

## STERESELECTIVE DIELS-ALDER REACTIONS OF A NEW CHIRAL CARBAMOYL NITROSO COMPOUND.\*\*

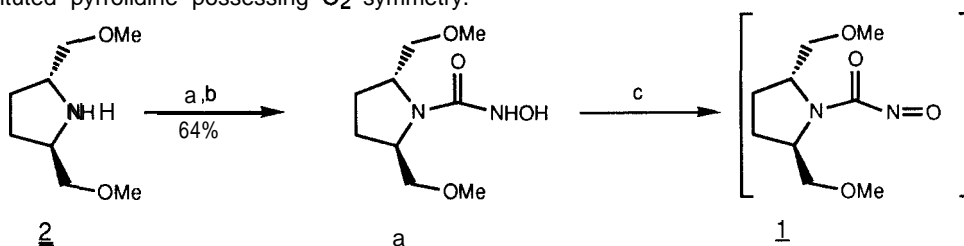
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Abstract: A new chiral carbamoylnitroso dienophile **1** has been prepared from a substituted pyrrolidine possessing  $C_2$  symmetry. Compound **1** reacts with dienes to yield (4 + 2) cycloadducts with very high diastereoisomeric excesses.

Diels-Alder reactions of chiral nitroso compounds are of great value for the synthesis of a large variety of homochiral nitrogen-containing organic products. Best results have been obtained with chiral  $\alpha$ -chloronitroso compounds derived from epiandrosterone or **D-mannose**.<sup>1</sup> However, we recently found that  $\alpha$ -chloronitroso compounds cannot be added to highly nucleophilic dienes which are decomposed under the reaction conditions.<sup>2</sup> The more reactive acylnitroso compounds derived from  $\alpha$ -hydroxyacids add to cyclopentadiene or cyclohexadiene somewhat less stereoselectively.<sup>3</sup> The group of Streith recently reported diastereoisomeric excesses ranging from 52 to 68 % in the reaction of cyclohexadiene with carbamoylnitroso compounds derived from **L-proline**.<sup>4</sup> We had made similar observations which were thought to result from the presence of two reacting conformations around the C-N bond. In this report, we show that much higher levels of diastereoselectivities can be obtained with a carbamoylnitroso compound derived from a disubstituted pyrrolidine possessing  $C_2$  symmetry.



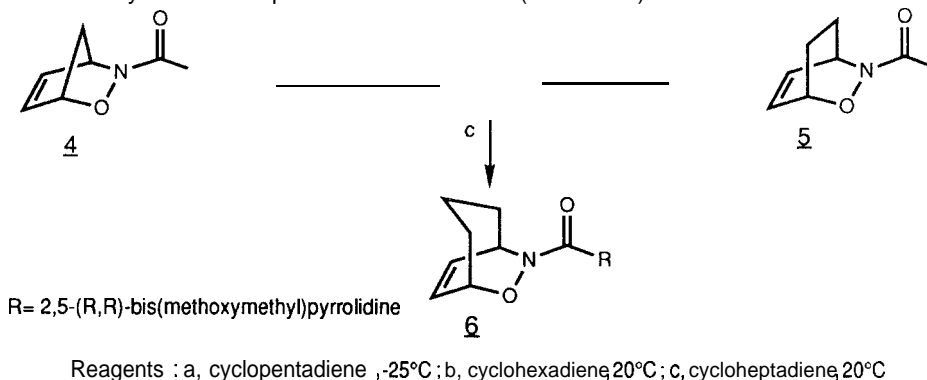
Reagents : a,  $\text{COCl}_2$  at  $-30^\circ\text{C}$  in ether ; b,  $\text{Me}_3\text{SiNHOSiMe}_3$ , neat,  $60^\circ\text{C}$  then  $\text{MeOH}$  ; c,  $\text{Et}_4\text{N}^+\text{IO}_4^-$ ,  $\text{MeOH}$

Scheme 1

The starting material for **3** is (2R, 5R) - bis (methoxymethyl) - pyrrolidine **2** which can be readily prepared in optically pure form.<sup>5</sup> Reaction of **2** with phosgene at  $-30^\circ\text{C}$  proceeded without rearrangement.<sup>6</sup> The resulting carbamoyl chloride was immediately transformed into hydroxamic

\*\* Dedicated to Professor Paul van Ragué Schleyer at the occasion of his 60th birthday.

acid **3**. The chiral carbamoylnitroso compound **1** was generated in situ by oxidation of **3** with a solution of tetraethylammonium periodate in methanol (Scheme 1).



### Scheme 2

**Table 1 :** Reactions of carbamoylnitroso compound **1** with dienes.

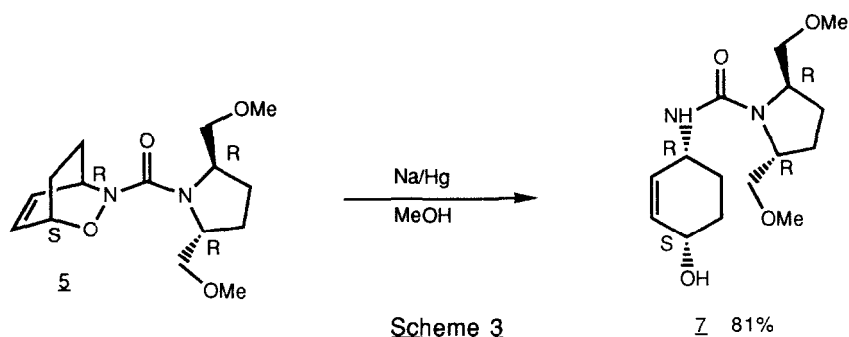
Diene	temp(°C)	Yield(%)	(a) de(%)	(b)	$[\alpha]_D^{25}$
A	Cyclopentadiene	- 25	83	87	+ 149.5 (c) c = 0.19 in MeOH
B	Cyclohexadiene	20	88	> 98	+ 106.8 c = 1.24 in MeOH
C	Cycloheptadiene	20	70	> 98	+ 94.9 c = 0.69 in MeOH

(a) Pure compounds after column chromatography;<sup>7</sup> (b) Diastereoisomeric excesses estimated by 500 MHz <sup>1</sup>H NMR on the crude products; (c)  $[\alpha]_D^{25}$  value of the major diastereoisomer.

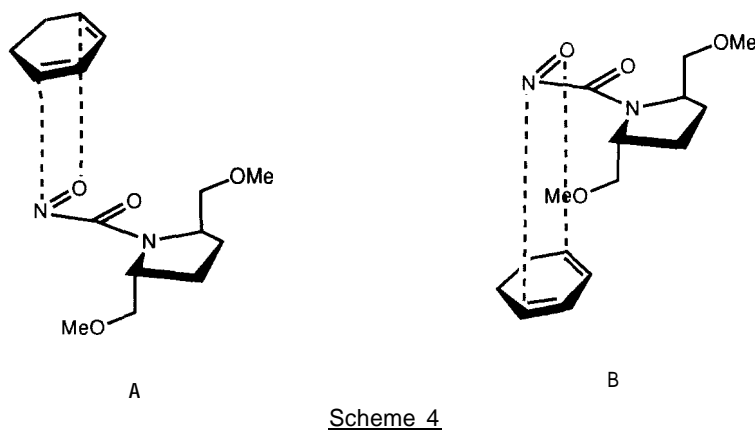
In the presence of a four-fold excess of diene, good chemical yields and excellent facial selectivities were observed (Scheme 2, Table 1). The <sup>1</sup>H NMR spectra of the crude mixtures of reactions B and C showed only one set of signals, suggesting that only one diastereoisomer was formed. A control experiment was performed : both diastereoisomers were prepared and separated by chromatography. An authentic mixture of both diastereoisomers showed well separated <sup>1</sup>H NMR signals.<sup>8</sup>

The absolute configuration of **adduct 5** has been determined by an X-Ray diffraction analysis <sup>9</sup> of the crystalline reduced product **7** (Scheme 3) by reference to the known absolute configuration of the asymmetric carbon atoms of the pyrrolidine ring.

The facial diastereoselectivity observed in these reactions is consistent with the transition state model depicted in Scheme 4. In contrast with other acylnitroso compounds<sup>10</sup>, the carbamoylnitroso **1** prefers a **syn** conformation. Ab initio calculations carried out by Dr G. Dive<sup>11</sup> predict this **syn** arrangement to be substantially more stable than the corresponding **anti** conformation. This obviously results from repulsive interactions between the oxygen atom of the N=O group and the bulky substituent on the pyrrolidine nitrogen atom.



In transition state **A**, the diene approaches in an *endo* fashion from the less hindered side of the dienophile. Transition state **A** is clearly lower in energy than transition state **B** and leads to the experimentally observed adduct **5**.



These preliminary results confirm that the introduction of a  $C_2$  symmetric carbamoyl group on a dienophilic double bond <sup>12</sup> leads to levels of facial selectivity which had not been obtained previously with other acylnitroso compounds. We shall report in due course an application of these findings to the synthesis of homochiral aminoacids.

### Acknowledgements

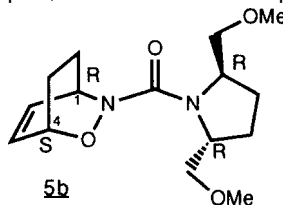
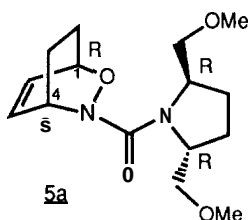
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### References and Notes

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This chiral pyrrolidine can now be readily prepared in large amounts. Chen, L.Y. and Ghosez, L.; unpublished results. Experimental procedure available on request.

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- All new products were characterized by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, elemental analysis and mass spectrometry.
- For example : 5a :  $\delta$  H5 = 6.68 ppm ,  $\delta$  H6 = 6.47 ppm ,  $\delta$  H1 = 4.77 ppm ,  $\delta$  H4 = 4.57 ppm  
5b :  $\delta$  H5 = 6.58 ppm ,  $\delta$  H6 = 6.52 ppm ,  $\delta$  H1 and H4 = 4.70 ppm



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- Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, 31, 1041.
- We thank Dr Dive, G. for the ab initio calculations (calculations with geometry optimisation of all degrees of freedom using STO-3G minimal basis set). The dihedral angle formed by the C=O and N=O planes is 4.17°.
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