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# Total Synthesis of (±)-Monomorine I and (±)-Indolizidine 195B by an Aza-[2,3]-Wittig Rearrangement of a Vinylaziridine

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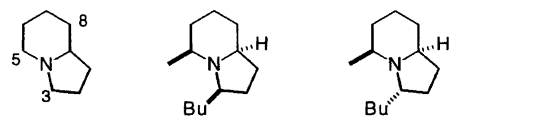
A novel synthesis of (±)-monomorine I (**1**) and (±)-indolizidine 195B (**2**) is described in which the key step is the highly efficient aza-[2,3]-Wittig rearrangement of vinylaziridine **12** into tetrahydropyridine **13**. Functional group manipulation then gave ketone **16** which could be converted into the target alkaloids by reductive amination (**1**:**2** 1.5:1).

Owing to their often potent biological activity and intriguing architectural features the indolizidine alkaloids, sometimes referred to as 'bicyclic gephyrotoxins', have become popular targets in organic synthesis.[1] Within this family of compounds the simplest members have a single substituent at the C5 position while in the more complex congeners the indolizidine nuclei are substituted at C3/C5 or C5/C8 (Fig. 1). We have previously shown that the aza-[2,3]-Wittig rearrangement in appropriately functionalized vinylaziridines[2] allows for a novel and efficient entry to this class of compounds which was exemplified by our enantioselective synthesis of (−)-indolizidines 209D, C5 monosubstituted, and 209B, C5/C8 disubstituted, both of which have been isolated from the skin secretion of neotropical frogs.[3,4] As a continuation of this investigation, and also to probe the potential of the strategy developed, we became interested in the preparation of C3/C5 disubstituted indolizidine alkaloids in which the aza-[2,3]-Wittig rearrangement was a key step. It should be noted that the implementation of such a project would demonstrate that the various types of indolizidine can be prepared by a common strategy. Consequently, as suitable targets we selected (+)-monomorine I (**1**), the trail-following pheromone of the Pharao ant (*Monomorin pharaonis*),[5] and (+)-indolizidine 195B (**2**), which is isolated from a dart-poison frog (*Dendrobates histrionicus*).[6] Both **1** and **2** have been prepared previously in racemic and enantiomerically pure forms,[7] and herein are detailed our results.

## Results and discussion

In our original approach towards alkaloids **1** and **2** it was envisioned that the bicyclic systems should be readily available from the acetal **3** by hydrogenation and concomitant reductive amination followed by functional group manipulations, albeit without any control over the C3 stereogenic center (route A, Scheme 1). Compound **3**, in turn, was recognized as the product of an aza-[2,3]-Wittig rearrangement of vinylaziridine **4**, which itself should be obtainable from epoxide **5** by standard procedures. Towards this end **6** was treated with *meta*-chloroperbenzoic acid (*m*-CPBA) using 2,6-di-*tert*-butylpyridine as a buffer to give epoxide **5** in 99% yield (Scheme 2).[8] Exposure of **5** to sodium azide gave the corresponding vicinal azido alcohols as a regioisomeric mixture which,[9] without separation, was converted into the aziridine **7** by $Ph_3P$ in refluxing toluene.[10,11] Subsequent alkylation of **7**, in order to install the necessary anion-stabilizing group for the projected aza-[2,3]-Wittig rearrangement, turned out to be an ordeal. Thus, subjecting **7** to *tert*-butyl bromoacetate ($K_2CO_3$, 18-crown-6, THF)[12] gave a complicated mixture of products, the $^1H$ NMR spectrum of which clearly indicated that the desired product was indeed present. Attempts




The indolizidine nuclei (+)-Monomorine I (**1**) (+)-Indolizidine 195B (**2**)

*Fig. 1.*

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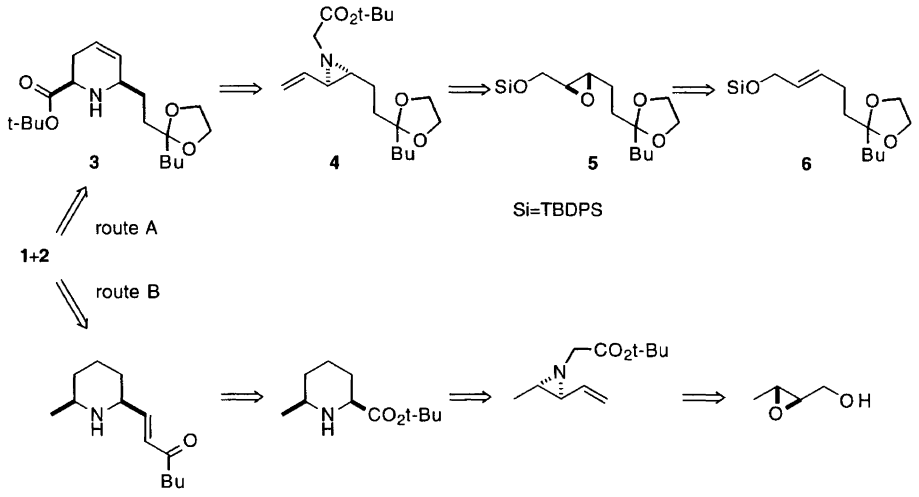
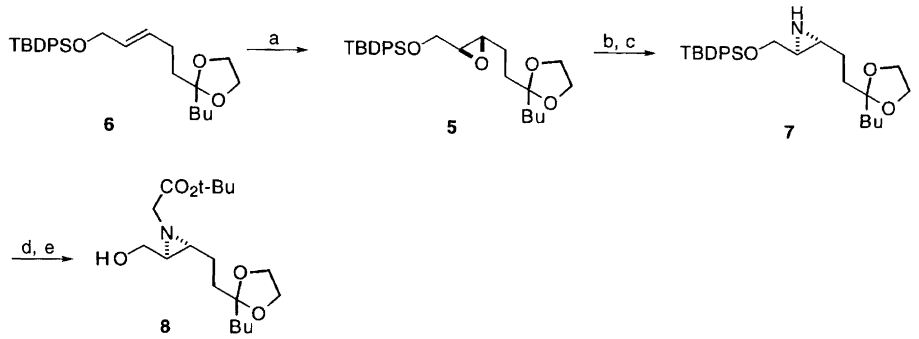


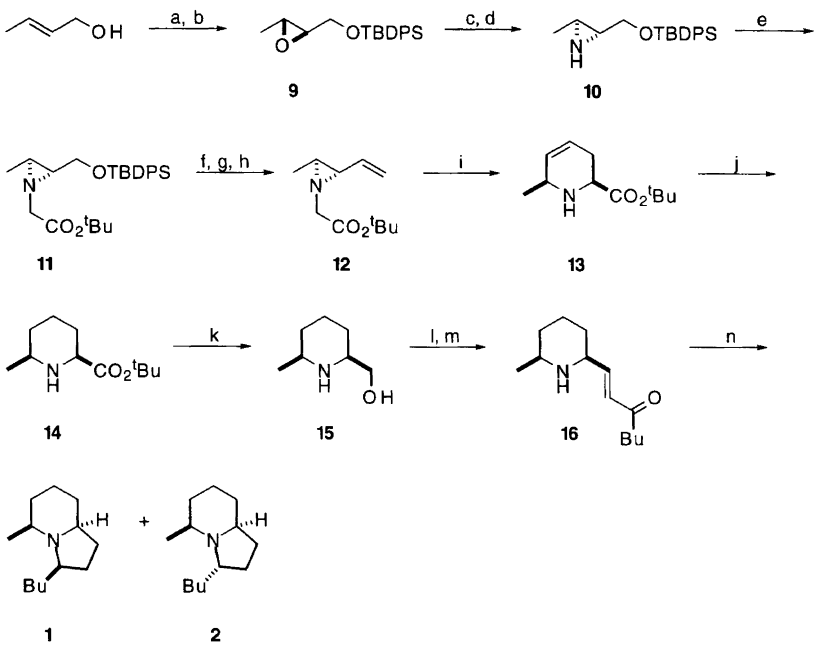

*Scheme 1.*




*Scheme 2.* TBDPS = *t*-BuPh$_2$Si. (a) *m*-CPBA, 2,6-di-*tert*-butylpyridine, $CH_2Cl_2$, 99%; (b) $NaN_3$, $NH_4Cl$, $MeOCH_2CH_2OH$, $H_2O$, reflux, 80%; (c) $Ph_3P$, PhMe, reflux, 82%; (d) *tert*-butyl bromoacetate, $K_2CO_3$, 18-crown-6, THF; (e) $Bu_4NF$, THF, 0 °C → RT, 37% (two steps).

to purify this mixture by flash chromatography on silica gel aggravated the situation and gave none of the desired product. Considering the number of aziridines that have been alkylated by using the above procedure the present result is surprising and can at present only be tentatively ascribed to the incompatibility of the acetal moiety to the reaction conditions. The above difficulties could, to some extent, be circumvented by desilylation of the crude reaction mixture to give the alcohol **8** as a 8:1 mixture of *N*-invertomers in 37% yield for two steps. Although **8** could uneventfully be converted into vinylaziridine **4** which, when treated with lithium diisopropylamide (LDA) (THF, −78 °C), smoothly rearranged to the corresponding *cis*-2,6-disubstituted tetrahydropyridine **3**,[13] the low yield obtained in the alkylation of **7**, which did not improve upon attempted optimization, led us to abandon this approach.

Instead a strategy was designed by which the required functionality for construction of the five-membered ring moiety in alkaloids **1** and **2** would be introduced at a late stage in the synthesis (route B, Scheme 1). Such a plan would then hopefully avoid the previous problems and, furthermore, closely mimics our previous synthesis of (−)-indolizidines 209B and 209D. Thus, protection of crotyl alcohol as its *tert*-butyldiphenylsilyl (TBDPS) ether followed by epoxidation gave **9** (88%, two steps) which was converted into aziridine **10** by using the two-step procedure discussed above (75%, two steps, Scheme 3). Not surprisingly, *N*-alkylation of **10** with *tert*-butyl bromoacetate turned out to be straightforward and gave ester **11** in 76% yield and as a 2:1 mixture of *N*-invertomers, in sharp contrast with the results obtained with aziridine **7** (*vide supra*). Having served its purpose the silyl group was next removed (83%) and the resultant primary alcohol was subjected to a Swern oxidation[14] followed, without isolation, by a Wittig olefination to give the key intermediate vinylaziridine **12** (72%, two steps). Subjecting **12** to LDA (THF, −78 °C) resulted in the rapid formation of the tetrahydropyridine **13** as the only detectable diastereomer in 99% yield, the result of an aza-[2,3]-Wittig rearrangement. At this stage the relative stereochemistry of **13** was only tentatively assigned as shown, which is in analogy with previous results.[2-4] Hydrogenation of **13** using a 5% Pd–C as catalyst turned out to be somewhat capricious affording piperidine **14** in moderate yields, at best. However, using rhodium-on-carbon as the catalyst for this transformation proved beneficial, as has been noted in similar




*Scheme 3.* TBDPS = *t*-$BuPh_2Si$. (a) TBDPSCl, $Et_3N$, DMAP, $CH_2Cl_2$, 94%; (b) *m*-CPBA, $CH_2Cl_2$, 94%; (c) $NaN_3$, $NH_4Cl$, $MeOCH_2CH_2OH$, $H_2O$, reflux, 96%; (d) $Ph_3P$, PhMe, reflux, 79%; (e) *tert*-butyl bromoacetate, $K_2CO_3$, 18-crown-6, $CH_3CN$, 76%; (f) $Bu_4NF$, THF, 0 °C → RT, 83%; (g) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −78 °C; (h) $Ph_3PCH_3Br$, KHMDS, THF, −20 °C 72% (two steps); (i) LDA, THF, −78 °C, 99%; (j) 5% Rh–C, $H_2$, MeOH, 91%; (k) $LiAlH_4$, THF, 93%; (l) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −78 °C; (m) $(MeO)_2P(O)CH_2COBu$, LiCl, i-$Pr_2NEt$, $CH_3CN$, 74% (two steps); (n) 5% Pd–C, $H_2$, MeOH, 73%.

systems, and gave **14** reproducibly in excellent yield (91%).[15] At this stage the relative stereochemistry of **14** was secured, thus confirming the outcome of the above rearrangement, by performing an NOE experiment, which showed a strong interaction (7%) between the α-amino protons in **14**. Subsequent reduction of **14** gave the amino alcohol **15** which was oxidized to the corresponding aldehyde using the Swern method. This aldehyde proved to be labile and was not amenable to prolonged storage and, as a consequence, was directly cannulated into a slurry of dimethyl (2-oxohexyl)phosphonate, LiCl and i-$Pr_2NEt$ in dichloromethane to give the *E*-configured α,β-unsaturated ketone **16** in 74% yield (two steps) with only trace amounts of the corresponding *Z* isomer.[16] Finally, hydrogenation and concomitant intramolecular reductive amination of **16** gave a separable 1.5:1 mixture of (±)-monomorine I (**1**) and (±)-indolizidine 195B (**2**), their spectral data being in excellent accord with literature data.[7] Although the present route does not allow for any control when introducing the stereogenic center at C3, similar ratios between **1** and **2** have been obtained previously when forming the bicyclic system by reductive amination.[7]

In conclusion, we have shown that C3/C5 disubstituted indolizidine alkaloids can be prepared using an aza-[2,3]-Wittig rearrangement as a key step. The present investigation also demonstrates that the three most common structural types of indolizidine alkaloid can be prepared by a common strategy. It should also be noted that although our first approach turned out to be unsuccessful, it nevertheless provides valuable information about the scope of our present preparation of vinylaziridines, a point that clearly needs to be improved.

## Experimental

$^1H$ and $^{13}C$ NMR spectra were obtained on a Varian XL-300 or a Bruker DRX 400 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. 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; acetonitrile was dried over 4 Å molecular sieves. All reactions were run in septum-capped, oven-dried flasks under an 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.[17]

*Aziridine* **7**. Epoxide **5**[13] (993 mg, 2.12 mmol) was dissolved in 2-methoxyethanol–$H_2O$ (8:1, 22.5 ml) and sodium azide (689 mg, 10.6 mmol) followed by ammonium chloride (227 mg, 4.24 mmol) was added. The reaction mixture was refluxed overnight and was then allowed to reach room temperature (RT). The reaction mixture was diluted with $Et_2O$, and the organic phase was separated, washed with water and brine, dried ($MgSO_4$) and concentrated. Flash chromatography

(heptane–ethyl acetate 6:1→3:1) of the residue gave the corresponding azido alcohols (881 mg, 80%) as a mixture of regioisomers. IR (film): 3400, 2950, 2100 $cm^{-1}$.

To a solution of the above azido alcohols (637 mg, 1.24 mmol) in toluene (10 ml) was added $PPh_3$ (391 mg, 1.49 mmol). The resultant mixture was refluxed overnight. The reaction mixture was cooled to RT and concentrated. Flash chromatography (heptane–ethyl acetate 1:1→2:1) of the residue gave the aziridine **7** (637 mg, 82%). $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 5 H), 7.35 (m, 5 H), 3.92 (s, 4 H), 3.75 (m, 2 H), 1.90–1.81 (m, 1 H), 1.80–1.40 (m, 6 H), 1.35–1.20 (m, 6 H), 1.05 (s, 9 H), 0.87 (t, 3 H, $J$=6.8 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 135.5, 133.3, 129.8, 127.7, 111.4, 64.9, 38.1, 37.0, 34.7, 27.7, 26.8, 26.0, 23.0, 19.2, 14.1. IR (film): 3220, 2920 $cm^{-1}$.

*Alcohol* **8**. The aziridine **7** (188 mg, 0.4 mmol) was dissolved in THF (5 ml) and *tert*-butyl bromoacetate (85 µl, 0.52 mmol) followed by $K_2CO_3$ (83 mg, 0.60 mmol) and 18-crown-6 (catalytic amount) was added. The resultant slurry was stirred at ambient temperature for 68 h. The reaction mixture was then poured into $Et_2O$ and water (1:1), the organic phase was separated and washed with brine and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the crude aziridine ester which was used in the next step without further purification.

To a solution of the above aziridine ester in THF (5 ml) at 0 °C was added tetrabutylammonium fluoride trihydrate (227 mg, 0.72 mmol). The reaction mixture was allowed to reach RT and stirred for an additional 45 min and then poured into $Et_2O$ and water. The organic phase was separated and washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (heptane–ethyl acetate 1:4 → 10% MeOH–ethyl acetate) gave **8** (61.4 mg, 37%, two steps) as an 8:1 mixture of N-invertomers. $^1H$ NMR (300 MHz, $CDCl_3$, major isomer): δ 3.88 (s, 4 H), 3.83 (m, 2 H), 3.56 (d, 2 H, $J$=16.8 Hz), 3.19 (m, 1 H), 2.88 (d, 1 H, $J$=17.4 Hz), 1.95 (m, 1 H), 1.80–1.50 (m, 4 H), 1.45 (s, 9 H), 1.31–1.19 (m, 6 H), 0.87 (t, 3 H, $J$=7.0 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3$, major isomer): δ 171.6, 111.2, 83.0, 65.2, 64.9, 64.7, 40.7, 36.9, 35.4, 28.3, 28.1, 27.9, 26.0, 22.9, 14.0. IR (film): 3440, 2950, 2880, 2250, 1750 $cm^{-1}$.

*Epoxide* **9**. To a solution of crotyl alcohol (2.3 ml, 27.1 mmol) in $CH_2Cl_2$ (80 ml) at 0 °C was added *tert*-butyldiphenylsilyl chloride (7.8 ml, 29.9 mmol), triethylamine (5.7 ml, 40.7 mmol) and *N*,*N*-dimethyl-4-aminopyridine (332 mg, 2.7 mmol) and the resultant mixture was stirred for 24 h at ambient temperature. The reaction mixture was poured into water (80 ml) and the organic layer was washed once with aq. $NH_4Cl$ (sat., 80 ml), dried ($MgSO_4$) and concentrated. Flash chromatography (heptane–EtOAc 1:0→15:1) of the residue gave the corresponding silyl ether (7.95 g, 94%) as a colorless oil. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.77–7.71 (m, 4 H), 7.47–7.38 (m, 6 H), 5.75–5.65 (m, 1 H), 5.63–5.56 (m, 1 H), 4.19–4.15 (m, 2 H), 1.72 (dd, 3 H, $J$=6.3, 1.4 Hz), 1.08 (s, 9 H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 136.0, 134.3, 130.4, 130.0, 128.0, 126.4, 65.1, 27.3, 19.7, 18.2. IR (neat): 2920, 2840, 1420, 1040, 1105 $cm^{-1}$.

To a solution of the above silyl ether (7.95 g, 25.6 mmol) in $CH_2Cl_2$ (100 ml) at 0 °C was added 2-chloroperbenzoic acid (9.47 g, 38.4 mmol, 70%) in small portions. The resultant mixture was stirred overnight at ambient temperature and was then poured into water (60 ml). The organic layer was washed with 10% aq. $Na_2SO_3$ (60 ml), water (2 × 60 ml), 10% aq. $NaHCO_3$ (60 ml) and brine (30 ml). Drying ($MgSO_4$), concentration and flash chromatography (heptane–EtOAc 1:0→15:1) gave the epoxide **9** (7.82 g, 94%) as white crystals (m.p. 32–34 °C). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.72–7.68 (m, 4 H), 7.47–7.38 (m, 6 H), 3.83–3.73 (m, 2 H), 2.90–2.85 (m, 2 H), 1.31 (d, 3 H, $J$=4.9 Hz), 1.07 (s, 9 H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 136.1, 136.0, 133.8, 130.2, 128.2, 128.1, 64.5, 59.9, 52.7, 27.2, 19.7, 17.8. IR (neat): 3060, 2940, 2860, 1465, 1425, 1390, 1110 $cm^{-1}$.

*Aziridine* **10**. Epoxide **9** (6.99 g, 21.4 mmol) was dissolved in 2-methoxy ethanol–water (8:1, 180 ml) and sodium azide (6.96 g, 107 mmol) and ammonium chloride (2.29 g, 42.8 mmol) were added sequentially. The resultant mixture was refluxed overnight and then cooled to RT. The reaction mixture was diluted with $Et_2O$ (500 ml) and the combined organic phases were washed with water (3 × 250 ml) and brine (250 ml). Drying ($MgSO_4$), concentration and flash chromatography (heptane–EtOAc 1:0→15:1) gave a mixture of the corresponding azido alcohols (7.51 g, 96%) as a colorless oil (maj:min 6.2:1). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.76–7.66 (m, 4 $H_{maj}$, 4 $H_{min}$), 7.50–7.40 (m, 6 $H_{maj}$, 6 $H_{min}$), 3.85 (d, 2 $H_{min}$, $J$=5.5 Hz), 3.77–3.74 (m, 2 $H_{maj}$), 3.72–3.50 (m, 2 $H_{min}$), 3.64–3.55 (m, 2 $H_{maj}$), 2.58 (d, 1 $H_{maj}$, $J$=4.6 Hz), 2.08 (d, 1 $H_{min}$, $J$=5.7 Hz), 1.31 (d, 3 $H_{maj}$, $J$=6.3 Hz), 1.18 (d, 3 $H_{min}$, $J$=6.4 Hz), 1.10 (s, 9 $H_{maj}$, 9 $H_{min}$). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 136.4, 136.1, 136.0, 135.9, 135.2, 133.2, 133.1, 130.5, 130.4, 128.3, 128.2, 128.1, 74.6, 68.6, 64.8, 64.7, 60.1, 58.7, 27.4, 27.3, 27.2, 19.7, 19.6, 19.5, 15.8, 15.3. IR (neat): 3420, 2920, 2090, 1455, 1250 $cm^{-1}$.

To a solution of the above mixture of azido alcohols (475 mg, 1.28 mmol) in toluene (20 ml) was added triphenylphosphine (404 mg, 1.54 mmol) and the resultant mixture was refluxed overnight. The reaction mixture was cooled to room temperature, concentrated and the residue flash chromatographed (heptane–EtOAc 1:0→15:1) to give the aziridine **10** (331 mg, 79%) as a colorless oil. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.69–7.64 (m, 4 H), 7.47–7.38 (m, 6 H), 3.78 (d, 2 H, $J$=3.4 Hz), 1.91 (br s, 1 H), 1.83 (br s, 1 H), 1.18 (d, 3 H, $J$=5.5 Hz), 1.07 (s, 9 H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ

136.0, 133.8, 130.2, 128.2, 68.4, 39.4, 27.3, 19.7, 19.0, 18.9. IR (neat): 2930, 2850, 1425, 1385, 1105 $cm^{-1}$.

*Aziridine* **11**. To a solution of aziridine **10** (2.54 g, 7.80 mmol) in acetonitrile (150 ml) was added 18-crown-6 (catalytic amount), $K_2CO_3$ (1.19 g, 8.58 mmol) and *tert*-butyl bromoacetate (1.39 ml, 8.58 mmol). The resultant slurry was stirred at ambient temperature for 9 h and then diluted with $Et_2O$ (300 ml). The combined organic phases were washed with water (150 ml) and brine (150 ml), dried ($MgSO_4$) and concentrated. Flash chromatography (heptane–EtOAc 4:1) of the residue gave the aziridine ester **11** (2.59 g, 76%) as a colorless oil. $^1H$ NMR ($CDCl_3$, 400 MHz, peaks assigned from a mixture of invertomers): δ 7.70–7.65 (m, 4 $H_{maj}$, 4 $H_{min}$), 7.46–7.36 (m, 6 $H_{maj}$, 6 $H_{min}$), 4.01–3.95 (m, 1 $H_{maj}$, 1 $H_{min}$), 3.84–3.78 (dd, 1 $H_{min}$, $J$=12.1, 7.1 Hz), 3.60 (d, 1 $H_{min}$, $J$=16.5 Hz), 3.44 (dd, 1 $H_{maj}$, $J$=11.0, 6.8 Hz), 3.17 (AB system, 2 $H_{maj}$, $J$=18.0, 16.6 Hz), 3.10 (d, 1 $H_{min}$, $J$=16.5 Hz), 2.05–2.01 (m, 1 $H_{min}$), 1.89–1.84 (m, 1 $H_{maj}$), 1.70–1.64 (m, 1 $H_{maj}$), 1.64–1.59 (m, 1 $H_{min}$), 1.50 (s, 9 $H_{min}$), 1.46 (s, 9 $H_{maj}$), 1.23 (d, 1 $H_{min}$, $J$= 5.5 Hz), 1.18 (d, 1 $H_{maj}$, $J$=6.1 Hz), 1.06 (s, 9 $H_{maj}$, 9 $H_{min}$). $^{13}C$ NMR ($CDCl_3$, 100 MHz, from a mixture of invertomers): δ 170.7, 136.0, 135.9, 134.3, 133.7, 130.2, 130.2, 130.0, 128.2, 128.1, 128.0, 81.3, 66.4, 60.9, 54.7, 54.1, 47.6, 44.3, 33.7, 37.1, 28.6, 28.5, 27.3, 27.2, 19.7, 19.6, 18.4, 11.4. IR (neat): 2930, 1735, 1420, 1360, 1150, 1100 $cm^{-1}$.

*Vinylaziridine* **12**. To a solution of aziridine ester **11** (139 mg, 0.32 mmol) in THF (10 ml) at 0 °C was added tetrabutylammonium fluoride trihydrate (150 mg, 0.47 mmol). The resultant mixture was stirred for 60 min at 0 °C and then concentrated (water bath at 0 °C). Flash chromatography (heptane–EtOAc 1:10→0:1) of the residue yielded the corresponding alcohol (53 mg, 83%) as a colorless oil. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 3.95 (dd, 1 H, $J$=11.1, 2.4 Hz), 3.65 (br s, 1 H), 3.51 (d, 1 H, $J$=17.0 Hz), 3.21 (dd, 1 H, $J$=11.1, 8.4 Hz), 2.88 (d, 1 H, $J$=17.1 Hz), 2.11–2.06 (m, 1 H), 1.57–1.52 (m, 1 H), 1.47 (s, 9 H), 1.26 (d, 3 H, $J$=6.1 Hz). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 172.1, 82.4, 65.0, 53.3, 48.9, 35.6, 28.5, 11.6. IR (neat): 3340, 2960, 1725, 1430, 1360, 1230, 1150 $cm^{-1}$.

To a solution of dimethyl sulfoxide (0.52 ml, 7.31 mmol) in $CH_2Cl_2$ (50 ml) at −78 °C was added oxalyl chloride (0.42 ml, 4.88 mmol). After 10 min the above alcohol (491 mg, 2.44 mmol) in $CH_2Cl_2$ (50 ml) was added dropwise over 10 min. The resultant mixture was stirred for 60 min at −78 °C and then $Et_3N$ (1.40 ml, 9.75 mmol) was added. Stirring was continued at −78 °C for 30 min followed by warming to room temperature over 1 h. The reaction mixture was diluted with $Et_2O$ (250 ml) and the combined organic phases were washed with brine–water (1:1, 3 × 75 ml). Drying ($MgSO_4$) and removal of the solvents (water bath at 0 °C) gave the crude aldehyde which was immediately used in the next step.

To a slurry of methyltriphenylphosphonium bromide (2.79 g, 7.80 mmol) in THF (40 ml) at −20 °C was added KHMDS (3.85 ml, 7.31 mmol, 1.90 M in THF) and stirring was continued for 60 min at room temperature. After recooling to −20 °C the above crude aldehyde in THF (50 ml) was added dropwise over 10 min. The resultant slurry was slowly warmed to room temperature (60 min) and then poured into brine (300 ml). The organic layer was separated and the aqueous phase extracted with $Et_2O$ (4 × 75 ml). The combined organic phases were dried ($MgSO_4$), concentrated (water bath at 0 °C) and the residue was flash chromatographed (pentane–$Et_2O$ 3:2) to yield the vinylaziridine **12** (345 mg, 72% from the alcohol) as a mixture of invertomers (maj:min 2:1). $^1H$ NMR ($CDCl_3$, 400 MHz, peaks assigned from a mixture of invertomers): δ 5.71–5.57 (m, 1 $H_{maj}$, 1 $H_{min}$), 5.41–5.26 (m, 2 $H_{maj}$, 1 $H_{min}$), 5.10 (d, 1 $H_{min}$, $J$=10.5 Hz), 3.29–3.18 (m, 1 $H_{maj}$, 2 $H_{min}$), 3.12 (d, 1 $H_{maj}$, $J$=16.5 Hz), 2.37 (dd, 1 $H_{maj}$, $J$=8.6, 3.3 Hz), 2.16–2.11 (m, 1 $H_{min}$), 1.76 (dd, 1 $H_{min}$, $J$=7.6, 3.2 Hz), 1.71–1.65 (m, 1 $H_{maj}$), 1.47 (s, 9 $H_{maj}$, 9 $H_{min}$), 1.30–1.25 (m, 3 $H_{maj}$, 3 $H_{min}$). $^{13}C$ NMR ($CDCl_3$, 100 MHz, from a mixture of invertomers): δ 170.5, 138.7, 133.1, 121.1, 116.4, 81.4, 55.5, 54.2, 48.7, 45.8, 42.9, 39.7, 32.4, 28.5, 23.1, 18.5, 14.6, 11.4. IR (neat): 2940, 1740, 1365 $cm^{-1}$.

*Tetrahydropyridine* **13**. To a solution of i-$Pr_2NH$ (53 µl, 0.37 mmol) in THF (5 ml) at −78 °C was added BuLi (268 µl, 0.34 mmol, 1.27 M in hexanes). The mixture was stirred at 0 °C for 60 min and then cooled to −78 °C. To this mixture was added the vinylaziridine **12** (33 mg, 0.17 mmol) in THF (5 ml) over 10 min to give a bright yellow solution. The reaction was stirred for an additional 10 min at −78 °C after which it 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 the crude tetrahydropyridine **13** (33 mg, 99%). This material was pure according to $^1H$ NMR analysis and was, owing to its sensitivity, used directly in the next step. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 5.76–5.71 (m, 1 H), 5.60–5.56 (m, 1 H), 3.56–3.51 (m, 1 H), 3.50 (ddd, 1 H, $J$=10.7, 4.5, 0.4 Hz), 2.32–2.24 (m, 1 H), 2.19–2.11 (m, 1 H), 1.84 (br s, 1 H), 1.48 (s, 9 H), 1.18 (d, 3 H, $J$=6.8 Hz).

*Pipecolinic ester* **14**. To a solution of the crude tetrahydropyridine **13** (107 mg, 0.543 mmol) in MeOH (5 ml) was added 5% Rh–C (catalytic amount) and the resultant slurry was hydrogenated at 50 psi for 13 h. The slurry was filtered through a pad of Celite, concentrated and flash chromatographed (heptane–EtOAc 3:1→1:2) to give the ester **14** (98 mg, 91%). $^1H$ NMR ($CDCl_3$, 300 MHz): δ 3.24 (dd, 1 H, $J$=11.3, 2.8 Hz), 2.61 (m, 1 H), 1.99 (m, 1 H), 1.82 (m, 1 H), 1.57 (m, 1 H), 1.42 (s, 9 H), 1.41–1.22 (m, 2 H), 1.11 (d, 3 H, $J$=6.3 Hz),

1.00 (m, 1 H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 172.5, 80.9, 59.6, 51.7, 33.7, 28.9, 28.0, 24.5, 22.6. IR (film): 3290, 2920, 1720 $cm^{-1}$.

*Amino alcohol* **15**. To a solution of the ester **14** (78 mg, 0.392 mmol) in THF (10 ml) at 0 °C was added $LiAlH_4$ (60 mg, 1.57 mmol). The slurry was stirred for 30 min at 0 °C to room temperature after which $H_2O$ (21 µl), 15% NaOH (21 µl) and $H_2O$ (41 µl) were added in sequence. 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, 9:1→1:1) of the residue gave **15** (47 mg, 93%) as white crystals (m.p. 64–66 °C). $^1$H NMR ($CDCl_3$, 300 MHz): δ 3.64 (dd, 1 H, $J$=11.0, 3.7 Hz), 3.45 (dd, 1 H, $J$=11.0, 7.9 Hz), 2.82–2.64 (m, 2 H), 1.81 (m, 1 H), 1.67 (m, 1 H), 1.55 (m, 1 H), 1.37 (m, 1 H), 1.21–1–05 (m, 2 H), 1.11(d, 3 H, $J$=6.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 65.8, 58.2, 52.2, 33.6, 27.4, 24.0, 22.2. IR (film): 3200, 2930 $cm^{-1}$.

*Ketone* **16**. To a solution of oxalyl chloride (61 µl, 0.698 mmol) in $CH_2Cl_2$ (10 ml) at −78 °C was added dimethyl sulfoxide (83 µl, 1.162 mmol). The reaction was stirred for 10 min after which **15** (30 mg, 0.232 mmol) in $CH_2Cl_2$ (5 ml) was added dropwise over 5 min. The resultant mixture was stirred for 20 min at −78 °C and then $Et_3N$ (0.227 ml, 1.628 mmol) 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 $Et_2O$ (10 ml) and water (5 ml) and the organic layer was separated, washed once with water and once with brine. Drying ($MgSO_4$) and removal of the solvents gave the crude aldehyde, which was used immediately in the next step.

To a solution of dimethyl (2-oxohexyl)phosphonate[18] (72 mg, 0.348 mmol) in $CH_3CN$ (10 ml) was added LiCl (15 mg, 0.348 mmol) and i-$Pr_2$NEt (52 µl, 0.302 ml) followed by the above crude aldehyde in $CH_3CN$ (1 ml). The resultant slurry was stirred at RT for 12 h and then poured into $Et_2O$ and water. The organic phase was separated and the aqueous phase extracted twice with $Et_2O$. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (heptane–EtOAc 5:1→1:1) of the residue gave **16** (36 mg, 74%, two steps). $^1$H NMR ($CDCl_3$, 300 MHz): δ 6.81 (dd, 1 H, $J$=16.1, 5.1 Hz), 6.12 (dd, 1 H, $J$=16.1, 1.9 Hz), 3.19 (m, 1 H), 2.54 (m, 1 H), 2.49 (t, 2 H, $J$=7.4 Hz), 1.91 (m, 1 H), 1.79–1.47 (m, 7 H), 1.38–1.24 (m, 2 H), 1.15 (d, 3 H, $J$=7.1 Hz), 0.89 (t, 3 H, $J$=7.3 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 200.5, 147.0, 129.5, 57.8, 56.5, 40.3, 29.9, 27.9, 26.2, 22.4, 20.5, 14.4, 13.9. IR (film) 3305, 1665 $cm^{-1}$.

*(±)-Monomorine I* (**1**) *and (±)-indolizidine 195B* (**2**). To a solution of **16** (56 mg, 0.268 mmol) in MeOH (5 ml) was added 10% Pd–C, and the resultant slurry was stirred for 48 h under an atmospheric pressure of $H_2$. The slurry was then filtered through a pad of Celite, and concentrated to give a 1.5:1 mixture of **1** and **2**, as judged from $^1$H NMR analysis. The isomers were separated by preparative TLC on basic aluminium oxide ($CHCl_3$–heptane 8:1) which gave pure **1** (24 mg, 46%) and **2** (14 mg, 27%). Monomorine I (**1**): $^1$H NMR ($CDCl_3$, 400 MHz): δ 2.47 (m, 1 H), 2.20 (m, 1 H, 2.10 (m, 1 H), 1.92–1.15 (m, 16 H), 1.11 (d, 3 H, $J$=6.4 Hz), 0.90 (t, 3 H, $J$=7.1 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 67.1, 62.9, 60.2, 39.7, 35.8, 30.9, 30.3, 29.8, 29.4, 24.9, 22.9, 22.8, 14.2. Indolizidine 195B (**2**): $^1$H NMR ($CDCl_3$, 400 MHz): δ 3.29 (m, 1 H), 2.53 (m, 1 H), 2.40 (m, 1 H), 1.97–1.17 (m, 16 H), 1.11 (d, 3 H, $J$=6.1 Hz), 0.91 (t, 3 H, $J$=7.0 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 59.0, 58.7, 52.0, 34.6, 32.4, 30.0, 29.2, 26.4, 24.9, 24.6, 23.1, 20.0, 14.2.

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