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Copper mediated scalemic organolithium reagents in alkaloid syntheses

R. Karl Dieter,* Ningyi Chen and Rhett T. Watson

Hunter Laboratory, Department of Chemistry, Clemson University, Clemson, SC 29634-0973, USA

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Dedicated to Professor Amos B. Smith, III on the occasion of his 60th birthday

Abstract—Scalemic 2-pyrrolidinylcuprates generated via asymmetric deprotonation of *N*-Boc-pyrrolidine followed by treatment with THF soluble CuCN·2LiCl react with ω-functionalized vinyl halides to afford 2-alkenyl-*N*-Boc-pyrrolidines. *N*-Boc deprotection and cyclization via intramolecular *N*-alkylation generates the pyrrolizidine or indolizidine skeletons. Subsequent functional group manipulation affords enantioenriched (+)-heliotridane, (+)-isoretronecanol, a formal synthesis of (+)-laburnine, (+)-(*R*)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine, (*R*)-1,2,3,5,6,8a-hexahydroindolizine, (+)-*ent*-δ-coniceine, (+)-tashiromine and (+)-5-epitashiromine.

1. Introduction

The pyrrolizidine (1-azabicyclo[3,3]octanes)[1] and indolizidine (1-azabicyclo[4,3]nonanes)[2] alkaloids are found in a wide variety of plants. Pyrrolizidine alkaloids are generally found in the genus *Senecio* (>1000 species) of the Compositae family and often consist of esters between an alkanolamine (i.e., necine base) and a necic acid.[1d] Although the pyrrolizidine alkaloids function as insect anti-feedents and insecticides, some insects sequester them for biological purposes.[1b–c] Both series of alkaloids display toxicity to mammals.[3–4] Plants containing pyrrolizidine alkaloids are the most common source of animal poisoning and pyrrolizidine macrocyclic diesters exhibit the more potent genotoxicity and tumorigenicity.[3a] The polyhydroxy indolizidine alkaloids swainsonine and castanospermine were shown to be agents of toxicity to grazing animals and the isolation of these causative agents led to the discovery of the aza sugars as glycosidase inhibitors.[4b]

Simple members of the two classes have been the subject of frequent total syntheses often serving as a testing ground for new synthetic methodology.[1a,d,2] Asymmetric syntheses abound[5–14] and enantioenriched pyrrolizidines **1–3** and indolizidines **6–8** have all been synthesized, while pyrrolizine **4**[15] and indolizine **5**[16] have only been prepared in racemic form. Of the nearly 50 asymmetric syntheses involving (−)-heliotridane,[5,7e–f,h] (+)-*ent*-heliotridane (**1**),[6] (−)-isoretronecanol,[7] (+)-isoretronecanol (**2**),[8] (+)-laburnine (**3**)[7a–c,n,9] and its enantiomer (−)-trachelanthamidine,[7d,i–k,m,10] (−)-coniceine,[11] (+)-coniceine,[12] (+)-tashiromine (**7**),[7b,13,14b] (−)-tashiromine[14] and (+)-5-epitashiromine (**8**) [or its (−) isomer][13b,17] all but six have involved the use of chiral auxiliaries[11d,f–h,12d] or molecules from the chiral pool [e.g., (*S*)-proline,[7d,f,h,i,k,m,11a,c,e] (*S*)-α-methylbenzylamine,[7b,g] α-D-glucosamine,[7l] (*R*)-phenylglycinol,[12d] L-glutamic acid,[14a] (+)-carvone,[5] (*S*)-pyroglutaminol,[11b] (*S*)-ethyl pyroglutamate,[7e] and (−)-4-hydroxy-L-proline[7n]] containing one or more of the stereocenters to be incorporated into the target molecules. The reported asymmetric syntheses involving enzymatic kinetic resolution,[12a] or asymmetric transformations [e.g., dihydroxylation,[12b] Heck,[12b] catalytic desymmetrization,[7c] and iminium ion cyclization[9b]] are also limited by scale, length of the synthetic route, or the enantioselectivity achieved. An elegant asymmetric catalyzed conjugate addition of a pyrrole moiety intramolecularly to a Michael acceptor was recently employed in an asymmetric synthesis of (−)-tashiromine.[14a]

A potentially rapid strategy for the synthesis of enantioenriched pyrrolizidines **1–2**, as well as indolizidines **7** and **8** (Fig. 1), could involve stereo- and regiocontrolled functional group manipulation of exo-cyclic alkenes **11a** and

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* Corresponding author. Tel.: +1 864 656 5025; fax.: +1 864 656 6613; e-mail: dieterr@clemson.edu

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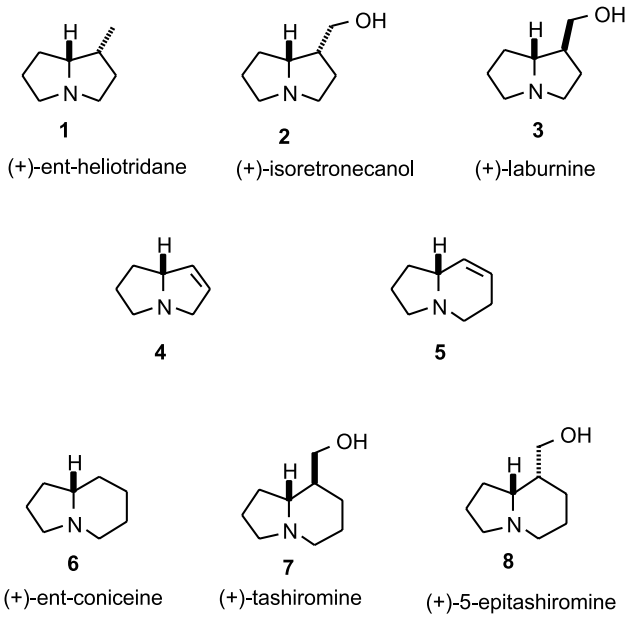
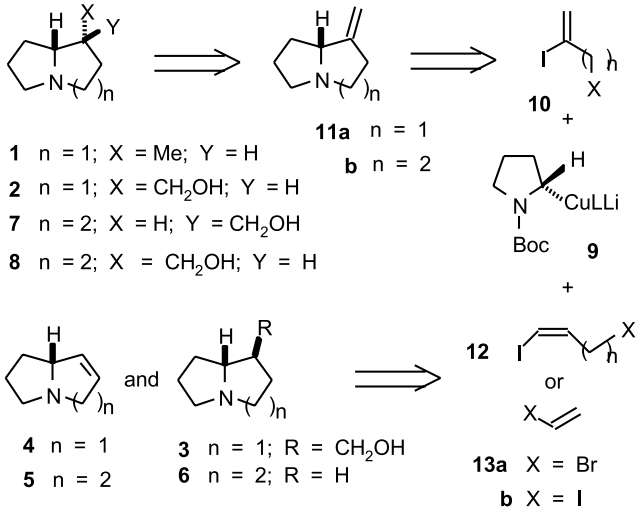


Figure 1. Pyrrolizidine and indolizidine synthetic targets.

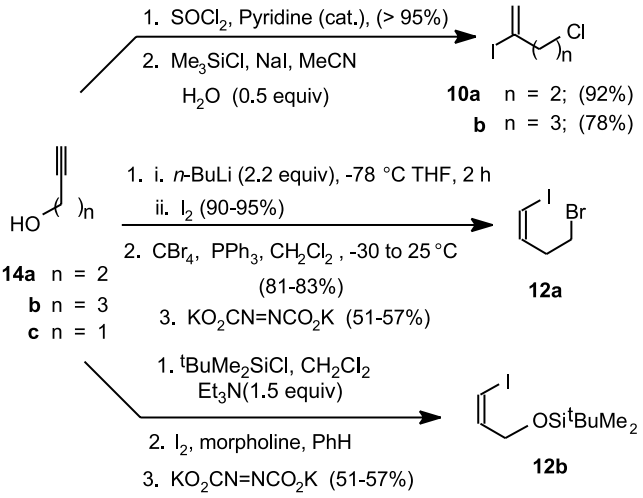
11b, respectively, which in turn could be constructed by sequential vinylation of cuprate **9**, generated from the scalemic stereogenic α-lithio carbamate,[18] followed by ring annulation (Scheme 1).[19] Extension of the strategy to pyrrolizine **4**, indolizine **5**, and indolizidine **6** would utilize 1-halo-1-alkenes **12a–b** with good leaving groups in the 3- or 4-positions for subsequent cyclization onto the *N*-atom. Variations on the strategy involving vinyl halides **13a–b** require subsequent radical cyclization of *N*-(2-iodo-1-oxoethyl)-2-vinylpyrrolidine to afford, after functional group manipulation, pyrrolizidine **3**. The success of this versatile asymmetric synthetic strategy relies upon the stereocontrolled formation of scalemic α-lithio and α-cuprio *N*-Boc-pyrrolidine and coupling of the cuprate reagent with vinyl halides in a highly enantioselective fashion. In this full report, we detail the rapid and efficient asymmetric syntheses of pyrrolizidines **1–3**, pyrrolizine **4**, indolizine **5**, and indolizidines **6–8**.



Scheme 1.

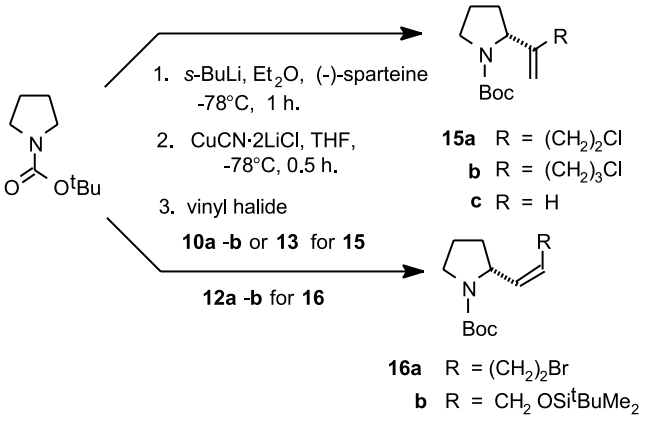
2. Results and discussion

The requisite 1- or 2-halo-1-alkenes containing ω-functionalization were readily prepared from commercially available 1-alkynes (Scheme 2). Conversion of alcohol **14a** into the alkyl chloride[20] followed by addition of in situ generated HI[21] to the chloro alkyne afforded vinyl iodide **10a**. Similar addition of HI to commercially available 5-chloro-1-pentyne (**14b**) afforded vinyl iodide **10b**. *cis*-Vinyl iodide **12a** was prepared by iodination of alkyne **14a**,[22] followed by conversion of the alcohol to the alkyl bromide[23] and diimide reduction[24] of the triple bond. Silylation of alkynyl alcohol **14c** followed by 1-alkynyl iodination and diimide reduction gave vinyl iodide **12b** in good overall yield.[25] Coupling of these readily prepared ω-functionalized vinyl iodides with metallated *N*-Boc-pyrrolidine provides all of the carbon atoms of the alkaloid skeletons (Scheme 3).



Scheme 2.

The key synthetic step involves the generation of scalemic *N*-Boc-2-pyrrolidinylcuprates and coupling with the vinyl iodides **10a–b** and **12a–b** or vinyl halides **13a–b** (Scheme 3). Asymmetric deprotonation of *N*-Boc-pyrrolidine according to Beak's procedure[26] followed by treatment with THF soluble CuCN·2LiCl afforded either the alkyl(cyano)cuprate (i.e., RCuCNLi) or dialkylcuprate (i.e., R_2CuLi) reagent depending upon the equivalents of CuCN employed.



Scheme 3.

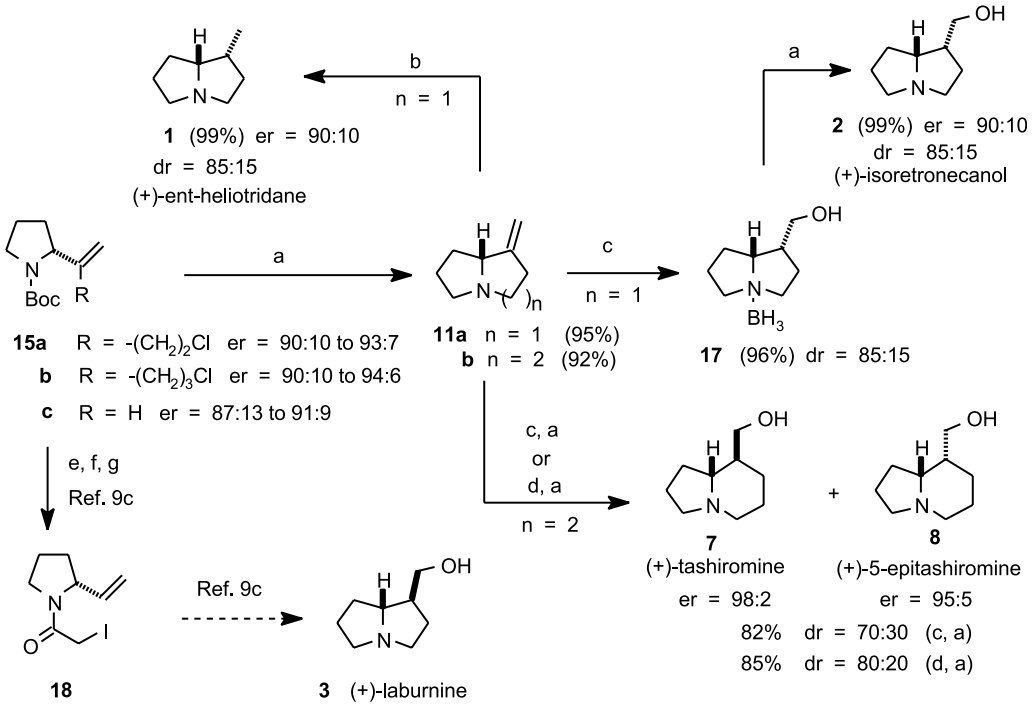
Table 1. Asymmetric deprotonation of *N*-Boc-pyrrolidine followed by cuprate formation and cuprate vinylation

Entry	Vinyl halide	CuCN·2LiCl (equiv)[a]	Product	% Yield[b]	er[c]
1	**10a**	1.0	**15a**	71–75	87:13–90:10
2	**10a**	0.5	**15a**	73–81	93:7–95:5
3	**10b**	1.0	**15b**	79	85:15–91:9
4	**10b**	0.5	**15b**	83	94:6–95:5
5	**12a**	1.0	**16a**	64–69	60:40–70:30
6	**12a**	0.5	**16a**	51–57	90:10–93:7
7	**12b**	1.0	**16b**	81	86:14
8	**12b**	0.5	**16b**	83	90:10
9	**13a**	0.5	**15c**	61–67	87:13
10	**13b**	0.5	**15c**	73	91:9

[a] Deprotonation of *N*-Boc-pyrrolidine [(i) *s*-BuLi, Et_2O, (−)-sparteine, −78 °C, 1 h; (ii) CuCN·2LiCl, 1.0 equiv=RCuCNLi, 0.5 equiv=R_2CuLi].
[b] Based upon isolated products purified by column chromatography.
[c] Enantiomeric ratio determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel].

As previously established,[26,27] high enantioselectivities require deprotonation of *N*-Boc-pyrrolidine in diethyl ether and formation of the cuprate reagents at low temperatures. This can be achieved by addition of a THF solution of CuCN·2LiCl to the cold solution of *N*-Boc-(*S*)-2-lithiopyrrolidine affording the scalemic cuprate reagent in a THF/Et_2O (1:1) solvent mixture. These reaction conditions afforded the *N*-Boc-2-alkenylpyrrolidines in modest to good chemical yields and with very good to excellent enantiomeric ratios as determined by chiral stationary phase HPLC (Table 1). In all instances the two reagents gave comparable chemical yields while the dialkylcuprate reagent gave higher enantiomeric ratios than the alkylcyanocuprate reagent. These very good to excellent enantiomeric ratios could be achieved on 1.0 mmol and on 10 mmol scale reactions. From previous studies, it had been established that the Li to Cu transmetallation as well as the vinylation reactions proceeded with retention of configuration.[27] It should be noted that in principle the opposite absolute configuration can be achieved by use of a (+)-sparteine analogue developed by O'Brien.[28]

N-Boc deprotection and cyclization of **15a–b** afforded **11a–b** as key intermediates for the preparation of the pyrrolizidine (i.e., **1** and **2**) and indolizidine (i.e., **7** and **8**) alkaloids (Scheme 4). Although the one-pot transformation could be achieved with either trimethylsilyl triflate (TMSOTf) or with TMSCl/NaI/MeCN, the most convenient procedure involved deprotection of **15a–b** with TMSCl/MeOH followed by neutralization with $NaHCO_3$ to effect cyclization. Simple hydrogenation of **11a** afforded (+)-*ent*-heliotridane (**1**) and its diastereomer (dr=85:15) while hydroboration–oxidation of **11a** afforded the amine–borane complex **17** after aqueous workup. The amine–borane complex **17** and its diastereomer (dr=85:15) were readily purified by column chromatography and gave ^1H and ^{13}C



Scheme 4. Reagents and conditions: (a) (i) Me_3SiCl, MeOH, 12 h, 25 °C; (ii) $NaHCO_3$. (b) H_2, Pd/C (10%), CH_2Cl_2, 12 h. (c) (i) BH_3·THF (2.2 equiv), THF, 0–25 °C, 1 h, then 60 °C, 1 h; (ii) 10 M NaOH (3 equiv), H_2O_2 (30%, 5 equiv), 0–25 °C, 12 h, (96%). (d) (i) BH_3·THF, THF, 0–25 °C, 1 h; (ii) 9-BBN (1.0 equiv), THF, 60 °C, 1 h; (iii) 10 M NaOH (3 equiv), H_2O_2 (30%, 5 equiv), 0–25 °C, 12 h. (e) CF_3COOH (20 equiv), CH_2Cl_2 (100%). (f) $ClCH_2COCl$, CH_2Cl_2, Et_3N (72%). (g) NaI, CH_3CN (95%).

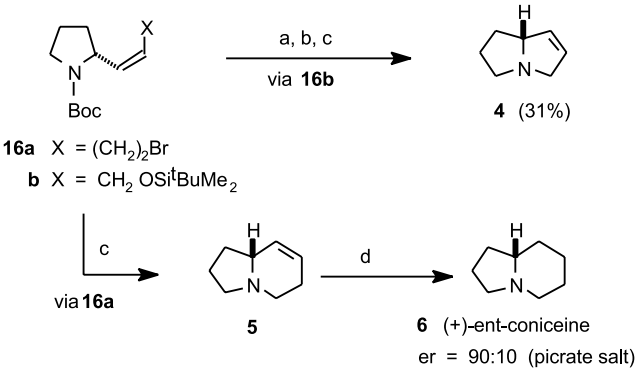
NMR spectra strikingly similar to isoretronecanol.[29] A broad absorption peak between δ 1.60 and 2.10 characteristic of the BH_3-protons was observed in the ^1H NMR spectrum. (+)-Isoretronecanol and its diastereomer (+)-laburnine (**3**) were obtained as an 85:15 mixture of diastereomers by treatment of **16** with TMSCl/MeOH. Previous reports on the hydroboration–oxidation of the lactam analogues of **11a** have not mentioned formation of diastereomeric mixtures of hydroxy lactams, although reported yields were low.[7e,h,29] Interestingly, hydrogenation of **11a** affords the same diastereomeric ratio as the hydroboration reaction, consistent with the 80:20 dr observed for hydrogenation of a lactam analogue of **11a**.[30]

Given that **1** and pseudoheliotridane are prepared from the same intermediate (i.e., **11a**) under the same reaction conditions, the er for each diastereomer is assumed to be the same. The specific rotation of the synthetic mixture of **1** [$[\alpha]_D^{25}=+57$ (*c* 0.5, EtOH)] and pseudoheliotridane when compared to reported values for pure **1** [(+)-heliotridane, $[\alpha]_D^{25}=+86$ (*c* 0.5, EtOH)][6a] and pure pseudoheliotridane ($[\alpha]_D^{25}=+7.0$ (*c* 0.5, EtOH))[6b] corresponds to an er= 88.4:11.6 taking into account the 85:15 diastereomeric ratios. The er is calculated from the expression $0.85\ [ax+(1-a)(-x)]+0.15\ [ay+(1-a)(-y)]=+57$ where *a* is the fraction of the major enantiomer, *x* is the specific rotation for pure heliotridane and *y* is the specific rotation for pure pseudoheliotridane obtained from the literature. Calculation of the optical purity from measured $[\alpha]_{mixture}$/theoretical $[\alpha]_{mixture}$ gave an optical purity of 77% (i.e., an er=88.5:11.5) where Theoretical $[\alpha]_{mixture}=(+86)(0.85)+(+7.0)(0.15)$. Since the specific rotation can be non-linear with concentration, the specific rotation of the synthetic mixture of diastereomers was determined at three different concentrations ($[\alpha]_D^{25}=+57.9$ (*c* 1.0, EtOH), +57.0 (*c* 0.5, EtOH) and +54.2 (*c* 0.25, EtOH)] over a four-fold range of concentrations and showed a small non-linearity.[31] Similarly, the specific rotation of the synthetic mixture of **2** and **3** ($[\alpha]_D^{25}=+60$ (*c* 0.5, EtOH)) when compared to the reported values for **2** ($[\alpha]_D^{25}=+70.2$ (*c* 5, EtOH))[7n] and **3** ($[\alpha]_D{}^{25}=+14.6$ (*c* 3.2, EtOH))[7n] corresponds to an er=95:5 when taking into account the 85:15 mixture of diastereomers. Consequently, within the limits of the method, no epimerization of the stereogenic center appears to occur during *N*-Boc deprotection, cyclization or subsequent functional group manipulations.

Execution of the same sequence with **15b** afforded **11b** which gave (+)-tashiromine (**7**) and (+)-5-epitashiromine (**8**) in a 70:30 ratio after sequential hydroboration–oxidation on the amine–BH_3 complex with BH_3–THF followed by cleavage of the BH_3-complex with TMSCl/MeOH. The two diastereomers could be separated by flash column chromatography and the measured optical rotations corresponded to an er=98:2 for **7** and an er=95:5 for **8**. The differences between the two values most likely reflect errors in measurement and/or some loss of the minor enantiomer during sequential operations and purifications. 5-Epitashiromine displayed a dextrorotatory rotation after initial isolation which changed to a levorotatory rotation after additional passage through a plug of silica gel as previously observed.[13b] Reaction of **11b** with 9-BBN followed by oxidation gave a low yield of organic material upon extraction with CH_2Cl_2, while 9-BBN hydroboration–oxidation of **11b**–BH_3 complex at reflux temperatures in THF gives an 80:20 ratio of **7**:**8** after BH_3 decomplexation with TMSCl/MeOH. Efforts to increase the diastereoselectivity with low temperature hydroboration or with more sterically hindered boranes were not pursued. Control experiments with one equivalent of BH_3-THF did show that amine complexation occurs before olefin hydroboration. The BH_3 complex thus facilitates isolation and purification of these highly water soluble amino alcohols.

This synthetic strategy also provides a synthetic route to (+)-laburnine (Scheme 4). Carbamate cleavage of **15c** followed by amide formation with α-chloroacetyl chloride and Finkelstein conversion of the α-chloroamide to the α-iodoamide afforded **18**.[9c] The enantiomer of **18** has been converted into (−)-trachelanthamidine which is the enantiomer of (+)-laburnine.[9c] The synthesis of **18** thus constitutes a formal total synthesis of (+)-laburnine.

Scalemic 2-alkenyl pyrrolidines **16a–b** are also readily converted to pyrrolizine **4** and indolizine **5**. Sequential silyl ether cleavage of **16b** with H_2SiF_6, mesylation of the alcohol and subsequent treatment of the mesyloxy carbamate with methanolic HCl followed by neutralization with $NaHCO_3$ yields pyrrolizine **4**. The low yield was a result of the volatility of the compound. Similar deprotection of carbamate **16a** and cyclization upon neutralization afforded **5**. Hydrogenation of the indolizine **5** affords (+)-δ-coniceine (**6**) (Scheme 5).



Scheme 5. Reagents and conditions. (a) H_2SiF_6, THF (79%). (b) MsCl, Et_3N, CH_2Cl_2 (87%). (c) (i) Me_3SiCl, MeOH, 12 h, 25 °C; (ii) $NaHCO_3$. (d) MeOH, $Pd(OH)_2$, H_2, 15 h.

3. Summary

In summary, *N*-Boc-2-pyrrolidinylcuprate chemistry offers a rapid entry into the pyrrolizidine and indolizidine carbon skeletons via a two pot process of cuprate coupling with a functionalized vinyl halide followed by a tandem *N*-Boc deprotection–cyclization sequence. The efficient asymmetric syntheses of (+)-*ent*-heliotridane, (+)-isoretronecanol, (+)-laburnine, (+)-**4**, (+)-**5**, (+)-*ent*-δ-coniceine, (+)-tashiromine and (+)-5-epitashiromine illustrate the synthetic power of scalemic α-(*N*-carbamoyl)alkylcuprate methodology and of the enantioenriched 2-lithiocarbamates from which they are derived. Scalemic α-lithiocarbamate methodology is thus significantly extended by copper mediated transformations. Although this strategy for

pyrrolizidine and indolizidine synthesis, as executed, required manipulation of functionality for elaboration and functional group substitution patterns of the natural products subsequent to the generation of the tertiary bridgehead amine, these transformations can in principle be conducted before *N*-Boc deprotection and cyclization. These strongly basic, nucleophilic and easily oxidized tertiary bridgehead nitrogen centers can be problematic in subsequent functional group manipulations. This difficulty can be circumvented if the nitrogen can be protected as the amine–borane or amine–BF_3 complexes.

These asymmetric syntheses employing scalemic stereogenic *N*-Boc-2-pyrrolidinyl metals represent one of the most efficient synthetic routes to these alkaloids to date and illustrates the synthetic power and potential of scalemic stereogenic organometallic reagents in organic synthesis.

4. Experimental

4.1. General

4.1.1. 4-Chloro-2-iodo-but-1-ene (10a). NaI (3.5 g, 23 mmol) was completely dissolved in dry acetonitrile (20 mL). To this solution was added chlorotrimethylsilane (TMSCl, 2.5 g, 23 mmol) which resulted in a cloudy white, fine suspension. After 5 min, water (0.20 g, 11.5 mmol) was added to generate anhydrous HI in situ. The mixture was stirred another 10 min and 4-chloro-1-butyne (2.0 g, 23 mmol) was added neat by syringe. The reaction mixture was stirred for 1 h at room temperature. Then *n*-pentane (40 mL) was added along with aqueous $NaHCO_3$ (saturated). After vigorous shaking, the layers were separated. The top organic layer was washed with sodium thiosulfate ($Na_2S_2O_3$, saturated aqueous), dried ($MgSO_4$) and concentrated in vacuo to give **10a** as a clear liquid (4.5 g, 92%), which was used without further purification: IR (neat) 3003, 1645, 875, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (t, J= 6.6 Hz, 2H), 3.62 (t, J=6.5 Hz, 2H), 5.83 (m, 1H), 6.12 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 42.9, 47.7, 104.2, 125.7; mass spectrum, *m/z* (rel. intensity) 218 (12, M^++2), 216 (40, M^+), 127 (48), 89 (48), 53 (100).

4.1.2. 5-Chloro-2-iodo-pent-1-ene (10b). Following the procedure described above for **10a** with 5-chloro-1-pentyne on a 5.0 mmol scale, gave **10b** as a clear liquid (0.90 g, 78%) that was used without further purification: IR (neat) 2956, 1612, 1432, 897, 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (quint, J=6.5 Hz, 2H), 2.55 (t, J=6.9 Hz, 2H), 3.51 (t, J= 6.8 Hz, 2H), 5.74 (m, 1H), 6.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 31.43, 42.10, 43.09, 109.60, 127.03; mass spectrum, *m/z* (rel. intensity) 232 (21, M^+ +2), 230 (56, M^+), 168 (16), 127 (15), 103 (20), 67 (100).

4.1.3. *cis* 4-Bromo-1-iodo-1-butene (12a). To a solution of 1.88 g of **14a** (26.8 mmol) in 80 mL THF at −78 °C was added 20 mL of 2.00 M *n*-BuLi (54.0 mmol). The thick suspension was vigorously stirred at −78 °C and then allowed to warm up to room temperature over 2 h. Then the suspension was again cooled to −78 °C and to it was added 6.70 g (52.0 mmol) I_2 in 40 mL of THF. After warming to room temperature overnight, the mixture was quenched with saturated aqueous NaCl (3×20 mL), washed with H_2O (2× 20 mL), and dried over anhydrous Na_2SO_4. A yellowish oil (4.72 g, 90% yield) was obtained. The crude product was used for the next reaction without further purification. 4-Hydroxy-1-iodo-1-butyne: IR (neat) 3341 (br), 2931, 1906 (vw), 1051, 683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (s, 1H), 2.61 (t, J=6.3 Hz, 2H), 3.70 (t, J=6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.05, 60.94, 91.05, 100.03; mass spectrum *m/z* (rel. intensity) EI 196 (100, M^+), 166 (68), 127 (33).

To a solution of 1.96 g of 4-hydroxy-1-iodo-1-butyne (10 mmol) in 30 mL of dry CH_2Cl_2 was added 3.97 g of CBr_4 (12 mmol) at −30 °C. The mixture was stirred vigorously, and a solution of PPh_3 (2.70 g, 10 mmol) in 10 mL of dry CH_2Cl_2 was added. The solution was stirred for 2 h at −30 °C, warmed to 0 °C, and then stirred another hour. The crude mixture was filtered through a thin layer of silica gel, and concentrated in vacuo. After column chromatography (100% Petroleum ether), 4-bromo-1-iodo-1-butyne (2.10 g, 81% yield) was obtained: IR (neat) 2100 (vw), 1430, 1322, 1268 (vs), 1208 (vs), 1142, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (t, J=7.2 Hz, 2H), 3.41 (t, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.12, 28.98, 91.70, 100.06; mass spectrum *m/z* (rel. intensity) EI 260 (100, M^++1), 258 (100, M^+−1), 179 (38), 165 (34), 127 (13), 51 (48).

Dipotassium azodicarboxylate was prepared by adding 9.0 g (77 mmol) of azodicarbonamide to a vigorously stirred 40% aqueous potassium hydroxide solution (30 mL), cooled by an ice water bath. After the addition was completed, the mixture was stirred for an additional 45 min at 0 °C and then filtered and the solid was washed with 100 mL of cold methanol. The solid potassium salt was placed in a 500 mL flask with 200 mL of methanol and 10 g (48 mmol) of 4-bromo-1-iodo-1-butyne was added. The mixture was stirred vigorously while a solution of 35 mL of acetic acid in 100 mL of methanol was added via a constant pressure addition funnel at such a rate as to cause gentle boiling. After the addition, the cloudy mixture turned colorless. The reaction mixture was transferred to a separatory funnel containing 500 mL of water and extracted with three 100 mL portions of pentane. The pentane fractions were combined, washed with two 100 mL portions of water, dried over anhydrous sodium sulfate, and filtered. The pentane was removed under reduced pressure to afford 7.14 g (57.0%) of **12a**: IR (neat) 3049, 1640 (w), 1614, 1444, 1282 (s), 1256 (vs), 703, 617; ^1H NMR ($CDCl_3$) δ 2.68–2.74 (m, 2H), 3.41 (t, J=6.9 Hz, 2H), 6.24–6.31 (m, 1H), 6.38–6.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 30.28, 37.70, 85.20, 137.88; mass spectrum *m/z* (relative intensity) EI 262 (20, M^++2), 260 (20, M^+), 167 (20), 135 (89), 133 (90), 53 (100).

4.1.4. *cis* 3-Dimethyl(1,1-dimethylethyl)silyloxy-1-iodo-1-propene (12b). Iodination and diimide reduction of the *tert*-butyldimethylsilyl ether of propargyl alcohol as described above for **12a** gave **12b** in 51% yield: IR (neat) 3420, 2996, 1642, 1455, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (dt, J=14.3, 4.4 Hz, 1H), 6.27 (dt, J=14.5, 1.8 Hz, 1H), 4.28 (dd, J=4.8, 1.8 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ −5.0, 18.3, 25.8, 66.8, 79.9, 142.0; mass spectrum *m/z* (relative intensity) 241 (100, M^+), 185 (65), 85 (90), 73 (55).

4.2. General procedure A: asymmetric vinylation of *N*-Boc-pyrrolidine for R_2CuLi

N-Boc-pyrrolidine (1.71 g, 10 mmol) was dissolved in freshly distilled ether (30 mL) along with (−)-sparteine (2.69 g, 11 mmol). The reaction mixture was cooled to −78 °C under an argon atmosphere and *sec*-BuLi (6.9 mL, 1.6 M, 11 mmol) was added dropwise by syringe. The resultant solution was stirred at −78 °C for 1 h. Then a solution containing CuCN (450 mg, 5 mmol) and LiCl (450 mg, 11 mmol) in THF (30 mL) was added portion-wise by syringe. The mixture was allowed to stir at −78 °C for 30 min before the vinyl iodide (11 mmol) was added neat. The reaction mixture was then allowed to warm to room temperature overnight. It was diluted with Et_2O (20 mL) and quenched with 5% aqueous HCl (15 mL). After shaking vigorously, the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give an oil which was purified by column chromatography on silica gel.

4.2.1. 1,1-Dimethylethyl (2*R*)-2-(3-chloro-1-methylene-propyl)-1-pyrrolidinecarboxylate (15a). Following general procedure A on a 10 mmol scale, carbamate **15a** was isolated [R_f 0.75, petroleum ether/EtOAc, 90:10, v/v] as a clear, colorless oil (2.11 g, 81%): IR (neat) 2964 (s), 1703 (vs), 1658 (s), 1436 (m), 892, 888 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.60–1.75 (m, 1H), 1.75–1.95 (m, 2H), 1.95–2.15 (m, 1H), 2.30–2.55 (m, 2H), 3.35–3.55 (m, 2H), 3.55–3.70 (m, 2H), 4.10–4.25 (m, 1H), 4.83 (br s with shoulder, 2H); ^{13}C NMR ($CDCl_3$) δ 22.6 (23.3), 28.4, (30.6) 31.3, 36.2, 42.6, 46.6, 61.1, 79.3, 110.2, 146.3, 154.3 (rotamers); mass spectrum, *m*/*z* (rel. intensity) 261 (0.1, $M^+ +2$), 259 (0.5, M^+), 203 (14), 186 (14), 167 (30), 114 (49), 70 (45), 57 (100).

The enantiomeric purity of **15a** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 95:5 (1 mmol scale) to 90–10 (10 mmol scale) er [hexane/^{i}PrOH, 99:1 (v/v), flow rate at 0.5 mL/min, detection at λ=210 nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 15.98 min followed by the (*S*)-isomer (minor) at 18.19 min.

4.2.2. 1,1-Dimethylethyl (2*R*)-2-(4-chloro-1-methylene-butyl)-1-pyrrolidinecarboxylate (15b). Following general procedure A on a 10 mmol scale, carbamate **15b** was isolated [silica gel, R_f 0.70, petroleum ether/Et_2O, 50;50, v/v] as a clear colorless oil (2.28 g, 83%): IR (neat) 2965 (s), 1702 (vs), 1680 (m), 1440 (m), 890 (s), 882 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.60–1.75 (m, 1H), 1.75–1.90 (m, 2H), 1.90–2.10 (m, 3H), 2.10–2.25 (m, 2H), 3.35–3.50 (br s, 2H), 3.55 (t, J=6.2 Hz, 2H), 4.15–4.35 (m, 1H), 4.77 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 23.4, 28.4, 32.8, 33.2, 36.1, 41.9, 47.6, 61.9, 79.8, 108.9, 146.5, 155.1; mass spectrum, *m*/*z* (rel. intensity) 275 (0.1, $M^+ +2$), 273 (0.4, M^+), 238 (0.1), 217 (15), 200 (14), 181 (28), 154 (32), 114 (56), 70 (57), 57 (100).

The enantiomeric purity of **15b** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 95:5 (1 mmol scale) to 90:10 (10 mol scale) er [hexane/^{i}PrOH, 99:1 (v/v), flow rate at 0.5 mL/min, detection at λ=210 nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 14.57 min followed by the (*S*)-isomer (minor) at 17.17 min.

4.2.3. 1,1-Dimethylethyl (2*R*)-2-ethenyl-1-pyrrolidine-carboxylate (15c). Following general procedure A on a 2 mmol scale, carbamate **15c** was isolated [R_f 0.65, petroleum ether/EtOAc, 90:10, v/v] as a clear, colorless oil (288 mg, 73%): IR (neat) 3049, 1690, 1660, 1340, 990, 892 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H), 1.56–2.10 (m, 4H), 3.12–3.37 (m, 2H), 4.10–4.30 (m, 1H), 4.85–5.10 (m, 2H), 5.62–5.80 (m, 1H);^{13}C NMR δ 23.1 (br s), 28.3, 31.2 (br s), 46.2, 58.7, 78.9, 113.7, 149.0, 154.4; mass spectrum *m*/*z* (rel. intensity) EI 197 (0.5, M^+), 141 (33), 124 (12), 96 (27).

The enantiomeric purity of **15c** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 91:9 er [hexane/^{i}PrOH, 99.5:0.5 (v/v), flow rate at 0.5 mL/min, detection at λ=210 nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 9.68 min followed by the (*S*)-isomer (minor) at 10.15 min.

4.2.4. 1,1-Dimethylethyl (2*R*)-2-[1-[(*Z*)-4-bromo-1-butenyl]]-1-pyrrolidinecarboxylate 16a. Following general procedure A on a 2 mmol scale, carbamate **16a** was isolated [R_f 0.70, petroleum ether/EtOAc, 90:10, v/v] as a clear, colorless oil (0.420 g, 69%); IR (neat) 2967, 2873, 1703 (vs), 1651, 1385 (vs), 1169; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.55–1.70 (m, 2H), 1.70–1.95 (m, 2H), 2.55–2.81 (m, 2H), 3.25–3.52 (m, 4H), 4.34–4.69 (m, 1H), 5.22–5.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.80, 28.54, 30.88, 31.50, 32.41, 46.46, 54.21, 79.16, 126.10, 134.40, 154.40.

The enantiomeric purity of **16a** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be a 90:10 er [hexane/^{i}PrOH, 99.5:0.5 (v/v), flow rate at 0.5 mL/min, detection at λ=210 nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 13.59 min followed by the (*S*)-isomer (minor) at 14.92 min.

4.2.5. 1,1-Dimethylethyl (2*R*)-2-[1-[(*Z*)-3-[dimethyl(1,1-dimethylethyl)silyloxy]-1-propenyl]]-1-pyrrolidinecarboxylate (16b). Following general procedure A on a 2 mmol scale, carbamate **16b** was isolated [R_f 0.75, petroleum ether/EtOAc, 90:10, v/v] as a clear, colorless oil (0.566 g, 83%): IR (neat) 2967, 1688 (vs), 1376 (vs), 1253, 1161, 1100, 843, 770; ^1H NMR ($CDCl_3$) δ −0.8 (s, 6H), 0.81 (s, 9H), 1.35 (s, 9H), 1.50–1.61 (m, 1H), 1.65–1.87 (m, 2H), 1.92–2.06 (m, 1H), 3.22–3.42 (m, 2H), 4.23 (br s, 2H), 4.39 (br s, 1H), 5.21–5.32 (m, 1H), 5.34–5.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.90, 18.15, 23.59, 25.83, 28.42, 33.33, 46.26, 54.33, 59.30, 76.72, 128.60, 132.50, 154.35; mass spectrum *m*/*z* (rel. intensity) 341 (1, M^+), 268 (7), 228 (48), 184 (46), 153 (74), 110 (100), 75 (59), 57 (81).

The enantiomeric purity of **16b** was determined by chiral stationary phase HPLC on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]

to be a 90:10 er [hexane/^{i}PrOH, 99:1 (v/v), flow rate) 0.5 mL/min, detection at $\lambda=210$ nm]. The (*R*)-enantiomer (major) eluted first with a retention time of 9.17 min followed by the (*S*)-isomer (minor) at 10.58 min.

4.2.6. (*R*)-Hexahydro-1-methylene-1*H*-pyrrolizine (11a). Carbamate **15a** (259 mg, 1.0 mmol) was dissolved in methanol (5.0 mL) at 25 °C, and trimethylsilylchloride (TMSCl, 540 mg, 5.0 mmol) was added dropwise by syringe. The mixture was stirred at room temperature overnight then quenched with saturated aqueous $NaHCO_3$ until pH>8. The mixture was diluted with methylene chloride, two layers were separated, and the organic layer was extracted three times with methylene chloride, and dried ($MgSO_4$). Concentration in vacuo afforded a clear yellow oil which was purified by Kugelrohr distillation (100 °C, 20 mm Hg) to give **11a** as a clear, colorless liquid (0.113 g, 92%): $[\alpha]_D^{22}=+53$ (*c* 1.0, $HCCl_3$); IR (neat) 3400 (vs), 2950 (m), 1660 (m), 1642, 1420 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48–1.60 (m, 1H), 1.60–1.80 (m, 2H), 1.90–2.15 (m, 1H), 2.35–2.50 (m, 2H), 2.50–2.60 (m, 2H), 2.80–3.10 (m, 2H), 3.77 (t, $J=6.6$ Hz, 1H), 4.75 (dd, $J=1.5$, 2.0 Hz, 1H), 4.87 (dd, $J=1.5$, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.5, 32.2, 32.5, 52.6, 54.1, 67.4, 104.6, 154.5; mass spectrum, *m/z* (rel. intensity) 123 (28, M^+), 122 (44), 108 (5), 95 (100), 80 (15), 67 (22), 55 (19).

4.2.7. (+)-*ent*-Heliotridane (1). Alkene **11a** (123 mg, 1 mmol) was dissolved in methylene chloride (10 mL) and 10% palladium on carbon (30 mg) was added. The round bottom flask (50 mL) was capped with a rubber septum, and sealed with parafilm. A balloon filled with hydrogen gas was attached via a syringe and the reaction mixture was stirred overnight at room temperature. Afterwards, the catalyst was removed by filtration through a thin layer of celite, and methylene chloride removed in vacuo to give a light brown oil which was purified by Kugelrohr distillation (100 °C, 20 mm Hg) to give (+)-*ent*-heliotridane (**1**) and its epimer (+)-pseudoheliotridane as a mixture of diastereomers (85:15, 99%): $[\alpha]_D^{25}=+57$ (*c* 0.5, EtOH), [lit.:[6a] (+)-heliotridane, $[\alpha]_D^{25}=+86$ (*c* 0.5, EtOH); lit.[6b] epimer (+)-pseudoheliotridane, $[\alpha]_D^{25}=+7.0$ (*c* 0.5, EtOH); calculated $[\alpha]_{mixture}=(+86)(0.85)+(+7.0)(0.15)=+74$ corresponding to an ee=77% or an er=88.5:11.5 assuming both diastereomers have the same er]; IR (neat) 3408 (vs), 2936 (m), 1642 (w), 1461 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, $J=6.8$ Hz, 3H), 1.55–1.80 (m, 2H), 1.80–2.20 (m, 4H), 2.40–2.55 (m, 1H), 2.65–2.75 (m, 1H), 2.90–3.10 (m, 1H), 3.50–3.70 (m, 1H), 3.80–4.00 (m, 1H), 4.15–4.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 25.7, 25.9, 30.7, 34.7, 53.6, 56.5, 69.9; mass spectrum, *m/z* (rel. intensity) 125 (19, M^+), 108 (4), 97 (10), 83 (100), 55 (52). Pseudoheliotridane: ^{13}C NMR δ 16.5, 24.9, 29.1, 34.1, 39.8, 54.51, 54.54, 72.9.

Heliotridane–BH_3 complex. ^{13}C NMR ($CDCl_3$) δ 13.80, 24.92, 27.40, 31.40, 34.76, 63.60, 65.02, 76.91 [lit.[1e] ^{13}C NMR δ 13.76, 24.88, 27.36, 31.37, 34.74, 63.54, 64.97, 76.88]. *Pseudoheliotridane–BH_3 complex.* ^{13}C NMR ($CDCl_3$) δ 17.63, 24.46, 30.99, 33.03, 41.60, 63.76, 65.02, 80.18 [lit.:[1e] ^{13}C NMR δ 17.60, 24.43, 30.07, 33.01, 41.60, 63.73, 64.27, 80.18].

4.2.8. (+)-Isoretronecanol (2). Alkene **11a** (123 mg, 1 mmol) was dissolved in THF (3 mL) and cooled to 0 °C under an inert argon atmosphere. Then a 1.0 M solution of $BH_3\cdot$THF in THF (1 mL, 1 mmol) was added and the reaction mixture was allowed to slowly warm to room temperature over 1 h. 9-BBN (2.0 mL, 1.0 mmol) was added dropwise. The reaction mixture was then heated at reflux for 1 h, cooled to 0 °C, and treated with 10 M NaOH (1.0 mL). H_2O_2 (1.0 mL, 30% aq) was added and stirring continued for 1 h while allowing the reaction mixture to warm to room temperature. The crude mixture was then diluted with Et_2O and the layers separated. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography on silica gel (petroleum ether/ether, 80:20, v/v) afforded the amine–borane complexes **17** as a 85:15 mixture of diastereomers: IR (neat) 3415 (s), 2976 (s), 2881 (s), 2365 (vs), 2314 (vs), 2271 (vs), 1634 (w), 1453 (s), 1170 (vs), 1015 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30–2.10 (vbr s, BH_3, 3H), 1.50–1.65 (m, 2H), 1.70–1.90 (m, 2H), 1.90–2.05 (m, 3H), 2.62–2.78 (m, 2H), 2.90–2.98 (m, 1H), 3.10–3.21 (m, 1H), 3.30–3.40 (m, 1H), 3.58–3.75 (m, 3H); ^{13}C NMR ($CDCl_3$). *Major diastereomer*: δ 24.4, 26.3, 26.6, 42.6, 61.6, 62.7, 64.1, 74.6. *Minor diastereomer*: δ 24.6, 28.0, 31.8, 49.0, 63.1, 64.0, 65.6, 76.2; mass spectrum, *m/z* (rel. intensity) 141 (28, M^+), 124 (14), 110 (9), 97 (3), 83 (100), 70 (10), 55 (48).

Decomposition of the amine–borane complexes **17** with methanolic HCl (chlortrimethylsilane in methanol) afforded **2** and its epimer (+)-laburnine (**3**) as a mixture of diastereomers (85:15, 80%): $[\alpha]_D^{25}=+60$ (*c* 0.5, EtOH), [lit.[7n] (+)-isoretronecanol $[\alpha]_D^{25}=+70.2$ (*c* 5, EtOH) and its epimer (+)-laburnine $[\alpha]_D^{25}=+14.6$ (*c* 3.2, EtOH);[7n] calculated $[\alpha]_{mixture}=(+70.2)(0.85)+(+14.6)(0.15)=+62$ corresponding to an ee=90% or an er=95:5 assuming both diastereomers have the same er]; ^1H NMR ($CDCl_3$) 1.35–1.55 (m, 2H), 1.55–2.20 (m, 6H), 2.40–2.75 (m, 2H), 3.00–3.15 (m, 1H), 3.15–3.30 (m, 1H), 3.59 (d, $J=7.4$ Hz, 2H), 5.25–6.50 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 26.4, 27.0, 44.1, 53.8, 55.5, 62.8, 66.5. *(+)-Laburnine*. ^{13}C NMR δ 25.6, 29.5, 31.7, 47.9, 54.4, 54.7, 64.5, 68.0; [lit.[7n] ^{13}C NMR ($CDCl_3$) δ 24.9, 30.0, 31.9, 48.3, 52.5, 54.6, 64.9, 67.5 and for the enantiomer (−)-trachelanthamide[13b] δ 25.7, 29.8, 31.8, 48.1, 54.5, 54.8, 65.6, 68.0].

4.2.9. 2,3,5,7a-Tetrahydro-1*H*-pyrrolizine (4). To the solution of **16b** (341 mg, 1.0 mmol) in THF (10 mL) was added H_2SiF_6 (1.0 mL, 2.2 mmol) under an Argon atmosphere. After addition was complete, the mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with Et_2O (20 mL) and quenched with brine (15 mL). After shaking vigorously, the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil (179 mg, 79%) which was purified by column chromatography on silica gel (petroleum ether/EtOAc, 70:30, v/v) to give pure *N*-Boc-2-(*Z*)-3-hydroxy-1-propenyl)pyrrolidine: IR (neat) 3360 (br), 1688 (vs), 1460 (s), 992, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.63–1.76 (m, 1H), 1.76–1.98 (m, 2H), 2.08–2.22 (m, 1H), 3.29–3.53 (m, 2H), 4.05–4.16 (m, 1H), 4.32 (br s, 1H), 4.50–5.61 (m, 1H), 5.49–5.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.86, 28.51, 32.99, 39.34, 46.48, 53.80, 79.51, 124.76, 136.57, 154.46.

Treatment of the alcohol (0.114 g, 0.5 mmol) with triethylamine (0.076 g, 0.75 mmol) and mesyl chloride (0.069 g, 0.60 mmol) in dry CH_2Cl_2 at −30 °C for 2 h followed by the $NaHCO_3$ work up afforded crude mesylate (0.133 g, 87%) which was used without further purification. The crude mesylate was dissolved in methanol (3 mL) and TMSCl (0.295 g, 2.5 mmol) was added slowly at room temperature and the mixture was stirred for 6 h followed by $NaHCO_3$ workup. The crude product was distilled under low pressure (30 mm Hg, 50 °C) to afford **4** (0.049 g, 31%): $[\alpha]_D^{25} = +2.1$ (*c* 1.5, $CHCl_3$); IR (neat) 3058 (vs), 1649 (w), 685 (br) cm^{-1}; ^1H NMR 1.75–2.04 (m, 4H), 2.10–2.29 (m, 2H), 2.87–2.98 (m, 1H), 3.61 (m, 2H), 4.40 (m, 1H), 4.83–4.93 (m, 1H); ^{13}C NMR 24.6, 29.9, 56.9, 61.4, 73.4, 124.3, 129.0; mass spectrum *m/z* (rel. intensity), EI 110 (5, $M^+ + 1$), 109 (49, M^+), 108 (42), 107 (25), 106 (42), 94 (5), 81 (100), 80 (94), 79 (18), 67 (11), 54 (28).

4.2.10. (+)-Coniceine (6). Carbamate **16a** (0.304 g, 1.0 mmol) was dissolved in methanol (5 mL) and TMSCl (0.540 g, 5.0 mmol) was added slowly at room temperature. The reaction mixture was stirred for 6 h followed by the addition of $NaHCO_3$ until pH > 8, stirred for another 2 h at room temperature. The crude material was extracted three times with 15 mL CH_2Cl_2, the combined organic phase was dried over Na_2SO_4, and concentrated in vacuo to afford (*R*)-**5** (0.106 g, 86%): IR (neat) 3073 (vs), 2995, 2315, 1639 (w), 1434; ^1H NMR ($CDCl_3$) δ 1.44–1.56 (m, 1H), 1.75–1.86 (m, 2H), 1.96–2.03 (m, 2H), 2.19–2.32 (m, 1H), 2.72–2.81 (m, 2H), 2.85–2.95 (m, 2H), 3.31–3.42 (m, 1H), 5.62–5.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.23, 22.74, 29.50, 46.07, 51.40, 59.26, 124.77, 128.38; mass spectrum *m/z* (rel. intensity) EI 123 (M^+, 51), 122 (100), 95 (47), 80 (24), 67 (27).

A suspension of (*R*)-**5** (123 mg, 1.0 mmol) and palladium hydroxide (35 mg) in methanol (5.0 mL) was stirred under a hydrogen atmosphere (50 psi) for 15 h. The catalyst was removed through Celite by filtration. After conc. HCl (0.20 mL) was added to the filtrate, the organic solvent was evaporated to yield a hydrochloride salt. The salt was treated with 10% K_2CO_3, and the mixture was extracted with diethyl ether twice. The combined ether extract was washed with brine, and dried over Na_2SO_4. After the solvent was removed, picric acid in EtOH was added. After slight heating, the mixture was cooled to room temperature and the solid was precipitated to yield the picrate salt (315 mg, 89%) of (+)-coniceine (**6**): $[\alpha]_D^{25} = +1.60$ (*c* 0.1, EtOH) for the picrate salt corresponding to an 80% ee or an er = 90:10, [lit.[11f] −2.0 (*c* 0.35, EtOH) for the enantiomer]; ^1H NMR ($CDC1_3$) δ 1.38–2.15 (10H, m), 2.50–2.67 (2H, m), 3.75–3.95 (3H, m), 10.38 (br s 2H), 10.88 (br s 1H); ^{13}C NMR ($CDC1_3$) δ 19.8, 22.9, 23.0, 27.3, 28.3, 53.7, 69.1, 126.6, 129.4, 142.3, 161.9; [lit.[12b] ^{13}C NMR δ 19.8, 23.0, 23.1, 27.3, 28.1, 53.6, 68.6, 126.8, 128.3, 141.8, 162.1]; mass spectrum (neat) *m/z* (rel. intensity) EI 125 (M^+, 51), 124 (100), 97 (94), 96 (96), 83 (61), 69 (67).

4.2.11. (*R*)-8-Methyleneoctahydroindolizine (11b). Carbamate **15b** (259 mg, 1.0 mmol) was dissolved in methanol (5 mL) at 25 °C and trimethylsilylchloride (TMSCl, 540 mg, 5.0 mmol) was added dropwise by syringe. The mixture was stirred at room temperature overnight and then quenched with saturated aqueous $NaHCO_3$ until pH > 8. The mixture was diluted with methylene chloride, two layers were separated and the organic layer extracted three times with methylene chloride, and dried ($MgSO_4$). Concentration in vacuo afforded a clear yellow oil which was purified by Kugelrohr distillation (100 °C, 20 mm Hg) to give **11b** as a clear colorless liquid (116 mg, 85%): $[\alpha]_D^{22} = +79$ (*c* 0.30, $HCCl_3$); IR (neat) 3395 (vs), 2955 (m), 1655 (m), 1644 (m), 1410 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53–1.80 (m, 6H), 1.96 (td, *J* = 5.2, 14.8 Hz, 1H), 2.00–2.20 (m, 2H), 2.20–2.30 (m, 1H), 2.30–2.45 (m, 1H), 3.08–3.20 (m, 2H), 4.68 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.72 (dd, *J* = 1.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2, 26.0, 26.7, 33.3, 52.7, 54.6, 66.6, 106.0, 147.1; mass spectrum, *m/z* (rel. intensity) 137 (58, M^+), 136 (96), 122 (100), 109 (98), 94 (23), 81 (44), 67 (28), 54 (28).

4.2.12. (+)-Tashiromine (7) and (+)-5-epitashiromine (8). Indolizidine olefin **11b** (137 mg, 1 mmol) was dissolved in THF (5 mL) and a 0.5 M solution of 9-BBN in THF (2.0 mL, 1.0 mmol) was added. The mixture was heated for 1 h at 60 °C and then cooled to room temperature before the addition of $BH_3 \cdot THF$ (1.0 mL, 1.0 mmol). After stirring for 30 min, the mixture was cooled to 0 °C and treated with 10 M NaOH (1.0 mL). Then H_2O_2 (35% aq, 1.0 mL) was added dropwise and allowed to stir for 1 h. The white cloudy reaction mixture was diluted with Et_2O, the combined ether phase was washed with $NaHCO_3$ twice, the combined organic phase was dried over Na_2SO_4, and concentrated in vacuo to afford a mixture of the BH_3-complexes of (+)-tashiromine and (+)-5-epitashiromine. Flash column chromatography (R_f 0.5, diethyl ether, 100%) gave a mixture of the BH_3-complexes. (+)-Tashiromine–BH_3 complex: ^{13}C NMR ($CDCl_3$) δ 18.74, 19.99, 20.92, 21.75, 35.43, 52.04, 64.28, 65.23, 66.82. (+)-epitashiromine–BH_3-complex: ^{13}C NMR ($CDCl_3$) δ 19.05, 20.44, 24.38, 28.11, 38.65, 55.30, 56.77, 64.69, 66.70.

Treatment of the BH_3 complexes of **7** and **8** with methanolic HCl (chlortrimethylsilane in methanol) afforded (+)-tashiromine (**7**) and its epimer (+)-5-epitashiromine (**8**) as a mixture of diastereomers (70:30, 85%). The two diastereomers were separated by column chromatography (flash silica gel, CH_2Cl_2/MeOH/NH_4OH, 95:4.75:0.25). (+)-Tashiromine (**7**): $[\alpha]_D^{22} = +41.9$ (*c* 1.1, EtOH) [lit.[13b] ($[\alpha]_D^{20} = +42.9$ (*c* 1.1, EtOH)]; IR (neat) 3560 (br), 2950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.48 (dd, *J* = 10.8, 6.1 Hz, 1H); 3.15–3.02 (m, 2H), 2.09–2.01 (m, 1H), 2.05–1.80 (m, 3H), 1.74–1.37 (m, 7H), 1.23–1.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 24.9, 27.4, 28.9, 44.3, 52.6, 53.5, 65.6, 65.6; [lit.[1e] ^{13}C NMR δ 20.2, 24.6, 27.1, 28.5, 44.1, 52.1, 53.6, 65.0, 65.8].

(+)-5-Epitashiromine (**8**). $[\alpha]_D^{22} = +1.48$ (*c* 1.5, EtOH) [lit. $[\alpha]_D^{20} = +1.1$ (EtOH),[13b] $[\alpha]_D = -0.96$ (*c* 0.31, EtOH);[14a] IR (neat) 3450, 2952 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.15 (dd, *J* = 10.9, 4.1 Hz, 1H), 3.71 (br d, *J* = 9.7 Hz, 1H), 3.11–3.05 (m, 1H), 3.03–2.91 (m, 1H), 2.36–2.24 (m, 1H), 2.12–1.93 (m, 3H), 1.90–1.61 (m, 6H), 1.60–1.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 23.2, 25.7, 30.5, 35.3, 54.0, 54.4, 66.5, 66.8; [lit.[1e] ^{13}C NMR δ 20.8, 23.3, 25.8, 30.6, 35.3, 53.5, 54.5, 65.7, 66.8]. A sample of **8** taken from the column chromatography gave $[\alpha]_D^{22} = +1.48$ (*c* 1.5, EtOH) and this sample upon passage through a pipette with a small

amount of silica gel gave $[\alpha]_D^{22} = -0.87$ (*c* 1.5, EtOH). This change in the sign of rotation as a function of sample history was previously noted.[13b]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.094. General experimental information, description of materials and ^1H and ^{13}C NMR spectra for compounds **1**–**5**, **7**–**8**, **2**–BH_3 (i.e., **17**)/**3**–BH_3, **7**–BH_3/**8**–BH_3, **11a**–**b**, **15a**–**c**, and **16a**–**b** are available.

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31. The specific rotation can vary with concentration, temperature, solvent and the presence of soluble impurities in the sample. The optical and enantiomeric purities may be nonequivalent (Horeau effect), although this is generally a small effect observed in weakly polar solvents that disappears in polar solvents. All these effects must be kept in mind when attempting to determine optical purity by polarimetry and rotations should be measured at the same concentration, temperature and in the same solvent when making comparisons with literature values. The 85:15 mixture of **1** (*c* 0.45) and pseudoheliotridane (*c* 0.07) were measured at $c=0.5$ (EtOH) giving the concentrations shown in parentheses for each species. Thus the concentration of **1** is close to the reported literature concentration of $c=0.5$ and pseudoheliotridane is at 1/6th the concentration of the reported value (i.e., *c* 0.5). See: Eliel, E. L.; Whilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 217–221 and 1071–1080.