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An Unexpected Reversal in the Stereochemistry of Transannular Cyclizations. A Stereoselective Synthesis of (±)–Epilupinine.

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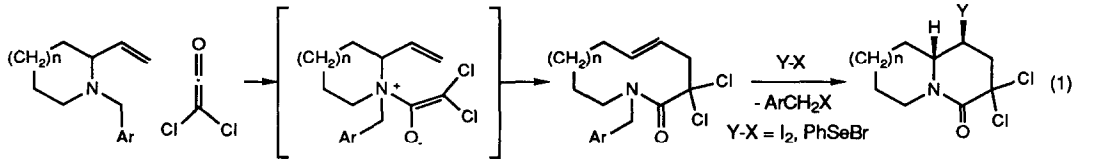
Key Words: Transannualar Cyclizations; Quinolizidine and Indolizidine synthesis; Epilupinine.

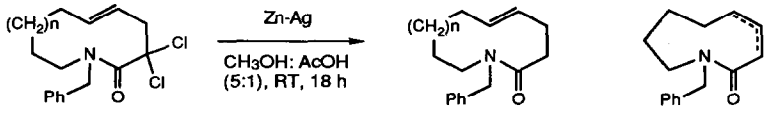
Abstract: *The transannular cyclizations of N–benzylhexahydroazec–5–en–2–one and N–benzylhexahydroazon–5–en–2–one using iodine or phenylselenenyl bromide affords substituted quinolizidines and indolizidines, respectively. In the case of the ten–membered ring lactams an unexpected reversal in stereochemistry was observed. These results were confirmed by elaboration of the iodo cycloadduct* **4a** *into (±)–epilupinine.*

We have recently reported[1] a new strategy for the synthesis of indolizidine and quinolizidine ring systems involving a zwitterionic variant of the aza–Claisen rearrangement[2] followed by transannular cyclization[3] from the intermediate macrocyclic lactams (eq 1). It was shown that these transannular cyclization events proceeded with complete regio– and stereocontrol in systems having geminal dichloride substituents at C-3. Thus, a net *anti*–addition across the *E*–double bond afforded cycloadducts having either an equatorial iodo- or phenylseleno-substituent. In the present study transannualar cyclizations of the unsubstituted macrocyclic lactams **2a,b** were explored in order to further define the stereochemical aspects of this process and to demonstrate the utility of our methodology in synthesis.



(1)

The requisite macrocyclic lactams **2a,b**[4] were obtained from the previously prepared dichloro adducts **1a,b** by reductive dechlorination using Zn–Ag alloy[5] (eq 2). Whereas the ten–membered ring lactam **2b** was readily isolated in 86% yield, the nine–membered compound **2a** was afforded in 45% yield along with 23% of a mixture of the α,β and β,γ double bond isomers **3**.[6]



1a, n = 0
b, n = 1

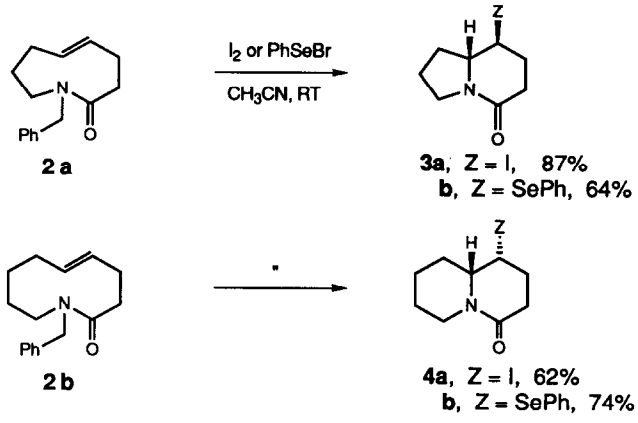
2a, n = 0, 45% +
b, n = 1, 86%

3, 23%

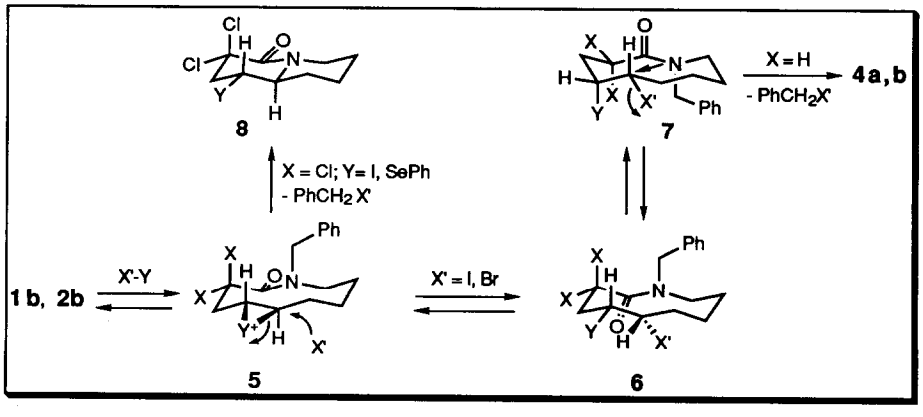
(2)

Transannular cylizations of **2a,b** were carried out in acetonitrile at room temperature for 1–2 h using either 2.0 equivalents of iodine or 1.1 equivalents of phenylselenyl bromide.[7] The resulting cycloadducts were isolated as a single species in generally good yields with complete regio– and stereoselectivity. In the case of the indolizidines

3a,b[4] the iodo– and phenylseleno-substituents were equatorial as indicated by the trans–diaxial coupling observed between the bridgehead and the adjacent methine protons (**3a**, J = 10.4 Hz; **3b**, J = 10.6 Hz). These results are consistent with the anti–addition of the electrophile and the nitrogen lone pair across the E–double bond in precursor **2a**.[8] On the other hand, quinolizidines **4a,b**[4] were found to have axial iodo– or phenylseleno-substituents as suggested by the axial–equatorial coupling detected between the hydrogens at C–5 and C–6 (**4a**, J = 5.9 Hz; **4b**, J = 7.3 Hz).[9] An explanation for the complete reversal in stereochemistry resulting from the transannular cylizations of **1b** versus **2b** is given in Scheme 1 below.

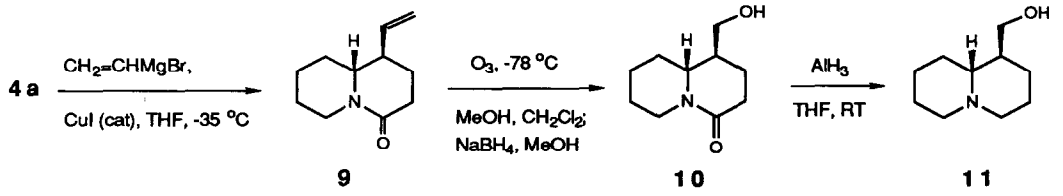


The bridged ion **5**, derived from attack of the electrophilic species X'-Y upon **1b** or **2b**, undergoes two different reaction pathways[10] dependant upon the substitution at C-3 (Scheme 1).[11] In the case of **2b** this species should be sufficiently long lived, due to the sluggish reactivity of the tertiary amide nitrogen, to undergo a reversible attack by the external halide in solution giving adduct **6**.[12] A macrocyclic ring inversion would then provide conformer **7** now having an equatorial like leaving group at C–6 suitably aligned for displacement by the transannular nitrogen which gives rise to the observed stereochemistry in **4a,b**. This conformation would likely be disfavored in the case of **1b** due to 1,3–diaxial type interactions between the axial chlorine substituent at C–3 and the iodo– or phenylseleno group at C–5. Therefore, the bridged ion **5** (X = Cl) derived from **1b** prefers to react directly with the transannular nitrogen affording cycloadduct **8** having an equatorial substituent at C–5.



Scheme 1

Confirmation of the stereochemistry observed in quinolizidine **4a** was provided by its expeditious conversion in the simple lupinus alkaloid (±) –epilupinine (**11**) of known configuration.[13] Thus, copper catalyzed addition of vinylmagnesium bromide to **4a** afforded the substitution adduct **9**[4] in 83% yield with clean inversion of stereochemistry at C-5. The vinyl adduct **9** was reacted with ozone at –78 °C and then directly converted into the alcohol **10** by quenching the cold reaction mixture with methanolic sodium borohydride. The amide function in **10** was then reduced (AlH_3/THF)[14] thus affording **11**[15] in 59% overall yield from **9**.



The stereochemical course of transannular cyclizations involving unsubstituted macrocyclic nine– and ten–membered ring lactams has been determined. In the case of the ten–membered ring systems the stereochemical outcome was dictated by the substitution at C–3. This consequence is of importance in future applications of this methodology for the synthesis of various indolizidine and quinolizidine alkaloids. Efforts to probe the intriguing conformational properties of these unusual medium ring systems using a combination of substituent effects and molecular modeling are currently underway.

Acknowledgements: This work was supported by funds from Utah State University and the Donors of the Petroleum Research Fund Administered by the American Chemical Society.

References and Notes

1. Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 0000.

2. For a related process, see: Baxter, E. W.; Labaree, D.; Ammon, Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 7682. Baxter, Labaree, D.; Chao, S.; Mariano, P. S. *J. Org. Chem.* **1989**, **54**, 2893. Chao, S.; Kunng, F. A.; Mariano, P. S. *ibid*, **1984**, **49**, 2708. Kunng, F. A.; Gu, J. M.; Chao, S.; Chen, Y.; Mariano, P. S. *ibid*, **1983**, *48*, 4262.

3. Transannular Cyclizations of eight and nine membered ring amines and amides has been explored. a) Wilson, S. R.; Sawicki, R. A. *J. Heterocyclic Chem.* **1982**, *19*, 81. b) *ibid. J. Org. Chem.* **1979**, *44*, 287. c) *ibid.* 330. d) Mariano, P. S.; Osborn, M. E.; Dunaway–Mariano, D.; Gunn, B. C.; Pettersen, R. C. *J. Org. Chem.* **1977**, *42*, 2903.

4. All new compounds have been fully characterized by ^1H and ^{13}C NMR, IR, and either elemental analysis or high resolution mass spectroscopy.

5. Heathcock, C. H.; Clark, R. D. *J. Org. Chem.* **1972**, *38*, 3658.

6. Separation of **2b** from **3** could be achieved by careful chromatographic separation using a 50 cm medium pressure column packed with 30-40 μ Davisil silica gel (150 Å pore size) with 10% ethyl acetate/hexanes as the eluant.

7. The cyclization of benzyl protected 5–hexen–2–ol derivatives using iodine has been documented. Rychonovsky, S. D.; Bartlett, P. A. *J. Am. Chem Soc.* **1981**, *103*, 3964. For the amidoselenation of unsaturated amides, see:

Toshimitsu, A.; Tereo, K.; Uemura, S.; *J. Org. Chem.* **1986**, *51*, 1724 and refs cited therein.

8. The structure for the 4-methoxybenzyl analog of **2b** has been unambiguously established by X-ray analysis and reveals an *E*-double bond and a cisoid arrangement about the planer amide bond. Comparison of the ^{1}H and ^{13}C NMR spectra for this compound with that for **2b** confirm that both compounds exist as similar, discrete conformational, species in solution.

9. In contrast, the coupling between the bridgehead and adjacent methine protons in the C-5 equatorial substituted systems, i.e. compounds **8** (Y = I, SePh), reveals coupling constants of 9.9 and 10.2 Hz, respectively.

10. Bromine-induced intramolecular cyclization reactions can proceed via two possible mechanistic pathways, i.e. formation of a bromonium ion followed by ring closure or initial formation of a dibromide, which then cyclizes. Staninets, V. I.; Shilow, E. A. *Russ. Chem. Rev.* **1971**, *40*, 272.

11. In this scheme we have drawn the macrocyclic precursors having a transoid amide bond in an extended chair-chair type arrangement. This is likely the predominate low energy conformation for **1b** and **2b** at room temperature. The ^{1}H and ^{13}C NMR spectra for macrocyles **1b** and **2b** reveal the presence of two species (2.6:1 ratio for **1b**) which coalesce at 100 °C. The most reasonable explanation would invoke a *cis-trans* interconversion about the planar amide bond. An analogous scheme can be drawn using the cisoid amide isomer in a cup shaped chair-chair type conformation. The stereochemical outcome for reactions evolving through this species would be the same. Examination of molecular models for **1b** or **2b** suggests that chair-boat, boat-chair, and boat-boat conformations are also possible for both amide geometries. However, the presence of various non-bonded steric interactions in these conformations should kinetically inhibit their reactivity.

12. This reaction pathway has been documented for the reaction of (*Z*)-1 *H*-2,3,6,7,8,9-hexahydroazonine with bromine (ref 4c). The regiochemistry for this mode of attack involving the heterogenous reagent, PhSeBr can be predicted. Examination of molecular models suggests that the bromide nucleophile is directed at C-6 due to steric shielding of the C-5 position by *N*-benzyl group. The C-10 methylene would fulfill a similar role in the conformation derived from the cisoid amide isomer (ref 11).

13. For recent syntheses of epilupinine see: a) Takahata, H; Yamabe, K.; Suzuki, T.; Yamazaki, T. *Chem. Pharm. Bull.* **1986**, *34*, 4523. b) Ihara, M.; Kirihara, T.; Fukumoto, K.; Kametani, T. *Heterocycles*, **1985**, *23*, 1097. c) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckcamp, W. C. *J. Org. Chem.* **1985**, *50*, 4014. d) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *ibid.* **1984**, 1682. e) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *ibid.* **1983**, *48*, 3661. f) Okita, M.; Wakamatsu, T.; Ban Y. *Heterocycles*, **1983**, *20*, 401. g) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037.

14. Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.

15. For **11** as a colorless solid, mp 78–79.5 °C (lit.[13a] mp 79–80 °C). The ^{1}H and ^{13}C NMR spectra for our material were identical to literature spectra (ref. 13c,d). We are grateful to Professor S. M. Weinreb for a ^{1}H spectra of (±)–epilupinine.

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