First International Electronic Conference on Synthetic Organic Chemistry (ECSOC-1), www.mdpi.org/ecsoc/, September 1-30, 1997

[A0014]

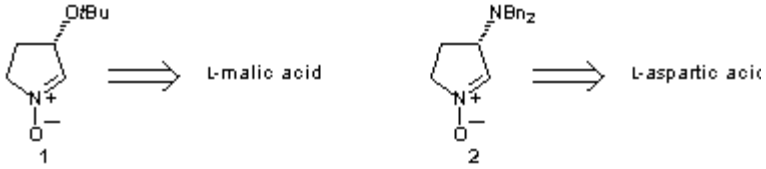
A Straightforward Route to Enantiopure Pyrrolizidines by Cycloaddition to Pyrroline N-Oxides Derived from the Chiral Pool

Valentina Fedi, Alberto Brandi, and Andrea Goti*

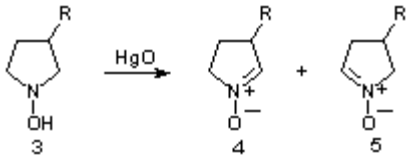
Centro di Studio C.N.R. sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni (CSCEA), Dipartimento di Chimica organica "Ugo Schiff", Universita di Firenze, via G. Capponi 9, I-50121 Firenze, Italy. Tel: (39) 55-2757610, Fax: (39) 55-2476964, goti@risc1.chimorg.unifi.it

Received: 15 July 1997 / Uploaded: 23 July 1997

We have recently reported the synthesis of enantiopure 3-heterosubstituted pyrroline *N*-oxides of type **1** and **2** (Scheme 1) obtained by oxidation of the corresponding hydroxylamines, in turn available in large amounts from L-malic and L-aspartic acids, respectively.[1]



Scheme 1.



Scheme 2.

The final oxidation step of hydroxylamines **3** produced two regioisomeric nitrones **4** and **5** (Scheme 2).[1] An unexpected high preference for oxidation at the position vicinal to the substituent to afford compound **4** has been found. The amount of this regioisomer increased consistently with the ability of the substituent to stabilize a negative charge. This effect was rationalized on the basis of the stabilizing stereoelectronic effect provided by an adjacent electronegative group in the TS of the rate-determining step of the oxidation, from the nitrosonium cation to the final nitrone, which requires the removal of a proton, as indicated in Figure 1.[1]

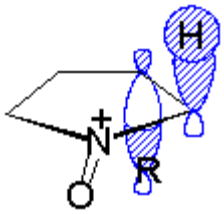
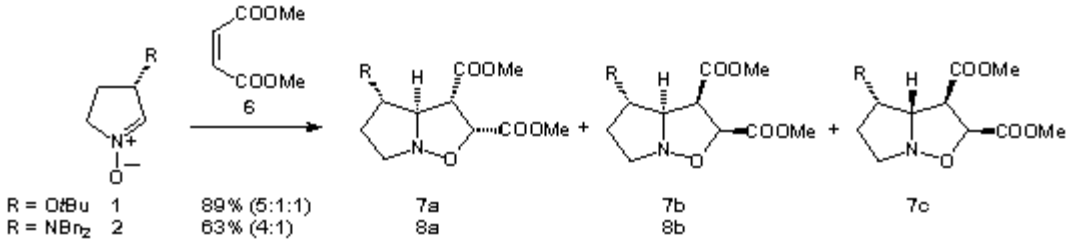


Figure 1.

In this communication we report the application of nitrones **1** and **2** to the synthesis of enantiopure pyrrolizidines and structurally related compounds by means of 1,3-dipolar cycloaddition reactions to dimethyl maleate and -crotonolactone. [2,3]

The reaction of nitrone **1** with dimethyl maleate (**6**) in benzene at room temperature for 3 days gave three cycloadducts in a 5:1:1 ratio (Scheme 3), which were assigned structures **7a-c**, respectively, on the basis of 2D-NMR NOESY spectra. As expected on the basis of previous findings on related cycloadditions of substituted pyrroline *N*-oxides,[1,3] the major adduct **7a** derived from the less encumbered *exo-anti* TS. The minor adducts **7b** and **7c** arose from roughly equi-energetic *endo-anti* and *exo-syn* TS, respectively, while formation of the fourth possible adduct was prevented by the sterically unfavored *endo-syn* approach (Figure 2).[4]



Scheme 3.

The analogous cycloaddition of nitrone **2** to **6** gave only two adducts **8a-b** in 4:1 ratio (Scheme 3), with structural assignment based on analogy and a NOESY spectrum of **8b**. The bulkier dibenzylamino group with respect to *tert*-butoxy can account for the lack of formation of products deriving from the sterically more hindered *syn* approaches at all (Figure 2).

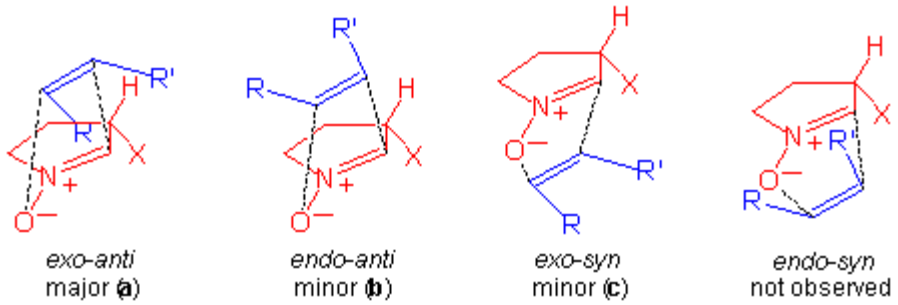
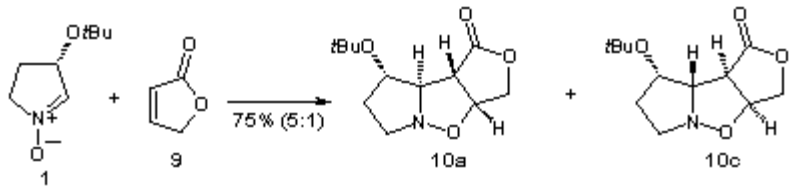


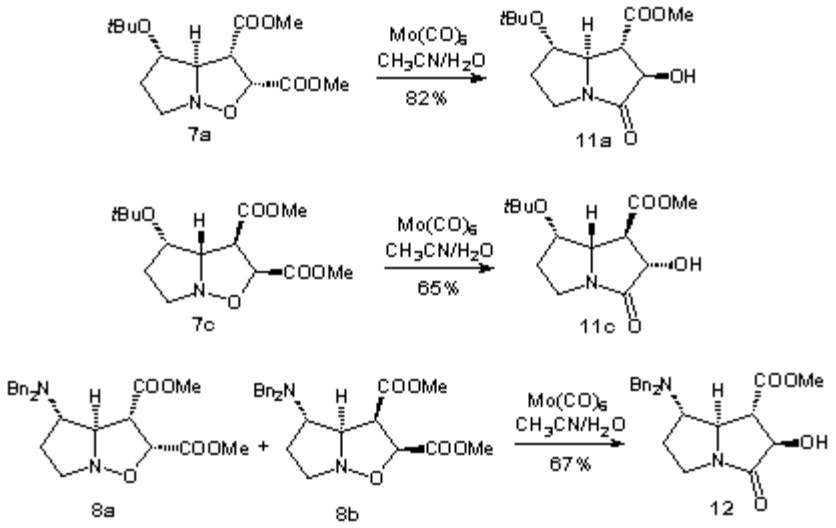
Figure 2

-Crotonolactone (**9**) has been chosen as another suitable dipolarophile for synthesizing the pyrrolizidine target compounds.[5] Indeed, **9** and butenolides in general are known to give an unique regioisomer,[5,6] usually with a better *exo/endo* selectivity in cycloadditions to cyclic nitrones than maleic acid derivatives,[5,6a] likely due to the loss of favorable secondary orbital interactions in the TS. Indeed, the reaction of nitrone **1** with **9** gave only two adducts in the same 5:1 ratio (Scheme 4). These compounds were assigned the structures **10a** and **10c**, as deriving from the two possible *exo* approaches, *anti* and *syn* to the substituent on nitrone, respectively, once again on the basis of NOESY spectra.



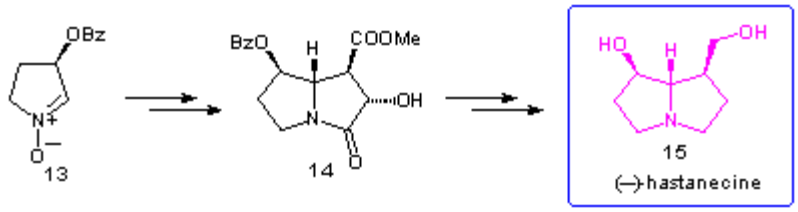
Scheme 4.

The transformation of adducts **7** and **8** into the desired pyrrolizine skeleton requires a simple opening of the isoxazolidine ring by reductive cleavage of the N-O bond, since re-closure to form a lactam moiety by attack of nitrogen to the -carboxylic carbon atom occurs spontaneously.[7,5] A mild method consisting in refluxing the isoxazolidine in aqueous acetonitrile in presence of molybdenum hexacarbonyl has been used to perform this transformation.[8] The separated isoxazolidines **7a** and **7c** gave good to excellent yields of **11a** and **11c**, respectively, in this step (Scheme 5). The mixture of isoxazolidines **8a-b** turned out to be inseparable by flash column chromatography and was subjected directly to the reductive ring-opening, which afforded only the pyrrolizidinone **12**, corresponding to the major adduct **8a** (Scheme 5).



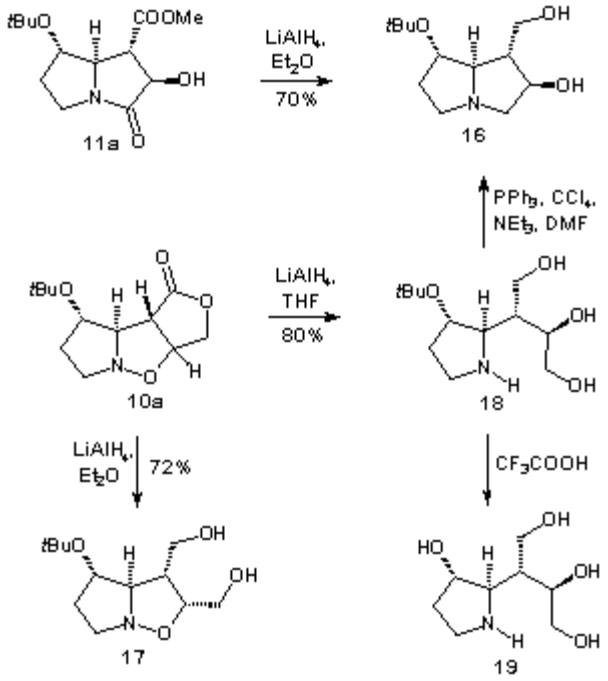
Scheme 5.

The same cycloaddition-reductive ring-opening procedure has been utilized very recently for a formal EPC synthesis of (-)-hastanecine (**15**),[9,10] the necine base of several pyrrolizidine alkaloids, starting from nitrone **13** (Scheme 6).



Scheme 6

Due to the biological relevance of polyhydroxypyrrolizidines and pyrrolidines as inhibitors of glycosidases and consequently as potential therapeutic (antibiotic, antiviral, antitumoral) agents,[11,12] we pursued the synthesis of such compounds and their structural analogues from the pyrrolizidinone **11a** and the cycloadduct **10a** (Scheme 7). Reduction of **11a** with $LiAlH_4$ in Et_2O gave the monoprotected pyrrolizidine triol **16**, which represents a new, non-natural stereoisomer of the necine bases rosmarinecine and croalbinecine. Reduction of the adduct **10a** under the same conditions was not able to accomplish the cleavage of the isoxazolidine ring, giving the pyrrolo[1,2-*b*]isoxazole derivative **17** in good yields. This compound is also interesting, representing a structural oxygenated analogue of polyhydroxypyrrolizidines. On the other hand, under reflux in THF, the reduction proceeded to give the monoprotected tetrahydroxypyrrolidine **18**, which in turn was deprotected to **19** or cyclized to **16** by treatment with PPh_3 in CCl_4 (Scheme 7).



Scheme 7.

In conclusion, a straightforward and versatile access to polyhydroxypyrrolizidines, pyrrolidines and structural analogues has been outlined. Application of related procedures to the synthesis of natural products and biologically interesting compounds is underway in our laboratories, as well as biological screening of the products against a variety of glycosidic enzymes.

Acknowledgment: The authors thank C.N.R. (Consiglio Nazionale delle Ricerche - Italy, Progetto Strategico "Tecnologie Chimiche Innovative") and M.U.R.S.T. (Ministero dell'Universit[daggerdbl] e della Ricerca Scientifica e Tecnologica - Italy) for financial support.

References and Notes

1. (a) Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119-3125. (b) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743-4748.

2. For a synthesis of hydroxyindolizidines from nitrone **1**, see ref. 1b.

3. For cycloadditions of related enantiomerically pure pyrroline *N*-oxides, see: (a) Mc Caig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939-3942. (b) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949-952. (c) Brandi, A.; Cicchi, S.; Goti, A.; Koprowski, A.; Pietrusiewicz, K. M. *J. Org. Chem.* **1994**, *59*, 1315-1318. (d) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806-6812. (e) Goti, A.; Cardona, F.; Brandi, A.; Picasso, S.; Vogel, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1659-1674. (f) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761-763. (g) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1863-1864. (h) Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. *Synlett* **1997**, 123-125.

4. *Syn* and *anti* refer to the approaches of dipolarophile from the same or the opposite face of the substituent at C-3 of the nitrone, respectively.

5. Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866-3869.

6. (a) Cid, P.; de March, P.; Figueredo, M.; Font, J.; Milan, S.; Soria, A.; Virgili, A. *Tetrahedron* **1993**, *49*, 3857-3870. (b) de Lange, B.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 5317-5320. (c) Banerji, A.; Basu, S. *Tetrahedron* **1992**, *48*, 3335-3344. (d) Saito, S.; Ishikawa, T.; Kishimoto, N.; Kohara, T.; Moriwake, T. *Synlett* **1994**, 282-284.r 7. Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2568-

2584.

8. Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351-3354.

9. Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *Synlett* **1997**, 577-579.

10. Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672-5680.

11. Reviews: (a) Elbein, A. D. *Ann. Rev. Biochem.* **1987**, *56*, 497-534. (b) Vogel, P. *Chimica Oggi* **1992**, *10 (August-September)*, 9-15. (c) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199-210. (d) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319-384.

12. (a) Hartmann, T.; Witte, L. *Chemistry, Biology and Chemoecology of the Pyrrolizidine Alkaloids* In *Alkaloids: Chemical & Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1995; vol. 9, p. 155-233. (b) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: New York, 1986.

Comments

During 1-30 September 1997, all comments on this poster should be sent by e-mail to ecsoc@listserv.arizona.edu with **A0014** as the message subject of your e-mail. After the conference, please send all the comments and reprints requests to the author(s).
