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INTRAMOLECULAR DIENOPHILE TRANSFER. DIELS-ALDER ADDUCTS OF ACYL-NITROSO COMPOUNDS AS USEFUL REAGENTS FOR INTRAMOLECULAR CYCLOADDITIONS.

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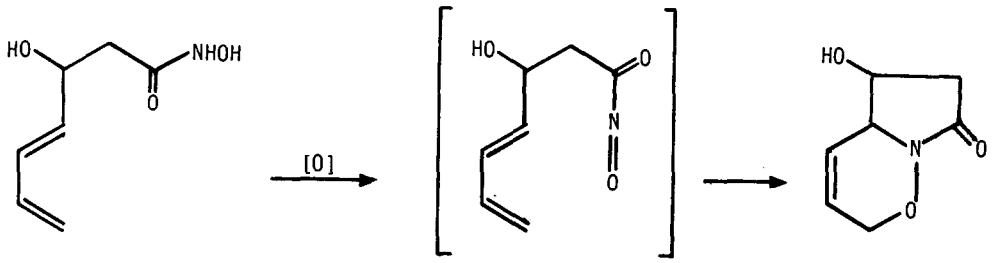
In connection with synthetic programs underway in these laboratories, we required certain 3-hydroxy-4,6-heptadiene-hydroxamic acids (1) for use as precursors to the corresponding acyl-nitroso compounds. Thus Kirby has reported that periodate oxidation of hydroxamic acids generates highly reactive acyl-nitroso compounds which can be trapped by dienes to afford products of [4 + 2] cycloaddition.[1] We envisioned, based upon the yields obtained for a series of bio-molecular processes (e.g. 65-70% for reaction of nitroso-carbonyl benzene with 1.2 eq of cyclohexa-diene at 23° in dimethylformamide[2]) that oxidation of hydroxamic acids such as 1 would furnish intramolecular Diels-Alder adducts in exceptionally high yield. Reductive cleavage of the nitrogen-



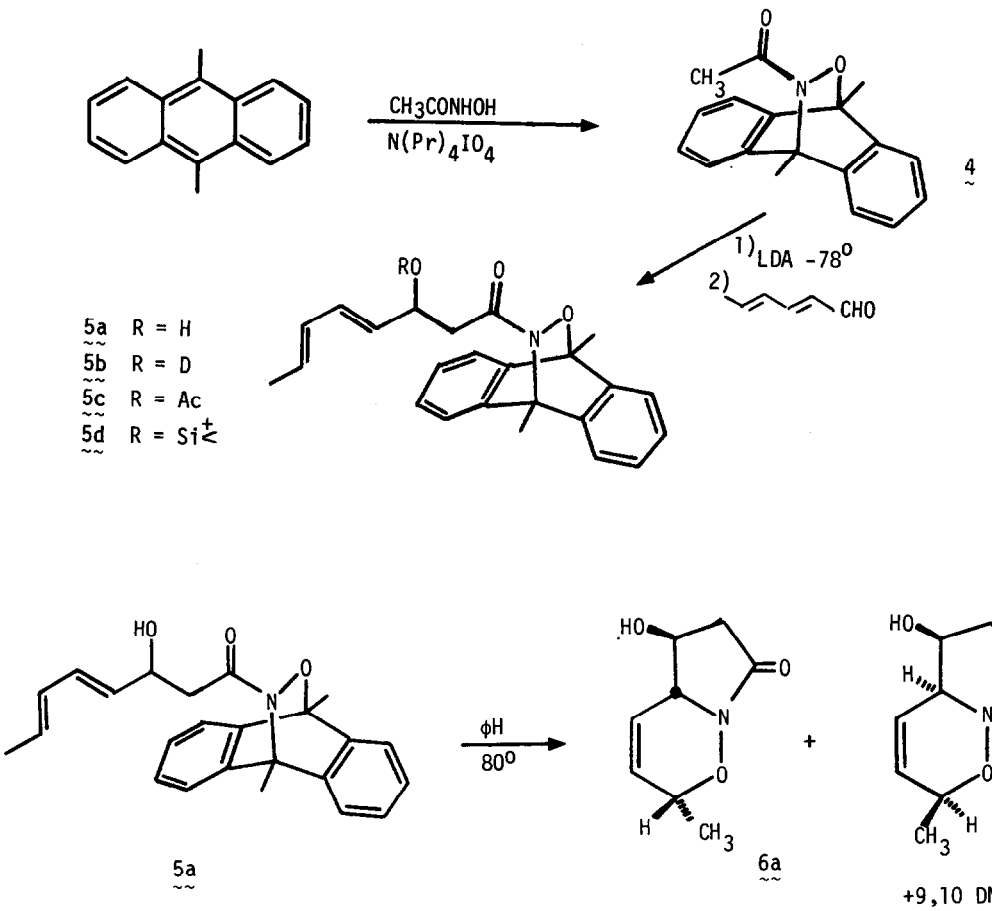
1 2 3

oxygen bond in 3 might then lead to a highly functionalized five-ring lactam, a structural moiety encountered in a large number of naturally occurring nitrogen containing materials.

Unfortunately, the β-hydroxyl substitution in 1 renders most standard approaches[3] to the preparation of hydroxamic acids inapplicable. Thus, we have devised a new approach, termed "intra-molecular dienophile transfer," directly to the desired acyl-nitroso compounds (2), which bypasses β-hydroxy hydroxamic acids, and the problems inherent in their construction, entirely.

Slow addition (via syringe pump) of a DMF solution of acetohydroxamic acid (2 eq) to a well-stirred chloroform solution of 1 eq of 9,10-dimethylanthracene and 2 eq tetra-N-propyl ammonium periodate,[1] at 23° under argon, gave, after normal extractive workup and purification by column chromatography (elution with 10-20% THF-hexane), Diels-Alder adduct 4, in > 90% yield.[4] Formation of the enolate of 4 with lithium diisopropylamide, in THF-HMPA(4:1) at -78°, followed by quenching with 2,4-hexadienal, then afforded the desired condensation product 5a in 85% isolated yield after purification by column chromatography over silica gel (elution with 25% THF-hexane).

Thermolysis of 5a in refluxing benzene (0.5 ml per mg of 5a) for 5 hours then afforded

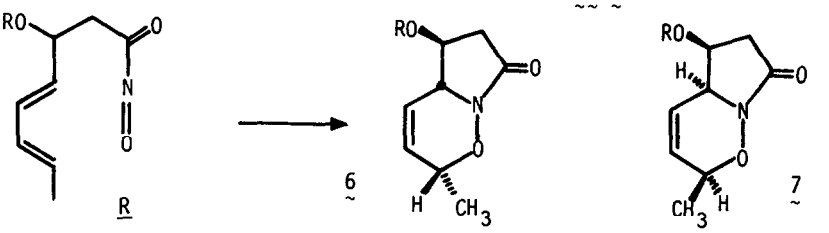


9,10-dimethylanthracene and two intramolecular Diels-Alder adducts (6a and 7a) in quantitative yield. Adducts 6a and 7a were readily separated from each other and recovered dimethylanthracene by column chromatography over silica gel, with 3% methanol in chloroform as eluting solvent. The gross structures of 6a and 7a as the desired [4 + 2] adducts were clearly revealed by their IR and NMR spectra, and by appropriate homonuclear decoupling experiments. The stereochemistry of 6a and 7a, however, could not be reliably assigned based on the observed spectra. An unambiguous assignment of stereochemistry proved possible from europium shift experiments, since in isomer 7a, the methyl group experience considerably more rapid downfield shifts than did the corresponding methyl group in 6a. Molecular models clearly reveal that a close approach of hydroxyl and methyl is possible only in adduct 7a.

Interestingly, only a very small effect of oxygen substitution on the distribution of Diels-Alder adducts was observed. Acetate 5c and tert-butyl dimethylsilyl ether 5d were prepared by

standard techniques[5] and decomposed as above in refluxing benzene to afford adducts 6c, 7c, and 6d, 7d, respectively, which were independently prepared from 6a and 7a. Chart I shows the product ratios obtained from 5a, 5c, and 5d, and also from O-deuterio 5a (5b).

CHART I: Product Ratios from Thermolysis of 5a-d

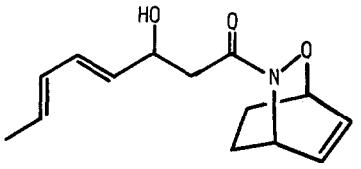


(a)	H	66 :	33
(b)	D	66 :	33
(c)	Ac	43 :	57
(d)	-Si	41 :	59

That oxygen substitution should have minimal stereochemical consequences for the course of the cycloaddition is not unexpected. The transition states leading to 6a and 7a differ only by rotation by 180° about the C_3C_4 single bond in the intermediate acyl nitroso compound. Careful inspection of molecular models reveals no unfavorable steric interactions in either transition state. A roughly 60:40 distribution of adducts at 80° indicates that any differences in steric interactions in the two transition states must amount to less than 1 kcal/mole. Interestingly, the stereochemical preference observed with free hydroxyl compound 5a is inverted when the hydroxyl is protected as either its acetate or tert-butyldimethylsilyl ether. Hydrogen bonding in the acyl-nitroso intermediate may thus be involved in determining the stereochemical outcome with the free hydroxyl compound. However, the effect could not be increased by deuterium substitution (note entry 2, Table I), even though deuterium is known[6] to hydrogen bond more strongly than protrium.

That the stereochemical preferences observed are the result of a kinetically controlled cycloaddition, rather than equilibration after an initial, rapid, cycloaddition process was indicated by the following observations. First of all, the distribution of products obtained in refluxing benzene was independent of time over the period of 5-14 hours. Secondly, if the crude product obtained from silyl ether 5d was rethermolyzed in refluxing toluene (110°) for 14 hours, no change in the 6d/7d ratio was observed. Finally, the reluctance of Diels-Alder adducts such as 6 and 7 (where an aromatic moiety cannot be formed in a retro Diels-Alder process) to equilibrate via a retro Diels-Alder, Diels-Alder sequence was substantiated by the observation that compound 8 was recovered essentially unchanged after thermolysis in refluxing xylene (140°)

for 14 hours.



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$\xrightarrow[14 \text{ hours}]{140^{o}}$ N.R.

Reductive cleavage of the N-O bond in silyl ether 7d with excess 6% sodium amalgam (ethanol, 0^{o}, 4 eq disodium hydrogen phosphate as buffer, 9 hours) gave the corresponding hydroxylactam in 82% isolated yield.[7]

In summary, we note that dienophile transfer, using Diels-Alder adducts of acyl-nitroso compounds as synthetic reagents, allows the preparation of otherwise difficultly accessible intramolecular [4 + 2] adducts with exceptionally high efficiency. Further studies on the stereochemistry of this process as a function of diene substitution, as well as application to natural products synthesis, are in progress in our laboratories and will be reported in due course.

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2. G. E. Keck and S. A. Fleming, unpublished results.

3. S. R. Sandler and W. Kera, "Organic Functional Group Preparations," A. T. Blomquist and H. Wasserman, Editors, Academic Press, New York and London, Volume II, Chapter 12.

4. The preparation of this material has been previously reported by Kirby, note reference 1(a).

5. Acetate 5c was prepared in quantitative yield by treatment of alcohol 5a with excess (5 eq) acetic anhydride in pyridine at 23^{o} for 23 hours. Silyl ether 5d was prepared (96% isolated yield) by reaction of 5a with tert-butyl dimethylsilylchloride (3 eq) and imidazole (6 eq) in dry DMF at 23^{o} for 19 hours. For the formation and removal of tert-butyldimethylsilyl ethers note E. J. Corey and A. Vankateswarlu, J. Am. Chem. Soc., 93, 2318 (1971).

6. The 25% greater viscosity of D_2O vrs. H_2O has been attributed to stronger hydrogen bonding with deuterium. See Isotope Effects in Chemical Reactions, C. J. Collins and N. S. Bowman, Eds., Van Nostrand Reinhold Co., New York, 1970, pp. 347-350.

7. This reagent has previously been employed by Trost to effect the reductive cleavage of carbon-sulfur bonds. Note B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, Tetrahedron Lett., 3477 (1976).

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