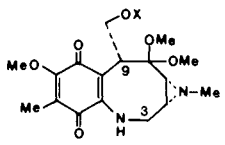
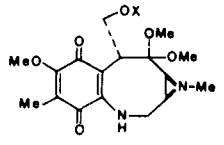
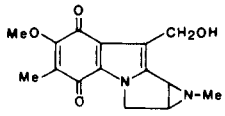


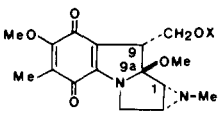
11, X = H
14, X = $CO_2C_6H_5$
16, X = C_6H_5



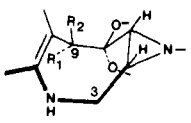
12, X = H
15, X = $CO_2C_6H_5$



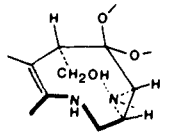
13



17, X = H
18, X = $CONH_2$



11a, R_1 = CH_2OH, R_2 = H
12a, R_1 = H, R_2 = CH_2OH



11b

droxymethyl group in the eight-membered quinone which cyclizes to the mitosene **13.** The following argument is proposed. Two tub conformations[12] **11a** and **11b** (slightly twisted) are considered as possible preferred conformations for **11.** There is no serious increase in steric hindrance in bringing **11a** or **11b** to the transition state for the transannular cyclization. Examination of a molecular model suggests that the preferred conformation of the trans compound **12** is most likely the tub conformation **12a** corresponding to **11a,** because the other tub conformation corresponding to **11b** experiences considerable steric compression between the aziridine and quinone rings, and also between the hydroxymethyl and amide NH groups. There is a serious increase in steric hindrance in bringing **12a** to the transition state for the transannular cyclization.

We anticipated that the preferred conformation of **11** would be **11b** because of the hydrogen-bond stabilization indicated. Valuable information was obtained from the difference in stability of phenyl carbonates **14**[7] and **15,**[7] synthesized, respectively, from **11** and **12** under standard conditions ($ClCO_2C_6H_5$/Py/0 °C). *cis*-Phenyl carbonate **14** decomposed to phenyl ether **16**[7] on standing at room temperature for 2 days, while *trans*-phenyl carbonate **15** was stable under the same conditions. Furthermore, a strong peak corresponding to (M^+ − 44) was observed in the mass spectrum of **14,** while no such peak was observed in the mass spectrum of **15.**[13] These results can be rationalized in terms of an intramolecular interaction between the aziridine and phenyl carbonate groups which is *only* possible in the conformation corresponding to **11b.** Thus, this conformation must exist at least to some extent even for **14.** All of the ^1H NMR signals of **11** in $CDCl_3$ are sharp, suggesting that **11** exists in one preferred conformation; i.e., **11b,** or that interconversion between two conformations **11a** and **11b** is rapid. The second possibility is unlikely because a serious interaction between the hydrogen atoms at C-3 and C-9 occurs during the interconversion. This analysis suggested that the transannular cyclization of **11** would result in the desired stereochemistry with respect to the C-1, C-9a, and C-9 positions.[14]

Trityl tetrafluoroborate[15,16] (CH_2Cl_2/25 °C) smoothly effected the transannular cyclization of **11** to yield exclusively decarbamoyl-*N*-methylmitomycin A (**17**)[7] (deep purple needles; mp 99–101 °C dec; M^+ obsd 320.1387, calcd for $C_{16}H_{20}O_5N_2$ 320.1372; ^1H NMR ($CDCl_3$) δ 1.84 (3 H, s), 2.26 (3 H, s), 3.16 (3 H, s), 4.04 ppm (3 H, s); UV (CH_3OH) λ_{max} 216 nm (log ϵ 4.20), 320 (3.97), 530 (3.08)) in 90% yield. The synthetic substance was identical with an authentic sample prepared from mitomycin A (**1a**)[17] in two steps (1, $NaOCH_3$/CH_3OH–C_6H_6/25 °C;[18] 2, CH_3I/K_2CO_3/acetone/reflux[11,19]) in all respects (^1H NMR, UV, mass spectrum, IR, and TLC). Decarbamoyl-*N*-methylmitomycin A (**17**) was converted to *N*-methylmitomycin A (**18**)[7,11] (mp 172–174 °C dec) in two steps (1, $COCl_2/C_6H_5N(CH_3)_2/CH_2Cl_2$–$C_6H_5CH_3$/25 °C; 2, NH_3/CH_2Cl_2–$C_6H_5CH_3$/0 °C) in 85% yield. The transformation of *N*-methylmitomycin A (**18**) to porfiromycin (**1d**) has been previously reported.[11]

The total synthesis of mitomycins A, B, and C by the route reported is in progress in our laboratory.

Acknowledgment. Financial assistance from National Institutes of Health, National Science Foundation, and Hoffmann-La Roche is gratefully acknowledged.

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(2) This paper was presented at the 25th National Organic Chemistry Symposium, Morgantown, W. Va., June 19–23, 1977, by Y. Kishi.
(3) See, for example, "The Merck Index", M. Windholz, Ed., 9th ed, Merck & Co., Rahway, N.J., 1976, p 807 ff and references cited therein.
(4) See the references cited in part I of this series.
(5) The structure of mitomycin B including its absolute configuration was recently confirmed by x-ray crystallography: R. Yahashi and I. Matsubara, *J. Antibiot.*, **29,** 104 (1976).
(6) G. O. Morton, G. E. Van Lear, and W. Fulmor, *J. Am. Chem. Soc.*, **92,** 2588 (1970).
(7) Satisfactory spectroscopic data were obtained for this substance.
(8) We have recently developed a method to transform diol **7** into epoxide **8** in six steps (1, $NaOCH_3/CH_3OH$/25 °C; 2, MsCl/Py–CH_2Cl_2/25 °C; 3, K_2CO_3/CH_2Cl_2/25 °C; 4. Ms_2O/Py/25 °C; 5. KOAc/18-crown-6/DMF/120 °C; 6, $NaOCH_3/CH_3OH$–CH_2Cl_2/25 °C). The overall yield was 56%.
(9) Numbering in this paper corresponds to that of the mitomycins.
(10) Apparently **12** exists as a mixture of two conformers.
(11) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84,** 3185 (1962).
(12) See, for example, *Top. Stereochem.*, **7,** 128 (1973).
(13) The corresponding phenyl carbonate in the deiminomitomycin A series is also stable, and does not give a peak of (M^+ − 44) in the mass spectrum.[1]
(14) One can reach the same conclusion about the stereochemistry outcome of the transannular cyclization of **11,** even for the second possibility.
(15) D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, and D. Zurr, *J. Chem. Soc., Perkin Trans. 1,* 542 (1972).
(16) We have recently discovered that HBF_4 (CH_2Cl_2/25 °C) or $HClO_4$ (CH_2Cl_2/25 °C) effects the transannular cyclization of **11** as well as $(C_6H_5)_3CBF_4$ does. The effective reagent under the trityl tetrafluoroborate conditions is most likely HBF_4 liberated from $(C_6H_5)_3CBF_4$ and moisture since 0.4 equiv of this reagent gave the best result. Hydrogen chloride or boron trifluoride etherate in methylene chloride at room temperature gave less satisfactory results because elimination of methanol from the produced mitosane **17** could not be controlled under these conditions. The conditions for the transannular cyclization used in the synthesis of deiminomitomycin A[1] could not be applied to **11,** because transketalization of **11** (and **14**) to the corresponding hemithioketal was unsuccessful under a variety of conditions. The trityl tetrafluoroborate condition was not successful for the synthesis of deiminomitomycin A because elimination of methanol from the produced deiminomitomycin A could not be controlled under these conditions.
(17) We are indebted to Dr. J. S. Webb, Lederle Laboratories, for a sample of mitomycin A.
(18) S. Kinoshita, K. Uzu, K. Nakano, and T. Takahashi, *J. Med. Chem.*, **14,** 109 (1971).
(19) S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, T. Takahashi, and M. Matsui, *J. Med. Chem.*, **14,** 103 (1971).
(20) D. W. Brattesani and C. H. Heathcock, *Tetrahedron Lett.*, 2279 (1974).

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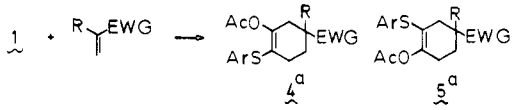
On the Regioselectivity of the Catalyzed and Uncatalyzed Diels–Alder Reaction

Sir:

We wish to report that the regioselectivity of the Diels–Alder reaction can be varied dramatically by a combination of the competing orientating influences of sulfur and oxygen on

Table I. Cycloadditions of **1**

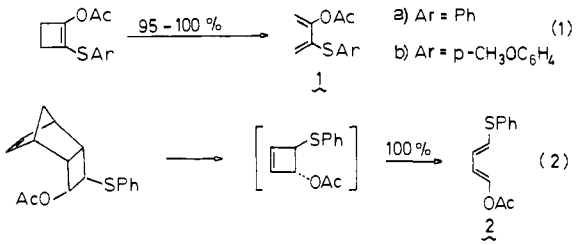


Ar	R	EWG	Conditions	% yield	Ratio of **4**:**5**
Ph	CH_3	CHO	Neat, reflux	84	10:1
4-$CH_3OC_6H_4$	CH_3	CHO	Neat, reflux	84	13:1
			BF_3 Et_2O,[b] rt[c]	94	>50:<31
			$MgBr_2$ Et_2O,[b] rt[c]	55	>50:<31
4-$CH_3OC_6H_4$	CH_3	CO_2CH_3	Neat, reflux	93	9:1
			BF_3 Et_2O,[b] rt[c]	95	>50:<31
4-$CH_3OC_6H_4$	H	$COCH_3$	Neat, reflux	86	10:1
4-$CH_3OC_6H_4$	H	CN	Neat, reflux	72	8:1
4-$CH_3OC_6H_4$	H	CO_2CH_3	Neat, reflux	91	10:1

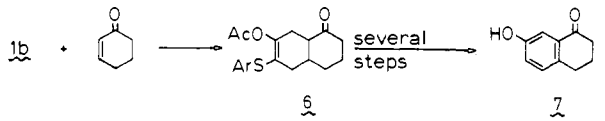
[a] See ref 5 and 9. [b] 5 mol % of catalyst is employed. [c] Room temperature.

thermal cycloadditions[1,2] and the effect of Lewis acids. *Most importantly, Lewis acids can either reinforce or oppose the effect of sulfur*—a result that is not anticipated using current concepts regarding factors affecting regiochemistry.[3] Thus, a degree of control that heretofore did not exist is available. Special interest derives from the application of these effects toward intermediates in the synthesis of the anthracycline antitumor agents.[4]

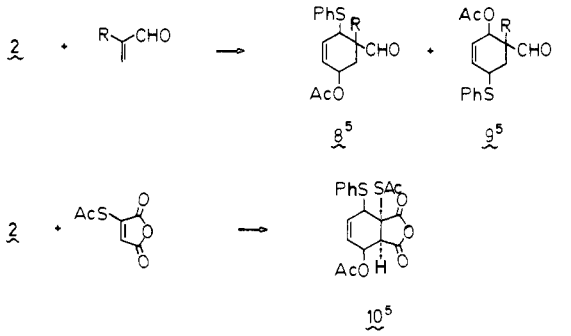
We examined the behavior of the dienes **1** and **2** available from the corresponding cyclobutenes as outlined in eq 1 and



eq 2. Diene **1**[5] is available in 40–65% overall yield from cyclobutanone[6] and diene **2**[5] in 30–33% overall yield from the Diels–Alder adduct of maleic anhydride and cyclopentadiene.[7,8] Diene **1** undergoes thermal cycloaddition at ~80 °C neat or in refluxing benzene or toluene (see Table I) with substantially higher regiocontrol by sulfur than was exercised by 2-methoxy-3-phenylthiobutadiene (**3**) (cf. ref 1). On the other hand, Lewis acids have a contrasting effect on the reactions of **1** compared with **3**. Whereas diene **3** showed an enhancement of regiocontrol by oxygen relative to sulfur upon addition of magnesium bromide,[1] diene **1** shows a reinforcement of the directive effect of sulfur.[9] For example, addition of boron trifluoride etherate or anhydrous magnesium bromide enhanced the ratios of **4**:**5** to >50:1. In addition, under catalyzed conditions 2-cyclohexenone underwent cycloaddition in 80–85% yields also with sulfur dominating as determined by conversion of **6** to **7**. Thus, sulfur can completely control the reaction.

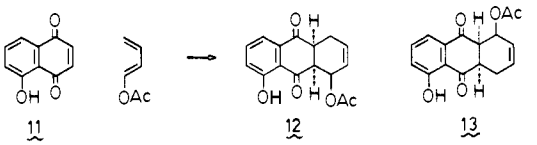


Diene **2** exhibits similar behavior. For example, reaction with methacrolein led to **8** as the dominant product (**8**:**9**, R = CH_3, 15:1) but in the presence of boron trifluoride etherate this ratio increases (**8**:**9**, R = CH_3, 20:1).[10] Thermal cycloaddition of acrolein and **2** led only to decomposition. In the presence of 0.9 equiv of boron trifluoride etherate only adduct **8**[5,10] (R = H) is obtained ($PhCH_3$, 0 °C). Thermal cycloaddition of **2** and



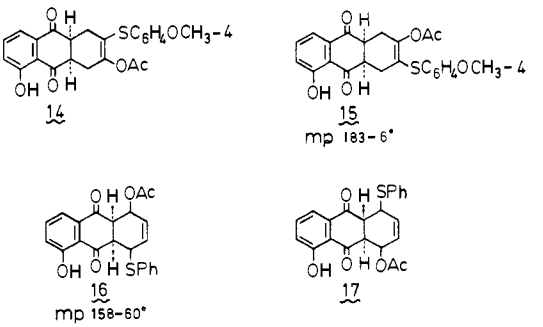
2-acetylthiomaleic anhydride led only to **10**.[5,10] Thus, sulfur is the controlling element.

Dramatically different results were obtained with juglone (**11**) as the dienophile. It is known that acetoxybutadiene adds to give **12** and **13** in a ratio of ~3:1.[11,12] Addition of 5 mol %

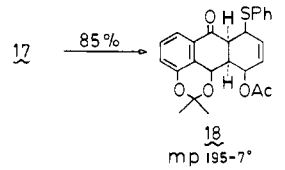


of boron trifluoride etherate at room temperature enhances this ratio so that essentially only **12** is obtained.[13] Thus, the carbonyl group ortho to the hydroxyl group determines the regiochemistry with respect to the dienophile.

Thermal addition of **1b** or **2** to juglone gives the adduct in which sulfur, not oxygen, dominates the regiochemistry, i.e., **14**:**15**,[5,9] 2:1 (82%); **16**[5,10]:**17**, 2.3:1 (69%). Addition of 0.1 to 1 equiv of boron trifluoride etherate completely *reverses* the regiochemistry so that **15** and **17** are the exclusive products;

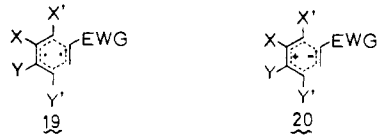


i.e., oxygen, not sulfur, completely dominates the regiochemistry. Adduct **17** was not characterized as such but reduced ($NaBH_4$, CH_3OH, 0 °C) and derivatized (2,2-dimethoxypropane, acetone, BF_3·Et_2O, room temperature) to give **18**.[5,14]



18
mp 195-7°

We attribute the differences to competing considerations of polar factors and odd electron distribution as illustrated by the two extreme forms **19** and **20** for the transition state. In the



19 20

thermal reaction, odd electron distribution as in **19** provides the dominating effect that determines regiochemistry. Since sulfur can stabilize a radical more effectively than oxygen,[15] it controls. However, if polar factors dominate, then oxygen would be anticipated to be the controlling element. In the Lewis acid catalyzed reaction polar factors should become more important relative to electron density. If the Lewis acid coordinates to the dienophile in promoting the Diels–Alder reaction, then a reversal from the thermal chemistry should be observed. Indeed, **1** and **2** show a complete reversal in regiochemistry of addition with juglone. On the other hand, the Lewis acid can coordinate with the diene in addition to or in lieu of the dienophile. Under such circumstances, it should preferentially coordinate to the acetoxy group and thus diminish the contributing effect of oxygen. In such a case, the reduced interaction of oxygen would enhance the observed regiochemical control exercised by sulfur. With dienophiles that don't tie up the Lewis acid as effectively as juglone, such as the acroleins and acrylates, the above effect leads to a reinforcement of the sulfur directing ability. Qualitatively, the magnitude of the catalytic rate enhancement supports this picture. Whereas the reaction of **1b** with juglone changes from 4 h at 110 °C (thermal) to 1.5 h at −10 °C (catalyzed), that of **1b** with α-methacrolein only changes from 16 h at 80 °C (thermal) to 16 h at room temperature (catalyzed).[16] While the frontier orbital PMO approach reaches the same conclusions with respect to the thermal reactions, it is unclear how such a rationale relates to the Lewis acid catalyzed reaction.[3]

In any event, by using sulfur as a control element and the effect of Lewis acids, great versatility in directing the orientation of Diels–Alder reactions is available.[17] The highly functionalized adducts obtained with dienes **1** and **2** are extremely valuable for further elaboration based upon β-keto sulfide chemistry[18] and sulfoxide pyrolyses[18] and sigmatropic rearrangements.[19] The juglone adducts have special applicability since they can serve as potential intermediates directed toward the tetracycline antibiotics and the anthracycline antitumor agents such as daunomycinone.[6] The asymmetry of ring A of juglone is translated to asymmetry of ring C which, in turn, can allow regiocontrolled introduction of the final ring.

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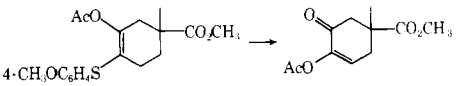
(5) This structure was fully supported by spectroscopic analysis and elemental analysis and/or high resolution mass spectroscopy.
(6) 2-Arylthiocyclobutanone[1] is acetylated (Ac_2O, $(C_2H_5)_3N$, room temperature) and pyrolyzed through a hot tube (350 °C at 1-mm pressure) mounted horizontally. **1b**: IR 1767 cm^{-1}; NMR δ 7.46 and 6.94 (AA'BB', 4 H), 5.61 (s, 2 H), 5.14 (br, 1 H), 5.06 (br, 1 H), 3.85 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR δ 168.2, 159.8, 150.4, 139.1, 134.5, 122.8, 115.1, 114.9, 105.6, 55.2, 20.5.
(7) Cf. preparation of 1,4-diacetoxybutadiene, M. E. Jung, *J. Chem. Soc., Chem. Commun.*, 956 (1974). For a correction of the stereochemical assignment of this diene, see J. F. W. Keanna and P. E. Eckler, *J. Org. Chem.*, **41**, 2625 (1976).
(8) The acyloin from the Diels–Alder adduct of cyclopentadiene and maleic anhydride has the hydroxyl group in the endo configuration in contrast to the assignment of Jung. Tosylation (TsCl, C_5H_5N, room temperature), displacement (PhSNa, $(C_6H_{13})_4NBr$, DMF, 0 °C), reduction ($NaBH_4$, ethanol, 0 °C), acetylation (Ac_2O, C_5H_5N, 0 °C), and pyrolysis (horizontal hot tube, 460 °C at 1 mm) gave **2**: mp 65–66 °C; IR 1771, 1646, 1571 cm^{-1}; NMR δ 7.32 (d, J = 12.1 Hz, 1 H), 6.31 (d, J = 14.7 Hz, 1 H), 6.23 (dd, J = 14.7, 10.3 Hz, 1 H), 6.06 (dd, J = 12.1, 10.3 Hz, 1 H); ^{13}C NMR δ 167.7, 138.9, 135.8, 129.8, 129.7, 128.3, 127.3, 125.6, 114.8, 20.4.
(9) Assignment of regiochemistry was established by spectroscopy and/or chemical behavior analogous to the methods employed for cycloadditions of **3**. See ref 1. For example 4 (R = CH_3, EWG = CO_2CH_3) was converted to i.



i

(10) Assignment of regiochemistry follows from spectroscopic data. For example in adduct **8** (R = CH_3) the methine adjacent to sulfur (δ 3.68) only shows coupling to the vinyl proton, whereas the methine adjacent to oxygen (δ 5.37) shows coupling to the methylene group and a vinyl proton.
(11) H. H. Inhoffen, H. Muxfeldt, H. Schaefer, and H. Kramer, *Croat. Chem. Acta*, **29**, 329 (1957); H. Musfeldt, *Angew. Chem.*, **74**, 825 (1962).
(12) Also see A. J. Birch and V. H. Powell, *Tetrahedron Lett.*, 3467 (1970).
(13) Experiment performed by C. Caldwell in these laboratories. A ratio of **12:13** of >20:1 is observed.
(14) The NMR spectrum of this compound clearly establishes the regiochemistry as well since the benzylic methine (δ 5.44 (d, J = 5.6 Hz) and acetoxy methine (δ 5.56 (dd, J = 5.5, 4.3 Hz)) couple to the same bridgehead proton at δ 3.14 as determined by spin decoupling. The methine next to sulfur (δ 3.90) couples (J = 5.0 Hz) to the bridgehead proton adjacent to the carbonyl group (δ 3.55).
(15) J. W. Timberlake, A. W. Garner, and M. L. Hodges, *Tetrahedron Lett.*, 309 (1973).
(16) The effect of Lewis acid complexation of the diene in addition to or in lieu of the dienophile on rate is difficult to predict. Using a frontier orbital PMO approach, it can be argued that a relative rate acceleration or deceleration will be observed.
(17) By modifying the substituents on S and O, control by O in the presence of Lewis acids with simple dienophiles as high as 10:1 can be obtained.
(18) B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976); D. Seebach and M. Teschner, *Chem. Ber.*, **109**, 1601 (1976).
(19) Cf. D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).

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Ab Initio Electronic Structure Calculations for Classical and Nonclassical Structures of the 2-Norbornyl Cation

Sir:

We report geometry optimized ab initio molecular orbital calculations employing both the STO-3G and the more flexible 4-31G basis sets[1] for the 2-norbornyl cation to help resolve the long-standing controversy as to whether the classical[2] or nonclassical[3] model best represents the known experimental data.

Geometry optimization for both ions was carried out at the STO-3G level using initial configurations obtained from the