Titanium-Mediated Cyclization of ω-Vinyl Imides in Alkaloid Synthesis: Isoretronecanol, Trachelanthamidine, 5-Epitashiromine, and Tashiromine

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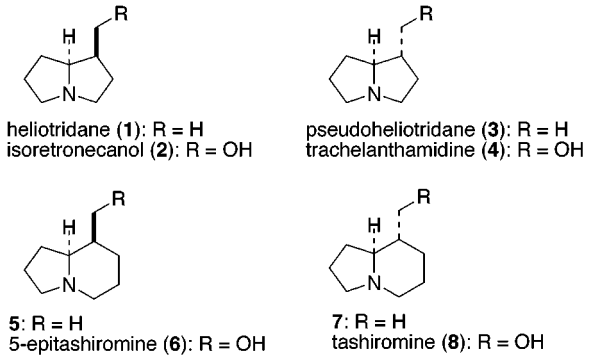
A new method for the stereocontrolled synthesis of pyrrolizidine and indolizidine alkaloids by means of titanium-mediated cyclization of ω-vinyl imides is described. The general procedure involves treatment of readily available ω-vinyl imides **9** and **10** with 2.5 equiv of cyclopentylmagnesium chloride in the presence of $ClTi(O\text{-}i\text{-}Pr)_3$ (1.1 equiv) and subsequent stereoselective reduction of the *N*-acylaminal group. The cis and trans ring junction stereoisomers can be stereoselectively prepared by catalytic hydrogenation (H_2, PtO_2, EtOAc) and $NaCNBH_3$ reduction (TFA, MeOH), respectively. Finally, treatment of the resulting lactams with LAH or diborane afforded the target alkaloids **1**−**8** in good yields.

Introduction

The pyrrolizidine or indolizidine alkaloids represent a diverse group of natural products that display a broad range of biological activity.[1,2] These alkaloids have been popular targets for total synthesis. In addition to interesting biological activity, they have provided a useful forum to develop a general, efficient method for the construction of the common azabicyclo[3.3.0] or azabicyclo-[4.3.0] skeleton. There are several elegant synthetic methods available for these relatively simple structural subunits.[3]

We recently developed a new, general route to the pyrrolizidine and indolizidine skeleton by means of titanium-mediated cyclization of ω-vinyl imides (Scheme 1),[4] which in turn evolved from the Kulinkovich titanacyclopropane intermediate.[5] As the first foray to pyrrolizidine and indolizidine alkaloids, we report herein the implementation of this annulation to the stereocontrolled synthesis of their simplest members, **1**−**8**.



Results and Discussion

Recently, we reported that treatment of readily available ω-vinyl imides **9** and **10** with 2.5 equiv of cyclopentylmagnesium chloride in the presence of $ClTi(O\text{-}i\text{-}Pr)_3$ (1.1 equiv) gave, upon hydrolysis, *N*-acylaminals **11** (55%) and **12** (55%), respectively.[4] The corresponding alcohols **13** (45%) and **14** (60%) were also readily prepared by simple oxidation with molecular oxygen prior to aqueous workup.[6a] It occurred to us that stereocontrolled reduction of the *N*-acylaminal function would provide a concise approach to the key structural elements of the pyrrolizidine and indolizidine alkaloids. A particularly attractive feature is the possibility of stereoselectively securing both diastereomers, i.e., lactams with cis-ring hydrogens (e.g., **15**, **17**, **19**, and **21**) and those with trans-ring hydrogens (e.g., **16**, **18**, **20**, and **22**), via common advanced inter-

(1) For pyrrolizidine alkaloids, see: (a) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 31, Chapter 6, p 193. (b) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465. (c) Robins, D. J. *Nat. Prod. Rep.* **1989**, *6*, 221. (d) Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. G. *Synlett* **1990**, 433. (e) Dai, W.-M.; Nagao, Y.; Fujita, E. *Heterocycles* **1990**, *30*, 1231. (f) Robins, D. J. *Nat. Prod. Rep.* **1993**, *10*, 487.

(2) For indolizidine alkaloids, see: (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4. (b) Rajeswari, S.; Chandrasekharan, S.; Govindachari, T. R. *Heterocycles* **1987**, *25*, 659. (c) Takahata, H.; Momose, T. In *The Alkaloids;* Brossi, A., Ed.; Academic Press: San Diego, 1993; Vol. 44, Chapter 3, p 189. (d) Michael, J. P. *Nat. Prod. Rep.* **1994**, *11*, 639.

(3) For some representative examples of previous work, see: (a) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373. (b) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (c) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993. (d) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430. (e) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959. (f) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014. (g) Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755. (h) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289. (i) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345. (j) Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K.-C.; Poon, Y.-F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5719 and references therein.

(4) Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127.

(5) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Prityts kaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. (c) Kulinkovich, O. G.; Sorokin, V. L.; Kel'in, A. V. *Zh. Org. Khim.* **1993**, *29*, 66.

(6) (a) For several imides, ether is the solvent of choice for the preparation of primary alcohols, whereas use of THF often results in varying amounts of the methyl compounds as byproducts: Sung, M. J.; Cha, J. K. Unpublished results. (b) Kim, S.-H.; Cha, J. K. Unpublished results.

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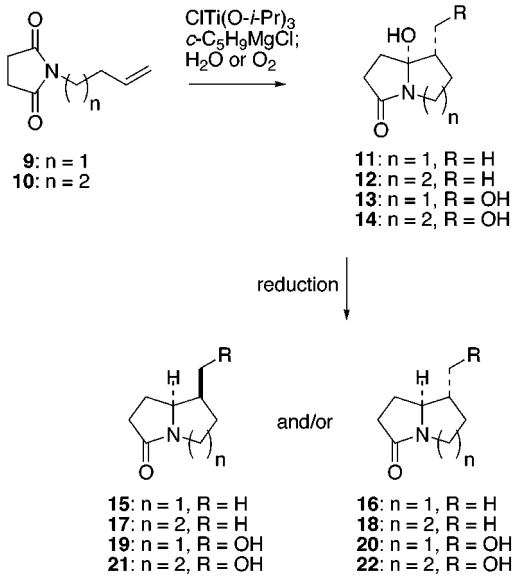
Scheme 1



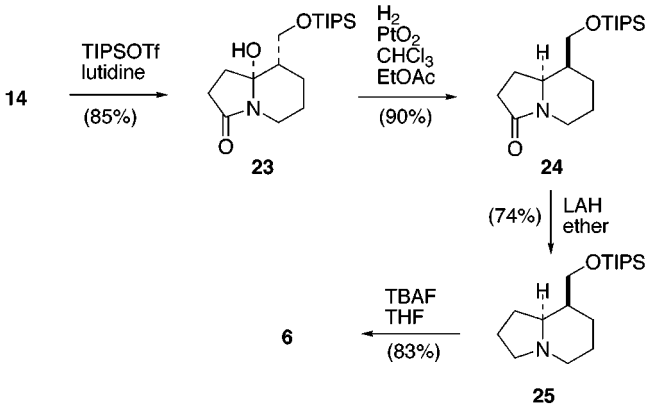
mediates. Such a divergent synthesis can be considered advantageous, since stereoisomers are frequently encountered in the naturally occurring alkaloids.

As prototypical examples, reduction of the methyl derivatives **11** and **12** was first examined.[7] Catalytic hydrogenation of **11** with PtO_2 (in EtOAc) in the presence of a small amount of chloroform as the source of HCl[8] afforded exclusively **15** in 90% yield.[9] Excellent diastereoselectivity (15:1) was also observed for hydrogenation of indolizidinone **12** to provide **17** (92%). Reduction with $NaCNBH_3$ (TFA, MeOH) furnished the corresponding trans[10] isomers **16** and **18** with high selectivity (**16**: 12:1, 78−85%; **18**: 10:1, 85%).

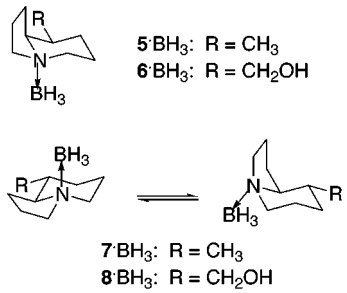
These reduction protocols were next extended to alcohols **13** and **14**. Catalytic hydrogenation of **13** under identical conditions (H_2, PtO_2, $CHCl_3$−EtOAc) produced the cis[10] isomer **19** in greater than 10:1 diastereoselectivity (85% yield). In contrast, hydrogenation of the homologue **14** proved to be troublesome due to concomitant overreduction of the desired product **21**; despite considerable experimentation under several different conditions, coproduction of **17** could not be avoided. This complication was circumvented by protection of the primary alcohol prior to reduction (Scheme 2). Thus, hydrogenation of the TIPS ether **23** took place smoothly to afford **24** as a single product (94%). Reduction of **13** and **14** with $NaCNBH_3$ reduction (TFA, MeOH) was uneventful, and good to excellent diastereoselectivity was observed to furnish the respective lactams **20** (>15:1, 60%-80%) and **22** (20:1, 55−75%).

Finally, treatment of the lactams **15**−**20** and **22** with LAH or diborane (ether, reflux) afforded the corresponding pyrrolizidines and indolizidines in good yields.

Scheme 2



5-Epitashiromine (**6**) was obtained by way of LAH reduction of lactam **24**, followed by desilylation (Scheme 2). These alkaloids were characterized most conveniently as the borane complexes.[11] In passing, we note that the borane complexes of the trans indolizidines **7** and **8** exist as two conformational isomers, while only one isomer is possible for those of the cis isomers **5** and **6**, as well as the pyrrolizidines **1**−**4**. Treatment of the borane complexes with acid furnished the target compounds. Spectroscopic data of these pyrrolizidine and indolizidine alkaloids were found to be in excellent agreement with literature values.[1−3,9−12]



Discussion

Hydrogenation in the presence of Adams catalyst was first employed for β-enamino esters during the preparation of pyrrolizidine alkaloids.[9a] Uniformly high diastereoselectivity was also found in additional examples on catalytic hydrogenation of related pyrrolizidine, indolizidine, and quinolizidine derivatives.[7,9] As outlined in Scheme 3, the enamides **27** are believed to be the substrates for hydrogenation. This is supported by our recent observation that hydrogenation of isomers **29** and **30** under identical conditions produces the same lactam **31** as a sole product.[6b] Facile formation of **17** in catalytic

(7) For a general review on reduction of enamines or enamides, see: Pitacco, G.; Valentin, E. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; Wiley: New York, 1994; Chapter 17, p 923.

(8) Cf. Secrist, J. A., III; Logue, M. W. *J. Org. Chem*. **1972**, *37*, 335.

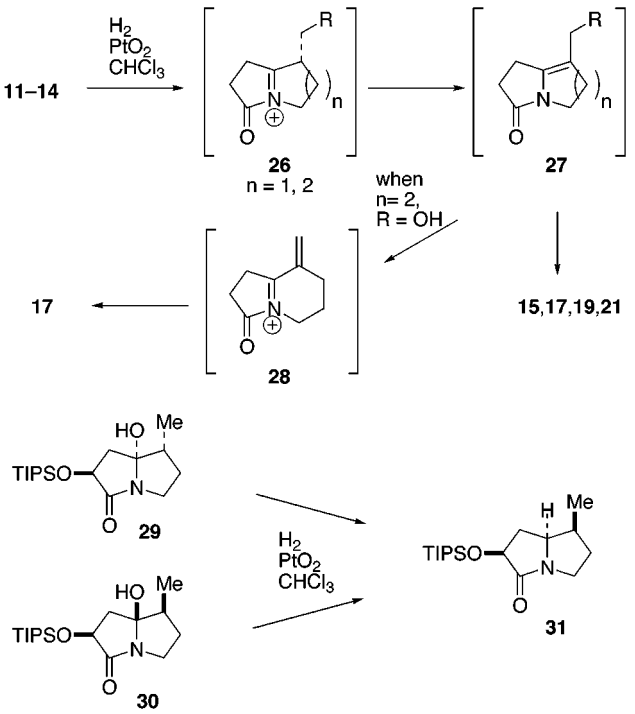
(9) For related hydrogenation of enamides or enamines, see: (a) Leonard, N. J.; Sato, T. *J. Org. Chem*. **1969**, *34*, 1066. (b) Muchowski, J. M.; Nelson, P. H. *Tetrahedron Lett*. **1980**, *21*, 4585. (c) Miyano, S.; Fujii, S.; Yamashita, O.; Toraishi, N.; Sumoto, K. *J. Org. Chem*. **1981**, *46*, 1737.

(10) (a) The cis/trans nomenclature refers to the relative stereochemistry of the two methine hydrogens. (b) For stereoselective $NaCNBH_3$ reduction of iminium compounds, see: Ohnuma, T.; Tabe, M.; Shiiya, K.; Ban, Y. *Tetrahedron Lett*. **1983**, *24*, 4249.

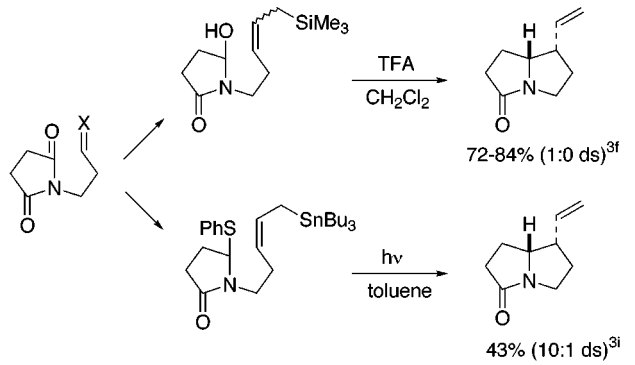
(11) For an elegant use of borane for blocking reactivity at the pyrrolizidine nitrogen, see: White, J. D.; Amedio, J. C., Jr.; Gut, S.; Ohira, S.; Jayasinghe, L. R. *J. Org. Chem*. **1992**, *57*, 2270.

(12) The spectroscopic data of these target alkaloids **1**−**8** were found to be in excellent agreement with those reported in the literature: (a) Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 219 and Pandey, G.; Reddy, G. D. *Tetrahedron Lett*. **1992**, *33*, 6533. (b) Knight, D. W.; Share, A. C.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2089. Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc*. **1984**, *106*, 8209. Mori, M.; Kanda, N.; Oda, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 5465. (c) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc*. **1996**, *118*, 5322. (d) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k.; Blickensdorf, J. D. *J. Am. Chem. Soc*. **1993**, *115*, 10183. (e) Paulvannan, K.; Stille, J. R. *J. Org. Chem*. **1994**, *59*, 1613.

Scheme 3



Scheme 4



hydrogenation of the alcohol **14** is believed to involve the intermediate **28** generated from the enamide.

The cyanoborohydride reduction of indolizidine **12** in acidic methanol was first reported by Ban and co-workers to take place with a high degree of trans stereoselectivity,[10] which complements cis stereochemistry produced by catalytic hydrogenation. The stereoselective formation of the trans indolizidine **18** can be rationalized in terms of a stereoelectronically preferred axial attack of hydride ion on the immonium ion bearing the equatorially placed methyl group. Under carefully controlled conditions at low temperatures, $NaCNBH_3$ reduction can be carried out without the involvement of the enamide. For example, no epimerization was observed at the methyl-bearing stereocenter during reduction (3.0 equiv of $NaCNBH_3$, 1.5 equiv of TFA, MeOH) of **30** at −78 °C in the preparation of the trans product (structure not shown).[6b]

Finally, it is noteworthy that the titanium-mediated coupling−reduction sequence of bicyclic ω-vinyl imides offers a viable, alternate approach to the well-known synthetic methods involving nucleophilic additions to *N*-acyliminium ions or α-acylamine radical cyclizations (Scheme 4). In the latter known approaches, the obligatory partial reduction and exchange (with an alcohol or a thiol) steps of imides precede the key carbon−carbon bond formation. On the other hand, the titanium-mediated annulation utilizes the imide function directly for ring closure. As illustrated in the present work, subsequent stereoselective reduction of the *N*-acylaminal group provides stereocontrolled access to several specific stereoisomers; the resulting stereochemistry is complementary to that available from nucleophilic additions to *N*-acyliminium ions or α-acylamine radical cyclizations. Moreover, the *N*-acylaminal functionality allows considerable flexibility for further elaboration (e.g., a new carbon−carbon bond construction).

In conclusion, the titanium-mediated annulation reaction of readily available vinyl tethered imides offers a new method for carbon−carbon bond construction in alkaloid synthesis. Synthetic studies toward structurally complex natural products, as well as the development of an enantioselective process, are currently under way and will be reported in due course.

Experimental Section

Representative Procedure for the Titanium-Mediated Coupling of ω-Vinyl Imides. Preparation of (1*R,2*R**)-1-Hydroxy-2-methyl-6-azabicyclo[4.3.0]nonan-7-one (12).** A solution of the imide **10** (167 mg, 1.0 mmol) in THF (10 mL) was treated with $ClTi(O\text{-}i\text{-}Pr)_3$ (1.0 mL of a 1 M hexane solution) at room temperature. After the reaction mixture was cooled to 0 °C, cyclopentylmagnesium chloride (1.5 mL of a 2 M Et_2O solution; commercially available from Aldrich) in THF (5 mL) was added during 30 min (via syringe pump). The mixture was stirred for 20 min, followed by addition of a mixture of water (0.9 mL) and Et_2O (10 mL) and subsequent stirring for an additional hour at room temperature and drying with $MgSO_4$. The resultant suspension was filtered through Celite, and the filter cake was thoroughly washed with Et_2O. The combined filtrate and washings were concentrated in vacuo to afford the crude product. Purification by column chromatography on silica gel (8:1.7:0.3 CH_2Cl_2−EtOAc−MeOH) afforded 93 mg (55%) of **12**: IR ($CHCl_3$) 3367, 1671 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.83 (br dd, J = 12.9, 4.9 Hz, 1 H), 3.45 (br s, −OH, 1 H), 2.84 (ddd, J = 12.9, 3.6, 1.1 Hz, 1 H), 2.50 (m, 1 H), 2.26 (ddd, J = 15.3, 10.0, 3.2 Hz, 1 H), 2.12−1.93 (m, 2 H), 1.68 (m, 1 H), 1.58−1.30 (m, 4 H), 0.98 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.6, 90.1, 41.7, 36.3, 32.6, 29.1, 27.9, 24.6, 15.2; HRMS (M^+) calcd for $C_9H_{15}NO_2$ 169.1103, found 169.1107.

(1*R,2*R**)-1-Hydroxy-2-methyl-5-azabicyclo[3.3.0]octan-6-one (11):** IR ($CHCl_3$) 3344, 1660 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.35 (m, 1 H), 3.20 (dd, J = 10.9, 9.9 Hz, 1 H), 2.96 (dt, J = 17.1, 9.3 Hz, 1 H), 2.39 (ddd, J = 17.1, 9.3, 2.7 Hz, 1 H), 2.20−1.93 (m, 4 H), 1.80 (m, 1 H), 1.05 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.8, 97.6, 43.2, 40.0, 33.7, 33.0, 32.5, 11.9; HRMS (M^+) calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0951.

Representative Procedure for the Titanium-Mediated Coupling of ω-Vinyl Imides, Followed by Oxidative Workup. Preparation of (1*R,2*S**)-1-Hydroxy-2-hydroxymethyl-6-azabicyclo[4.3.0]nonan-7-one (14).** To a solution of the imide **10** (58 mg, 0.35 mmol) in THF (4 mL) was added $ClTi(O\text{-}i\text{-}Pr)_3$ (0.35 mL of a 1 M hexane solution) at room temperature. After the reaction mixture was cooled to 0 °C, cyclopentylmagnesium chloride (0.6 mL of a 2 M Et_2O solution; commercially available from Aldrich) in THF (5 mL) was added during 20 min (via syringe pump). The mixture was then stirred for an additional 20 min, and oxygen was bubbled through the mixture for 20 min. A mixture of water (0.5 mL) and Et_2O (5 mL) was added. The resulting suspension was filtered through Celite, and the filter cake was thoroughly washed with Et_2O. The combined filtrate and washings were concentrated in vacuo to afford the crude product. The residue was purified using basic alumina column chromatography (8:

1.6:0.4 CH_2Cl_2−EtOAc−MeOH) to provide 39 mg (60%) of the acylaminal **14**, which was used immediately for the next step: IR (neat) 3350, 1668, 1450 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.11 (s, −OH, 1 H), 4.02 (dd, J = 11.2, 2.1 Hz, 1 H), 3.91 (br dd, J = 13.0, 4.9 Hz, 1 H), 3.73 (br d, J = 11.2 Hz, 1 H), 2.92 (ddd, J = 13.0, 13.0, 2.9 Hz, 1 H), 2.61−2.53 (m, 1 H), 2.51−2.44 (br s, −OH, 1 H), 2.38−2.20 (m, 2 H), 2.16−1.92 (m, 2 H), 1.89−1.81 (m, 1 H), 1.59−1.40 (m, 3 H); HRMS ($M^+ - H_2O$) calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0964.

(1*R,2*S**)-1-Hydroxy-2-hydroxymethyl-5-azabicyclo-[3.3.0]octan-6-one (13):** IR (neat) 3365, 1673, 1454 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.92 (dd, J = 12.3, 3.8 Hz, 1 H), 3.78 (dd, J = 12.3, 6.6 Hz, 1 H), 3.53−3.45 (m, 1 H), 3.28 (br t, J = 9.9 Hz, 1 H), 3.02−2.92 (m, 1 H), 2.43 (td, J = 5.9, 16.9 Hz, 1 H), 2.27−2.22 (m, 3 H), 2.18−2.01 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.7, 98.1, 60.5, 49.3, 39.8, 34.0, 33.6, 27.3. This compound was also characterized as the mono-TIPS ether: ^1H NMR (360 MHz, $CDCl_3$) δ 4.19 (br s, 1 H, −OH), 4.07 (dd, J = 10.5, 3.5 Hz, 1 H), 3.91 (dd, J = 10.5, 5.5 Hz, 1 H), 3.53 (dt, J = 11.7, 8.3 Hz, 1 H), 3.31 (br t, J = 11.7 Hz, 1 H), 2.99 (dt, J = 16.8, 9.2, 1 H), 2.41 (ddd, J = 16.8, 9.2, 2.4 Hz, 1 H), 2.30 (m, 1 H), 2.22 (m, 2 H), 2.13 (m, 1 H), 2.04 (m, 1 H), 1.06 (m, 21 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.2, 97.8, 61.6, 49.0, 39.5, 34.3, 33.5, 27.4, 17.9, 11.7; HRMS ($M^+ - H_2O$) calcd for $C_{17}H_{31}NO_2Si$ 309.2124, found 309.2120.

(1*R,2*S**)-1-Hydroxy-2-triisopropylsiloxymethyl-6-azabicyclo[4.3.0]nonan-7-one (23).** To a solution of the alcohol **14** (24 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) were added NEt_3 (0.1 mL, 1.0 mmol) and TIPSOTf (43 μL, 0.16 mmol) sequentially at 0 °C. The mixture was stirred at room temperature for 8 h, quenched with water (5 mL), and extracted with CH_2Cl_2 (2 × 15 mL). The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by short column chromatography (1:1 hexanes−EtOAc) to give 37 mg (85%) of **23**: IR (neat) 3390, 1674, 1464 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.70 (s, −OH, 1 H), 4.17 (dd, J = 10.3, 2.6 Hz, 1 H), 3.89 (br dd, J = 13.1, 4.9 Hz, 1 H), 3.80 (dd, J = 10.3, 2.7 Hz, 1 H), 2.94 (td, J = 13.1, 2.6 Hz, 1 H), 2.61 (m, 1 H), 2.35−2.16 (m, 2 H), 2.15−1.97 (m, 2 H), 1.83 (m, 1 H), 1.62−1.41(m, 3 H), 1.11 (m, 21 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.6, 90.2, 64.4, 46.6, 36.0, 33.7, 29.0, 24.4, 23.6; HRMS ($M^+ - H_2O$) calcd for $C_{18}H_{33}NO_2Si$ 323.2281, found 323.2271.

Representative Procedure for Catalytic Hydrogenation of *N*-Acylaminals. Preparation of (1*S,2*S**)-2-Triisopropylsiloxymethyl-6-azabicyclo[4.3.0]nonan-7-one (24).** A solution of **23** (7 mg, 0.02 mmol) in EtOAc (3.5 mL) was treated with PtO_2 (3.5 mg) and $CHCl_3$ (3.8 μL, 0.04 mmol). The mixture was stirred under an atmosphere of hydrogen (balloon) for 4 h and filtered through Celite, and the filter cake was rinsed thoroughly with EtOAc. The combined filtrates were concentrated in vacuo to afford 6 mg (90%) of **24**: IR (neat) 1694, 1462 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.11 (br d, J = 12.0, 1 H), 3.85 (dd, J = 10.2, 6.8 Hz, 1 H), 3.68 (m, 1 H), 3.59 (dd, J = 10.2, 6.6 Hz, 1 H), 2.65 (td, J = 12.0, 5.4 Hz, 1 H), 2.39−2.28 (m, 2 H), 2.14 (m, 1 H), 2.08−1.95 (m, 3 H), 1.54−1.41 (m, 3 H), 1.05 (m, 21 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.3, 60.7, 59.3, 40.3, 39.6, 30.5, 26.8, 20.5, 19.3, 18.2, 11.9.

(1*S,2*S**)-2-Methyl-5-azabicyclo[3.3.0]octan-6-one (15):** IR (neat) 1683, 1456 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.98 (td, J = 7.4, 5.7 Hz, 1 H), 3.49 (dt, J = 11.5, 7.6 Hz, 1 H), 3.03 (br t, J = 11.5 Hz, 1 H), 2.68 (td, J = 16.7, 9.5 Hz, 1 H), 2.41 (ddd, J = 16.7, 9.8, 2.8 Hz, 1 H), 2.23−2.13 (m, 2 H), 2.05−1.96 (m, 1 H), 1.88−1.80 (m, 1 H), 1.78−1.69 (m, 1 H), 0.84 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.9, 64.5, 39.3, 34.9, 34.7, 33.0, 20.8, 13.4.

(1*S,2*S**)-2-Methyl-6-azabicyclo[4.3.0]nonan-7-one (17):** IR (neat) 1668, 1442 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.11 (ddd, J = 12.5, 4.6, 3.8 Hz, 1 H), 3.64 (ddd, J = 8.2, 4.6, 3.9 1 H), 2.63 (td, J = 12.5, 4.4 Hz, 1 H), 2.36−2.31 (m, 2 H), 2.03 (m, 1 H), 1.92 (m, 1 H), 1.80−1.56 (m, 4 H), 1.45−1.39 (m, 1 H), 0.90 (d, J = 7.1 Hz 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.9, 60.3, 40.2, 31.2, 30.8, 30.3, 20.6, 18.2, 11.1; HRMS (M^+) calcd for $C_9H_{15}NO$ 153.1154, found 153.1179.

(1*S,2*S**)-2-Hydroxymethyl-5-azabicyclo[3.3.0]octan-6-one (19):** IR (neat) 3390, 1662, 1424 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.08 (apparent q, J = 7.2 Hz, 1 H), 3.63 (dd, J = 10.6, 7.1 Hz, 1 H), 3.54 (dd, J = 10.6, 7.7 Hz, 1 H), 3.55−3.50 (m, 1 H), 3.03−2.96 (m, 1 H), 2.70−2.60 (m, 2 H), 2.41 (dd, J = 7.8, 3.9 Hz, 1 H), 2.41 (dd, J = 7.8, 4.2 Hz, 1 H), 2.31−2.24 (m, 1 H), 2.17−2.04 (m, 2 H), 1.95−1.87 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.0, 63.3, 61.5, 40.6, 40.1, 34.8, 30.0, 21.4.

(1*S,2*S**)-2-Hydroxymethyl-6-azabicyclo[4.3.0]nonan-7-one (21):** ^1H NMR (360 MHz, $CDCl_3$) δ 4.10 (m, 1 H), 3.81 (dd, J = 10.6, 6.5 Hz, 1 H), 3.70 (td, J = 3.6, 7.0 Hz, 1 H), 3.59 (dd, J = 10.6, 6.9 Hz, 1 H), 2.66 (td, J = 5.2, 12.4 Hz, 1 H), 2.35−2.30 (m, 2 H), 2.09−1.94 (m, 4 H), 1.87 (br s, 1 H, −OH), 1.60−1.41 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.3, 59.9, 59.3, 40.3, 39.1, 30.4, 26.5, 20.5, 19.1.

Representative Procedure for Sodium Cyanoborohydride Reduction of *N*-Acylaminals. Preparation of (1*S,2*R**)-2-Hydroxymethyl-6-azabicyclo[4.3.0]nonan-7-one (22).** A mixture of **14** (140 mg, 0.76 mmol) and $NaBH_3$-CN (143 mg, 2.27 mmol) in methanol (5 mL) was cooled to −78 °C, and TFA (0.25 mL of a 3.0 M MeOH solution) was added. The mixture was stirred at −78 °C for 2 h and then at room temperature for an additional 10 h. After water (3 mL) was added, the mixture was extracted with CH_2Cl_2 (2 × 10 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 chromatography (9:1 CH_2Cl_2−MeOH) to afford 71 mg (55%) of **22**: IR (neat) 1694, 1462 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.11 (br dd, J = 11.4, 4.3 Hz, 1 H), 3.66 (dd, J = 10.8, 4.5 Hz, 1 H), 3.58 (dd, J = 10.8, 5.4 Hz, 1 H), 3.25 (m, 1 H), 2.56 (td, J = 12.7, 3.2 Hz, 1 H), 2.38−2.23 (m, 3 H), 1.97−1.89 (m, 1 H), 1.88−1.68 (m, 3 H), 1.43−1.25 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.8, 64.3, 59.0, 46.0, 39.9, 30.5, 27.0, 24.5, 24.0; HRMS (M^+) calcd for $C_9H_{15}NO_2$ 169.1103, found 169.1080.

(1*S,2*R**)-2-Methyl-5-azabicyclo[3.3.0]octan-6-one (16):** IR (neat) 1670, 1458 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.46 (dt, J = 11.7, 8.1 Hz, 1 H), 3.39 (td, J = 8.0, 7.2 Hz, 1 H), 3.10 (br t, J = 11.7 Hz, 1 H), 2.66 (m, 1 H), 2.39 (ddd, J = 16.7, 9.7, 2.2 Hz, 1 H), 2.26−2.15 (m, 2 H), 1.73−1.53 (m, 3 H), 0.99 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.6, 68.1, 40.9, 40.5, 35.5, 34.8, 25.1, 15.2; HRMS (M^+) calcd for $C_8H_{13}NO$ 139.0997, found 139.1003.

(1*S,2*R**)-2-Methyl-6-azabicyclo[4.3.0]nonan-7-one (18):** IR (neat) 1687 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.07 (ddt, J = 12.8, 4.8, 1.3 Hz, 1 H), 2.90 (td, J = 9.3, 7.5 Hz, 1 H), 2.52 (td, J = 12.8, 3.5 Hz, 1 H), 2.31 (m, 2 H), 2.19 (m, 1 H), 1.77 (br d, J = 12.9 Hz, 1 H), 1.65 (br d, J = 12.8 Hz, 1 H), 1.55 (m, 1 H), 1.35 (qdd, J = 12.8, 4.8, 3.6 Hz, 1 H), 1.16 (m, 1 H), 1.09 (m, 1 H), 0.88 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.5, 63.0, 39.8, 38.7, 32.5, 30.4, 24.4, 23.9, 17.3; HRMS (M^+) calcd for $C_9H_{15}NO$ 153.1154, found 153.1151.

(1*S,2*R**)-2-Hydroxymethyl-5-azabicyclo[3.3.0]octan-6-one (20):** IR (neat) 3380, 1666, 1443 cm^{-1}; ^1H NMR (360 MHz, acetone-d_6) δ 3.78 (t, J = 5.1 Hz, 1 H, −O*H*), 3.66 (m, 2 H), 3.55 (m, 1 H), 3.45 (dt, J = 11.1, 8.6 Hz, 1 H), 2.97 (m, 1 H), 2.51 (m, 1 H), 2.32−2.08 (m, 3 H), 1.88−1.76 (m, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.7, 65.2, 63.5, 47.9, 40.6, 34.9, 30.0, 26.7; HRMS (M^+) calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0949.

Representative Procedure for LAH Reduction of Lactams. Preparation of (1*S,2*S**)-2-Triisopropylsiloxymethyl-6-azabicyclo[4.3.0]nonane (25).** To a solution of the lactam **24** (8 mg, 25 μmol) in Et_2O (4 mL) was added LAH (8 mg, 0.2 mmol, 8.0 equiv) at 0 °C. The reaction mixture was refluxed for 10 min and quenched with water followed by 15% NaOH solution. The resulting mixture was then stirred for an additional 10 min, diluted with THF (10 mL), dried with $MgSO_4$, and filtered through Celite. The filter cake was rinsed thoroughly with THF. The combined filtrate and rinsings were concentrated *in vacuo* to afford 5.7 mg (74%) of **25**. The crude product was used for the next step without purification: IR (neat) 1462 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.88 (dd, J = 9.9, 5.3 Hz, 1 H), 3.72 (dd, J = 9.9, 8.0 Hz, 1 H), 3.03−2.93 (m, 2 H), 2.13−1.88 (m, 5 H), 1.73−1.27 (m, 7 H), 1.20 (m, 21 H).

(±)-Heliotridane (1).[12a] Characterized as the borane complex: IR (neat) 2965, 2360, 2266, 1168 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.57 (td, J = 8.7, 7.6 Hz, 1 H), 3.42 (m, 1 H), 3.17 (td, J = 12.0, 6.2 Hz, 1 H), 2.93 (ddd, J = 12.0, 7.4, 1.5 Hz, 1 H), 2.74 (td, J = 10.4, 6.0 Hz, 1 H), 2.54 (m, 1 H), 2.02 (m, 1 H), 1.94−1.78 (m, 2 H), 1.64−1.49 (m, 3 H), 1.01 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 76.9, 65.0, 63.5, 34.7, 31.4, 27.4, 24.9, 13.8; HRMS (M^+ − H) calcd for $C_8H_{17}BN$ 138.1454, found 138.1460.

(±)-Isoretronecanol (2).[12b] Characterized as the free base and also as the borane complex: IR (neat) 3420, 2972, 2371, 2311, 2264, 1166 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.76−3.64 (m, 3 H), 3.43 (m, 1 H), 3.24 (td, J = 11.6, 6.6 Hz, 1 H), 2.99 (ddd, J = 11.6, 7.7, 2.4 Hz, 1 H), 2.83−2.69 (m, 2 H), 2.12−1.97 (m, 3 H), 1.87 (m, 1 H), 1.71−1.55 (m, 2 H), 1.34 (t, J = 5.0 Hz, 1 H, −O*H*); ^{13}C NMR (90 MHz, $CDCl_3$) δ 74.8, 64.5, 62.9, 62.4, 43.0, 27.1, 26.7, 24.8; HRMS (M^+ − H) calcd for $C_8H_{17}BNO$ 154.1403, found 154.1406.

(±)-Pseudoheliotridane (3).[12c] Characterized as the borane complex: IR (neat) 2963, 2360, 2874, 2361, 2313, 2266, 1457, 1169 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.45−3.39 (m, 1 H), 3.22 (m, 1 H), 3.13 (ddd, J = 11.4, 9.9, 6.2 Hz, 1 H), 2.93 (ddd, J = 11.4, 6.6, 4.2 Hz, 1 H), 2.77 (m, 1 H), 2.14 (m, 1 H), 2.00−1.75 (m, 5 H), 1.63 (m, 1 H), 1.18 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 80.5, 64.2, 63.7, 41.6, 33.0, 30.1, 24.4, 17.6; HRMS (M^+ − H) calcd for $C_8H_{17}BN$ 138.1454, found 138.1463.

(±)-Trachelanthamidine (4).[12b] As the free base: ^{13}C NMR (90 MHz, $CDCl_3$) δ 68.0, 65.6, 54.8, 54.5, 48.1. 31.8, 29.8, 25.7. Also characterized as the borane complex: IR (neat) 3438, 2972, 2877, 2361, 2316, 1167 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.72 (dd, J = 10.4, 6.4 Hz, A of AB q, 1 H), 3.70 (dd, J = 10.4, 6.4 Hz, B of AB q, 1 H), 3.48−3.37 (m, 2 H), 3.19 (ddd, J = 10.8, 8.8, 6.4 Hz, 1 H), 2.98−2.82 (m, 2 H), 2.18 (m, 1 H), 2.11−1.85 (m, 5 H), 1.75 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 76.2, 64.6, 63.9, 63.1, 49.0, 31.8, 28.0, 24.5; HRMS (M^+ − H) calcd for $C_8H_{17}BNO$ 154.1403, found 154.1411.

(±)-Methylindolizidine (5).[12d] Characterized as the borane complex: IR (neat) 2959, 1462 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.24 (m, 1 H), 3.14−2.98 (m, 2 H), 2.75 (br d, J = 11.6 Hz, 1 H), 2.59−2.43 (m, 2 H), 2.26 (qt, J = 13.5, 4.5 Hz, 1 H), 1.96−1.75 (m, 4 H), 1.57−1.43 (m, 2 H), 1.15 (qd, J = 13.5, 4.3 Hz, 1 H), 0.86 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 70.2, 64.5, 51.6, 27.3, 25.1, 21.8, 21.7, 19.0, 18.5; HRMS (M^+ − H) calcd for $C_9H_{19}BN$ 152.1611, found 152.1597.

(±)-5-Epitashiromine (6).[12e] A solution of **25** (5.3 mg) in THF (4 mL) was treated with a solution of TBAF (0.037 mL of a 1.0 M solution in THF). After the mixture was stirred at room temperature for 6 h, it was concentrated in vacuo to afford the crude product. The residue was purified using silica gel column chromatography (10:2:0.2 CH_2Cl_2−MeOH−NH_4OH) to provide **6** (2.8 mg, 83%): IR (neat) 3373, 1462, 1379, 1327 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.18 (dd, J = 10.7, 4.0 Hz, 1 H), 3.74 (br d, J = 10.7 Hz, 1 H), 3.15−3.07 (m, 1 H), 3.05−3.00 (m, 1 H), 2.32−2.24 (m, 1 H), 2.12−1.96 (m, 3 H), 1.95−1.67 (m, 6 H), 1.63−1.45 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 66.8, 65.7, 54.5, 53.5, 35.3, 30.6, 25.8, 23.3, 20.8; HRMS (M^+) calcd for $C_9H_{17}NO$ 155.1310, found 155.1320.

(±)-Methylindolizidine (7).[12a] Characterized as the borane complex: IR (neat) 2957, 1462 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.14−3.03 (m, 3 H), 2.93 (td, J = 10.1, 2.9 Hz, 1 H), 2.82 (dd, J = 10.7, 7.3 Hz, 1 H), 2.54 (m, 1 H), 2.22 (m, 1 H), 1.86 (m, 1 H), 1.77−1.54 (m, 4 H), 1.27 (m, 1 H), 1.12 (qd, J = 12.3, 4.1 Hz, 1 H), 0.91 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 72.2, 56.2, 54.0, 31.9, 31.2, 27.8, 20.6, 20.0, 19.6; HRMS (M^+ − H) calcd for $C_9H_{19}BN$ 152.1611, found 152.1584.

(±)-Tashiromine (8):[12e] IR (neat) 3356, 2931, 1460 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.61 (dd, J = 10.9, 4.7 Hz, 1 H), 3.44 (dd, J = 10.9, 6.5 Hz, 1 H), 3.09−3.02 (m, 2 H), 2.04 (q, J = 9.1 Hz, 1 H), 1.97−1.82 (m, 3 H), 1.80−1.40 (m, 7 H), 1.02 (qd, J = 12.8, 4.7 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 65.8, 65.0, 53.6, 52.1, 44.1, 28.5, 27.1, 24.6, 20.2; HRMS (M^+) calcd for $C_9H_{17}NO$ 155.1310, found 155.1314.

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Supporting Information Available: Photocopies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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