A Stereospecific Synthesis of (±)-5,8-Disubstituted Indolizidines and (±)-1,4-Disubstituted Quinolizidines Found in Poison Frog Skins

Patrick Michel and André Rassat*

Ecole Normale Supérieure, Département de Chimie, UMR CNRS 8640, 24, rue Lhomond, F-75231 Paris, Cedex 05, France

John W. Daly and Thomas F. Spande

Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, 20892-0820

Andre.Rassat@ens.fr

Received May 1, 2000

An efficient, high-yield stereospecific route to three (±)-5,8-disubstituted indolizidines, (**209B** (***I***), **209I** (***II***), **223J** (***III***)) and two (±)-1,4-disubstituted quinolizidines (**207I** (***IV***), **233A** (***V***)), racemates of alkaloids found in the skins of neotropical and Madagascan poison frogs is reported. The structures of the natural alkaloids were thereby established by chiral GC comparison with the exception of indolizidine **209B** (***I***) for which a natural **209B** could no longer be detected.

Introduction

Skins of certain genera of frogs/toads of the Dendrobatidae, Bufonidae, Mantellinae, and Myobatrachidae families contain a wide variety of alkaloids, chiefly bi- and tricyclic structures with a single nitrogen.[1] Many are of the "izidine" class, with disubstituted pyrrolizidines, di- and trisubstituted indolizidines and disubstituted quinolizidines having been characterized. Occasionally, sufficient natural material has permitted NMR analysis, but more frequently, as in the present study, we are forced to rely upon GC−mass spectrometry and GC−FTIR spectroscopy for structural elucidation and comparison of natural and synthetic materials. In fact, many proposed structures[1] are based solely on analogy and GC data.

Certain alkaloids of the "izidine" type have been detected in ants, which, along with other arthropods, appear the likely source of most of the over 500 alkaloids detected so far in amphibian skin. Of the indolizidines, two disubstituted patterns have been observed, namely 3,5- and 5,8-, while a 5,6,8-trisubstituted class with several members has also been recently characterized. Both 1,4- and 4,6-disubstituted quinolizidines have been found. The 5,8-disubstituted indolizidines (58 examples[1] with structures either established or proposed) and 1,4-disubstituted quinolizidines (six examples[1] with structures either established or proposed) are the more common structural patterns found in amphibian skin and have received the greatest attention in characterization and synthesis.[1] None of these alkaloids has so far been reported from any other source.

Bohlmann band patterns in the infrared spectra allow the assignment of the relative *E* or *Z* stereochemistry at positions 5 and 9 in the 5,8-disubstituted indolizidines and positions 4 and 10 in the 1,4-disubstituted quinolizidines[1] but no other spectral methods at present, short of ^{1}H NMR spectroscopy, permit the assignment of the relative stereochemistry of the substituent at C-8 in the 5,8-disubstituted indolizidines or that at C-1 in the 1,4-disubstituted quinolizidines. For such assignments, where insufficient material exists for NMR characterization, as is true in the present study, synthesis of the possible stereoisomers is the only option. Simple analogy to the stereochemistry of well-characterized natural 5,8-indolizidines or 1,4-quinolizidines is not justified, since naturally occurring examples of both C-8 epimers in the indolizidine case are known and an example of naturally occurring 1-epimers has also been found in frog skin 1,4-quinolizidines.[2]

Nearly all previous syntheses in the 5,8-series were restricted to the 8-methyl analogues; enantioselective syntheses have proved the equatorial *R* configuration for that substituent in all cases examined.[3] Although the structure postulated for the 5,8-indolizidine **209B**, having an 8*R* methyl configuration, was previously synthesized by several groups[4] identity was never confirmed by direct comparison with natural material. The present synthesis provides a new route to synthetic (±)-**209B** (***I***) and provided us the racemic material necessary to compare the two enantiomers with natural **209B** using chiral GC columns.

Syntheses of two (±)-5,8-indolizidines having an 8-*n*-propyl substituent (**209I** (***II***), **223J** (***III***)) and syntheses

(1) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In Alkaloids: Chemical and Biological Perspectives; Pelletier S. W. Ed.; Pergamon: New York, 1999; Vol. 13. Chapter 1, pp 1−161.

(2) The quinolizidine **217A** and its 1-epimer both occur in a Madagascan frog. Unpublished work. For their syntheses, see: Pearson, W. H.; Suga, H. *J. Org. Chem.* **1998**, *63*, 9910−9918.

(3) Comins, D. L.; LaMunyon, D. H.; Chen, X. H. *J. Org. Chem.* **1997**, *62*, 8182−8187 and references cited therein.

(4) Comins, D. L.; Zeller, E, *Tetrahedron Lett.* **1991**, *32*, 5889−5892; Holmes, A. B.; Smith, A. L.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393−1405; Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2883; Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, *59*, 943−945; Aehman, J.; Somfai, P. *Tetrahedron* **1995,** *51*, 9747−9756.

10.1021/jo000666b CCC: $19.00
Published on Web 12/05/2000

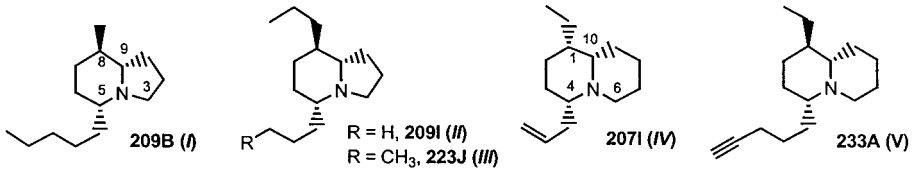
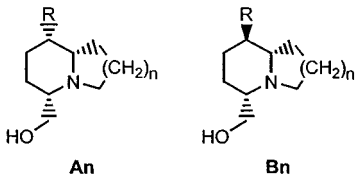


Figure 1. Racemic frog skin alkaloids synthesized in this work.

Scheme 1



of two (±)-1,4-quinolizidines having a 1-ethyl substituent (**207I** (***IV***), **233A** (***V***)) were also undertaken as a means of completing or confirming the tentative structural assignments (Figure 1) of those natural alkaloids and permitting, if possible, the elucidation of the absolute stereochemistry of the natural materials. The synthetic route described below would in principle allow the synthesis of any disubstituted indolizidine or quinolizidine with saturated C-8 or C-1 substituents, respectively. Furthermore the syntheses are compatible with any indolizidine C-5 substituent or C-4 quinolizidine substituent, whether saturated or unsaturated.

Results and Discussion

Since we wanted to selectively control the relative configuration of alkyl substituents at indolizidine C-8 and quinolizidine C-1, we looked for a versatile method that could be used to prepare selectively the two epimeric series **An** and **Bn**, (indolizidine, n, = 1; quinolizidine, n = 2), where R could be a methyl, ethyl, or *n*-propyl group (Scheme 1); the other side chain being elaborated from the hydroxymethyl substituent. The key intermediates chosen were **7** and **9** (Scheme 2) and **20**, **21**, **24a**, **24b**, and **25** (Scheme 3). The 9-azabicyclo[3.3.1]nonane derivative **1**, easily obtained in large quantities,[5] was a convenient starting material. Opening of either ring would ensure cis substituents at piperidine C-2 and C-6, so that the substituent at the indolizidine C-8 or quinolizidine C-1 positions could be stereospecifically introduced. Structures of intermediates (**26-51**) along with synthetic details and properties of most such intermediates, are provided in the Supporting Information.

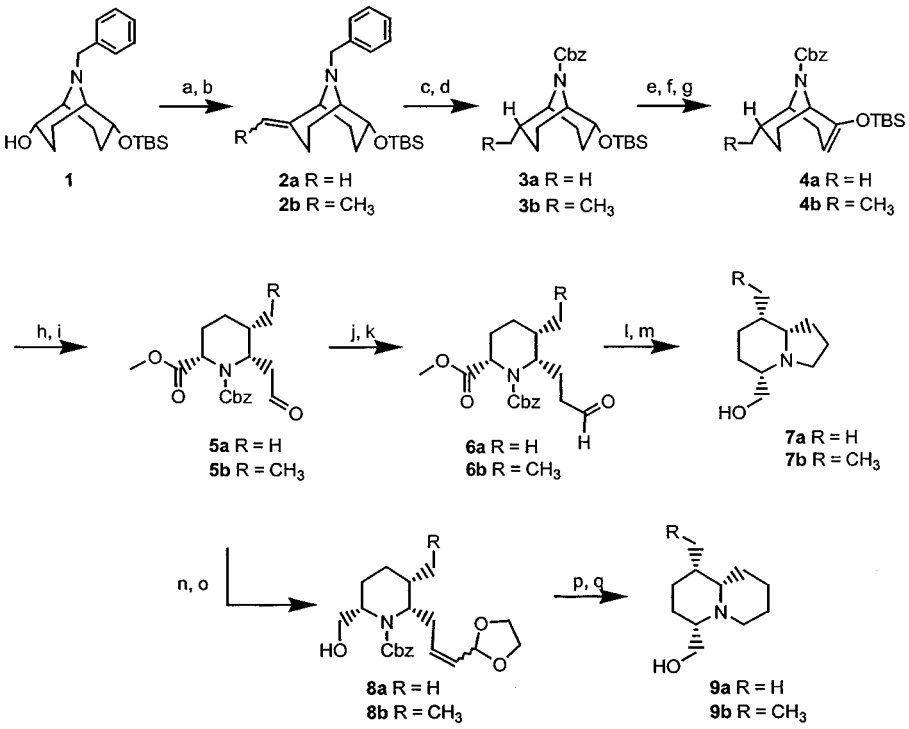
A_n Series. In this series, the axial substituents at the indolizidine C-8 or quinolizidine C-1 are thermodynamically unstable and thus we decided to control this stereochemistry at the bicyclo[3.3.1]nonane stage. Swern oxidation of **1** followed by a Wittig reaction afforded **2a/b** (Scheme 2). **2b** was obtained as a 1/9 mixture of *Z* and *E* isomers which was easily separated by column chromatography. However, hydrogenation of **2a** or **2b** in methanol afforded homogeneous saturated debenzylated amines. When this reaction was followed by ^{1}H NMR, an initial hydrogenolysis of the benzyl group was observed, followed by reduction of the double bond. The stereospecificity for exo attack may be possibly related to coordination of the secondary nitrogen atom with the platinum catalyst. The equatorial OTBS group probably also increases steric hindrance from the endo side by locking the other ring in a chair conformation. The experimental conditions were critical at this stage: if the concentration of **2a/b** was greater than 0.2 M, phase-separation occurred and the reduced secondary amine was not obtained. This amine was then protected by carbobenzyloxylation to afford the alcohols **3a/b** (**3a** 92%, **3b** 82% overall from **2a/b**) which were converted in three steps to the silyl enol ethers **4a/b**. The bicyclo[3.3.1]nonane skeleton was then opened by ozonolysis of **4a/b** to give, after three classical steps, the substituted piperidine acetaldehyde esters **5a/b**. One carbon was then added by a Wittig reaction and the enol ether initially formed was converted to the piperidine priopionaldehyde esters **6a/b**. Cyclization to the indolizidines **7a/b** was then effected in two steps.

Quinolizidines **9a/b** were obtained after a two-carbon homologation of the aldehyde esters **5a/b**. In this case, the methoxycarbonyl function could be reduced at an earlier stage, because the presence of the resulting alcohol does not interfere with the removal of the dioxolane protecting group. Thus we could retain the easier-to-purify carbamates for an additional step. At this stage, the stereochemistry of the hydrogenation products **9a**/**9b** was confirmed by the coupling constants observed for H-10. The ddd signals observed for H-10 in **9a** (δ 2.11) or **9b** (δ 2.14) (see Experimental Section for **9a**) were each observed to be comprised of one large and two small and equal couplings. The small couplings are assigned to axial−equatorial couplings H-10−H-$1_{eq.}$ and H-10−H-$9_{eq.}$ and the large coupling to H-10−H-9_{ax}, confirming an axial orientation for the 1-methyl group. ^{13}C-signals for the 1-methyl (12.8 ppm) of **9a** and the methylene of the 1-ethyl (17.9 ppm) of **9b** likewise confirm an axial orientation for both substituents.

B_n Series. Since the R substituents in this series will have the thermodynamically stable equatorial orientation, we decided to control the configuration at the izidine stage by epimerization of the aldehyde **16** or **17** (Scheme 3). Using a sequence of reactions similar to those of Scheme 1, alcohol **1** was converted into the indolizidine **12** (or quinolizidine **13**) and transformed by Swern oxidation and Wittig reaction into the enol ethers **14** (or **15**). The aldehyde **16** (or **17**) was selectively obtained by treatment with a 4 N HCl/THF solution until a single aldehyde proton signal was observed by ^{1}H NMR. The aldehydes were directly reduced to **18** (or **19**) then converted into **20** (or **21**), or homologated to **22** (or **23**) to afford the indolizidines **24** (or the quinolizidine **25**). The ^{1}H NMR spectrum of **209B** obtained from **20** is identical to that reported [4] confirming that the thermodynamically most stable orientation for the aldehydo group after equilibration is exclusively the equatorial configuration. ^{13}C-signals for the 8-methyl group of indolizidine **20** (18.6 ppm) or the 1-methyl group of quinolizidine **21** (18.9 ppm) indicated equatorial configurations.[2]

(5) Michel, P.; Rassat, A. *J. Org. Chem.* **2000**, *65*, 2572−2573.

Scheme 2[a]



[a] Key: (a) Swern oxidation (93% **26**); (b) (Ph_3PCH_2R)Br, *t*-BuOK, THF (92% **2a**; 98% **2b**); (c) H_2, Pd/C 10% (wet), MeOH; (d) CbzCl, K_2CO_3, acetone (95% in two steps **3a**); (e) 40% HF, CH_3CN (97% **27a**); 82% in three steps **27b**); (f) Swern oxidation (86% **28a**; 81% **28b**); (g) KH, THF, TBDMSCl (93% **4a**; 88% **4b**); (h) (i) O_3, MeOH/CH_2Cl_2, (ii) $NaBH_4$, (iii) CH_2N_2 (71% **29a**; 71% **29b**); (i) Swern oxidation (80% **5a**; 81% **5b**); (j) ($Ph_3PCH_2OCH_3$)Cl, *t*-BuOK, THF (51% **30a**); (k) *p*-TsOH, acetone (58%, **6a**); (l) H_2, Pd/C 10%, MeOH/H_2O (47% **31a**; 13% in three steps **31b**); (m) Super-Hydride, THF, 0 °C (76% **7a**; 45% **7b**); (n) ($Ph_3PCH_2CH(OCH_2CH_2O)$)Br, *t*-BuOK, THF (79% **32a**; 95% **32b**); (o) Super-Hydride, THF, 0 °C (79% **8a**; 94% **8b**); (p) THF, 1.2 N HCl (96% **33a**; 89% **33b**); (q) H_2, Pd/C 10%, MeOH/H_2O (70% **9a**; 78% **9b**). For structures of intermediates see Scheme 8 (Supporting Information).

Side Chains. In each series, transformation to the desired natural product (Schemes 4−7) was easily accomplished by introduction of the appropriate side chains using Wittig reactions on the aldehydes obtained in turn from the alcohols **20**, **24b**, **25**, or **9b**. Racemic indolizidines **209B**, **209I**, and **223J** with an 8-equatorial configuration were prepared from **20** or **24b**, while for quinolizidine **207I**, a second Wittig reaction was used. For quinolizidine **233A**, the aldehyde from the Wittig reaction was converted into the desired alkyne in a one-pot reaction using dibromomethyltriphenylphosphonium bromide.[6] Below we have indicated the final key steps of each synthetic sequence and the methods used to establish identity with the naturally occurring alkaloid.

Synthesis of Indolizidines.

Indolizidine (±)-209B (*I*). This was prepared in 27% overall yield from **20** by Swern oxidation and Wittig reaction of *n*-butyltriphenylphosphonium bromide with the resulting aldehyde followed by hydrogenation (Scheme 4). Both enantiomers of our synthetic (±)-**209B** having the previously proposed[1] 8-equatorial methyl of the natural **209B** separated on a chiral column. A natural material **209B** [7] could no longer be detected in extracts from dendrobatid frogs and its presence and identity remain in question. A sample of (±)-**205A** on hydrogenation (2.5 h; Pd/C/MeOH) was indistinguishable on the chiral column from our synthetic (±)-**209B** (***I***) confirming earlier work of Kibayashi[4] that his (−)-**209B** had the same absolute stereochemistry as (−)-**205A** and (−)-**207A**, i.e., an 8*R* configuration.

Indolizidine (±)-209I (*II*). This was prepared in 41% overall yield from **24b** by Swern oxidation and Wittig reaction of ethyltriphenylphosphonium bromide with the resulting aldehyde followed by hydrogenation (SCHEME 5). It proved to be identical with the natural material[1] by the criteria of GC co-injection and identical mass and GC−FTIR spectra.

Indolizidine (±)-223J (*III*). This was prepared in 35% overall yield from **24b** via the aldehyde above followed by Wittig reaction with *n*-propyltriphenylphosphonium bromide followed by hydrogenation. It was identical with the natural material[1] by the criteria of GC co-injection and identical mass and GC−FTIR spectra. An 8*R* equatorial configuration for the 8-*n*-propyl group of the 5,8-indolizidine **223J** had earlier been tentatively assigned by analogy to several C-8 methyl alkaloids (**205A**, **207A, 235B′**) where synthesis by a number of groups[4] had established an equatorial 8*R* configuration. Our synthesis of (±)-**223J** with an 8-equatorial propyl substituent proved on comparison with natural **223J** that the tentative equatorial assignment for an 8-*n*-propyl substituent was correct. The absolute configuration appears likely to be 8*R* in analogy to **205A**, **207A**, and **235B′**.

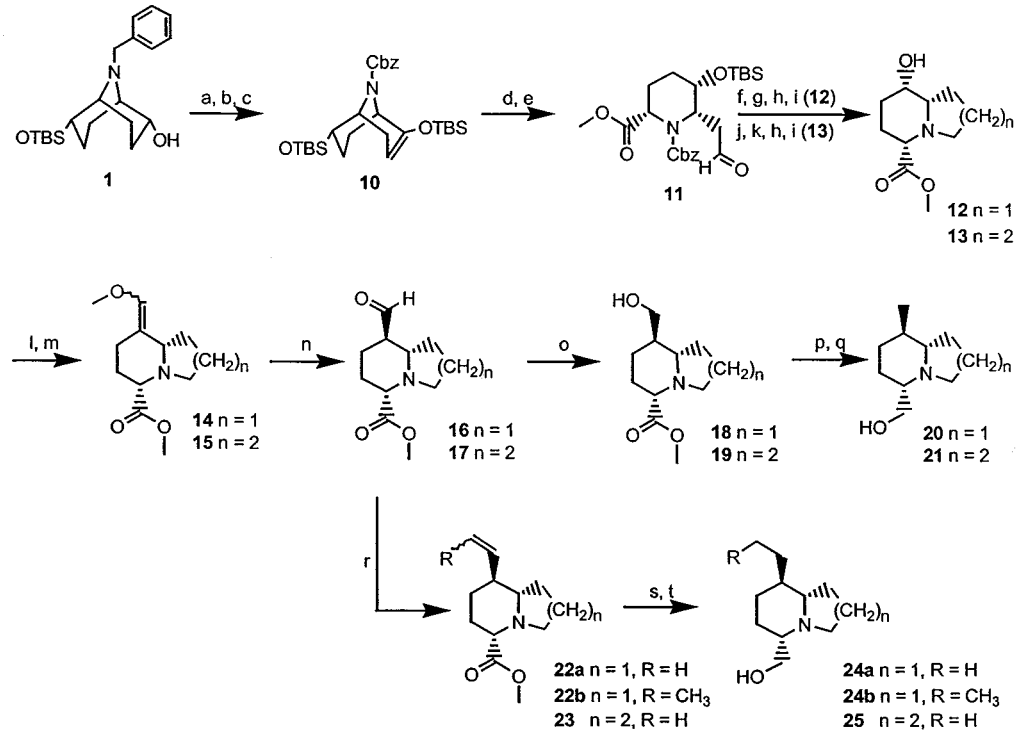
Synthesis of Quinolizidines.

Quinolizidine (±)-207I (*IV*). This was prepared in 26% overall yield from **9b** via the 8-ethyl-5-carboxalde-

(6) Optimization of this reaction on model compounds has shown that the 35% yield could have been improved by quenching the reaction with saturated brine instead of pure water. Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* **1999**, *40*, 8575−8578.

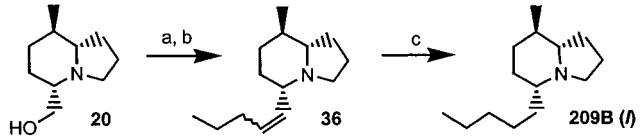
(7) Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023−1095.

Scheme 3[a]



[a] Key: (a) (i) H_2, Pd/C 10% (wet), MeOH, (ii) CbzCl, K_2CO_3, acetone (86% **43**); (b) Swern oxidation (87% **44**); (c) KH, THF, TBDMSCl (98% **10**); (d) (i) O_3, MeOH/CH_2Cl_2, (ii) $NaBH_4$, (iii) CH_2N_2 (90% **45**); (e) Swern oxidation (88% **11**); (f) ($Ph_3PCH_2OCH_3$)Cl, *t*-BuOK, THF (82% **46**); (g) *p*-TsOH, acetone (98% **47**); (h) H_2, Pd/C 10%, MeOH/H_2O; (i) MeOH/HCl (72% up to intermediate **12**); (80% up to intermediate **13**); (j) ($Ph_3PCH_2CH(OCH_2CH_2O)$)Br, *t*-BuOK, THF (90% **48**); (k) THF, 1.2 N HCl (97% **49**); (l) Swern oxidation; (m) ($Ph_3PCH_2OCH_3$)Cl, *t*-BuOK, THF (57% in two steps **14**); 68% in two steps **15**); (n) THF, 4 N HCl; (o) $NaBH_4$, MeOH (58% in two steps **18**); 63% in two steps **19**); (p) MsCl, Et_3N, CH_2Cl_2 (88% **50**; 73% **34**; (q) Super-Hydride, THF, 0 °C (85% **20**; 81% **21**); (r) (Ph_3PCH_2R)Br, *t*-BuOK, THF (53% in two steps **22a**; 50% in two steps **22b**; 68% in two steps **23**); (s) H_2, Pd/C 10%, MeOH (91% **51a**; 88% **51b**; 86% **35**); (t) Super-Hydride, THF, 0 °C (92% **24a**; 93% **24b**; 96% **25**). For structures of intermediates see Scheme 8 (Supporting Information).

Scheme 4[a]



[a] Key: (a) Swern oxidation; (b) ($Ph_3P(CH_2)_3CH_3$)Br, *t*-BuOK, THF (41% in two steps **36**); (c) H_2, Pd/C 10%, MeOH (66%, (±)-**209B (*I*)**).

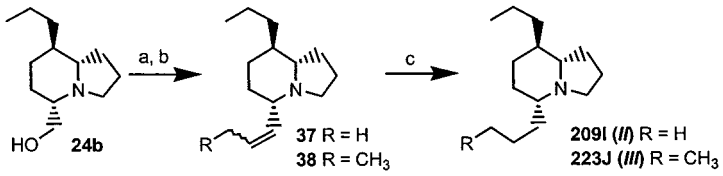
hyde **39** from Swern oxidation of **9b** followed by Wittig reaction with methoxymethyltriphenylphosphonium bromide to **40**, then acid hydrolysis and a second Wittig reaction with methyltriphenylphosphonium bromide (Scheme 6). It was identical to the natural material[8] by GC co-injection and identical mass and GC−FTIR spectra. A preliminary report on the synthesis of (±)-**207I** has appeared.[9] It should be noted that in the case of the 1-ethyl substituted 1,4 quinolizidines, the structural analogy mentioned above between the equatorial 8-propyl and 8-methyl substituted indolizidines breaks down, for Momose's enantioselective synthesis[10] of a (−)-quinolizidine with an equatorial 1-ethyl substituent having the 1*R*,4*S*,10*S* stereochemistry tentatively proposed for **207I**, was not identical with the natural material. The present synthesis afforded the (±)-1,4-quinolizidine **207I** with an axial 8-ethyl configuration and proved identical in all respects with the natural **207I**. Thus, the natural material is confirmed to be the 1-epimer of the structure originally considered likely for **207I.**

Quinolizidine (±)-233A (*V*). This was prepared in 16% overall yield from **25** by Swern oxidation followed by Wittig reaction with 2-(1,3-dioxolan-2-yl)-ethyltriphenylphosphonium bromide to yield **41**, hydrolysis of the hydrogenated product **42** and another Wittig reaction with dibromomethyltriphenylphosphonium bromide and concomitant dehydrobromination with potassium *tert*-butoxide to create the terminal acetylene (Scheme 7). The synthetic material was identical to the natural material[8] by GC co-injection and comparison of mass and FTIR spectra. The relative configuration of the 1-ethyl group of quinolizidine **233A** had been left unspecified[1]. Our synthetic (±)-**233A** with a 1-equatorial ethyl proved identical in all respects with natural **233A**, including vapor-phase FTIR spectra (Figure 2). In contrast **207I**, also naturally occurring, has an axial 1-ethyl group. We could not separate the enantiomers of our synthetic (±)-**233A** using four chiral columns.

The enantiomers of quinolizidine (±)-**207I** and indolizidines (±)-**209I** or (±)-**223J** separated on chiral gas chromatographic columns. On co-injection on chiral column A (see Experimental Section) with natural indolizidines **209I** and **223J**, the earlier eluting peak of each pair of peaks from (±)-**209I** and (±)-**223J** was enhanced, while the later eluting peak for a co-injection

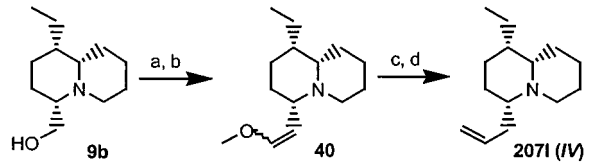
(8) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **1993**, *56*, 1016−1038.
(9) Michel, P.; Rassat, A. *Chem Commun.* **1999**, 2281−2283.
(10) Toyooka, N.; Tanaka, K.; Momose, T.; Daly J. W.; Garraffo, H. M. *Tetrahedron*, **1997,** *53*, 9553−9574.

Scheme 5[a]



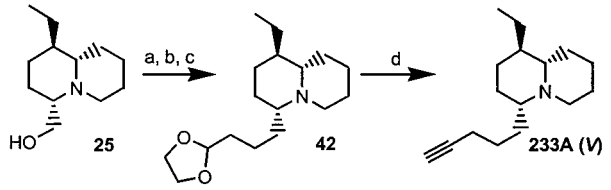
[a] Key: (a) Swern oxidation; (b) $(Ph_3P(CH_2)_2R)Br$, *t*-BuOK, THF (64% in two steps (R = H, **37**); 45% in two steps (R = CH_3, **38**)); (c) H_2, Pd/C 10%, MeOH (64% (±)-**209I (*II*)**; 78% (±)-**223J (*III*)**).

Scheme 6[a]



[a] Key: (a) Swern oxidation (75% **39**); (b) $(Ph_3PCH_2OCH_3)Cl$, *t*-BuOK, THF (83% **40**); (c) THF, 4N HCl; (d) $(Ph_3PCH_3)Br$, *t*-BuOK, THF (41% in two steps (±)-**207I** (***IV***)). For structure of intermediate **39**, see Scheme 8 (Supporting Information).

Scheme 7[a]



[a] Key: (a) Swern oxidation (75%); (b) $Ph_3PCH_2CH_2CH(OCH_2CH_2O)Br$, *t*-BuOK, THF (57% in two steps **41**); (c) H_2, Pd/C 10%, MeOH (82% **42**); (d) (i) THF, 4N HCl; (ii) $(Ph_3PCHBr_2)Br$, *t*-BuOK, THF (35% (±)-**233A** (***V***)). For structure of intermediate **41**, see Scheme 8 (Supporting Information).

of quinolizidine (±)-**207I** with natural **207I** was enhanced. When pure enantiomers of these three alkaloids become available, their absolute stereochemistry can easily be determined.

Conclusion

In summary, we have established relative configurations at C-1 in the quinolizidines **207I** and **233A** and at C-8 in the indolizidines **209I** and **223J**. By choosing any convenient Wittig reagent, these transformations may easily be modified to obtain selectively almost any saturated substituent, in an axial or equatorial configuration at the indolizidine C-8 or quinolizidine C-1 positions and saturated or unsaturated substituents in an equatorial configuration at the indolizidine C-5 or quinolizidine C-4 positions.

In the course of this work, we also made an empirical observation that may prove general and permit the assignment of stereochemistry to C-1 substitutents in quinolizidines by noting the shape of their Bohlmann band patterns in GC−FTIR spectroscopy, a technique requiring less material than ^1H NMR spectroscopy. Natural **207I** with an axial C-1 ethyl configuration has a pair of bands at 2789 cm^{-1} of even intensity, while its C-1 epimer (as is also the case with (±)-**233A**) has a pair of bands at 2789 cm^{-1} where the higher frequency band of the pair is roughly 30% more intense (see Figures 2 and 3). A sample of the C-1 epimer of (±)-**217A**,[2] with

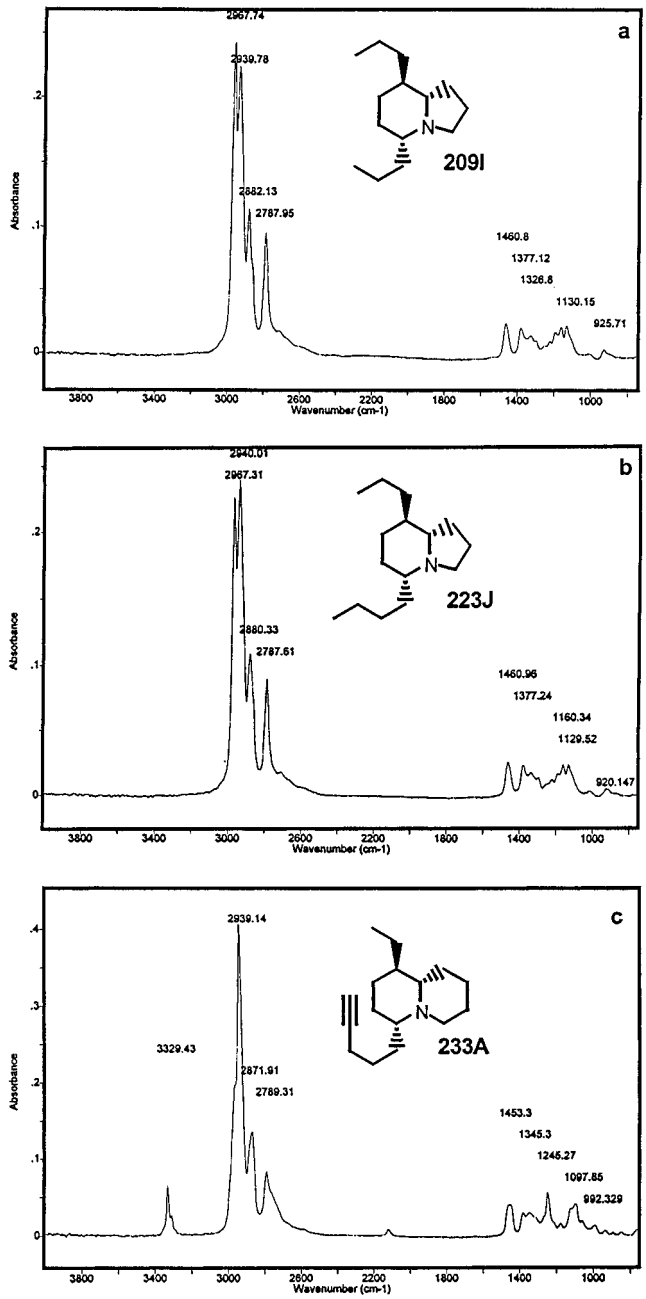


Figure 2. Vapor-phase FTIR spectra of (a) indolizidine (±)-**209I (*II*)**, (b) indolizidine (±)-**223J (*III*)**, and (c) quinolizidine (±)-**233A (*V*)**.

an axial C-1 methyl, a minor byproduct in a synthesis of (±)-**217A**, also showed the same split bands of even intensity as did (±)-**207I**, while (±)-**217A** with an equatorial 1-methyl showed Bohlmann bands of the same type as (±)-**233A** (Figures 2 and 3).

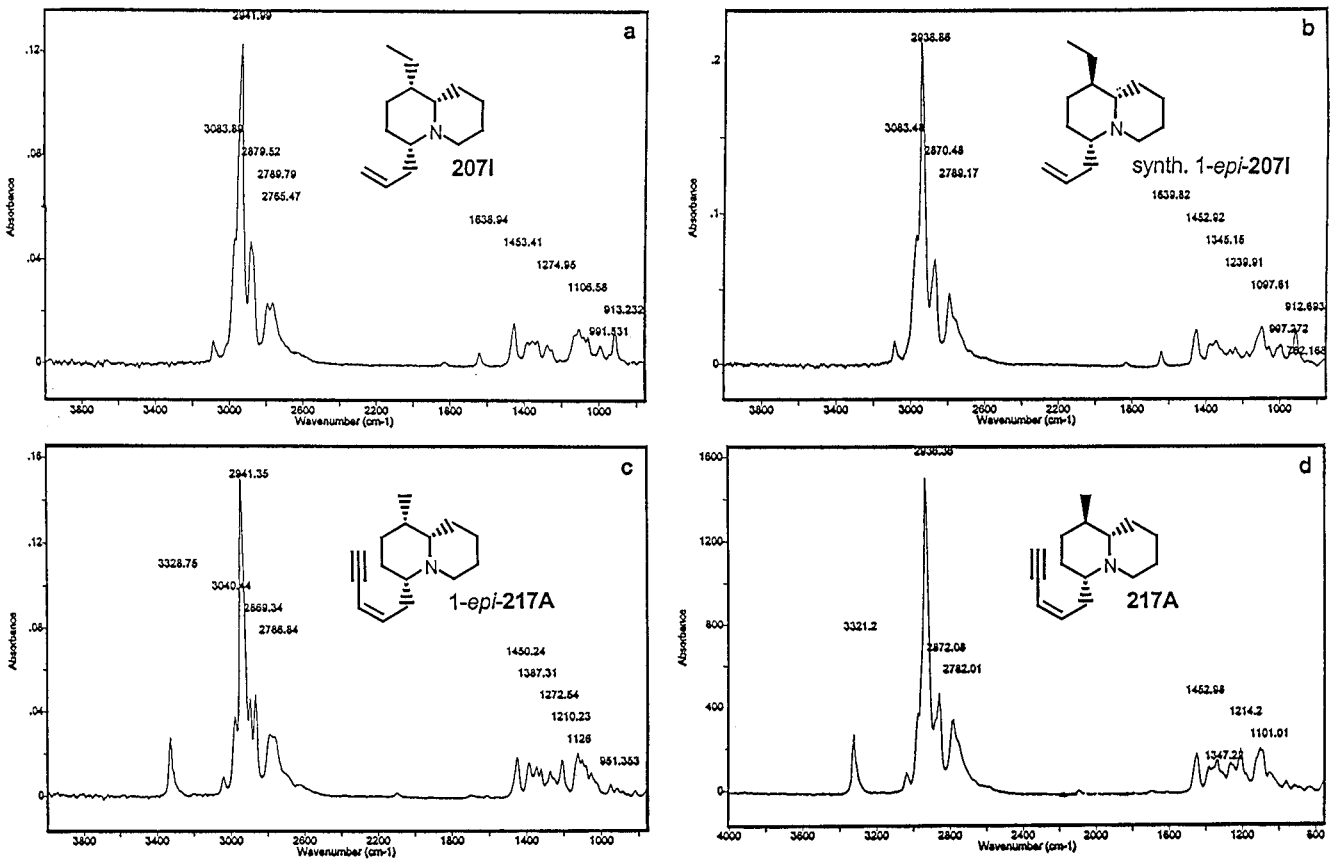


Figure 3. Vapor-phase FTIR spectra of (a) quinolizidine (−)-**207I**, (b) quinolizidine 1-*epi*-(±)-**207I (*IV*)**, (c) quinolizidine (±)-**217A**, and (d) quinolizidine 1-*epi*-(±)-**217A**.

Experimental Section

Unless specified, materials were commercial and used without purification. CH_2Cl_2 and Et_3N were distilled from CaH_2. THF was distilled from Na-benzophenone ketyl radical immediately before use. ^{1}H NMR spectra were recorded in $CDCl_3$ or CD_3OD at 400 MHz for ^{1}H and 50 MHz for ^{13}C using $CDCl_3$ (7.30 ppm for ^{1}H, 77.00 ppm for ^{13}C) as reference unless otherwise stated. Analytical TLC was performed with Merck SiO_2 plates (60 F254). Flash chromatography was performed using Merck SiO_2 (Geduran SI 60, 0.040−0.063 mm) or Merck Al_2O_3 90 (active neutral (III), 0.063−0.200 mm). Elemental analyses were performed by the Service Régional de Microanalyses de l'Université Pierre et Marie Curie. "As described" means that the quantities of reagents and solvents have been proportionally adjusted, mutatis mutandis. Vapor-phase FTIR spectra and EIMS were obtained with a Hewlett-Packard (HP) model 5890 GC having a 25 m × 0.32 mm i.d. HP-5 fused-silica capillary column programmed from 100° to 280° at the rate of 10 °C/min, interfaced with an HP model 5971 mass selective detector and an HP model 5965B IR instrument with narrow band (4000−750 cm^{-1}) detector and an HP ChemStation (DOS based). GC-EIMS co-injections used a Restek RTX-5MS column (30 m, 0.25 mm i.d., 0.25μm film thickness). A β-Dex-120 cyclodextrin-based column (A) (Supelco Inc., Bellefonte, PA; 30 m × 0.25 mm i.d., 25 um film thickness) or a permethylated β-cyclodextrin column (B)-(25QC2/CYDEX-B; 25 m × 0.22 mm i.d., 0.25 um film thickness, made by SGE, Inc and a GC with a flame ionization detector was employed for the chiral separations. A program of 100−165 °C at 1.5 °C/min was used for A; 100−145 °C at 1.5 °C was used for B. Helium was used as the carrier gas at 20 psi.

9-Benzyl-6-*endo*-[(*tert*-butyldimethylsilyl)oxy]-9-azabicyclo[3.3.1]nonan-2-one (26). To a solution of oxalyl chloride (2.01 mL, 23.07 mmol) in CH_2Cl_2 (100 mL) at −60 °C was added dropwise DMSO (3.27 mL, 46.13 mmol). The mixture was stirred for 2 min, and a solution of alcohol **1** (7.57 g, 20.97 mmol) in CH_2Cl_2 (10 mL) was then added. After the mixture was stirred for 15 min, Et_3N (15 mL, 106.73 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. H_2O (100 mL) was then added, and the aqueous layer was extracted with additional CH_2Cl_2 (100 mL). The organic layers were combined, washed sequentially with solutions of saturated NaCl (200 mL), 0.4 N HCl (200 mL), H_2O (100 mL), saturated $NaHCO_3$ (200 mL), and H_2O (100 mL), dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on SiO_2 (hexane/EtOAc 90:10) to give the corresponding ketone **26** (7.03 g, 95%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.51 (dddd, J = 13.8, 13.8, 11.5, 5.1 Hz, 1H), 1.77 (dddd, J = 13.6, 5.1, 2.1, 2.1 Hz, 1H), 1.81−1.88 (m, 1H), 1.91−2.01 (m, 1H), 2.12−2.23 (m, 1H), 2.30 (dddd, J = 14.5, 8.9, 5.0, 1.4 Hz, 1H), 2.43 (ddd, J = 17.8, 8.7, 7.3 Hz, 1H), 2.66 (ddd, J = 17.8, 9.8, 5.0 Hz, 1H), 3.00 (br t, J = 6.2 Hz, 1H), 3.09 (br d, J = 4.0 Hz, 1H), 3.89 (s, 2H), 4.07 (ddd, J = 11.4, 5.1, 5.1 Hz, 1H), 7.27−7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.9, −4.7, 17.8, 17.9, 25.7, 25.7, 28.3, 36.9, 55.3, 58.0, 63.4, 68.9, 127.1, 128.2, 138.3, 215.9; IR (neat) ν = 3086, 3028, 2951, 2932, 2886, 2859, 1713, 1470, 1254, 1119, 1092, 838 cm^{-1}; MS (CI, NH_3) m/z 360 (100) $[M + H]^+$. Anal. Calcd for $C_{21}H_{33}NO_2Si$ (359.6): C, 70.15; H, 9.25; N, 3.90. Found: C, 69.99; H, 9.24; N, 3.86.

9-Benzyl-6-*endo*-[(*tert*-butyldimethylsilyl)oxy]-6-methylidene-9-azabicyclo[3.3.1]nonane (2a). To Ph_3PCH_3Br (18.05 g, 50.52 mmol) and *t*-BuOK (5.59 g, 49.81 mmol) under argon, THF (150 mL) was added and the mixture heated to reflux. After 1 h, a solution of ketone **26** (8.89 g, 24.76 mmol) obtained from **1**[5] in THF (15 mL) was added dropwise. The solution was stirred overnight and then allowed to cool to room temperature. H_2O (150 mL) was added, and the solution was extracted with Et_2O (2 × 100 mL). The organic layers were combined, dried over Na_2SO_4 and evaporated. The crude

product was purified by flash chromatography on SiO_2 (hexane/EtOAc 97.5:2.5 then 90:10) to give **2a** (8.22 g, 92%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 1.67 (dddd, J = 12.9, 5.8, 1.7, 1.7 Hz, 1H), 1.71−2.06 (m, 5H), 2.37 (br dd, J = 15.6, 7.1 Hz, 1H), 2.63 (ddddd, J = 15.5, 12.0, 8.6, 2.5, 2.5 Hz, 1H), 2.76 (br t, tl, J = 5.1 Hz, 1H), 3.03 (br d, J = 4.4 Hz, 1H), 3.69 (d, J = 13.7 Hz, 1H), 3.81 (d, J = 13.7 Hz, 1H), 4.20 (ddd, J = 11.3, 5.6, 5.6 Hz, 1H), 4.62 (br t, J = 2.4 Hz, 1H), 4.88 (br t, J = 2.2 Hz, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.9, −4.7, 17.9, 18.2, 25.7, 29.9, 30.1, 30.3, 56.8, 56.9, 58.0, 71.4, 110.0, 126.5, 128.0, 128.3, 139.9, 146.4; IR (KBr) ν 3063, 3022, 2961, 2935, 2859, 1643 cm^{-1}; HRMS calcd for $C_{22}H_{36}NOSi$ [M + H] 358.2566, found 358.2572.

Benzyl 2-*endo*-[(*tert*-Butyldimethylsilyl)oxy]-6-*endo*-methyl-9-azabicyclo[3.3.1]nonane-9-carboxylate (3a). Argon was bubbled through a solution of amine **2a** (2.58 g, 7.22 mmol) and 10% Pd/C wet (50%, 1.07 g) in MeOH (500 mL). The resultant suspension was stirred overnight under a balloon pressurized with hydrogen. After filtration through Celite, the solvent was removed under reduced pressure. To the residual intermediate amine in acetone (100 mL), K_2CO_3 (3.58 g, 25.9 mmol) and benzyl chloroformate (1.4 mL, 9.8 mmol) were added, and the solution was refluxed overnight. Acetone was then evaporated under reduced pressure, and H_2O (100 mL) was added to the residual solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the organic layers were combined, dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on SiO_2 (hexane/EtOAc 90:10) to afford **3a** (2.77 g, 95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.040, 0.044, 0.10 and 0.12 (s, 6H), 0.90 and 0.93 (s, 9H), 0.95−1.00 (m, 3H), 1.56−2.00 (m, 8H), 2.10−2.18 (m, 1H), 3.79−3.94 (m, 1H), 3.97 (br t, J = 4.4 Hz, 0.5H), 4.03 (br t, J = 4.8 Hz, 0.5H), 4.11 (br t, J = 4.8 Hz, 0.5H), 4.20 (br t, J = 5.1 Hz, 0.5H), 5.09−5.27 (m, 2H), 7.33−7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.0, −4.9, −4.8, 17.9, 19.0, 19.1, 22.3, 22.7, 23.4, 25.7, 28.9, 29.0, 30.7, 33.7, 34.0, 49.9, 50.4, 50.6, 51.1, 66.7, 69.4, 69.9, 127.5, 127.6, 127.7, 128.3, 128.4, 136.7, 154.40; IR (neat) ν 3090, 3067, 3034, 2955, 2932, 2856, 1699, 1421, 1300, 1090, 837, 775 cm^{-1}; MS (CI, CH_4) m/z 404 (100) [M + H]$^+$, 388(23), 272(35). Anal. Calcd for $C_{23}H_{37}NO_3Si$ (403.6): C, 68.44; H, 9.24; N, 3.47. Found: C, 68.54; H, 9.38; N, 3.35.

The intermediate amine, **2-*endo*-[(*tert*-butyldimethylsilyl)oxy]-6-*endo*-methyl-9-azabicyclo[3.3.1]nonane**, could be obtained from the above residue by chromatography on Al_2O_3 (CH_2Cl_2/MeOH 100:0 then 98:2) to afford a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 0.91 (d, J = 6.7 Hz, 3H), 1.46−1.97 (m, 9H), 2.09−2.14 (m, 1H), 2.70 (br t, J = 3.9 Hz, 1H), 2.89 (br t, J = 4.7 Hz, 1H), 3.94 (ddd, J = 10.9, 5.6, 5.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.0, −4.6, 17.6, 19.6, 24.1, 24.6, 25.6, 29.3, 31.1, 35.4, 50.5, 51.5, 71.5; IR (neat) ν 3370, 2953, 2930, 2885, 2856, 1250, 1107, 1086, 1013, 856, 837, 773 cm^{-1}; HRMS calcd for $C_{15}H_{32}NOSi$ [M + H] 270.2253, found 270.2242.

Benzyl 2-*endo*-Hydroxy-6-*endo*-methyl-9-azabicyclo-[3.3.1]nonane-9-carboxylate (27a). To a solution of **3a** (5.3 g, 13.15 mmol) in MeCN (100 mL) was added 40% hydrofluoric acid (5 mL). After the mixture was stirred overnight, a saturated $NaHCO_3$ solution (100 mL) was added and the resulting solution extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/acetone 90:10) to give **27a** (3.69 g, 97%) as a colorless oil: 1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 7.1 Hz, 1.5H), 0.99 (d, J = 7.1 Hz, 1.5H), 1.51−2.03 (m, 8H), 2.07−2.20 (m, 1.5H), 2.78 (d, J = 4.0 Hz, 0.5H), 3.89−4.06 (m, 2H), 4.24 (br t, J = 5.2 Hz, 0.5H), 4.29 (br t, J = 5.3 Hz, 0.5H), 5.13−5.20 (m, 2H), 7.32−7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0, 19.1, 22.3, 22.8, 23.3, 28.8, 29.1, 29.6, 33.6, 34.1, 50.0, 50.4, 50.7, 50.8, 66.8, 66.9, 127.5, 127.7, 127.8, 128.3, 128.3, 136.7, 136.8, 154.5, 154.6; IR (neat) ν 3420, 3090, 3065, 3034, 2955, 2936, 2872, 1670, 1427, 1340, 1302, 1215, 1109, 1063, 989, 895 cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_3$ [M + H] 290.1756, found 290.1754.

Benzyl 2-*endo*-Methyl-6-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (28a). The alcohol **27a** (3.5 g, 12.11 mmol) was oxidized as described for **26**. The crude product was purified by flash chromatography on SiO_2 (hexane/EtOAc 80:20) to afford **28a** (3.01 g, 86%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 7.3 Hz, 1.2H), 0.94 (d, J = 6.9 Hz, 1.8H), 1.14−1.29 (m, 1H), 1.53−1.58 (m, 1H), 1.63−1.82 (m, 2H), 1.85−1.98 (m, 1H), 1.98−2.08 (m, 1H), 2.16−2.36 (m, 2H), 2.46−2.57 (m, 1H), 4.40−4.52 (m, 1H), 4.57−4.68 (m, 1H), 5.14−5.26 (m, 2H), 7.34−7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7, 17.8, 18.1, 18.7, 25.2, 28.0, 28.4, 34.1, 34.5, 36.4, 49.6, 50.2, 59.1, 59.6, 67.1, 127.6, 127.9, 128.1, 128.2, 128.4, 136.3, 136.5, 154.5, 154.8, 212.8; IR (neat) ν 3089, 3065, 2957, 2930, 2874, 1732, 1697, 1422, 1304, 1101, 989 cm^{-1}; MS (CI, CH_4) m/z 288 (100) [M + H]$^+$, 154(24). Anal. Calcd for $C_{17}H_{21}NO_3$ (287.4): C, 71.06; H, 7.36; N, 4.87. Found: C, 70.98; H, 7.46; N, 4.81.

Benzyl 2-[(*tert*-Butyldimethylsilyl)oxy]-6-*endo*-methyl-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate (4a). Potassium hydride (35% in oil, 6.05 g, 52.79 mmol) was suspended in THF (80 mL) after being washed with THF (2 × 30 mL). The ketone **28a** (2.84 g, 9.89 mmol) in THF (5 mL) was added dropwise. After 2 h, a solution of *tert*-butyldimethylsilyl chloride (2.80 g, 18.57 mmol) in THF (15 mL) was added and the mixture was stirred overnight. H_2O (80 mL) was then added at 0 °C, and the solution extracted with Et_2O (2 × 80 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on SiO_2 (hexane/EtOAc 95:5) to give **4a** (3.72 g, 93%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15, 0.16, 0.18 and 0.22 (s, 6H), 0.91−0.96 (m, 12H), 1.44−1.56 (m, 2H), 1.60−1.75 (m, 2H), 1.79−1.92 (m, 1H), 2.04−2.12 (m, 1H), 2.31−2.45 (m, 1H), 4.10−4.24 (m, 1H), 4.39 (br s, 0.5H), 4.49 (br s, 0.5H), 4.87−4.93 (m, 1H), 5.15−5.24 (m, 2H), 7.32−7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.9, −4.8, −4.4, −4.3, 17.8, 18.6, 18.7, 21.7, 22.4, 25.3, 25.5, 26.7, 27.2, 35.0, 35.3, 49.9, 50.6, 50.7, 51.2, 66.6, 66.7, 101.4, 102.1, 127.5, 127.6, 127.7, 128.3, 136.9, 137.0, 148.3, 148.8, 154.1; IR (neat) ν 3115, 3090, 3065, 3032, 2957, 2930, 2887, 2858, 1705, 1674, 1425, 1329, 1304, 1207, 1099, 841 cm^{-1}; MS (CI, CH_4) m/z 402 (100) [M + H]$^+$. Anal. Calcd for $C_{23}H_{35}NO_3Si$ (401.6): C, 68.78; H, 8.78; N, 3.49. Found: C, 68.71; H, 8.87; N, 3.47.

1-Benzyl 2-Methyl (2*S,5*S**,6*S**)-6-(2-Hydroxyethyl)-5-methylpiperidine-1,2-dicarboxylate (29a).** Ozone was bubbled through a stirred solution of **4a** (3 g, 7.5 mmol) in CH_2Cl_2−MeOH (10:1; 55 mL) at −78 °C for 30 min, and the excess was displaced by a stream of argon. $NaBH_4$ (300 mg, 7.93 mmol) was then added at −78 °C. After the mixture was stirred for 30 min, a second portion of $NaBH_4$ (350 mg, 9.25 mmol) was added, and the solution was allowed to warm to room temperature. The solvent was evaporated and the residue was triturated with 1.2 N HCl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to give an oil, which was used directly in the next step. To a stirred solution of the previous oil in Et_2O (20 mL), CH_2N_2 in Et_2O, was added at 0 °C, and the mixture was stirred at room temperature for 30 min; excess CH_2N_2 was destroyed with AcOH, and the mixture was evaporated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/MeOH 95:5) to give **29a** (1.80 g, 71%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.00 (m, 3H), 1.28−1.54 (m, 3H), 1.65−1.76 (m, 2H), 1.80−1.96 (m, 1H), 2.28−2.42 (m, 1H), 3.63 (s, 3H), 3.60−3.82 (m, 3H), 4.25−4.32 (m, 0.2H), 4.42 (ddd, J = 12.7, 5.1, 2.7 Hz, 0.8H), 4.90 (dd, J = 6.6, 2.0 Hz, 1H), 5.07−5.33 (m, 2H), 7.34−7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.8, 23.8, 25.7, 25.9, 28.1, 28.4, 33.8, 34.2, 51.4, 51.8, 52.0, 58.0, 59.4, 67.6, 127.7, 127.9, 128.1, 128.3, 136.2, 157.0, 156.2, 172.3, 172.9; IR (neat) ν 3466, 3096, 3065, 3032, 2959, 2874, 1738, 1693, 1416, 1304, 1213, 1111, 1061 cm^{-1}; MS (CI, CH_4) m/z 336 (100) [M + H]$^+$, 292 (100), 202 (25). Anal. Calcd for $C_{18}H_{25}NO_5$ (335.4): C, 64.46; H, 7.51; N, 4.18. Found: C, 64.61; H, 7.60; N, 4.07. Asterisks on *R*- or *S*-designators indicate that these are arbitrary, used only to indicate relative configurations of one enantiomer of racemates.

1-Benzyl 2-Methyl (2*S,5*S**,6*S**)-5-Methyl-6-(2-oxoethyl)piperidine-1,2-dicarboxylate (5a).** The alcohol **29a** (1.65 g, 4.92 mmol) was oxidized as described for **26** and the crude product purified by flash chromatography on SiO_2 (hexane/EtOAc 80:20) to afford **5a** (1.32 g, 80%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.93 (m, 3H), 1.25−1.38 (m, 1H), 1.51 (dddd, J = 13.9, 3.4, 3.4, 3.4 Hz, 1H), 1.74 (br s, 1H), 1.90 (br s, 1H), 2.33−2.65 (m, 3H), 3.68 (s, 1.5H), 3.74 (s, 1.5H), 4.83−5.07 (m, 2H), 5.13−5.26 (m, 2H), 7.30−7.42 (m, 5H), 9.74 (br s, 0.5H), 9.84 (br s, 0.5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.4, 23.6, 25.8, 33.7, 41.6, 50.8, 51.7, 52.0, 67.3, 67.7, 127.6, 127.9, 128.3, 136.0, 136.2, 155.7, 172.5, 201.0, 201.5; IR (neat) ν 3065, 3034, 2957, 2936, 2876, 2725, 1724, 1699, 1408, 1306, 1215, 1111, 1061 cm^{-1}; MS (CI, CH_4) m/z 334 (82) $[M + H]^+$, 290 (100), 246 (90), 156 (46). Anal. Calcd for $C_{18}H_{23}NO_5$ (333.4): C, 64.85; H, 6.95; N, 4.20. Found: C, 64.77; H, 7.00; N, 4.11.

1-Benzyl 2-Methyl (2*S,5*S**,6*S**)-6-(3-Methoxyprop-2-enyl)-5-methylpiperidine-1,2-dicarboxylate (30a).** To $Ph_3PCH_2OCH_3Cl$ (1.64 g, 4.78 mmol) and *t*-BuOK (507 mg, 4.51 mmol) under argon was added THF (50 mL) and then, after 2 min, a solution of the aldehyde **5a** (1.2 g, 3.6 mmol) in THF (5 mL). After the mixture was stirred for 90 min, H_2O (50 mL) was added, and the resulting solution was extracted with Et_2O (2 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on SiO_2 (hexane/EtOAc 80:20) to give **30a** (664 mg, 51%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−2.35 (m, 12H), 3.39−6.30 (m, 10H), 7.32−7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.1, 18.3, 18.4, 18.5, 18.8, 19.1, 20.6, 21.8, 23.5, 23.8, 24.8, 25.5, 25.8, 25.9, 27.7, 27.8, 32.4, 34.4, 34.5, 36.5, 38.2, 50.9, 51.0, 51.7, 53.6, 54.6, 55.2, 55.6, 55.8, 56.3, 56.9, 59.2, 60.0, 64.8, 66.3, 66.9, 67.2, 99.7, 100.2, 103.7, 126.7, 127.1, 127.7, 127.8, 128.0, 128.2, 128.4, 136.3, 136.6, 146.0, 147.4, 147.5, 148.5, 153.3, 172.7, 172.8; IR (neat) ν 3065, 3034, 2955, 2934, 2874, 1736, 1699, 1414, 1304, 1213, 1109 cm^{-1}; MS (CI, CH_4) m/z 362 (100) $[M + H]^+$, 318 (49), 286 (26), 196 (37). Anal. Calcd for $C_{20}H_{27}NO_5$ (361.4): C, 66.46; H, 7.53; N, 3.88. Found: C, 66.43; H, 7.50; N, 4.00.

1-Benzyl 2-Methyl (2*S,5*S**,6*S**)-5-Methyl-6-(2-oxopropyl)piperidine-1,2-dicarboxylate (6a).** To a stirred solution of **30a** (600 mg, 1.66 mmol) in acetone (20 mL) was added *p*-toluenesulfonic acid monohydrate (166 mg, 0.87 mmol). After the mixture was stirred for 10 min, H_2O (20 mL) was added and the solution extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on SiO_2 (hexane/EtOAc 90:10 then 80:20) to give **6a** (336 mg, 58%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94−0.99 (m, 3H), 1.36−1.53 (m, 3H), 1.64−1.89 (m, 3H), 2.32−2.71 (m, 3H), 3.65−3.75 (m, 3H), 4.14−4.39 (m, 1H), 4.91−5.34 (m, 3H), 7.30−7.42 (m, 5H), 9.57 (br s, 0.5H), 9.83 (br s, 0.5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8, 18.1, 18.8, 23.7, 25.8, 26.0, 34.2, 34.3, 40.8, 41.0, 51.0, 51.3, 52.0, 54.8, 55.1, 67.3, 67.6, 127.6, 127.7, 128.2, 128.3, 136.1, 136.5, 156.0, 156.3, 172.7, 201.9, 202.3; IR (neat) ν 3065, 3034, 2957, 2874, 2829, 2723, 1736, 1697, 1414, 1302, 1109, 1061, 1001 cm^{-1}; MS (CI, CH_4) m/z 348 (61) $[M + H]^+$, 304 (48), 196 (100). Anal. Calcd for $C_{19}H_{25}NO_5$ (347.4): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.54; H, 7.33; N, 4.03.

Methyl (5*S,8*S**,9*S**)-8-Methylindolizidine-5-carboxylate (31a).** Argon was bubbled through a solution of **6a** (300 mg, 0.86 mmol) containing 10% Pd/C (70 mg) in MeOH (20 mL) and H_2O (1 mL). The resultant suspension was stirred overnight under a balloon pressurized with hydrogen. After filtration through Celite, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 80:20) to give **31a** (80 mg, 47%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, J = 7.1 Hz, 3H), 1.53−1.86 (m, 8H), 1.87−1.99 (m, 2H), 2.07−2.12 (m, 1H), 2.72 (dd, J = 11.5, 2.9 Hz, 1H), 3.21 (br t, J = 8.4 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0, 20.1, 24.6, 26.0, 29.0, 31.2, 51.7, 52.8, 66.7, 68.3, 173.8; IR (neat) ν 2951, 2880, 2856, 2791, 2727, 1751, 1437, 1387, 1279, 1204, 1169, 1144, 1084, 1028 cm^{-1}; HRMS calcd for $C_{11}H_{20}NO_2$ $[M + H]$ 198.1494, found 198.1504.

(5*S,8*S**,9*S**)-8-Methylindolizidine-5-methanol (7a).** To a stirred solution of **31a** (22 mg, 0.11 mmol) in THF (20 mL) was added Super-Hydride (2.6 mL, 2.6 mmol) at 0 °C. The reaction mixture was stirred for 2 h and then allowed to warm to room temperature. H_2O (10 mL) was added, and the resulting solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on Al_2O_3 (CH_2Cl_2/MeOH 100:0 then 98:2) to give **7a** (14.5 mg, 76%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 7.0 Hz, 3H), 1.37−1.44 (m, 1H), 1.51−1.75 (m, 6H), 1.78−2.03 (m, 3H), 2.04−2.10 (m, 1H), 2.18−2.24 (m, 1H), 2.50 (br s, 1H), 3.21−3.27 (m, 1H), 3.45 (dd, J = 10.7, 1.7 Hz, 1H), 3.81 (dd, J = 10.6, 3.9 Hz, 1H,); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.7 (expected position for an axial methyl), 20.4, 22.8, 26.5, 29.1, 31.3, 51.6, 64.1, 64.5, 66.7; IR (neat) ν 3369, 2963, 2928, 2878, 2855, 2789, 2725, 2596, 1655, 1460, 1387, 1142, 1072, 1053 cm^{-1}; HRMS calcd for $C_{10}H_{20}NO$ $[M + H]$ 170.1545, found 170.1545.

1-Benzyl 2-Methyl (2*S,5*S**,6*S**)-6-[3-(1,3-Dioxolan-2-yl)prop-2-enyl]-5-methylpiperidine-1,2-dicarboxylate (32a).** To [(1,3-dioxolan-2-yl)methyl]triphenylphosphonium bromide (2.48 g, 5.66 mmol) and *t*-BuOK (615 mg, 5.48 mmol) under argon was added THF (50 mL), followed after 30 min by a solution of aldehyde **5a** (1.19 g, 3.58 mmol) in THF (5 mL). The solution was stirred for 1 h, H_2O (50 mL) was added, and the solution was extracted with Et_2O (2 × 50 mL). The organic layers were combined, dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on SiO_2 (hexane/EtOAc 70:30) to give **32a** (1.15 g, 79%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89−1.05 (m, 3H), 1.46−1.52 (m, 2H), 1.62−1.75 (m, 1H), 1.75−1.87 (m, 1H), 2.08−2.27 (m, 1H), 2.29−2.41 (m, 1H), 2.43−2.51 (m, 1H), 3.65−3.74 (m, 3H), 3.87−4.06 (m, 4H), 4.20−4.52 (m, 1H), 5.00−5.55 (m, 5H), 5.80−6.05 (m, 1H), 7.33−7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.9, 19.0, 23.7, 24.5, 25.7, 29.1, 34.4, 34.5, 51.0, 51.8, 56.1, 64.6, 67.4, 99.2, 103.8, 126.3, 127.8, 128.3, 136.4, 136.4, 156.1, 172.7; IR (neat) ν 3065, 3022, 2957, 2878, 1736, 1697, 1412, 1306, 1213, 1111, 1059, 1003, 959 cm^{-1}; MS (CI, CH_4) m/z 404 (35) $[M + H]^+$, 290 (100), 246 (46), 156 (22). Anal. Calcd for $C_{22}H_{29}NO_6$ (403.5): C, 65.49; H, 7.24; N, 3.47. Found: C, 65.36; H, 7.33; N, 3.38.

Benzyl (2*S,5*S**,6*S**)-2-[3-(1,3-Dioxolan-2-yl)prop-2-enyl]-6-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (8a).** To a stirred solution of **32a** (1.1 g, 2.72 mmol) in THF (30 mL) was added Super-Hydride (7 mL, 7 mmol) at 0 °C. The reaction mixture was stirred for 90 min and then allowed to warm to room temperature. H_2O (10 mL) was added and the solution extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2/acetone 95:5 then 90:10) to give **8a** (813 mg, 79%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 7.0 Hz, 3H), 1.41−1.47 (m, 2H), 1.63−1.89 (m, 3H), 2.33−2.53 (m, 3H), 3.58−3.76 (m, 2H), 3.87−4.08 (m, 4H), 4.40−4.51 (m, 2H), 5.14−5.21 (m, 2H), 5.42−5.51 (m, 1H), 5.55−5.57 (m, 1H), 5.80−6.00 (m, 1H), 7.33−7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.9, 22.7, 25.1, 27.8, 34.4, 51.5, 54.8, 63.7, 64.7, 64.8, 67.1, 99.1, 103.5, 126.7, 127.4, 127.7, 128.3, 128.5, 134.7, 136.6, 156.6; IR (neat) ν 3447, 3065, 3032, 2957, 2930, 2876, 1686, 1414, 1308, 1113, 1051, 957 cm^{-1}; MS (CI, CH_4) m/z 376 (22) $[M + H]^+$, 262 (100), 218 (18). Anal. Calcd for $C_{21}H_{29}NO_5$ (375.5): C, 67.18; H, 7.78; N, 3.73. Found: C, 67.03; H, 7.94; N, 3.73.

Benzyl (2*S,5*S**,6*S**)-6-(Hydroxymethyl)-3-methyl-2-(4-oxobut-2-enyl)piperidine-1-carboxylate (33a).** To a stirred solution of **8a** (750 mg, 2 mmol) in THF (20 mL) was added 1.2 N HCl (1 mL). After the mixture was stirred for 10 min, H_2O (20 mL) was added, and the resulting solution was extracted with Et_2O (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on SiO_2 CH_2Cl_2/acetone 90:10) to afford **33a** (640 mg, 96%) as a colorless

oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95−1.02 (m, 3H), 1.36−1.52 (m, 2H), 1.65−1.77 (m, 1H), 1.83−1.96 (m, 2H), 2.40−2.65 (m, 3H), 3.57−3.75 (m, 2H), 4.30−4.58 (m, 2H), 5.03−5.30 (m, 2H), 6.07−6.14 (m, 1H), 6.75−7.00 (m, 1H), 7.37−7.41 (m, 5H), 9.05−9.42 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.8, 22.4, 24.8, 33.4, 34.3, 51.3, 54.2, 63.8, 67.3, 127.7, 128.1, 128.5, 134.1, 136.2, 156.5, 193.9; IR (neat) ν 3443, 3090, 3065, 3034, 2959, 2934, 2874, 2822, 2739, 1689, 1412, 1308, 1115, 972 cm^{-1}; HRMS calcd for $C_{19}H_{26}NO_4$ [M + H] 332.1856, found 332.1962.

(1*S,4*S**,10*S**)-1-Methylquinolizidine-4-methanol (9a).** The aldehyde **33a** (589 mg, 1.77 mmol) was hydrogenated as described for **31a**. The crude product was purified by flash chromatography on Al_2O_3 (CH_2Cl_2/MeOH 100:0 then 98:2) to afford **9a** (229 mg, 70%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 6.9 Hz, 3H), 1.28 (ddddd, J = 12.5, 12.5, 12.5, 4.1, 4.1 Hz, 1H), 1.36−1.53 (m, 4H), 1.57−1.68 (m, 4H), 1.70−1.80 (m, 2H), 1.94−2.08 (m, 2H), 2.11 (H-10, ddd, J = 9.9, 3.3, 3.3 Hz, 1H), 3.05 (br s, 1H), 3.19−3.27 (m, 2H), 3.93 (dd, J = 10.5, 3.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.8, 23.9, 24.7, 26.2, 31.1, 31.3, 32.7, 52.1, 62.5, 63.4, 64.6; IR (neat) ν 3402, 2968, 2934, 2882, 2856, 2797, 2762, 2617, 1653, 1448, 1391, 1109, 1053, 1024 cm^{-1}; HRMS calcd for $C_{11}H_{22}NO$ [M + H] 184.1701, found 184.1702.

Methyl (4*S,10*S**)-1-(Methoxyethylidene)quinolizidine-4-carboxylate (15).** To a solution of oxalyl chloride (725 μL, 8.31 mmol) in CH_2Cl_2 (80 mL) at −60 °C was added dropwise DMSO (1.18 mL, 16.63 mmol). The mixture was stirred for 2 min, and a solution of alcohol **13** (1.61 g, 7.55 mmol) in CH_2Cl_2 (5 mL) was then added. After the mixture was stirred for 15 min, Et_3N (3.2 mL, 22.77 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. H_2O (80 mL) was then added, and the aqueous layer was extracted with additional CH_2Cl_2 (80 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to give an oil, which was used directly in the next step without further purification. To $Ph_3PCH_2OCH_3Cl$ (5.45 g, 15.89 mmol) and *t*-BuOK (1.72 g, 15.33 mmol) under argon was added THF (80 mL). After 2 min, the crude oil in THF (5 mL) was added. The solution was stirred for 10 min, H_2O (80 mL) was added and the resulting solution was extracted with Et_2O (2 × 80 mL). The organic layers were combined, dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 50:50 then 20:80) to give **15** (1.23 g, 68%) as a pale yellow solid. Major stereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26−1.40 (m, 1H), 1.60−1.88 (m, 7H), 1.89−1.96 (m, 1H), 1.98−2.07 (m, 1H), 2.41 (br d, J = 10.8 Hz, 1H), 2.82−2.89 (m, 1H), 2.90−2.98 (m, 2H), 3.59 (s, 3H), 3.75 (s, 3H), 5.92 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.4, 24.1, 25.2, 27.4, 29.8, 51.5, 54.7, 59.1, 61.8, 69.4, 115.6, 141.0, 173.7; IR (KBr) ν 2999, 2943, 2845, 2793, 2731, 2687, 1728, 1682, 1450, 1281, 1213, 1134, 1105, 1045, 845, 773 cm^{-1}; HRMS calcd for $C_{13}H_{22}NO_3$ [M + H] 240.1600, found 240.1604.

Methyl (1*R,4*S**,10*S**)-1-(hydroxymethyl)quinolizidine-4-carboxylate (19).** To a stirred solution of **15** (400 mg, 1.67 mmol) in THF (30 mL), 4 N HCl (1 mL) was added. After the mixture was stirred overnight, saturated $NaHCO_3$ solution (20 mL) was added, and the resulting solution was extracted with Et_2O (2 × 30 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to give **17** as an oil, which was used directly in the next step without further purification. The crude aldehyde **17** was dissolved in MeOH (20 mL), and $NaBH_4$ (140 mg, 3.7 mmol) was added to the stirred solution. After 4 h, H_2O (20 mL) was added, and the resulting solution was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on Al_2O_3 (CH_2Cl_2/MeOH 100:0 then 98:2) to give **19** (239 mg, 63%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1.48 (m, 3H), 1.51−1.72 (m, 3H), 1.73−2.01 (m, 8H), 2.80−2.87 (m, 2H), 3.57−3.74 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3, 25.2, 27.0, 29.1, 29.2, 42.7, 51.7, 54.5, 63.5, 63.9, 68.8, 174.4; IR (KBr) ν 3200, 3020, 2934, 2850, 2775, 2682, 1744, 1454, 1300, 1198, 1167, 1146, 1107, 1016 cm^{-1}; HRMS calcd for $C_{12}H_{22}NO_3$ [M + H] 228.1600, found 228.1607.

Methyl (1*R,4*S**,10*S**)-1-[(Methylsulfonyl)oxy]quinolizidine-4-carboxylate (34).** The alcohol **19** (227 mg, 1 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon was treated dropwise with methanesulfonyl chloride (154 μL, 2 mmol) followed by Et_3N (562 μL, 4 mmol). The solution was stirred for 1 h and then allowed to warm to room temperature. Saturated $NaHCO_3$ solution (20 mL) was added and the aqueous layer extracted with additional CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on Al_2O_3 (CH_2Cl_2/MeOH 100:0 then 99.5:0.5) to give **34** (224 mg, 73%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.47 (m, 3H), 1.58−1.71 (m, 2H), 1.71−1.83 (m, 3H), 1.83−2.02 (m, 5H), 2.79−2.86 (m, 2H), 3.02 (s, 3H), 3.74 (s, 3H), 4.17−4.24 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.0, 25.1, 26.8, 28.8, 29.0, 36.9, 40.4, 51.8, 54.3, 62.4, 68.3, 70.8, 173.9; IR (neat) ν 3018, 2939, 2860, 2808, 2764, 2675, 1742, 1638, 1443, 1354, 1281, 1200, 1175, 949, 924, 856, 831 cm^{-1}; HRMS calcd for $C_{13}H_{24}NO_5S$ [M + H] 306.1375, found 306.1393.

(1*R,4*S**,10*S**)-1-Methylquinolizidine-4-methanol (21).** The ester **34** (200 mg, 0.65 mmol) was reduced as described for **7a**. The crude product was purified by flash chromatography on Al_2O_3 (CH_2Cl_2/MeOH 100:0 then 98:2) to afford **21** (97 mg, 81%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J = 6.5 Hz, 3H), 1.01−1.19 (m, 2H), 1.20−1.33 (m, 2H), 1.53 (ddddd, J = 12.7, 12.7, 12.7, 3.9, 3.9 Hz, 1H), 1.60−1.72 (m, 4H), 1.73−1.89 (m, 3H), 1.93−2.00 (m, 1H), 2.13 (dddd, J = 11.7, 3.6, 3.6, 1.3 Hz, 1H), 2.85 (br s, 1H), 3.19−3.26 (m, 1H), 3.34 (d, J = 10.4 Hz, 1H), 3.93 (dd, J = 10.6, 3.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.9, 24.5, 26.0, 29.1, 30.1, 33.0, 35.8, 51.2, 62.9, 63.1, 68.6; IR (KBr) ν 3375, 3202, 2970, 2951, 2936, 2855, 2795, 2596, 1489, 1456, 1443, 1375, 1273, 1119, 1070, 1059, 962, 928, 777 cm^{-1}; HRMS calcd for $C_{11}H_{22}NO$ [M + H] 184.1701, found 184.1703.

Methyl (1*S,4*S**,10*S**)-1-Ethenylquinolizidine-4-carboxylate (23).** To a stirred solution of **15** (970 mg, 4.05 mmol) in THF (60 mL) was added 4 N HCl (3 mL). After the mixture was stirred overnight, saturated $NaHCO_3$ solution (60 mL) was added, and the resulting solution was extracted with Et_2O (2 × 60 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to give **17** as an oil, which was used directly in the next step without further purification. To Ph_3PCH_3Br (2.73 g, 7.64 mmol) and *t*-BuOK (844 mg, 7.52 mmol) under argon was added THF (50 mL). After 30 min, a solution of aldehyde **17** in THF (5 mL) was then added. The solution was stirred 1 h, H_2O (50 mL) was added and then the solution was extracted with Et_2O (2 × 50 mL). The organic layers were combined, dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 80:20) to give **23** (614 mg, 68%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17−1.39 (m, 3H), 1.57−2.00 (m, 9H), 2.01−2.12 (m, 1H), 2.80−2.87 (m, 2H), 3.76 (s, 3H), 5.01 (dd, J = 10.2, 1.9 Hz, 1H), 5.05 (dd, J = 17.1, 1.9 Hz, 1H), 5.58 (ddd, J = 17.1, 10.2, 9.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3, 25.3, 29.0, 30.1, 30.5, 46.7, 51.6, 54.3, 65.3, 68.6, 115.2, 140.4, 174.0; IR (neat) ν 3076, 2991, 2936, 2856, 2801, 2756, 2725, 2592, 1749, 1639, 1443, 1275, 1232, 1196, 1169, 1140, 1113, 1016, 914 cm^{-1}; HRMS calcd for $C_{13}H_{22}NO_2$ [M + H] 224.1651, found 224.1645.

Methyl (1*R,4*S**,10*S**)-1-Ethylquinolizidine-4-carboxylate (35).** The alkene **23** (550 mg, 2.46 mmol) was hydrogenated as described for **31a**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 80:20 then 50:50) to afford **35** (480 mg, 86%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 3H), 1.01−1.17 (m, 2H), 1.17−1.38 (m, 3H), 1.51−1.66 (m, 4H), 1.66−1.82 (m, 2H), 1.82−2.00 (m, 4H), 2.77−2.84 (m, 2H), 3.75 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.1, 24.2 (expected position for methylene of an equatorial ethyl), 24.4, 25.2, 28.3, 28.8, 29.4, 41.1, 51.4, 54.5, 66.1, 68.9, 174.2; IR (neat) ν 2936, 2858, 2801, 2756, 1751, 1736, 1441, 1167, 1024 cm^{-1}; HRMS calcd for $C_{13}H_{24}NO_2$ [M + H] 226.1807, found 226.1796.

(1*R,4*S**,10*S**)-1-Ethylquinolizidine-4-methanol (25).** The ester **35** (440 mg, 1.95 mmol) was reduced as described for **7a**. The crude product was purified by flash chromatography on Al_2O_3 (CH_2Cl_2/MeOH 100:0 then 98:2) to afford **25** (372 mg, 96%) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 0.98−1.20 (m, 4H), 1.28 (ddddd, J = 12.7, 12.7, 12.7, 4.0, 4.0 Hz, 1H), 1.47−1.62 (m, 2H), 1.62−1.72 (m, 2H), 1.72−1.91 (m, 5H), 1.96−2.03 (m, 1H), 2.09−2.16 (m, 1H), 2.85 (br s, 1H), 3.20−3.27 (m, 1H), 3.34 (br d, J = 10.5 Hz, 1H), 3.93 (dd, J = 10.6, 3.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.3, 24.5, 24.7 (expected position for methylene of an equatorial ethyl), 26.0, 28.6, 29.0, 29.8, 41.5, 51.4, 62.8, 63.1, 66.4; IR (KBr) ν 3404, 3219, 2967, 2934, 2856, 2791, 2748, 1632, 1489, 1445, 1383, 1348, 1273, 1236, 1153, 1124, 1065, 984, 920, 779 cm^{-1}; HRMS calcd for $C_{12}H_{24}NO$ [M + H] 198.1858, found 198.1852.

(5S*,8R*,9S*)-8-Methyl-5-pent-1-enylindolizidine (36): To a solution of oxalyl chloride (131 μL, 1.5 mmol) in CH_2Cl_2 (15 mL) at −60 °C was added dropwise DMSO (213 μL, 3 mmol). The mixture was stirred for 2 min, and a solution of alcohol **20** (172 mg, 1.01 mmol) in CH_2Cl_2 (2 mL) was then added. After the mixture was stirred for 15 min, Et_3N (700 μL, 4.98 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. H_2O (15 mL) was then added, and the aqueous layer was extracted with additional CH_2Cl_2 (20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to give a crude oil, which was used directly in the next step without further purification. To $Ph_3P(CH_2)_3CH_3Br$ (1.23 g, 3.08 mmol) and *t*-BuOK (320 mg, 2.85 mmol) under argon was added THF (20 mL). After 30 min, the crude oil dissolved in THF (3 mL) was added. The solution was stirred for 2 h, H_2O (20 mL) was then added, and the resulting solution was extracted with Et_2O (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 90:10) to give **36** (86 mg, 41%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87−0.97 (m, 6H), 0.98−1.11 (m, 1H), 1.30−1.82 (m, 10H), 1.91−2.04 (m, 2H), 2.05−2.15 (m, 2H), 2.79−2.85 (m, 1H), 3.17 (ddd, J = 8.9, 8.9, 1.9 Hz, 1H), 5.37−5.47 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 18.7, 20.0, 22.7, 28.8, 29.7, 32.6, 33.3, 36.3, 52.7, 60.4, 70.5, 130.2, 132.8; IR (neat) ν 3005, 2959, 2928, 2872, 2849, 2781, 1458, 1377, 1350, 1312, 1285, 1200, 1182, 1130 cm^{-1}; HRMS calcd for $C_{14}H_{26}N$ [M + H] 208.2065, found 208.2070.

Indolizidine (±)-209B (*I*). The alkene **36** (86 mg, 0.41 mmol) was hydrogenated as described for **31a**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 90:10) to afford (±)-**209B (*I*)** (57 mg, 66%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J = 6.5 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 0.92−1.03 (m, 1H), 1.19−1.58 (m, 11H), 1.59−1.81 (m, 5H), 1.84−2.03 (m, 3H), 3.29 (ddd, J = 8.8, 8.8, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.8, 20.3, 22.6, 25.5, 29.0, 31.1, 32.2, 33.6, 34.5, 36.4, 51.8, 63.6, 71.4; IR (neat) ν 2955, 2930, 2872, 2777, 2700, 1458, 1375, 1132 cm^{-1}; HRMS calcd for $C_{14}H_{28}N$ [M + H] 210.2222, found 210.2216. The above NMR data are identical with that reported[4] for synthetic (−)- or (±)-**209B**.

A β-cyclodextrin chiral GC column resolved the above racemate into two chromatographic peaks with retention times of 27.85 and 28.43 min. The peak of longer retention time co-chromatographed with (−)-**209B** provided by Kibayashi's or Holmes' groups.[4] Natural **209B** could no longer be detected in extracts from *Dendrobates pumilio* (Isla Colon, Panama, 1986) or *D. histrionicus* (Chocó, Colombia, 1983). An alkaloid, previously thought to be **209B** in two extracts of *D. pumilio* (Chiriqui Grande, Panama, 1981) proved to be a different alkaloid entirely.

(5S*,8R*,9S*)-5-Prop-1-enyl-8-propylindolizidine (37). **37** was obtained from **24b** (136 mg, 0.69 mmol) as described for **36**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 90:10) to afford **37** (92 mg, 64%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.1 Hz, 3H), 0.90−1.15 (m, 2H), 1.21−1.35 (m, 2H), 1.35−1.52 (m, 4H), 1.56−1.83 (m, 7H), 1.86−2.02 (m, 3H), 2.84 (ddd, J = 10.9, 8.9, 2.9 Hz, 1H), 3.17 (ddd, J = 8.8, 8.8, 1.8 Hz, 1H), 5.39−5.46 (m, 1H), 5.47−5.56 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.2, 14.2, 19.5, 20.0, 28.9, 30.0, 32.1, 35.4, 40.9, 52.6, 60.0, 69.3, 124.1, 133.6; IR (neat) ν 3013, 2959, 2930, 2870, 2849, 2781, 1458, 1128 cm^{-1}; HRMS calcd for $C_{14}H_{26}N$ [M + H] 208.2065, found 208.2062. An alkaloid corresponding to this indolizidine has not as yet been detected in frog skin extracts.

Indolizidine (±)-209I (*II*): The alkene **37** (85 mg, 0.41 mmol) was hydrogenated as described for **31a**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 90:10) to afford (±)-**209I (*II*)** (55 mg, 64%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81−0.94 (m, 7H), 0.96−1.10 (m, 1H), 1.13−1.51 (m, 9H), 1.52−1.82 (m, 5H), 1.82−2.01 (m, 4H), 3.27 (br t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.5, 19.0, 19.6, 20.3, 29.1, 30.3, 31.0, 35.5, 36.8, 41.1, 51.8, 63.3, 70.2; IR (neat) ν 2957, 2932, 2872, 2777, 2702, 1458, 1379, 1159, 1132 cm^{-1}; HRMS calcd for $C_{14}H_{28}N$ [M + H] 210.2222, found 210.2225. Retention times on chiral columns A and B, respectively: 28.26, 28.77 min; 26.58, 26.94 min. The enantiomer of shorter retention time is identical with the natural material.

(5S*,8R*,9S*)-5-But-1-enyl-8-propylindolizidine (38). **38** was obtained from **24b** (130 mg, 0.66 mmol) as described for **36**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 95:5) to afford **38** (67 mg, 45%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H), 0.90−1.00 (m, 1H), 1.00−1.08 (m, 1H), 1.17−1.31 (m, 2H), 1.31−1.48 (m, 4H), 1.52−1.64 (m, 3H), 1.65−1.77 (m, 1H), 1.82−2.03 (m, 3H), 2.03−2.16 (m, 2H), 2.77 (ddd, J = 10.9, 8.6, 3.0 Hz, 1H), 3.13 (ddd, J = 8.8, 8.8, 1.8 Hz, 1H), 5.29−5.43 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 14.2, 19.5, 20.0, 20.9, 28.9, 30.0, 32.5, 35.4, 40.9, 52.7, 60.3, 69.3, 131.9, 132.1; IR (neat) ν 3007, 2961, 2932, 2872, 2849, 2781, 2689, 1460, 1128 cm^{-1}; HRMS calcd for $C_{15}H_{28}N$ [M + H] 222.2222, found 222.2220. An alkaloid corresponding to this indolizidine has not as yet been detected in frog skin extracts.

Indolizidine (±)-223J (*III*). The alkene **38** (60 mg, 0.27 mmol) was hydrogenated as described for **31a**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 95:5) to afford (±)-**223J (*III*)** (45 mg, 78%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81−0.93 (m, 7H), 0.98−1.10 (m, 1H), 1.14−1.49 (m, 11H), 1.53−2.00 (m, 9H), 3.27 (ddd, J = 8.7, 8.7, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.4, 19.6, 20.3, 23.1, 28.0, 29.1, 30.4, 31.1, 34.2, 35.6, 41.2, 51.8, 63.5, 70.2; IR (neat) ν 2957, 2932, 2862, 2777, 2702, 1458, 1377, 1337, 1227, 1194, 1159, 1132 cm^{-1}; HRMS calcd for $C_{15}H_{30}N$ [M + H] 224.2378, found 224.2383. Retention times on chiral columns A and B, respectively: 34.67, 35.18 min; 33.06, 33.49 min. The enantiomer of shorter retention time is identical with the natural material. An earlier report[10] contains a typographical error in the abstract indicating (−)-**223J** had been prepared. This should have read (−)-**223I**.

(1S*,4S*,10S*)-1-Ethylquinolizidine-4-carboxaldehyde (39). To a solution of oxalyl chloride (130 μL, 1.5 mmol) in CH_2Cl_2 (25 mL) at −60 °C was added dropwise DMSO (213 μL, 3 mmol). The mixture was stirred for 2 min, and a solution of the alcohol **9b** (218 mg, 1.1 mmol) in CH_2Cl_2 (2 mL) was then added. After the mixture was stirred for 15 min, Et_3N (1 mL, 7.11 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. H_2O (25 mL) was then added, and the aqueous layer was extracted with additional CH_2Cl_2 (20 mL). The organic layers were combined, washed with saturated NaCl solution (50 mL), dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on SiO_2 (CH_2Cl_2) to give **39** (162 mg, 75%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 3H), 1.19−1.66 (m, 11H), 1.70−1.78 (m, 1H), 1.86−1.93 (m, 2H), 2.00 (ddd, J = 11.4, 2.6, 2.6 Hz, 1H), 2.45 (ddd, J = 12.0, 4.0, 4.0 Hz, 1H), 2.66−2.72 (m, 1H), 9.44 (d, J = 4.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.2, 17.9, 20.7, 24.7, 25.7, 25.8, 30.2, 39.2, 56.4, 64.7, 73.8, 204.2; IR (neat) ν 2936,

2874, 2799, 1732, 1690, 1445, 1134, 1111, 1074, 1049 cm^{-1}; HRMS calcd for $C_{12}H_{22}NO$ [M + H] 196.1701, found 196.1706.

(1*S,4*S**,10*S**)-1-Ethyl-4-(2-methoxyethenyl)quinolizidine (40). 40** was obtained from **39** (277 mg, 1.42 mmol) as described for **30a**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0 then 80:20) to afford **40** (263 mg, 83%) as a colorless oil. *E* isomer :^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 3H), 1.16−1.82 (m, 14H), 1.90−1.99 (m, 1H), 2.18−2.25 (m, 1H), 3.30−3.38 (m, 1H), 3.50 (s, 3H), 4.66 (dd, J = 12.5, 9.5 Hz, 1H), 6.38 (d, J = 12.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 18.3, 25.0, 26.0, 27.0, 29.5, 30.8, 40.3, 54.5, 55.4, 65.2, 66.4, 106.5, 147.9; IR (neat) ν 3057, 2934, 2872, 2858, 2831, 2785, 2756, 1656, 1447, 1247, 1211, 1167, 1109, 935 cm^{-1}; HRMS calcd for $C_{14}H_{26}NO$ [M + H] 224.2014, found 224.2033. *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 3H), 1.17−1.80 (m, 14H), 1.97−2.07 (m, 1H), 2.84−2.91 (m, 1H), 3.29 (br d, J = 11.6 Hz, 1H), 3.56 (s, 3H), 4.38 (dd, J = 9.3, 6.4 Hz, 1H), 5.90 (d, J 6.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 18.3, 25.1, 25.9, 26.7, 27.4, 30.7, 40.3, 54.2, 59.4, 60.2, 66.4, 110.4, 146.6; IR (neat) ν 3034, 2934, 2858, 2824, 2787, 2754, 2735, 1668, 1450, 1254, 1101 cm^{-1}.

Quinolizidine (±)-207I (*IV*). To a stirred solution of **40** (260 mg, 1.16 mmol) in THF (10 mL) was added 4 N HCl (10 mL). After being stirred overnight, 2.5 N NaOH (20 mL) was added, and the resulting solution was extracted with Et_2O (2 × 30 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to give a crude oil, which was used directly in the next step without further purification. To Ph_3PCH_3Br (708 mg, 1.98 mmol) and *t*-BuOK (215 mg, 1.91 mmol) under argon, THF (20 mL) was added. After 1 h, the crude oil dissolved in THF (5 mL) was added. The solution was stirred overnight, H_2O (20 mL) was added and the resulting solution extracted with Et_2O (2 × 30 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0, 97.5:2.5 then 95:5) to give (±)-**207I (*IV*)** (99 mg, 41%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 3H), 1.20−1.83 (m, 14H), 1.85−1.93 (m, 1H), 1.97 (ddd, J = 11.4, 2.6, 2.6 Hz, 1H), 2.12−2.22 (m, 1H), 2.44 (ddddd, J = 14.2, 6.5, 3.2, 1.6, 1.6 Hz, 1H), 3.32−3.38 (m, 1H), 5.02−5.09 (m, 2H), 5.85 (dddd, J = 17.0, 10.3, 7.5, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 18.4, 25.0, 26.2, 26.3, 27.1, 31.0, 38.3, 40.6, 53.0, 64.1, 66.7, 115.9, 136.2; IR (neat) ν 3074, 2963, 2934, 2872, 2860, 2789, 2760, 2739, 1639, 1448, 1128, 1109, 908 cm^{-1}; HRMS calcd for $C_{14}H_{26}N$ [M + H] 208.2065, found 208.2051. Retention times on chiral columns A and B, respectively: 29.41, 30.03 min; 26,59, 27.11 min. The enantiomer of longer retention time is identical with the natural material.

(1*R,4*S**,10*S**)-4-[3-(1,3-Dioxolan-2-yl)prop-1-enyl]-1-ethylquinolizidine (41). 41** was obtained from **25** (350 mg, 1.77 mmol) as described for **36**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 80:20 then 50:50) to afford **41** (283 mg, 57%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3H), 1.03−1.35 (m, 5H), 1.41−1.66 (m, 6H), 1.70−1.82 (m, 3H), 1.93−2.01 (m, 1H), 2.46−2.52 (m, 2H), 2.78 (ddd, J = 11.2, 8.5, 3.1 Hz, 1H), 3.17−3.23 (m, 1H), 3.83−4.05 (m, 4H), 4.91 (t, J = 4.7 Hz, 1H), 5.45−5.57 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.2, 24.5, 24.7, 25.7, 28.8, 29.5, 32.0, 32.5, 41.8, 53.6, 61.5, 64.6, 64.7, 66.7, 103.6, 122.7, 136.9; IR (neat) ν 3013, 2957, 2930, 2876, 2856, 2787, 2747, 1464, 1450, 1441, 1398, 1381, 1308, 1234, 1202, 1132, 1045, 1015, 941, 843, 752 cm^{-1}; HRMS calcd for $C_{17}H_{30}NO_2$ [M + H] 280.2277, found 280.2281.

(1*R,4*R**,10*S**)-4-[3-(1, 3-Dioxolan-2-yl)propyl]-1-ethylquinolizidine (42).** The alkene **41** (283 mg, 1.01 mmol) was hydrogenated as described for **31a**. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 80:20 then 50:50) to afford **42** (233 mg, 82%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3H), 0.91−1.95 (m, 22H), 3.18−3.27 (m, 1H), 3.78−3.99 (m, 4H), 4.83 (t, J = 4.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.2, 20.1, 24.4, 24.7, 25.9, 29.2, 29.5, 31.0, 33.8, 34.0, 41.5, 51.2, 62.9, 64.5, 67.0, 104.2; IR (neat) ν 2930, 2874, 2858, 2785, 2760, 1463, 1450, 1441, 1410, 1379, 1360, 1346, 1312, 1267, 1236, 1173, 1128, 1053, 1040, 943 cm^{-1}; HRMS calcd for $C_{17}H_{32}NO_2$ [M + H] 282.2433, found 282.2430.

Quinolizidine (±)-233A (*V*). To a stirred solution of **42** (225 mg, 0.8 mmol) in THF (20 mL) was added 4 N HCl (1 mL). After the mixture was stirred for 1 h, H_2O (20 mL) was added, and the resulting solution extracted with Et_2O (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to give an oil, which was used directly in the next step without further purification. To $Ph_3PCH_2Br_2Br$ (1.11 g, 1.99 mmol) and *t*-BuOK (215 mg, 1.91 mmol) under argon was added THF (20 mL). After 1 min, the previous oil, dissolved in THF (3 mL), was added followed after 10 min by 1 M *t*-BuOK in THF (6 mL). The solution was stirred for 10 min, H_2O (20 mL) was added, and the resulting solution extracted with Et_2O (2 × 30 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography on Al_2O_3 (hexane/Et_2O 100:0, 95:5 then 90:10) to give (±)-**233A (*V*)** (66 mg, 35%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7.4 Hz, 3H), 0.94−1.27 (m, 5H), 1.33−1.44 (m, 1H), 1.45−1.79 (m, 12H), 1.85−1.92 (m, 2H), 1.94 (t, J = 2.7 Hz, 1H), 2.17 (td, J = 6.7, 2.7 Hz, 2H), 3.19−3.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4, 18.7, 24.5, 24.6, 24.9, 26.1, 29.4, 29.7, 31.1, 33.1, 41.6, 51.4, 62.7, 67.2, 68.2, 84.3; IR (neat) ν 3312, 2959, 2930, 2874, 2874, 2856, 2787, 2760, 2118, 1460, 1450, 1441, 1379, 1346, 1312, 1265, 1236, 1171, 1124, 1103, 1090, 1059, 1042, 988, 935, 897, 847, 760 cm^{-1}; HRMS calcd for $C_{16}H_{28}N$ [M + H] 234.2222, found 234.2221. This material proved identical on GC co-injections with natural **233A** and had an identical vapor-phase FTIR spectrum.

Source of Natural Extracts. Quinolizidine **207I**: In the alkaloidal fraction from *Mantella expectata* collected January 1993 at Massif Isalo, Madagascar. Indolizidines **209I, 223J**: Together in a 3:1 ratio in the alkaloidal fraction from *Dendobates pumilio* frogs collected Feb., 1992 at Peninsula Aguacate, Bocas Province, Panama. Quinolizidine **233A**: In the alkaloidal fraction from *Mantella pulchra* collected Jan., 1993 at An'Ala, Madagascar. Co-injections were performed at two concentrations of added synthetic alkaloid mixed with the natural alkaloidal fraction in methanol and the program specified at the start of the Experimental section was used.

Acknowledgment. This work was supported by the French Ministry of Education and CNRS. We thank Matthieu Kirchhoffer and Romain Duboc for the large-scale preparation of **1** and Dr. W. Pearson for synthetic samples of racemic **217A** and 1-*epi*-**217A** and Drs. C. Kibayashi and A. B. Holmes for samples of (−)-**209B** and its hydrochloride, respectively.[4]

Supporting Information Available: ^{1}H and ^{13}C NMR, MS, HRMS, and IR data for all intermediates of Schemes 2 and 3 not characterized above. Scheme 8 has the structures of intermediates **26**−**51** referred to in the Experimental Section and the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000666B