Flexible syntheses of 5,8-disubstituted indolizidine poisonous-frog alkaloids *via* a Michael-type conjugate addition

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The efficient and flexible syntheses of 5,8-disubstituted indolizidine poisonous-frog alkaloids is described using a highly stereoselective Michael-type conjugate addition reaction as the key step. In this work, syntheses of the 5,8-disubstituted indolizidine poisonous-frog alkaloids **(−)-231C**, **(−)-221I** and the proposed structure for **(−)-193E** are reported.

Keywords: efficient and flexible synthesis, 5,8-disubstituted indolizidine, poisonous-frog alkaloids, Michael-type conjugate addition

Various biologically active alkaloids have been found in amphibian skin. These include over 20 structural classes and more than 800 alkaloids.[1,2] A great number of these alkaloids show interesting biological activities, such as pharmacological effects at neuronal nicotinic acetylcholine receptors.[3,4] A great need for the development of efficient synthetic routes to these poisonous-frog alkaloids has arisen in order to determine the structures of these natural products and investigate their biological activities. However, these alkaloids have been isolated in only micro amounts from the skin of poisonous frogs. Consequently, we report here synthetic efforts directed at these alkaloids.

5,8-Disubstituted indolizidines constitute the largest subclass of these alkaloids, and over 80 alkaloids have been detected to date.[1,2] In our previous work, we found that **(−)-235B'**, one of this class of alkaloids, acts as a selective and noncompetitive antagonist for α4β2 nicotinic acetylcholine receptors.[5] These interesting results suggest that the alkaloid **(−)-235B'** is a promising lead compound for drugs designed to treat cholinergic disorders such as autosomal dominant nocturnal frontal lobe epilepsy. In this study, we synthesised the 5,8-disubstituted indolizidines **(−)-231C**, **(−)-221I** and the proposed structure **(−)-193E**.[6,7]

This synthetic strategy began with the enantiomerically pure piperidone **1**,[8] which was converted to the Cbz-urethane **2**. Treatment of **2** with LiHMDS followed by addition of 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent)[9] to the resulting lithium enolate gave the enol triflate **3**, which was subjected to a palladium-catalysed carbonylation to provide the enaminoester **4**. The key Michael-type conjugate addition reaction[10] at the 3-position of **4** proceeded smoothly to obtain the desired trisubstituted piperidine **5** in a highly stereoselective manner. Reduction of the ester moiety with lithium triethylborohydride (Super-Hydride®) afforded the corresponding alcohol **6**, which was converted to α,β-unsaturated ester **7** using a Swern oxidation followed by a Horner-Emmons reaction of the resulting aldehyde. Hydrogenation of **7** over palladium hydroxide followed by treatment of amino ester with trimethylaluminum under Weinreb's reaction conditions[11] provided the key lactam **8**. Removal of the silyl group with TBAF yielded the corresponding alcohol **9**, which was subjected to a Swern oxidation followed by a Wittig reaction to provide the olefin **10**. Hydrogenation and cleavage of the silylether with TBAF afforded the corresponding alcohol **11**, which was treated with Swern oxidation and a Wittig reaction to give the (*Z*)-iodoolefin **12** under Stork's reaction conditions.[12] A Sonogashira coupling reaction[13] of **12** with TMS-acetylene followed by removal of the trimethylsilyl group with K_2CO_3 obtained the desired **(−)-231C**. In the FTIR spectra, there was a strong, sharp Bohlmann band[14] at about 2787 cm^{-1}, which established the 5,9-*Z* configuration and is same as the natural **(−)-231C** obtained from extracts of the dendrobatid frog. The relative stereochemistry was determined to be 5,8-*E* and 5,9-*Z* configurations based on the GC-FTIR and GC-MS data[1] (Scheme 1).

The stereoselectivity of the key Michael-type conjugate addition reaction was rationalised as follows. The conformation of **4** will be restricted to **A** due to $\mathbf{A}^{(1,3)}$ strain[15] between the side chain on the α-position and the *N*-Cbz group. The anion attacks from the α-axial face owing to stereoelectronic effects,[16] bringing about the protonation of the enolate to obtain trisubstituted piperidine as a single isomer. This remarkable stereoselectivity can be also explained by Cieplak's hypothesis.[17] In the preferred conformation A, the developing σ* of the transition state is stabilised by the antiperiplanar donor σ_{C-H} of the C4 position (Fig. 1).

The reaction conditions for the synthesis of the trisubstituted piperidine **5** were studied and the results are given in Table 1. THF was used as the solvent for the reaction in the initial experiment, either at −78 °C for 2 h or at −78 °C to room temperature over 0.8 h. The yields were 71% and 75%, respectively (Table 1, entries 1 and 4). After several experiments, it was determined that ether was the best solvent for these conjugate addition reactions, and at −78 °C to −10 °C over 1 h gave the desired compound **5** quantitatively (Table 1, entry 5).

In a similar manner, the Michael-type conjugate addition reaction of **4** with lithium divinylcuprate gave the trisubstituted piperidine **13**. The carbon-chain extension at the 2-position of **13** was performed *via* the alcohol **14**, which was converted to the α,β-

Table 1 Optimisation of the reaction conditions for the synthesis of the trisubstituted piperidine **5** from compound **4**

Entry	Me_2CuLi/equiv.	Solvent	Temperature/°C	Time/h	Yield/%
1	2	THF	−78	2.0	71
2	2	Et_2O	−78	2.0	70
3	5	Et_2O	−78 to r.t.	0.8	93
4	5	THF	−78 to r.t.	0.8	75
5	5	Et_2O	−78 to −10	1.0	99
6	5	Et_2O	−78 to −30	1.5	91

All the reactions were performed with 100 mg of the substrate **4**, and the reactions were stopped when the substrate disappeared.

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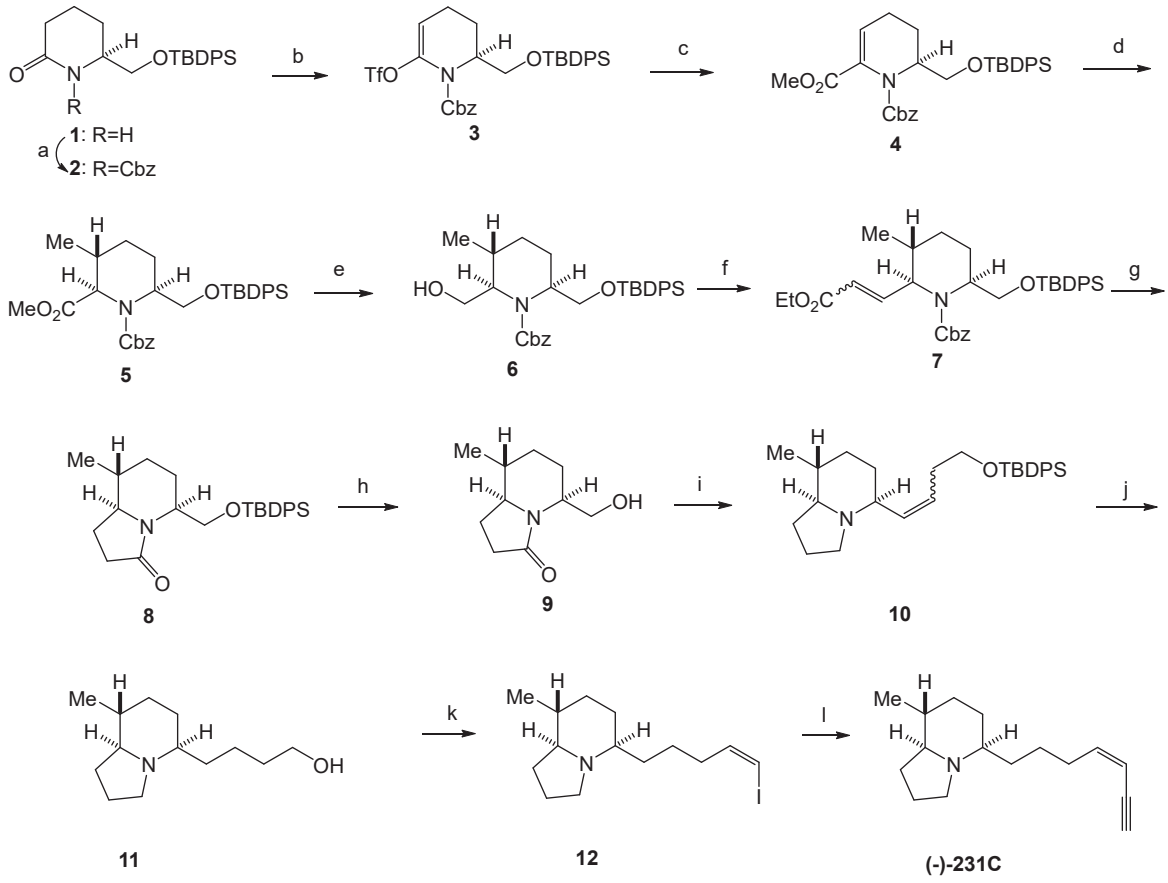


Reagents and conditions: (a) *n*-BuLi, CbzCl, THF, (86%); (b) LiHMDS, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloro-pyridine (Comins' reagent), THF, −78 to −50 °C (91%); (c) $Pd(PPh_3)_4$, Et_3N, MeOH, DMF, CO balloon, 75 °C (78%); (d) Me_2CuLi, Et_2O, −78 to −10 °C (99%); (e) Super-Hydride®, THF, 0 °C (92%); (f) (1) Swern oxidation, (2) NaH, $(EtO)_2P(O)CH_2CO_2Et$, 0 °C to r.t. (97%); (g) 20% $Pd(OH)_2/C$, MeOH, 4 atm then Me_3Al, CH_2Cl_2, reflux (71%); (h) TBAF, THF, r.t. (99%); (i) (1) $LiAlH_4$, THF, reflux; (2) Swern oxidation; (3) $TBDPSO(CH_2)_3P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C to r.t. (83%); (j) (1) 10% Pd/C, H_2, EtOAc, 1 atm; (2) TBAF, THF, r.t. (79%); (k) (1) Swern oxidation; (2) $ICH_2P^+Ph_3I^-$, NaHMDS, HMPA, THF, −78 °C to r.t. (61%); (l) (1) CuI, TMS-acetylene, $Pd(Ph_3P)_4$, *i*-Pr_2NH, THF, r.t. (90%); (2) K_2CO_3, MeOH, r.t. (89%).

Scheme 1 Synthesis of **(–)-231C**.

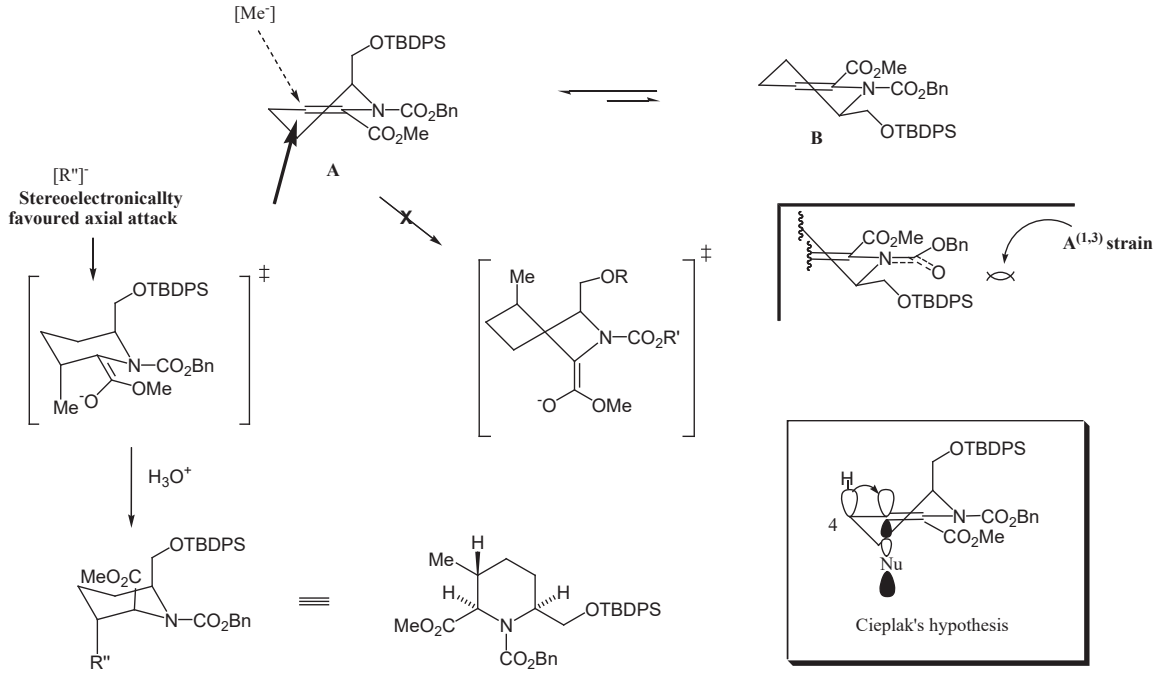


Fig. 1 Stereoselectivity of the key Michael-type conjugate addition reaction.

unsaturated ester **15** using Swern oxidation followed by a Horner-Emmons reaction of the corresponding aldehyde. Hydrogenation of **15** followed by treatment of the resulting amino ester under Weinreb's reaction conditions[11] yielded the key intermediate **16**. Cleavage of the silyl group provided compound **17**, which was subjected to a two-step oxidation followed by Arndt-Eistert reaction[15] of the resulting carboxylic acid to give the homologated ester **18**. The ester moiety of **18** was reduced with LAH. Swern oxidation and Wittig olefination afforded the desired alkaloid **(–)-221I**. The relative stereochemistry of natural **(–)-221I** was shown to be the same as that of synthetic **(–)-221I** by GC-MS and GC-FTIR. In addition, the ester **18** was transformed to the proposed structure for **(–)-193E** in a similar three-step sequence to that used in the synthesis of alkaloid **(–)-221I**. However, comparison of the synthetic material with natural **(–)-193E** on GC analysis showed that the synthetic material had a slightly longer GC retention time than the natural product. The GC-mass spectra of the synthetic compound and natural material were almost identical and the GC-FTIR spectra were very similar in the Bohlmann band region (indicating 5,9-*Z* configurations).[14] Consequently, it is most likely that the natural alkaloid **193E** is the 8-epimer of the synthetic product.[4] The synthesis of the 8-epimer of **193E** would confirm this interesting result (Scheme 2).

Conclusion

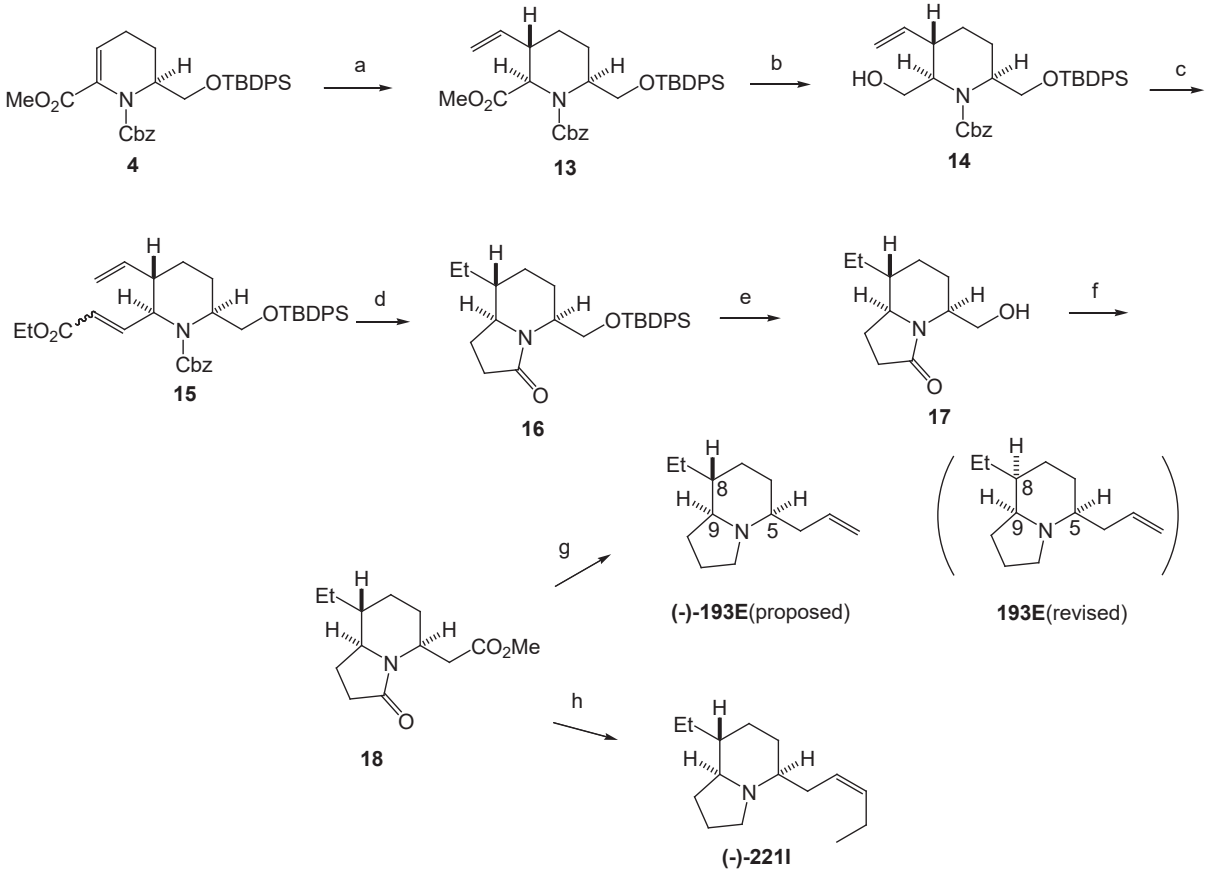
We have achieved the total synthesis of (–)-**231C**, (–)-**221I** and an epimer of **193E** starting from common chiral lactams. The relative stereochemistry of (–)-**231C** and (–)-**221I** was also determined. The present asymmetric synthesis of the proposed structure for **193E** revealed that the C8 configuration of natural **193E** should be revised.

Experimental

All chemical reagents were obtained from commercial suppliers (Aldrich, Kanto Chemical, Tokyo Chemical Industry, Aladdin, Wako Pure Chemical Industries) and used without further purification. Anhydrous solvents were obtained by commercial protocols. All non-aqueous reactions were carried out under an Ar atmosphere. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} glass plates pre-coated with 0.25-mm-thick silica gel (Merck). Column chromatography was carried out on Cica silica gel 60N (spherical, neutral, 40–50 μm or 63–210 μm). ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian UNITY plus 300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) instrument, with $CDCl_3$, CD_3OD or DMSO-d_6 as an internal reference. IR spectra were measured on a JNM FT/IR-460Plus spectrometer. Mass spectra were recorded on a JEOL D-200, JEOL JMS-GCmate II, Shimadzu GC-MS-QP 500 or JEOL AX 505 spectrometer. Melting points were taken with a Yanagimoto micro-melting point apparatus and are uncorrected.

Phenylmethyl 2-(tert-butyldiphenylsilyloxymethyl)-6-oxopiperidine-1-carboxylate (**2**)

A stirred solution of **1** (5.2 g, 14.2 mmol) in THF (30 mL) was treated with a solution of *n*-BuLi (1.6 M in hexane, 9.74 mL, 15.6 mmol) at –78 °C, and the resulting mixture was stirred at –78 °C for 30 min.



Reagents and conditions: (a) $(vinyl)_2CuLi$, Et_2O, −78 to −10 °C (99%); (b) Super-Hydride®, THF, 0 °C (92%); (c) (1) Swern oxidation; (2) NaH, $(EtO)_2P(O)CH_2CO_2Et$, 0 °C to r.t. (97%); (d) 20% $Pd(OH)_2$/C, MeOH, 4 atm then Me_3Al, CH_2Cl_2, reflux (68%); (e) TBAF, THF, r.t. (91%); (f) (1) Swern oxidation; (2) $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O, 0 °C to r.t.; (3) $ClCO_2Et$, Et_3N, THF, 0 °C; (4) CH_2N_2, Et_2O, r.t.; (5) $PhCO_2Ag$, Et_3N, MeOH, r.t. (81%); (g) (1) $LiAlH_4$, THF reflux; (2) Swern oxidation; (3) $MeP^+Ph_3I^-$, *n*-BuLi, THF, 0 °C to r.t. (63%); (h) (1) $LiAlH_4$, THF reflux; (2) Swern oxidation; (3) *n*-$Pr_3P^+Ph_3I^-$, NaHMDS, THF, −78 °C to r.t. (62%).

Scheme 2 Syntheses of **(–)-221C** and the proposed structure of **(–)-193E**.

$ClCO_2Bn$ (2.23 mL, 15.6 mmol) was added to the reaction mixture at the same temperature. The reaction mixture was stirred at ~–78 to 0 °C for 3 h, and quenched with saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (100 g, hexane:acetone = ~20:1–15:1) to afford compound **2** as colourless oil; yield 6.1 g (86%); IR (neat) (cm^{-1}): 3069, 2956, 1772, 1716, 1255; ^1H NMR (500 MHz): δ 1.09 (9H, s), 1.73–1.78 (1H, m), 1.90–2.00 (2H, m), 2.15–2.19 (1H, m), 2.55 (2H, t, *J* = 7.0 Hz), 3.77 (2H, d-like, *J* = 5.5 Hz), 4.45–4.49 (1H, m), 5.24 (2H, ABq, *J* = 12.0 Hz), 7.35–7.48 (11H, br m), 7.66–7.70 (4H, m); ^{13}C NMR (75 MHz): δ 17.61 (t), 19.13 (s), 24.42 (t), 26.78 (q), 34.87 (t), 56.26 (d), 64.22 (t), 68.25 (t), 127.56 (d), 127.72 and 127.95 (each d), 128.31 (d), 129.60 (d), 129.63 (s), 132.54 and 132.76 (each s), 135.18 (s), 135.31 and 135.38 (each d), 153.80 (s), 171.60 (s); MS *m/z*: 444 (M^+ – 57); $[\alpha]_D^{26}$ –52.3 (*c* 1.25, $CHCl_3$). HRMS calcd for $C_{26}H_{26}NO_4Si$: 444.1629; found: 444.1643.

*Phenylmethyl 2-(tert-butyldiphenylsilyloxymethyl)-6-trifluoromethanesulfonyl- oxy-3,4-dihydro-2*H*-pyridine-1-carboxylate* (**3**)

A stirred solution of **2** (6.1 g, 12.2 mmol) in THF (15 mL) was treated with a solution of LiHMDS (prepared from 1,1,1,3,3,3-hexamethyldisilazane (3.1 mL, 14.6 mmol) and *n*-BuLi (1.6 M in hexane, 9.2 mL, 14.6 mmol) in THF (12 mL) at 0 °C for 30 min) at –78 °C, and the reaction mixture was stirred at the same temperature for 30 min. A solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent) (5.25 g, 13.4 mmol) in THF (6 mL) was added dropwise to the reaction mixture *via* a double-tipped stainless steel needle at –78 °C, and the resulting mixture was stirred at ~–78 to –40 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous mixture was extracted with Et_2O (3 × 50 mL). The ethereal layers were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (100 g, hexane:acetone = ~60:1–50:1) to afford compound **3** as: Colourless oil; yield 7.0 g (91%); IR (neat) (cm^{-1}): 3071, 2958, 1730, 1683, 1215; ^1H NMR (500 MHz): δ 1.12 (9H, s), 1.73–1.80 (1H, m), 1.96–2.08 (2H, br m), 2.17–2.23 (1H, br m), 3.62–3.67 (1H, m), 3.85–3.92 (1H, m), 4.75–4.80 (1H, m), 5.22–5.42 (3H, m), 7.38–7.49 (11H, br m), 7.67–7.74 (4H, m); ^{13}C NMR (75 MHz): δ 19.03 (s), 19.24 (t), 22.22 (t), 26.76 (q), 55.77 (d), 60.80 (t), 68.47 (t), 106.41 (d), 126.06 (d), 127.58 and 128.16 (each d), 128.22 and 128.35 (each d), 129.63 (d), 133.03 and 133.08 (each s), 135.15 (s), 135.34 and 135.38 (each d), 135.64 (s), 138.00 and 139.16 (each s), 149.13 (d), 153.17 (s); MS *m/z*: 576 (M^+ – 57); $[\alpha]_D^{26}$ –57.2° (*c* 1.26, $CHCl_3$). HRMS calcd for $C_{27}H_{25}F_3NO_6SSi$: 576.1122; found: 576.1127.

*1-Phenylmethyl 2-methyl 6-(tert-butyldiphenylsilyloxymethyl)-5,6-dihydro-4*H*- pyridine-1,2-dicarboxylate* (**4**)

A stirred solution of **3** (7 g, 11.1 mmol) in DMF (45 mL) was treated with $Pd(Ph_3P)_4$ (640 mg, 0.55 mmol), and the resulting mixture was stirred at room temperature under a CO balloon pressure for 30 min. Et_3N (6.3 mL, 45.3 mmol) and MeOH (18 mL, 445.3 mmol) was added to the reaction mixture, and then the mixture was stirred at 75 °C under a CO balloon pressure for 15 h. After cooling, the reaction mixture was diluted with H_2O (100 mL) and brine (25 mL), and the aqueous mixture was extracted with Et_2O (4 × 50 mL). The organic layers were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (80 g, hexane:acetone = ~50:1–30:1) to afford compound **4** as: Pale yellow oil; yield 4.7 g (78%); IR (neat) (cm^{-1}): 3069, 2955, 1737, 1714, 1269; ^1H NMR (500 MHz): δ 1.09 (9H, s), 1.82–1.89 (1H, m), 1.95–2.03 (1H, m), 2.06–2.15 (1H, m), 2.17–2.19 (1H, m), 3.48 (3H, br), 3.57 (1H, t-like, *J* = 6.5 Hz), 3.81–3.84 (1H, m), 4.68 (1H, br), 5.08 and 5.26 (2H, ABq, *J* = 11.9 Hz), 6.01 (1H, t-like, *J* = 3.8 Hz), 7.33–7.49 (11H, br m), 7.65–7.73 (4H, m); ^{13}C NMR (75 MHz): δ 19.24 (t), 19.48 (s), 22.44 (t), 26.76 (q), 51.73 (q), 52.60 (d), 61.24 (t), 67.89 (t), 126.75 (d), 127.51 (d), 128.00 (d), 128.29 (d), 129.54 (d), 130.39 (s), 133.11 and 133.26 (each s), 135.38 (d), 135.64 (s), 153.79 (s), 165.21 (s); MS *m/z*: 543 (M^+); $[\alpha]_D^{26}$ –37.4 (*c* 1.30, $CHCl_3$). HRMS calcd for $C_{32}H_{37}NO_5Si$: 543.2442; found: 543.2465.

1-Phenylmethyl 2-methyl 6-(tert-butyldiphenylsilyloxymethyl)-3-methylpiper- idine-1,2-dicarboxylate (**5**)

A stirred suspension of CuI (8.2 g, 43.1 mmol) in Et_2O (50 mL) was treated with a solution of MeLi (0.98 M in Et_2O, 88 mL, 87 mmol) at –78 °C, and the resulting suspension was stirred at –78 to –35 °C for 20 min. The resulting solution was cooled to –78 °C, and a solution of **4** (4.7 g, 8.7 mmol) in Et_2O (15 mL) was added dropwise *via* a double-tipped stainless steel needle to the above reaction mixture at –78 °C. The temperature was gradually raised to –10 °C, and then the reaction was quenched with saturated aqueous NH_4Cl. The aqueous mixture was diluted with CH_2Cl_2, and the insoluble material was removed through a Celite pad. The filtrate was separated and the aqueous layer was extracted with CH_2Cl_2. The filtrate and organic layers were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (70 g, hexane:acetone = ~50:1–30:1) to afford compound **5** as: Colourless oil; yield 4.8 g (99%); IR (neat) (cm^{-1}): 3070, 2954, 1746, 1703; ^1H NMR (500 MHz) δ 1.09 (9H, s), 1.10 (3H, d, *J* = 7.4 Hz), 1.22–1.28 (1H, m), 1.57–1.62 (1H, m), 1.88–1.92 (2H, m), 2.49 (1H, br), 3.42 (3H, s), 3.52 (1H, t-like, *J* = 10.4 Hz), 3.79 (1H, dd, *J* = 10.4, 4.6 Hz), 4.43 (1H, br), 4.52 (1H, br), 5.14 and 5.21 (2H, ABq, *J* = 12.6 Hz), 7.26–7.47 (11H, br m), 7.66–7.70 (4H, m); ^{13}C NMR (75 MHz): δ 18.16 (q), 18.25 (t), 19.30 (s), 21.97 (t), 26.88 (q), 28.06 (d), 51.74 (q), 52.18 (d), 58.62 (d), 62.41 (t), 67.24 (t), 127.38 and 127.45 (each d), 127.67 (d), 128.24 (d), 129.41 and 129.44 (each d), 130.12 (d), 133.37 and 133.47 (each s), 135.33 and 135.36 (each d), 136.46 (s), 156.47 (s), 172.49 (s); MS *m/z*: 502 (M^+ – 57); $[\alpha]_D^{26}$ –0.43 (*c* 2.73, $CHCl_3$). HRMS calcd for $C_{29}H_{32}NO_5Si$: 502.2048; found: 502.2039.

Phenylmethyl 6-(tert-butyldiphenylsilyloxymethyl)-2-hydroxymethyl-3-methyl- piperidine-1-carboxylate (**6**)

A stirred solution of **5** (4.8 g, 8.6 mmol) in THF (30 mL) was treated with a solution of lithium triethylborrohydride (Super-Hydride®, 1 M in THF, 18.9 mL, 18.9 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2h. The reaction was quenched with small pieces of ice, and the mixture was diluted with CH_2Cl_2. The organic layer was dried and evaporated to give a colourless oil, which was chromatographed on silica gel (80 g, hexane:acetone = ~10:1–8:1) to afford compound **6** as: Colourless oil; yield 4.2 g (92%); IR (neat) (cm^{-1}): 3445, 3070, 2957, 1697, 1112; ^1H NMR (500 MHz): δ 1.06–1.07 (12H, br s-like), 1.15–1.22 (1H, m), 1.46 (1H, br), 1.65 (1H, br), 1.85 (2H, br), 2.92 (1H, br), 3.54–3.75 (4H, br m), 4.10 (1H, br), 4.50 (1H, br), 5.10 (1H, br), 5.21 (1H, d-like, *J* = 12.4 Hz), 7.34–7.47 (11H, br m), 7.69 (4H, br); ^{13}C NMR (75 MHz): δ 19.17 (q), 19.37 (s), 19.82 (t), 22.73 (t), 26.80 (q), 27.52 (d), 51.03 (d), 59.07 (d), 65.03 (t), 67.29 (t), 126.75 (d), 127.58 and 127.61 (each d), 127.71 (d), 128.31 (d), 129.62 (d), 132.85 (s), 135.33 and 135.39 (each d), 136.53 (s), 157.57 (s); MS *m/z*: 474 (M^+ – 57); $[\alpha]_D^{26}$ +8.80 (*c* 1.59, $CHCl_3$). HRMS calcd for $C_{28}H_{32}NO_4Si$: 474.2099; found: 474.2093.

Phenylmethyl 6-(tert-butyldiphenylsilyloxymethyl)-2-(2-ethoxycarbonylvinyl)- 3-methylpiperidine-1-carboxylate (**7**)

A stirred solution of $(COCl)_2$ (1.04 mL, 11.86 mmol) in CH_2Cl_2 (15 mL) was treated with DMSO (1.68 mL, 23.73 mmol) at –78 °C, and the resulting mixture was stirred at the same temperature for 5 min. A solution of **6** (4.2 g, 7.91 mmol) in CH_2Cl_2 (6 mL) was added dropwise to the reaction mixture *via* a double-tipped stainless steel needle at –78 °C. The resulting solution was stirred at –78 °C for 30 min, and then triethylamine (4.92 mL, 35.59 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (3 × 50 mL), and the organic extracts were combined, dried and evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred suspension of NaH (60%, 350 mg, 8.7 mmol) in THF (15 mL) was treated with $(EtO)_2P(O)CH_2CO_2Et$ (1.74 mL, 8.7 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. A solution of the above aldehyde in THF (6 mL) was added dropwise to the resulting mixture *via* a double-tipped stainless steel needle

at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (4 × 40 mL). The organic extracts were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (80 g, hexane:acetone = ~20:1–10:1) to afford compound **7** as a 2:1 mixture of the *E*- and *Z*-isomers as: Pale yellow oil; yield 4.6 g (97%); ^{1}H NMR (500 MHz): δ 1.03–1.07 (12H, br s-like), 1.21 (3H, t, *J* = 7.1 Hz), 1.50–1.66 (3H, br m), 1.80–1.94 (2H, br m), 3.44–3.68 (2H, br m), 4.05–4.18 (2H, m), 4.48–4.54 (2H, br m), 5.01–5.20 (2H, m), 5.62 and 5.87 (1H, m), 6.22 and 6.89 (1H, m), 7.28–7.43 (11H, br m), 7.64 (4H, t-like, *J* = 7.4 Hz).

5-(tert-Butyldiphenylsilyloxymethyl)-8-methylhexahydroindolizin-3-one (**8**)

A stirred solution of **7** (4.6 g, 7.68 mmol) in MeOH (20 mL) was treated with 20% $Pd(OH)_2$/C (500 mg), and the resulting suspension was hydrogenated at 4 atm under a hydrogen atmosphere for 44 h. The catalyst was filtered off and the filtrate was evaporated to give a pale yellow oil. The solution of this oil in CH_2Cl_2 (50 mL) was treated with a solution of Me_3Al (1 M in hexane, 9.2 mL, 9.2 mmol) at 0 °C, and then refluxed for 15 h. After cooling, the reaction mixture was quenched with 10% aqueous HCl, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layer and extracts were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (60 g, hexane:acetone = ~20:1–10:1) to afford compound **8** as: Colourless solid; m.p. ~78–80 °C; yield 2.3 g (71%); IR (KBr) (cm^{-1}): 3066, 2958, 1752, 1688, 1109, 1088; ^{1}H NMR (500 MHz): δ 0.91 (3H, d, *J* = 6.4 Hz), 1.12 (9H, s), 1.13–1.21 (1H, m), 1.29–1.35 (1H, m), 1.52–1.59 (2H, m), 1.85–1.89 (1H, m), 2.11–2.16 (2H, m), 2.25–2.28 (2H, m), 2.95 (1H, m), 3.34–3.38 (1H, m), 4.17–4.21 (1H, m), 4.60–4.64 (1H, m), 7.38–7.45 (6H, m), 7.72–7.74 (4H, br); ^{13}C NMR (75 MHz): δ 17.61 (q), 19.27 (s), 24.09 (t), 26.89 (q), 27.59 (t), 31.20 (t), 31.34 (t), 37.26 (d), 57.55 (d), 63.67 (t), 64.36 (d), 127.35 and 129.29 (each d), 133.53 and 133.58 (each d), 135.31 (s), 135.36 (d), 174.37 (s); MS *m/z*: 364 (M^+ – 57); $[\alpha]_D^{26}$ –62.5 (*c* 1.74, $CHCl_3$). HRMS calcd for $C_{22}H_{26}NO_2Si$: 364.1731; found: 364.1755.

5-Hydroxymethyl-8-methylhexahydroindolizin-3-one (**9**)

A stirred solution of **8** (300 mg, 0.71 mmol) in THF (5 mL) was treated with a solution of TBAF (1M in THF, 0.78 mL, 0.78 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 13 h. The solvent was evaporated, and the residue was chromatographed on silica gel (10 g, hexane:acetone = ~20:1–2:1) to afford compound **9** as: Colourless oil; yield 129 mg (99%); IR (neat) (cm^{-1}): 3342, 2929, 1663; ^{1}H NMR (500 MHz): δ 0.86 (3H, d, *J* = 6.5 Hz), 1.09–1.25 (2H, br m), 1.28–1.37 (1H, m), 1.53–1.63 (2H, m), 1.76–1.80 (1H, m), 2.15–2.21 (1H, m), 2.30–2.37 (2H, m), 2.92–2.97 (1H, m), 3.06 (1H, br), 3.72 (1H, d-like, *J* = 12.9 Hz), 3.81–3.86 (1H, m), 4.77 (1H, br); ^{13}C NMR (75 MHz): δ 17.28 (q), 23.90 (t), 28.12 (t), 31.44 (t), 32.30 (t), 38.10 (d), 60.48 (d), 63.70 (t), 65.84 (d), 175.39 (s); MS *m/z*: 183 (M^+); $[\alpha]_D^{26}$ –53.6 (*c* 1.25, $CHCl_3$). HRMS calcd for $C_{10}H_{17}NO_2$: 183.1258; found: 183.1269.

5-[4-(tert-Butyldiphenylsilyloxy)but-1-enyl]-8-methyl-octahydroindolizine (**10**)

A stirred solution of **9** (470 mg, 2.57 mmol) in THF (30 mL) was treated with $LiAlH_4$ (292 mg, 7.70 mmol) at 0 °C, and the resulting suspension was refluxed for 15 h. After cooling, the reaction was quenched with 10% aqueous NaOH, and the aqueous mixture was extracted with hot $CHCl_3$ (10 × 15 mL). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a colourless oil, which was used directly in the next step.

A stirred solution of $(COCl)_2$ (0.34 mL, 3.86 mmol) in CH_2Cl_2 (6 mL) was treated with DMSO (0.55 mL, 7.71 mmol) at –78 °C, and the reaction mixture was stirred at –78 °C for 5 min. A solution of the above alcohol in CH_2Cl_2 (9 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at –78 °C, and the mixture was then stirred at the same temperature for 30 min. Triethylamine (1.6 mL, 11.57 mmol) was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the organic layer was separated. The aqueous mixture was extracted with CH_2Cl_2 (2 × 15 mL), and the organic layer and extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred suspension of $TBDPSO(CH_2)_3P^+Ph_3Br^-$ (5.4 g, 8.45 mmol) in THF (30 mL) was treated with a solution of *n*-BuLi (1.6 M in hexane, 5 mL, 7.97 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 10 min. A solution of the above aldehyde in THF (9 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at 0 °C. After stirring the reaction mixture for 18 h, the reaction was quenched with H_2O. The aqueous mixture was extracted with Et_2O (3 × 30 mL), and the organic extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was chromatographed on silica gel (50 g, hexane:acetone = ~100:1–20:1) to afford compound **10** as: Pale yellow oil; yield 949 mg (83%); ^{1}H NMR (500 MHz): δ 0.90 (3H, d, *J* = 6.4 Hz), 0.99–1.04 (1H, m), 1.07 (9H, s), 1.36–1.61 (6H, br m), 1.70–1.74 (2H, m), 1.84 (1H, q-like, *J* = 8.9 Hz), 1.93–1.97 (1H, m), 2.36–2.41 (2H, m), 2.70–2.74 (1H, m), 3.10 (1H, t-like, *J* = 8.5 Hz), 3.68 (2H, t, *J* = 6.9 Hz), 5.41–5.48 (2H, m), 7.38–7.46 (6H, m), 7.69–7.71 (4H, m).

4-(8-Methyloctahydroindolizin-5-yl)butan-1-ol (**11**)

A stirred solution of **10** (121 mg, 0.27 mmol) in EtOAc (5 mL) was treated with 10% Pd/C (50 mg), and the resulting suspension was hydrogenated at 1 atm under a hydrogen atmosphere for 37 h. The catalyst was filtered off and the filtrate was evaporated to give a pale yellow oil. A solution of this oil in THF (8 mL) was mixed with a solution of TBAF (1 M in THF, 0.7 mL, 0.68 mmol), and the reaction mixture was stirred at room temperature for 14 h. The solvent was evaporated and the residue was chromatographed on silica gel (10 g, hexane:acetone = ~30:1–1:1) to afford compound **11** as: Pale yellow oil; yield 45 mg (79%); IR (neat) (cm^{-1}): 3309, 2928, 2870, 2785; ^{1}H NMR (500 MHz): δ 0.87 (3H, d, *J* = 6.8 Hz), 0.95 (1H, qd, *J* = 12.8, 4.3 Hz), 1.26–1.77 (15H, br m), 1.91–1.97 (2H, br), 2.00 (1H, q-like, *J* = 9.0 Hz), 3.28 (1H, t-like, *J* = 8.6 Hz), 3.65 (2H, t-like, *J* = 6.8 Hz); ^{13}C NMR (75 MHz): δ 18.95 (q), 20.39 (t), 22.09 (t), 29.01 (t), 31.07 (t), 33.17 (t), 33.64 (t), 34.30 (t), 36.39 (d), 51.79 (t), 62.78 (t), 63.49 (d), 71.39 (d); MS *m/z*: 211 (M^+); $[\alpha]_D^{26}$ –112.2 (*c* 1.98, $CHCl_3$). HRMS calcd for $C_{13}H_{25}NO$: 211.1935; found: 211.1944.

5-(5-Iodopent-4-enyl)-8-methyloctahydroindolizine (**12**)

A stirred solution of $(COCl)_2$ (0.35 mL, 4 mmol) in CH_2Cl_2 (10 mL) was treated with DMSO (0.58 mL, 8 mmol) at –78 °C, and the resulting mixture was stirred at the same temperature for 5 min. A solution of **11** (210 mg, 1.00 mmol) in CH_2Cl_2 (3 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at –78 °C, and the reaction mixture was stirred at –78 °C for 30 min. Triethylamine (1.66 mL, 12 mmol) was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred suspension of $ICH_2P^+Ph_3I^-$ (1.33 g, 2.5 mmol) in THF (15 mL) was treated with a solution of NaHMDS (1M in THF, 2.5 mL, 2.5 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 1 min. HMPA (0.6 mL) was added to the mixture followed by dropwise a solution of the above aldehyde in THF (6 mL) *via* a double-tipped stainless steel needle at –78 °C. The reaction mixture was stirred at ~–78 °C to room temperature for 2 h and quenched with saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with Et_2O (4 × 25 mL), and the organic extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane:acetone = ~80:1–20:1) to afford compound **12** as: Pale yellow oil; yield 203 mg (61%); IR (neat) (cm^{-1}): 2926, 2869, 2778, 2457; ^{1}H NMR (500 MHz): δ 0.88 (3H, d, *J* = 6.8 Hz), 0.96 (1H, qd-like, *J* = 12.0, 4.2 Hz), 1.22–1.41 (5H, br m), 1.42–1.58 (2H, m), 1.61–1.78 (5H, m), 1.89–1.95 (2H, m),

1.97 (1H, q-like, *J* = 8.9 Hz), 2.12–2.17 (2H, m), 3.26 (1H, t-like, *J* = 8.6 Hz), 6.15–6.21 (2H, m); ^{13}C NMR (75 MHz): δ 18.96 (q), 20.42 (t), 24.22 (t), 29.09 (t), 31.18 (t), 33.67 (t), 34.04 (t), 35.00 (t), 36.57 (d), 51.86 (t), 63.17 (d), 71.31 (d), 82.50 (d), 140.96 (d); MS *m/z*: 333 (M^+); $[\alpha]_D^{26}$ –67.4 (*c* 1.67, $CHCl_3$). HRMS calcd for $C_{14}H_{24}IN$: 333.0953; found: 333.0973.

8-Methyl-5-[7-(trimethylsilyl)hept-4-en-6-ynyl]octahydroindolizine (**12***)

A stirred suspension of CuI (11 mg, 0.057 mmol) and $Pd(Ph_3P)_4$ (23 mg, 0.02 mmol) in THF (2 mL) was treated with *i*-Pr_2NH (0.2 mL, 1.44 mmol) at room temperature. A solution of **12** (65 mg, 0.2 mmol) and TMS-acetylene (0.1 mL, 0.93 mmol) in THF (3 mL) was added dropwise to this solution *via* a double-tipped stainless steel needle. The reaction mixture was stirred at room temperature for 17 h, and then quenched with saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with Et_2O (4 × 10 mL), and the organic extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was chromatographed on silica gel (10 g, hexane:acetone = ~100:1–20:1) to afford compound **12*** as: Pale yellow oil; yield 41 mg (90%); IR (neat) (cm^{-1}): 3017, 2958, 2778, 2148, 843; ^{1}H NMR (500 MHz): δ 0.21 (9H, s), 0.88 (3H, d, *J* = 6.4 Hz), 0.97 (1H, qd-like, *J* = 12.0, 3.9 Hz), 1.27–1.53 (8H, br m), 1.67–1.78 (4H, m), 1.94–2.18 (3H, m), 2.33 (2H, q-like, *J* = 6.9 Hz), 3.29 (1H, br), 5.49 (1H, d-like, *J* = 11.1 Hz), 5.95 (1H, dt-like, *J* = 11.1, 7.7 Hz); ^{13}C NMR (75 MHz): δ 12.33 (q), 18.96 (q), 20.37 (t), 22.73 (t), 24.93 (t), 29.04 (t), 30.57 (t), 31.07 (t), 33.66 (t), 36.42 (d), 51.81 (t), 63.23 (d), 71.42 (d), 98.57 (s), 102.01 (s), 109.34 (d), 144.99 (d); MS *m/z*: 303 (M^+); $[\alpha]_D^{26}$ –57.9 (*c* 1.11, $CHCl_3$). HRMS calcd for $C_{19}H_{33}NSi$; 303.2380; found: 303.2372.

5-Hept-4-en-6-ynyl-8-methyloctahydroindolizine (**231C**)

A stirred solution of **12*** (20 mg, 0.066 mmol) in MeOH (0.6 mL) was treated with K_2CO_3 (20 mg, 0.15 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O, and the insoluble material was filtered off. The filtrate was evaporated to give indolizidine **231C** as: Colourless oil; yield 14 mg (89%); IR (neat) (cm^{-1}): 3328, 3034, 2787, 1457, 1249, 851; ^{1}H NMR (500 MHz): δ 0.87 (3H, d, *J* = 6.8 Hz), 0.95 (1H, qd, *J* = 12.0, 4.3 Hz), 1.20–1.56 (3H, br m), 1.51–1.57 (7H, br m), 1.60–1.78 (5H, br m), 1.86–1.91 (2H, m), 1.92 (1H, q-like, *J* = 9.0 Hz), 2.28–2.40 (2H, m), 3.08 (1H, br s), 3.26 (1H, t-like, *J* = 8.6 Hz), 5.45 (1H, d-like, *J* = 9.9 Hz), 6.01 (1H, dt-like, *J* = 9.9, 6.7 Hz); ^{13}C NMR (75 MHz): δ 18.98 (q), 20.44 (t), 25.02 (t), 29.13 (t), 30.58 (t), 31.26 (t), 33.70 (t), 34.16 (t), 36.63 (d), 51.87 (t), 63.18 (d), 71.29 (d), 80.48 (s), 81.27 (d), 108.15 (d), 145.68 (d); MS *m/z*: 231 (M^+); $[\alpha]_D^{26}$ –107.67 (*c* 0.68, $CHCl_3$). HRMS calcd for $C_{16}H_{25}N$: 231.1986; found: 231.1999.

1-Phenylmethyl2-methyl6-(tert-butyldiphenylsilyloxymethyl)-3-vinylpiperidine-1,2-dicarboxylate (**13**)

A stirred solution of tetravinyltin (4 mL, 24.5 mmol) in Et_2O (10 mL) was treated with a solution of MeLi (0.98 M in Et_2O, 100 mL, 98 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. A stirred suspension of CuI (9.33 g, 49.0 mmol) in Et_2O (20 mL) was treated with a solution of vinyllithium (prepared as above) at –78 °C, and the resulting mixture was stirred at ~–78 to –35°C for 30 min. A solution of **4** (6.1 g, 11.2 mmol) in Et_2O (20 mL) was added dropwise to the reaction mixture *via* a double-tipped stainless steel needle at –78 °C. The reaction mixture was stirred at ~–78 to –10 °C for 1 h, and then the reaction was quenched with saturated aqueous NH_4Cl. The aqueous mixture was diluted with CH_2Cl_2, and the insoluble material was filtered off. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The organic layer and extracts were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (100 g, hexane:acetone = ~25:1–20:1) to afford compound **13** as: Pale yellow oil; yield 6.3 g (99%); IR (neat) (cm^{-1}): 3074, 2953, 1744, 1698, 1269, 1113; ^{1}H NMR (500 MHz): δ 1.05 (9H, s), 1.21 (1H, br), 1.44 (1H, br), 1.80 (1H, m), 1.87 (1H, br), 3.02 (1H, br), 3.40 (3H, s), 3.47 (1H, t-like, *J* = 9.9 Hz), 3.74 (1H, m), 4.40 (1H, br), 4.82 (1H, br), 5.11–5.19 (4H, m), 5.82–5.89 (1H, m), 7.28–7.45 (11H, br m), 7.64 (4H, d-like, *J* = 6.4 Hz); ^{13}C NMR (75 MHz): δ 18.43 (t), 19.26 (s), 20.70 (t), 26.84 (q), 36.66 (d), 51.84 (q), 52.13 (d), 55.81 (d), 61.97 (t), 67.26 (t), 115.28 (t), 127.37 and 127.45 (each d), 127.67 (d), 128.06 (d), 128.21 (d), 129.41 and 129.44 (each d), 133.26 and 133.37 (each s), 135.30 and 135.33 (each d), 136.38 (s), 138.55 (d), 156.10 (s), 172.17 (s); MS *m/z*: 514 (M^+ – 57); $[\alpha]_D^{26}$ –8.80 (*c* 1.69, $CHCl_3$). HRMS calcd for $C_{30}H_{32}NO_5Si$: 514.2048; found: 514.2067.

Phenylmethyl6-(tert-butyldiphenylsilyloxymethyl)-2-hydroxymethyl-3-vinylpiperidine-1-carboxylate (**14**)

A stirred solution of **13** (6.04 g, 10.58 mmol) in THF (80 mL) was treated with a solution of Super-Hydride® (1 M in THF, 23 mL, 23.0 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 2 h. The reaction was quenched with small pieces of ice, and the mixture was diluted with CH_2Cl_2. The organic layer was dried and evaporated to give a colourless oil, which was chromatographed on silica gel (70 g, hexane:acetone = ~20:1–8:1) to afford compound **14** as: Colourless oil; yield 5.3 g (92%); IR (neat) (cm^{-1}): 3445, 3070, 2932, 2858, 1695, 1112; ^{1}H NMR (500 MHz): δ 1.09 (9H, s), 1.30–1.43 (1H, m), 1.47 (1H, br), 1.67–1.72 (1H, m), 1.84–1.90 (1H, m), 2.43 (1H, br), 3.14 (1H, br), 3.58–3.75 (4H, br m), 4.36 (1H, br m), 4.51 (1H, br), 5.09–5.24 (4H, m), 5.89 (1H, m), 7.33–7.48 (11H, m), 7.70–7.71 (4H, br); ^{13}C NMR (75 MHz): δ 19.14 (s), 20.15 (t), 22.67 (t), 26.78 (q), 36.79 (d), 50.98 (d), 56.36 (d), 64.41 (t), 67.33 (t), 115.04 (t), 127.58 (d), 127.72 (d), 128.29 (d), 129.62 (d), 132.79 (s), 135.31 (d), 135.36 (d), 136.41 (s), 140.02 (d), 157.15 (s); MS *m/z*: 486 (M^+ – 57); $[\alpha]_D^{26}$ +14.2 (*c* 1.11, $CHCl_3$). HRMS calcd for $C_{29}H_{32}NO_4Si$: 486.2099; found: 486.2107.

Phenylmethyl 6-(tert-butyldiphenylsilyloxymethyl)-2-(2-ethoxycarbonylvinyl)-3-vinyl-piperidine-1-carboxylate (**15**)

A stirred solution of $(COCl)_2$ (1.28 mL, 14.64 mmol) in CH_2Cl_2 (20 mL) was treated with DMSO (2.1 mL, 29.28 mmol) at –78 °C, and the resulting mixture was stirred at the same temperature for 5 min. A solution of **14** (5.3 g, 9.76 mmol) in CH_2Cl_2 (9 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at –78 °C. The resulting solution was stirred at –78 °C for 30 min and then triethylamine (6.1 mL, 43.92 mmol) was added to the reaction mixture, which was then warmed to 0 °C for 1 h, and quenched with H_2O. The aqueous mixture was extracted with Et_2O (3 × 50 mL), and the organic extracts were combined, dried and evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred suspension of NaH (60%, 430 mg, 10.74 mmol) in THF (30 mL) was treated with $(EtO)_2P(O)CH_2CO_2Et$ (2.2 mL, 10.74 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. A solution of the above aldehyde in THF (9 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at 0 °C. The reaction mixture was stirred at room temperature for 22 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (4 × 50 mL). The organic extracts were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (80 g, hexane:acetone = ~20:1–10:1) to afford compound **15** as a 2:1 mixture of the *E*- and *Z*-isomers as: Pale yellow oil; yield 5.78 g (97%); ^{1}H NMR (500 MHz): δ 1.03 (9H, s), 1.22 (3H, t, *J* = 7.1 Hz), 1.51–1.85 (4H, br m), 2.51 (1H, br), 3.44–3.68 (2H, br m), 4.03–4.18 (2H, m), 4.48 (1H, br m), 4.84 (1H, br), 5.01–5.22 (4H, br m), 5.62 and 5.87 (1H, m), 5.71–5.86 (1H, m), 6.22 and 6.89 (1H, m), 7.28–7.43 (11H, br m), 7.64 (4H, t-like, *J* = 7.4 Hz).

5-(tert-Butyldiphenylsilyloxymethyl)-8-ethylhexahydroindolizin-3-one (**16**)

A stirred solution of **15** (1.6 g, 2.61 mmol) in MeOH (10 mL) was treated with 20% $Pd(OH)_2/C$ (100 mg), and the resulting suspension was hydrogenated at 4 atm under a hydrogen atmosphere for 44 h. The catalyst was filtered off and the filtrate was evaporated to give a pale yellow oil. A solution of this oil in CH_2Cl_2 (30 mL) was treated with a solution of Me_3Al (1 M in hexane, 3.1 mL, 3.1 mmol) at 0 °C, and the resulting solution was refluxed for 17 h. After cooling, the reaction was

quenched with 10% aqueous HCl, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layer and extracts were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on silica gel (50 g, hexane:acetone = ~20:1–10:1) to afford compound **16** as: Colourless solid; m.p. ~84–87 °C; yield 771 mg (68%); IR (KBr) (cm^{-1}): 3070, 2931, 1690, 1112; ^{1}H NMR (500 MHz): δ 0.88 (3H, t, *J* = 7.3 Hz), 0.90–1.18 (3H, m), 1.11 (9H, s), 1.44–1.60 (3H, br m), 1.87–1.91 (1H, m), 2.04–2.11 (2H, m), 2.19–2.22 (2H, m), 3.00 (1H, q-like, *J* = 7.7 Hz), 3.40–3.43 (1H, m), 4.11 (1H, t-like, *J* = 9.0 Hz), 4.56 (1H, dd, *J* = 9.0, 4.2 Hz), 7.35–7.40 (6H, m), 7.71–7.74 (4H, m); ^{13}C NMR (75 MHz): δ 10.44 (q), 18.92 (s), 24.22 (t), 24.26 (t), 26.31 (t), 26.59 (q), 30.89 (t), 43.10 (d), 56.36 (d), 61.94 (d), 63.22 (t), 127.04 (d), 128.99 (d), 133.13 (d), 134.96 and 135.00 (each s), 173.96 (s); MS *m/z*: 378 (M^+ – 57); $[\alpha]_D^{26}$ –63.1 (*c* 1.71, $CHCl_3$). HRMS calcd for $C_{23}H_{28}NO_2Si$: 378.1888; found: 378.1897.

8-Ethyl-5-hydroxymethylhexahydroindolizin-3-one (**17**)

A stirred solution of **16** (783 mg, 1.8 mmol) in THF (12 mL) was treated with a solution of TBAF (1M in THF, 2.7 mL, 2.7 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was evaporated, and the residue was chromatographed on silica gel (20 g, hexane:acetone = ~20:1–2:1) to afford compound **17** as: Colourless solid; m.p. ~54–57 °C; yield 340 mg (91%); IR (KBr) (cm^{-1}): 3298, 2941, 1656; ^{1}H NMR (500 MHz): δ 0.92 (3H, t, *J* = 7.7 Hz), 1.02–1.13 (3H, m), 1.30–1.38 (1H, m), 1.50–1.57 (1H, m), 1.61–1.69 (2H, m), 1.96–2.01 (1H, m), 2.21–2.28 (1H, m), 2.34–2.46 (2H, m), 3.06–3.11 (2H, m), 3.76 (1H, dd, *J* = 12.8, 2.1 Hz), 3.90 (1H, dd, *J* = 12.8, 7.2 Hz), 4.57 (1H, br); ^{13}C NMR (75 MHz): δ 10.53 (q), 23.93 (t), 23.98 (t), 27.85 (t), 28.30 (t), 31.33 (t), 44.24 (d), 60.34 (d), 63.62 (t), 64.25 (d), 175.26 (s); MS *m/z*: 197 (M^+). HRMS calcd for $C_{11}H_{19}NO_2$: 197.1415; found: 197.1401.

Methyl (8-ethyl-3-oxooctahydroindolizin-5-yl)acetate (**18**)

A stirred solution of $(COCl)_2$ (0.25 mL, 2.82 mmol) in CH_2Cl_2 (10 mL) was treated with DMSO (0.40 mL, 5.63 mmol) at –78 °C, and the resulting mixture was stirred at the same temperature for 5 min. A solution of **17** (340 mg, 1.73 mmol) in CH_2Cl_2 (3 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at –78 °C, and the reaction mixture was stirred at –78 °C for 30 min. Triethylamine (1.17 mL, 8.45 mmol) was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (3 × 25 mL). The organic layers were combined, dried and evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred solution of the above aldehyde in *t*-BuOH (9 mL) were treated with 2-methyl-2-butene (7.9 mL, 75.13 mmol), NaH_2PO_4•$2H_2O$ (2.93 g, 18.78 mmol), and then a solution of $NaClO_2$ (80%, 1.27 mg, 11.27 mmol) in H_2O (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous $NaHSO_3$ at 0 °C. The aqueous mixture was acidified with 10% aqueous HCl, saturated with solid NaCl and extracted with EtOAc (10 × 10 mL). The organic extracts were combined, dried and evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred solution of the above carboxylix acid in THF (15 mL) was treated with Et_3N (0.29 mL, 2.07 mmol) and $ClCO_2Et$ (0.2 mL, 2.07 mmol) at 0 °C, and the resulting suspension was stirred at the same temperature for 1 h. The insoluble material was filtered off, and the filtrate was evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred solution of the above oil in Et_2O (30 mL) was treated with a solution of CH_2N_2 in Et_2O at 0 °C, and the yellow mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was dissolved in MeOH (12 mL). $PhCO_2Ag$ (43 mg, 0.19 mmol) and Et_3N (0.52 mL, 3.76 mmol) were added to the MeOH solution, and the resulting suspension was stirred at room temperature in the dark for 15 h. The insoluble material was filtered off, and the filtrate was evaporated to give a pale brown oil, which was chromatographed on silica gel (25 g, hexane:acetone = ~30:1–10:1) to afford compound **18** as: Pale yellow oil; yield 335 mg (81%); IR (neat) (cm^{-1}): 2964, 1739, 1688, 1173; ^{1}H NMR (500 MHz): δ 0.86 (3H, t, *J* = 7.2 Hz), 0.97–1.15 (3H, m), 1.34–1.66 (4H, br m), 1.88–1.94 (1H, m), 2.06–2.21 (1H, m), 2.22–2.27 (2H, m), 2.41 (1H, dd, *J* = 16.5, 4.7 Hz), 3.03 (1H, q-like, *J* = 7.4 Hz), 3.41 (1H, dd, *J* = 16.5, 8.8 Hz), 3.52–3.61 (1H, m), 3.66 (3H, s); ^{13}C NMR (75 MHz): δ 10.73 (q), 24.03 (t), 24.19 (t), 28.41 (t), 31.46 (t), 31.84 (t), 37.89 (t), 44.24 (d), 51.39 (q), 52.57 (d), 63.62 (d), 171.97 (s), 175.05 (s); MS *m/z*: 239 (M^+). HRMS calcd for $C_{13}H_{21}NO_3$: 239.1520; found: 239.1544.

5-Allyl-8-ethyloctahydroindolizine [**193E** *(proposed)*]

A stirred solution of **18** (167 mg, 0.71 mmol) in THF (8 mL) was treated with $LiAlH_4$ (80 mg, 2.1 mmol) at 0 °C, and the resulting suspension was refluxed for 13 h. After cooling, the reaction was quenched with 10% aqueous NaOH, and the aqueous mixture was extracted with $CHCl_3$ (10 × 10 mL). The organic extracts were combined, dried over K_2CO_3 and evaporated to give a colourless oil, which was used directly in the next step.

A stirred solution of $(COCl)_2$ (0.1 mL, 1.14 mmol) in CH_2Cl_2 (1 mL) was treated with DMSO (0.17 mL, 2.40 mmol) at –78 °C, and the reaction mixture was stirred at –78 °C for 5 min. A solution of the alcohol obtained above in CH_2Cl_2 (2 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at –78 °C, and the reaction mixture was stirred at –78 °C for 30 min. Triethylamine (0.5 mL, 3.61 mmol) was added to the reaction mixture, which was then warmed to 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred suspension of $MeP^+Ph_3I^-$ (1.27 g, 3.15 mmol) in THF (15 mL) was treated with a solution of *n*-BuLi (1.6 M in hexane, 1.84 mL, 2.94 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for 5 min. A solution of the aldehyde obtained above in THF (3 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at 0 °C. The reaction mixture was stirred at room temperature for 17 h, and the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with Et_2O (4 × 15 mL), and the organic extracts were combined, dried over K_2CO_3 and evaporated to give pale yellow oil, which was chromatographed on silica gel (20 g, hexane:acetone = ~100:1–20:1) to afford a product with the proposed structure of **193E** as: Pale yellow oil; yield 85 mg (63%); IR (neat) (cm^{-1}): 3083, 2963, 2933, 2788, 910; ^{1}H NMR (500 MHz): δ 0.83–0.92 (1H, m), 0.88 (3H, t, *J* = 7.7 Hz), 1.03–1.09 (1H, m), 1.13–1.28 (2H, m), 1.41–1.52 (2H, m), 1.57–1.69 (2H, m), 1.74–1.78 (2H, m), 1.85–2.02 (4H, m), 2.08–2.12 (1H, m), 2.44 (1H, m), 3.29 (1H, t, *J* = 9.0 Hz), 5.00–5.07 (2H, m), 5.77–5.85 (1H, m); ^{13}C NMR (75 MHz): δ 11.17 (q), 20.53 (t), 25.99 (t), 29.08 (t), 29.79 (t), 31.21 (t), 39.53 (t), 42.99 (d), 51.95 (t), 63.05 (d), 70.01 (d), 116.37 (t), 135.76 (d); MS *m/z*: 193 (M^+); $[\alpha]_D^{26}$ –68.7 (*c* 3.30, $CHCl_3$). HRMS calcd for $C_{13}H_{23}N$: 193.1829; found: 193.1833.

8-Ethyl-5-pent-2-enyloctahydroindolizine (**221I**)

A stirred solution of **18** (167 mg, 0.71 mmol) in THF (8 mL) was treated with $LiAlH_4$ (80 mg, 2.1 mmol) at 0 °C, and the resulting suspension was refluxed for 13 h. After cooling, the reaction was quenched with 10% aqueous NaOH, and the aqueous mixture was extracted with $CHCl_3$ (10 × 10 mL). The organic extracts were combined, dried over K_2CO_3 and evaporated to give a colourless oil, which was used directly in the next step.

A stirred solution of $(COCl)_2$ (0.1 mL, 1.14 mmol) in CH_2Cl_2 (1 mL) was treated with DMSO (0.17 mL, 2.40 mmol) at –78 °C, and the reaction mixture was stirred at –78 °C for 5 min. A solution of the alcohol obtained above in CH_2Cl_2 (2 mL) was added dropwise to this mixture *via* a double-tipped stainless steel needle at –78 °C, and the reaction mixture was stirred at –78 °C for 30 min. Triethylamine (0.5 mL, 3.61 mmol) was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step.

A stirred suspension of *n*-$PrP^+Ph_3Br^-$ (1.21 g, 3.15 mmol) in THF (15 mL) was treated with a solution of NaHMDS (1 M in THF, 2.8 mL, 2.8 mmol)

at room temperature, and the resulting mixture was stirred at the same temperature for 1 min. HMPA (0.8 mL) was added to the mixture followed by dropwise a solution of the aldehyde obtained above in THF (3 mL) *via* a double-tipped stainless steel needle at –78 °C. The reaction mixture was stirred at ~–78 °C to room temperature for 22 h, and the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous mixture was extracted with Et_2O (4 × 15 mL), and the organic extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane:acetone = ~100:1–20:1) to afford compound **221I** as: Pale yellow oil; yield 96 mg (62%); IR (neat) (cm^{-1}): 3015, 2963, 2932, 2787, 1459; ^1H NMR (500 MHz): δ 0.86–0.91 (1H, m), 0.89 (3H, t, J = 7.2 Hz), 0.96 (3H, t, J = 7.6 Hz), 1.03–1.09 (1H, m), 1.11–1.27 (2H, m), 1.42–1.52 (2H, m), 1.58–1.70 (2H, m), 1.74–1.82 (2H, m), 1.84–1.97 (3H, m), 2.00–2.15 (4H, m), 2.40 (1H, br), 3.32 (1H, t, J = 8.9 Hz), 5.32–5.47 (2H, m); ^{13}C NMR (75 MHz): δ 11.17 (q), 14.30 (q), 20.53 (t), 20.78 (t), 26.00 (t), 29.09 (t), 29.82 (t), 31.26 (t), 32.60 (t), 42.96 (d), 51.98 (t), 63.64 (d), 70.06 (d), 125.70 (d), 133.00 (d); MS *m/z*: 221 (M^+); $[\alpha]_D^{26}$ –77.8 (*c* 3.75, $CHCl_3$). HRMS calcd for $C_{15}H_{27}N$: 221.2142; found: 221.2165.

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