Total Synthesis of (±)-Quinolizidine 217A

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Several 1,4-disubstituted quinolizidines have been isolated in minute quantities from the skin of certain poisonous frogs and toads. The structures of these alkaloids have been proposed mainly on the basis of MS and IR spectroscopic data. We report the first total synthesis of a naturally occurring alkaloid of this type, quinolizidine 217A. After examination of several azide-based routes, the cyclization of an azide onto an ester-bearing alkene provided a 3,4,5,6-tetrahydropyridine that was reduced in a stereoselective fashion to produce a *cis*-2,6-disubstituted piperidine (**25** → **31** → **32**). Transformation of **32** into quinolizidine 217A (**2**) and its C(1) epimer (**41**) were accomplished in a straightforward fashion. Synthetic quinolizidine 217A was found to be identical to the natural alkaloid, confirming its stereostructure. Compound **41** has the same stereostructure as that proposed for the alkaloid quinolizidine 207I, a compound whose configuration was recently revised as a result of synthetic studies by Momose et al., who synthesized a 1,4-disubstituted quinolizidine with the configuration previously proposed for quinolizidine 207I and found the synthetic material to be epimeric with the natural material. Compound **41** should provide a useful point of comparison for future studies on the stereostructure of natural or synthetic quinolizidine 207I.

Introduction

Extracts from the skin of certain poison frogs and toads have yielded many pharmacologically active alkaloids, including a variety of azabicyclic compounds of the "izidine" type, i.e., pyrrolizidines, indolizidines, and, most recently, quinolizidines.[1] While the structures of the 5,8-disubstituted indolizidines (**1**) are well-known and have in many cases been confirmed by synthesis,[2−4] the 1,4-disubstituted quinolizidines (e.g., **2**−**4**) are a relatively new class of alkaloids isolated from these amphibians (Figure 1).[5−7] GC−FTIR and GC−MS analysis have been used to provide evidence of the structure of the 1,4-disubstituted quinolizidines due to the minute quantities involved, and thus there is uncertainty about their exact structure and stereochemistry. Quinolizidine 217A (**2**) is the only 1,4-disubstituted quinolizidine that has been isolated in sufficient quantities to allow ^{1}H NMR spectroscopic analysis, resulting in the proposed structure shown in Figure 1.[7] Although the absolute configuration

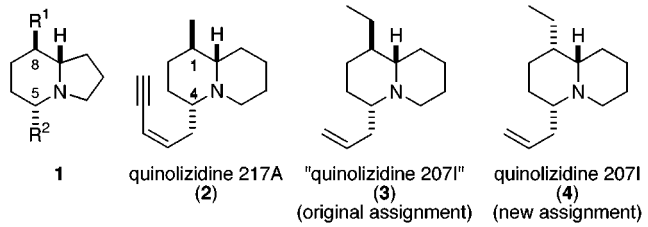

Figure 1. Representative structures of "izidine" alkaloids from frogs and toads.

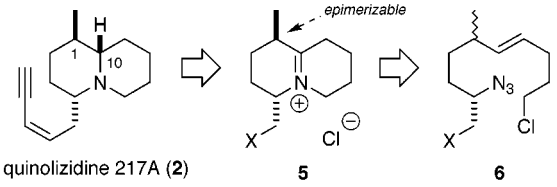

Figure 2. Retrosynthetic analysis of quinolizidine 217A (**2**).

of this and other quinolizidines is not known, the relative configuration is proposed to parallel that of the known 5,8-disubstituted indolizidines. Only one report of a synthesis of a 1,4-disubstituted quinolizidine has appeared to date. Momose and co-workers[4] reported a synthesis of **3**, originally proposed to be quinolizidine 207I. However, the synthetic material was found to be epimeric with the natural alkaloid, prompting a tentative reassignment of 207I as **4**. The scarcity of 1,4-disubstituted quinolizidines and the uncertainty surrounding their structure prompted us to attempt a synthesis of quinolizidine 217A (**2**). We report herein the synthesis of this alkaloid, confirming the structural assignment of the natural alkaloid to be as shown.

A retrosynthetic analysis of quinolizidine 217A is shown in Figure 2. Equatorial attack of hydride on the iminium ion **5** should give the appropriate C(10) configuration of **2**. We planned to generate the iminium ion **5** by double cyclization of the chloro azidoalkene **6**, a one-

(1) (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, pp 1−274. (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 43, pp 185−288. (c) Daly, J. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1997; Vol. 50.

(2) Michael, J. P. *Nat. Prod. Rep.* **1994**, *11*, 17−39.

(3) Leading recent references: (a) Bardou, A.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1998**, *39*, 5189−5192. (b) Michael, J. P.; Gravestock, D. *Pure Appl. Chem.* **1997**, *69*, 583−588. (c) Aehman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747−9756. (d) Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511−1124. (e) Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, *59*, 943−945. (f) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141−1147.

(4) Toyooka, N.; Tanaka, K.; Momose, T.; Daly, J. W.; Garraffo, H. M. *Tetrahedron* **1997**, *53*, 9553−9574.

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(6) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016−1038.

(7) Jain, P.; Garraffo, H. M.; Yeh, H. J. C.; Spande, T. F.; Daly, J. W.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1996**, *59*, 1174−1178.

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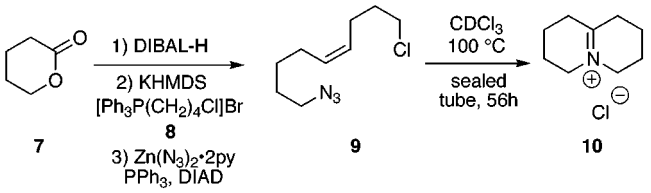
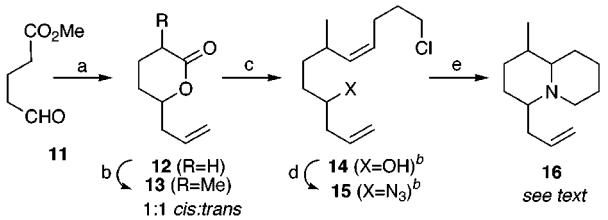
Scheme 1. Model Study for Quinolizidine Synthesis



Scheme 2. Attempted synthesis of a 1,4-Disubstituted Quinolizidine[a]



[a]Key: (a) CH_2=$CHCH_2TMS$, $TiCl_4$; TsOH, PhH, Dean-Stark (73%).; (b) LDA; MeI (93%); (c) DIBAL-H; $[Ph_3P(CH_2)_4Cl]Br$, KHMDS (53%); (d) $Zn(N_3)_2$•2py, PPh_3, DIAD (86%); (e) C_6D_6, sealed tube, 100-110 °C, 15h; $NaBH_4$, MeOH; (f) $CDCl_3$, 100 °C, 37h; $NaBH_4$, MeOH.
[b]Inseparable 1:1 mixture of diastereomers, both with *Z*-alkene.

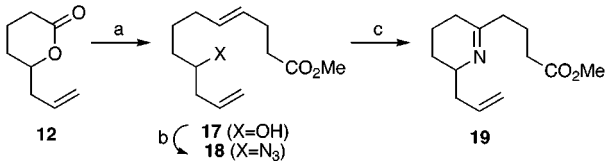
pot thermal process we have developed for alkaloid synthesis.[8−10] The configuration of the allylic methyl group of **6** was not considered to be important, since epimerization under the cyclization conditions should occur to provide the most stable diastereomer of **5**.[9]

Results and Discussion

A simple model cyclization was carried out to test the ability of the chloro azidoalkene cyclization to generate quinolizidines (Scheme 1). Reduction of δ-valerolactone to the lactol followed by a Wittig reaction employing the phosphonium salt **8**[8] and a Mitsunobu reaction with zinc azide[11] afforded the chloro azidoalkene **9**. Heating this azide at 100 °C in a sealed tube cleanly produced the iminium salt **10** as the sole product as judged by ^{1}H NMR spectroscopy.

Our first attempt at using the chloro azidoalkene cyclization to synthesize a 1,4-disubstituted quinolizidine is outlined in Scheme 2. An allyl group was chosen for the eventual C(4) substituent, since several quinolizidines have such a substituent (e.g., **3**/**4** above) and other quinolizidines might be accessible by manipulation of the allyl group. Addition of allyltrimethylsilane to the aldehyde **11**[12] followed by cyclization of the resultant hydroxy-ester gave the lactone **12**. Methylation of the enolate of **12** afforded a 1:1 mixture of diastereomeric lactones **13**, which were subjected to the same sequence of reactions used in Scheme 1 to produce the chloro azidoalkene **15** as an inseparable mixture of diastereomers. Cyclization of **15** in a variety of solvents and at different temperatures followed by sodium borohydride reduction led to highly viscous materials. Chromatography allowed the isolation of very small amounts (2−10% yield) of a material that was consistent with **16** by GC−MS. Unfortunately, this material was found to be a mixture of several compounds, presumably diastereomers. Following the progress of the cyclization process by ^{1}H NMR spectroscopy indicated that the desired iminium ion was not being produced cleanly (cf. Scheme 1). While we were aware that simple homoallylic azides produce resinous materials upon thermolysis,[13] we felt that such decomposition might be avoided if a second alkene were present that was capable of a favorable dipolar cycloaddition. The failure of the cyclization of **15** may be in part due to the involvement of the homoallylic double bond in the cycloaddition (see, however, Scheme 3 below). We considered preparing compounds related to **15** that did not have the terminal vinyl group. However, the observation of several different diasteromers of **16** was troubling, indicating nonselectivity in the epimerization (see Figure 2) and/or hydride reduction step. Hence, we abandoned the chloro azidoalkene approach in favor of a stepwise cyclization process.

Scheme 3. Model Study for Cycloaddition Step Only[a]



[a]Key: (a) DIBAL-H; CH_2=$CHMgBr$; $MeC(OMe)_3$, $EtCO_2H$, toluene, reflux; NaOMe, MeOH, CH_2Cl_2 (26% overall, *E*-only).; (b) $Zn(N_3)_2$•2py, PPh_3, DIAD (30%); (e) C_6D_6, sealed tube, 130-135 °C (41%).

Cha has studied the cycloaddition of ester-bearing azidoalkenes for the synthesis of indolizidines.[14] To examine the use of this method for the current application, we prepared the ester-bearing azidoalkene **18** (Scheme 3). The allylic methyl group needed for a synthesis of quinolizidine 217A is purposely missing in **18**, since we wished to study the stereochemistry of the reduction of the imine **19** without complications from a second stereocenter. Reduction of the lactone **12** and addition of vinylmagnesium bromide to the resultant lactol gave a secondary alcohol, which was converted to **17** by a Johnson ortho ester Claisen rearrangement.[15] Transformation of **17** to the azide **18** followed by heating afforded the imine **19** in 41% yield after considerable optimization. Unfortunately, reduction of **19** with a variety of hydridic reagents gave complex mixtures of amino alcohols. Nonetheless, the cyclization of **18** shows that a homoallylic azide may indeed be used for a cycloaddition with a second double bond with moderate efficiency (cf. Scheme 2). However, the low overall yield of **19** and the potential problems inherent in transforming the terminal vinyl group into the desired enyne side chain of quinolizidine 217A led us to consider a less problematic substituent.

After considerable experimentation, we settled on a 1,3-dioxolane group as a masked aldehyde. The synthesis

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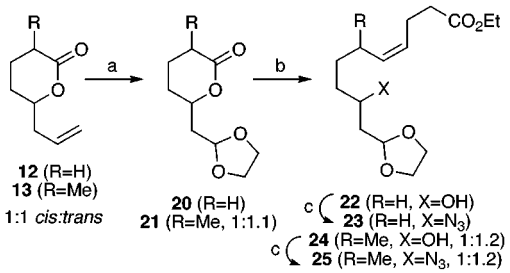
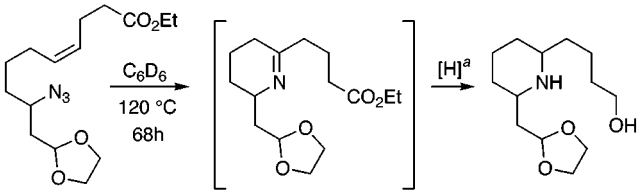
(10) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **1994**, *50*, 12293−12304.
(11) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130−132.
(12) (a) Huckstep, M.; Taylor, R. J. K. *Synthesis* **1982**, 881−882. (b) Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942−1943. (c) Burgstahler, A. W.; Weigel, L. O.; Shaefer, C. G. *Synthesis* **1976**, 767−768.
(13) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749−754.
(14) Bennett, R. B., III; Choi, J.-R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580−2582.
(15) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743.

Scheme 4. Synthesis of Cycloaddition Precursors[a]



[a]Key: For **12**→**20**→**22**→**23**: (a) OsO_4, NMO; $NaIO_4$; $HOCH_2CH_2OH$, TMSCl (15%); (b) DIBAL-H; $[Ph_3P(CH_2)_3CO_2Et]Br$ (**26**), KHMDS (39%). (c) MsCl, NEt_3; Bu_4NN_3 (84%). For **13**→**21**→**24**→**25**: (a) 35%; *p*-TsOH·H_2O/Dean-Stark trap used for acetal formation; (b) 52%; (c) 87%.

Scheme 5. Cyclization of Model Azide 23



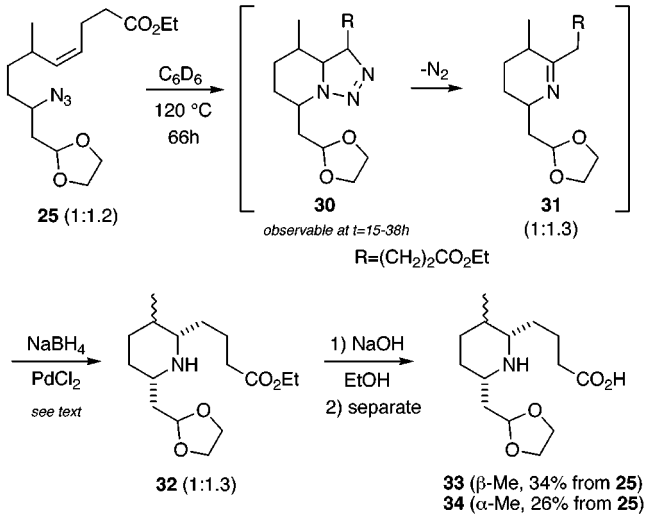
[a][H] = $LiAlH_4$, $AlMe_3$: 68% of **28** as a single diastereomer
[H] = DIBAL-H: 28% of **29** as a single diastereomer

of the key cycloaddition precursors **25** and **23** (with and without the allylic methyl group) are shown in Scheme 4. The lactones **12** and **13** were subjected to ozonolysis and protection to give **20** and **21**, which were reduced to the lactols and converted to the alkenes **22** and **24** with the ylide derived from the phosphonium salt **26**.[14] Standard displacement chemistry was used to install the azido groups, producing **23** and **25**.

The cyclization of **23** was studied first (Scheme 5), since the absence of the allylic methyl group simplifies development of a stereoselective hydride reduction of the imine **27**. Heating **23** in a sealed tube produced **27**, which was then treated with a variety of hydride reagents. Following literature precedent,[16] we found that $LiAlH_4/AlMe_3$ and DIBAL-H were the most diastereoselective reagents, producing the *trans*- and *cis*-piperidines **28** and **29** as single diastereomers as judged by ^{1}H NMR spectroscopy in good to modest overall yield (unoptimized). The assignment of the relative configurations of these two piperidines relies on close literature precedent[17] (see Experimental Section).

With the model piperidines **28** and **29** assigned and in hand, we turned our attention to the more complex cyclization of the azide **25**, which bears the allylic methyl group necessary for a synthesis of quinolizidine 217A (Scheme 6). Heating the azide **25** (an inseparable 1:1.2 mixture of diastereomers) produced the triazoline **30** initially, which decomposed as planned to the imine **31**, which was found to be a 1:1.3 mixture of diastereomers by ^{1}H NMR spectroscopy. Reduction of **31** with DIBAL-H (see above) gave a 1:2 mixture of the two possible *cis*-

Scheme 6. Cyclization of Azide 25



2,6-disubstituted piperidines **32**, but the overall yield from **25** could not be optimized above 27%. Fortunately, work by Lhommet[18] and co-workers on the stereoselective reduction of pyrrolines to 2,5-disubstituted pyrrolidines provided us with a solution to this problem. Thus, reduction of the crude imine **31** with $NaBH_4/PdCl_2$ provided **32** efficiently (vide infra) as an inseparable 1:1.3 mixture of the two possible *cis*-2,6-disubstituted piperidines, which were best used without purification. Surprisingly, we were not able to induce the cyclization of **32** to the lactams under a variety of conditions. For example, heating **32** with sodium cyanide or freshly prepared sodium ethoxide in anhydrous ethanol produced the acids **33** and **34** rather than the lactams. Ultimately, we found it convenient to simply saponify **32** to **33** and **34** and close the second ring using other nonacylative chemistry (see Scheme 7). Fortunately, the crystalline acids **33** and **34** were easily separated and were formed in 34 and 26% overall yield, respectively, from the azide **25**. Thus, the three-step sequence (cycloaddition, reduction, and saponification) had been quite efficient, i.e., a 60% overall yield of **33**/**34** after separation. Assignment of the relative configurations of **33** and **34** was made at a later stage (vide infra).

The acids **33** and **34** were converted to quinolizidine 217A (**2**) and its C(1) epimer **41** as shown in Scheme 7. Reduction of the acids produced the alcohols **35** and **36**. At this point, we were able to use the stereochemical assignments of the simpler piperidines **28** and **29** along with literature precedent and coupling constant analysis to assign the stereostructures of **35** and **36** and thus **33** and **34**. A full discussion of these assignments may be found in the Experimental Section. Cyclization of **35** and **36** to the quinolizidines **37** and **38** using phosphorus-based methods proceeded without difficulty. Hydrolysis of the dioxolanes to the aldehydes and olefination using Yamamoto's method[19] afforded the silyl enynes **39** and **40**. Desilylation afforded racemic quinolizidine 217A (**2**) and its C(1) epimer **41**. The ^{1}H NMR spectroscopic and mass spectrometric data for **2** matched the literature values (see Supporting Information),[7] as did the IR

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(17) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990−5994.

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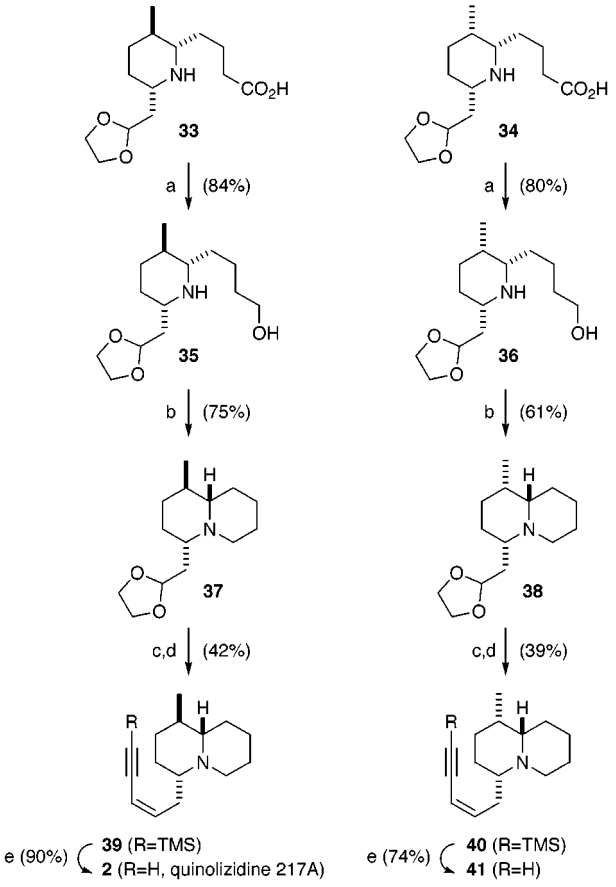
(19) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768−2776.

Scheme 7. Synthesis of Quinolizidine 217A (2) and Epimer (41).[a]



[a]Key: (a) $LiAlH_4$; (b) PPh_3, CCl_4, NEt_3; (c) aq. THF; (d) $TMSCCCH_2SiMe_2tBu$, *t*BuLi, $Ti(OiPr)_4$; (e) nBu_4NF

spectal data.[6] Both **2** and **41** show the presence of Bohlmann bands in their infrared spectra, consistent with *trans*-decalin-like structures with a cis relationship of the C(10) and C(4) methine hydrogens.[20] A sample of our synthetic quinolizidine 217A was provided to Daly and Spande,[21] who found an exact match with natural quinolizidine 217A by GC−FTIR. Further, analysis of our synthetic material by GC on a chiral column resolved the racemate into two enantiomers. The most highly retained enantiomer cochromatographed with natural quinolizidine 217A.[21] The ^{1}H NMR spectrum of **2** is also similar to that of synthetic (1*R*,4*S*,10*S*)-4-allyl-1-ethylquinolizidine (**3**, Figure 1).[4] The quinolizidine **41** exhibited ^{1}H NMR resonances that were clearly different from those reported for natural quinolizidine 217A.[7] Note that **41** has the same relative configuration as that proposed for the newly revised structure of quinolizidine 207I (**4**, Figure 1). Unfortunately, due to the miniscule amounts of natural quinolizidine 207I isolated from frogs,[6] NMR spectroscopic data are not available for comparison with synthetic **41**. However, should such material become available, either by isolation or synthesis, our synthetic **41** will serve as a useful point of comparison.

Conclusion

In summary, our synthesis of quinolizidine 217A (**2**) represents the first synthesis of a naturally occurring 1,4-disubstituted quinolizidine alkaloid and confirms the literature assignment of the relative configuration of this substance. The C(1) epimeric compound **41** represents the first synthetic 1,4-disubstituted quinolizidine with the same relative configuration as that recently proposed for quinolizidine 207I (**4**).

Experimental Section

General. Methods. Reagents and starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Methylene chloride (CH_2Cl_2), triethylamine, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and benzene were distilled from calcium hydride under a nitrogen atmosphere. Methanol (MeOH) was distilled from magnesium turnings under a nitrogen atmosphere. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone ketyl under a nitrogen atmosphere. Chloroform was filtered through basic alumina. Alkyllithiums were titrated by the method of Gilman and Haubein[22] or Ronald et al.[23] All reactions were conducted in oven- or flame-dried glassware under an anhydrous nitrogen atmosphere with standard precautions taken to exclude moisture. Chromatography refers to flash chromatography on silica gel (230−400 mesh) unless otherwise noted.

6-Allyltetrahydropyran-2-one (12). This is a known compound[24] but was prepared by an alternative procedure. Thus, a solution of $TiCl_4$ (45.6 mL, 45.6 mmol, 1.0 M solution in CH_2Cl_2) in dry CH_2Cl_2 (120 mL) was added to a solution of methyl 5-oxopentanoate (**11**)[12] (4.94 g, 38.0 mmol) and allyltrimethylsilane (5.21 g, 7.24 mL, 45.6 mmol) in dry CH_2Cl_2 (70 mL) over a period of 1.5 h at −78 °C. The mixture was allowed to warm to −20 °C over a period of 3 h, where it was held another 30 min. Water (100 mL) was added, the layers were separated, and the organic layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed (3:1 hexane/ethyl acetate) to give 4.43 g of pale yellow oil, which was dissolved in benzene (450 mL) and heated at reflux for 3 h in the presence of *p*-TsOH·H_2O (0.53 g), removing water with a Dean−Stark trap. The mixture was cooled and concentrated to about 30 mL and chromatographed (3:1 hexane/ethyl acetate) to give 3.90 g (73%) of the title compound as pale yellow oil. R_f = 0.20 (3:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48−1.98 (m, 4H), 2.34−2.65 (m, 4H), 4.30−4.39 (m, 1H), 5.12−5.18 (m, 2H), 5.82 (ddt, J = 17.1, 10.2, 7.3, Hz, 1H). These spectral data matched the literature data.[24]

6-Allyl-3-methyltetrahydropyran-2-one (13). *n*-Butyllithium (7.44 mL, 17.1 mmol, 2.3 M solution in hexane) was added to a solution of diisopropylamine (1.73 g, 2.40 mL, 17.1 mmol) in dry THF (25 mL) at −78 °C. After 30 min at 0 °C, the solution was cooled to −78 °C and a solution of **12** (2.00 g, 14.3 mmol) in dry THF (25 mL) was added. After 1 h, iodomethane (6.08 g, 2.67 mL, 42.8 mmol) was added. After stirring at −78 °C for 1 h, the mixture was quenched with THF/H_2O (1:1, 100 mL) and extracted with CH_2Cl_2 (100 mL × 3). The organic extracts were dried ($MgSO_4$) and concentrated. Chromatography (10:1 hexane/ethyl acetate) provided 1.73 g of the title compound as colorless oil. The aqueous washes from the extraction were treated with 1 M HCl (15 mL) and extracted with CH_2Cl_2 (100 mL × 3). The organic extract was dried ($MgSO_4$) and concentrated. The resulting oil

(20) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157−2167.

(21) Personal communication with John W. Daly and T. Spande, NIDDK (National Institutes of Health). The GC−FTIR data was obtained on an HP-5 fused silica-bonded capillary column (25 m × 0.32 mm). The chiral GC analysis was performed using a Supelco Beta-DEX 120 fused silica capillary column (30 m, 0.25 mm i.d., 0.25 μm film thickness).

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was heated for 3 h with *p*-TsOH·H_2O (45 mg) in benzene (40 mL) at reflux with water removal using a Dean −Stark trap for 3 h to cyclize the hydroxy acid to the lactone. The solution was cooled and concentrated, and the resultant oil was chromatographed (10:1 hexane/ethyl acetate) to give 0.295 g of additional product for a combined yield of 2.021 g (93%) of the title compound as an inseparable 1:1 mixture of diastereomers as determined by ^{1}H NMR analysis. R_f = 0.33 (4:1 hexane/ethyl acetate); IR (neat) 1732 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (d, J = 6.7 Hz, 3H × $^1/_2$), 1.30 (d, J = 7.1 Hz, 3H × $^1/_2$), 1.47−1.72 (m, 2H), 1.88−2.15 (m, 2H), 2.30−2.64 (m, 3H), 4.31−4.39 (m, 1H), 5.11−5.18 (m, 2H), 5.75−5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.30, 17.45, 25.59, 26.16, 28.46, 28.58, 33.26, 36.18, 39.63, 40.54, 77.51, 81.04, 118.42, 118.56, 132.73, 132.91, 174.32, 176.17; MS (CI, NH_3) *m*/*z* (rel intense) 155 [(M + H)$^+$, 100], 137 (21), 130 (5); HRMS (CI, NH_3) calcd for $C_9H_{14}O_2H$ [(M + H)$^+$] 155.1072, found 155.1066.

6-[(1,3-Dioxolan-2-yl)methyl]tetrahydropyan-2-one (20). Osmium tetraoxide (0.85 mL of a 2.5 wt % solution in *tert*-butyl alcohol) was added to a solution of **12** (0.794 g, 5.66 mmol) and *N*-methylmorpholine-*N*-oxide (NMO, 0.995 g, 8.49 mmol) in THF/*t*-BuOH (5:2, 11.2 mL). After 73 h, additional portions of osmium tetraoxide (0.20 mL of a 2.5 wt % solution in *t*-BuOH) and NMO (0.498 g, 4.25 mmol) were added. After 90 h, 10% aqueous $NaHSO_4$ (5 mL) was added at 0 °C. After 30 min, brine (50 mL) was added and the mixture was extracted with ethyl acetate (50 mL × 5) and CH_2Cl_2 (50 mL × 3). The organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by passing through a short plug of silica gel (9:1 $CHCl_3$/MeOH) to give 0.385 g of colorless oil, which was immediately dissolved in ether/H_2O (9 mL, 2:1) and was treated with $NaIO_4$ (0.637 g, 2.98 mmol) at 0 °C. After 15 min, the mixture was warmed to room temperature and stirred for 2 h. Brine (10 mL) was added to the mixture, and the product was extracted with ethyl acetate (20 mL × 5). The organic layer was dried ($MgSO_4$) and concentrated to give 0.277 g of colorless oil, which was dissolved in dry CH_2Cl_2 (12 mL) and stirred with ethylene glycol (0.133 g, 0.12 mL, 2.15 mmol) and (TMS)Cl (TMS = trimethylsilyl (0.466 g, 0.54 mL, 4.29 mmol) at room temperature for 6 h. The solution was diluted with CH_2Cl_2 (100 mL) and washed with brine (50 mL), and the organic phase was dried ($MgSO_4$) and concentrated. Chromatography (3:1 hexane/ethyl acetate) provided 0.157 g (15% from **12**) of the title compound as colorless oil. R_f = 0.17 (1:1 hexane/ethyl acetate); IR (neat) 1734 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55−1.67 (m, 1H), 1.81−2.05 (m, 4H), 2.16 (ddd, J = 3.3, 7.7, 13.9 Hz, 1H), 2.45 (ddd, J = 7.0, 8.4, 17.6 Hz, 1H), 2.60 (ddd, J = 1.1, 6.6, 17.6 Hz, 1H), 3.82−3.91 (m, 2H), 3.93−4.02 (m, 2H), 4.53 (dddd, J = 2.9, 4.8, 7.7, 11.0 Hz, 1H), 5.08 (dd, J = 3.7, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 18.62, 28.42, 29.54, 40.36, 65.00, 65.12, 77.23, 101.29, 171.66; MS (CI, NH_3) *m*/*z* (rel intense) 187 [(M + H)$^+$, 100], 185 (4), 169 (3); HRMS (CI, NH_3) calcd for $C_9H_{14}O_4H$ [(M + H)$^+$] 187.0970, found 187.0961.

6-[(1,3-Dioxolan-2-yl)methyl]-3-methyltetrahydropyran-2-one (21). Osmium tetraoxide (3.53 mL of a 2.5 wt % solution in *tert*-butyl alcohol) was added to a solution of **13** (3.30 g, 21.68 mmol) and *N*-methylmorpholine-*N*-oxide (NMO, 7.26 g, 65.04 mmol) in THF/*t*-BuOH (5:2, 55 mL). After 20.5 h, ethyl acetate (200 mL) was added to the mixture and the organic layer was separated and washed with 10% $NaHSO_3$ solution (40 mL). The aqueous layer was extracted with ethyl acetate (100 mL × 5) and CH_2Cl_2 (100 mL × 5). The combined organic phases were dried ($MgSO_4$) and concentrated to give pale yellow oil, which was dissolved in ether/H_2O (162 mL, 2:1) and was treated with $NaIO_4$ (6.03 g, 28.2 mmol) at 0 °C. After 15 min, the mixture was warmed to room temperature, stirred for 1 h, then diluted with water (60 mL), and extracted with ethyl acetate (100 mL × 5). The organic phase was dried ($MgSO_4$) and concentrated to give colorless oil, which was dissolved in benzene (108 mL) and heated with ethylene glycol (1.35 g, 1.21 mL, 21.68 mmol) and *p*-TsOH·H_2O (0.325 g) at reflux for 30 min using a Dean−Stark trap for water removal. The solution was cooled and concentrated. The residue was chromatographed (3:1 hexane/ethyl acetate) to give 1.54 g of the title compound (35% from **13**) as colorless oil, which was found to be an inseparable 1:1.1 mixture of diastereomers as determined by ^{1}H NMR analysis. R_f = 0.12 (3:1 hexane/ethyl acetate); IR (neat) 1731 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (d, J = 6.7 Hz, 3H × 1/2.1), 1.30 (d, J = 7.1 Hz, 3H × 1.1/2.1), 1.47−2.19 (m, 6H), 2.40−2.68 (m, 1H), 3.82−4.03 (m, 4H), 4.49−4.58 (m, 1H), 5.04−5.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.25, 17.57, 25.64, 27.29, 28.64, 29.76, 33.23, 36.21, 39.82, 40.76, 64.93, 65.06, 74.69, 78.48, 101.25, 101.29, 174.08, 176.07; MS (CI, NH_3) *m*/*z* (rel intense) 201 [(M + H)$^+$, 100], 200 (0.3) 199 (2), 183 (4), 157 (4); HRMS (CI, NH_3) calcd for $C_{10}H_{16}O_4H$ [(M + H)$^+$] 201.1127, found 201.1123. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.08. Found: C, 59.66; H, 8.15.

Ethyl (*Z*)-10-(1,3-Dioxolan-2-yl)-9-hydroxy-4-decenoate (22). DIBALH (0.09 mL, 0.131 mmol, 1.5 M solution in toluene) was added to a cold (−78 °C) solution of **20** (20.3 mg, 0.109 mmol) in dry CH_2Cl_2 (1 mL). After 1 h, methanol (0.05 mL) and water (0.05 mL) were added sequentially. After being warmed to room temperature, the mixture was diluted with ether (5 mL) and $MgSO_4$ was added. After stirring vigorously for 1 h, the mixture was filtered and the filter cake was washed with ether (20 mL). The filtrate was concentrated to give 24.0 mg of the crude lactol as colorless oil. Potassium bis(trimethysilyl)amide (0.52 mL, 0.262 mmol, 0.5 M solution in toluene) was added to a suspension of $[Ph_3P(CH_2)_3CO_2Et]Br$ (**26**, 126 mg, 0.273 mmol)[14] in dry THF (2.0 mL) at 0 °C. After 30 min, the mixture was cooled to −78 °C and the lactol in dry THF (2.0 mL) was added. After 30 min at −78 °C, the mixture was warmed to 0 °C, stirred for 1 h, then quenched with saturated aqueous NH_4Cl (5 mL), and extracted with ether (10 mL × 3). The organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified chromatographed (3:1 hexane/ethyl acetate) to give 12.1 mg (39%) of the title compound as colorless oil, which was found to be only the *Z*-isomer by ^{1}H NMR spectroscopy. R_f = 0.40 (1:1 hexane/ethyl acetate); IR (neat) 3511 (br), 1734 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.3 Hz, 3H), 1.36−1.57 (m, 4H), 1.78 (ddd, J = 5.1, 9.2, 14.3 Hz, 1H), 1.88 (ddd, J = 2.2, 3.7, 14.3 Hz, 1H), 2.05−2.13 (m, 2H), 2.30−2.40 (m, 4H), 2.94 (br, 1H), 3.83−3.94 (m, 3H), 3.98−4.05 (m, 2H), 4.13 (q, J = 7.3 Hz, 2H), 5.04 (dd, J = 3.7, 5.1 Hz, 1H), 5.31−5.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.46, 23.04, 25.65, 27.26, 34.59, 37.06, 40.37, 60.51, 64.95, 65.15, 67.89, 103.84, 127.96, 131.26, 173.46; MS (CI, NH_3) *m*/*z* (rel intense) 287 [(M + H)$^+$, 30], 269 (12), 216 (35), 297 (11), 199 (100); HRMS (CI, NH_3) calcd for $C_{15}H_{26}O_5H$ [(M + H)$^+$] 287.1858, found 287.1858. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.72; H, 9.12.

Ethyl (*Z*)-9-Azido-10-(1,3-dioxolan-2-yl)-4-decenoate (23). Methanesulfonyl chloride (166 mg, 0.11 mL, 1.45 mmol) was added to a cold (−40 °C) solution of **22** (83 mg g, 0.290 mmol) and triethylamine (162 mg, 0.22 mL, 1.60 mmol) in dry CH_2Cl_2 (4.0 mL). After 1 h at room temperature, ether (20 mL) was added and the mixture was washed with ice-cold 2% HCl (20 mL) and then saturated $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$) and concentrated to give pale yellow oil that was dissolved in dry THF (1.4 mL) and treated with tetra-*n*-butylammonium azide (1.16 mL, 1 M solution in THF, 1.16 mmol). After stirring for 17 h at room temperature, the mixture was diluted with dichloromethane and washed with water (20 mL) and then the organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed (10:1 hexane/ethyl acetate) to give 76.2 g (84%) of the title compound as colorless oil. R_f = 0.50 (3:1 hexane/ethyl acetate); IR (neat) 2103 (s), 1732 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.3 Hz, 3H), 1.38−1.61 (m, 4H), 1.79 (ddd, J = 4.4, 5.9, 14.3 Hz, 1H), 1.91 (ddd, J = 3.6, 8.8, 14.3 Hz, 1H), 2.06−2.13 (m, 2H), 2.34−2.37 (m, 4H), 3.52 (m, 1H), 3.85−3.92 (m, 2H), 3.95−4.01 (m, 2H), 4.13 (q, J = 7.3 Hz, 2H), 4.99 (dd, J = 3.7, 5.9 Hz, 1H), 5.33−5.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.48, 23.05, 26.10, 27.00, 34.52, 34.70, 38.92, 59.20, 60.55, 65.06, 65.18, 102.23, 128.45, 130.67, 173.41; MS (CI, NH_3) *m*/*z* (rel intense) 284 [(M + H − N_2)$^+$, 100], 212 (56), 198 (28), 196 (61), 182 (24), 156 (25); HRMS (CI, NH_3) calcd for

$C_{15}H_{25}O_4N_3H-N_2$ [$(M + H - N_2)^+$] 284.1862, found 284.1875. Anal. Calcd for $C_{15}H_{25}O_4N_3$: C, 57.86; H, 8.09; N, 13.49. Found: C, 57.83; H, 8.03; N, 13.20.

Ethyl (*Z*)-10-(1,3-Dioxolan-2-yl)-9-hydroxy-6-methyl-4-decenoate (24). DIBALH (0.63 mL, 0.941 mmol, 1.5 M solution in toluene) was added to a cold (−78 °C) solution of **21** (0.157 g, 0.784 mmol) in dry CH_2Cl_2 (3.7 mL). After 1 h, methanol (0.1 mL) and water (0.1 mL) were added sequentially. After being warmed to room temperature, the mixture was diluted with ether (5 mL) and $MgSO_4$ was added. After being stirred vigorously for 1 h, the mixture was filtered and the filter cake was washed with ether (20 mL). The filtrate was concentrated to give 0.154 g (97% crude) of the lactol as colorless oil. Potassium bis(trimethysilyl)amide (3.64 mL, 1.82 mmol, 0.5 M solution in toluene) was added to a suspension of $[Ph_3P(CH_2)_3CO_2Et]Br$ (**26**, 824 mg, 1.82 mmol)[14] in dry THF (4.4 mL) at 0 °C. After 30 min, the mixture was cooled to −78 °C and the lactol in dry THF (9.0 mL) was added. After 30 min at −78 °C, the mixture was warmed to 0 °C, stirred for 2 h, then quenched with saturated aqueous NH_4Cl (20 mL), and extracted with ether (20 mL × 3). The organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified chromatographed (3:1 hexane/ethyl acetate) to give 0.124 g (52%) of the title compound as colorless oil, which was found to be a 1:1.2 mixture of diastereomers (both *Z*-alkenes) by ^{1}H NMR spectroscopy. R_f = 0.38 (1:1 hexane/ethyl acetate); IR (neat) 3504 (br), 1732 (s) cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 0.90 (d, J = 6.6 Hz, 3H × 1.2/2.2), 0.91 (d, J = 6.5 Hz, 3H × 1/2.2), 0.947 (t, J = 7.2 Hz, 3H × 1.2/2.2), 0.954 (t, J = 7.1 Hz, 3H × 1/2.2), 1.15−1.60 (m, 4H), 1.80−1.84 (m, 2H), 2.15−2.50 (m, 5H), 2.75 (d, J = 2.5 Hz, 1H × 1/2.2), 2.83 (d, J = 2.7 Hz, 1H × 1.2/2.2), 3.18−3.44 (m, 4H), 3.93 (m, 1H), 3.94 (q, J = 7.2 Hz, 2H × 1/2.2), 3.95 (q, J = 7.1 Hz, 2H × 1.2/2.2), 4.86−4.90 (m, 1H), 5.12−5.18 (m, 1H), 5.23−5.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.45, 21.48, 21.59, 23.27, 31.86, 31.94, 33.18, 33.41, 34.76, 35.33, 35.45, 40.36, 60.50, 64.93, 65.13, 68.05, 68.25, 103.81, 126.46, 126.49, 137.61, 137.69, 179,71; MS (CI, NH_3) m/z (rel intense) 301 [$(M + H)^+$,23], 230 (33), 214 (14), 213 (38), 200 (18), 199 (100), 196 (14), 195 (20), 186 (12), 185 (76); HRMS (CI, NH_3) calcd for $C_{16}H_{28}O_5H$ [$(M + H)^+$] 301.2015, found 301.2018. Anal. Calcd for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40. Found: C, 63.60; H, 9.49.

Ethyl (*Z*)-9-Azido-10-(1,3-dioxolan-2-yl)-6-methyl-4-decenoate (25). Methanesulfonyl chloride (0.278 g, 0.19 mL, 2.43 mmol) was added to a cold (−40 °C) solution of **24** (0.146 g, 0.486 mmol) and triethylamine (0.270 g, 0.37 mL, 2.67 mmol) in dry CH_2Cl_2 (6.7 mL). After 1 h at room temperature, ether (20 mL) was added and the mixture was washed with ice-cold 2% HCl (20 mL) and then saturated $NaHCO_3$ (20 mL). The organic phase was dried ($MgSO_4$) and concentrated to give pale yellow oil that was dissolved in dry THF (2.4 mL) and treated with tetra-*n*-butylammonium azide (1.94 mL, 1 M solution in THF, 1.94 mmol). After being stirred for 17 h at room temperature, the mixture was diluted with dichloromethane and washed with water (20 mL) and then the organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed (10:1 hexane/ethyl acetate) to give 0.137 g (87%) of the title compound as colorless oil, which was found to be an inseparable 1:1.2 mixture of diastereomers (both with the *Z*-alkene geometry) by ^{1}H NMR spectroscopy. R_f = 0.48 (3:1 hexane/ethyl acetate); IR (neat) 2102 (s), 1732 (s) cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 0.82 (d, J = 6.6 Hz, 3H × 1/2.2), 0.83 (d, J = 6.2 Hz, 3H × 1.2/2.2), 0.96 (t, J = 7.1 Hz, 3H), 1.00−1.46 (m, 4H), 1.69−1.75 (m, 1H), 1.86−1.94 (m, 1H), 2.14 −2.35 (m, 5H), 3.31−3.37 (m, 2H), 3.43−3.53 (m, 3H), 3.96 (q, J = 7.1 Hz, 2H), 4.91−4.94 (m, 1H), 5.01−5.07 (m, 1H), 5.21−5.29 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 14.66, 21.76, 21.88, 23.76, 32.09, 32.19, 33.51, 33.60, 34.04, 34.12, 34.91, 39.53, 39.60, 59.87, 60.08, 60.48, 65.11, 65.25, 102.62, 127.51, 127.58, 137.41, 137.52, 172.72; MS (CI, NH_3) m/z (rel intense) 298 [$(M + H - N_2)^+$, 100], 282 (2), 254 (2), 227 (8), 226 (38); HRMS (CI, NH_3) calcd for $C_{16}H_{27}O_4N_3H-N_2$ [$(M + H - N_2)^+$] 298.2018, found 298.2023. Anal. Calcd for $C_{16}H_{27}O_4N_3$: C, 59.06; H, 8.36; N, 12.91. Found: C, 59.25; H, 8.16; N, 12.88.

***trans*-2-[(1,3-Dioxolan-2-yl)methyl]-6-(4-hydroxybutyl)-piperidine (28).** A solution of **23** (26.8 mg, 0.0860 mmol) in C_6D_6 (1.0 mL) in a sealable NMR tube was degassed using three freeze/thaw cycles and then sealed under vacuum. The tube were heated in an oil bath to 120 °C for 68.5 h, when NMR spectroscopic analysis showed complete formation of the tetrahydropyridine **27** [^{1}H NMR (C_6D_6, 300 MHz) δ 0.95 (t, J = 7.1 Hz, 3H), 1.10−2.40 (m, 14H), 3.34−3.65 (m, 4H), 3.67 (br, 1H), 3.96 (q, J = 7.1 Hz, 2H), 5.48 (dd, J = 3.7, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.65, 19.69, 21.80, 28.83, 29.45, 34.17, 39.73, 43.30, 55.05, 60.28, 65.07 (overlap), 103.69, 167.85, 173.43]. After cooling the tube to 0 °C and unsealing, the contents were washed from the tube with dichloromethane (10 mL) and the solvent was removed under reduced pressure to give **27** as a colorless oil. A solution of **27** in dry THF (1.5 mL) was added to a suspension of $LiAlH_4$ (32.6 mg, 0.860 mmol) in dry THF (1.5 mL) at −78 °C, followed by the addition of trimethylaluminum (0.43 mL, 0.860 mmol, 2.0 M solution in hexane).[16] After 30 min, the solution was warmed to −40 °C for 1 h, then −20 °C for 1 h, and finally 0 °C for 1 h. The mixture was diluted with ether (2 mL) and treated with sodium fluoride (68 mg, 1.63 mmol) followed by the cautious dropwise addition of water (0.05 mL). After 15 min, the resulting slurry was filtered through Celite, washing the filter pad with ether (20 mL). The combined filtrates were dried (Na_2SO_4) and concentrated. The residue was chromatographed (90:9:1, $CHCl_3$/MeOH/NH_4OH) to give 14.2 mg (68%) of **28** as a colorless oil, which was found to be a single diastereomer by ^{1}H and ^{13}C NMR spectroscopy. R_f = 0.12 (90:9:1, $CHCl_3$/MeOH/NH_4OH); IR (neat) 3332 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24−1.74 (m, 13H), 1.95 (ddd, J = 5.5, 8.7, 14.2 Hz, 1H), 2.64 (br s, 2H), 2.80−2.95 (m, 1H), 3.10−3.25 (m, 1H), 3.64 (t, J = 6.5 Hz, 2H), 3.80−4.01 (m, 4H), 4.93 (t, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 20.09, 22.56, 31.22, 32.03, 32.99, 34.19, 37.80, 47.42, 50.71, 62.84, 64.87, 65.10, 104.00; MS (CI, NH_3) m/z (rel intense) 244 [$(M + H)^+$, 39], 242 (20), 224 (8), 171 (12), 170 (75); HRMS (CI, NH_3) calcd for $C_{13}H_{25}O_3H$ [$(M + H)^+$] 244.1913, found 244.1917.

Assignment of the Relative Configuration of 28. According to literature precedent, the C*H*N methine protons in simple *cis*-2,6-dialkylpiperidines typically appear at δ 2.4−2.7 ppm, whereas these protons appear at approximately δ 2.8−3.3 ppm in the trans diastereomers.[17] In **28**, the appearance of the two C*H*N methine protons at ca. δ 2.9 and 3.2 ppm is most consistent with the *trans*-2,6 diastereomer. In the other possible diastereomer (**29**, see below), these protons appear at ca. δ 2.5 and 2.7 ppm, consistent with the *cis*-2,6 diastereomer.

***cis*-2-[(1,3-Dioxolan-2-yl)methyl]-6-(4-hydroxybutyl)piperidine (29).** A solution of **23** (25.3 mg, 0.0813 mmol) in C_6D_6 (1.0 mL) in a sealable NMR tube was degassed and heated as above. After cooling the tube to 0 °C and unsealing, the contents were washed from the tube with benzene (10 mL) and the solvent was removed under reduced pressure to give **27** as a colorless oil. A solution of **27** in dry CH_2Cl_2 (0.5 mL) was treated with DIBALH (0.27 mL, 0.41 mmol, 1.5 M solution in toluene) at −78 °C.[16] After 30 min, the solution was warmed to −40 °C for 1 h, then −20 °C for 1 h, and finally 0 °C for 1 h. The mixture was diluted with ether (2 mL) and treated with sodium fluoride (68 mg, 1.63 mmol) followed by the cautious dropwise addition of water (0.05 mL). After 15 min, the resulting slurry was filtered through Celite, washing the filter pad with ether (20 mL). The combined filtrates were dried (Na_2SO_4) and concentrated. The residue was chromatographed (90:9:1, $CHCl_3$/MeOH/NH_4OH) to give 5.5 mg (28%) of **27** as a colorless oil, which was found to be a single diastereomer by ^{1}H and ^{13}C NMR spectroscopy. R_f = 0.21 (90:9:1, $CHCl_3$/MeOH/NH_4OH); IR (neat) 3334 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98−1.85 (m, 14H), 2.13 (br, 2H), 2.43−2.55 (m, 1H), 2.69−2.80 (m, 1H), 3.64 (t, J = 6.5 Hz, 2H), 3.80−4.02 (m, 4H), 4.97 (dd, J = 4.1, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 22.21, 24.97, 32.39, 32.96, 33.19, 36.98, 40.92, 53.68, 57.02, 62.83, 64.87, 65.12, 103.82; MS (CI, NH_3) m/z (rel intense) 244 [$(M + H)^+$, 100], 242 (16), 171 (11), 170 (56); HRMS (CI, NH_3) calcd

for $C_{13}H_{25}O_3H$ [$(M + H)^+$] 244.1913, found 244.1901. See above for the assignment of the relative configuration of **27**.

2-(3-Carboethoxypropyl)-6-[(1,3-dioxolan-2-yl)methyl]-3-methylpiperidine (32), (2*R,3*S**,6*R**)-2-(3-Carboxypropyl)-6-[(1,3-dioxolan-2-yl)methyl]-3-methylpiperidine (33), and (2*R**,3*R**,6*R**)-2-(3-Carboxypropyl)-6-[(1,3-dioxolan-2-yl)methyl]-3-methylpiperidine (34).** Three solutions of **25** [46.6 mg (0.143 mmol), 44.9 mg (0.138 mmol), and 42.1 mg (0.129 mmol)] in C_6D_6 (3 × 1.0 mL) in sealable NMR tubes were degassed using three freeze/thaw cycles and then sealed under vacuum. The tubes were heated in an oil bath to 130 °C for 66 h. After ca. 15 h, an intermediate was observed by ^{1}H NMR spectroscopy, assigned as the triazolines **30** [partial: δ 4.9 (dd), 4.7 (brq), 0.5 (d)]. After the full 66 h, the imine **31** was observed as the major product (dioxolanyl methine proton appears as a multiplet at ca. δ 5.5 ppm), accompanied by another compound, believed to be the aziridine (dioxolanyl methine proton appears as a multiplet at ca. δ 5.2 ppm).[25] The tubes were cooled to 0 °C and unsealed, and the contents were rinsed out with CH_2Cl_2 (5 mL each). The combined solutions were concentrated and immediately dissolved in dry ethanol (6.6 mL) and mixed with $PdCl_2$ (94.7 mg, 0.534 mmol) followed by $NaBH_4$ (46.4 mg, 1.233 mmol) at 0 °C.[18] The mixture was allowed to warm to room temperature and, after 1 h, was filtered through Celite, washing the filter cake with ethyl acetate (20 mL × 3). The filtrate was washed with 15% NaOH (50 mL), dried (Na_2SO_4), concentrated, and passed through a short plug of silica gel (160:8:1, $CHCl_3$/MeOH/NH_4OH) to give 87.4 mg of the ester **32** as colorless oil, which was found to be a 1:1.3 mixture of diastereomers by ^{1}H NMR spectroscopy. This material was saponified without further purification (see below). In a previous run, a sample of the pure ester **32** was obtained by careful chromatography (160:8:1, $CHCl_3$/MeOH/NH_4OH), again as an inseparable 1:1.3 mixture of diastereomers (1:1.3): R_f = 0.27 (90:9:1, $CHCl_3$/MeOH/NH_4OH); IR (neat) 3340 (w), 1731 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (d, J = 6.3, 3H × 1.3/2.3), 0.90 (d, J = 6.6 Hz, 3H × 1/2.3), 1.06−1.41 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.41−1.80 (m, 7H), 1.90 (br, 1H), 2.13 (dt, J = 2.6, 9.2 Hz, 1H × 1.3/2.3), 2.24−2.42 (m, 2H), 2.65 (dt, J = 2.7, 6.9 Hz, 1H × 1/2.3), 2.68−2.78 (m, 1H), 3.81−3.89 (m, 2H), 3.93−4.01 (m, 2H), 4.126 (q, J = 7.1 Hz, 2H), 4.129 (q, J = 7.1 Hz, 2H), 4.96 (t, J = 6.2 Hz, 1H × 1/2.3), 4.97 (t, J = 6.0 Hz, 1H × 1.3/2.3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.63, 14.47, 18.58, 21.44, 21.85, 30.41, 32.45, 33.58, 33.90, 34.54, 34.66, 36.14, 40.80, 41.15, 53.55, 54.44, 59.36, 60.42, 62.68, 64.83, 64.87, 65.14, 103.83, 103.88, 173.83; MS (CI, NH_3) m/z (rel intense) 300 [$(M + H)^+$, 62], 212 (42), 184 (100), 166 (25); HRMS (CI, NH_3) calcd for $C_{16}H_{29}O_4NH$ [$(M + H)^+$] 300.2175, found 300.2170.

Sodium hydroxide (29.2 mg, 0.731 mmol) was added to a solution of the ester **32** from above (87.4 mg) in ethanol (26 mL), and the mixture was heated at reflux for 1 h. After cooling to room temperature, the mixture was concentrated and chromatographed (2:1, $CHCl_3$/MeOH) without further workup to give 37.5 mg (34% from **25**) of **33** as a colorless solid and 29.2 mg (26% from **25**) of **34** as a colorless solid. See below (reductions of **33** and **34** to **35** and **36**) for assignment of the relative configurations. Data for **33**: R_f = 0.28 (2:1 $CHCl_3$/MeOH); colorless prisms ($CHCl_3$−hexane); mp = 160−162 °C; IR (KBr) 3422 (br), 1638 (w), 1560 (s) cm^{-1}; ^{1}H NMR [$CDCl_3$/methanol-d_6 (1:1), 360 MHz] δ 1.00 (d, J = 6.5 Hz, 3H), 1.45−2.22 (m, 12H), 2.41 (m, 1H), 2.61 (br t, J = 7.8 Hz, 1H), 3.17 (m, 1H), 3.87−4.04 (m, 4H), 5.04 (t, J = 4.0 Hz, 1H); MS (CI, NH_3) m/z (rel intense) 272 [$(M + H)^+$, 70], 271 (28), 270 (100), 254 (64), 252 (26), 185 (15), 184 (100), 182 (24), 166 (30); HRMS (CI, NH_3) calcd for $C_{14}H_{25}O_4NH$ [$(M + H)^+$] 272.1862, found 272.1873. Anal. Calcd for $C_{14}H_{25}O_4N$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.75; H, 9.23; N, 5.14. Data for **34**: R_f = 0.18 (2:1 $CHCl_3$/MeOH); colorless prisms (MeOH−ether); mp 204−207 °C (dec); IR (KBr) 3434 (br), 1638 (w), 1546 (s) cm^{-1}; ^{1}H NMR [$CDCl_3$/methanol-d_6 (1:1), 200 MHz] δ 1.01(d, J = 7.3 Hz, 3H), 1.45−2.40 (m, 13H), 3.07−3.30 (m, 2H), 3.85−4.06 (m, 4H), 5.02 (t, J = 4.9 Hz, 1H); MS (CI, NH_3) m/z (rel intense) 271 [$(M + H - N_2)^+$, 87], 271 (16), 270 (70), 254 (26), 185 (15), 184 (100), 182 (24), 166 (30); HRMS (CI, NH_3) calcd for $C_{14}H_{25}O_4NH$ [$(M + H)^+$] 272.1862, found 272.1852. Anal. Calcd for $C_{14}H_{25}O_4N$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.67; H, 8.97; N, 5.13.

(2*R,3*S**,6*R**)-6-[(1,3-Dioxolan-2-yl)methyl]-2-(4-hydroxybutyl)-3-methylpiperidine (35).** Lithium aluminum hydride (17.3 mg, 0.456 mmol) was added to a solution of **33** (42.8 mg, 0.158 mmol) in dry THF (4.5 mL) at 0 °C, and the mixture was allowed to warm to room temperature. After 17.5 h, the mixture was cooled to 0 °C and more lithium aluminum hydride (10.2 mg, 0.269 mmol) was added. After 7 h at room temperature, the mixture was cooled to 0 °C, diluted with ether (15 mL), and treated with sodium fluoride (0.133 g, 3.16 mmol) and water (0.1 mL). After 10 min, the resulting slurry was filtered through a pad of Celite and sodium sulfate, washing the filter cake with ether (50 mL). Concentration of the filtrate and chromatography of the residue (90:9:1 $CHCl_3$/MeOH/NH_4-OH) provided 34.1 mg (84%) of **35** as colorless oil. R_f = 0.31 (90:9:1 $CHCl_3$/MeOH/NH_4OH); IR (neat) 3334 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84 (d, J = 6.2 Hz, 3H), 1.08 (dq, J = 4.0, 13.2 Hz, 1H), 1.15−1.39 (m, 4H), 1.47−1.80 (m, 8H), 1.91 (br, 2H), 2.14 (dt, J = 2.1, 9.2 Hz, 1H), 2.71 (m, 1H), 3.62−3.70 (m, 2H), 3.82−3.88 (m, 2H), 3.94−4.00 (m, 2H), 4.98 (dd, J = 3.7, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.62, 21.85, 32.96, 33.23, 33.52, 34.52, 36.26, 40.75, 53.53, 62.69, 62.79, 64.87, 65.11, 103.91; MS (CI, NH_3) m/z (rel intense) 258 [$(M + H)^+$, 100], 257 (1), 241 (1), 240 (5), 238 (3), 184 (10), 170 (6); HRMS (CI, NH_3) calcd for $C_{14}H_{27}O_3NH$ [$(M + H)^+$] 258.2069, found 258.2064. See below for a discussion of the relative configuration of **35**.

(2*R,3*R**,6*R**)-6-[(1,3-Dioxolan-2-yl)methyl]-2-(4-hydroxybutyl)-3-methylpiperidine (36).** Lithium aluminum hydride (79.6 mg, 2.10 mmol) was added to a solution of **34** (0.114 g, 0.419 mmol) in dry THF (21 mL) at 0 °C, and the mixture was allowed to warm to room temperature. After 26 h, the mixture was cooled to 0 °C, diluted with ether (30 mL), and treated with sodium fluoride (0.352 g, 8.38 mmol) and water (0.2 mL). After 10 min, the resulting slurry was filtered through a pad of Celite and sodium sulfate, washing the filter cake with ether (100 mL). Concentration of the filtrate and chromatography of the residue (90:9:1 $CHCl_3$/MeOH/NH_4OH) provided 86.1 mg (80%) of **36** as colorless oil. R_f = 0.16 (90:9:1 $CHCl_3$/MeOH/NH_4OH); IR (neat) 3360 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (d, J = 7.3 Hz, 3H), 1.24−1.48 (m, 5H), 1.55−1.83 (m, 10H), 2.65 (dt, J = 2.9, 7.0 Hz, 1H), 2.73 (m, 1H), 3.65 (t, J = 6.6 Hz, 2H), 3.81−3.90 (m, 2H), 3.91−4.03 (m, 2H), 4.96 (dd J = 4.4, 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.84, 22.59, 28.21, 30.64, 32.54, 33.08, 34.09, 41.17, 54.47, 59.60, 62.98, 64.86, 65.16, 103.79; MS (CI, NH_3) m/z (rel intense) 258 [$(M + H)^+$, 100], 256 (14), 238 (16), 185 (12), 184 (61), 170 (29); HRMS calcd for $C_{14}H_{27}O_3NH$ [$(M + H)^+$] 258.2069, found 258.2062.

Assignment of Relative Configurations of 35 and 36. (1) Cis relationship at C(2) and C(6). For both **35** and **36**, the ^{1}H NMR chemical shifts of the C*H*N methine protons appear in the appropriate range for *cis*-2,6-disubstituted piperidines (see the discussion above for **28** and **29**). A comparison to **29** is informative (Figure 3). H_b appears consistently at ca. 2.7−2.8 ppm in **29**, **35**, and **36**. H_a appears at ca. 2.5 ppm in **29**, but **35** and **36** (H_a = 2.14 and 2.65 ppm, respectively) show considerable variation from this value, although still within the expected range for *cis*-2,6-disubstituted piperidines.[17] However, correcting the H_a shifts in **35** and **36** for the effect of a neighboring equatorial or axial methyl

(25) In a separate experiment, chromatography of the imine **28** was attempted (2:1 ethyl acetate/hexane followed by methanol/chloroform). Although a pure sample of **28** could not be obtained due to its decomposition, an impure byproduct was isolated in 15% yield that had spectral data consistent with an aziridine. This material exhibited the same multiplet at δ 5.2 ppm as that observed in the sealed tube experiments.

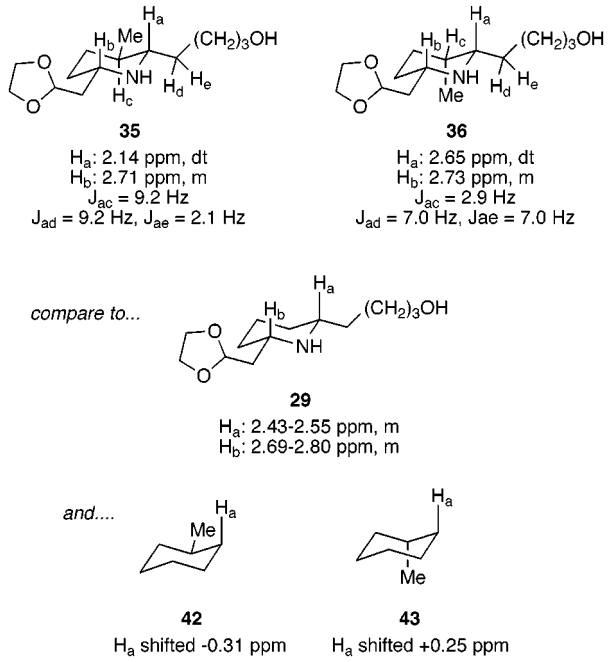


Figure 3. Assignment of relative configurations of **35** and **36**.

group (see **42** and **43**)[26] allows an excellent correlation with the value for H_a in **29** (i.e., 2.14 + 0.31 = 2.45 for **35**; 2.65−0.25 = 2.40 for **36**; compared with ca. 2.5 for **29**). Finally, the corresponding *trans*-2,6-disubstituted piperidines **44** (see below) were also synthesized, each showing C*H*N methine chemical shifts ($H_a + H_b$ = 2.8−2.95 ppm for the minor trans diastereomer and 2.46 + 3.28 ppm for the major trans diastereomer) downfield in value from **35/36**, again consistent with literature data and the assignments for **28** and **29** above.[17]

(2) Configuration of C(3) methyl group. Beyond the consistency of the effect of the C(3) methyl configuration on the chemical shifts of H_a discussed above, typical axial−axial and axial−equatorial coupling constants are observed for **35** (J_{ac} = 9.2 Hz) and **36** (J_{ac} = 2.9 Hz), respectively.

(2*R,3*R**/*S**,6*S**)-6-[(1,3-Dioxolan-2-yl)methyl]-2-(4-hydroxybutyl)-3-methylpiperidine (44).** A solution of **25** (40.5 mg, 0.124 mmol) in C_6D_6 (1.0 mL) in a sealable NMR tube was degassed using three freeze/thaw cycles and then sealed under vacuum. The tube was then heated in an oil bath at 120 °C for 67 h and then cooled to 0 °C and opened, and the contents were rinsed out with CH_2Cl_2 (10 mL). After concentration, the residue was dissolved in THF (1.5 mL) and added to a suspension of lithium aluminum hydride (47.1 mg, 1.24 mmol) in dry THF (1.5 mL) at −78 °C. Trimethylaluminum (0.62 mL, 1.24 mol, 2.0 M solution in hexane) was then added.[16] After 30 min, the mixture was held at −40 °C for 1 h, −20 °C for 1 h, and 0 °C for 1 h. The mixture was diluted with ether (2 mL) and treated with sodium fluoride (68 mg, 1.63 mmol) followed by the cautious dropwise addition of water (0.05 mL). After 15 min, the resulting slurry was filtered through a short pad of Celite, washing with ether (20 mL). The combined filtrates were dried (Na_2SO_4), and concentrated. The residue was chromatographed (90:4:1, $CHCl_3$/MeOH/NH_4OH) to give 10.3 mg (32%) of the title compound as colorless oil, which was found to be an inseparable 1:1.4 mixture of diastereomers as determined by ^{1}H NMR analysis, both with the trans relative configuration at C(2) and C(6). IR (neat) 3333 (br) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84 (d, J = 6.8 Hz, 3H × 1/2.4), 0.93 (d, J = 6.6 Hz, 3H × 1.4/2.4), 0.87−2.30 (m, 15H), 2.46 (dt, J = 3.4, 8.3 Hz, 1H × 1.4/2.4), 2.80−2.95 (m, 2H × 1/2.4), 3.28 (m, 1H × 1.4/2.4), 3.64 (t, J = 6.3 Hz, 2H × 1.4/2.4), 3.66 (t, J = 6.6 Hz, 2H × 1/2.4), 3.80−3.90 (m, 2H), 3.93−4.02 (m, 2H), 4.93 (t, J = 4.6 Hz, 1H × 1.4/2.4), 4.96 (t, J = 4.9 Hz, 1H × 1/2.4); MS (CI, NH_3) *m*/*z* (rel intense) 258 [(M + H)$^+$, 100], 256 (14), 240 (13), 238 (10), 184 (23), 170 (41); HRMS calcd for $C_{14}H_{27}O_3NH$ [(M + H)$^+$] 258.2069, found 258.2057. See above for a discussion of the methods used to determine the relative configuration at C(2) and C(3).

(1*S,4*R**,10*R**)-4-[(1,3-Dioxolan-2-yl)methyl]-1-methylquinolizidine (37).** Carbon tetrachloride (40.8 mg, 0.026 mL, 0.265 mmol) was added to a solution of **35** (34.1 mg, 0.132 mmol), triphenylphosphine (69.5 mg, 0.265 mmol), and Et_3N (26.8 mg, 0.037 mL, 0.265 mmol) in dry MeCN (2 mL) at 0 °C. After being stirred at room temperature for 20 h, the mixture was concentrated and chromatographed (160:8:1 $CHCl_3$/MeOH/NH_4OH) to give 23.7 mg (75%) of the title compound as colorless oil. R_f = 0.43 (90:9:1 $CHCl_3$/MeOH/NH_4OH); IR (neat) 2876 (m), 2854 (m), 2787 (m), 2756 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, J = 6.2 Hz, 3H), 1.00−2.14 (m, 16H), 3.26 (br d, J = 11.1 Hz, 1H), 3.79−3.88 (m, 2H), 3.92−4.01 (m, 2H), 4.93 (t, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.47, 24.76, 26.35, 30.31, 32.76, 33.92, 36.13, 39.01, 51.99, 60.14, 64.87, 64.96, 69.92, 103.65; MS (CI, NH_3) *m*/*z* (rel intense) 240 [(M + H)$^+$, 73], 238 (6), 167 (19), 153 (17), 152 (100); HRMS (CI, NH_3) calcd for $C_{14}H_{25}NO_2H$ [(M + H)$^+$] 240.1963, found 240.1928.

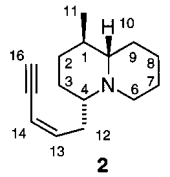
(1*R,4*R**,10*R**)-4-[(1,3-Dioxolan-2-yl)methyl]-1-methylquinolizidine (38).** Carbon tetrachloride (0.208 g, 0.13 mL, 1.35 mmol) was added to a solution of **36** (34.7 mg, 0.135 mmol), triphenylphosphine (0.354 g, 1.35 mmol), and Et_3N (0.137 g, 0.19 mL, 1.35 mmol) in dry MeCN (2 mL) at 0 °C. After stirring at room temperature for 47 h, the mixture was concentrated and chromatographed (160:8:1 $CHCl_3$/MeOH/NH_4OH) to give 19.7 mg (61%) of the title compound as pale yellow oil. R_f = 0.42 (90:9:1 $CHCl_3$/MeOH/NH_4OH); IR (neat) 2880 (m), 2856 (m), 2790 (w), 2758 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, J = 6.9 Hz, 3H), 1.18−2.08 (m, 16H), 3.29 (br d, J = 11.1 Hz, 1H), 3.82−3.88 (m, 2H), 3.92−4.00 (m, 2H), 4.94 (dd, J = 4.3, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.57, 25.22, 26.56, 27.81, 3.86, 32.12, 33.48, 38.66, 53.30, 61.34, 64.83, 64.95, 66.38, 103.64; MS (CI, NH_3) *m*/*z* (rel intense) 240 [(M + H)$^+$, 24], 167 (12), 166 (7), 153 (17), 152 (100); HRMS (CI, NH_3) calcd for $C_{14}H_{25}NO_2H$ [(M + H)$^+$] 240.1964, found 240.1957.

(1*S,4*R**,10*R**)-1-Methyl-4-(*Z*)−(5-(trimethylsilyl)pent-2-en-4-ynyl)quinolizidine (39).** A solution of **37** (32.9 mg, 0.137 mmol) in THF and 1 M HCl (4:1, 8.4 mL) was heated at 50 °C for 25 h. After the solution was cooled to room temperature, saturated $NaHCO_3$ (20 mL) was added to the mixture, which was then extracted with ethyl acetate (30 mL × 3). The organic phase was dried (Na_2SO_4) and concentrated to give pale yellow oil. In a separate flask, *tert*-butyllithium (0.16 mL, 0.274 mmol, 1.7 M solution in pentane) was added to a solution of 3-(*tert*-butyldimethylsilyl)-1-(trimethylsilyl)-1-propyne (77.7 mg, 0.343 mmol)[19] in dry THF (2.9 mL) at −78 °C. After 1 h, titanium tetraisopropoxide (96.3 mg, 0.10 mL, 0.339 mmol) was added to the mixture. After 10 min, a solution of the crude aldehyde in dry THF (2.9 mL) was added to the organotitanium reagent and the resulting mixture was held at −78 °C for 1 h, −20 °C for 2 h, and at room temperature for 2 h, after which saturated NH_4Cl (20 mL) was added and the mixture was extracted with ethyl acetate (30 mL × 3). The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (20:1 $CHCl_3$/MeOH) provided 16.6 mg (42%) of the title compound as colorless oil. R_f = 0.47 (90:9:1 $CHCl_3$/MeOH/NH_4OH); IR (neat) 2852 (m), 2784 (w), 2747 (w), 2149 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 9H), 0.85 (d, J = 6.6 Hz, 3H), 0.94−1.76 (m, 12H), 1.88−1.94 (m, 1H), 2.01−2.08 (m, 1H), 2.44−2.51 (m, 1H), 2.59−2.66 (m, 1H), 3.30 (br d, J = 11.3 Hz, 1H), 5.54 (dt, J = 10.7, 1.3 Hz, 1H), 6.04 (dt, J = 10.7, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.24, 19.42, 24.77, 26.29, 30.22, 32.00, 33.99, 35.08, 36.40, 52.02, 63.69, 69.87, 99.14, 102.36, 110.65, 142.83; MS (CI, NH_3) *m*/*z* (rel intense) 290 [(M + H)$^+$, 39], 289 (3), 288 (9), 275 (3), 274 (10), 153 (15), 152 (100); HRMS (CI, NH_3) calcd for $C_{18}H_{31}$-NSiH [(M + H)$^+$] 290.2304, found 290.2308.

(26) Pretsh, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin, 1989.

(1*R,4*R**,10*R**)-1-Methyl-4-(*Z*)-(5-(trimethylsilyl)pent-2-en-4-ynyl)quinolizidine (40).** A solution of **38** (17.0 mg, 0.0710 mmol) in THF and 1 M HCl (4:1, 5 mL) was heated at 50 °C for 22 h. After the solution was cooled to room temperature, saturated $NaHCO_3$ (20 mL) was added to the mixture, which was then extracted with ethyl acetate (30 mL × 3). The organic phase was dried (Na_2SO_4) and concentrated to give pale yellow oil. In a separate flask, *tert*-butyllithium (0.07 mL, 0.119 mmol, 1.7 M solution in pentane) was added to a solution of 3-(*tert*-butyldimethylsilyl)-1-(trimethylsilyl)-1-propyne (32.4 mg, 0.143 mmol)[19] in dry THF (1.5 mL) at −78 °C. After 1 h, titanium tetraisopropoxide (38.5 mg, 0.04 mL, 0.136 mmol) was added to the mixture. After 10 min, a solution of the crude aldehyde in dry THF (2.9 mL) was added to the organotitanium reagent and the resulting mixture was held at −78 °C for 1 h, −40 °C for 2 h, −20 °C for 1 h, and room temperature for 2.5 h, after which saturated NH_4Cl (10 mL) was added and the mixture was extracted with ethyl acetate (10 mL × 3). The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (30:1 $CHCl_3$/MeOH) provided 8.1 mg (39%) of the title compound as colorless oil. R_f = 0.23 (20:1 $CHCl_3$/MeOH); IR (neat) 2856 (m), 2788 (w), 2755 (w), 2149 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 9H), 0.97 (d, J = 6.9 Hz, 3H), 1.18−1.97 (m, 14H), 2.47 (ddd, J = 7.4, 7.4, 14.6 Hz, 1H), 2.60 (dd, J = 7.4, 14.6 Hz, 1H), 3.32 (br d, J = 11.5 Hz, 1H), 5.54 (d, J = 11.0 Hz, 1H), 6.07 (dt, J = 11.0, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.25, 13.61, 25.25, 26.61, 26.96, 31.73, 32.23, 33.59, 34.74, 53.09, 64.47, 66.13, 98.88, 102.56, 110.44, 143.06; MS (CI, NH_3) *m*/*z* (rel intense) 290 [(M + H)$^+$, 100], 289 (2), 288 (6), 182 (2), 164 (2); HRMS (CI, NH_3) calcd for $C_{18}H_{31}NSiH$ [(M + H)$^+$] 290.2304, found 290.2312.

(1*S,4*R**,10*R**)-1-Methyl-4-(*Z*)-(pent-2-en-4-ynyl)quinolizidine (2). Quinolizidine 217A.** Tetra-*n*-butylammonium fluoride (0.53 mL, 0.53 mmol, 1.0 M solution in THF) was added to a solution of **39** (15.4 mg, 0.0532 mmol) in dry DMF (2 mL) at room temperature. After 1.5 h, the solution was



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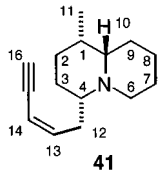
diluted with ethyl acetate (50 mL) and washed with water (50 mL × 5). The organic phase was dried (Na_2SO_4) and concentrated. Chromatography (15:1 $CHCl_3$/MeOH) gave 10.4 mg (90%) of the title compound as pale yellow oil. R_f = 0.24 (15:1 $CHCl_3$/MeOH); IR (neat) 3311 (m), 2972 (w), 2927 (s), 2870 (w), 2851 (m), 2784 (w), 2747 (w), 1451 (w), 1441 (w), 1336 (w), 1263 (w), 1127 (w), 1108 (w), 1085 (w), 1056 (w), 963 (w), 754 (m), 634 (m), 500 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, J = 6.6 Hz, 3H), 0.94−1.80 (m, 12H), 1.91 (m, 1H), 2.07 (m, 1H), 2.50−2.65 (m, 2H), 3.07 (d, J = 1.6 Hz, 1H), 3.27 (br d, J = 11.0 Hz, 1H), 5.52 (ddt, J = 1.9, 10.7, 1.6 Hz, 1H), 6.10 (dt, J = 10.7, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.44, 24.76, 26.34, 30.28, 31.85, 33.99, 35.07, 36.39, 51.88, 63.24, 69.75, 80.83, 81.79, 109.51, 143.54. MS (EI) *m*/*z* (rel intense) 217 (0.3), 216 (0.8), 202 (0.5), 153 (11.5), 152 (100), 150 (2), 136 (2.2), 110 (8.8), 91 (2.4), 84 (2.4), 67 (2.0), 65 (2.3), 56 (2.7), 55 (5.3), 54 (2.1), 41 (5.8), 39 (3.2); HRMS (EI) calcd for $C_{15}H_{23}N$ [M$^+$] 217.1830, found 217.1837. Data for DCl salt: ^1H NMR (acetone-d_6, 500 MHz) δ 0.95 (d, J = 6.6 Hz, 1H, H-11), 1.33 (qd, J = 12.4, 3.7 Hz, 1H, Hax-2), 1.49 (tq, J = 4.0, 13.2 Hz, 1H, Hax-8), 1.74−1.88 (m, 4H, Heq-2, Heq-3, Heq-7, Heq-8), 1.88−2.00 (m, 1H, Heq-9), 2.00−2.14 (m, 1H, Hax-9), 2.14−2.31 (m, 3H, H-1, Hax-3, Hax-7), 2.67−2.78 (m, 2H, Hax-6, H-10), 2.89 (dddd, J = 15.0, 7.7, 7.3, 1.5 Hz, H-12b), 2.95−3.14 (m, 2H, H-4, H-12a), 3.73 (d, J = 1.8, 1H, H-16), 3.82 (dtt, J = 12.1, 4.0, 1.8 Hz, 1H, Heq-6), 5.65 (dddd, J = 11.0, 2.2, 1.8, 1.5 Hz, 1H, H-14), 6.31 (dddd, J = 11.0, 7.3, 7.0, 7.0 Hz, 1H, H-13). The ^1H NMR spectroscopic and mass spectrometric data matched the literature values (see Supporting Information),[7] as did the IR spectal data.[6]

(1*R,4*R**,10*R**)-1-Methyl-4-(*Z*)-(pent-2-en-4-ynyl)quinolizidine (41).** Tetra-*n*-butylammonium fluoride (0.23 mL, 0.23 mmol, 1.0 M solution in THF) was added to a solution of **40** (6.7 mg, 0.0231 mmol) in dry DMF (2 mL) at room temperature. After 2 h, the solution was diluted with ethyl acetate



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(30 mL) and washed with water (30 mL × 5). The organic phase was dried (Na_2SO_4) and concentrated. Chromatography (15:1 $CHCl_3$/MeOH) gave 3.7 mg (74%) of the title compound as pale yellow oil. R_f = 0.24 (15:1 $CHCl_3$/MeOH); IR (neat) 3311 (w), 2933 (s), 2854 (m), 2753 (w), 1442 (w), 1378 (w), 1342 (w), 1321 (w), 1125 (w), 1102 (w), 1054 (w), 742 (w), 632 (w), 604 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97 (d, J = 6.9 Hz, 3H), 1.18−1.80 (m, 12H), 1.88−2.00 (m, 2H), 2.50−2.60 (m, 2H), 3.07 (d, J = 1.6 Hz, 1H), 3.28 (br d, J = 11.5 Hz, 1H), 5.51 (dq, J = 10.1, 1.9 Hz, 1H), 6.14 (dt, J = 10.1, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.63, 25.22, 26.60, 26.83, 31.71, 32.22, 33.57, 34.68, 52.98, 64.10, 66.06, 81.60, 109.28, 128.55, 143.69; MS (EI) *m*/*z* (rel intense) 217 (0.4), 216 (0.9), 202 (0.6), 153 (12), 152 (100), 150 (2.5), 136 (2.4), 110 (8.6), 91 (2.8), 84 (2.9), 82 (2.5), 77 (2.3), 67 (2.6), 65 (2.6), 56 (2.7), 55 (6.3), 54 (2.5), 41 (6.5), 39 (3.9); HRMS (EI) calcd for $C_{15}H_{23}N$ [M$^+$] 217.1830, found 217.1830.

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Supporting Information Available: Text describing experimental procedures for the preparation of **9**, **10**, and **14**−**19**, a table comparing ^1H NMR spectroscopic data for synthetic vs natural quinolizidine 217A (**2**), and photocopy figures showing of ^1H NMR spectra of new compounds without elemental analysis, including ^1H and ^{13}C NMR spectra of synthetic quinolizidine 217A (**2**), its DCl salt, and its C(1) epimer **41** (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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