AN APPROACH TO OPTICALLY ACTIVE PYRROLIZIDINES BY AN INTRAMOLECULAR MICHAEL REACTION

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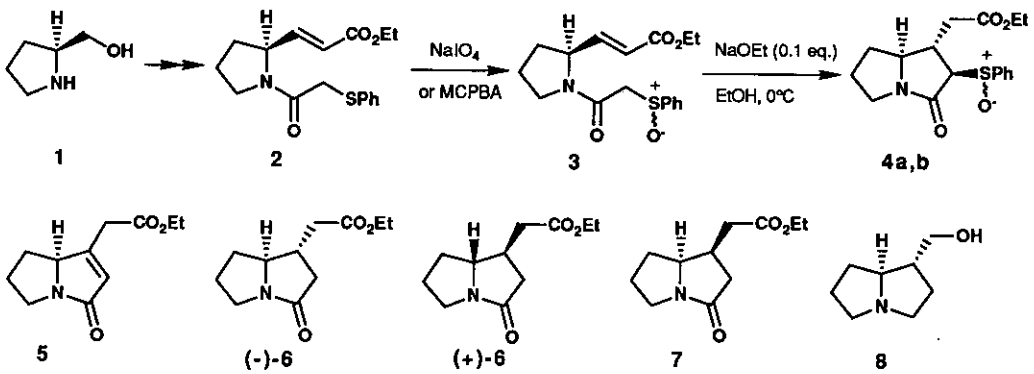
Abstract——Treatment of a diastereomeric mixture (5:3) of the α-phenylsulfinylacetamide (**3**) with a catalytic amount of sodium ethoxide in ethanol at 0°C for 10 min gave the bicyclic lactams (**4a**) and (**4b**) in high total yield but with extensive racemization. The cyclization of the diastereomerically pure sulfoxide (**3**) followed by chromatographic separation of the resulting lactams (**4a**) and (**4b**) and desulfurization of each lactam gave (1*S*,8*S*)-(-)- and (1*R*,8*R*)-(+)-ethyl hexahydro-3-oxo-3*H*-pyrrolizin-1-ylacetates (**6**), respectively. The (-)-isomer of **6** has already been transformed into (-)-trachelanthamidine (**8**).

Pyrrolizidine alkaloids have still attracted the attention of synthetic organic chemists because of a wide variety of biological activities.[1] In connection with our interests in this area,[2] we reported several approaches to the optically active pyrrolizidines starting from L-prolinol.[2c-f] We have now examined an intramolecular Michael reaction of the suitably functionalized α-phenylsulfinylacetamide (**3**), in the hope that a new route to the optically active pyrrolizidines might result. In this paper we describe some aspects of this reaction.

The starting sulfoxide (**3**) was prepared as a *ca.* 5:3 mixture of two diastereomers by oxidation of the α-phenylthioacetamide (**2**),[2e] which was in turn synthesized in three steps from L-prolinol (**1**). The isomeric ratios of the sulfoxide (**3**) were not affected by the nature of the oxidizing agents and reaction conditions used (sodium metaperiodate in aqueous acetone at room temperature and *m*-chloroperbenzoic acid in dichloromethane at 0°C).

Cyclization was effected by treatment of the sulfoxide (**3**) with sodium ethoxide (0.1 eq.) in ethanol at 0°C for 10 min to give a crude mixture of the bicyclic lactams (**4**).[3] Column chromatography of the crude material on silica

gel followed by one recrystallization from hexane and ethyl acetate gave a less polar product (**4a**)(41%), mp 127-128°C, and a polar product (**4b**)(34%), mp 114-115°C. Heating each isomer (**4a**) and (**4b**) in boiling toluene in the presence of sodium bicarbonate afforded the same α,β-unsaturated lactam (**5**)[2e] in 96 and 93% yields, respectively. The results indicated that the stereochemical relationship between the ethoxycarbonylmethyl and phenylsulfinyl groups of **4a,b** is trans. Desulfurization of **4a** and **4b** with Raney nickel in ethanol gave the same lactam (**6**)[2e] in 92 and 84% yields, respectively, suggesting that the sulfoxides (**4a**) and (**4b**) differ in the configuration of the S-O bond. In view of the fact that **4a** and **4b** were recovered unchanged upon treatment under the cyclization conditions, this cyclization reaction is considered to be a kinetically controlled process.

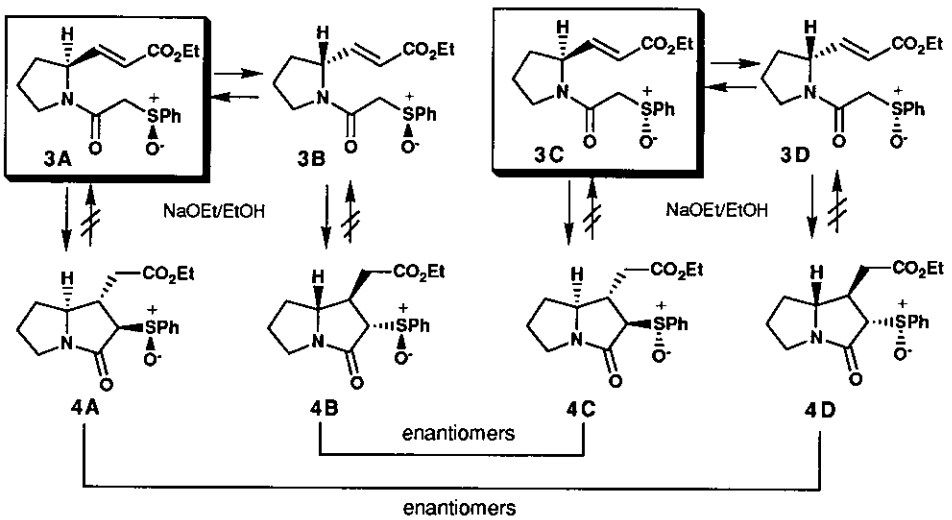


Scheme 1

Surprisingly, the desulfurized lactams (**5**) and (**6**) obtained from the less polar sulfoxide (**4a**) showed almost complete loss of the optical activity ($[\alpha]_D^{24}$ -1.8° (c=1.08, EtOH) for **5** and +0.2° (c=0.66, EtOH) for **6**), and **5** and **6** obtained from the polar sulfoxide (**4b**) showed 60-70% loss of the activity ($[\alpha]_D^{24}$ -9.9° (c=1.05, EtOH) for **5** and -9.8° (c=0.44, EtOH) for **6**)[4]. These results are rationalized in terms of partial epimerization of the α-phenylsulfinylacetamides (**3**) at the C-2 position prior to cyclization, which produces the four possible stereoisomers (**3A**)-(**3D**). Subsequent cyclization of each stereoisomer gives the four isomeric lactams (**4A**)-(**4D**) which are two pairs of enantiomers as shown in Scheme 2.

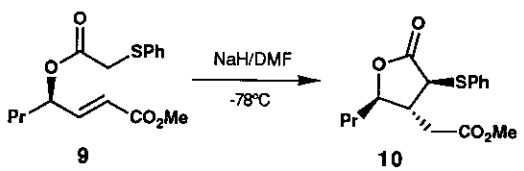
In order to prove this view, the diastereomeric sulfoxides (**3**) were separated by preparative tlc on silica gel (hexane-ethyl acetate, 2:1) but with difficulty. Only the major isomer of the two sulfoxides (**3**) was obtained as a pure compound.[5] Cyclization of this sulfoxide (**3**) gave a diastereomeric mixture of the lactams (**4**), which was

readily separated by chromatography on silica gel to give **4a** (42%), mp 119-121°C, and **4b** (39%), mp 123-124°C. Each isomer was then separately desulfurized with Raney nickel in ethanol to give each optical isomer (-)-(**6**), $[\alpha]_D^{24}$ -32° (c=0.44, EtOH), and (+)-(**6**), $[\alpha]_D^{24}$+30° (c=0.5, EtOH). The lactam (-)-(**6**) has already been transformed into (-)-trachelanthamidine (**8**) in four steps.[2e]



Scheme 2

In summary, the described procedure provides an efficient route to the hexahydro-3*H*-pyrrolizin-3-ones (**4**) but with extensive racemization. This is in contrast to the behavior of the ester (**9**) which has been reported to undergo a base-catalyzed Michael reaction to give the lactone (**10**) without racemization.[6] We found, however, that the internal chiral sulfinyl group can serve as a removable resolving agent and both the enantiomers of the lactam (**6**) are obtained from the single enantiomer of prolinol by a combination of the cyclization of **3**, chromatographic separation of the resulting diastereomeric lactams (**4a,b**), and desulfurization. For the practical purpose, however, it is desirable to improve the stereoselectivity of the oxidation of **2**.



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2. a) H. Ishibashi, K. Sato, K. Maruyama, M. Ikeda, and Y. Tamura, *Chem. Pharm. Bull.*, 1985, **33**, 4593; b) M. Ikeda, S. Harada, A. Yamasaki, K. Kinouchi, and H. Ishibashi, *Heterocycles*, 1988, **27**, 943; c) H. Ishibashi, H. Ozeki, and M. Ikeda, *J. Chem. Soc., Chem. Commun.*, 1986, 654.; d) H. Ishibashi, T. Sato, M. Irie, S. Harada, and M. Ikeda, *Chem. Lett.*, 1987, 795; e) T. Sato, K. Tsujimoto, K. Matsubayashi, H. Ishibashi, and M. Ikeda, *Chem. Pharm. Bull.*, 1992, **40**, 2308; f) H. Ishibashi, N. Uemura, H. Nakatani, M. Okazaki, T. Sato, N. Nakamura, and M. Ikeda, *J. Org. Chem.*, in press.
3. Desulfurization of the crude cyclized products (**4**) with Raney nickel in ethanol gave **6** and its diastereomer (**7**) in a ratio of *ca.* 3:1 (ratio determined by the glc analysis as well as the ^{1}H and ^{13}C nmr spectroscopy).
4. These are based on the optical rotations of **5** and **6** obtained by a radical cyclization route ($[\alpha]_D$ -23.5° for **5** and -35.8° for **6**).[2e]
5. Attempts to determine the absolute stereochemistry of the sulfoxides (**3**) and (**4**), including an X-ray analysis, were unsuccessful, so that the stereostructures of **3A-D** and **4A-D** shown in Scheme 2 are arbitrary.
6. C. M. Rodriguez and V. S. Martin, *Tetrahedron Lett.*, 1991, **32**, 2165.

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