Pergamon

Tetrahedron Letters 43 (2002) 7725–7728

TETRAHEDRON LETTERS

Synthesis of (±)-isoretronecanol, (±)-curassanecine, (±)-heliotridane, (±)-tashiromine and (±)-5-epitashiromine via α-(*N*-carbamoyl)alkylcuprate chemistry

R. Karl Dieter* and Rhett Watson

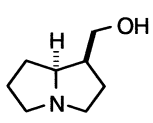
Department of Chemistry, Hunter Laboratory, Clemson University, Clemson, SC 29634-0973, USA

Received 13 August 2002; accepted 29 August 2002

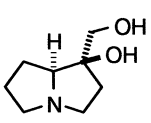
Abstract—Vinylation of *N*-Boc-2-pyrrolidinylcuprate reagents with functionalized vinyl iodides followed by *N*-Boc deprotection and cyclization affords 1-methylidine pyrrolizidine and indolizidine carbon skeletons. Functional group manipulation of the *exo*-cyclic olefin provides direct synthetic entries to the pyrrolizidine alkaloids (±)-isoretronecanol, (±)-curassanecine, (±)-heliotridane or the indolizidine alkaloids (±)-tashiromine and (±)-epitashiromine. This synthetic approach to pyrrolizidine and indolizidine alkaloids requires masking of the tertiary amine during functional group interconversions involving the alkene functionality. © 2002 Published by Elsevier Science Ltd.

Pyrrolizidine[1] and indolizidine[2] alkaloids are important classes of biologically active natural products. Several pyrrolizine imides display amnesia-reversal activity[3] while the antineoplastic pyrrolizidine *N*-oxide, indicine *N*-oxide, was examined in clinical trials.[4] Indolizidine alkaloids have been isolated from poison dart frogs and many have neurological properties.[5] The pyrrolizidine alkaloids isoretronecanol (**1**),[6] trachelanthamidine,[6c,7] and heliotridane (**3**)[8] and the indolizidines tashiromine (+)-(**4**)[6b,c,9] and (+)-5-epitashiromine (**5**)[6c,9] have provided a framework for testing new synthetic methodologies applicable to alkaloid total synthesis. Although several short syntheses have been devised for these simple alkaloids, a number of annulation strategies have involved long linear sequences. Our recent development of α-(*N*-carbamoyl)alkylcuprate chemistry[10] provided a synthetic methodology that could, in principle, be exploited for the rapid construction of the bicyclic framework. The syntheses of (±)-isoretronecanol (**1**), (±)-curassanecine (**2**), (±)-heliotridane (**3**), (±)-tashiromine (**4**) and (±)-5-epitashiromine (**5**) were undertaken to examine the utility of α-(*N*-carbamoyl)alkylcuprate chemistry in alkaloid synthesis and to explore issues of stereocontrol resulting from this strategy. Successful development of this approach to alkaloids **1**–**5** is amenable to asymmetric synthesis employing stereogenic α-(*N*-carbamoyl)alkylcuprates.[11]

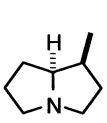
The α-(*N*-carbamoyl)alkylcuprate annulation strategy required the preparation of functionalized vinyl iodides **8** and **11** (Scheme 1). Hydroxy vinyl iodide **7**, readily prepared by addition of in situ generated HI[12] to alkynyl alcohol **6a**, was converted to either the mesylate **8a** or bromide **8b**. Initial efforts to prepare **13** focused on the alkylation of acetate enolates with propargyl bromide. Although the enolate of ethyl acetate gave complex mixtures, excellent yields of **12b** (95%) were obtained via alkylation of the enolate of *tert*-butyl acetate with propargyl bromide. Addition of HI to **12b**, however, resulted in ester cleavage. A synthetic approach to **11** involving addition of HI to alkynyl alcohol **6b** yielded a mixture of **9** and **10**, the latter product arising via acid promoted intramolecular addition of the hydroxyl group to the triple bond followed



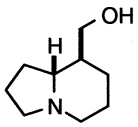
1
(-)-isoretronecanol



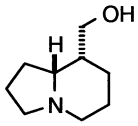
2
curassanecine



3
(-)-heliotridane



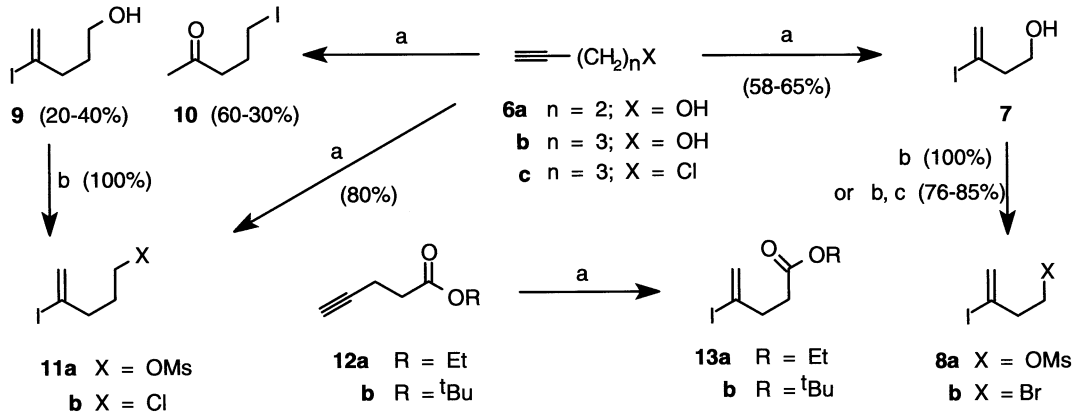
4
(+)-tashiromine



5
(+)-5-epitashiromine

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

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01835-X

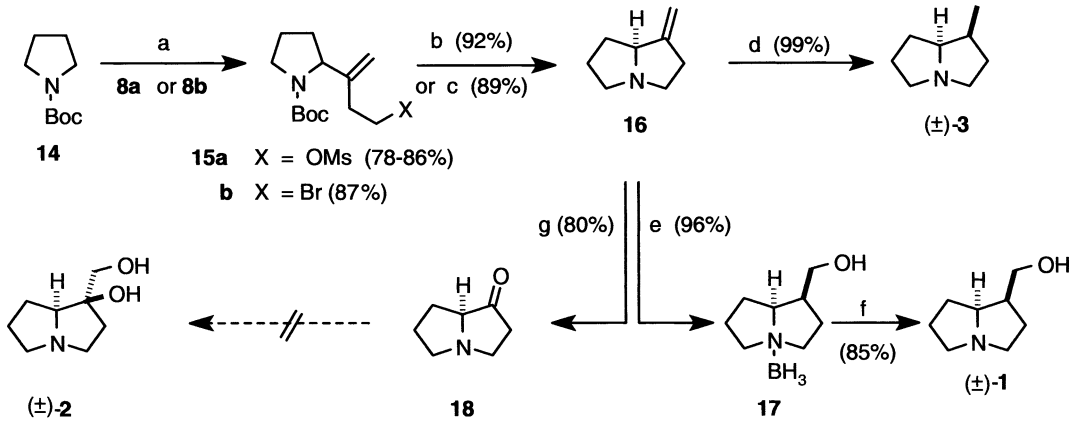


Scheme 1. *Reagents and conditions*: (a) Me_3SiCl, NaI, CH_3CN, H_2O (0.5 equiv.), 25°C. (b) (i) MsCl (1.1 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, –40°C; (ii) $NaHCO_3$, Et_2O. (c) LiBr, DMF, reflux, 1 h.

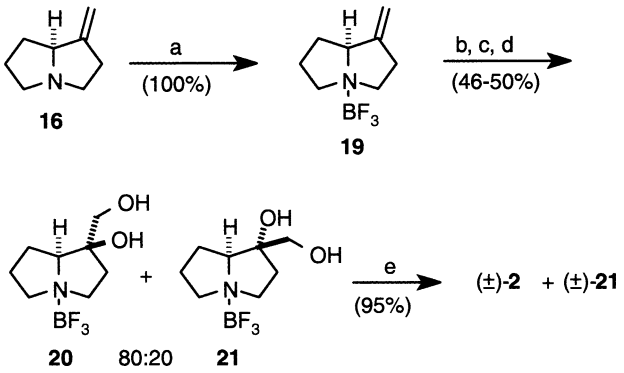
by iodide ion cleavage of the resulting α-methylene tetrahydrofuran intermediate. The ratio of **9**:**10**:**6b** varied as a function of HI employed [20:60:20 with 2.0 equiv. of HI and 40:30:30 with 1.0 equiv.]. Commercially available **6c** was easily converted to **11b** by addition of HI generated in situ.

The pyrrolidinyl cuprate generated from **14** afforded excellent yields of the vinylation products **15a** or **15b** uneventfully (Scheme 2).[10b,c] Utilization of the alkylcyanocuprate reagent (i.e. RCuCNLi) efficiently conserves the α-(*N*-carbamoyl)alkyl ligand. *N*-Boc deprotection and cyclization[13] of **15a** or **15b** to **16** could be effected with either trimethylsilyl triflate (TMSOTf) or with TMSCl/NaI/MeCN. Simple hydrogenation of **16** afforded (±)-heliotridane (**3**) and its diastereomer (85:15) while hydroboration–oxidation afforded amine–borane complex **17** after aqueous work-up. The amine–borane complex **17** and its diastereomer were readily purified by column chromatography. (±)-Isoretronecanol (**1**) [^{1}H NMR δ 3.60 (d, J=7.3 Hz, 2H); lit.:[6d] δ 3.60 (d, J=7.0 Hz, 2H)] and its diastereomer, (±)-lauburnine [^{13}C NMR δ 67.5, 64.7, 54.8, 54.2, 48.0, 32.0, 30.0, 25.0 (lit.:[6b] δ 67.5, 64.9, 54.7, 52.7, 48.5, 32.0, 30.1, 25.7)], were obtained as an 85:15 mixture by treatment of the borane–amine complexes with TMSCl/MeOH.

Initial approaches to (±)-curassanecine envisioned utilization of an epoxide derived from **16**. Efforts to epoxidize **16** with either *m*-chloroperbenzoic acid,[14] oxone[15a] or peroxytrifluoroacetic acid[14b] were unsuccessful as were attempts to effect either halohydrin formation[16] or dihydroxylation.[14b,15a] Ozonolysis of **16** in trifluoroacetic acid/CH_2Cl_2 (2:1)[17] afforded ketone **18**[18] in excellent yield. Reaction of **18** with benzyloxymethyllithium generated from the corresponding stannane[19,20] or with dimethyl sulfonium methylide[21] yielded, after workup, black chloroform insoluble materials. With these carbanions, the reaction mixture turned black immediately upon addition of ketone **18**, although the 1,2-nucleophilic addition of *n*-BuLi appeared to occur uneventfully. Unable to execute 1,2-nucleophilic addition to ketone **18**, an effort to epoxidize the BF_3 complex of **16** was undertaken.[22] Treatment of neat **16** with $BF_3{\cdot}Et_2O$ quantitatively afforded **19** (Scheme 3) which upon reaction with *m*-chloroperbenzoic acid (CH_2Cl_2, 25°C, 7 days) gave a complex mixture after treatment with 10% aqueous



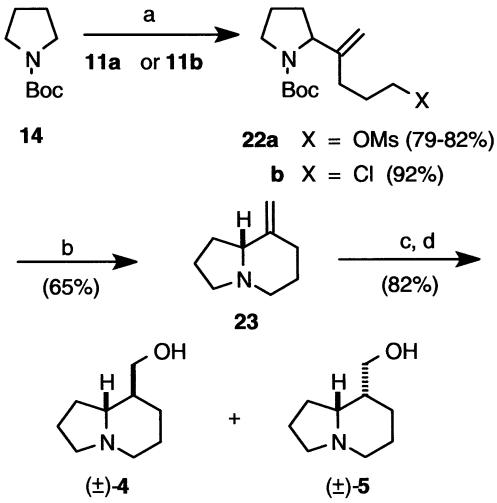
Scheme 2. *Reagents and conditions*: (a) (i) *sec*-BuLi, THF, TMEDA, –78°C, 1.25 h; (ii) CuCN·2LiCl (1.0 equiv.), –78°C, 1 h; (iii) **8a** or **8b**, –78°C, 4 h. (b) TMSOTf (1.0 equiv.), CH_2Cl_2, under Ar, –20 to 25°C, 12 h (92%). (c) TMSCl, NaI, CH_3CN (dry) (89%). (d) H_2, Pd/C (10%), CH_2Cl_2, 12 h (99%). (e) (i) $BH_3{\cdot}THF$, THF, 0–25°C, 1 h; (ii) 10 M NaOH (3 equiv.), H_2O_2 (30%, 5 equiv.), 0–25°C, 12 h, (96%). (f) MeOH, TMSCl, 1 h, 25°C. (g) CF_3COOH, O_3, –78°C, 20 min, (80%).



Scheme 3. *Reagents and conditions*: (a) (i) $BF_3{\cdot}Et_2O$ (2.0 equiv.), 12 h; (ii) high vacuum, remove excess $BF_3{\cdot}Et_2O$ (100%). (b) *m*-CPBA (2.0 equiv.), CH_2Cl_2, 25°C, 7 days. (c) 10% aq. HCl, 12 h. (d) 6 M HCl, 2 h (46–50%). (e) CsF, CH_3CN, reflux, 12 h.

HCl in contrast to literature suggestions of low epoxidation yields.[22] The ^{13}C NMR spectrum of this mixture displayed 32 absorption peaks. Further treatment of this material with 6 M HCl afforded material that displayed 16 absorption peaks in the ^{13}C NMR spectrum while the ^{19}F NMR spectrum indicated the continued presence of an amine–borane complex. These results are consistent with the initial formation of a mixture of diastereomeric epoxides and diols (four compounds each with eight carbon atoms) which are converted to the two diastereomeric diols upon treatment with 6 M HCl. DEPT, COSY, NOESY and difference NOE NMR experiments on the two component sample supported structural assignments as the BF_3-complexes of (±)-curassanecine **20** and its diastereomer **21**. Efforts to cleave the BF_3-complexes with 10% NaOH (80°C, 30 min) or concentrated NH_4OH (80°C, 12 h) yielded only recovered complex.[23] Treatment of the **20**+**21** mixture with CsF in acetonitrile gave (±)-**2** [^{13}C NMR δ 80.1, 70.5, 68.1, 55.7, 53.3, 39.1, 27.8, 25.3 (lit.:[24] δ 80.3, 70.8, 68.3, 55.7, 53.3, 39.2, 27.8, 25.4)] and recovered (±)-**21** [^{19}F NMR δ −150.5 and identical ^{13}C NMR absorptions as before treatment with CsF] as a 75:25–80:20 mixture, respectively.

The same strategy can be employed for construction of the indolizidine skeleton (Scheme 4). Vinylation of the cuprate generated from **14** with **11a** or **11b** affords **22a** or **22b**, respectively, both of which undergo *N*-Boc deprotection and cyclization to give **23** in excellent yields. Hydroboration–oxidation of **23** with $BH_3{\cdot}THF$ gives a 70:30 mixture of (±)-tashiromine (**4**) [^1H NMR δ 3.62 (dd, $J=10.7$, $J=4.6$ Hz, 1H), 3.48 (dd, $J=10.8$, $J=6.1$ Hz, 1H); lit.:[6c] δ 3.61 (dd, $J=10.9$, $J=4.7$ Hz, 1H), 3.44 (dd, $J=10.9$, $J=6.5$ Hz, 1H)] and (±)-5-epitashiromine (**5**) [^1H NMR δ 4.15 (dd, $J=10.9$, $J=4.1$ Hz, 1H), 3.71 (bd, $J=9.7$, 1H); lit.:[6c] δ 4.18 (dd, $J=10.7$, $J=4.0$ Hz, 1H), 3.74 (dd, $J=10.7$, 1H)] after cleavage of the initially formed amine–borane complexes [i.e. (±)-**4**-BH_3 and (±)-**5**-BH_3]. Reaction of **23** 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 **23**-BH_3 complex at



Scheme 4. *Reagents and conditions*: (a) (i) *sec*-BuLi, THF, TMEDA, −78°C, 0.75–1.25 h; (ii) CuCN·2LiCl (1.0 equiv.), −78°C, 1 h; (iii) **11a** or **11b**, −78°C, 4 h. (b) TMSOTf, CH_2Cl_2, −40°C, 12 h. (c) (i) $BH_3{\cdot}THF$, THF, 0–25°C, 1 h; (ii) 10 M NaOH (3 equiv.), H_2O_2 (30%, 5 equiv.), 0–25°C, 12 h. (d) MeOH, TMSCl, 1 h, 25°C.

reflux temperatures in THF gives a 66:34 ratio of **4**:**5** after BH_3 decomplexation with TMSCl/MeOH. The BH_3 complex thus facilitates isolation and purification of these highly water soluble amino alcohols. Additional efforts to maximize this stereoselectivity were not made.

In summary, α-(*N*-carbamoylalkyl)cuprate chemistry offers a rapid entry into the pyrrolizidine and indolizidine carbon skeletons via a two pot process of cuprate coupling with a functionalized vinyl iodide followed by a tandem *N*-Boc deprotection–cyclization sequence. This strategy requires manipulation of functionality for elaboration of the stereochemistry and functional group substitution patterns of the natural products subsequent to the generation of the tertiary bridgehead amine. 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 complex or as a salt by reaction with a strong protic acid or with a Lewis acid such as BH_3 or $BF_3{\cdot}Et_2O$. The amine–borane complexes are quite useful for the isolation and characterization of reaction products and can be easily converted to the free amines by treatment with either TMSCl–MeOH or CsF. The α-(*N*-carbamoylalkyl)cuprate is particularly attractive because the cuprate coupling reaction can be achieved with high enantioselectivity.[11]

Acknowledgements

This work was generously supported by the National Institutes of Health (GM-60300-01). Support of the

NSF Chemical Instrumentation Program for purchase of a JEOL 500 MHz NMR instrument is gratefully acknowledged (CHE-9700278).

References

1. Wróbel, J. T. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: San Diego, 1985; Vol. 26, Chapter 7, p. 327 and references cited therein.
2. (a) Michael, J. P. In *The Alkaloids*: *Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic Press: San Diego, 2001; Vol. 55, p. 92 and references cited therein; (b) Takahata, H.; Momose, T. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 44, Chapter 3, p. 189 and references cited therein; (c) Howard, A. S.; Michael, J. P. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: San Diego, 1986; Vol. 28, Chapter 3, p. 183 and references cited therein.
3. (a) Hartman, J. D.; Dodd, J. H.; Hicks, J. L.; Hershenson, F. M.; Huang, C. C.; Butler, D. E. *J. Labelled Compd. Radiopharm.* **1985**, *22*, 583; (b) Butler, D. E.; Leonard, J. D.; Caprathe, B. W.; L'Italien, Y. J.; Pavia, M. R.; Hershenson, F. M.; Poschel, P. H.; Marriott, J. G. *J. Med. Chem.* **1987**, *30*, 498.
4. Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1987**, *30*, 2144.
5. For reviews on amphibian 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, Chapter 1, p. 1; (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 43, Chapter 3, p. 185.
6. (a) Le Coz, S.; Mann, A.; Thareau, F.; Taddei, M. *Heterocycles* **1993**, *36*, 2073; (b) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Haviari, G.; Célérier, J.-P.; Lhommet, G.; Gramain, J.-C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122; (c) Kim, S.-H.; Kim, S.-I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771; (d) Iwashita, T.; Kusumi, T.; Kakisawa, H. *J. Org. Chem.* **1982**, *47*, 230.
7. Sato, T.; Tsujimoto, K.; Matsubayashi, K.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1992**, *40*, 2308.
8. Honda, T.; Yamane, S.; Naito, K.; Suzuki, Y. *Heterocycles* **1995**, *40*, 301.
9. Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613.
10. (a) Dieter, R. K.; Dieter, J. W.; Alexander, C. W.; Bhinderwala, N. S. *J. Org. Chem.* **1996**, *61*, 2930; (b) Dieter, R. K.; Sharma, R. R. *Tetrahedron Lett.* **1997**, *38*, 5937; (c) Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Org. Chem.* **2001**, *66*, 2302.
11. Dieter, R. K.; Topping, C. M.; Chandupatla, K. R.; Lu, K. *J. Am. Chem. Soc.* **2001**, *123*, 5132.
12. Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.
13. Dieter, R. K.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847.
14. (a) Diez, A.; Vilaseca, L.; López, I.; Rubiralta, M. *Heterocycles* **1991**, *32*, 2139; (b) Hanselmann, R.; Benn, M. *Tetrahedron Lett.* **1993**, *34*, 3511.
15. (a) Kennedy, R. J.; Stock, A. M. *J. Org. Chem.* **1960**, *25*, 1901; (b) Emmons, W.; Pagano, A. S.; Freeman, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 3472.
16. (a) Srikrishna, A.; Reddy, T. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2137; (b) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005.
17. Carretero, J. C.; Arrayás, R. G. *J. Org. Chem.* **1998**, *63*, 2993.
18. Christine, C.; Ikhiri, K.; Ahond, A.; Mourabit, A. A.; Poupat, C.; Potier, P. *Tetrahedron* **2000**, *56*, 1837.
19. Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.
20. Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151.
21. Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5307.
22. Ferrer, M.; Sánchez-Baeza, F.; Messeguer, A.; Diez, A.; Rubiralta, M. *J. Chem. Soc., Chem. Commun.* **1995**, 293.
23. Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5469.
24. (a) Mohanraj, S.; Herz, W. *J. Nat. Prod.* **1982**, *45*, 328; (b) Gramain, J.-C.; Remuson, R.; Vallee-Goyet, D. *J. Nat. Prod.* **1991**, *54*, 1062.