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A Short, Enantioselective Synthesis of (-)-Epilupinine from Proline via a Spirocyclic Ammonium Ylide

B. N. Naidu[1] and F. G. West*

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

Abstract: Diazoketone **5b**, available in one step from proline benzyl ester, underwent conversion to quinolizidine **8b** with high diastereoselectivity (19:1 **8b/7b**) and in surprisingly high enantiomeric excess (75%). The key step presumably occurs via spirocyclic ylide **6b**, which undergoes [1,2]-shift with retention. Rearrangement product **8b** was converted to (-)-epilupinine **2** via an efficient, 3-step sequence.
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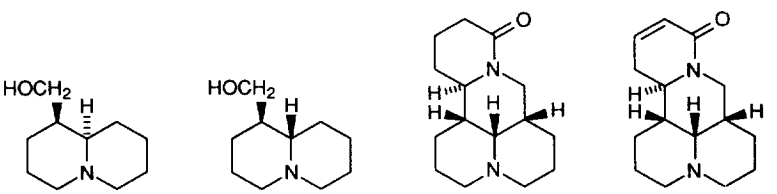
The quinolizidine skeleton is frequently encountered in nature, particularly among the lupin alkaloids.[2] Members of this class range in structural complexity from the relatively simple natural products lupinine (**1**) and epilupinine (**2**) to more elaborate substances, such as matrine (**3**) and sophocarpine (**4**) (Fig. 1). The latter compounds are of particular interest, given the range of their biological activity.[3] A considerable body of work exists concerning the synthesis of quinolizidines, with most of it centered on the prototypical examples **1** and **2**.[4] Reported here is a complete account of our route to **2**, employing a diastereo- and enantioselective rearrangement of a proline-derived ammonium ylide.[5]



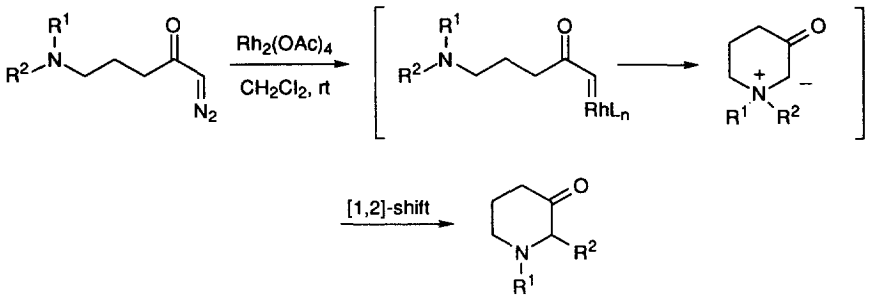
(-)-**1** (-)-**2** **3** **4**

Figure 1. Representative lupin alkaloids.

Our interest in targets containing the quinolizidine nucleus arose from prior studies involving the rearrangement chemistry of ammonium ylides. We have shown that acyclic[6] and cyclic[7] ammonium ylides, generated from metal carbenoids and tertiary amines, can furnish a variety of useful intermediates via [1,2]-shift (Stevens rearrangement) of one of the nitrogen substituents of the intermediate ylide. In particular, 2-substituted piperidine-3-ones could be prepared in high yield from acyclic 5-dialkylamino-1-diazopentan-2-one precursors and catalytic rhodium(II) acetate (Scheme 1).[7a,8]

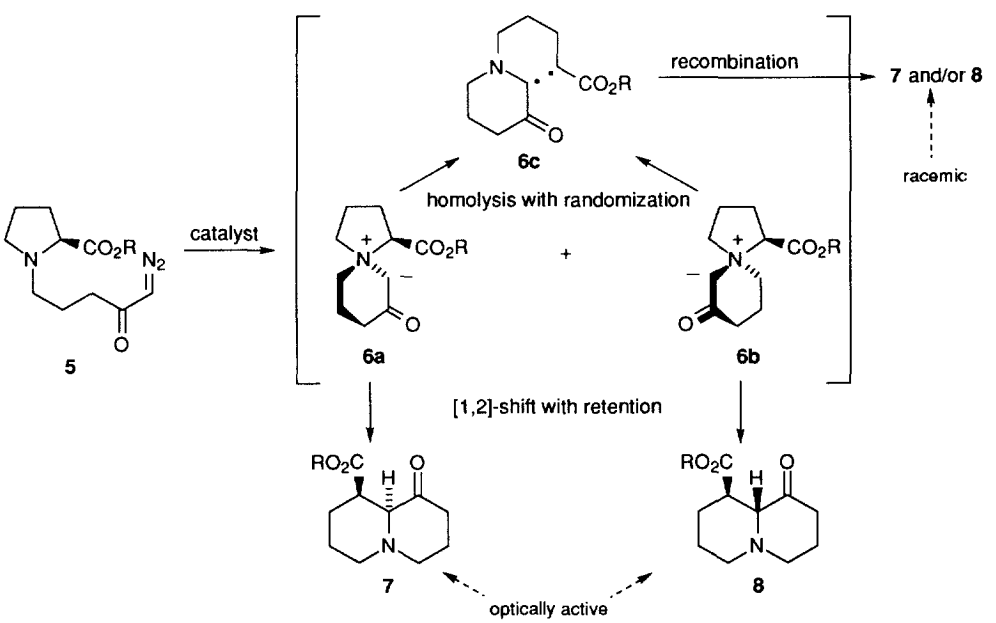
The notion of using a chiral migrating group derived from a readily available amino acid in this process was intriguing. Prior studies provided some evidence that significant levels of stereochemical retention could be realized in [1,2]-shifts of ammonium[9] or oxonium[10] ylides. Moreover, an amino acid derived ester substituent would likely offer sufficient stabilization to permit efficient rearrangement.[11] While probing the issue of retention during migration of an optically pure migrating group, we hoped to explore relative stereocontrol as well. Proline esters (**5**) were attractive in this regard, as the two possible diastereomeric [1,2]-shift products **7** and **8** correspond to the lupinine or the epilupinine stereochemistry, respectively (Scheme 2). Diastereoselectivity in this transformation could arise in one of two possible ways. Carbenoid addition to the proline nitrogen may occur from the opposite face as the ester group, or from the same face, leading to diastereomeric spirocyclic ylides **6a** and **6b**. If this process were stereoselective, and if **6a** and **6b** each

Scheme 1

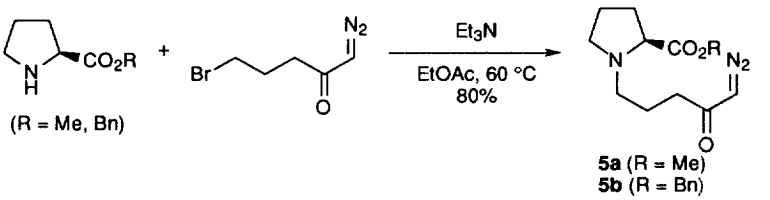


underwent [1,2]-shift with retention, the initial ratio of ylides would be reflected in the ratio of **7** and **8**. Alternatively, randomization could occur via a biradical intermediate. Considerable mechanistic evidence exists for the intermediacy of radical pairs during Stevens [1,2]-shifts of ammonium ylides.[7a,9,12] If bond rotation were faster than radical recombination, achiral biradical **6c** could intervene. Any diastereoselectivity in the formation of **7** and **8** would then result from a preferred orientation of the reacting radical centers, and the initial ratio of **6a** and **6b** would be moot. An important distinction between these two pathways can be found in their enantioselectivity. While rearrangement of **6a** and **6b** with retention should furnish optically pure **7** and **8**, reaction via achiral **6c** should lead to racemic **7** and **8**. Thus, the optical purity of the product quinolizidines offered a convenient mechanistic probe.

Scheme 2



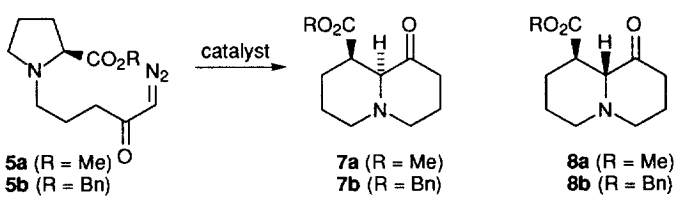
Substrates **5a** and **5b** could be efficiently prepared in one step from 5-bromo-1-diazo-2-pentanone[7a] and L-proline methyl ester or L-proline benzyl ester in the presence of triethylamine (eq 1). Although excess proline ester was required in this process, its recovery after the reaction was possible.[13] A more serious concern was the possibility of racemization during the N-alkylation step. In the case of methyl ester **5a**, ^{1}H NMR analysis (methyl ester singlet) using the chiral shift reagent Eu(hfc)$_3$ indicated no racemization. A comparable study with **5b** could not be carried out, due to the lack of easily resolved signals. However, given its close structural analogy to **5a**, it was presumed to be formed without racemization as well.



(1)

Several catalysts were examined for effecting the key ylide formation/[1,2]-shift step (Table). As with simple 5-amino diazoketones, Rh$_2$(OAc)$_4$ furnished [1,2]-shift products **7** and **8** in good yield for both **5a** and **5b** (entries 1 and 4).[7a] Unfortunately, the diastereoselectivity was only modest (89:11 and 75:25, respectively). The identity of the two diastereomers was not readily apparent, and it was determined that conversion to either lupinine or epilupinine would resolve this question. Since copper-based catalysts had been shown to be especially effective for carbenoid generation in the presence of basic amines,[6,7b-d] both copper powder and copper(II) acetylacetonate were also examined. With methyl ester **5a**, little effect was seen from the catalyst change (entries 2 and 3). In contrast, both the overall yield and the diastereoselectivity were substantially increased for benzyl ester **5b** (entries 5-7), with the best results (84%, 19:1) obtained using Cu(acac)$_2$.

Table. Effect of Catalyst on Rearrangement of Diazoketones 5a and 5b.



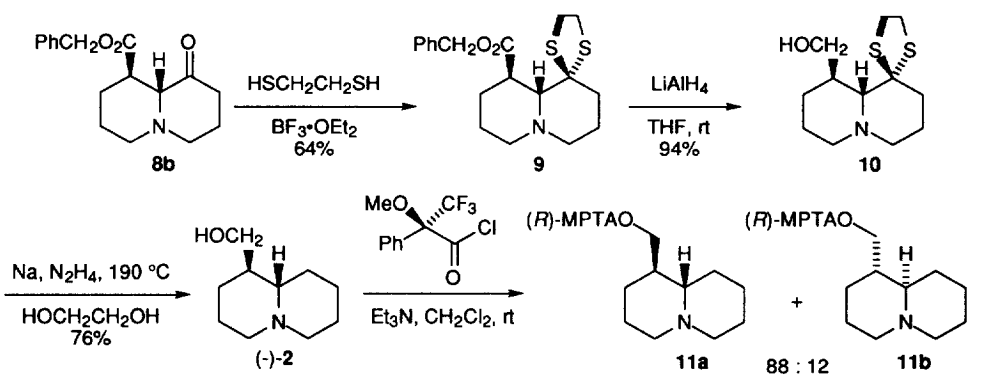
Entry	Substrate	Catalyst (mol%)/solvent/Temp	Chemical Yield (%)	Diastereoselectivity (**7**:**8**)
1	**5a**	Rh$_2$(OAc)$_4$ (3)/CH$_2$Cl$_2$/rt	76	11:89
2	**5a**	Cu(acac)$_2$ (5)/PhCH$_3$/reflux	82	16:84
3	**5a**	Cu powder (50) /PhCH$_3$/reflux	83	18:82
4	**5b**	Rh$_2$(OAc)$_4$ (3)/CH$_2$Cl$_2$/rt	74	25:75
5	**5b**	Cu(acac)$_2$ (5)/PhCH$_3$/reflux	84	5:95
6	**5b**	Cu powder (50) /PhCH$_3$/reflux	87	6:94
7	**5b**	Cu powder (15) /PhCH$_3$/reflux	87	7:93

With high levels of diastereoselectivity realized for the benzyl ester, we now sought to determine to what extent the [1,2]-shift had occurred with retention. Proton NMR analysis of the major product via chiral shift

reagents proved difficult for the same reasons seen with **5b**. Nonetheless, with the acidic shift reagent BNPPA a qualitative assessment could be made by examining the partially resolved benzylic protons. For the major product **8b** obtained under the optimal conditions (entry 5), an enantiomeric excess in the range of 65-75% was measured. Surprisingly, **8b** was obtained in only 40-55% ee under the $Rh_2(OAc)_4$ conditions (entry 4). One might have, *a priori*, expected a higher degree of retention under these conditions, since the reaction was carried out at a lower temperature. The enantiomeric excess of the minor product **7b** was difficult to determine, since it could not be obtained entirely free of **8b**. However, crude measurements indicated that its optical purity was highly variable.

To identify the relative stereochemistry of the major quinolizidine isomer, as well as obtain a more reliable value for its optical purity, we now wished to convert **8b** to either **1** or **2**. This would require reduction of both the ketone (to methylene) and the benzyl ester (to primary alcohol). Direct reduction of the ketone was problematic, leading mainly to inseparable mixtures of partially reduced products. Instead, we opted to proceed through the dithioketal **9**, which could be prepared in good yield via $HSCH_2CH_2SH/BF_3{\cdot}OEt_2$ (Scheme 3).[14] Reduction to primary alcohol **10** with $LiAlH_4$ proceeded without incident; however, both **10** and **9** proved resistant to standard desulfurization procedures, such as RaNi[14] or $Bu_3SnH/AIBN$.[15] Ultimately, we found that treatment of **10** with hydrazine and Na^0 in hot ethylene glycol[16] led to clean desulfurization to give (-)-epilupinine **2** in good yield.[17] Analysis of **2** by optical rotation, and its MPTA esters **11a/11b** by ^{19}F NMR spectroscopy, showed that it was formed in 75-76% ee. This constitutes a concise and efficient synthesis of epilupinine in five steps from proline benzyl ester.

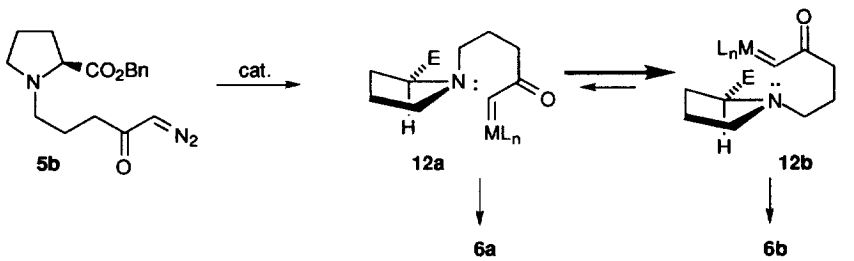
Scheme 3



It is interesting to note that, in contrast to these results, previously described acyclic ammonium ylides bearing chiral migrating groups gave a 1:1 ratio of diastereomeric [1,2]-shift products, albeit often with excellent levels of retention.[9e] The intermediate level of enantiomeric excess obtained in the conversion of **5b** to **8b** suggests that the high diastereoselectivity in favor of **8b** over **7b** must arise from both pathways discussed above (see Scheme 2). The majority of **8b** presumably is formed as a result of selective generation of spirocyclic ylide **6b** in preference to its diastereomer **6a**, followed by migration with retention. However, the 25% of **8b** which is formed as a racemate must occur via achiral biradical **6c**. The stereospecific formation of **8b** from **5b** via **6b** represents an underutilized method for chirality transfer, in which a temporary chiral center at nitrogen ultimately leads to one at carbon via [1,2]-shift. A similar result employing a [2,3]-shift of a N-chiral ammonium ylide been described by Clark and Hodgson in relation to their approach to the Manzamine A ring skeleton.[18]

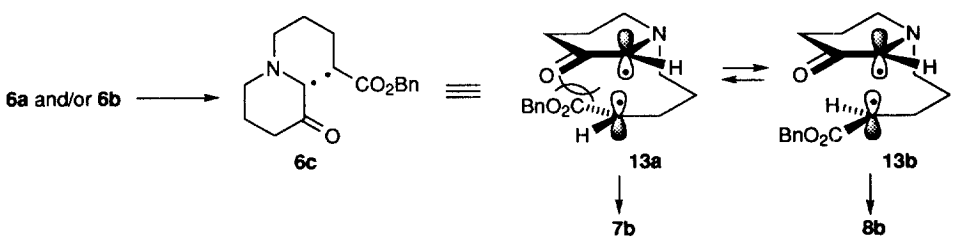
Selective generation of spirocyclic ylide **6b** in preference to its diastereomer **6a** may appear superficially surprising, since it requires approach of the metal carbenoid from the same face of the pyrrolidine ring as the large ester substituent. However, it is reasonable to assume that the pyramidal form in which the ring nitrogen exists dominates over simple steric approach issues with regard to facial selectivity for attack of the carbenoid. The two possible nitrogen pyramidal isomers **12a** and **12b** (Scheme 4) may be envisioned as rapidly interconverting diastereomers, with the available nitrogen lone pair directed either trans or cis to the ester group. Isomer **12b**, in which the vicinal ester and carbenoid side-chain are trans, should be favored and leads to ylide diastereomer **6b**. A similar observation has been reported in the diastereoselective quaternization of 2-vinylpiperidines.[19]

Scheme 4



As noted above, racemic **8b** presumably derives from the intervention of achiral biradical **6c**, which obtains if the rate of migration is slow relative to bond rotation. Since the amount of racemic **8b** formed far exceeds the total yield of **7b** (both racemic and optically active), recombination of **6c** also appears to be a diastereoselective process.[20] Two reactive rotamers, **13a** and **13b**, can be envisioned (Scheme 5), in which the planar ester-substituted radical approaches the piperidone ring with either the smaller hydrogen or the larger ester under the ring. Rotamer **13b**, which leads to **8b**, minimizes unfavorable steric interactions and should be preferred.

Scheme 5



In summary, we have described a conceptually novel approach to the quinolizidine skeleton via diastereoselective generation of a spirocyclic ammonium ylide. The stereochemical information temporarily resident at nitrogen is largely transferred to the adjacent carbon through [1,2]-shift with retention. To the extent that the intermediate randomizes to an achiral biradical, the recombination process is also diastereoselective, albeit racemic. The utility of this approach was demonstrated by the 5-step conversion of proline benzyl ester to the quinolizidine alkaloid epilupinine. Application of this methodology to other alkaloid targets will be reported elsewhere.

EXPERIMENTAL SECTION

General. Reactions were conducted in oven-dried (120 °C) or flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannula. Solvents were distilled before use: dichloromethane from calcium hydride; toluene from sodium; diethyl ether and tetrahydrofuran from sodium benzophenone ketyl. Thin layer chromatography (TLC) was performed on plates of silica precoated with 0.25 mm Kieselgel 60 F_{254} (Merck). Flash columns were packed with 230-400 mesh silica gel (Merck or Baxter). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 75 MHz and are reported (ppm) relative to the center line of a triplet at 77.0 ppm for deuteriochloroform. Infrared (IR) spectra were measured with a Mattson FT-IR 3000 spectrophotometer. Mass spectra (E.I. @ 70 eV) were determined on a VG Micromass 7050E mass spectrometer equipped with a VG 2000 Data system. Combustion analyses were performed by Atlantic Microlabs, Norcross, GA.

Diazoketone 5a. A mixture of proline methyl ester (1.04 g, 8.0 mmol), Et_3N (0.28 mL, 2.0 mmol) and 5-bromo-1-diazo-2-pentanone (0.382 g, 2.0 mmol) in EtOAc (8.0 mL) was stirred overnight at 60 °C. The reaction mixture was then transferred to a separatory funnel along with 100 mL of EtOAc, and washed with saturated $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, filtered and concentrated to give a yellow liquid. Flash column chromatography (silica gel, 3.5-cm x 24-cm column, 1:1 followed by 7:3 EtOAc/hexanes, EtOAc and 1:19 MeOH/EtOAc) provided 0.362 g (76%) of **5a** as a yellow oil: $[\alpha]^{22}_D$ = -61.5 ° (c 0.5, $CHCl_3$); R_f 0.11 (EtOAc); IR (neat) 2953, 2103, 1738, 1642, 1373, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.33 (s, 1H), 3.71 (s, 3H), 3.19-3.14 (m, 1H), 3.16 (dd, 1H, *J* = 8.9, 5.8 Hz), 2.69 (dt, 1H, *J* = 11.9, 7.7 Hz), 2.42 (m, 3H), 2.32 (dd, 1H, *J* = 16.7, 8.1 Hz), 2.17-2.03 (m, 1H), 1.98-1.86 (m, 3H), 1.81 (quintet, 2H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.7, 174.5, 65.9, 54.2, 54.0, 53.1, 51.6, 38.4, 29.2, 23.9, 23.1. Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.03; H, 7.19; N, 17.64. Found: C, 55.11; H, 7.20; N, 17.36.

Determination of optical purity using Eu(hfc)$_3$. About 10 mg of the diazo ketone **5a** was dissolved in 0.5 mL of $CDCl_3$ and its ^{1}H NMR spectrum was taken. To this solution was added 0.05 equiv of a solution of $Eu(hfc)_3$ in $CDCl_3$. The sample was shaken well and its ^{1}H NMR was recorded. This process was repeated, each time adding 0.05 equiv of $Eu(hfc)_3$ solution, until the baseline resolution was obtained. Careful integration of the methyl ester singlets indicated no racemization within the limits of detection.

Diazoketone 5b. Treatment of proline benzyl ester (2.05 g, 10.0 mmol) with 5-bromo-1-diazo-2-pentanone (0.478 g, 2.5 mmol) according to the above procedure gave a yellow liquid. Flash column chromatography (silica gel, 3.5-cm x 24-cm column, 2:3 EtOAc/hexanes followed by 1:1 and 3:2 EtOAc/hexanes) provided 0.628 g (80%) of **5b** as a yellow oil: $[\alpha]^{22}_D$ = -38.2 ° (c 0.59, $CHCl_3$); R_f 0.10 (1:1 EtOAc/hexanes); IR (neat) 2955, 2101, 1738, 1642, 1373, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.30 (m, 5H), 5.20 (s, 1H), 5.16 (d, 1H, J_{AB} = 12.3 Hz), 5.13 (d, 1H, J_{AB} = 12.3 Hz), 3.20 (dd, 1H, *J* = 8.8, 5.7 Hz), 3.13 (dd, 1H, *J* = 7.7, 3.1, Hz), 2.67 (dt, 1H, *J* = 11.9, 7.6 Hz), 2.47-2.26 (m, 4H), 2.17-2.03 (m, 1H), 1.98-1.84 (m, 3H), 1.78 (quintet, 2H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.8, 174.0, 135.9, 128.4, 128.1, 128.0, 66.2, 65.9, 54.2, 54.0, 53.2, 38.5, 29.3, 24.1, 23.3. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.75; H, 6.71; N, 13.32. Found: C, 64.68; H, 6.76; N, 13.16.

Ketoesters 7a and 8a. *Method A.* To a stirred solution (degassed) of $Rh_2(OAc)_4$ (13.3 mg, 3 mol%) in 70 mL of dry CH_2Cl_2 was added dropwise a solution (degassed) of **5a** (0.238 g, 1.0 mmol) in 20 mL of dry CH_2Cl_2 over 20 min, then the addition flask was rinsed with 10 mL of dry CH_2Cl_2 and added to the reaction mixture. After stirring for an additional 30 min, the reaction mixture was transferred to a separatory funnel, washed with brine (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give a yellow liquid. Flash column chromatography (silica gel, 3.5-cm x 15-cm column, 2:3 EtOAc/hexanes followed by EtOAc)

provided 0.160 g (76%) of **7a/8a** as a colorless oil that proved to be a 11:89 mixture of diastereomers by ^{1}H NMR analysis of the integration of methyl ester singlets.

Method B. To a refluxing solution (degassed) of $Cu(acac)_2$ (13.1 mg, 5 mol%) in 70 mL of dry toluene was added dropwise a solution (degassed) of **5a** (0.238 g, 1.0 mmol) in 20 mL of dry toluene over 45 min, then the addition flask was rinsed with 10 mL of dry toluene and added to the reaction mixture. After stirring for an additional 30 min at reflux, the reaction mixture was cooled, concentrated and purified to provide 0.173 g (82%) of **7a/8a** as a colorless oil that proved to be a 16:84 mixture of diastereomers by ^{1}H NMR analysis of the integration of methyl ester singlets.

Method C. A mixture of **5a** (0.238 g, 1.0 mmol) and Cu powder (32 mg, 50 mol%) in 50 mL of dry toluene (degassed) was stirred at reflux for 2.5 h, cooled, concentrated and purified to provide 0.175 g (83%) of **7a/8a** as a colorless oil that proved to be a 18:82 mixture of diastereomers by ^{1}H NMR analysis of the integration of methyl ester singlets. (A clean ^{1}H NMR spectrum for **7a** could not be obtained.)

7a: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.1, 172.6, 71.5, 56.0, 55.0, 53.3, 41.4, 37.8, 26.1, 22.9, 22.0.

8a: R_f 0.20 (EtOAc); IR (neat) 2947, 1726, 1439, 1323, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3H), 2.96 (dt, 1H, J = 11.9, 4.2 Hz), 2.91 (d, 1H, J = 10.2 Hz), 2.59-2.32 (m, 5H), 2.23 (td, 1H, J = 11.5, 3.0 Hz), 2.09-1.85 (m, 3H), 1.75-1.51 (m, 2H), 1.40 (qd, 1H, J = 12.6, 4.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.3, 175.1, 71.2, 56.0, 55.0, 51.6, 42.1, 39.5, 28.1, 24.8, 24.2; HRMS calcd for $C_{11}H_{17}NO_3$ *m/e* 211.1208, found *m/e* 211.1210.

Ketoesters 7b and 8b. *Method A*. Treatment of **5b** (0.315 g, 1.0 mmol) with $Rh_2(OAc)_4$ (13.3 mg, 3 mol%) in CH_2Cl_2 according to method A and purification by flash column chromatography (silica gel, 3.5-cm x 15-cm column, 2:3 EtOAc/hexanes followed by 1:1 and 3:2 EtOAc/hexanes) provided 0.213 g (74%) **7b/8b** as a colorless oil that proved to be a 25:75 mixture of diastereomers by ^{1}H NMR analysis of the integration of benzyl ester singlets.

Method B. Treatment of **5b** (0.315 g, 1.0 mmol) with $Cu(acac)_2$ (13.1 mg, 5 mol%) in toluene according to method B and purification provided 0.242 g (84%) of **7b/8b** as a colorless oil that proved to be a 5:95 mixture of diastereomers by ^{1}H NMR analysis of the integration of benzyl ester singlets.

Method C. Treatment of **5b** (0.315 g, 1.0 mmol) with Cu powder (32 mg, 50 mol%) in toluene according to method C and purification provided 0.236 g (82%) of **7b/8b** as a colorless oil that proved to be a 6:94 mixture of diastereomers by ^{1}H NMR analysis of the integration of benzyl ester singlets.

Method D. A mixture of **5b** (0.315 g, 1.0 mmol) and Cu powder (9.5 mg, 15 mol%) in 10 mL of dry toluene (degassed) was stirred at reflux for 1 h, cooled, concentrated and purified to provide 0.232 g (81%) of **7b/8b** as a colorless oil that proved to be a 7:93 mixture of diastereomers by ^{1}H NMR analysis of the integration of benzyl ester singlets.

7b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.28 (m, 5H), 5.11 (d, 1H, J_{AB} = 12.2 Hz), 5.04 (d, 1H, J_{AB} = 12.2 Hz), 3.16 (ddd, 1H, J = 13.2, 9.8, 3.3 Hz), 3.05-2.96 (m, 1H), 2.93-2.75 (m, 3H), 2.83 (d, 1H, J = 10.3), 2.36 (ddd, 1H, J = 16.2, 9.6, 6.5 Hz), 2.36 (dtd, 1H, J = 13.4, 5.8, 1.0 Hz), 2.27-2.07 (m, 2H), 2.00-1.89 (m, 1H), 1.85-1.67 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.6, 170.4, 135.6, 128.4, 128.2, 128.1, 66.5, 52.2, 45.9, 41.4, 36.9, 32.5, 29.7, 23.4, 21.6.

8b: $[\alpha]^{22}_D$= -34.1 ° (c 0.29, $CHCl_3$); R_f 0.14 (1:1 EtOAc/hexanes); IR (neat) 2944, 1726, 1321, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.26 (m, 5H), 5.13 (s, 2H), 2.97-2.92 (m, 2H), 2.95 (d, 1H, J = 9.7 Hz), 2.66-2.31 (m, 4H), 2.21 (td, 1H, J = 11.6, 3.1 Hz), 2.10-1.80 (m, 3H), 1.73-1.62 (m, 1H), 1.56 (tt, 1H, J = 12.6, 3.6 Hz), 1.40 (qd, 1H, J = 12.5, 4.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.3, 174.6, 136.1, 128.4, 127.9, 128.3, 71.2, 66.1, 56.1, 55.1, 42.2, 39.6, 28.2, 24.9, 24.6; HRMS calcd for $C_{17}H_{21}NO_3$ *m/e* 203.1158, found *m/e* 203.1158.

Determination of optical purity using BNPPA. About 10 mg of **8b** was dissolved in 0.5 mL of $CDCl_3$ and its ^{1}H NMR spectrum was taken. To this solution was added 0.5 equiv of (*R*)-(-)-1,1'-binaphthyl-2,2'-

diylphosphoric acid ((*R*)-(-)-BNPPA), the sample was shaken well and its ^{1}H NMR spectrum was recorded. Careful integration of the partially resolved benzyl ester protons furnished an approximate ratio of enantiomers.

Dithiolane 9. To a stirred solution of **8b** (0.287 g, 1.0 mmol) in 1 mL of 1,2-ethanedithiol was added 1 mL of BF_3•Et_2O and the resulting mixture was stirred for 48 h at rt. The reaction mixture was then poured into an ice cold saturated $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (5 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated to give a yellow liquid. Flash column chromatography (silica gel, 3.5-cm x 15-cm column, 1:9 EtOAc/hexanes followed by 1:3 EtOAc/hexanes) provided 0.232 g (64%) of **9** as a colorless syrup: R_f 0.13 (15:85 EtOAc/hexanes); IR (neat) 2940, 1726, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.26 (m, 5H), 5.14 (d, 1H, J_{AB} = 12.3 Hz), 5.00 (d, 1H, J_{AB} = 12.2 Hz), 3.18-2.98 (m, 5H), 2.85-2.78 (m, 2H), 2.74 (d, 1H, J = 9.8 Hz), 2.34-1.89 (m, 6H), 1.64-1.51 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6, 135.8, 128.5, 128.3, 128.0, 72.7, 69.8, 66.3, 56.7, 55.8, 44.7, 44.5, 39.7, 37.5, 30.1, 25.0, 23.8. Anal. Calcd for $C_{19}H_{25}NO_2S_2$: C, 62.77; H, 6.93; N, 3.85. Found: C, 62.66; H, 6.87; N, 3.78.

Alcohol 10. To a stirred solution of **9** (0.364 g, 1.0 mmol) in THF (10 mL) at 0 °C was added $LiAlH_4$ (0.042 g, 1.1 mmol) and the resulting mixture was stirred for 3 h at rt. The reaction mixture was then diluted with 100 mL of Et_2O, carefully quenched with 15% aq NaOH (1.0 mL) and H_2O (1.0 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give a yellow oil. Flash column chromatography (silica gel, 3.5-cm x 15-cm column, 1:1 EtOAc/hexanes followed by 3:2, 7:3 and 4:1 EtOAc/hexanes) provided 0.244 g (94%) of **10** as a crystalline white solid: $[\alpha]^{22}_D$ = -9.0 ° (c 0.20, $CHCl_3$); mp 131-133 °C (recrystallized from hexanes/Et_2O/CH_2Cl_2); R_f 0.14 (1:1 EtOAc/hexanes); IR (KBr) 3387, 2922, 1431, 1281, 1119, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.73 (dd, 1H, J = 10.7, 6.1 Hz), 3.58 (dd, 1H, J = 10.6, 7.0 Hz), 3.40-3.12 (m, 4H), 2.83-2.74 (m, 2H), 2.28 (s, 1H), 2.24-1.47 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.1, 70.0, 66.4, 56.0, 52.3, 44.6, 39.1, 38.6, 38.0, 24.9, 21.9, 19.7. Anal. Calcd for $C_{12}H_{21}NOS_2$: C, 55.56; H, 8.16; N, 5.40. Found: C, 55.37; H, 8.21; N, 5.30.

(-)-Epilupinine 2. A mixture of **10** (0.156 g, 0.60 mmol), 1.2 mL of anhydrous hydrazine, and a solution of 23 mg of Na in 6 mL of ethylene glycol was heated at 190-195 °C for 16 h under an atmosphere of N_2. The reaction mixture was then cooled, diluted with 25 mL of H_2O, and extracted with CH_2Cl_2 (5 x 25 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated to give a yellow liquid. Flash column chromatography (silica gel, 3.5-cm x 10-cm column, 1:9 MeOH/EtOAc followed by 1:3 MeOH/EtOAc) provided 0.077 g (76%) of (-)-**2** as a crystalline white solid whose spectral properties were identical with those previously reported:[21] $[\alpha]^{22}_D$ = -24.09 ° (c 0.22, EtOH) [Lit.[20] $[\alpha]^{22}_D$ = +32.0° (c 0.86, EtOH)]; mp 79-80 °C (recrystallized from hexanes/Et_2O) [Lit.[20] 78-79 °C]; R_f 0.14 (1:3, MeOH/EtOAc); IR (KBr) 3335, 3169, 2944, 2859, 1448, 1364, 1066, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64 (dd, 1H, J = 10.8, 3.6 Hz), 3.57 (dd, 1H, J = 10.9, 5.5 Hz), 2.92 (t, 2H, J = 12.5 Hz), 2.16 (tdd, 2H, J = 11.7, 3.6, 2.1 Hz), 1.99-1.24 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.6, 63.7, 56.6, 56.3, 43.2, 29.0, 27.8, 24.9, 24.4, 24.1; HRMS calcd for $C_{10}H_{19}NO$ *m/e* 169.1467, found *m/e* 169.1458.

Determination of optical purity of 2 via MPTA ester. To a solution of about 25 mg of **2** in 10 mL of CH_2Cl_2 was added excess Et_3N and 1.0 equiv of (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride. The reaction mixture was stirred over night at room temperature and concentrated under reduced pressure. Then the resulting slurry was taken up into 25 mL of ethyl ether, and washed with saturated $NaHCO_3$ (2 x 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give pale yellow oil which was passed through a plug of silica gel. The filtrate was concentrated under reduced pressure to give an inseparable mixture of **11a** and **11b** as a colorless oil whose ^{19}F NMR was recorded, and the ratio of the integrals for the CF_3 singlets was measured as 88:12.

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