Piperidines via Ammonium Ylide [1,2]-Shifts: A Concise, Enantioselective Route to (–)-Epilupinine from Proline Ester

F. G. West* and B. N. Naidu

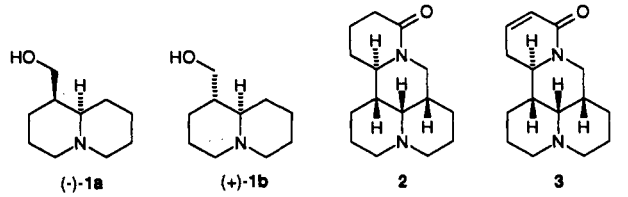
Department of Chemistry, University of Utah
Salt Lake City, Utah 84112

Received June 6, 1994

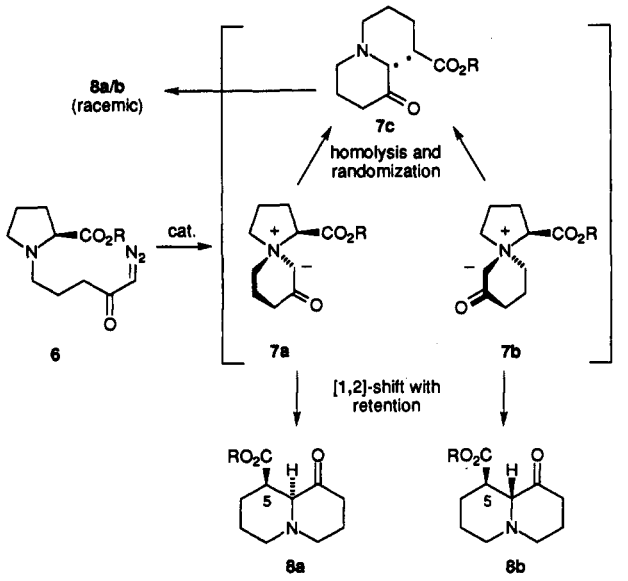
We have recently developed a new route to substituted piperidines from simple acyclic diazo ketone precursors by way of the Stevens [1,2]-shift of cyclic ammonium ylides.[1] Previous reports of moderate to high levels of stereochemical retention by *chiral* migrating groups[2] suggested the examination of diazo ketones bearing pendant, optically active α-amino acid derivatives. Further, the use of a cyclic amino acid such as proline would permit the rapid construction of more elaborate, bicyclic skeletons. Potential application to various lupin alkaloids[3,4] (Chart I) can be envisioned, ranging from the simple quinolizidines lupinine (**1a**) and epilupinine (**1b**) to more elaborate, biologically active compounds such as matrine (**2**) and sophocarpine (**3**). Reported herein are the preliminary results of these studies, including the use of the carbenoid/ylide/[1,2]-shift methodology in the diastereoselective and enantioselective synthesis of epilupinine in five steps from proline benzyl ester.

In analogy to the simple monocyclic examples, [1,2]-shift of spiro[4,5] ammonium ylide **7** should give the corresponding fused bicyclic quinolizidine skeleton **8** (Scheme 1). Placement of a carbalkoxy group adjacent to the nitrogen in the five-membered ring would ensure migration of that carbon[1] and would leave in place a suitable precursor to the primary alcohol of lupinine or epilupinine. Our previous results suggested that the desired ylides **7** could be formed from monocyclic diazo ketone **6** via $Rh_2(OAc)_4$ catalysis.[5] Both relative and absolute stereochemistry are important issues in the key transformation of **6** to **8**. The Stevens [1,2]-shift can apparently occur with high stereochemical retention, despite the fact that a substantial body of mechanistic evidence suggests that it proceeds through a radical pair intermediate.[6] If this held for diastereomeric ylides **7a** and **7b**, quinolizidines **8a** and **8b** each would be formed in significant enantiomeric excess. Starting with natural (L)-proline would furnish products enriched in the (*R*)-configuration at C-5. On the other hand, if the biradical intermediates survived long enough to randomize, **8a,b** would be formed as racemates.

Chart 1. Representative Quinolizidine Alkaloids



Scheme 1



Treatment of 5-bromo-1-diazo-2-pentanone (**5**) with (L)-proline benzyl ester (**4a**) (4 equiv)[7] and triethylamine at 60 °C gave diazo ketone **6** in 80% yield (Scheme 2). Although attempts to determine the optical purity of **6** using chiral NMR shift reagents were unsuccessful, no racemization was detected in the analysis of the analogously prepared methyl ester **9**.[8] Exposure of diazo ketone **6** to catalytic $Rh_2(OAc)_4$ (3 mol %) in dichloromethane provided quinolizidines **8a** and **8b** in 74% yield as a 1:3 mixture of diastereomers.[9] On the other hand, addition of a toluene solution of **6** to a refluxing mixture of Cu^0 powder (0.5 equiv) in toluene or a refluxing solution of $Cu(acac)_2$ (5 mol %) in toluene gave **8a** and **8b** in 81–84% yield and as 6:94 and 5:95 ratios of

(1) (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177. (b) For a general review of the Stevens rearrangement, see: Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 913–73.

(2) (a) Campbell, A.; Houston, A. H. J.; Kenyon, J. *J. Chem. Soc.* **1947**, 93. (b) Brewster, H. H.; Kline, M. W. *J. Am. Chem. Soc.* **1952**, *74*, 5179. (c) Millard, B. J.; Stevens, T. S. *J. Chem. Soc.* **1963**, 3397. (d) Schöllkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.* **1969**, 3415. (e) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009.

(3) Reviews: (a) Lupine alkaloids: Aslanov, H. A.; Kushmuradov, Y. U.; Sadykov, A. S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press, Inc.: San Diego, CA, 1987; Vol. 31, Chapter 5, p 117. (b) Michael, J. P. *Nat. Prod. Rep.* **1991**, *8*, 553. (c) Michael, J. P. *Nat. Prod. Rep.* **1993**, *10*, 51.

(4) (±)-Lupinine: (a) Al-awar, R. S.; Joseph, J. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732. (b) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215. (c) Kurihara, T.; Matsubara, Y.; Osaki, H.; Harusawa, S.; Yoneda, R. *Heterocycles* **1990**, *30*, 885. (d) Haddad, M.; Célérier, J.-P.; Lhommet, G. *Heterocycles* **1987**, *26*, 2335. (e) Iwashita, T.; Kusumi, T.; Kahisawa, H. *J. Org. Chem.* **1982**, *47*, 230. (±)-Epilupinine: (f) Edstrom, E. D. *Tetrahedron Lett.* **1991**, *32*, 5709. (g) Beckwith, A. L. J.; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269. (h) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 2219. (i) Takahata, H.; Yamabe, K.; Suzuki, T.; Yamazaki, T. *Heterocycles* **1986**, *24*, 37. (j) Ihara, M.; Kirihara, T.; Fukumoto, K.; Kametani, T. *Heterocycles* **1985**, *23*, 1097. (k) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014. (l) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (m) Okita, M.; Wakamatsu, T.; Ban, Y. *Heterocycles* **1983**, *20*, 401. (n) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661. Both (±)-lupinine and (±)-epilupinine: (o) Gesson, J. P.; Jacquesy, J. C.; Rambaud, D. *Tetrahedron Lett.* **1992**, *33*, 3633. (p) Célérier, J. P.; Haddad, M.; Lhommet, G.; Dhimane, H.; Pommelet, J. C.; Chuche, J. *Tetrahedron* **1989**, *45*, 6161. (q) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325. (r) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037 and references cited therein. Asymmetric syntheses: (s) Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J. *Synthesis* **1991**, 970. (t) Morley, C.; Knight, D. W.; Share, A. C. *Tetrahedron Asymmetry* **1990**, *1*, 147. (u) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289.

(5) Reviews: (a) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091. (b) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (c) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (d) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

(6) Ammonium ylides: See refs 1 and 2e. Sulfonium ylides: Baldwin, J. E.; Erickson, W. F.; Hackler, R. E.; Scott, R. M. *J. Chem. Soc., Chem. Commun.* **1970**, 576. Oxonium ylides: Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479.

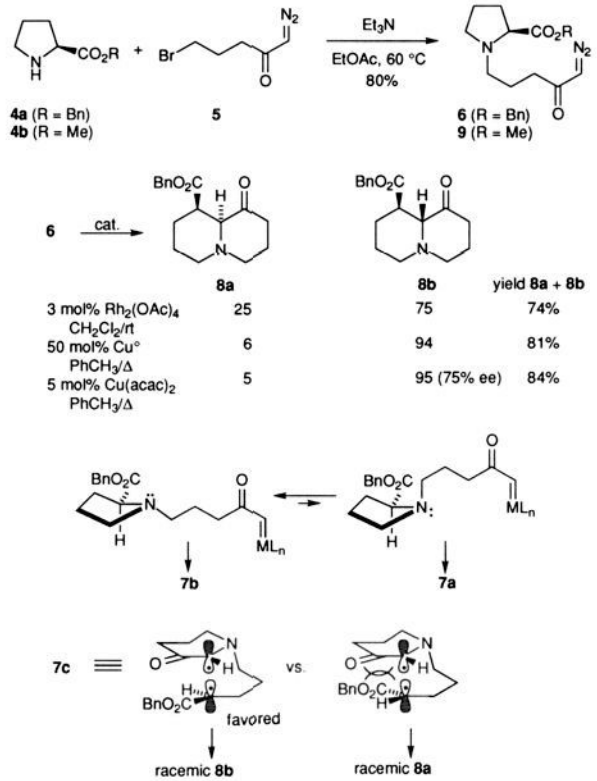
(7) Although an excess of **4a** was required, it could be recovered at the end of the reaction in ca. 50% yield. On larger scale reactions (≥20 mmol of **5**), 3 equiv of **4a** could be used with little or no diminution in yield.

(8) Diazo ketone **9** derived from optically pure **4b** was analyzed via ^1H NMR using $Eu(hfc)_3$, and the spectra were compared with those of racemic **9**. See supplementary material for details.

(9) Ratios of **8a/8b** were determined via integration of the benzyl ester methylene resonances in the ^1H NMR spectra.

0002-7863/94/1516-8420$04.50/0

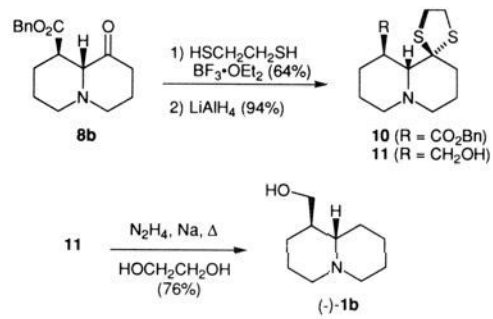
Scheme 2



diastereomers, respectively.[10] Methyl ester substrate **9** furnished the corresponding methyl ester substituted quinolizidines in comparable yields, and with diastereomer ratios of 16:84–11:89.

Analysis of major diastereomer **8b** by chiral NMR shift reagent indicated that it was formed in ca. 65–75% ee.[11] This level of stereochemical retention suggests that the high diastereoselectivity observed derives predominantly from preferential formation of ylide diastereomer **7b** with stereospecific [1,2]-shift to give optically pure **8b**. Formation of **7b** requires approach of the metal carbenoid from the same face of the proline ring as the ester substituent. Prior to nucleophilic attack on the carbenoid the configuration of the amine nitrogen is mutable, and it may preferentially reside in a pyramidal form placing the vicinal groups trans, thus requiring approach of the carbenoid cis to the ester group.[12] The racemic portion of **8b** presumably arises from achiral biradical **7c**, and since the yield of racemate far exceeded the total yield of **8a**, the overall diastereoselectivity of this process may also derive in part from an intrinsic selectivity in the

Scheme 3



recombination of **7c**.[13] Diastereoselective recombination by **7c** to give racemic **8b** may proceed through a transition state placing the hydrogen of the migrating carbon under the piperidone ring to minimize steric interactions involving the ester group.

Conversion of **8b** to epilupinine **1b** was carried out in three steps (Scheme 3). Thioketalization afforded dithiolane **10**, which could be cleanly reduced to primary alcohol **11**. Attempts to desulfurize **10** or **11** using Raney nickel or free radical conditions were unsuccessful. However, treatment of **11** with hydrazine/Na^0 in hot ethylene glycol[14] led to (–)-**1b** in good yield. Analysis of the product both by optical rotation and via its MTPA ester confirmed that it was formed in 75% ee.[15]

In summary, we have reported the synthesis of epilupinine in five steps and 30% overall yield, starting from readily available proline benzyl ester. The key rearrangement step to generate the quinolizidine skeleton proceeds with high levels of diastereoselectivity and moderate enantiospecificity. This route demonstrates the potential of ammonium ylide [1,2]-shift methodology for the efficient construction of polycyclic alkaloid skeletons. Efforts to understand and optimize the stereospecific shift of chiral migrating groups and to apply this chemistry to the enantioselective construction of more elaborate targets will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (BRSG Grant No. S07 RR07092) for partial support of this work, the American Cancer Society for a Junior Faculty Research Award (F.G.W.), and Eli Lilly and Company for a Granteeship (F.G.W.).

Supplementary Material Available: Experimental procedures and physical data for **6**, **8a**,**b**, **9**–**11**, and **1b** and ^{19}F NMR spectrum of the MTPA ester of **1b** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) Significant catalyst effects on both carbenoid and ylide reactivity have been observed in several other instances: West, F. G.; Naidu, B. N.; Tester, R. W. Submitted for publication.

(11) *A priori*, one might expect higher levels of retention using Rh(II) catalysis, since the lower temperature might reduce the likelihood of biradical randomization. Surprisingly, the major quinolizidine **8b** was formed in only 40-55% ee in $Rh_2(OAc)_4$-catalyzed reactions. Analysis of minor diastereomer **8a** was difficult, as it could not be obtained free of **8b**. However, crude measurements indicate that its optical purity was highly variable (0–40% ee).

(12) For a related example involving diastereoselective quaternization of 2-vinylpiperidines, see Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831. See also: *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992.

(13) (a) Porter, N. A.; Arnett, E. M.; Brittain, W. J.; Johnson, E. A.; Krebs, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 1014. (b) Porter, N. A.; Krebs, P. J. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1988; Vol. 18. (c) In contrast to the results described here, previously reported *acyclic* ammonium ylides bearing chiral migrating groups gave a 1:1 ratio of diastereomeric [1,2]-shift products.[2e]

(14) (a) Georgian, V.; Harrisson, R.; Gubisch, N. *J. Am. Chem. Soc.* **1959**, *81*, 5834. (b) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatenkencherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 478.

(15) (a) $[\alpha]^{22}_D = -24.09°$ (*c* 0.22, EtOH) [lit.[7c] $[\alpha]^{22}_D = +32.0°$ (*c* 0.86, EtOH)]. (b) Compound **1b** was treated with excess Et_3N and 1.0 equiv of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride to furnish the corresponding diasteremeric esters, whose ratio was determined via integration of the CF_3 singlets in the ^{19}F NMR spectrum.