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Highly Stereoselective Construction of 4,6-*cis*-Substituted Quinolizidine Ring Core: An Application to Enantioselective Total Synthesis of the Marine Alkaloid Clavepictines A, B and Pictamine

Naoki Toyooka,* Yasuhito Yotsui, Yasuko Yoshida, Takefumi Momose, and Hideo Nemoto*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan

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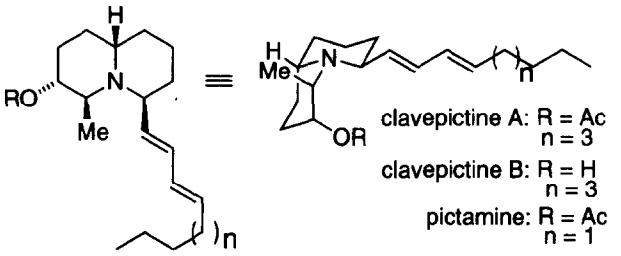
Abstract: The enantioselective total synthesis of the marine alkaloids clavepictines A, B and pictamine has been achieved through the highly stereocontrolled quinolizidine ring closure of the conformationally constrained piperidine ring system (**2**), which bears the chiral centers and appropriate functionality needed for the synthesis of target alkaloids. The absolute stereochemistry of clavepictines and pictamine was verified to be 3*R*, 4*S*, 6*S*, 9a*S* by the present synthesis.

Recently the group of Cardellina, II reported the isolation of the quinolizidine alkaloids clavepictines A and B from the tunicate *Clavelina picta*, which are the first quinolizidine alkaloids from a tunicate.[1] Clavepictines A and B inhibited growth of murine leukemia and human solid tumor cell lines (P-388, A-539, U-251, and SN12K1) at concentrations less than 9 ug/mL (IC_{50} = 1.8-8.5 μg/mL). Although their relative stereochemistry has been determined on the basis of extensive NMR studies for clavepictine A in conjunction with an X-ray diffraction analysis for clavepictine B as shown below, the absolute stereochemistry is unknown. Pictamine has also been isolated from the same marine species, and its gross structure has been determined to be a bis-nor analog of clavepictine A.[2]



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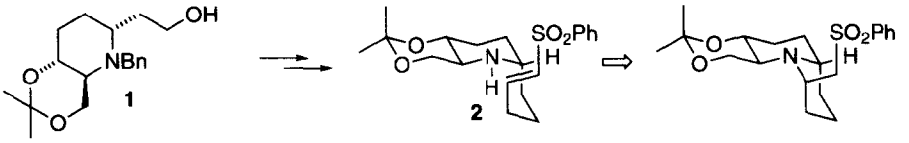
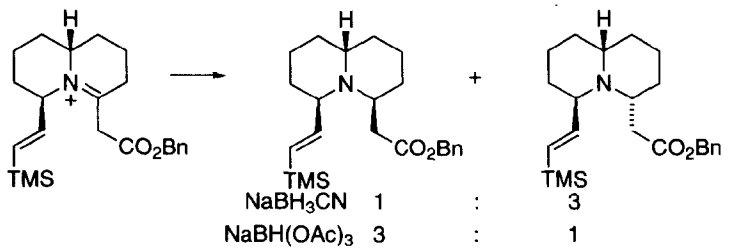
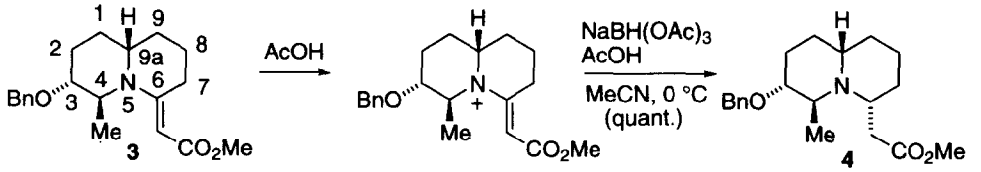
We envisioned a synthetic approach to the above alkaloids starting with a piperidine derivative (-)-(**1**), which is readily available from 2-piperidone type of chiral building block by using method previously developed in our labolatory.[3] The synthetic strategy involved is based on the highly stereocontrolled intramolecular Michael type of ring closure[4] of conformationally constrained piperidine (**2**) to give a quinolizidine ring system as the key step and ultimately led to the enantioselective total synthesis of clavepictines A, B and pictamine to verify the absolute configuration of both alkaloids. This paper presents full details of these results.[5]



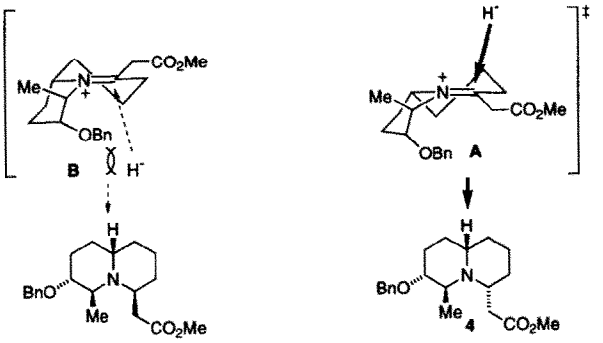
Recently, Hart *et al.* reported the stereochemical course of reduction of iminium ions with sodium borohydride or sodium triacetoxyborohydride in model studies directed toward the synthesis of clavepictine A.[6]



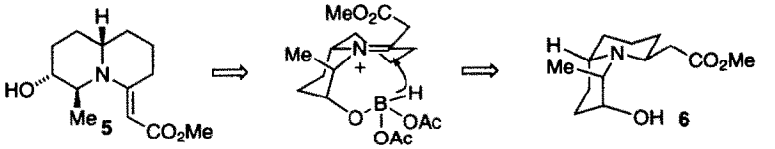
At first, we applied this methodology for the construction of key quinolizidine core. Reduction of iminium ion, generated from vinylogous urethane **3**,[7] took place smoothly to provide the reduced product (**4**) as a single isomer in a nearly quantitative yield.



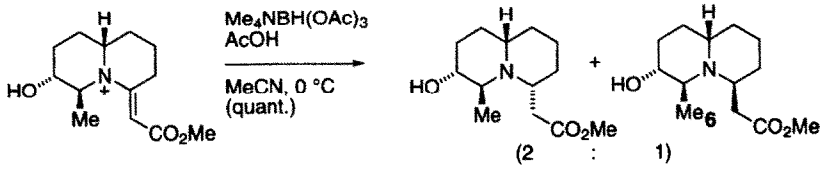
Inspection of its ^{1}H NMR spectra[8] revealed that the product was not desired quinolizidine but the C-6 epimer. The conformers **A** and **B** are considered as the transition state for the reduction of above iminium ion, where the α-methyl substituent occupies pseudo-axial orientation due to the $A^{(1,3)}$ strain[9] with methoxycarbonlmethyl group on the iminium moiety. Thus, the preferred β-axial attack of hydride[10] proceeds smoothly *via* the conformer **A** to give the C_6 epimer. On the other hand, no preferred α-axial attack of hydride[10] *via* the conformer **B** proceeds dut to the steric hindrance of the benzyloxy group to give a desired reduction product.



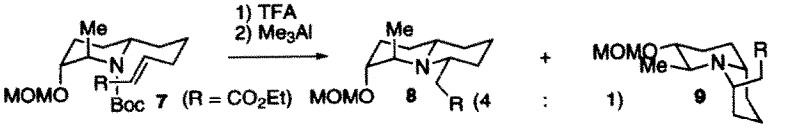
Next we decided to examine the reduction of iminium ion of vinylogous urethane **5**[11] on the basis of the above assumption. We anticipated that the exchange of one of acetoxyl in reducing agent with the hydroxyl in **5** occurs, and intramolecular hydride attack proceeds from the α-face in **5** to form desired product **6**.



Thus, the reduction of **5** with tetramethylammonium triacetoxyborohydride under tha acidic condition was examined, however, C_6 epimer of **6** was obtained again as the major product in a ratio of 2:1. Thus, we were forced to develop an alternative strategy for construction of the key quinolizidine core.

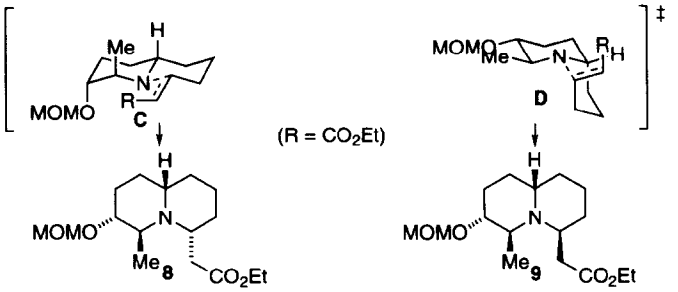


Next, we planned the intramolecular Michael type of ring closure of functionalized piperidine system **7**[12] to give 3,4,6-trisubstituted quinolizidine. Deprotection of the Boc group in **7** with TFA followed by treatment of the resulting amine with Me_3Al afforded a 4:1 mixture of *trans*(4,6)- and *cis*(4,6)-quinolizidines (**8**,**9**), whose structures were verified by the comparison of ^1H NMR spectra with quinolizidine **4** and **6** obtained by the above iminium reductions.

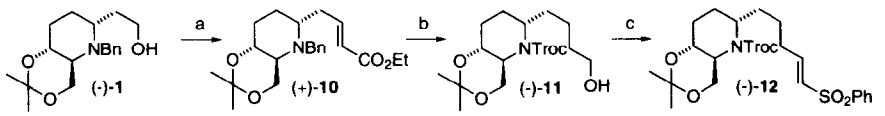


One conceivable reason for the stereoselectivity of this reaction is as follow. The conformers **C** and **D** are considered for the transition state for this ring closure. The *trans*(4,6)-quinolizidine **8** is obtained *via* the conformer **C**, where the nitrogen nucleophile reacts from the *re*-face of α,β-unsaturated ester moiety to avoid

steric interaction with the α-methyl group on the piperidine ring. The *cis*(4,6)-quinolizidine **9** is obtained from the conformer **D**, where the nitrogen nucleophile reacts from the *si*-face as mentioned above.

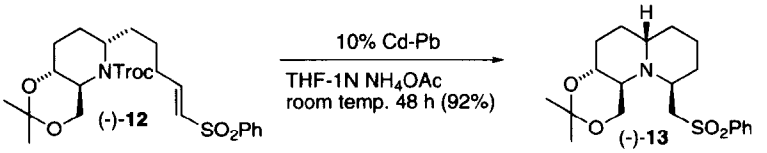


These results imply that the product in this cyclization will converge to desired *cis*(4,6)-quinolizidine if the conformation of the piperidine ring is fixed to the conformer **D**. With this result in mind, we designed the piperidine (**2**), which was fixed to the conformation preferable for obtaining the desired *cis*(4,6)-quinolizidine by protection of the glycol system on the pipridine ring with the acetonide group. The piperidine (-)-**12** was prepared from alcohol (-)-**1**[3] in the usual manner. Swern oxidation of (-)-**1** and subsequent Wittig-Horner reaction of the resulting aldehyde afforded the homologated α,β-unsaturated ester (+)-**10**, which was transformed to alcohol (-)-**11** in three-step sequence {catalytic hydrogenation over $Pd(OH)_2$, $LiAlH_4$ reduction, and protection of the resulting amine with 2,2,2-trichloroethyl chloroformate (TrocCl)}. Further carbon-chain elongation at the 6-position of (-)-**11** was performed by Wittig-Horner reaction, after Swern oxidation of (-)-**11**, using $(EtO)_2P(O)CH_2SO_2Ph$ to give (-)-**12** (**Scheme 1**).



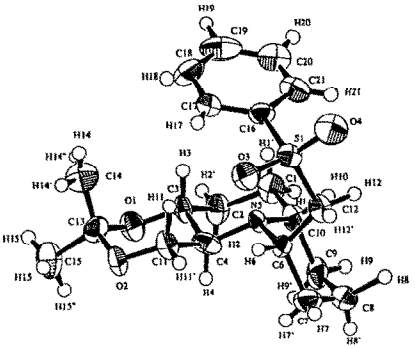
Scheme 1 *Reagents and conditions*: a: Swern ox., then $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (80% in 2 steps); b: H_2, $Pd(OH)_2$, EtOH, then $LiALH_4$, THF, reflux, then TrocCl, K_2CO_3, $CHCl_3$-H_2O = 10:1 (65% in 3 steps); c: Swern ox., then $(EtO)_2P(O)CH_2SO_2Ph$, NaH, THF (80% in 2 steps)

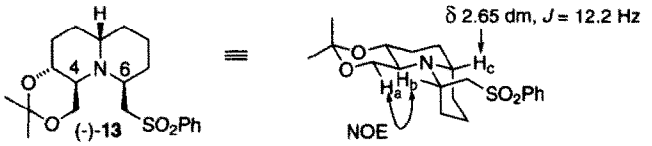
With the requisite sulfone (-)-**12** in hand, we next focused our attention on the construction of the quinolizidine core by using the intramolecular Michael reaction. Deprotection of the Troc group in (-)-**12** with 10% Cd-Pb[13] at room temperature took place smoothly, and subsequent intramolecular cyclization proceeded nicely to afford the quinolizidine (-)-**13** in 92% yield as the only cyclized product.



The stereochemistry of (-)-**13** was initially assigned on the basis of the following NMR study. The observation of an NOE between H_a and H_b on the NOESY experiment for (-)-**13** suggested *cis* relation

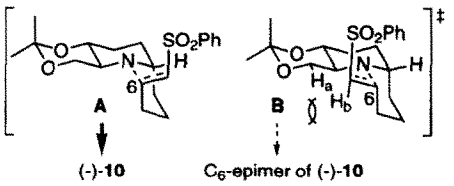
between the substituents at the C_4-and C_6-position. Moreover, analysis of the coupling pattern (doublet of multiplets) and the coupling constant (J = 12.2 Hz) of the bridge head proton (H_c) indicated that H_c was situated axially with respect to the ring bearing the benzenesulfonylmethyl and equatorially to the second ring, implying a *cis* ring fusion. This assignment was confirmed by an X-ray diffraction analysis,[14] and the result confirmed the absolute configuration of (-)-**13** as shown below.





This high-kinetic stereoselectivity on the Michael cyclization can be rationalized as shown in **Figure 3**. Comparison of two kinds of folded chair-like transition states (**E** and **F**) leading to (-)-**13** and its C_6-epimer, respectively, reveals a potential steric repulsion between H_a and H_b for **F**. Therefore, the cyclization occurs *via* the transition state **E** to give the desired product (-)-**13**.

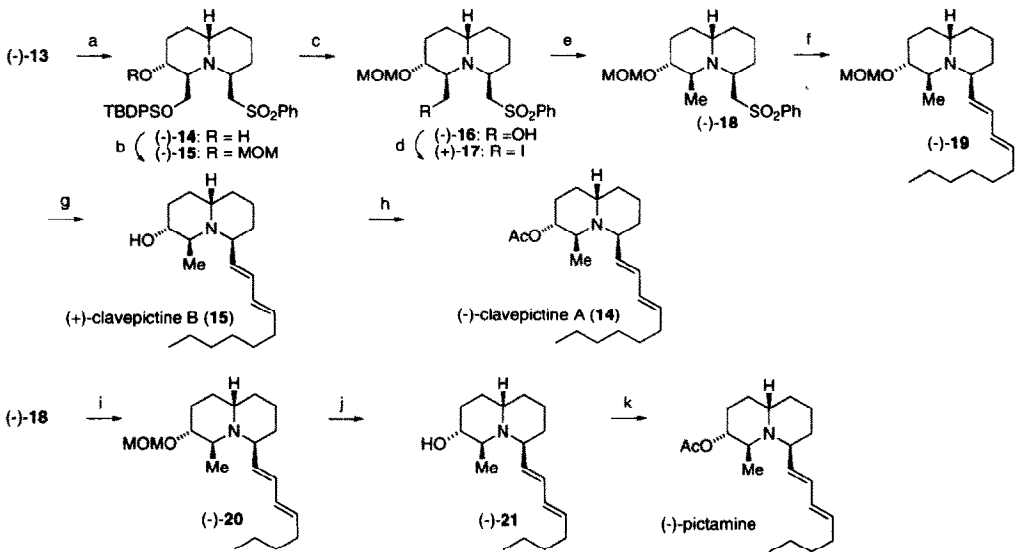
Figure 3



Completion of the synthesis of clavepictines A, B and pictamine is shown in **Scheme 2**. Treatment of (-)-**13** with 10% HCl in EtOH followed by *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole gave alcohol (-)-**14**. Protection of the secondary hydroxyl in (-)-**14** with methoxymethyl chloride (MOMCl) afforded ether (-)-**15**, and deprotection with HF-pyridine provided alcohol (-)-**16**. Iodination of (-)-**16** to give (+)-**17** and radical reduction of (+)-**17** afforded quinolizidine (-)-**18**. Finally, the decadienyl moiety was installed by the Julia coupling. Thus, treatment of (-)-**18** with *n*-BuLi at -80 °C followed by addition of *trans*-2-nonenal to the resulting anion at -80~-50 °C gave the β-hydroxy sulfone, which on sodium amalgam reduction provided the diene (-)-**19**. Deprotection of the MOM group with concentrated HCl in refluxing MeOH resulted in (+)-clavepictine B {$[\alpha]^{26}_D$ +25.7 (*c* 0.61 CH_2Cl_2), lit.[1] $[\alpha]_D$ +27.1 (*c* 0.03 CH_2Cl_2)}, and

acetylation of clavepictine B afforded (-)-clavepictine A {$[\alpha]^{26}_D$ -74.5 (*c* 0.55, CH_2Cl_2), lit.[1] $[\alpha]_D$ -75.6 (c 0.7, CH_2Cl_2)}. The spectral data for synthetic clavepictines A and B were identical with those for natural products.[1] In an analogous fashion, quinolizidine (-)-**18** was transformed to pictamine. Julia coupling of (-)-**18** with *trans*-2-heptenal gave diene (-)-**20**, which was treated with concentrated HCl in refluxing MeOH to afford alcohol (-)-**21**. Protection of the hydroxyl group in (-)-**21** with Ac_2O provided pictamine {$[\alpha]^{26}_D$ -83.5 (*c* 0.89, EtOAc), lit.[2] $[\alpha]_D$ -87 (*c* 0.1, EtOAc)}, whose spectral data were identical with those of natural product.[2]

Scheme 2



Scheme 2 *Reagents and conditions*: a: 10% HCl, EtOH, reflux, then TBDPSCl, imidazole, DMF, 80 °C (85% in 2 steps); b: MOMCl, Hünig base, $CHCl_3$, reflux (93%); c: 40% HF, pyridine, THF (95%); d: I_2, Ph_3P, imidazole, benzene (89%); e: *n*-Bu_3SnH, AIBN, toluene, reflux (94%); f: *n*-BuLi, *trans*-2-nonenal, -80~-50 °C, then 5% Na-Hg, Na_2HPO_4, MeOH, rt (53% in 2 steps); g: c. HCl, MeOH, reflux (82%); h: Ac_2O, pyridine (90%); i: *n*-BuLi, *trans*-2-heptenal, -80~-50 °C, then 5% Na-Hg, Na_2PO_4, MeOH, rt, (48% in 2 steps); j: c. HCl, MeOH, reflux (84%); k: Ac_2O, pyridine (92%)

In conclusion, a general synthetic route to 3-substituted *cis*(4,6)-quinolizidine ring system has been established using highly stereocontrolled intramolecular Michael reaction of conformationally constrained piperidine ring system as the key step. The enantioselective total synthesis of the marine alkaloids clavepictines A, B and pictamine was achieved by this methodology, and the absolute configurations of both alkaloids were determined as depicted in **Scheme 2** by the present synthesis.

Experimental

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. ^{1}H NMR spectra were recorded at the indicated field stregth as solutions in $CDCl_3$ unless otherwise indicated.

Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. Carbon signals were assigned by a DEPT pulse sequence, q = methyl, t = methylene, d = methine, and s = quaternary carbons. Infrared spectra (IR) were measured with a Perkin-Elmer 1600 series FT-IR spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 or JMS-AX505HAD mass spectrometer. Optical rotations were measured on a JASCO DIP-140 or DIP-1000 digital polarimeter. Column chromatography was performed on Merck silica gel 60 (No 7734-5B) or (No 9385).

Reduction of the vinylogous urethane 3 with $NaB(OAc)_3H$: To a stirred solution of **3** (41 mg, 0.125 mmol) in MeCN (1 mL) and AcOH (1 mL) was added $NaB(OAc)_3H$ (56 mg, 0.24 mmol) at 0 °C, and then the resulting suspension was stirred at 0 °C for 3 h. The reaction was quenched with 10% Na_2CO_3 (aq), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 4). The organic extracts were combined, dried, and evaporated to give **4** (41 mg, quant.) as a colorless oil.

IR (neat) 1720 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, d, J = 6.8 Hz), 1.24-1.37 (4H, br m), 1.43-1.74 (6H, br m), 1.87 (2H, br), 2.23 (1H, dd, J = 14.0, 8.3 Hz), 2.40 (1H, tt, J = 11.0, 3.0 Hz), 2.73-2.81 (2H, m), 3.32 (1H, br), 3.36-3.38 (1H, m), 3.67 (3H, s), 4.54 & 4.61 (2H, ABq, J = 13.0 Hz), 7.25-7.37 (5H, m); ^{13}C NMR (75 MHz) δ 8.10, 22.72, 23.84, 28.90, 32.45, 33.97, 38.92, 51.58, 52.03, 53.06, 55.00, 69.85, 76.62, 127.32, 127.56, 128.27, 139.16, 173.33; MS 331 (M^+); HRMS Calcd. For $C_{20}H_{29}NO_3$: 331.2146, Found 331.2139.

Reduction of the vinylogous urethane 5 with $NaB(OAc)_3H$: To a stirred solution of **5** (31 mg, 0.13 mmol) in MeCN (3 mL) and AcOH (0.1 mL) was added a solution of $Me_4NB(OAc)_3H$ (35 mg, 0.15 mmol) in MeCN (1 mL) at 0 °C, and then the resulting solution was stirred at 0 °C for 2 h. The reaction was quenched with 10% Na_2CO_3 (aq), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 4). The organic extracts were combined, dried, and evaporated to give a 1:2 mixture of the quinolizidine **6** and its C_6 epimer.

Intramolecular Michael reaction of 7: To a stirred solution of **7** (66 mg, 0.17 mmol) in CH_2Cl_2 (4 mL) was added TFA (0.18 mL, 1.65 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with solid K_2CO_3, and the K_2CO_3 was filtered off. The filtrate was evaporated to give **4** (give a pale yellow oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=20:1~7:1) to give **8** (16 mg, 32%) and **9** (4 mg, 8%) as a colorless oil, respectively.

Quinolizidine **8**: IR (neat) 1718 cm^{-1}; ^1H NMR (500 MHz) δ 0.96 (3H, d, J = 7.0 Hz), 1.24 (3H, t-like, J = 7.0 Hz), 1.25-1.31 (2H, m), 1.35-1.70 (7H, br m), 1.86 (1H, br), 2.16 (1H, dd, J = 14.0, 8.0 Hz), 2.40 (1H, t-like, J = 10. 0 Hz), 2.74 (1H, dd, J = 14.0, 4.5 Hz), 2.77-2.82 (1H, m), 3.31 (1H, q-like, J = 7.0 Hz), 3.36 (3H, s), 3.61 (1H, br), 4.08-4.15 (2H, m), 4.67 & 4.70 (2H, ABq, J = 6.5 Hz); ^{13}C NMR (75 MHz) δ 8.14, 14.21,

23.27, 23.82, 29.01, 32.49, 34.02, 39.23, 52.79, 52.95, 54.90, 55.23, 60.30, 75.14, 94.47, 172.86; MS 299 (M^+); HRMS Calcd. For $C_{16}H_{29}NO_4$: 299.2095, Found 299.2098.

Quinolizidine **9**: IR (neat) 1718 cm^{-1}; ^1H NMR (500 MHz) δ 1.07 (1H, br), 1.13 (1H, br), 1.16 (3H, d, J = 6.0 Hz), 1.24 (3H, t-like, J = 7.0 Hz), 1.25-1.36 (1H, m), 1.41-1.75 (5H, br m), 1.81-1.90 (2H, m), 2.45 (1H, dd, J = 14.0, 7.0 Hz), 2.77 (1H, dd, J = 14.0, 8.0 Hz), 2.88-2.93 (1H, m), 3.03-3.08 (1H, m), 3.09-3.13 (1H, m), 3.38 (3H, s), 3.72 (1H, br), 4.07-4.16 (2H, m), 4.62 & 4.73 (2H, ABq, J = 6.5 Hz); MS 299 (M^+); HRMS Calcd. For $C_{16}H_{29}NO_4$: 299.2095, Found 299.2072.

Ethyl (4a*S*,6*R*,8a*R*)-(+)-hexahydro-2,2-dimethyl-5-(phenylmethyl)-4*H*-1,3-dioxino-[5,4-b]pyridine-6-but-(2*E*)-enoate [(+)-10]: To a stirred solution of $(COCl)_2$ (0.19 mL, 2.28 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.32 mL, 4.56 mmol) at –78 °C, and the resulting mixture was stirred for 5 min. To the mixture was added a solution of (-)-**1** (347 mg, 1.14 mmol) in CH_2Cl_2 (5 mL) at –78 °C, and the stirring was continued for 30 min. Triethylamine (0.95 mL, 6.84 mmol) was added to the resulting mixture at –78 °C, and the temperature was gradually increased to 0 °C. The reaction was quenched with sat. aqueous $NaHCO_3$, and the aqueous layer was extracted with Et_2O (20 mL x 3). The combined Et_2O layer was dried and evaporated to give the crude aldehyde as a pale yellow oil. This aldehyde was used directly in the next step. To a stirred suspension of NaH (60%, 68 mg, 1.71 mmol) in THF (10 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.37 mL, 1.82 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the aldehyde obtained above in THF (5 mL) at 0 °C, and the mixture was stirred at room temperature for 40 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 5). The combined CH_2Cl_2 layer was dried and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=50:1) to give (+)-**10** (338 mg, 80%) as a colorless oil.

IR (neat) 1716, 1652 cm^{-1}; ^1H NMR (500 MHz) δ 1.27 (3H, t, J = 7.0 Hz), 1.40 & 1.47 (each 3H, each s), 1.52-1.64 (2H, m), 1.68-1.74 (2H, m), 2.47-2.52 (2H, m), 2.69 (1H, td, J = 10.5, 4.5 Hz), 2.82-2.86 (1H, m), 3.52 & 3.69 (2H, ABq, J = 14.0 Hz), 3.59 (1H, t, J = 10.0 Hz), 3.72 (1H, ddd, J = 11.0, 9.0, 4.5 Hz), 3.88 (1H, dd, J = 10.9, 4.5 Hz), 4.16 (2H, q, J = 7.0 Hz), 5.79 (1H, dt-like, J = 15.0, 1.0 Hz), 6.72 (1H, dt, J = 15.0, 8.0 Hz), 7.22-7.31 (5H, m); ^{13}C NMR (75 MHz) δ 14.17 (q), 19.17 (q), 25.02 (t), 25.46 (t), 26.25 (t), 29.50 (q), 52.95 (t), 55.18 (d), 55.91 (d), 60.13 (t), 63.93 (t), 72.11 (d), 98.47 (s), 122.89 (d), 126.99 (d), 127.98 (d), 128.29 (d), 139.33 (s), 146.88 (d), 166.19 (s); MS 373 (M^+), 91 (100); HRMS Calcd. For $C_{22}H_{31}NO_4$: 373.2251, Found 373.2232; $[\alpha]^{26}_D$ +62.6 (*c* 1.00, $CHCl_3$).

Trichloroethyl (4a*S*,6*S*,8a*R*)-(-)-hexahydro-6-(4-hydroxybutyl)-2,2-dimethyl-4*H*-1,3-dioxino-[5,4-b]pyridine-5-carboxylate [(-)-11]: To a stirred solution of (+)-**10** (300 mg, 0.80 mmol) in EtOH (10mL) was added $Pd(OH)_2$ (20 mg), and the resulting suspension was hydrogenated at 1 atm for 15 h. The catalyst was filtered through a celite pad, and the filtrate was evaporated to give a colorless oil. To a stirred solution of the oil obtained above in THF (10 mL) was added $LiAlH_4$ (61 mg, 1.60 mmol), and the resulting suspension was was refluxed for 12 h. After cooling the reaction was quenched with 10% aqueous NaOH,

and the residue was extracted with hot $CHCl_3$ (10 mL x 6). The combined $CHCl_3$ layer was dried and evaporated to afford a colorless oil, which was used directly in the next step. To a stirred solution of the oil obtained above in $CHCl_3$ (20 mL) were added H_2O (2 mL), K_2CO_3 (220 mg, 1.60 mmol) and TrocCl (0.22 mL, 1.60 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 8 h. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 5). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=11:1) to give (-)-**11** (220 mg, 65%) as a colorless oil.

IR (neat) 3446, 1717 cm^{-1}; ^1H NMR (500 MHz) δ 1.31-1.42 (2H, m), 1.39 & 1.51 (each 3H, each s), 1.55-1.70 (6H, m), 1.74-1.88 (3H, m), 3.23 (1H, td, J = 10.0, 4.5 Hz), 3.63 (2H, t-like, J = 6.2 Hz), 3.71 (1H, td, J = 10.5, 4.5 Hz), 4.36 & 4.44 (1H, br), 4.59 (1H, t, J = 11.0 Hz), 4.66 & 4.72 (1H, br); ^{13}C NMR (75 MHz) δ 19.07 (q), 22.49 (t), 26.03 (t), 29.15 (t), 29.39 (q), 32.34 (t), 53.39 (d), 53.46 (d), 62.36 & 62.45 (each t, due to rotamers), 62.52 (t), 70.63 (d), 74.94 (s), 95.41 (s), 98.49 (s), 153.25 (s); MS 417 (M^+); HRMS Calcd. For $C_{16}H_{26}Cl_3NO_5$: 417.0875, Found 417.0855; $[\alpha]^{26}_D$ -9.3 (*c* 2.24, $CHCl_3$).

(-)-Phenyl sulfone [(-)-12]: To a stirred solution of $(COCl)_2$ (0.1 mL, 1.22 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.17 mL, 2.44 mmol) at -78 °C, and the resulting mixture was stirred for 5 min. To the mixture was added a solution of (-)-**11** (255 mg, 0.61 mmol) in CH_2Cl_2 (2 mL) at -78 °C, and the stirring was continued for 30 min. Triethylamine (0.51 mL, 3.66 mmol) was added to the resulting mixture at -78 °C, and the temperature was gradually increased to 0 °C. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (20 mL x 3). The combined Et_2O layer was dried and evaporated to give the crude aldehyde as a pale yellow oil. This aldehyde was used directly in the next step. To a stirred suspension of NaH (60%, 27 mg, 0.67 mmol) in THF (5 mL) was added $(EtO)_2P(O)CH_2SO_2Ph$ (214 mg, 0.73 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the aldehyde obtained above in THF (5 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 5). The combined CH_2Cl_2 layer was dried and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=15:1) to give (-)-**12** (266 mg, 80%) as a colorless oil.

IR (neat) 1715, 1446, 1266, 1234 cm^{-1}; ^1H NMR (500 MHz) δ 1.37 & 1.48 (each 3H, each s), 1.40-1.51 (3H, m), 1.55-1.64 (2H, m), 1.73-1.86 (3H, m), 2.26 (2H, q, J = 7.0 Hz), 3.14 (1H, td, J = 10.0, 4.5 Hz), 3.65-3.72 (1H, m), 4.29 (1H, br), 4.39 (1H, br), 4.56 (1H, br t-like, J = 11.0 Hz), 4.52-4.66 (1H, br), 4.71 (1H, d-like, J = 11.0 Hz), 6.30 (1H, dd-like, J = 14.0, 1.0 Hz), 6.93 (1H, dtd, J = 14.0, 6.5, 1.0 Hz), 7.52 (2H, tm, J = 8.0 Hz), 7.59 (1H, tm, J = 8.0 Hz), 7.84 (2H, dm, J = 8.0 Hz); ^{13}C NMR (75 MHz) δ 9.01 (q), 22.53 (t), 24.18 (t), 25.95 & 26.46 (each t, due to rotamers), 28.66 & 29.34 (each t, due to rotamers), 29.34 (q), 30.97 & 31.45 (each t, due to rotamers), 52.93 (d), 53.37 (d), 62.20 (t), 63.93 (t), 70.40 (d), 74.75 (t), 95.47 (s), 98.45 (s), 127.45 (d), 129.20 (d), 130.84 (d), 133.25 (d), 140.38 (s), 145.98 (d); MS 553 (M^+); HRMS Calcd. For $C_{23}H_{30}Cl_3NO_6S$: 553.0858, Found 553.0882; $[\alpha]^{26}_D$ -3.77 (*c* 4.10, $CHCl_3$).

(-)-Quinolizidine [(-)-13]: To a stirred solution of (-)-**12** (278 mg, 0.5 mmol) in THF (6 mL) were added 1N NH_4OAc (6 mL) and 10% Cd-Pb (440 mg), and the resulting suspension was stirred at room temperature for 24 h. To the suspension was added an additional 10% Cd-Pb (440 mg), and the stirring was continued an additional 24 h. The reaction was quenched with 15% aqueous K_2CO_3, and the insoluble material was removed through a celite pad. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (15 mL x 4). The organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give a colourless solid, which was recrystallized from *i*-Pr_2O-benzene-hexane to afford (-)-**13** (127 mg, 67%) as a colorless needles (mp 194~195 °C). The mother liquor was evaporated, and the residue was chromatographed on SiO_2 (10 g, hexane:acetone=17:1) to give (-)-**13** (48 mg, 25%) as an additional crops.
IR (KBr) 1291, 1268 cm^{-1}; ^1H NMR (500 MHz) δ 0.95 (1H, dm, *J* = 13.5 Hz), 1.00 (1H, tt, *J* = 14.0, 5.0 Hz), 1.25 (2H, tm, *J* = 17.0 Hz), 1.32-1.46 (2H, m), 1.38 & 1.44 (each 3H, each s), 1.48 & 1.53 (each 1H, each dt, *J* = 14.0, 4.0 Hz), 1.72 (1H, dm, *J* = 13.5 Hz), 1.75-1.89 (2H, m), 2.65 (1H, dm, *J* = 12.2 Hz), 2.78 (1H, td-like, *J* = 9.5, 4.5 Hz), 3.14 (1H, dd, *J* = 15.0, 5.0 Hz), 3.23 (1H, ddd, *J* = 11.0, 9.0, 4.2 Hz), 3.40 (1H, br dt-like, *J* = 8.0, 4.0 Hz), 3.48 (1H, t, *J* = 11.0 Hz), 3.74 (1H, dd, *J* = 14.0, 8.0 Hz), 3.90 (1H, dd, *J* = 11.0, 4.5 Hz), 7.56 (2H, t-like, *J* = 8.0 Hz), 7.65 (1H, tt-like, *J* = 8.0, 1.1 Hz), 7.92 (2H, dm, *J* = 8.0 Hz); ^{13}C NMR (75 MHz) δ 19.07 (q), 20.48 (t), 21.33 (t), 22.23 (t), 25.59 (t), 27.82 (t), 29.42 (q), 48.42 (d), 49.21 (d), 52.79 (d), 57.27 (t), 62.60 (t), 71.84 (d), 98.09 (s), 127.86 (d), 128.86 (d), 133.20 (d), 140.67 (s); MS 379 (M^+), 138 (100); HRMS Calcd. For $C_{20}H_{29}NO_4S$: 379.1817, Found 379.1839; $[\alpha]^{26}_D$ -44.5 (*c* 1.06, $CHCl_3$).

(3*R*,4*S*,6*S*,9a*S*)-(-)-4-{[(2,2-Dimethylethyl)diphenylsiloxy]methyl}-3-hydroxy-6-(phenylsulfonylmethyl)-octahydro-2*H*-quinolizine [(-)-14]: To a stirred solution of (-)-**13** (583 mg, 1.54 mmol) in EtOH (40 mL) was added 10% aqueous HCl (3 mL), and the resulting mixture was refluxed for 30 min. After cooling, the solvent was removed, and the residue was dissolved in $CHCl_3$ (30 mL). To the solution was added K_2CO_3 (3 g), and the stirring was continued at room temperature for 1 h. Filtration of K_2CO_3 and then evaporation of the filtrate gave a colourless oil, which was used directly in the next step. To a stirred solution of the oil obtained above in DMF (5 mL) were added imidazole (160 mg, 2.35 mmol) and TBDPSCl (0.41 mL, 1.58 mmol), and the resulting mixture was stirred at 80 °C for 40 min. After cooling, the reaction mixture was diluted with $CHCl_3$ (20 mL) and 15% aqueous K_2CO_3 (5 mL), and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (10 mL x 5), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=10:1) to give (-)-**14** (755 mg, 85%) as a colorless solid (mp 160~163 °C).
IR (KBr) 3501, 1289 cm^{-1}; ^1H NMR (500 MHz) δ 0.93 (1H, dd, *J* = 13.0, 4.5 Hz), 1.06 (9H, s), 1.19 (1H, dm, *J* = 13.0 Hz), 1.24-1.34 (2H, m), 1.39 (1H, qm, *J* = 13.0 Hz), 1.50 (1H, qt-like, *J* = 12.0, 4.5 Hz), 1.59 (1H, dq, *J* = 13.0, 4.5 Hz), 1.67-1.77 (3H, m), 2.61 (1H, dm, *J* = 11.0 Hz), 2.89 (1H, q-like, *J* = 7.5 Hz), 3.18 (1H, dd, *J* = 14.0, 5.5 Hz), 3.20 (1H, br s), 3.18-3.25 (1H, m), 3.61 (1H, dd, *J* = 15.0, 7.0 Hz), 3.69-3.75 (1H, br), 3.71 (1H, dd, *J* = 11.0, 5.5 Hz), 3.88 (1H, dd, *J* = 11.0, 5.0 Hz), 7.34 (2H, t-like, *J* = 7.5 Hz), 7.42-7.49 (7H,

m), 7.70-7.74 (6H, m); ^{13}C NMR (75 MHz) δ 19.03 (s), 20.34 (t), 22.99 (t), 23.70 (t), 26.74 (q), 26.86 (t), 27.63 (t), 49.48 (d), 49.94 (d), 58.38 (t), 60.44 (d), 66.84 (t), 71.45 (d), 127.81 (d), 127.86 (d), 128.82 (d), 129.92 (d), 129.97 (d), 132.62 (s), 132.81 (s), 133.09 (d), 135.63 (d), 135.65 (d), 140.25 (s); MS 577 (M^+), 520 (M^+-57), 69 (100); HRMS Calcd. For $C_{33}H_{43}NO_4S_1Si$: 577.2700, Found 577.2658; $[\alpha]^{26}_D$ -1.01 (*c* 1.02, $CHCl_3$).

(3*R*,4*S*,6*S*,9a*S*)-(-)-4-{[(2,2-Dimethylethyl)diphenylsiloxy]methyl}-3-(methoxymethoxy)-6-(phenylsulfonylmethyl)octahydro-2*H*-quinolizine [(-)-15]: To a stirred solution of (-)-**14** (755 mg, 1.31 mmol) in $CHCl_3$ (15 mL) were added MOMCl (0.31 mL, 4.08 mmol) and (*i*-Pr)$_2$EtN (0.83 mL, 4.74 mmol), and the resulting mixture was refluxed for 40 min. After cooling, the solvent was removed to give a pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=12:1) to give (-)-**15** (753 mg, 93%) as a colorless oil.

IR (neat) 1305, 1036 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.81 (1H, tt, *J* = 14.0, 4.5 Hz), 1.05 (9H, s), 1.22-1.44 (4H, m), 1.56 (1H, qd, *J* = 12.5, 4.0 Hz), 1.66-1.76 (2H, m), 1.82 (1H, dq, *J* = 12.5, 4.0 Hz), 2.18 (1H, tt, *J* = 14.0, 4.9 Hz), 2.64 (1H, dm, *J* = 11.5 Hz), 2.75 (1H, td, *J* = 10.0, 4.5 Hz), 3.02 (3H, s), 3.06 (1H, dd, *J* = 9.0, 6.0 Hz), 3.26 (1H, dd, *J* = 14.5, 5.5 Hz), 3.79 (1H, dd, *J* = 10.0, 4.5 Hz), 3.81 (1H, dd, *J* = 14.0, 7.5 Hz), 3.98 (1H, d, *J* = 11.0 Hz), 4.23 & 4.39 (2H, ABq, *J* = 7.0 Hz), 4.46-4.53 (1H, m), 7.36-7.46 (5H, m), 7.54 (1H, tt, *J* = 7.5, 1.2 Hz), 7.74 (2H, dm, *J* = 7.5 Hz), 7.81-7.84 (2H, m), 7.88 (2H, dm, J = 7.5 Hz); ^{13}C NMR (75 MHz) δ 19.11 (s), 20.65 (t), 22.59 (t), 22.63 (t), 22.97 (t), 25.70 (t), 26.69 (q), 26.91 (t), 31.56 (t), 49.31 (d), 50.63 (d), 55.42 (q), 58.22 (t), 61.64 (d), 65.69 (t), 74.61 (d), 95.26 (t), 127.46 (d), 127.70 (d), 127.95 (d), 128.75 (d), 129.44 (d), 129.56 (d), 132.92 (d), 133.37 (s), 133.47 (s), 135.80 (d), 135.85 (t), 141.24 (s); MS 621 (M^+), 564 (M^+-57), 352 (100); HRMS Calcd. For $C_{35}H_{47}NO_5S_1Si$: 621.2973, Found 621.2932; $[\alpha]^{26}_D$ -4.58 (*c* 1.24, $CHCl_3$).

(3*R*,4*S*,6*S*,9a*S*)-(-)-4-(Hydroxymethyl)-3-(methoxymethoxy)-6-(phenylsulfonylmethyl)-octahydro-2*H*-quinolizine [(-)-16]: To a stirred solution of (-)-**15** (753 mg, 1.21 mmol) in THF (15 mL) were added pyridine (3.6 mL, 44.5 mmol) and 47% aqueous HF (0.91 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched with 30% aqueous K_2CO_3, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 8). The combined $CHCl_3$ layer was dried over K_2CO_3, and evaporated to give a colourless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=5:1) to give (-)-**16** (443 mg, 95%) as a colorless oil.

IR (neat) 3502, 1301,1212, 1144 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.89-1.00 (2H, m), 1.14 (1H, br d, *J* = 14.5 Hz), 1.20 (1H, dq, *J* = 14.0, 3.0 Hz), 1.41 (1H, qm, *J* = 12.0 Hz), 1.49 (1H, qt, *J* = 13.0, 4.5 Hz), 1.70 (1H, dm, *J* = 14.0 Hz), 1.73-1.84 (3H, m), 2.65-2.70 (2H, br m), 3.08 (1H, dd, *J* = 14.0, 3.0 Hz), 3.35 (1H, br), 3.38 (3H, s), 3.55 (1H, ddd, *J* = 11.0, 9.0, 4.5 Hz), 3.82-4.00 (4H, m), 4.70 & 4.72 (2H, ABq, *J* = 6.5 Hz), 7.55 (2H, tm, *J* = 8.0 Hz), 7.62 (1H, tt, *J* = 8.0, 1.2 Hz), 7.94 (2H, dm, *J* = 8.0 Hz); ^{13}C NMR (75 MHz) δ 20.60 (t), 21.70 (t), 22.71 (t), 25.79 (t), 26.84 (t), 48.72 (d), 49.06 (d), 55.49 (q), 57.16 (t), 59.10 (d), 73.36 (d), 96.13 (t), 127.83

(d), 129.07 (d), 133.41 (d), 140.67 (s); MS 383 (M^+), 352 (100); HRMS Calcd. For $C_{19}H_{29}NO_5S$: 383.1730, Found 383.1751; $[\alpha]^{26}_D$ -3.06 (*c* 1.18, $CHCl_3$).

(3*R*,4*S*,6*S*,9a*S*)-(+)-4-(Iodomethyl)-3-(methoxymethoxy)-6-(phenylsulfonylmethyl)-octahydo-2*H*-quinolizine [(+)-17]: To a stirred solution of (-)-**16** (443 mg, 1.16 mmol) in benzene (20 mL) were added imidazole (195 mg, 2.87 mmol), Ph_3P (757 mg, 2.89 mmol) and I_2 (584 mg, 2.30 mmol), and the resulting suspension was stirred at room temperature for 20 min. The reaction was quenched with 10% $Na_2S_2O_3$ in sat. aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 1, 10 mL x 5). The combined CH_2Cl_2 layer was dried over K_2CO_3 and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=15:1) to give (+)-**17** (510 mg, 89%) as a pale yellow oil.

IR (neat) 1302, 1199, 1036 cm^{-1}; ^1H NMR (500 MHz) δ 1.09 (1H, br d, *J* = 12.0 Hz), 1.22-1.32 (1H, br m), 1.39-1.55 (3H, m), 1.61-1.81 (4H, m), 1.86-1.93 (1H, br m), 2.16 (1H, br d, *J* = 8.0 Hz), 2.82 (1H, br d, *J* = 12.0 Hz), 3.12-3.19 (2H, m), 3.33-3.39 (1H, m), 3.36 (3H, s), 3.43 (1H, br d, *J* = 10.0 Hz), 3.70 (1H, d-like, *J* = 10.0 Hz), 3.73 (1H, dd, *J* = 13.0, 11.0 Hz), 4.64 & 4.69 (2H, ABq, *J* = 6.8 Hz), 7.55 (2H, t-like, *J* = 7.5 Hz), 7.63 (1H, t-like, *J* = 7.5 Hz), 7.93 (2H, d-like, *J* = 7.5 Hz); ^{13}C NMR (75 MHz) δ 11.08 (t), 19.77 (t), 19.78 (t), 23.49 (t), 24.93 (t), 27.64 (t), 48.41 (d), 50.24 (d), 55.77 (q), 56.06 (d), 58.71 (t), 76.75 (d), 95.58 (t), 128.06 (d), 129.29 (d), 133.63 (d), 139.94 (s); MS 493 (M^+), 366 (100); HRMS Calcd. For $C_{19}H_{28}INO_4S$: 493.0747, Found 493.0787; $[\alpha]^{26}_D$ +30.9 (*c* 2.78, $CHCl_3$).

(3*R*,4*S*,6*S*,9a*S*)-(-)-3-(Methoxymethoxy)-4-methyl-6-(phenylsulfonylmethyl)-octahydro-2*H*-quinolizine [(-)-18]: To a stirred solution of (+)-**17** (510 mg, 1.03 mmol) in toluene (15 mL) were added *n*-Bu_3SnH (0.35 mL, 1.24 mmol) and AIBN (34 mg, 0.21 mol), and the resulting solution was refluxed for 16 h. After cooling, the solvent was removed, and the residue was dissolved in MeCN (25 mL). The MeCN solution was washed with hexane (6 mL x 8) and then evaporated. The residue was chromatographed on SiO_2 (15 g, hexane:acetone=14:1) to give (-)-**18** (358 mg, 94%) as a colorless oil.

IR (neat) 1304, 1148, 1106 cm^{-1}; ^1H NMR (500 MHz) δ 0.89-0.94 (1H, m), 0.99 (1H, tt, *J* = 15.0, 5.0 Hz), 1.04 (3H, d, *J* = 5.9 Hz), 1.22-1.37 (3H, m), 1.54 (1H, tt, *J* = 13.0, 4.0 Hz), 1.67-1.83 (4H, m), 2.61 (1H, dm, *J* = 12.5 Hz), 2.72-2.78 (1H, m), 2.82 (1H, tt, *J* = 11.0, 4.5 Hz), 3.26 (1H, dd, *J* = 14.5, 6.0 Hz), 3.35 (3H, s), 3.63 (1H, dd, *J* = 14.5, 7.0 Hz), 3.82 (1H, br q, *J* = 5.5 Hz), 4.56 & 4.68 (2H, ABq, *J* = 7.0 Hz), 7.53 (2H, t-like, *J* = 8.0 Hz), 7.60 (1H, tt-like, *J* = 8.0, 1.0 Hz), 7.91 (2H, dm, *J* = 8.0 Hz); ^{13}C NMR (75 MHz) δ 15.39 (q), 20.45 (t), 20.97 (t), 22.23 (t), 25.82 (t), 27.70 (t), 48.93 (d), 49.15 (d), 53.02 (d), 55.54 (q), 58.13 (t), 79.31 (d), 95.58 (t), 128.07 (d), 128.84 (d), 133.16 (d), 140.53 (s); MS 367 (M^+), 212 (100); HRMS Calcd. For $C_{19}H_{29}NO_4S$: 367.1796, Found 367.1830; $[\alpha]^{26}_D$ -10.95 (*c* 0.81, $CHCl_3$).

(3*R*,4*S*,6*S*,9a*S*)-(-)-6-(Deca-1,3-dienyl)-3-(methoxymethoxy)-4-methyloctahydro-2*H*-quinolizine [(-)-19]: To a stirred solution of (-)-**18** (76 mg, 0.21 mmol) in THF (2 mL) was added *n*-BuLi (10% in hexane, 0.15 mL, 0.23 mmol) at -80 °C, and the resulting solution was stirred for 10 min. To the solution was added *trans*-2-nonenal (0.07 mL, 0.42 mmol) at -80 °C, and the reaction mixture was stirred at -50 °C for 1 h. The

reaction was quenched with 15% aqueous K_2CO_3, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 5). The combined $CHCl_3$ layer was dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the oil obtained above in MeOH (5 mL) were added Na_2HPO_4 (220 mg, 1.55 mmol) and 5% Na-Hg (1.8 g), and the resulting suspension was stirred at room temperature for 2 h. The reaction was quenched with 15% aqueous K_2CO_3, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 4). The combined $CHCl_3$ layer was dried over K_2CO_3 and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=20:1) to give (-)-**19** (38 mg, 53%) as a colorless oil.

IR (neat) 1654, 1560, 1543 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, *J* = 7.0 Hz), 1.12 (3H, d, *J* = 6.5 Hz), 1.24-1.31 (7H, m), 1.36 (2H, quint-like, *J* = 7.0 Hz), 1.45-1.56 (3H, m), 1.57-1.64 (2H, m), 1.70-1.76 (2H, m), 1.87 (1H, tt-like, *J* = 12.5, 3.8 Hz), 1.91-1.99 (1H, m), 2.05 (2H, br q, *J* = 6.5 Hz), 3.18-3.23 (1H, m), 3.27-3.33 (1H, m), 3.35 (3H, s), 3.39 (1H, q, *J* = 4.0 Hz), 3.84 (1H, td, *J* = 8.0, 3.0 Hz), 4.61 (2H, s), 5.52 (1H, dd, *J* = 14.0, 7.5 Hz), 5.58 (1H, dt, *J* = 14.0, 7.1 Hz), 6.03 (1H, dd, *J* = 14.0, 10.0 Hz), 6.09 (1H, dd, *J* = 14.0, 10.0 Hz); ^{13}C NMR (75 MHz) δ 14.10 (q), 17.12 (q), 19.68 (t), 22.05 (t), 22.59 (t), 25.92 (t), 28.91 (t), 29.32 (t), 29.38 (t), 31.24 (t), 31.72 (t), 32.63 (t), 49.13 (d), 52.95 (d), 55.27 (q), 57.64 (d), 75.44 (d), 94.22 (t), 130.13 (d), 131.01 (d), 133.35 (d), 136.26 (d); MS 349 (M^+), 334 (100); HRMS Calcd. For $C_{22}H_{39}NO_2$: 349.3018, Found 349.3001; $[\alpha]^{26}_D$ -20.7 (*c* 0.81, $CHCl_3$).

(+)-Clavepictine B: To a stirred solution of (-)-**19** (38 mg, 0.11 mmol) in MeOH (2 mL) was added c. HCl (2 drops), and the resulting solution was refluxed for 4 h. After cooling, the reaction was quenched with 15% aqueous K_2CO_3, and the solvent was removed. The residue was extracted with hot $CHCl_3$ (5 mL x 10), and the $CHCl_3$ layer was combined and evaporated to give a colourless oil, which was chromatographed on SiO_2 (10 g, $CHCl_3$:MeOH=10:1) to give (+)-clavepictine B (27 mg, 82%) as a colorless solid (mp 70~72 °C, lit[1] mp 70~72 °C).

IR (KBr) 3202, 3019, 2923, 2855, 1659, 1443, 1368, 1340, 1278, 1202, 1151, 1055, 1039, 1029, 990 cm^{-1}; ^1H NMR (500 MHz, C_5D_5N) δ 0.81 (3H, t, *J* = 7.0 Hz), 1.15-1.27 (7H, br m), 1.29 (3H, d, *J* = 6.5 Hz), 1.29-1.35 (2H, m), 1.36-1.43 (1H, m), 1.48-1.59 (2H, m), 1.60-1.72 (3H, m), 1.77-1.86 (2H, m), 1.90-1.96 (1H, m), 2.05 (2H, q, *J* = 7.0 Hz), 3.11-3.16 (1H, m), 3.32 (1H, quint, *J* = 6.0 Hz), 3.62 (1H, quint-like, *J* = 5.0 Hz), 4.04 (1H, br q, *J* = 5.0 Hz), 5.65 (1H, dt, *J* = 15.0, 7.0 Hz), 5.78 (1H, d, *J* = 5.5 Hz), 5.87 (1H, dd, *J* = 15.0, 7.0 Hz), 6.22 (1H, dd, *J* = 15.0, 10.0 Hz), 6.38 (1H, dd, *J* = 15.0, 10.0 Hz); ^{13}C NMR (125 MHz, C_5D_5N) δ 14.24 (q), 16.79 (q), 20.60 (t), 22.84 (t), 26.07 (t), 27.87 (t), 28.10 (t), 29.12 (t), 29.34 (t), 29.70 (t), 31.92 (t), 32.95 (t), 49.47 (d), 56.67 (d), 57.21 (d), 71.87 (d), 130.87 (d), 131.23 (d), 133.02 (d), 137.03 (d); $[\alpha]^{26}_D$ +25.7 (*c* 0.61, CH_2Cl_2), lit[1] $[\alpha]^{26}_D$ +27.1 (*c* 0.03, CH_2Cl_2).

(-)-Clavepictine A: To a stirred solution of (+)-clavepictine B (25 mg, 0.082 mmol) in pyridine (0.3 mL) was added Ac_2O (0.1 mL), and the resulting mixture was stirred at room temperature for 5 h. The volatiles

were removed, and the residue was chromatographed on SiO_2 (10 g, hexane:acetone=16:1) to give (-)-clavepictine A (26 mg, 90%) as a colorless oil.

IR (neat) 3016, 2928, 2856, 1736, 1654, 1560, 1458, 1376, 1246, 1162, 1108, 1029, 990, 962 cm^{-1}; ^1H NMR (500 MHz, C_5D_5N) δ 0.80 (3H, t, J = 7.0 Hz), 0.95 (1H, dq-like, J = 12.6, 3.0 Hz), 1.10 (3H, d, J = 7.1 Hz), 1.12-1.24 (6H, m), 1.26-1.35 (3H, m), 1.42-1.50 (4H, br m), 1.58 (1H, dm, J = 13.0 Hz), 1.75 (1H, dq, J = 13.0, 4.0 Hz), 1.84 (1H, tt, J = 11.0, 4.0 Hz), 1.93 (1H, qd-like, J = 13.0, 4.0 Hz), 2.04 (2H, q-like, J = 6.0 Hz), 2.15 (3H, s), 3.11 (1H, dm, J = 10.0 Hz), 3.50 (1H, qd-like, J = 7.0, 2.5 Hz), 3.85 (1H, td, J = 8.0, 3.0 Hz), 4.70 (1H, q, J = 3.0 Hz), 5.66 (1H, dd, J = 15.0, 7.0 Hz), 5.73 (1H, dt, J = 15.0, 7.0 Hz), 6.17 (1H, dd, J = 15.0, 10.5 Hz), 6.31 (1H, dd, J = 15.0, 10.5 Hz); ^{13}C NMR (125 MHz, C_5D_5N) δ 14.10 (q), 17.20 (q), 19.68 (t), 20.59 (t), 21.60 (t), 22.59 (t), 25.68 (q), 28.96 (t), 29.29 (t), 31.72 (t), 32.63 (t), 49.00 (d), 52.89 (d), 58.01 (d), 73.29 (d), 129.97 (d), 130.95 (d), 133.58 (d), 136.15 (d), 170.34 (s); $[\alpha]^{26}_D$ –74.5 (*c* 0.55, CH_2Cl_2), lit[1] $[\alpha]^{26}_D$ -75.6 (*c* 0.7, CH_2Cl_2).

(3*R*,4*S*,6*S*,9a*S*)-(-)-3-(Methoxymethoxy)-4-methyl-6-(octa-1,3-dienyl)octahydro-2*H*-quinolizine [(-)-20]: To a stirred solution of (-)-**18** (120 mg, 0.33 mmol) in THF (2 mL) was added *n*-BuLi (10% in hexane, 0.26 mL, 0.39 mmol) at -80 °C, and the resulting solution was stirred for 10 min. To the solution was added *trans*-2-heptenal (0.085 mL, 0.65 mmol) at –80 °C, and the reaction mixture was stirred at –50 °C for 1 h. The reaction was quenched with 15% aqueous K_2CO_3, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 4). The combined $CHCl_3$ layer was dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the oil obtained above in MeOH (10 mL) were added Na_2HPO_4 (350 mg, 2.45 mmol) and 5% Na-Hg (2.8 g), and the resulting suspension was stirred at room temperature for 2 h. The reaction was quenched with 15% aqueous K_2CO_3, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 4). The combined $CHCl_3$ layer was dried over K_2CO_3 and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=20:1) to give (-)-**20** (51 mg, 48%) as a colorless oil.

IR (neat) 1654, 1458 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t, J = 7.0 Hz), 1.12 (3H, d, J = 6.9 Hz), 1.13-1.18 (1H, m), 1.24-1.38 (5H, m), 1.45-1.63 (5H, m), 1.70-1.76 (1H, m), 1.84-1.90 (1H, m), 1.96 (1H, qm, J = 11.0 Hz), 2.06 (2H, br q, J = 7.0 Hz), 3.18-3.23 (1H, m), 3.28-3.33 (1H, m), 3.35 (3H, s), 3.39 (1H, q-like, J = 4.0 Hz), 3.84 (1H, td, J = 8.0, 3.0 Hz), 4.61 (2H, s), 5.52 (1H, dd, J = 14.0, 7.5 Hz), 5.58 (1H, dt, J = 14.0, 7.0 Hz), 6.03 (1H, ddt-like, J = 14.0, 10.0, 1.0 Hz), 6.09 (1H, dd, J = 14.0, 10.0 Hz); ^{13}C NMR (75 MHz) δ 13.95 (q), 17.12 (q), 19.69 (t), 22.06 (t), 22.26 (t), 25.92 (t), 29.38 (t), 31.26 (t), 31.50 (t), 32.29 (t), 49.14 (d), 52.95 (d), 55.26 (q), 57.64 (d), 75.46 (d), 94.44 (t), 130.17 (d), 131.02 (d), 133.28 (d), 136.23 (d); MS 321 (M^+), 334 (100); HRMS Calcd. For $C_{20}H_{35}NO_2$: 321.2666, Found 321.2648; $[\alpha]^{26}_D$ -36.8 (*c* 0.73, $CHCl_3$).

(3R,4S,6S,9aS)-(+)-3-Hydroxy-4-methyl-6-(octa-1,3-dienyl)octahydro-2H-quinolizine [(+)-21]: To a stirred solution of (-)-**20** (38 mg, 0.12 mmol) in MeOH (2 mL) was added c. HCl (3 drops), and the resulting solution was refluxed for 4 h. After cooling, the reaction was quenched with 15% aqueous K_2CO_3, and the

solvent was removed. The residue was extracted with hot $CHCl_3$ (5 mL x 10), and the $CHCl_3$ layer was combined and evaporated to give a colourless oil, which was chromatographed on SiO_2 (10 g, $CHCl_3$:MeOH=10:1) to give (+)-**21** (29 mg, 84%) as a colorless solid (mp 67~69 °C).

IR (KBr) 3200, 1655, 1460 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t, *J* = 7.0 Hz), 1.05 (3H, d, *J* = 6.9 Hz), 1.27-1.38 (5H, m), 1.39-1.64 (6H, m), 1.68-1.80 (3H, br m), 2.06 (2H, q, *J* = 7.0 Hz), 2.89 (1H, br), 2.93-2.98 (1H, ddd, *J* = 13.0, 6.5, 4.0 Hz), 3.00-3.05 (1H, m), 3.44-3.50 (2H, m), 5.58-5.64 (1H, m), 5.91-5.97 (1H, m), 5.99-6.04 (2H, m); ^{13}C NMR (125 MHz) δ 13.95 (q), 14.30 (q), 19.21 (t), 22.27 (t), 25.89 (t), 27.09 (t), 31.48 (t), 32.33 (t), 32.59 (t), 32.79 (t), 47.06 (d), 58.98 (d), 61.08 (d), 70.51 (d), 129.86 (d), 129.99 (d), 133.74 (d), 134.43 (d); MS 277 (M^+); HRMS Calcd. For $C_{18}H_{31}NO$: 277.2404, Found 277.2433; $[\alpha]^{26}_D$ +29.6 (*c* 0.74, $CHCl_3$).

(-)-Pictamine: To a stirred solution of (+)-**21** (16 mg, 0.055 mmol) in pyridine (0.3 mL) was added Ac_2O (0.1 mL), and the resulting mixture was stirred at room temperature for 16 h. The volatiles were removed, and the residue was chromatographed on SiO_2 (10 g, hexane:acetone=16:1-10:1) to give (-)-pictamine (17 mg, 92%) as a colorless oil.

IR (neat) 3015, 2931, 2861, 1736, 1246, 1162, 1030, 990 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.86-0.91 (1H, m), 0.88 (3H, t, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 7.0 Hz), 1.24-1.37 (4H, m), 1.38-1.44 (2H, m), 1.45-1.56 (3H, br m), 1.65 (1H, dq-like, *J* = 12.5, 3.7 Hz), 1.69-1.77 (2H, m), 1.87 (3H, s), 1.92 (1H, qm, *J* = 11.0 Hz), 2.04 (2H, q, *J* = 7.5 Hz), 3.05 (1H, dq, *J* = 10.5, 3.0 Hz), 3.52 (1H, qd, *J* = 7.0, 3.0 Hz), 3.86 (1H, td, *J* = 8.0, 3.0 Hz), 4.76 (1H, q, *J* = 3.0 Hz), 5.67 (1H, dt, *J* = 15.0, 8.0 Hz), 5.72 (1H, dd, *J* = 15.0, 8.0 Hz), 6.13 (1H, dd, *J* = 14.0, 10.0 Hz), 6.26 (1H, dd, *J* = 15.0, 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.94 (q), 17.17 (q), 19.63 (t), 20.50 (t), 21.58 (t), 22.28 (t), 25.64 (q), 29.99 (t), 31.45 (t), 32.26 (t), 32.81 (t), 48.97 (d), 52.86 (d), 58.00 (d), 73.22 (d), 129.95 (d), 130.94 (d), 133.50 (d), 136.08 (d), 170.32 (s); $[\alpha]^{26}_D$ -83.5 (*c* 0.89, EtOAc), lit[2] $[\alpha]^{26}_D$ -87 (*c* 0.1, EtOAc).

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We are grateful to Doctor John H. Cardellina, II, National Cancer Institute, for kindly providing us with ^1H and ^{13}C NMR spectra of natural clavepictines A and B, and indebted to Professor D. John Faulkner, University of California, San Diego, for his kindly providing us with ^1H and ^{13}C NMR spectra of natural pictamine.

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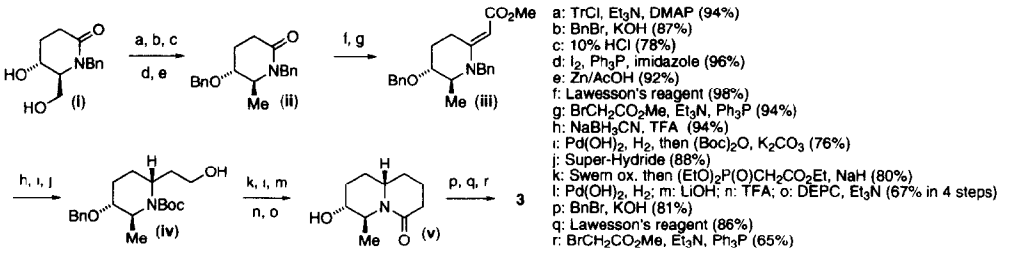
7. The vinylogous urethane **3** was prepared from diol (**i**)[3] as follows:



8. Decoupling experiments of **4** revealed that the protons at the C_6 position and the bridge-head are axial orientation. This observation means that the relative stereochemistry of methyl and methoxycarbonylmethyl groups is *trans* relationship, and the ring juncture is also *trans* relationship.

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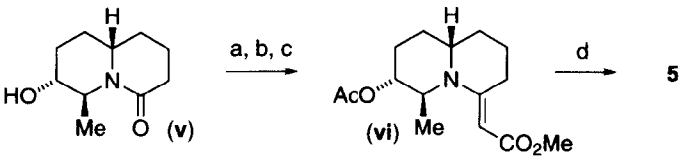
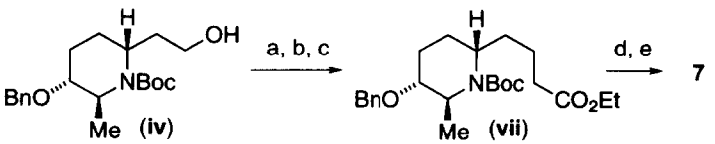
11. The vinylogous urethane **5** was prepared from (**v**) obtained above as follows:



a: Ac_2O, pyridine (89%); b: Lawesson's reagent (99%);
c: $BrCH_2CO_2Me$, Et_3N, Ph_3P (80%); d: K_2CO_3, MeOH (quant.)

12. The piperidine **7** was prepared from (**iv**) obtained above as follows:



a: Swern ox. then $(EtO)_2P(O)CH_2CO_2Et$, NaH (80%); b: $Pd(OH)_2$, H_2;
c: MOMCl, Hünig base (95%); d: Super-Hydride (93%);
e: Swern ox. then $(EtO)_2P(O)CH_2CO_2Et$, NaH (57%)

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14. Crystallographic data for (-)-**13**: orthorhombic, space group $P2_12_12_1$, with a = 14.160(3) Å, b = 15.825(3) Å, c = 8.616(3) Å^3, and Z = 4 (D_{calcd} = 1.306 g cm^{-3}), μ (Mo Kα) = 1.92 cm^{-1} absorption corrected by ω scans; 966 with $I>3.00\sigma(I)$ were used in refinement; R = 5.2%, R_w = 6.4 %.