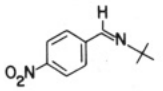
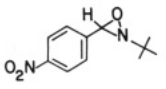
Table I. ^{18}O-Labeled *m*-Chloroperoxybenzoic Acid Oxidations[a]

substrate	reaction time, h	temp, °C	product	% yield	(M + 2)$^+$/M$^+$ ratio
	2	0		70[b]	0.38
	3	25		84[c]	0.36[d]
	3	25		92[c]	0.39[d]

[a] 1.2 equiv of *m*-chloroperoxybenzoic acid used in CH_2Cl_2. [b] Isolated yield. [c] GLC yield. [d] GLC/MS analysis.

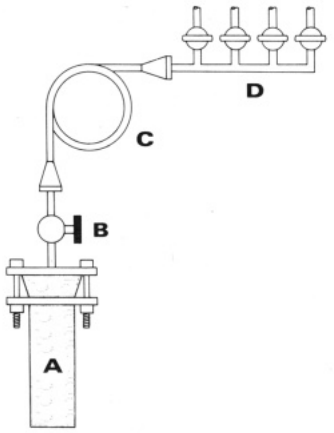


Figure 1. Apparatus for the preparation of $Na_2{}^{18}O_2$: (A) aluminum reaction vessel with Teflon gasket, (B) isolation valve, (C) copper tubing coil, (D) Swagelok manifold with stopcocks to vacuum, manometer, N_2, and $^{18}O_2$. The vessel outer dimensions are 110 mm × 35 mm (40 mm at top), and the wall thickness is 4 mm. Vessel temperature is determined by wrapping a thermometer in heating tape to the outer surface.

Preparation of ^{18}O-Labeled Na_2O_2. Cleaned sodium (1.50 g, 65.2 mmol) was placed into an aluminum reaction vessel (Figure 1; note that *Pyrex will not withstand the extreme reaction conditions*!) which was then evacuated and heated to 300–325 °C, using heating tape. $^{18}O_2$ (1 L, 44.6 mmol, 50% enriched) was opened to the reaction vessel. The vessel was agitated to break the initial oxide coating after which further oxidation proceeded rapidly. When oxygen was no longer being consumed, the vessel was cooled and opened under a nitrogen atmosphere. The powdery contents were finely ground and returned to the vessel. After evacuation and reheating (300–325 °C) of the vessel, additional $^{18}O_2$ (1 L, 44.6 mmol, 50% enriched) was opened to the vessel and allowed to react overnight. The resulting yellow $Na_2{}^{18}O_2$ (2.24 g, 34% based on $^{18}O_2$; active oxygen content 71%, determined by iodometric titration) was used immediately.

Preparation of ^{18}O-Labeled *m*-Chloroperoxybenzoic Acid.[6] THF (5 mL) was placed into a 100-mL, three-necked, round-bottomed flask fitted with an addition funnel and thermometer. $Na_2{}^{18}O_2$ (2.17 g, 20.7 mmol) was added, and the mixture was cooled to −20 °C in a CCl_4–dry ice bath. Into the funnel was placed *m*-chlorobenzoyl chloride (3.36 g, 19.2 mmol) and THF (5 mL). This solution (1.5 mL) was slowly added to the $Na_2{}^{18}O_2$ mixture. $MgSO_4 \cdot 7H_2O$ (50 mg, 0.2 mmol) in H_2O (0.5 mL) was cooled to 0 °C and slowly added to the reaction mixture.[7] The remaining acid chloride solution was added dropwise over 30 min, keeping the reaction temperature between −10 and −5 °C. After the addition was complete, the funnel was rinsed with THF (2 mL). H_2O (30 mL) was cooled to 0 °C and slowly added to the reaction mixture, maintaining the internal temperature below 0 °C. The entire mixture was poured into H_2SO_4 (20% aqueous solution, 25 mL) cooled to 0 °C. The resulting white suspension was extracted with Et_2O (2 × 50 mL). The combined ether layers were sequentially washed with H_2O (50 mL) and sodium phosphate buffer (pH 7.0, 50 mM, 3 × 50 mL). Drying ($MgSO_4$) and evaporation of the solvent in vacuo yielded peroxy acid (2.87 g, 85.5%) as a white powder (mp 85–87 °C) which was found to contain 99% active oxygen (iodometric titration): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.39–7.51 (m, 1 H), 7.58–7.67 (m, 1 H), 7.87–8.09 (m, 2 H); IR (Nujol) 3250, 1735, 1710, 1275, 1255, 1075, 900, 810, 730 cm^{-1}; MS, *m/e* (M$^+$, relative intensity) 172 ($C_7H_5{}^{35}Cl{}^{16}O_3$, 29), 174 ($C_7H_5{}^{37}Cl{}^{16}O_3$ and $C_7H_5{}^{35}Cl{}^{16}O_2{}^{18}O$, 45), 176 ($C_7H_5{}^{37}Cl{}^{16}O_2{}^{18}O$ and $C_7H_5{}^{35}Cl{}^{16}O{}^{18}O_2$, 22), 178 ($C_7H_5{}^{37}Cl{}^{16}O{}^{18}O_2$, 4); total active ^{18}O, 39%.

Acknowledgment is made to the National Cancer Institute (Grant No. 2 RO1 CA-20574) and the Alfred P. Sloan Foundation for support of this work.

(6) Adapted from the procedure of: Vilkas, M. *Bull. Soc. Chim. Fr.* **1959**, 1501.
(7) Moyer, J. R.; Manley, N. C. *J. Org. Chem.* **1964**, *29*, 2099.

Communications

Competition between Endocyclic and Exocyclic Periselectivity in Cycloadditions of *o*-Xylylenes to Fulvenes

Summary: The reactions of *o*-xylylenes with fulvenes produce [6 + 4], spiro [4 + 2], or ring [4 + 2] adducts, depending upon the substituents on the xylylene or fulvene.

Sir: We have described the propensity of "neutral" and electron-deficient dienes to cycloadd in a Diels–Alder ([4 + 2]) fashion to endocyclic double bonds of fulvenes.[1] On the basis of a consideration of the frontier molecular orbitals of fulvenes, we predicted,[1,2] and later found experimentally,[3,4] that electron-rich dienes undergo [6 + 4] cycloadditions to fulvenes. Padwa and co-workers found that a nitrile ylide undergoes both [6 + 4] and [4 + 2] cyclo-

(1) Houk, K. N.; Luskus, L. J. *J. Org. Chem.* **1973**, *38*, 3836.
(2) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301. Houk, K. N.; George, J. K.; Duke, R. E., Jr. *Tetrahedron* **1974**, *30*, 523. Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

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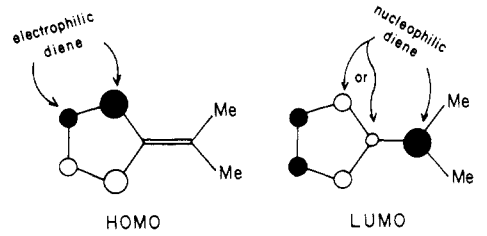
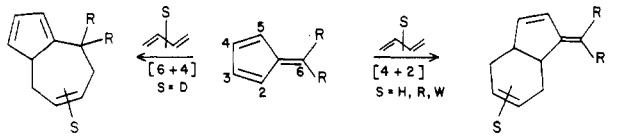


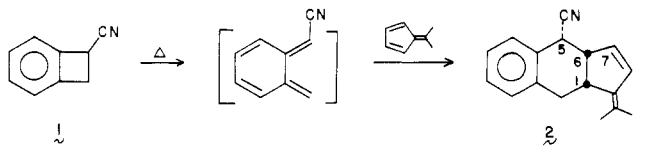
Figure 1. Frontier molecular orbitals of dimethylfulvene and predicted sites of attack by dienes.

additions to dimethylfulvene;[5] these results are in agreement with the prediction that the nucleophilic terminus of an electron-rich 4π cycloaddend should attack atom 6 of the fulvene, accompanied by bonding at either atoms 2 or 1, both of which modes are thermally allowed. The more electron-rich 1,3-dipole, diazomethane, adds to fulvenes mainly in the [6 + 4] sense.[6] Moss found that nucleophilic carbenes add to the exocyclic double bond, while electrophilic carbenes add to an endocyclic double bond.[7]



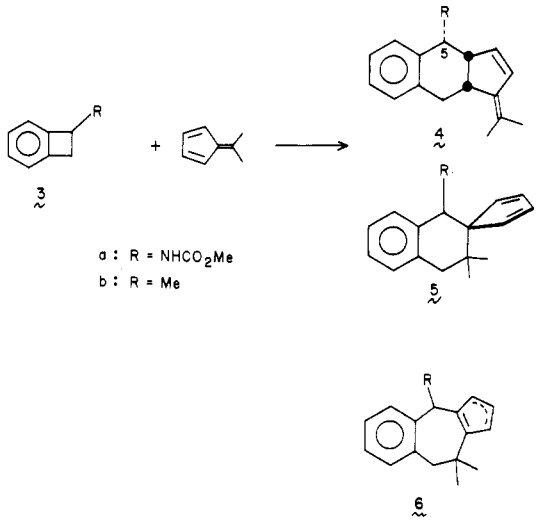
Although these periselectivity patterns have been amply demonstrated for reactions of a variety of 4π addends and fulvenes,[1-4] there have been no previous studies of changes in periselectivity induced by substituent changes on a single type of diene. We herein report such a study and the surprising finding that electron-rich *o*-xylylenes add primarily in a [4 + 2] fashion to the exocyclic double bond of fulvenes.

When cyanobenzocyclobutene, **1**,[8] was refluxed in xylene with a threefold excess of dimethylfulvene for 5 h, a single 1:1 adduct, **2**, mp 107–108 °C, was isolated in 67% yield after column chromatography.[9] The structure of the adduct, **2**, was established by 300-MHz NMR spectroscopy.



The regiochemistry is compatible with the union of the site of highest fulvene HOMO coefficient (C-2) with the site of the largest *o*-xylylene terminal LUMO coefficient (the unsubstituted carbon). The parent system, *o*-xylylene, generated from benzodihydrothiophene dioxide, also gives only the endocyclic [4 + 2] cycloadduct. The rearranged aromatized adduct, isopropylnaphthocyclopentene, is also obtained in this reaction.[9]

When [(methoxycarbonyl)amino]benzocyclobutene, **3a**, prepared from **1**,[10] was heated in toluene with 1.5 equiv of dimethylfulvene for 4 h, column chromatography gave two adducts, **4a** (mp 175–177 °C) and **5a** (mp 139 °C) in 28% and 66% yield, respectively.[9] The structure of **5a** was proven by a single-crystal X-ray structure determination.[11]



Pyrolysis of **3b**[12] with dimethylfulvene in a sealed tube in toluene at 185 °C for 5 h gave the [4 + 2] adduct **4b**[13] in 50% yield, the spiro adduct **5b** in 9% yield, and the [6 + 4] adduct **6b** in 18% yield. The [6 + 4] adduct consists of an inseparable mixture of two cyclopentadiene isomers in a ratio of 1.6:1, according to NMR. Pyrolysis of **5b** at 200 °C for 2 h does not give the [6 + 4] adduct, indicating that **6b** does not arise by a 1,5 sigmatropic shift of **5b**.

Thus, a donor substituent on the *o*-xylylene causes the preferred mode of cycloaddition to shift from endocyclic [4 + 2] to union of the most nucleophilic terminus of the diene to the exocyclic carbon of the fulvene, as predicted from frontier molecular orbital considerations,[2] with formation of either the spiro [4 + 2] or the [6 + 4] adducts in specific cases. This result is consistent with the reactions of acyclic dienes in that the most nucleophilic diene terminus attacks the site of largest LUMO coefficient (Figure 1), but contrasts to the acyclic diene case, since the latter appear to give only the [6 + 4] adducts.[3,4,14] Only fulvenes in which the ring carbons are blocked from entering into cycloadditions have previously been found to undergo cycloadditions across the exocyclic double bond.[15]

Electron-withdrawing substituents on atom 6 of the fulvene should further enhance nucleophilic attack at C-6.[2] Indeed, the reaction of **3a** with 6-[(*p*-nitrobenzoyl)oxy]-fulvene, **7**,[16] gave only the spiro adduct **8** (mp 190–191 °C), in 93% yield, after refluxing the reactants for 4 h in toluene.

In spite of the spiro nature of **8**, it can be converted to an azulene. Thus, treatment of **8** with 5% KOH in methanol produced benzo[*f*]azulene, **9**,[17] in 41% yield. This transformation must involve elimination of acid, 6π electrocyclic opening, and 10π electrocyclic reclosure to the dihydroazulene, which subsequently loses amine. The last

(3) Dunn, L. C.; Chang, Y.-M.; Houk, K. N. *J. Am. Chem. Soc.* **1976**, *98*, 7095.
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(5) Padwa, A.; Nobs, F. *Tetrahedron Lett.* **1978**, 93.
(6) Houk, K. N.; Luskus, L. J. *Tetrahedron Lett.* **1970**, 4029.
(7) Moss, R. A.; Young, C. M.; Perez, L. A.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1981**, *103*, 2413.
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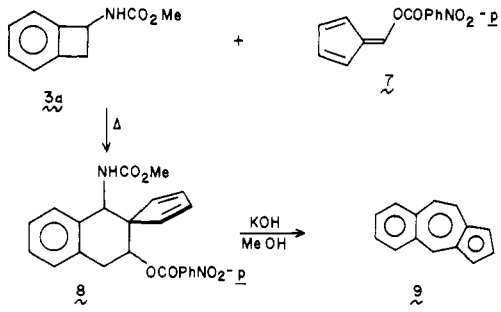
(10) Skorcz, J. A.; Robertson, J. E. *J. Med. Chem.* **1965**, *8*, 255.
(11) Details of the X-ray crystallographic data are given as supplementary material.
(12) Horner, L.; Subramanian, P. V.; Eiben, K. *Justus Liebigs Ann. Chem.* **1968**, *714*, 91.
(13) Adduct **4b** was contaminated with a 2:1 adduct under these conditions. When the reaction was carried out in dibutyl phthalate solvent, none of the 2:1 adduct was obtained, although the material balance was much poorer under these conditions.
(14) The possible role of spiro [4 + 2] adducts as precursors to apparent [6 + 4] adducts in previously reported acyclic diene reactions[3,4] is the subject of current study.
(15) Wieland, H.; Probst, O. *Justus Liebigs Ann. Chem.* **1937**, *530*, 274.
(16) Gupta, Y. N.; Mani, S. R.; Houk, K. N. *Tetrahedron Lett.* **1982**, *23*, 495.
(17) Plattner, Pl. A.; Furst, A.; Keller, W. *Helv. Chim. Acta* **1949**, *32*, 2464.



two steps find analogy in the Hafner–Ziegler azulene synthesis.[18]

The subtle factors that control the competition between spiro [4 + 2] and [6 + 4] cycloadditions are currently under investigation.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for financial support of this research. The 300-MHz spectrometer (Pittsburgh) and X-ray diffractometer (LSU) were acquired with funds from the National Science Foundation, to whom we are triply grateful.

Supplementary Material Available: ORTEP drawing of **5a**, crystallographic data for **5a**, and table of positional and thermal parameters (6 pages). Ordering information is given on any current masthead page.

(18) Ziegler, K.; Hafner, K. *Angew. Chem.* **1955**, *67*, 301. Hafner, K. *Justus Liebigs Ann. Chem.* **1957**, *606*, 79.

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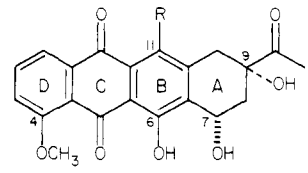
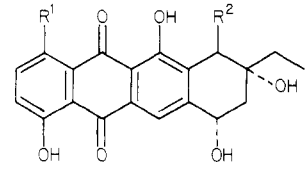
Regiospecific Total Synthesis of 6-Deoxyanthracyclines: 4-Demethoxy-6-deoxydaunorubicin

Summary: A regiospecific approach to 6-deoxyanthracyclinones, which has resulted in the synthesis of the novel anthracycline 4-demethoxy-6-deoxydaunorubicin, is reported. The construction of aglycone entails the coupling of the metalated 1,4-dimethoxynaphthalene with 2-carbomethoxy-4-acetylcyclohexanal. The new aldehyde was prepared from cis tetrahydrophthalic monoester via a regioselective acylation followed by conversion of the carboxylic group to a formyl group. The daunosaminyl glycoside showed on HeLa cells the same cytotoxicity as daunorubicin.

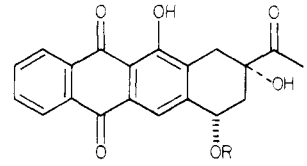
Sir: Recent advances in the regiospecific synthesis of anthracyclines have provided several new routes to aglycones with ring B as in daunomycinone (**1**)[1] or in its 11-deoxy analogue (**2**).[2] Little attention has been focused on the synthesis of 6-deoxyanthracyclinones represented hitherto by naturally occurring pigments δ-rhodomycinone (**3**),[3] α_2-rhodomycinone (**4**), α-citromycinone (**5**), and γ-citromycinone (**6**).[4] In this communication we report the synthesis of the novel anthracycline 4-demethoxy-6-deoxydaunorubicin (**7**).



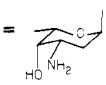
1, R = OH
2, R = H



3, R^1 = OH; R^2 = CO_2CH_3
4, R^1 = R^2 = OH
5, R^1 = H; R^2 = OH
6, R^1 = R^2 = H

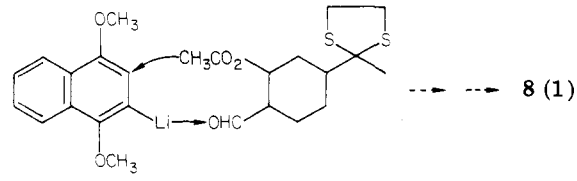


7, R =

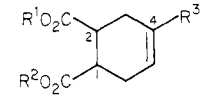


8, R = H

Our original synthetic approach for the construction of the aglycone **8** entails the coupling of the metalated 1,4-dimethoxynaphthalene (**9**), which formally represents the CD rings, with the new aldehyde **10**, the ring A precursor, followed by cyclization affording ring B as illustrated in eq 1.



9 **10**



11, R^1 = CH_3; R^2 = R^3 = H
12, R^1 = CH_3; R^2 = H; R^3 = $COCH_3$
13, R^1 = R^2 = CH_3; R^3 = $COCH_3$

The substrate **11**[5] was chosen as inexpensive starting material for the preparation of **10**. The reaction of **11** with CH_3COCl (i, $CHCl_3$, 3 equiv of $AlCl_3$, −5 °C, 8 h; ii, K_2CO_3, room temperature, 5 h) gave regioselectively **12**[6] (mp 117–121 °C) in 65% overall yield after crystallization. The regioselectivity of this reaction, affording only **12**, is probably due to the polarization induced on the double bond of **11** by an intermediate aluminum carboxylate. The structure of **12** was supported by spectroscopic[7] and chemical[8] evidence. Compound **12** was readily transformed into **10**, obtained as an oil in 45% overall yield (i, EtOH,

(1) For a comprehensive review, see: Arcamone, F. *Med. Chem. (Academic)* **1981**, *17*.

(2) (a) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561. (b) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799.

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(4) (a) Brockmann, H.; Niemeyer, J. *Chem. Ber.* **1968**, *101*, 1341. (b) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1981**, 1337. (c) Kende, A. S.; Gesson, J. P.; Demuth, T. P. *Ibid.* **1981**, 1667.

(5) Yadav, J.; Corey, P.; Hsu, C. T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, 811.

(6) All products showed ^1H and ^{13}C NMR, IR, and mass spectra consistent with the assigned structures. Melting points are uncorrected; the yields are unoptimized.

0022-3263/83/1948-0405$01.50/0