transfer mechanism can account both for the highly selective formation of the more stable α-amino radical (Scheme I) and the failure of simple trialkyl amines such as **1** to yield stilbene–amine adducts in nonpolar solvents. The failure of amine **2** to yield a type b adduct in nonpolar solvent is, at first, surprising. However, nonbonded interactions between an *N*-methyl group and an ortho hydrogen of the phenyl group may prevent through-conjugation in the α-(dimethylamino)benzyl radical. Steric inhibition of resonance should be much less pronounced for the α-amino radicals from amines **3**–**5**. As we have previously reported, a proton-transfer mechanism can account for the selective formation of the less stable α-amino radical in polar solvents.[1,4] At present we cannot distinguish between hydrogen-transfer and proton-transfer mechanisms for the formation of type b adducts in moderately to highly polar solvents. The solvent dependence of the deuterium isotope effect on the formation of adduct **4b** is more consistent with a solvent-induced change in mechanism, as is the solvent dependence of the quantum yield for formation of **3b** (Figure 1).

The orientation of oxidation of amines **3**–**5** may prove to be a useful chemical diagnostic of radical vs. one-electron-transfer mechanisms for amine oxidation. For example, the triplet state of flavins (isoalloxazines) oxidizes the methylene carbon of *N*,*N*-dimethylglycine (free-radical mechanism?), whereas the flavoenzyme monoamine oxidase oxidizes the methyl carbons (electron-transfer mechanism?).[9] Further studies of selective amine oxidations are in progress in our laboratory.[10,11]

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(10) The use of primary vs. tertiary radical formation from *p*-cymene as a probe of hydrogen atom vs. proton-transfer mechanisms has recently been described: Wagner, P. J.; Puchalski, A. E. *J. Am. Chem. Soc.* **1980**, *102*, 6177.
(11) Support of this work by the National Science Foundation (CHE78-01120) is gratefully acknowledged.

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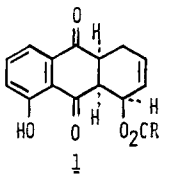
Received June 5, 1980

A Model for Asymmetric Induction in the Diels–Alder Reaction

Sir:

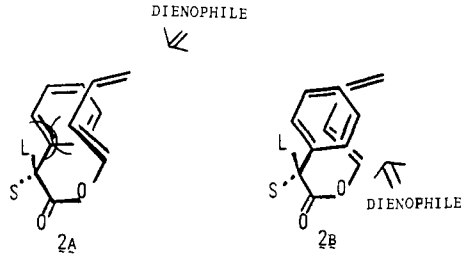
The Diels–Alder reaction continues to stimulate much thought from a synthetic, mechanistic, and theoretical point of view. The application of this reaction to chiral synthesis has had mixed results, but some of the recent work has been highly encouraging.[1] The development of a model for enantioselectivity in such a reaction would serve to enhance the utility of this reaction in natural product synthesis. We wish to report the development of such a model and its application to the asymmetric formation of adduct **1**, a key intermediate toward several classes of important tetracycline natural products.[2,3]

(1) David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron* **1978**, *34*, 299; David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230. David, S.; Eustache, J.; Lubineau, A. *Ibid.* **1979**, 1795. Korolev, A.; Mur, V. *Dokl. Akad. Nauk. S.S.S.R.* **1948**, *59*, 251; *Chem. Abstr.* **1949**, *42*, 6776+. Most work has dealt with chiral dienophiles. See Boeckman, R. K., Jr.; Naegeby, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 754. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908; Jurczak, J.; Tracy, M. *J. Org. Chem.* **1979**, *44*, 3347; Hashimoto, S.; Komeshima, N.; Koga, K. *Chem. Commun.* **1979**, 437; Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, 6359; Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333.
(2) For some recent studies of Diels–Alder reactions of juglone, see: (a) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554. (b) Trost, B. M.; Ippen, J.; Vladuchick, W. C. *Ibid.* **1977**, *99*, 8116. (c) Boeckman, R. K., Jr.; Jr.; Dolak, T. M.; Culos, K. U. *Ibid.* **1978**, *100*, 7098. (d) Kelly, T. R.; Montury, M. *Tetrahedron Lett.* **1978**, 4309, 4311.



1

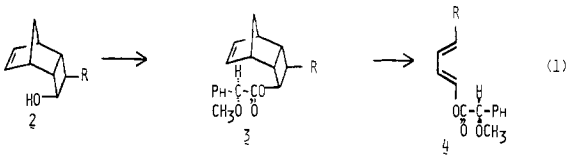
On the basis of a π-stacking model, two conformations can be envisioned for a diene such as **2**. In the folding represented by **2a**, the large group L projects toward the diene, encountering a



2A 2B

severe nonbonded interaction. Such a nonbonded interaction is between the small group S and the diene in conformer **2b**. On this basis, the latter would be favored. Effectively, the aromatic ring then serves as a steric steering group to direct the incoming dienophile to one of the two enantiotopic faces of the diene. Indeed, this simple model nicely predicts the observations.

The requisite dienes were synthesized according to eq 1.[4]

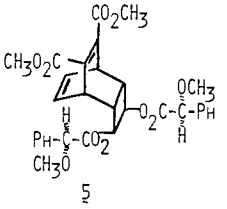


(1)

2 3 4

Esterification of **2** with (*S*)-*O*-methylmandeloyl chloride[5] or (*S*)-*O*-methylmandelic acid in the presence of dicyclohexylcarbodiimide and DMAP[6] led to the esters **3** (R = H, C_2H_5). Thermolysis liberated the dienes **4** (R = H, C_2H_5), quantitatively.

The diene **4** (R = (*S*)-*O*-methylmandeloxy) was available by the thermolysis of **5**.[7] Because of the possibility of racemization,



5

especially in the esterification step, the optical purity of diene **4** (R = H), $[\alpha]_D^{23}$ +14.4° (*c* 0.025, $CHCl_3$), was determined independently. Use of the chiral shift reagent Eu(hfbs)$_3$[8] showed no doubling of peaks whereas the racemic compound, prepared identically from racemic O-methylmandelic acid, showed two methoxy singlets of equal intensity at δ 4.09 and 4.20 with 20 mol % shift reagent. Thus, on this basis, we estimate the optical purity of **4** to be >95% and, probably, ~97% based upon the fact that the starting mandelic acid is 97% optically pure.

(3) Stork, G.; Hadedorn A. A., III. *J. Am. Chem. Soc.* **1978**, *100*, 3609. (b) Trost, B. M.; Caldwell, C., unpublished work.
(4) Trost, B. M.; Godleski, S. A.; Ippen, J. *J. Org. Chem.* **1978**, *43*, 4559.
(5) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732.
(6) Hassner, A.; Alexian, V. *Tetrahedron Lett.* **1978**, 4475.
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(8) Goering, H. L.; Eickenberry, J. N.; Koermer, G. S.; Lattimer, C. J. *J. Am. Chem. Soc.* **1974**, *96*, 1493.

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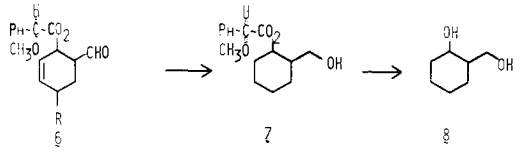
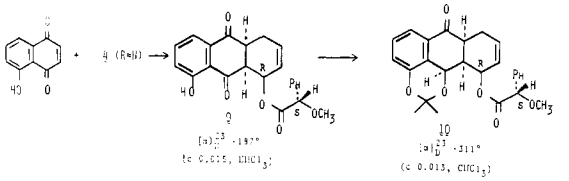
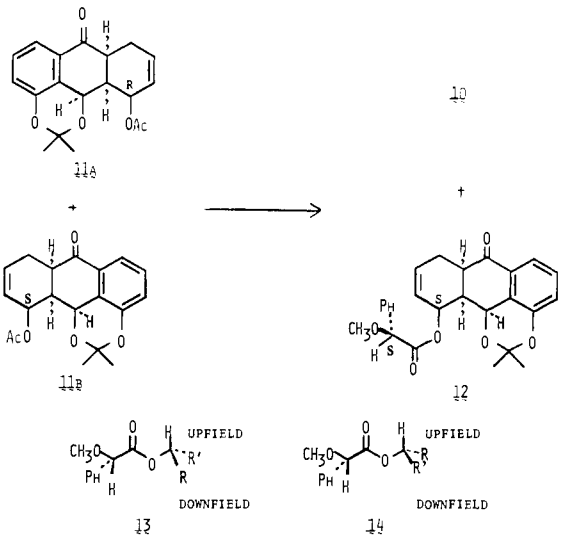
Cycloaddition of **4** (R = H) with acrolein in toluene in the presence of 15 mol % boron trifluoride etherate at −20 °C for 48 h led to a 98% yield of adduct **6** (R = H). The absorptions for



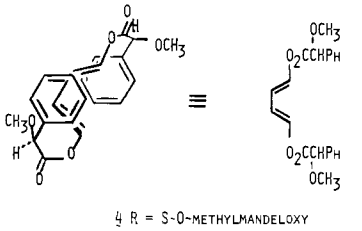
the aldehydic protons at δ 9.65 and 9.20 in an 82:18 ratio represent the degree of asymmetric induction. To confirm this assessment and to determine the absolute configuration, the adduct **6** (R = H) was reduced ($NaBH_4$, C_2H_5OH, 0 °C, 86%; then 10% Pd/C, C_2H_5OAc, 1 atm of H_2, room temperature, 84%) to give **7** and then hydrolyzed (AGl-X2 hydroxide resin base, H_2O, 50 °C) to the known diol **8**,[9] $[\alpha]_D^{23}$−17.7° (*c* 0.01, H_2O). From the known rotation and configuration of **8**, the observed rotation corresponds to a 75:25 ratio of the 1*R*,2*R* to 1*S*,2*S* isomer. Similarly, diene **4** (R = C_2H_5) reacted with acrolein to give adduct **6** (R = C_2H_5) with the 3*R*,4*S*,6*R* configuration depicted as the major isomer (80:20) as determined by the aldehydic proton absorptions (δ 9.56 and 9.07) and subsequent correlation.[9] Most significant is the reaction of diene **4**, R = H, with juglone in the presence of 1.6 equiv of boron triacetate[2d] ($CHCl_3$, 0 °C, room temperature).



The adduct **9**, isolated in 98% yield, showed a single set of absorptions in the 270-MHz NMR spectrum suggestive of complete asymmetric induction. The instability of the adduct led us to convert it to the more stable derivative **10**,[11] mp 130–0.5°C ($NaBH_4$, C_2H_5OH, 0 °C; $CH_3C(OCH_3)_2CH_3$, DMF, TsOH, room temperature). Not only did the 270-MHz ^1H NMR spectrum show only a single set of absorptions, the 67-MHz ^{13}C NMR spectrum showed cleanly 23 absorptions (24 different C, thus one degeneracy). Either complete asymmetric induction occurred or the nonequivalence of the two diastereomers was not being revealed by high-field NMR spectroscopy. To rule out the latter possibility, the acetate of a racemic mixture of **11** was cleaved (1.1 equiv of vitride, $PhCH_3$, 0 °C),[3b] and the racemic alcohol esterified with (*S*)-*O*-methylmandelic acid (PCC, DMAP, ether, room temperature) to give a mixture of **10** and **12**. As expected, clear doubling of absorptions occurred in both the 270-MHz ^1H and 67-MHz ^{13}C spectra. The optical purity of **10** was assessed at >97%. The absolute configuration of **10** was assigned on the basis of Mosher's model[12] for mandelate esters as represented in **13** and **14**. The vinyl protons of the two diastereomers **10** and **12** appear at δ 5.39 and 5.77 for one and δ 5.93 and 5.96 for the other, in agreement with the assignment of the higher field signals to **10**. Thus, the product from the cycloaddition corresponds to the absolute configuration depicted in **10**.



In all three cases, the absolute configuration corresponds to reaction of the diene from the conformer represented by **2b**. It is interesting to note the increase in asymmetric induction as a function of the dienophile. This effect can be interpreted in terms of the importance of charge-transfer intermediates in the Diels–Alder reaction.[13] It can be argued that the importance of the π-stacking interaction increases with increased charge transfer between the diene and dienophile. The fact that juglone should form stronger charge-transfer complexes than acrolein then accounts for the increase in asymmetric induction from 60% to 100% with the two dienophiles. Further evidence that such a π-stacking interaction may be important arose in the complete inertness of diene **4** (R = (*S*)-*O*-methylmandeloxy) toward cycloaddition.



4 R = S-O-METHYLMANDELOXY

Apparently the diene is sandwiched between the two aromatic rings, and thereby both faces of the diene are shielded. We believe the above represents a useful working model for designing asymmetric partners in the Diels–Alder reaction. The fact that adduct **9** is available with complete control of absolute stereochemistry enhances its importance as a synthetic intermediate in tetracycline-type natural products.

Acknowledgment. We wish to thank the National Institutes of Health (National Cancer Institute) for generous support of our programs. We thank Mr. C. Caldwell for helpful discussions and a generous sample of **11**.

Supplementary Material Available: ^{13}C spectra for optically active **9** and the racemic series **9** and **11** (1 page). Ordering information is given on any current masthead page.

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(11) 270-MHz ^1H NMR ($CDCl_3$) δ 7.71 (dd, 1 H, *J* = 8, 1 Hz), 7.33 (t, 1 H, *J* = 8 Hz), 7.26–7.33 (m, 3 H), 7.03 (dd, 1 H, *J* = 7.5, 1 Hz), 6.96–7.00 (m, 2H), 5.83 (ddd, 1 H, *J* = 10, 5, 2.5 Hz), 5.61 (t, 1 H, *J* = 4 Hz), 5.46 (m, 2 H), 3.26 (s, 1 H), 3.25 (dm, 1 H, *J* = 17.5 H z), 3.20 (s, 3 H), 3.07 (dd, 1 H, *J* = 10, 5 Hz), 2.99 (t, 1 H, *J* = 6.5 Hz), 2.22 (dm, 1 H, *J* = 17.5 Hz), 1.67 (s, 3 H), 1.61 (s, 3 H). 67 MHz ^{13}C NMR ($CDCl_3$): 214.8 (C=O), 169.0 (C=O), 150.6 (HC=), 136.0 (HC=), 131.0 (Ar), 131.4 (Ar), 128.2 (Ar), 128.1 (Ar), 126.5 (Ar), 125.2 (Ar), 122.8 (Ar), 121.0 (Ar), 118.3 (Ar), 101.5 (O–C–O), 81.3 (COCHO), 66.0 (ArCHO*), 64.2 (COOCH*), 57.3 (OCH_3), 42.1 (CH), 42.06 (CH), 28.3 (CH_2), 23.6 (CH_3), 23.3 (CH_3). Assignments indicated by * may be reversed. IR ($CHCl_3$) 1740, 1687, 1599, 1382 cm^{-1} Anal. Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 72.09; H, 6.06.

(12) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(13) This subject was first discussed by Woodward. [Woodward, R. B.; *J. Am. Chem. Soc.* **1942**, *64*, 9058. Woodward, R. B.; Baer, H. *Ibid.*, **1944**, *66*, 645.] Also see Sauer, J. *Angew Chem., Int. Ed. Engl.* **1967**, *6*, 16.

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