tively little C_α–C_β double-bond character. The higher value of the $^\alpha$C than the $^\beta$C isotope effect is readily interpreted in terms of extensive delocalization of the developing negative charge at C_β into the aromatic ring (added C_β-ring bond formation).

Further experiments are planned to study the variation of the $^\alpha$C and $^\beta$C isotope effects with ring substituents and as the solvent is charged to the diglyme system, for which Kwart's group proposes a changeover from a linear (large ring–Me_2SO involved) β-proton transfer to a nonlinear transfer. Model calculations comparing syn and anti mechanisms and linear (Me_2SO involved) vs. nonlinear proton transfers are also planned. The carbon isotope effect data place stringent constraints on the structures and geometries of the acceptable transition-state models.

Acknowledgment. We are indebted to Drs. John R. I. Eubanks and M. Kanska for preparation of some of the labeled compounds.

Registry No. (2-(*p*-Methoxyphenyl)ethyl)dimethylamine *N*-oxide, 34875-26-8; (2-(*p*-methylphenyl)ethyl)dimethylamine *N*-oxide, 85662-27-7; (2-(*p*-chlorophenyl)ethyl)dimethylamine *N*-oxide, 34875-27-9; (2-phenylethyl)dimethylamine *N*-oxide, 19270-13-4; (2-(*p*-nitrophenyl)-ethyl)dimethylamino *N*-oxide, 85662-28-8; carbon-14, 14762-75-5.

Mild Lewis Acid Catalysis: Eu(fod)$_3$-Mediated Hetero-Diels–Alder Reaction

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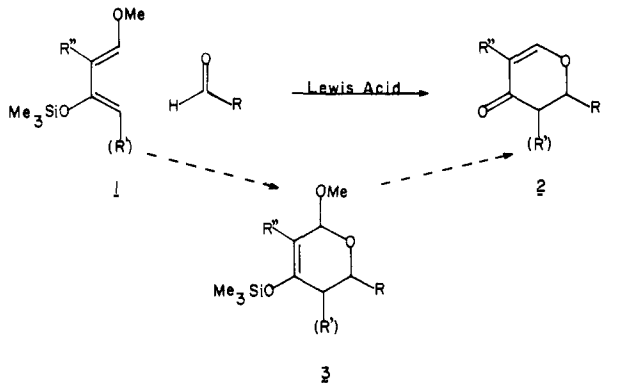
Under Lewis acid catalysis, cyclocondensations of dienes (cf. **1**, Scheme I) with aldehydes afford dihydropyrones (**2**). This process has been explored as to scope,[1,2] applications,[3] and mechanism.[4] Initially, the intermediacy of cycloadducts was presumed but not demonstrated. More recently, as part of our mechanistic investigations the acid-labile intermediates, **3**, could be detected and even isolated in modest yield.

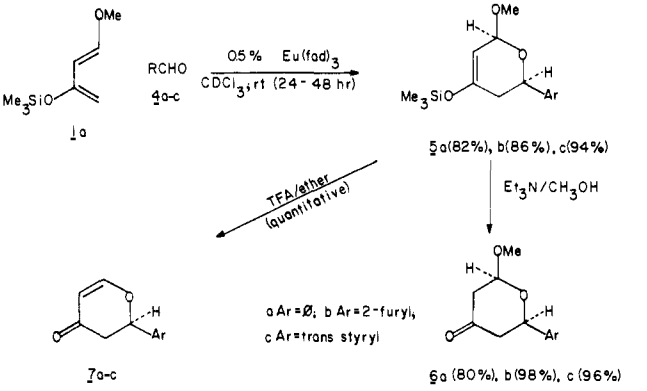
There occurred to one of us the notion that the oxaphilicity of rare-earth cations,[5] suitably complexed with solubilizing ligands,[6] might so perturb an aldehyde[7,8] as to render it a potent heterodienophile. In this communication we report on the experimental realization of this hypothesis, using trace amounts of tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium (Eu(fod)$_3$) as the catalyst.

Our findings, using diene **1a** (Scheme II) with aromatic aldehydes, are provided below. With these substrates the *cis*[9]-methyl glycosides **5** were produced with good selectivity.[10] With a high

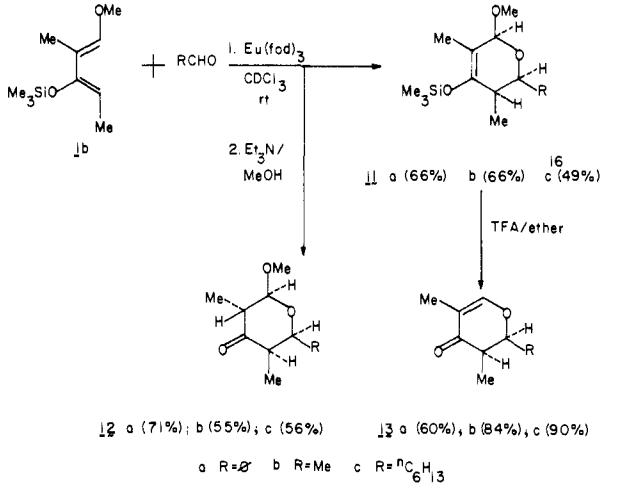
Scheme I



Scheme II



Scheme III



(1) Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457 and references therein.

(2) For thermal cycloadditions to activated (cf. glyoxalate, chloral, etc.) aldehydes see ref 1, footnotes 6–10. For some recent findings from other laboratories that have followed our disclosures see: (a) Belanger, J.; Landry, N. T.; Pare, R. J.; Jankowski, K. *J. Org. Chem.* **1982**, *47*, 3649. (c) Aben, R. W.; Scheeren, H. W. *Synthesis* **1982**, 779. (c) Brady, W. T.; Agho, M. O. *Ibid.* **1982**, 500.

(3) (a) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360. (b) Danishefsky, S.; Kerwin, J. F., Jr. *Ibid.* **1982**, 3183 and references therein.

(4) (a) Larson, E. R.; Danishefsky, S. *Tetrahedron Lett.* **1982**, *23*, 1975. (b) Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1982**, *104*, 6458.

(5) For recent discussions of the coordination properties of various lanthanides see: (a) Rueben, J. In "Handbook on the Physics and Chemistry of Rare Earths"; Gschneidner, K. A., Jr., Eyring, L., Eds.; North-Holland: Amsterdam, 1979; Chapter 39. (b) Richardson, F. S. *Chem. Rev.* **1982**, *82*, 541. (c) Marks, T. J. *Prog. Inorg. Chem.* **1978**, *24*, 51.

(6) In selecting ligands for the lanthanide in this and related ongoing investigations, we were influenced by considerations of demonstrated efficacy as NMR shift reagents; see: (a) Dyer, D. S.; Cunningham, J. A.; Brooks, J. J.; Sievers, R. E.; Rondeau, R. E. In "Nuclear Magnetic Resonance Shift Reagents"; Academic Press: New York, 1973; Chapter 2. (b) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Aam. Chem. Soc.* **1974**, *96*, 1038. The uses of other ligands are under investigation.

(7) To the best of our knowledge the concept and findings described here are novel. For previous apparent manifestations of the Lewis acidity of lanthanides in reactions of carbonyl compounds see: Trost, B. M.; Bogdonowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 2040. Luche, J. L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976. Forsberg, J. H.; Belasubramanian, T.; Spaziano, V. T. *Ibid.* **1976**, 1060. For a very recent listing of the applications of lanthanides in catalysis see: Marks, T. J.; Ernst, R. D. "Comprehensive Organometallic Chemistry", in press. We thank Professor Marks for providing us with a preprint of this valuable compilation.

(8) For the use of divalent lanthanides as reducing agents see: Natale, N. R. *Tetrahedron Lett.* **1982**, *23*, 5009.

(9) The stereochemical assignment of the pseudoglycal ethers, **5a–c** is best determined by their conversion to the β-methoxy ketones, **6a–c**, respectively. In the NMR spectra of the cis compounds **6a** and **6b**, the anomeric (C_1) proton appears as an apparent triplet, J-7–8 Hz, while the C_5 methine appears as a doublet of doublets $J_1 \simeq$ **11**–12 Hz, $J_2 \simeq$ 2–3 Hz, implying an axial-like disposition for both of these hydrogens. The assignment of configuration at C_5 in compounds **12** (and, therefore, in silyl enol ethers **11**) relies on the assumption of suprafaciality in the sense of addition to diene **1b**.[4b]

(10) The cis/trans ratios in compounds **6** are for **6a** 12:1, for **6b** ~ 6:1, and **6c** 8:1.

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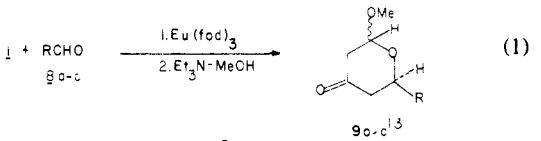
yield route to these silyl enol ethers (**5**) in hand, procedures for their smooth transformation to products of the type **6**[11] or **7**[11] were devised.

In the cyclocondensation reaction of the "parent" diene **1a** with saturated aliphatic aldehydes, endo selectivity is eroded. Aldehydes **8** react with **1a** (eq 1) in the presence of 0.5–5 mol % of $Eu(fod)_3$[12]



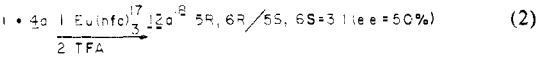
(1)

9 a R=Me (81%), b R=^{n}C$_6$H$_{13}$ (55%), c R=^{i}Pr (40%)

in chloroform at room temperature. Methanolysis of the crude reaction mixture afforded compounds **9**[11] in the indicated yields as mixtures[13] of methyl acetals. Where studied, it was shown that the composition of the pyranosides reflects the ratio of their precursor silyl enol ethers.

The power of the method for the stereospecific synthesis of carbon-branched pyranose derivates is seen from the reaction of the substituted diene **1b**[14] with aldehydes **4a**, **8a**, and **8b**. Unlike the case with unsubstituted diene **1a**, virtually total endo specificity is maintained in the reaction of **1b** with a range (both aromatic and aliphatic) of aldehydes, giving rise to enol ethers **10**. Thus, three chiral centers are established through this suprafacial[4b,9] endo-cycloaddition process. A fourth center at C_2 is controlled through apparent axial protonation of the silyl enol ethers, which gives rise to the methoxyketones **11** (Scheme III).[11,15] Alternatively, the enol ethers **11** can be converted to cis-disubstituted pyrones **12**[11] in the usual way. Of course, for strictly preparative purposes, **11** and **12** could be obtained in higher yield by avoiding purification of the very sensitive vinylogous ortho esters **10**.

We have begun to explore the possibility that a Eu^{3+} salt, bearing chiral ligands, might exhibit topological biases as it orchestrates the cyclocondensation reaction. This proposition has been reduced to practice. While the ultimate potentialities of this method for asymmetric induction will only be revealed after the sort of methodical investigations that are now in progress, the following finding is suggestive:



(2)

The various results reported above have ramifications which are of continuing interest to our laboratory.

Acknowledgment. This research was supported by NIH Grant A1-16943-03. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University.

(11) The structure of this compound is consistent with its infrared, NMR, and mass spectra. Spectral data for all new compounds are provided in the supplementary material.

(12) As expected, increases in the amounts of $Eu(fod)_3$ lead to an increased reaction rate. In the case of aldehyde **8a**, 0.5 mol % of catalyst was employed for 14 h (room temperature); for aldehyde **8b**, 5 mol % catalyst and 12 h (room temperature) were used, while in the case of aldehyde **8c** reaction was carried out with 1 mol % of catalyst for 100 h (room temperature).

(13) The cis/trans ratios in compounds **9** were for **9a** 2.8:1, for **9b** 1.2:1, and for **9c** 1.5:1.

(14) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

(15) Traces of another isomer, too minor for isolation, are suggested in the NMR spectra of compounds **12**. It is not clear whether this isomer is that arising from cycloaddition or from α-protonation.

(16) Silyl enol ether **11c** was obtained as a ca. 1:1 mixture with the dihydropyrone **13c**. The latter was obtained as a pure compound on treatment of "**11c**" with trifluoroacetic acid (TFA) as shown.

(17) This is the trade name for tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium, which is commercially available from Aldrich.

(18) **12a** was degraded to methyl 2-methyl-3-phenyl-3-hydroxybutyrate as previously[3a] described. The agreement of the optical rotation[19] and NMR ($Eu(hfc)_3$) measurements on this erythro ester serve to define both the sense and magnitude of the asymmetric induction. Details of the NMR method will be provided in the full paper.

(19) Cf.: Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127 and references therein.

Registry No. **1a**, 54125-02-9; **1b**, 72486-93-2; **2a**, 100-52-7; **2b**, 98-01-1; **4c**, 14371-10-9; **5a**, 85612-97-1; **5b**, 85612-98-2; **5c**, 85612-99-3; **6a**, 85613-00-9; **6b**, 85613-01-0; **6c**, 85613-02-1; **7a**, 40989-96-6; **7b**, 85613-03-2; **7c**, 85613-04-3; **8a**, 75-07-0; **8b**, 111-71-7; **8c**, 78-84-2; *cis*-**9a**, 85613-05-4; *trans*-**9a**, 85613-06-5; *cis*-**9b**, 85613-07-6; *trans*-**9b**, 85613-08-7; *cis*-**9c**, 85613-09-8; *trans*-**9c**, 85613-10-1; **11a**, 85613-11-2; **11b**, 85613-12-3; **11c**, 85613-13-4; **12a** (isomer 1), 85613-14-5; **12a** (isomer 2), 85648-05-1; **12b**, 85613-15-6; **12c**, 85613-16-7; **13a**, 83378-98-7; **13b**, 85613-17-8; **13c**, 85613-18-9; $Eu(fod)_3$, 17631-68-4.

Supplementary Material Available: Infrared, NMR (^1H and ^{13}C), and mass spectral data for all new compounds (3 pages). Ordering information is given on any current masthead page.

DNA Major–Minor Groove Binding Specificity of Daunorubicin: Anthramycin-Modified and T-4 Bacteriophage DNA Studies

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The major vs. minor groove binding specificity of substituents on intercalating drugs is an important aspect of their interaction with DNA, which is not well understood and for which methods for systematic evaluation are not readily available.[1] With antitumor anthracycline drugs, adriamycin and daunorubicin, for example, fiber diffraction,[2] model building, and drug analogue activity[3] studies have led to proposals for binding of the nonaromatic A ring and its substituents in the major groove. An X-ray crystallographic structure of daunorubicin intercalated into a complementary double-helical nucleotide segment[4] and derivative binding analysis[5] have resulted in proposals for minor groove binding specificity for these drugs. We report here a method for evaluating major vs. minor groove binding specificity for many intercalators and use the method to establish that the A-ring substituents to daunorubicin bind in the minor groove under the solution conditions of these experiments.

Anthramycin (AM) is an antitumor antibiotic that reacts covalently with the 2-amino group of guanine in the minor groove of DNA.[6,7] Work by Kohn and co-workers[6] and by Hurly and co-workers[7] has shown that AM is topologically matched to the minor groove of DNA and covers approximately three base pairs to produce an uncharged adduct with very little perturbation of the double-helix structure. We prepared two samples with different AM to DNA-P ratio and conducted binding and viscometric studies of the interaction of daunorubicin with these modified DNA samples.[8] The binding results, shown in Figure 1A, il-

(1) Wilson, W. D.; Jones, R. L. In "Intercalation Chemistry"; Academic Press; New York, 1982; Chapter 14.

(2) Pigram, W. J.; Fuller, W.; Hamilton, L. D. *Nature (London) New Biol.* **1972**, *235*, 17.

(3) Henry, D. W. In "Cancer Chemotherapy"; American Chemical Society: Washington, DC, 1976; pp 15–57.

(4) Quigley, G.; Wang, A.; Ughetto, G.; van der Marel, G.; van Boom, J.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 7204.

(5) Gabbay, E. J.; Grier, D.; Fingerle, R.; Reimer, R.; Levy, R.; Pearce, S. W.; Wilson, W. D. *Biochemistry* **1976**, *15*, 2062.

(6) (a) Kohn, K. W.; Spears, C. L. *J. Mol. Biol.* **1970**, *51*, 551. (b) Kohn, K. W.; Glaubiger, D.; Spears, C. L. *Biochim. Biophys. Acta* **1974**, *361*, 288. (c) Glaubiger, D.; Kohn, K. W.; Charney, E. *Biochim. Biophys. Acta* **1974**, *361*, 303.

(7) (a) Petrusek, R. L.; Anderson, G. L.; Garner, T. F.; Fannin, Q. L.; Kaplan, D. J.; Zimmer, S. G.; Hurley, L. H. *Biochemistry* **1981**, *20*, 1111. (b) Kaplan, D. J.; Hurley, L. H. *Ibid.* **1981**, *20*, 7572.

(8) Samples I and II were prepared by addition of 3.2×10^{-3} and 2.3×10^{-2} mmol, respectively, of anthramycin methyl ether to 7.6×10^{-2} mmol of sonicated calf thymus DNA in 2.0 mL of PIPES buffer (0.01 M piperazine-*N*,*N*'-bis(2-ethanesulfonic acid), 0.001 M EDTA, pH 7.0). The reaction mixture was stirred at room temperature for 3 h and at 4 °C for 4 h, extracted with octanol, and extensively dialyzed at 4 °C against the desired buffer. The anthramycin to phosphate ratios, determined spectrophotometrically,[7] were 0.0352 and 0.106 for samples I and II, respectively. Samples were also characterized by ^{31}P NMR, Tm, and viscometric analysis. Binding studies were conducted as previously described.[9]

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