Tetrahedron Letters,Vol.23,No.20,pp 2081-2084,1982 0040-4039/82/202081-04$03.00/0
Printed in Great Britain

DIASTEREOFACE SELECTION IN THE INOC REACTION

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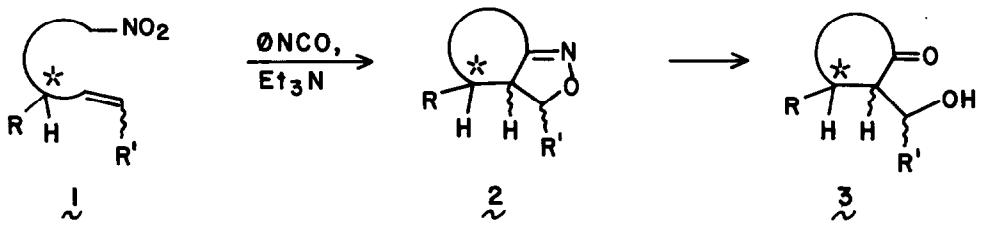
Summary: The effect of an "inside" allylic asymmetric center on the course of the intramolecular nitrile oxide cycloaddition reaction has been studied.

We have been concerned recently with the ability of an allylic asymmetric center to control diastereoface selection during the dipolar cycloaddition of nitrile oxides to olefins.[1] While in some of the intermolecular cases we have examined to date the stereocontrol varies from negligible to fairly good,[2] we felt that the highest degree of such asymmetric induction might best be achieved for an intramolecular [3+2] cycloaddition in which the allylic asymmetric center is present within the new carbocyclic ring being formed (Scheme 1).[3]

SCHEME I.



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Since the isoxazolines 2 generated in this way can be cleaved by hydrogen to β-hydroxyketones,[4] it would appear that the demonstration of such stereoselection would offer a possible synthetic route to cyclic ketones bearing three contiguous asymmetric centers. Additionally, the further elaboration of such materials (3) through conventional alkylation/Baeyer-Villiger type chemistry could afford a route to stereodefined lactones, and thus to part structures of the macrolide antibiotics. Overall, the process would provide a new strategy for acyclic stereocontrol.

To create the experimental basis for these notions, we prepared the two nitroalkenes 5 and 7 by routes displayed in the accompanying Schemes.

In regard to these relatively straightforward sequences, we only wish to mention that although the aldehydes prepared from the esters 4 and 6 by Dibal reduction co-distilled with the toluene used as the reaction solvent, the toluene

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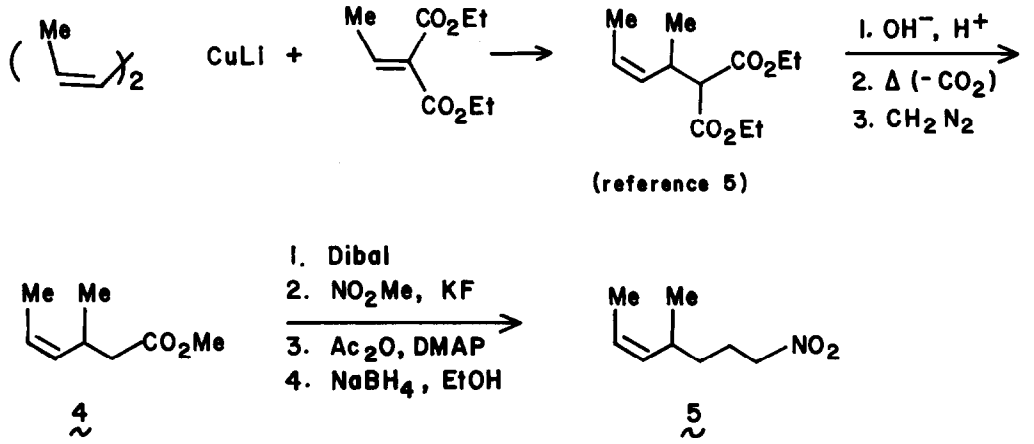
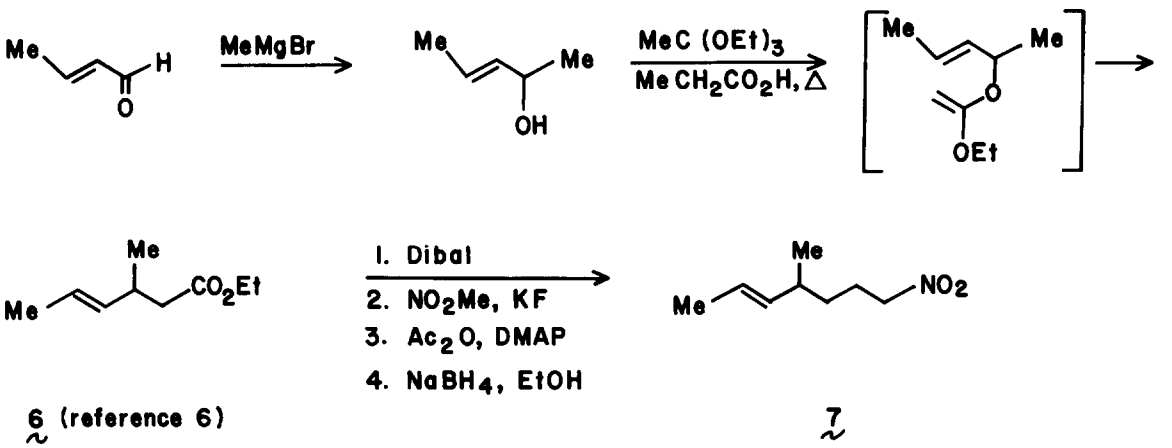
SCHEME 2. Preparation of the Z-nitroalkene



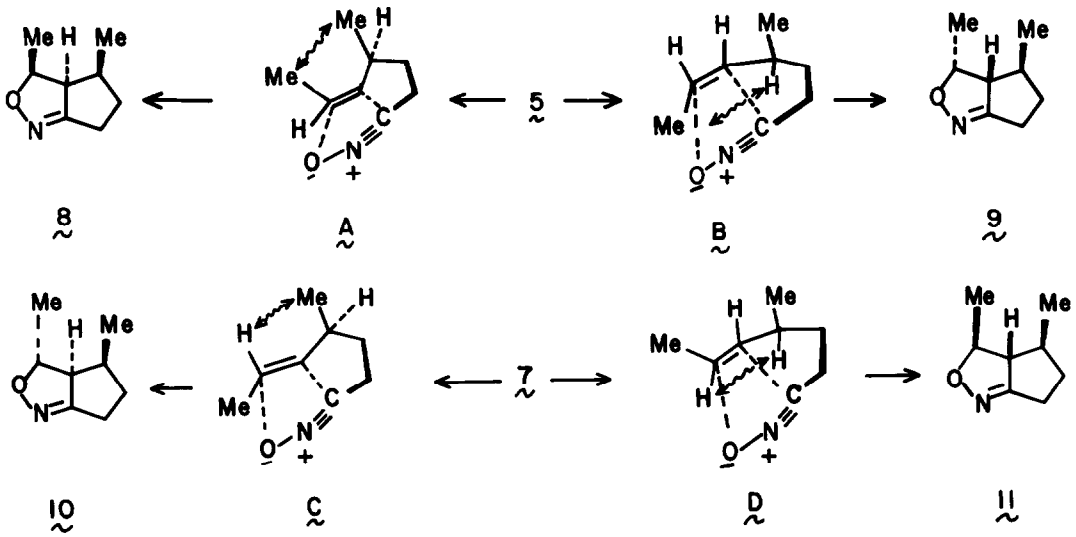
SCHEME 3. Preparation of the E-nitroalkene



solutions of these aldehydes could be used directly in the nitromethane condensation step (Henry reaction) without any difficulty.[7] The purity of these olefins was assured through examination of their 300 MHz ^{1}H NMR spectra.

Subjection of 5 and 7 individually to phenylisocyanate/triethylamine[8] at room temperature led to the desired dipolar cycloaddition products in high yield. Quite interestingly, the Z-nitroalkene led to the generation of only a single isoxazoline (>98% purity) whereas the E-nitroalkene gave a 3:1 mixture of two cycloadducts. These results are easily understandable in terms of $A^{1,3}$ strain present in the transition state for cycloaddition.[9] For the cis olefin, an

examination of Dreiding models reveals that one mode of cycloaddition (A) would involve a severe methyl-methyl interaction, whereas the other (B) contains a less serious methyl-hydrogen interaction. Clearly then, transition state B should win out even in the case of a reaction involving a relatively energetic intermediate like a nitrile oxide.



NOE experiments did substantiate that 9 was indeed the sole product of this INOC reaction.[10,11]

For the trans olefin, the two possible transition states are C and D. A methyl-hydrogen interaction is present in C, whereas a less serious hydrogen-hydrogen interaction is found in D. Since these steric interactions are much less serious than a methyl-methyl interaction, the trans-nitroalkene would be anticipated to be less discriminating in going on to isoxazoline. A mixture of products favoring the one arising from transition state D would be anticipated, a fact indeed borne out by experiment. NOE experiments did again serve to substantiate the assignment of structure 11 to the major product of the INOC reaction of 7.[12]

These experiments thus reveal that it is possible to achieve high diastereoface selectivity in intramolecular nitrile oxide cycloaddition reactions, as long as an allylic asymmetric center is present within the non-isoxazoline ring being formed (this ring need not, of course, be comprised only of carbon atoms). Future experiments will serve to define the utility of this process of stereocontrol for the synthesis of macrolide and ansamycin antibiotics.

Acknowledgements: We are indebted to the National Institutes of Health (Grant No. HL-20579) for support of these investigations. We thank Dr. F. T. Lin for performing the NOE experiments.

References and Notes

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2. The ability of an allylic asymmetric center to control the course of intermolecular nitrile oxide cycloaddition reactions will be published separately. M. Adamczyk and A. Ghosh, unpublished results, 1981.

3. The effect of an asymmetric center on the course of the Diels-Alder reaction is a well studied phenomenon. See, for example: W. R. Roush and S. M. Peseckis, J. Am. Chem. Soc., 103, 6696 (1981).

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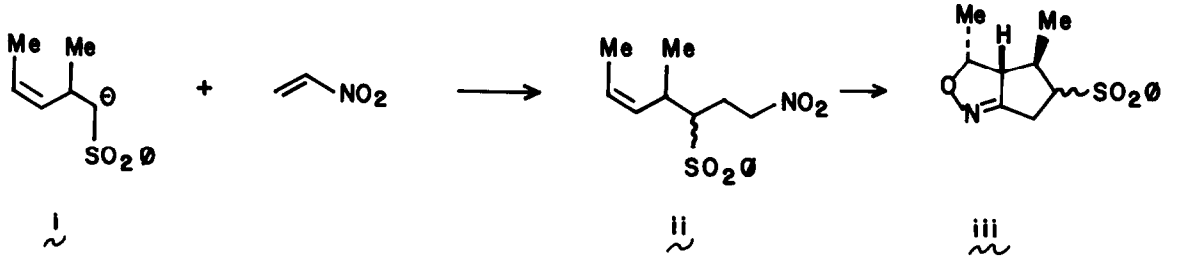
10. The [3+2] dipolar cycloaddition of the Z-nitroalkene ii, prepared by addition of the sulfone anion i to nitroethylene, has also been examined. LDA induced



i ii iii

elimination of the sulfone group of iii led to a single product whose ^{1}H NMR characteristics were quite similar to those of 9. Thus, it is assumed that even in this case, A^{1,3} strain controls the reaction course and that the additional asymmetric center plays little if any role in determining diastereoface selection.

11. The NOE values were measured by the time dependence enhancement technique on a Bruker WH-300 NMR spectrometer. The experimental conditions were 10 sec delay time (about 10X average T_1), 90° pulse width with 4.98 sec aquisition time, and the NOE irradiation from the peak frequency of either of the methyl groups with near saturation power.

12. All new products displayed satisfactory IR, NMR and high resolution mass spectral data.

(Received in USA 29 January 1982)