via* oven-dried syringes. Potassium hexamethyldisilazide (KHMDS) was freshly prepared in THF prior to use.[23]

Azido diols **7a** *and* **8a**. Epoxy alcohol **6a** was dissolved in 2-methoxyethanol/H_2O (8/1, 36 ml) and sodium azide (11.5 g, 0.18 mol) followed by ammonium chloride (3.70g, 0.69 mol) was added. The resulting mixture was refluxed overnight and then cooled to room temperature. The reaction mixture was diluted with Et_2O (200 ml) and the organic phase was separated, washed with H_2O (3 x 100 ml) and brine (1 x 100 ml). Drying ($MgSO_4$) and concentration gave a mixture of crude azido diols **7a** and **8a** (6.8g, 96%) that was taken on to the next step without further purification. IR (film) 3480, 2930, 2110, 1460, 1270 cm^{-1}.

Azido diols **7b** *and* **8b**. Prepared from **6b** in 89% yield as detailed above for compounds **7a/8a**. IR (film) 3440, 2900, 2100, 1460, 1250 cm^{-1}.

Aziridine **9a**. To a solution of azido diols **7a** and **8a** (6.80 g, 33.8 mmol) in CH_2Cl_2 (50 ml) was added *tert*-butyldimethylsilyl chloride (5.60 g, 37.2 mmol), triethylamine (7.1 ml, 50.7 mmol) and *N*, *N*-dimethyl-4-aminopyridine (cat.) and the resultant mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (100 ml) and poured into water (100 ml) The organic phase was separated and washed once with aq. NH_4Cl (sat, 100 ml), dried ($MgSO_4$) and concentrated. Flash chromatography (heptane/EtOAc: 15/1→10/1) of the residue gave the corresponding mixture of silyl ethers as a colorless oil (10.1 g, 94%).

To a solution of the mixture of silyl ethers (6.29 g, 19.9 mmol) from above in toluene (40 ml) was added triphenylphosphine (6.29g, 23.9 mmol) and the resultant mixture was refluxed overnight. The reaction mixture was cooled to room temperature, concentrated and the residue flash chromatographed (heptane/EtOAc: 6/1→1/1) to give aziridine **9a** (5.20g, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (m, 2H), 1.78 (m, 2H), 1.41-1.27 (m, 11H), 0.87 (s, 9H), 0.85 (t, 3H, J=9.0 Hz), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.9, 38.5, 33.9, 32.2, 29.5, 28.0, 26.3, 23.0, 18.7, 14.5, -4.92, -4.95; IR (film) 2920, 2850,1460, 1250, 1105 cm^{-1}; $[\alpha]_D$= +22.51 (*c* 1.48, $CHCl_3$); HRMS (FAB+) Exact mass Calc for $C_{15}H_{34}NOSi$ (M+H): 272.2410 Found: 272.2416.

Aziridine **9b**. Prepared from **7b/8b** in 90% yield as detailed above for **9a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (m, 2H), 1.84 (m, 2H), 1.51-1.30 (m, 9H), 0.87 (m, 12H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 63.0, 38.1, 34.0, 33.4, 31.6, 27.2, 25.9, 22.6, 18.3, 14.0, -5.4, -5.4; IR (film) 2920, 2850, 1250, 1095 cm^{-1}; $[\alpha]_D$= +24.83 (*c* 0.600, $CHCl_3$); HRMS (FAB+) Exact mass Calc for $C_{14}H_{32}NOSi$ (M+H): 258.2253. Found: 258.2256.

Aziridine ester **10a**. To a solution of aziridine **9a** (5.1g, 18.8 mmol) in THF (50 ml) was added *tert*-butyl bromoacetate (4.50 ml, 23.9 mmol), K_2CO_3 (3.55 g, 25.7 mmol) and 18-crown-6 (cat.). The resultant slurry was stirred at ambient temperature for 40 h and then diluted with Et_2O (100 ml). The combined organic phases were washed once with water (50 ml) and once with brine (50 ml), dried ($MgSO_4$) and concentrated. Flash chromatography (heptane/EtOAc: 10/1→1/1) of the residue gave aziridine ester **10a** (4.84 g, 67%).^{1}H NMR ($CDCl_3$, 300 MHz, peaks assigned from a mixture of invertomers) δ 3.91 (m, $1H_{maj}$, $1H_{min}$), 3.79 (dd, $1H_{maj}$, J=12.0, 6.3 Hz), 3.45 (d, $1H_{maj}$, J=16.4 Hz), 3.32 (dd, $2H_{min}$, J=10.8, 6.9 Hz), 3.32 (d, $1H_{maj}$, J=16.4 Hz), 3.31 (d, $1H_{min}$, J=16.4 Hz), 2.04 (m, $1H_{min}$), 1.93 (m, $1H_{maj}$), 1.75-1.58 (m, $1H_{maj}$,$1H_{min}$), 1.55-1.21 (m, $10H_{maj}$, $10H_{min}$), 1.49 (s, $9H_{maj}$, $9H_{min}$), 0.98-0.85 (m, $12H_{maj}$, $12H_{min}$), 0.10 (s, $6H_{maj}$, $6H_{min}$); ^{13}C NMR ($CDCl_3$, 75 MHz, from a mixture of invertomers) δ 170.7, 170.2, 80.9, 80.7, 65.9, 59.4, 54.3, 54.0, 46.8, 43.2, 42.7, 42.0, 32.7, 31.8, 31.7, 29.1, 29.0, 28.1, 27.2, 26.0, 25.8, 25.7, 22.6, 22.5, 18.3, 18.1, 14.1, -5.3, -5.4, -5.5; IR (film, from a mixture of invertomers) 2960, 1795, 1255, 1155 cm^{-1}; HRMS (FAB+) Exact mass Calc for $C_{21}H_{44}NO_3Si$ (M+H): 386.3090. Found: 386.3107.

Aziridine ester **10b**. Prepared from **9b** in 64% yield as detailed above for **10a**. ^{1}H NMR ($CDCl_3$, 300 MHz, peaks assigned from a mixture of invertomers) δ 3.93 (m, $1H_{maj}$, $1H_{min}$), 3.81 (dd, $1H_{maj}$, J=6.3, 12.1 Hz), 3.46 (d, $1H_{maj}$, J=16.3 Hz), 3.34 (dd, $1H_{min}$, J=6.9, 10.9 Hz), 3.15 (d, $1H_{maj}$, J=16.3 Hz), 3.14 (d, $1H_{min}$, J=16.6 Hz), 2.00 (m, $1H_{maj}$, $1H_{min}$), 1.99 (m, $1H_{maj}$,$1H_{min}$), 1.75-1.28 (m, $8H_{maj}$, $8H_{min}$) 1.49 (s, $9H_{maj}$, $9H_{min}$), 0.84 (m, $12H_{maj}$, $12H_{min}$), 0.10 (s, $9H_{maj}$, $9H_{min}$); ^{13}C NMR ($CDCl_3$, 75 MHz, from a mixture of invertomers) δ 170.7, 170.2, 0.9, 80.7, 65.7, 59.4, 54.4, 54.0, 46.8, 43.2, 42.7, 42.0, 32.6, 31.6, 31.5, 30.9, 28.1, 27.8, 25.9, 25.8, 22.6, 22.5, 18.3, 18.1, 14.0, 14.0, -5.3, -5.3, -5.4, -5.5; IR (film, from a mixture of invertomers) 2930, 1745, 1465, 1365, 1150 cm^{-1}; HRMS (FAB+) Exact mass Calc for $C_{20}H_{42}NO_3Si$ (M+H): 372.2934. Found: 372.2921.

Vinylaziridine **11a.** To a solution of ester **10a** (1.10 g, 2.85 mmol) in THF (40 ml) was added tetrabutylammonium fluoride trihydrate (1.35 g, 4.28 mmol). The resultant mixture was stirred for 30 min and then poured into Et_2O (100 ml) and water (100 ml). The organic phase was separated and washed with brine (50 ml), dried ($MgSO_4$) and concentrated. Flash chromatography (heptane/EtOAc: 1/1→1/4) of the residue yielded the corresponding alcohol (0.692 g, 89%) as a mixture of invertomers. ^{1}H NMR ($CDCl_3$, 300 MHz, peaks assigned from a mixture of invertomers) δ 4.60 (app q, $1H_{min}$, J=12.6 Hz), 3.91 (m, $1H_{maj}$), 3.71 (m, $1H_{maj}$), 3.57 (d, $1H_{maj}$, J=16.9 Hz), 3.55 (m, $1H_{min}$), 3.18 (dd, $2H_{min}$, J=10.5, 9.3 Hz), 2.85 (d, $1H_{maj}$, J=16.9 Hz), 2.22 (m, $1H_{min}$), 2.00 (m, $1H_{maj}$, $1H_{min}$), 1.74-1.23 (m, $12H_{maj}$, $11H_{min}$), 1.52 (s, $9H_{maj}$, $9H_{min}$), 0.87 (m, $3H_{maj}$, $3H_{min}$); ^{13}C NMR ($CDCl_3$, 75 MHz, from a mixture of invertomers) δ 171.7, 82.0, 64.8, 63.4, 53.1, 51.3, 47.7, 40.7, 37.2, 35.2, 31.8, 31.5, 29.0, 28.2, 28.1, 27.0, 22.6, 14.0 ; IR (film, from a mixture of invertomers) 3380, 2930, 1735, 1460, 1370, 1160 cm^{-1}.

To a solution of oxalylchloride (377 µl, 4.31 mmol) in CH_2Cl_2 (30 ml) at -78 °C was added dimethylsulfoxide (764 µl, 10.77 mmol). After 10 min the alcohol from above in CH_2Cl_2 (10 ml) was added dropwise over 10 min. The resultant mixture was stirred for 40 min at -78 °C and then Et_3N (25.7 mmol, 3.60 ml) was added. Stirring was continued at -78 °C for 30 min followed by warming to room temperature over 1 h. The mixture was poured into Et_2O (150 ml) and water (100 ml) and the organic layer was separated, washed once with water (100 ml) and once with brine (100 ml). Drying ($MgSO_4$) and removal of the solvents gave the crude aldehyde that was immediately taken on to the next step.
To a slurry of methyltriphenylphosphonium bromide (2.53 g, 7.10 mmol) in toluene (20 ml) at -20 °C was added KHMDS (9.2 ml, 6.45 mmol, 0.7 M in THF) and stirring was continued for 1 h at room temperature. After recooling to -20 °C the crude aldehyde from above in THF (10 ml) was added dropwise over 10 min. The resultant slurry was slowly warmed to room temperature (30 min) and then poured into brine (100 ml). The organic layer was separated and the aqueous phase extracted with Et_2O (3x75 ml). The combined organic phases were dried (Na_2SO_4), concentrated (water bath at 0 °C) and the residue was flash chromatographed (heptane/EtOAc: 6/1→3/1) to yield vinyl aziridine **11a** (0.470 g, 82% from **10a**) as a mixture of invertomers. ^1H NMR ($CDCl_3$, 300 MHz, peaks assigned from a mixture of invertomers) δ 5.63 (m, $1H_{maj}$, $1H_{min}$), 5.36 (dd, $1H_{maj}$, J=1.5, 16.8 Hz,), 5.28 (m, $1H_{min}$), 5.25 (dd, $1H_{maj}$, J=1.7, 10.3 Hz), 5.07 (d, $1H_{min}$, J=10.6 Hz), 3.32-3.10 (m, $2H_{maj}$, $2H_{min}$), 2.39 (dd, $1H_{maj}$, J=2.7, 8.6 Hz), 1.98 (m, $1H_{min}$), 1.75 (m, $1H_{min}$), 1.70-1.10 (m, $11H_{maj}$, $10H_{min}$), 1.45 (s, $9H_{maj}$, $9H_{min}$), 0.88 (m, $3H_{maj}$, $3H_{min}$); ^{13}C NMR ($CDCl_3$, 75 MHz, from a mixture of invertomers) δ 170.0, 138.3, 132.8, 120.5, 115.7, 80.9, 55.4, 54.1, 47.7, 47.5, 44.6, 44.5, 32.7, 31.8, 31.7, 29.1, 28.1, 28.0, 27.0, 26.0, 22.6, 14.0; IR (film, from a mixture of invertomers) 2920, 1740, 1375, 1155 cm^{-1}; HRMS (CI+) Exact mass Calc for $C_{16}H_{30}NO_2$ (M+H): 268.2277. Found: 268.2283.
Vinylaziridine **11b**. Prepared from **10b** in 65% yield as detailed above for **11a**. ^1H NMR ($CDCl_3$, 300 MHz, peaks assigned from a mixture of invertomers and only major isomer reported) δ 5.80 (dq, 1H, J=11.0, 6.8 Hz), 5.21 (app. t, 1H, J=11.0 Hz), 3.22 (d, 1H, J=11.5 Hz), 3.09 (d, 1H, J=11.5 Hz), 2.55 (dd, 1H, J=2.5, 8.5 Hz) 1.77 (dd, 3H, J=2.0, 7.2 Hz) 1.76-1.20 (m, 9H), 1.46 (s, 9H), 0.88 (t, 3H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, from a mixture of invertomers and only major isomer reported) δ 170.2, 131.4, 124.5, 80.8, 55.7, 48.7, 39.2, 32.9, 31.7, 28.1, 26.8, 22.6, 14.0, 13.4; IR (film, from a mixture of invertomers) 2920, 1750, 1365, 1155 cm^{-1}; HRMS (CI+) Exact mass Calc for $C_{16}H_{30}NO_2$ (M+H): 268.2277. Found: 268.2268.
Tetrahydropyridine **12a**. To a solution of $^iPr_2NH$ (0.11 ml, 0.79 mmol) in THF (6 ml) at 0 °C was added BuLi (0.49 ml, 0.72 mmol, 1.48 M in hexanes). The mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. To this mixture was added vinylaziridine **11a** (96.5 mg, 0.36 mmol) in THF (4 ml) *via* cannula over 5 min to give a red-brown solution. After stirring for an additional 10 min at -78 °C the reaction was terminated by addition of pH 7 phosphate buffer (3 ml) and the mixture was poured into Et_2O (20 ml) and phosphate buffer (20 ml). The organic phase was separated, dried ($MgSO_4$) and concentrated to give crude **12a** (95.1 mg, 98%). This material was pure according to ^1H NMR analysis and was, due to its acid sensitivity, taken on directly to the next step. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.71 (m, 1H), 5.58 (m, 1H), 3.45 (dd, 1H, J=4.6, 10.7 Hz), 3.35 (m, 1H), 2.24-2.05 (m, 3H), 1.20-1.1 (m, 10H), 1.45 (s, 9H), 0.87 (m, 3H).
Tetrahydropyridine **12b**. Prepared from **11b** in 97% yield as detailed above for **12a**. ^1H NMR ($CDCl_3$, 300 MHz) δ 5.55 (m, 2H), 3.25 (m, 1H), 2.98 (d, 1H, J=9.5 Hz), 2.29 (m, 1H), 1.55-1.15 (m, 7H), 1.48 (s, 10H), 1.04 (d, 3H, J=7.5 Hz), 0.87 (m, 3H).
Pipecolinic ester **13a**. To a solution of crude tetrahydropyridine **12a** (343 mg, 1.28 mmol) in EtOH (10 ml) was added 10% Pd/C (cat.) and the resultant slurry was stirred overnight under an atmospheric pressure of H_2. The slurry was filtered through a pad of Celite, concentrated and flash chromatographed (heptane/EtOAc: 20/1→6/1) to give pipecolinic ester **13a** (266 mg, 83%). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.19 (dd, 1H, J=11.5, 2.5 Hz), 2.45 (m, 1H), 2.97 (m, 1H), 2.84 (m, 2H), 2.62 (m, 1H), 1.52-1.18 (m,

12H), 1.45 (s, 9H), 1.02 (m, 1H), 0.86 (t, 3H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 80.8, 59.8, 56.4, 37.2, 32.1, 29.5, 29.4, 28.1, 25.9, 24.7, 22.6, 14.1; IR (film) 3340, 2930, 1760, 1455, 1368, 1160 cm^{-1}; $[\alpha]_D$=+12.2 (*c* 3.21, $CDCl_3$); HRMS (FAB+) Exact mass Calc for $C_{16}H_{32}NO_2$ (M+H): 270.2433. Found: 270.2438.

Pipecolinic ester **13b**. Prepared from **12b** in 55% yield as detailed above for **13a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.85 (d, 1H, J=10.1 Hz), 2.43 (m, 1H), 1.79 (m, 1H), 1.65 (m, 1H), 1.54-0.95 (m, 12H) 1.45 (s, 9H), 0.88 (d, 3H, J=7.5 Hz), 0.85, (t, 3H, J= 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 80.9, 67.2, 55.8, 37.0, 35.0, 33.6, 32.8, 32.0, 28.1, 25.7, 22.6, 18.7, 14.0; IR (film) 2920, 1730, 1455, 1370, 1150 cm^{-1}; $[\alpha]_D$=-7.7 (*c* 1.67, $CHCl_3$); HRMS (FAB+) Exact mass Calc for $C_{16}H_{32}NO_2$ (M+H): 270.2433. Found: 270.2422.

Amino alcohol **14a**. To a solution of pipecolinic ester **13a** (173 mg, 0.64 mmol) in THF (10 ml) at 0 °C was added $LiAlH_4$ (7.2 mg, 0.18 mmol). After stirring the slurry for 30 min at 0 °C to room temperature H_2O (7.5 µl), 15% NaOH (7.5 µl) and H_2O (21.5 µl) were added. After 10 min Na_2SO_4 was added and the mixture was stirred for an additional 30 min and then filtered through a pad of Celite. The filter cake was washed thoroughly with EtOAc and the combined organic phases were concentrated. Flash chromatography (EtOAc/MeOH: 1/0→1/1) of the residue gave **14a** (120 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.58 (dd, 1H, J=11.0, 3.5 Hz), 3.39 (dd, 1H, J=11.0, 8.4 Hz), 3.36 (br s, 2H), 2.69 (m, 1H), 2.58 (m, 1H), 1.79 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H) 1.45-1.20 (m, 11H), 1.15-0.95 (m, 2H), 1.85 (t, 3H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.4, 58.3, 56.6, 36.9, 32.1, 31.8, 29.4, 28.1, 25.8, 24.1, 22.6, 14.0; IR (KBr) 3140, 2930, 1575, 1470, 1075, 1010 cm^{-1}; $[\alpha]_D$=-3.95 (*c* 0.73, $CDCl_3$); HRMS (FAB+) Exact mass Calc for $C_{12}H_{26}NO$ (M+H): 200.2014. Found: 200.2016.

Amino alcohol **14b**. Prepared from **13b** in 90% yield as detailed above for **14a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77 (dd, 1H, J=3.2, 10.7 Hz), 3.45 (dd, 1H, J=7.7, 10.7 Hz), 2.47 (m, 1H), 2.32 (ddd, 1H, J=3.2, 7.6, 9.6 Hz), 2.05 (br s, 2H), 1.69 (m, 2H), 1.30 (m, 9H), 1.07 (m, 2H), 0.88 (t, 3H, J=5.9 Hz), 0.85 (d, 3H, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.3, 63.9, 56.4, 37.2, 34.0, 33.2, 32.9, 32.0, 25.7, 22.6, 18.1, 14.1; IR (film) 3280, 2930, 1560 cm^{-1}; $[\alpha]_D$=-18.6 (*c* 0.845, $CHCl_3$); HRMS (FAB+) Exact mass Calc for $C_{12}H_{26}NO$ (M+H): 200.2014. Found: 200.2020.

Ester **15a**. To a solution of oxalylchloride (52 µl, 0.625 mmol) in CH_2Cl_2 (10 ml) at -78 °C was added dimethylsulfoxide (84 µl, 1.20 mmol). After stirring for 10 min **14a** in CH_2Cl_2 (10 ml) was added dropwise over 10 min. The resultant mixture was stirred for 20 min at -78 °C and then Et_3N (0.348 ml, 2.50 mmol) was added. After stirring for an additional 40 min at -78 °C ethyl (triphenylphosphoranylidene)acetate (457 mg, 1.5 mmol) was added and the resultant slurry was allowed to slowly warm to room temperature. The mixture was then poured into CH_2Cl_2 (40 ml) and brine/pH 7 buffer (1/1, 40 ml) and the phases were separated. The aqueous phase was extracted once with CH_2Cl_2 (20 ml) and the combined organic phases were dried ($MgSO_4$), concentrated and flash chromatographed (heptane/EtOAc: 6/1→2/3) to yield the **15a** (66 mg, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (dd, 1H, J=6.0, 15.8 Hz), 5.92 (dd, 1H, J= 1.4, 15.8 Hz), 4.15 (q, 2H, J=7.2 Hz), 3.26 (m, 1H), 2.52 (m, 1H), 1.89-1.59 (m, 3H), 1.54 (br s, 1H), 1.50-0.94 (m, 13H), 1.26 (t, 3H, J=7.2 Hz), 0.85 (t, 3H, J=6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7, 150.9, 119.9, 60.3, 58.1, 56.7, 37.3, 32.0, 32.0, 31.8, 29.5, 25.8, 24.6, 22.6, 14.2, 14.0; IR (film) 3310, 2920, 2850, 1715, 1655, 1450, 1265 cm^{-1}; $[\alpha]_D$=+49.5 (*c* 1.02, CH_2Cl_2); HRMS (FAB+) Exact mass Calc for $C_{16}H_{30}NO_2$ (M+H): 268.2277. Found: 268.2287.

Ester **15b**. Prepared from **14b** in 75% yield as detailed above for **15a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.90 (dd, 1H, J=15.7, 8.0 Hz), 5.93 (d, 1H, J=15.7 Hz), 4.18 (q, 2H, J=7.1 Hz), 2.83 (br t, 1H, J=8.6 Hz) 2.49 (m, 1H), 1.79 (m, 1H), 1.67 (m, 1H), 1.50 (m, 1H), 1.39-1.18 (m, 9H), 1.27 (t, 3H, J=7.1 Hz), 1.11 (m, 2H), 0.87, (m, 3H), 0.83 (d, 3H, J=6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 149.8, 122.1, 65.3, 60.3, 56.4, 37.1, 35.9, 33.7, 32.5, 32.0, 25.6, 22.6, 18.6, 14.2, 14.0; IR (film) 3350, 2980, 1720, 1660, 1465, 1270 cm^{-1}; $[\alpha]_D$=-0.81 (*c* 1.60, $CHCl_3$); HRMS (FAB+) Exact mass Calc for $C_{16}H_{30}NO_2$ (M+H): 268.2277. Found: 268.2277.

Amino ester **16a**. To a solution of ester **15a** (57 mg, 0.21 mmol) in EtOH (10 ml) was added 10% Pd/C (30 mg) and the resultant slurry was shaken under a hydrogen atmosphere (4 kg/cm^2) overnight. The slurry was then filtered through a pad of Celite and concentrated to give amino ester **16a** (52 mg, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.09 (q, 2H, J=7.1 Hz), 2.65 (m, 2H), 2.40 (m, 2H), 2.03-1.08 (m, 22H), 0.84 (t, 3H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 60.4, 57.8, 57.0, 35.7, 31.8, 30.7, 30.6, 29.3, 25.8, 24.0, 22.6, 14.2, 14.0; IR (film) 3020, 2930, 2880, 1725, 1215 cm^{-1}; $[\alpha]_D$=-1.29 (*c* 1.01, $CHCl_3$).
Amino ester **16b**. Prepared from **15b** in 84% yield as detailed above for **16a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.11 (q, 2H, J= 7.3 Hz), 2.40 (m, 1H), 2.13 (dt, 1H, J=8.5, 3.0 Hz), 2.03 (m, 1H), 1.69 (m, 3H), 1.54-1.05 (m, 12H), 1.24 (t, 3H, J=7.0 Hz), 0.87 (t, 3H, J=7.0 Hz), 0.85 (d, 3H, J=6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.2, 62.4, 60.4, 57.3, 36.4, 35.5, 33.9, 32.0, 31.9, 30.8, 28.2, 25.6, 22.6, 18.4, 14.2, 14.0; IR (film) 2910, 1725, 1450, 1365, 1175 cm^{-1}; $[\alpha]_D$=-26.92 (*c* 3.88, $CHCl_3$); HRMS (FAB+) Exact mass Calc for $C_{16}H_{32}NO_2$ (M+H): 270.2433. Found: 270.2430.
Amide **17a**. To a solution of ester **16a** (49 mg, 0.81 mmol) in benzene (10 ml) was added 2M trimethylaluminum (0.20 ml, 0.40 mmol, in hexanes). The pale yellow solution was stirred for 2 h at ambient temperature and then refluxed overnight. The mixture was then cooled to room temperature and aq. HCl (5 ml, 0.1 M) was added followed by stirring for an additional 30 min. The phases were separated and the aqueous phase extracted with EtOAc (3x10 ml), then diluted with saturated $NaHCO_3$ (5 ml) and extracted once more with EtOAc (10 ml). The combined organic phases were dried ($MgSO_4$), concentrated and flash chromatographed (heptane/EtOAc: 2/3→0/1) to give **15a** (19 mg, 69%).^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.38 (m, 1H), 3.16 (m, 1H), 2.32 (m, 3H), 2.08 (m, 1H), 1.88-1.63 (m, 4H), 1.57-1.20 (m, 12H), 0.87 (t, 3H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.4, 59.7, 57.6, 32.5, 32.0, 31.9, 29.5, 29.4, 26.9, 25.1, 22.7, 22.7, 14.1; IR (film) 2925, 2855, 1680, 14.25, 1250 cm^{-1}; $[\alpha]_D$=-19.8 (*c* 1.15, $CDCl_3$); HRMS (FAB+) Exact mass Calc for $C_{14}H_{26}NO$ (M+H): 224.2014. Found: 224.2005.
Amide **17b**. Prepared from **16b** in 88% yield as detailed above for **17a**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.11 (m, 1H), 2.92 (dt, 1H, J=10.4, 6.6 Hz), 2.36-2.20 (m, 3H), 2.05 (m, 1H), 1.88-1.05 (m, 13H), 0.87 (d, 3H, J=6.4 Hz), 0.84 (t, 3H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 65.4, 57.2, 36.7, 32.2, 31.9, 31.8, 29.7, 26.6, 23.5, 22.7, 17.8, 14.1; IR (film) 2910, 1680, 1455, 1410, 1355 cm^{-1}; $[\alpha]_D$=-63.29 (*c* 2.13, $CHCl_3$); HRMS (FAB+) Exact mass Calc for $C_{14}H_{26}NO$ (M+H): 224.36654. Found: 224.2009.
Indolizidine 209 D (**1**). To a solution of amide **17a** (16 mg, 0.069 mmol) in THF (5 ml) was added $LiAlH_4$ (10 mg) and the slurry was refluxed for 2 h. After cooling to room temperature H_20 (10 µl), 15% NaOH (10 µl) and H_2O (30 µl) were added sequentially and the resultant slurry was stirred for 10 min followed by addition of Na_2SO_4. After stirring for 30 min the mixture was filtered, the filter cake was washed thoroughly with EtOAc and the combined organic phases were concentrated. Flash chromatography of the residue on deactivated silica gel (heptane/EtOAc: 99/1→9/1) yielded **1** (13 mg, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.25 (dt, 1H, J=9.0, 2.0 Hz), 2.96 (q, 1H, J=9.0 Hz), 1.90-1.05 (m, 22H), 0.86 (t, 3H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 65.0, 63.9, 51.6, 34.7, 31.9, 31.1, 30.9, 30.6, 29.8, 25.8, 24.7, 22.6, 20.4, 14.1; IR (film) 2920, 2860, 2780, 1455, 1375 cm^{-1}; $[\alpha]_D$=-83.6 (*c* 0.77, CH_2Cl_2) [lit.[4b] $[\alpha]_D$=-80.4 (*c* 1, CH_2Cl_2); lit.[4c] $[\alpha]_D$=-76.5 (*c* 0.74, CH_2Cl_2)].
Indolizidine 209B (**2**). Prepared from **17b** in 70% yield as detailed above for **1**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.26 (dt, 1H, J=8.6, 2.2 Hz), 2.00-0.88 (20H, m), 0.87 (t, 3H, J=6.5 Hz), 0.87 (d, 3H, J=6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.3, 63.6, 51.8, 36.5, 34.6, 33.7, 32.3, 31.2, 29.0, 25.5, 22.6, 20.3, 18.9, 14.1; IR (film) 2950, 2910, 2850 cm^{-1}; $[\alpha]_D$=-91.0 (*c* 0.55, MeOH) [lit.[5b] $[\alpha]_D$=-94.3 (*c* 1.85, MeOH), lit.[5e] $[\alpha]_D$=-91.3 (*c* 0.58, MeOH)].

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