1-(1-Carboxy-1-methylethyl)-3-(methylthio)-4-(phenoxyacetamido)-2-azetidinone (17). To a solution of the phosphinimine **16** (87 mg, 0.18 mmol) and triethylamine (40 mg, 0.4 mmol) in CH_2Cl_2 (3 mL), at 0 °C under argon, was added a solution of phenoxyacetyl chloride (34 mg, 0.2 mmol) in CH_2Cl_2 (0.5 mL) during 10 min. After 2 h a cold 4% aqueous $KHCO_3$ solution was added with stirring. The organic phase was extracted with water, and the combined aqueous extracts were mixed with ether and then acidified to pH 2.5 with 10% H_3PO_4. The aqueous fraction was extracted with ether, and the combined etheral fractions were dried and evaporated to give the title compound **17** (28 mg, 44 %): oil; IR ($CHCl_3$) 1760, 1710, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.70 (s, 6 H), 2.19 (s, 3 H), 4.54 (s, 2 H), 4.90 (m, 2 H), 6.0 (br, 2 H), 6.7–7.8 (m, 5 H). Treatment of a sample of **17** in CH_2Cl_2 with diphenyldiazomethane in acetone gave the diphenylmethyl ester **13**, identical in its physical data with an authentic sample prepared as described in a previous section.

Conversion of the *trans*-Azidolactam 9 to the *cis*-(Acylamino)lactam 14 through the Intermediacy of 11, 19, 20, 21, and 23. To a solution of **11** obtained as previously described from 164 mg (0.4 mmol) of **9**, in benzene (4 mL) was added *p*-nitrobenzaldehyde (65 mg, 0.43 mmol). After 2 h the mixture was evaporated under reduced pressure, and the residue was washed with ether to give the Schiff base **19** (180 mg, 87%): oil; IR ($CHCl_3$) 1760, 1740, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.76 (s) and 1.80 (s) (6 H), 2.04 (s, 3 H), 4.77 (d, 1 H, J = 2 Hz), 5.00 (d, 1 H, J = 2 Hz), 6.93 (s, 1 H), 7.37 (br s, 10 H), 7.88 (d, 2 H, J = 9 Hz), 8.25 (d, 2 H, J = 9 Hz), 8.57 (s, 1 H). To the Schiff base **19** (150 mg, 0.29 mmol) in THF (4 mL), under argon at −68 °C, was added a solution of PhLi (0.29 mmol) in ether. After 5 min, DMF (5 mL) was added followed by an immediate quenching with a solution of AcOH (0.3 mL) and H_2O (0.3 mL) in THF (2 mL). The reaction mixture was brought to room temperature and then diluted with benzene (20 mL) and washed with water, pH 4.4 buffered phosphate solution, pH 8 buffered phosphate solution, and again water. The NMR spectrum of the residue obtained after drying and evaporation indicated the presence of a 1:1 mixture of the Schiff bases **19** and **21**. NMR ($CDCl_3$) of **21**: δ 1.74 (s), 1.80 (s), 2.00 (s), 5.04 (formal q). The *p*-nitrobenzylidene grouping was removed from **19** and **21** with 2,4-dinitrophenylhydrazine (60 mg, 0.3 mmol) and *p*-toluenesulfonic acid (59 mg, 0.3 mmol) in ethanol (4 mL),[1] to give a mixture of the amines **22** and **23**. To a solution of the crude product and triethylamine (37 mg, 0.37 mmol) in CH_2Cl_2, under argon at 0 °C, was added a solution of phenoxyacetyl chloride (51 mg, 30 mmol) in CH_2Cl_2 (0.5 mL) during 15 min. After another 2 h the mixture was washed with 5% aqueous H_3PO_4, 4% aqueous $KHCO_3$, and water, dried, and evaporated. The NMR spectrum of the residue indicated the presence of a 1:1 mixture of **13** and **14**. Treatment of the product with ether resulted in the crystallization of **13** (48 mg). The mother liquor was evaporated, and the residue was chromatographed on a silica gel plate (hexane–acetone) to give **14** (56 mg, 38% yield based on **21**) and a second portion (12 mg) of **13**. The spectral data of these samples of **13** and **14** were identical with those of the fully characterized compounds described in previous sections.

Registry No. **6**, 71537-37-6; **7**, 71537-38-7; **8**, 71537-39-8; **9**, 71537-40-1; **10**, 71537-41-2; **11**, 71537-42-3; **12**, 71537-43-4; **13**, 71537-44-5; **14**, 71537-45-6; **15**, 71537-46-7; **16**, 71565-59-8; **16** trifluoroacetate salt, 71565-60-1; **17**, 71537-47-8; **19**, 71537-48-9; **21**, 71537-49-0; **22**, 71537-50-3; **23**, 71537-51-4; 2-aminoisobutyric acid, 62-57-7; ethyl thionoformate, 29392-46-9; diphenyldiazomethane, 883-40-9; azidoacetyl chloride, 30426-58-5; trifluoroacetic acid, 354-32-5; triphenylphosphine, 603-35-0; phenoxyacetyl chloride, 701-99-5; *p*-nitrobenzaldehyde, 555-16-8.

Diels–Alder Cycloaddition of Juglone Derivatives. 2. Regiospecificity of Reactions Leading to Tetracyclic Anthracyclinone Systems[1]

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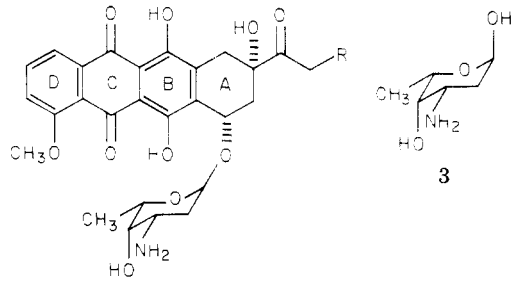
Received May 30, 1979

The regiospecificity of the reaction of several juglone derivatives with two complex dienes derived from bicyclic dimethoxycyclobutenes has been examined as part of a series of model studies leading toward the synthesis of the anthracyclinone antibiotics adriamycin and daunorubicin. In general, regiospecificity appears governed primarily by diene polarization factors. The structural assignments have been confirmed by a single-crystal X-ray analysis of one of the tetracyclic adducts from juglone methyl ether and related by chemical interconversion.

The development of synthetic approaches to the anthracyclinone class of antitumor antibiotics has been the object of intense study by a number of research groups in this country and abroad. The clinical importance of adriamycin (**1**) and to a lesser extent daunorubicin (**2**) as antitumor agents has been a major stimulus of this activity.[3] In addition, though, the unreliability of biochemical sources of the active substances[4] and the discovery of significant and potentially severe side effects, especially acute cardiac toxicity resulting from therapeutic administration of **1** and **2**, have further encouraged the exploration of methods to prepare not only **1** and **2** but a variety of analogues which are unavailable by chemical modification of **1** and **2**.



3

1, R = OH
2, R = H

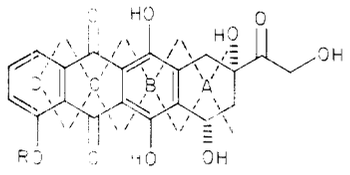
The total synthesis of **1** and related systems poses three independent problems: (1) aglycone synthesis, (2) synthesis of the requisite carbohydrate, and (3) methodology for

(1) For previous studies see: Boeckman, Jr., R. K.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.
(2) (a) Fellow of the Alfred P. Sloan Foundation, 1976–1980. (b) Recipient of a Career Development Award (CA-00273) from the National Cancer Institute of the National Institutes of Health (1976–1981).
(3) Henry, D. W. *ACS Symp. Ser.* **1976**, *No.* 30.
(4) Arcamone, F.; Cassinelli, G.; Fantini, G.; Grein, A.; Orezzi, P.; Pol, P.; Spalla, C. *Biotech. Bioeng.* **1969**, *11*, 1101.

0022-3263/79/1944-4396$01.00/0

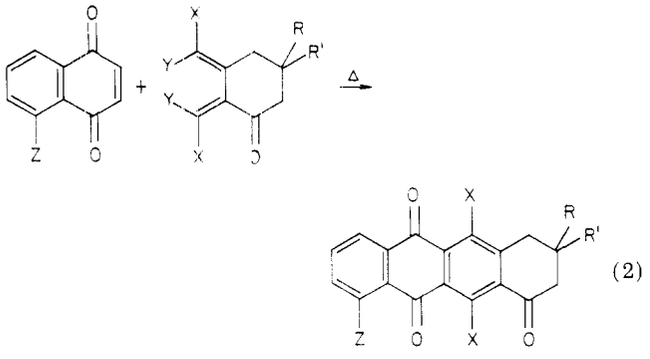
conjugation of the above components to the active glycosides. Progress in the synthesis of anthracyclines has been recently documented by several excellent reviews.[5-7] In our case, the entire effort has been devoted to the challenges posed by synthesis of the aglycones.

Retrosynthetic analysis of the problem reveals a number of potentially feasible bond-dissection schemes as indicated in eq 1. To date, nearly all of the indicated schemes have been attempted or reduced to practice.[5-7] Thus far, however, the most numerous approaches have utilized the Diels–Alder reaction in the key bond-forming operation(s).



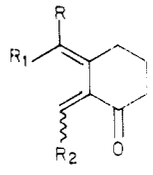
(1)

Recently, we have reported results of our initial studies directed toward aglycone synthesis.[8] Our approach, which constructs aromatic ring B, involves a Diels–Alder reaction of a napthoquinone synthon (rings C and D) and a diene component derived from a bicyclic cyclobutene (eq 2).

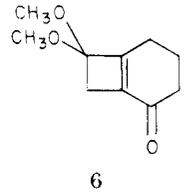


(2)

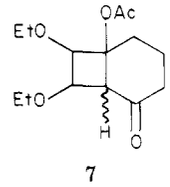
The attractive feature of this route is the potential for regioselectivity which may be realized by manipulation of the polarization of the diene and dienophile. The studies described in this paper have determined the regiochemical tendencies for complex dienes such as **4** and **5** and to a limited extent the feasibility of alteration of the regiochemistry by alteration of the dienophile structure.



4, R = R_1 = OCH_3; R_2 = H
5, R = R_2 = OEt; R_1 = H



6



7

As in our earlier studies,[8] the dienes **4** and **5** were generated in situ by thermolysis of the cyclobutene **6** and acetate **7**. If one examines the structure of the diene **4**, the expected mode of polarization is evident. The terminal oxygen substituents should dominate regioselectivity as has been observed by Kelly[9] and Birch.[10] To the extent that the carbonyl influences regiocontrol, one would expect it to enhance the net polarization of **4**. On the other hand, **5** is likely to be relatively unpolarized since the alkoxy groups' influence oppose one another. The effect of the carbonyl group should then result in lower net polarization of **5** relative to **4** but in the opposite sense.[11]

Table I

dienophile + diene $\xrightarrow{\Delta}$ adducts

case	dienophile	diene	adducts	ratio	yield,[a] %
1	8	4	14 + 15	1:2.5	77
2	9	4	16 + 17	3:1	88
3	10	4	18 + 19[b]	1:1	70
4	8	5	26 + 27	1.55:1.0	59
5	9	5	28 + 29	1.0:1.6	48
6	10	5	30 + 31[c]	1.35:1.0	61
7	11	5[d]	20 + 21	2.2:1	39
8	12	5[d]	22 + 23	1:2	39
9	13	5[d]	24 + 25[b]	1.2:1	22

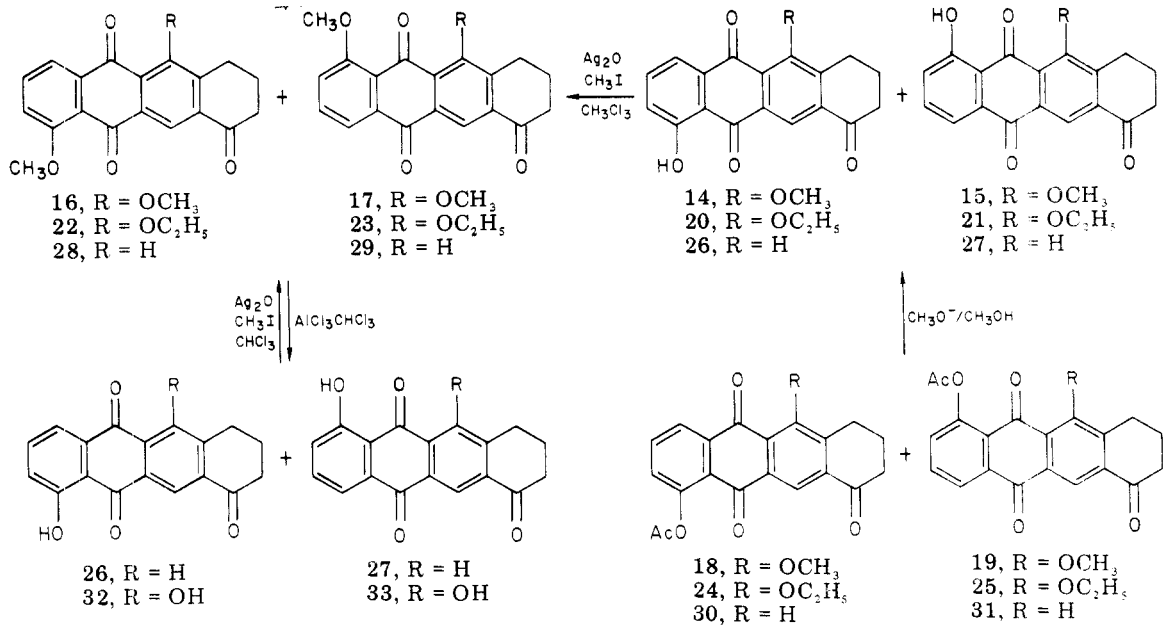
[a] Yields cited are for chromatographically purified materials and are unoptimized. [b] Adducts **18** and **19** were routinely converted to a mixture of **14** and **15** for analysis by ^{1}H NMR (integration of the phenolic proton; accuracy ±5%). [c] Analyzed as a mixture of **28** and **29** by NMR integration of H_a after hydrolysis and methylation (Ag_2O, CH_3I). [d] These reactions were run in the presence of 1–3 equiv of Li_2CO_3 and excess anhydrous $MgSO_4$.

Diels–Alder Reactions of Diene 4. The thermal Diels–Alder reactions were conducted in *o*-dichorobenzene (bp 179 °C) or xylene (bp 144 °C) at reflux for periods of 1–5 h. Generally reaction periods of ≤2 h were sufficient and the shorter reaction periods usually greatly facilitated isolation of pure products from the reaction mixture.

The results of the reactions of juglone (**8**) and derivatives **9** and **10** with diene **4** are given in Table I. As can be seen, the product distributions for **8** and **9** are in accord with our expectation (vide supra) based upon anticipated diene polarization, although the magnitude of the regiocontrol is smaller than expected. This lower regiospecificity can be partially understood by consideration that the overall regiochemical outcome results from a combination of primary and secondary orbital effects. For diene **4**, secondary orbital effects oppose the direction of control indicated by primary orbital effects (the two terminal methoxyls). The orbital coefficient for the internal atom bearing the alkyl residue of diene **4** is estimated to be larger than that bearing the carbonyl.[11] The larger carbonyl carbon coefficients in the dienophiles **8–10** are such that the coefficient of the carbonyl nearest the OH is larger and the carbonyl remote from OMe and OAc is larger. This effect to the extent that it is important opposes the orientation predicted by the larger coefficient of the terminal diene coefficients (unsubstituted carbon larger). Normally, primary effects dominate, as they have in this case. The expected reversal of orientation occurs upon going from **8** to **9**, in accord with the idea that subtle changes in dienophile polarization are manifested for dienes which are relatively strongly polarized.[11] These changes in polarization are too small to be observed in a molecular orbital calculation of **8–10** (CNDO/2).[11] It is not clear, however, why acetate **10**, expected to exhibit some degree of selectivity,[11] shows almost no observable regioselectivity. Since the acetates **10**, **18**, and **19** were sensitive to hydrol-

(5) (a) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley Interscience: Somerset, N.J., 1979; Vol. 1, Chapter 2. (b) Arcamone, F. "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Halsted Press: New York, 1978; Vol. 2, Chapter 3.
(6) Brown, J. R. *Prog. Med. Chem.* **1978**, *15*, 165.
(7) Kelly, T. R. *Annu. Rep. Med. Chem.*, in press.
(8) Boeckman, Jr., R. K.; Delton, M. H.; Nagasaka, T.; Watanabe, T. *J. Org. Chem.* **1977**, *42*, 2946.
(9) Kelly, T. R.; Gillard, J. W.; Goerner, Jr., R. N.; Lyding, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 5513.
(10) Birch, A. J.; Powell, V. *Tetrahedron Lett.* **1970**, 3467.
(11) Boeckman, Jr., R. K.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.

Scheme I



16, R = OCH_3
22, R = OC_2H_5
28, R = H

17, R = OCH_3
23, R = OC_2H_5
29, R = H

14, R = OCH_3
20, R = OC_2H_5
26, R = H

15, R = OCH_3
21, R = OC_2H_5
27, R = H

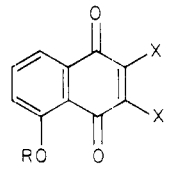
26, R = H
32, R = OH

27, R = H
33, R = OH

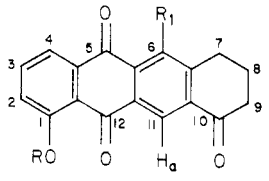
18, R = OCH_3
24, R = OC_2H_5
30, R = H

19, R = OCH_3
25, R = OC_2H_5
31, R = H

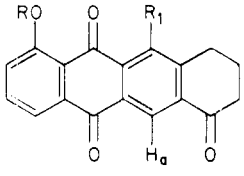
ysis and since the mixtures of **18** and **19** were converted to mixtures of **14** and **15** for characterization and analysis, care was taken to ensure that no observable change in ratios occurred when comparing the crude products after hydrolysis and the purified acetates which had been subsequently hydrolyzed. This ruled out the possibility that partial hydrolysis of **10** prior to cycloaddition had resulted in the observed lack of regiocontrol, since cycloaddition of **8** and **10** was expected to lead to different regiochemical results.



8, R = X = H
9, R = CH_3; X = H
10, R = Ac; X = H
11, R = H; X = Cl
12, R = CH_3; X = Cl
13, R = Ac; X = Cl

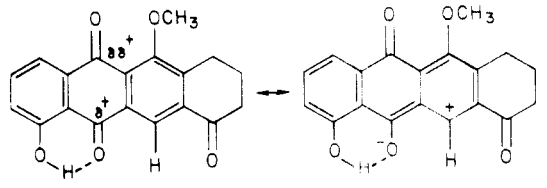


14, R = H; R_1 = OCH_3
20, R = H; R_1 = OC_2H_5
16, R = CH_3; R_1 = OCH_3
22, R = CH_3; R_1 = OC_2H_5
18, R = Ac; R_1 = OCH_3
24, R = Ac; R_1 = OC_2H_5
26, R = R_1 = H
28, R = CH_3; R_1 = H
30, R = Ac; R_1 = H



15, R = H; R_1 = OCH_3
21, R = H; R_1 = OC_2H_5
17, R = CH_3; R_1 = OCH_3
23, R = CH_3; R_1 = OC_2H_5
19, R = Ac; R_1 = OCH_3
25, R = Ac; R_1 = OC_2H_5
27, R = R_1 = H
29, R = CH_3; R_1 = H
31, R = Ac; R_1 = H

Correlations and Structure Assignments of the Tetracyclic Adducts. The structures of adducts **14–19** were correlated, as shown in Scheme I, by mutual chemical interconversion. Generally, ratios were assigned by utilizing NMR integration of the well-resolved phenolic protons of adducts **14** (δ 12.42) and **15** (δ 12.72). Several other spectral features of **14–19** deserve comment. Proton H_a due to its position, flanked on both sides by peri carbonyl groups, lies at significantly lower field (**14**, δ 9.03; **15**, δ 8.65) than the ring-D protons since it lies within the deshielding region of the anisotropic fields of the two carbonyl groups. Consequently, it is readily identified and led to our assignment of the position of the methoxyl in adducts **14–19**. A further diagnostic feature is that H_a appears at lower field when the ring-D OH is syn (**14**, δ 9.03), presumably due to the increased polarization of the carbonyl by the hydrogen bond and the resulting increase in deshielding via greater contribution of the resonance form shown in eq 3. This permits one to assign the structures of adducts



(3)

14–19 as those shown in Table I. The regiochemical results obtained for the remaining adducts will be discussed below. In spite of the internal self-consistency of the data, the inability to make a direct comparison of adducts **14–19** with a naturally derived tetracyclic substance of known structure led us to attempt to confirm our structure assignments unambiguously. It was possible to separate the isomeric dimethoxy adducts **16** and **17** by careful column chromatography or, more conveniently, by fractional crystallization from $CHCl_3/CH_3CH_2OH$ (or CH_3OH) to afford the major adduct **16** (mp 215–216 °C). Suitable crystals of this material were grown from $CHCl_3/CH_3OH$ and subjected to a single-crystal X-ray analysis.

Structure Determination of Adduct 16. Tetracyclic ketone **16** crystallized in the triclinic crystal class with unit cell dimensions a = 9.010 (1) Å, b = 10.215 (2) Å, c = 8.577 (2) Å, α = 81.50 (1)°, β = 97.52 (1)°, and γ = 85.74 (1)°. An approximate density of 1.45 g/cm^3 (measured and calculated) indicated two molecules of $C_{20}H_{16}O_5$ per unit cell of $P1$ or $P\bar{1}$. All unique data with $2\theta \leq 45°$ were collected by using graphite-monochromated Mo Kα (0.710669 Å) X-rays. A total of 2266 diffraction maxima were surveyed, and after correction for Lorentz, polarization, and back-

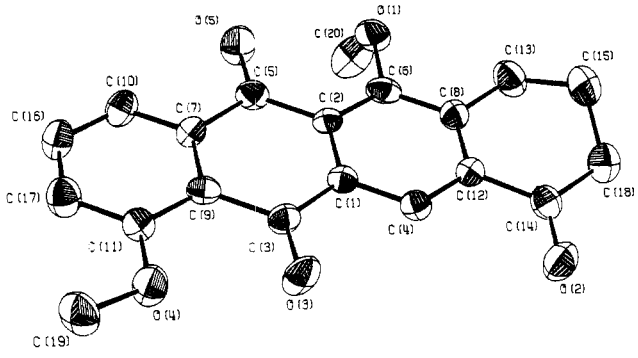


Figure 1. Computer-generated perspective drawing of tetracycle **16**. Hydrogens are omitted for clarity.

ground effects, 1056 (47%) were judged observed ($F_o^2 \leq 2.50F_o^2$).

Intensity statistics suggested the centric space group $P\bar{1}$ and solution of the crystal structure was undertaken in this space group.[13] Signs were determined for the 250 largest normalized structure factors by using a multisolution weighted sign determination process (MULTAN 74).[14] The most consistent set of phase relationships failed to produce the expected molecular fragment upon a three-dimensional E synthesis but rather provided a fragment displaced on one of the crystallographic axes. This problem was resolved by recycling the most consistent (highest CFOM) phase set, using Karle iteration[15] in the lower symmetry space group $P1$.[16] The resulting three-dimensional E synthesis revealed all the carbon framework atoms. Before least-squares refinement was begun, the $P\bar{1}$ symmetry was regenerated by calculation of the coordinates of the second molecule in the unit cell related by the inversion symmetry, utilizing the unit cell origin indicated from the coordinates derived from the recycling process. The remaining nonhydrogen atoms were located in space group $P\bar{1}$ by utilizing in two successive difference E syntheses. This final set of phases isotropic full-matrix least-squares refinement proceeded smoothly for all 25 nonhydrogen atoms through three cycles. All hydrogen atoms were then included in the model at the calculated positions,[17] and refinement was continued with anisotropic thermal parameters for nonhydrogen atoms and isotropic thermal parameters for the hydrogen atoms to a current unweighted crystallographic residual of 0.051 for observed reflections.[18] Bond distances and angles generally agree well with accepted values. Additional crystallographic details are available as supplementary material.

(12) A combination of primary and secondary orbital effects seems to be required to account for the observed results; cf. ref 11. See also: Alston, P. V.; Ottenbrite, R. M. *J. Org. Chem.* **1975**, *40*, 1111.

(13) (a) Wilson, A. J. C. *Acta Crystallogr.* **1949**, *2*, 318. (b) Hamptmann, H.; Karle, J. "ACA Monograph No. 3"; Polycrystal Book Service: Pittsburgh, Pa., 1953.

(14) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.

(15) Hamptmann, H.; Karle, J. *Acta Crystallogr.* **1956**, *9*, 635.

(16) This procedure permitted location of a single molecular fragment rather than multiple fragments.

(17) The following library of crystallographic programs was used: the Wayne State modification of the W. R. Busing, K. O. Martin, and H. A. Levy program "A Fortran Crystallographic Least Squares Program" (USAES Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965); the A. Zalkin program to calculate hydrogen positions, HFINDR (Lawrence Berkeley Laboratory); W. R. Busing, K. O. Martin, and H. A. Levy's ("ORFFE, A Fortran Crystallographic Function and Error Program", Report ORNL-TM-306, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1964); M. Glick's STDDEV; C. Johnson's ORTEP ("ORTEP, A Commission Report", Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965).

(18) Additional crystallographic details are available as supplementary material.

Table II

R	R_1	compound	$\delta(H_a)$	compound	$\delta(H_a)$
H	OCH_3	14	9.03	15	8.65
H	OC_2H_5	20	8.95	21	8.73
H	H	26	8.95	27	8.92
CH_3	OCH_3	16	8.67	17	8.58
CH_3	OC_2H_5	22	8.75	23	8.65
CH_3	H	28	8.87	29	8.83

Figure 1 is a computer-generated drawing of the final X-ray model excluding hydrogens. It is important to note that the substitution pattern of **16** is unambiguously the syn regioisomer, as predicted and previously assigned. Therefore, the remaining structural assignments are confirmed as indicated in Table I and Scheme I.

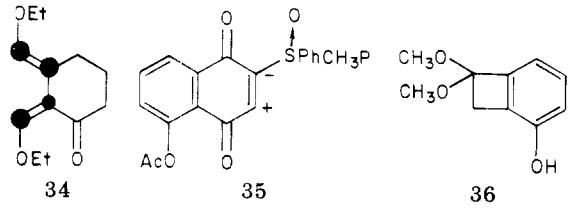
Diels–Alder Reactions of Diene 5. It was also of interest to examine the potential for regiocontrol stemming from the cycloadditions of diene **5**. In spite of the expected lower degree of polarization of **5**, this diene had the potential to permit the preparation of adducts containing both ring-B oxygen functions. Since the cyclobutene derived from **7** proved difficult to characterize and handle, cycloaddition reactions were conducted directly on the mixture of diastereomers **7**, generating **5** in situ by elimination and ring opening.[8] Bases were added to scavenge methanol and promote elimination (LiH or $LiCO_3$). Generally, reaction temperatures of 200–210 °C were required for this transformation since the trans ring junction isomer was particularly resistant to elimination. Overall the reactions of **8–13** in this series (particularly with chloroquinones **11–13**) were less clean and provided lower yields of tetracyclic adducts. Even with the chloroquinones **11–13**, we were unsuccessful, as before, in obtaining dioxygenated adducts.[8] The regiochemical results are given in Table I, and the chemical correlation of adducts **20–31** is given in Scheme I.

The *tentative* structural assignments of adducts **26–31** have been made on the basis of a correlation of the chemical shifts of the proton H_a. In both the D-ring OH and OCH_3 series, the regioisomer corresponding to **14** has the higher field absorption for H_a and the regioisomer corresponding to **15** has the lower field absorption for H_a, as shown in Table II. These correlations coupled with the X-ray structural data strongly suggest the structural assignment of the regioisomers in the series **26–31** indicated in Table I.

The regiochemical results for diene **5** and chloroquinones **11–13** are in the opposite direction as those for diene **4**, although of lower magnitude. This implies an electron distribution in **5** opposite to that expected on the basis of a simple frontier orbital analysis as shown for **34**. Qualitative analysis of the orbital coefficients expected for **5** indicates that the terminal coefficients are nearly equal. Secondary orbital effects should now dominate, and the larger coefficient (the difference is rather small) now appears on the internal atom of **5** bearing the carbonyl. This result leads to a prediction of a reversal of the orientation observed experimentally and is in accordance with those obtained for simple dienes.[12] The results for quinones **8–10** with **5** exhibit the same general trends but with the magnitude still further reduced. This can conceivably be attributed to the relatively higher reactivity of **8–10**, leading to reduced regioselectivity. The results for acetates **10** and

13 are, however, opposite to those expected, although internally consistent for both. In fact, the reactions of the acetate derivatives **10** and **13** exhibit anomalous regiochemical behavior with **4** and **5** which is not readily accommodated by theory. The magnitude of these effects is small, but it seems clear that thermal reactions of the acetate-blocked quinones will not provide synthetically useful regioselectivities in this series.

A brief investigation of the effects of quinone substitution upon regioselectivity with **4** was conducted. From our previous studies, acetoxy sulfoxide **35** is known to be



34 35 36

strongly polarized as indicated (NMR data).[11] The polarizations of **35** and **4** were expected to be complementary, and regiocontrol was expected to be enhanced. However, substitution of strongly electron-withdrawing groups on the quinone results in enhancement of the oxidation potential. Reaction of **35** with **6** at 160 °C afforded a relatively low yield of tetracyclic adducts **14** and **15** after workup (27%). Substantial amounts of products ascribed to oxidation of the cyclobutene **4** to phenol **36** and further transformations were obtained. The regioselectivity observed was also much lower and in the opposite sense to that anticipated for [**14**]/[**15**] = 1.5:1.0. We presently are investigating modifications of quinones **8**–**10** which will enhance the polarization of the system without enhancing the oxidation potential of the system as well as the potential for increasing the observed regiochemical control through Lewis acid catalysis.

Experimental Section

All infrared spectra were recorded on a Perkin-Elmer 137 spectrometer. Proton magnetic resonance spectra were determined on a Varian T-60 spectrometer, and chemical shifts are reported in δ units relative to tetramethylsilane. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All boiling points are uncorrected. The mass spectra, both high and low resolution, were determined on an AEI MS-9 spectrometer. Ether and THF were distilled from CAH and aromatic solvents, amines, hydrocarbon solvents, and alcohols were distilled from calcium hydride. Unless otherwise stated, all reactions were conducted under argon. For routine TLC analysis, microscope slides were prepared by dipping them in a slurry of EM silica gel GF-254 in chloroform. Unless otherwise stated, all preparative chromatography was performed on EM silica gel 60 (200–400 mesh) by utilizing a medium-pressure chromatographic apparatus. The Florisil used was supplied by Fisher (100–200 mesh). Microanalyses were conducted by Midwest Microlab, Ltd.

1-Acetoxy-8,8-dimethoxybicyclo[4.2.0]octan-5-one. A solution of 3-acetoxy-2-cyclohexen-1-one (20 g, 0.130 mol) and ketene dimethyl acetal (57 g, 0.65 mol) in dry ether (450 mL) was degassed with a stream of argon for 30 min. This mixture was then irradiated with a 450-nm Hanovia medium-pressure lamp through a Corex filter at room temperature. The progress of the reaction was monitored by TLC (silica gel with petroleum ether–ether (3:2)) and IR (disappearance of the C=O band at 1630 cm^{-1}). After 48 h it appeared that all of the 3-acetoxy-2-cyclohexen-1-one had been consumed and irradiation was stopped. The reaction mixture was washed with 10% aqueous potassium carbonate (150 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel with hexane–ethyl acetate (2:1), affording four fractions. Fraction 1: 5.4 g of orange oil; R_f 0.90 (silica gel, hexane–ethyl acetate (2:1)). The ^1H NMR spectrum indicated that this material was a mixture of methoxy hydrocarbons resulting from photolytic coupling of the ketene dimethyl acetal. Fraction 2: 3.8 g of yellow oil (16% yield of 7,7-dimethoxybicyclo[4.2.0]-1($\Delta^{1,6}$)-octen-2-one); R_f 0.61 (silica gel, hexane–ethyl acetate (2:1)); ^1H NMR ($CDCl_3$) δ 3.44 (s, 6 H), 2.84 (m, 2 H), 2.44 (m, 6 H); IR (film) 2900, 1680 (C=O), 1250, 1130, 1060, 860 cm^{-1}; low-resolution mass spectrum (70 eV) m/e 182 (P^+). Fraction 3: 14.10 g of yellow oil (45% yield of 1-acetoxy-8,8-dimethoxybicyclo[4.2.0]octan-5-one; 64% based upon recovered dione); R_f 0.46 (silica gel, hexane–ethyl acetate (2:1)); ^1H NMR ($CDCl_3$) δ 3.35 (s, 3 H), 3.29 (s, 3 H), 2.88 (q, J = 5 Hz, 2 H), 2.35 (m, 4 H), 2.10 (m, 3 H), 2.06 (s, 3 H); IR (film) 2900, 1740, 1705, 1250, 1160, 1080, 1040 cm^{-1}; low-resolution mass spectrum (70 eV) m/e 242 (P^+). Fraction 4: 4.45 g of yellow oil (recovered 1,3-cyclohexanedione); R_f 0.04 (silica gel, hexane–ethyl acetate (2:1)).

7,7-Dimethoxybicyclo[4.2.0]-1($\Delta^{1,6}$)-octen-2-one (6). Method A. 1,5-Diazabicyclo[5.4.0]undec-5-ene (DBU) (17.4 g, 115 mM) was added to a solution of 1-acetoxy-8,8-dimethoxybicyclo[4.2.0]octan-5-one (18.5 g, 76.5 mM) in ether (150 mL) and pyridine (50 mL) at room temperature. After 16 h of stirring, the mixture was diluted with water (300 mL) and extracted with ether (4 × 150 mL). The combined extracts were washed with water (3 × 200 mL), dried ($MgSO_4$), and evaporated in vacuo, affording 9.56 g of a yellow oil (69% yield of **6**): ^1H NMR ($CDCl_3$) δ 3.44 (s, 6 H), 2.84 (m, 2 H), 2.44 (m, 6 H); IR (film) 2900, 1680, 1250, 1125, 1050, 860 cm^{-1}; low-resolution mass spectrum (70 eV) m/e 182 (P^+).

Method B. Thallium ethoxide (0.77 g, 3.09 mM) was added to a solution of 1-acetoxy-8,8-dimethoxybicyclo[4.2.0]octan-5-one (0.5 g, 2.06 mmol) in ether (10 mL) at room temperature. A light yellow precipitate was immediately deposited. After 16 h of stirring at room temperature, the resulting orange suspension was filtered. The filtrate was diluted with ether (20 mL), washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated in vacuo, affording 0.266 g of a yellow oil (71% yield of 7,7-dimethoxybicyclo[4.2.0]-1($\Delta^{1,6}$)-octen-2-one).

Method C. A solution of 1-acetoxy-8,8-dimethoxybicyclo[4.2.0]octan-5-one (0.5 g, 2.06 mM) in methylene chloride (15 mL) was treated with sodium methoxide (0.28 g, 4.12 mM) at room temperature. The resulting suspension was stirred at room temperature for 24 h and filtered. The filtrate was washed with H_2O (15 mL), dried ($MgSO_4$), and evaporated in vacuo, affording 0.310 g of yellow oil (82% yield of 7,7-dimethoxybicyclo[4.2.0]-1-($\Delta^{1,6}$)-octen-2-one).

5-Hydroxy-2-(phenylsulfinyl)-1,4-naphthaquinone Acetate. To a solution of 5-hydroxy-2-(phenylthio)-1,4-naphthaquinone acetate (0.5 g, 1.54 mM) in methylene chloride (10 mL) was added *m*-chloroperbenzoic acid (0.33 g, 1.62 mM) at room temperature. After 90 min the reaction was quenched with 10% aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The layers were separated, and the aqueous phase was extracted with methylene chloride (20 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo, affording 0.520 g of yellow crystals: mp 197–199 °C; 99% yield of **35**; ^1H NMR ($CDCl_3$) δ 7.85 (m, 4 H), 7.55 (m, 5 H), 2.48 (s, 3 H); low-resolution mass spectrum (70 eV) m/e 340 (P^+).

7,8-Dihydro-6-ethoxy-1-hydroxy-5,10,12(9*H*)-naphthacenetrione (20) and 9,10-Dihydro-11-ethoxy-1-hydroxy-5,7,12(8*H*)-naphthacenetrione (21). A suspension of 2,3-dichloro-5-hydroxy-1,4-naphthaquinone (100 mg, 0.412 mM), 1-acetoxy-7,8-diethoxybicyclo[4.2.0]octan-5-one (134.0 mg, 0.495 mM),[8] lithium carbonate (74 mg, 1.23 mM), and lithium hydride (7 mg) in *o*-dichlorobenzene (2 mL) was degassed with a stream of argon for 15 min and then immersed in an oil bath preheated to 200–210 °C. After 2 h of stirring at 200–216 °C, the dark suspension was cooled, diluted with 5% hydrochloric acid, and extracted with methylene chloride (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was warmed at 40 °C under high vacuum (0.5–1.0 torr) to remove residual *o*-dichlorobenzene. The resulting dark solid was chromatographed on silica gel with benzene/ethyl acetate (19:1) and afforded 30.0 mg of an orange crystalline solid, recovered 5-hydroxy-1,4-naphthaquinone (30% recovery), and 54.0 mg of a yellow crystalline solid: mp 210–219 °C; 39% yield of tetracyclic isomers **20** and **21**; ^1H NMR ($CDCl_3$) δ 12.67, 12.53 (2 s, OH, 1 H), 8.95, 8.73 (2 s, 1 H), 7.73 (m, 2 H), 7.40 (m, 1 H), 4.30 (q, J

= 7 Hz, 2 H), 3.20 (m, 2 H), 2.80 (m, 2 H), 2.32 (m, 2 H), 1.53 (t, J = 7 Hz, 3 H); low-resolution mass spectrum (70 eV) m/e 336 (P^+).

7,8-Dihydro-6-ethoxy-1-methoxy-5,10,12(9*H*)-naphthacenetrione (22) and 9,10-Dihydro-11-ethoxy-1-methoxy-5,7,12(8*H*)-naphthacenetrione (23). Reaction of 2,3-dichloro-5-methoxy-1,4-naphthaquinone (50 mg, 0.195 mM) with 1-acetoxy-7,8-diethoxybicyclo[4.2.0]octan-5-one (63.2 mg, 0.234 mM) yielded the following: 39% yield of tetracyclic isomers **22** and **23**; ^1H NMR ($CDCl_3$) δ 8.75, 8.65 (2 s, 1 H), 7.80–7.20 (m, 3 H), 4.20 (q, J = 7 Hz, 2 H), 4.07 (s, 3 H), 3.15 (m, 2 H), 2.77 (m, 2 H), 2.30 (m, 2 H), 1.53 (t, J = 7 Hz, 3 H); low-resolution mass spectrum (70 eV) m/e 350 (P^+).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.16; H, 5.16.

7,8-Dihydro-6-ethoxy-1-hydroxy-5,10,12(9*H*)-naphthacenetrione (20) and 9,10-Dihydro-1-ethoxy-1-hydroxy-5,7,12(8*H*)-naphthacenetrione (21). Reaction of 2,3-dichloro-5-hydroxy-1,4-naphthaquinone acetate (200 mg, 0.71 mM) with 1-acetoxy-7,8-diethoxybicyclo[4.2.0]octan-5-one (230 mg, 0.85 mM) as described above followed by treatment of the product with concentrated hydrochloric acid (5 mL) in 95% ethanol (10 mL) at reflux for 10 min afforded 52.5 mg of a yellow crystalline solid: mp 209–216 °C; 22% yield of a mixture of isomeric tetracyclic phenols **20** and **21**; ^1H NMR ($CDCl_3$) δ 12.67, 12.53 (2 s, OH, 1 H), 8.95, 8.73 (2 s, 1 H), 7.73 (m, 2 H), 7.40 (m, 1 H), 4.30 (q, J = 7 Hz, 2 H), 3.20 (m, 2 H), 2.80 (m, 2 H), 2.32 (m, 2 H), 1.53 (t, J = 7 Hz, 3 H); low-resolution mass spectrum (70 eV) m/e 336 (P^+).

Methylation of the Tetracyclic Phenols. General Procedure. Silver oxide (144 mg, 0.62 mM) was added to a solution of **14** and **15** (50 mg, 0.15 mM) and methyl iodide (32 mg, 0.22 mM) in chloroform (15 mL). The resulting suspension was heated at reflux for 10 h. Filtration of the cooled mixture, evaporation of the filtrate in vacuo, and chromatography of the resulting residue on silica gel with chloroform afforded 48.3 mg of a yellow crystalline solid, a mixture of the isomeric tetracycles **16** and **17** (92% yield).

7,8-Dihydro-1,6-dimethoxy-5,10,12(9*H*)-naphthacenetrione (16) and 9,10-Dihydro-1,11-dimethoxy-5,7,12(8*H*)-naphthacenetrione (17). A solution of 5-methoxy-1,4-naphthaquinone (0.78 g, 4.13 mM) and 7,7-dimethoxybicyclo-[4.2.0]-$\Delta^{1,6}$-octen-2-one (1.0 g, 4.13 mM) in dry xylene (10 mL) was degassed for 15 min with a stream of argon. The mixture was immersed in an oil bath preheated to 180–190 °C. The reaction was followed by TLC (silica gel with benzene–EtOAc (4:1)). After 2 h all of the quinone starting material had been consumed, and the dark solution was cooled to room temperature. The solvent was removed in vacuo and the residue was suspended in methanol (20 mL). Sodium methoxide (0.10 g) was added and the mixture was treated with a stream of dry air at room temperature for 25 min. Excess 5% HCl (15 mL) was added and the mixture extracted with methylene chloride (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo, and the residue was washed through a plug of Florisil (10 g) with methylene chloride–ethyl acetate (2:1). Evaporation of the filtrate in vacuo afforded 1.22 g of a yellow crystalline solid (88% crude yield). Recrystallization of this material from chloroform–ethanol (9:1) first afforded 0.687 g of yellow needles (**16**): mp 211–214 °C; ^1H NMR ($CDCl_3$) δ 8.67 (s, 1 H), 7.85 (d, J = 1.5 Hz, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.33 (dd, J = 1.5 and 8 Hz, 1 H), 4.08 (s, 3), 4.00 (s, 3), 3.13 (t, J = 5 Hz, 2 H), 2.75 (t, J = 6 Hz, 2 H), 2.22 (m, 2 H); mass spectrum (70 eV) m/e 336 (P^+).

Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.64; H, 4.61.

The mother liquor then afforded 0.21 g of small red needles (**17**): mp 216–219 °C; ^1H NMR ($CDCl_3$) δ 8.58 (s, 1 H), 7.85 (d, J = 1.5 Hz, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.33 (dd, J = 1.5 and 8 Hz, 1 H), 4.08 (s, 3 H), 4.02 (s, 3 H), 3.15 (t, J = 6 Hz, 2 H), 2.75 (t, J = 6 Hz, 2 H), 2.28 (p, J = 6 Hz, 2 H); mass spectrum (70 eV) m/e 336 (P^+).

7,8-Dihydro-1-hydroxy-6-methoxy-5,10,12(9*H*)-naphthacenetrione (14) and 9,10-Dihydro-1-hydroxy-11-methoxy-5,7,12(8*H*)-naphthacenetrione (15). Method A. Reaction of 5-hydroxy-1,4-naphthaquinone acetate (0.100 g, 0.46 mM) with 7,7-dimethoxybicyclo[4.2.0]-$\Delta^{1,6}$-octen-2-one (0.11 g, 0.46 mM) as described above afforded 0.104 g of yellow crystals, a 1:1 mixture of **14** and **15** in 70% yield.

Method B. Upon reaction of **6** (182 mg, 1.0 mmol) and **8** (174 mg, 1.0 mmol), a 77% yield of the title compounds in a ratio of 1.0:2.5, respectively, was obtained by the previously described procedure: ^1H NMR ($CDCl_3$) δ 12.72 (s, 0.72 H), 12.42 (s, 0.28 H), 8.68 (s, 0.28 H), 8.65 (s, 0.72 H), 7.75 (m, ~1 H), 7.38 (m, 2 H), 4.05 (s, <3 H), 4.02 (s, <3 H), 3.17 (t, J = 5 Hz, 2 H), 2.77 (t, J = 5 Hz, 2 H), 2.22 (p, J = 5 Hz, 2 H); mass spectrum (70 eV) m/e 322 (P^+).

Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 71.14; H, 4.34.

Method C. Reaction of 5-hydroxy-2-(phenylsulfinyl)-1,4-naphthaquinone acetate (0.340 g, 1.0 mM) with 7,7-dimethoxybicyclo[4.2.0]-Δ^{16}-octen-2-one (0.242 g, 1.0 mM) as described above afforded 86 mg of an orange crystalline solid (27% yield of a mixture of isomeric tetracycles **14** and **15**).

Also isolated were 100 mg of a brown solid identical by TLC and ^1H NMR with an authentic sample of 5-hydroxy-2-(phenylthio)-1,4-naphthaquinone and a polar fraction, 121 mg of brown oil, which was a mixture of the starting cyclobutane **6** and its oxidation product, phenol **36**.

7,8-Dihydro-1-methoxy-5,10,12(9*H*)-naphthacenetrione (28) and 9,10-Dihydro-1-methoxy-5,7,12(8*H*)-naphthacenetrione (29). General Procedure. A suspension of 5-methoxy-1,4-naphthaquinone (**9**) (100 mg, 0.53 mM), 1-acetoxy-7,8-diethoxybicyclo[4.2.0]octan-5-one (**7**) (145 mg, 0.54 mM), lithium carbonate (118 mg, 1.59 mM), and lithium hydride (9 mg, 1.06 mM) in xylene (5.0 mL) was degassed with a stream of argon for 15 min and then immersed in an oil bath preheated to 200–210 °C. After 8 h of stirring at 200–210 °C, the mixture was cooled to room temperature, poured into 5% hydrochloric acid (10 mL), and extracted with chloroform (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo, and the residue was treated with potassium methoxide and air in methanol (20 mL) at room temperature for 30 min. The resulting dark solution was poured into 5% hydrochloric acid (20 mL) and extracted with chloroform (3 × 25 mL). After drying ($MgSO_4$), the combined extracts were evaporated in vacuo and the residue was chromatographed on silica gel with chloroform, affording 78 mg of yellow crystals: mp 209–216 °C; ^1H NMR ($CDCl_3$) δ 8.87, 8.83 (2 s, 1 H), 8.10 (s, 1 H), 7.80 (m, 2 H), 7.03 (m, 1 H), 4.05 (s, 3 H), 3.13 (t, J = 6 Hz, 2 H), 2.75 (t, J = 6 Hz, 2 H), 2.17 (p, J = 6 Hz, 2 H); low-resolution mass spectrum (70 eV) m/e 360 (P^+); 48% yield of the isomeric tetracycles **28** and **29**.

7,8-Dihydro-1-hydroxy-5,10,12(9*H*)-naphthacenetrione (26) and 9,10-Dihydro-1-hydroxy-5,7,12(8*H*)-naphthacenetrione (27). Method A. Reaction of 5-hydroxy-1,4-naphthaquinone (**8**; 10 mg, 0.575 mM) with 1-acetoxy-7,8-diethoxybicyclo[4.2.0]octan-5-one (**7**; 155 mg, 575 mM) as described above afforded 99 mg of a yellow crystalline solid: mp 215–222 °C; ^1H NMR ($CDCl_3$) δ 12.63, 12.49 (2 s, 1 H), 8.95, 8.92 (2 s, 1 H), 8.23 (s, 1 H), 7.72 (m, 2 H), 7.40 (m, 1 H), 3.22 (m, 2 H), 2.83 (m, 2 H), 2.23 (m, 2 H); low-resolution mass spectrum (70 eV) m/e 292 (P^+); 59% yield of the isomeric tetracycles **26** and **27**.

This material was methylated with silver oxide and methyl iodide by the procedure described above to give, after chromatography on silica gel with chloroform, 95 mg of yellow crystals, a 92% yield of a mixture of **28** and **29**.

Method B. Reaction of 5-hydroxy-1,4-naphthaquinone acetate (**10**; 100 mg, 0.463 mM) with 1-acetoxy-7,8-diethoxybicyclo-[4.2.0]octan-5-one (**7**; 125 mg, 0.463 mM) as described above afforded 82 mg of a yellow crystalline solid (mp 214–222 °C), a 61% yield of the isomeric tetracycles **26** and **27**.

This material was methylated with silver oxide and methyl iodide by the procedure described above to give, after chromatography on silica gel with chloroform, 78 mg of yellow crystals, a 91% yield of a mixture of **28** and **29**.

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Registry No. **6**, 18926-93-7; **7**, 63876-92-6; **8**, 481-39-0; **9**, 4923-61-9; **10**, 5196-28-1; **11**, 4923-60-8; **12**, 71700-71-5; **13**, 71700-72-6; **14**,

71700-73-7; **15**, 71700-74-8; **16**, 71700-75-9; **17**, 71700-76-0; **18**, 71700-77-1; **19**, 71700-78-2; **20**, 71700-79-3; **21**, 71700-80-6; **22**, 71700-81-7; **23**, 71700-82-8; **24**, 71700-83-9; **25**, 71700-84-0; **26**, 71700-85-1; **27**, 71700-86-2; **28**, 71700-87-3; **29**, 71700-87-3; **30**, 71700-88-4; **31**, 71700-89-5; **35**, 71700-90-8; **36**, 71700-91-9; 3-acetoxy-2-cyclohexen-1-one, 57918-73-7; ketene dimethyl acetal, 922-69-0; 1-acetoxy-8,8-dimethoxybicyclo[4.2.0]octan-5-one, 18926-91-5; 5-hydroxy-2-(phenylthio)-1,4-naphthaquinone acetate, 71700-92-0; 5-hydroxy-2-(phenylthio)-1,4-naphthaquinone, 71700-93-1.

Supplementary Material Available: Fractional coordinates (Table III), bond distances (Table IV), and bond angles (Table V) for tetracycle **16** (3 pages). Ordering information is given on any current masthead page.

In Situ Vinylindole Synthesis of Carbazoles[1a,b]

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The condensation of indole with ketones catalyzed by maleic acid has been utilized as a synthesis of 3-vinylindoles which, acting as dienes, are trapped by in situ Diels–Alder addition to the maleic acid. The resulting tetrahydrocarbazoles undergo double-bond isomerization and selective decarboxylation of the carboxyl group in the indole-2-acetic acid configuration to form 3-R^3- and 4-R^4-substituted-1,2,3,4-tetrahydrocarbazole-2-carboxylic acids which were the products isolated [$R^3 = R^4 = CH_3$; $R^3 = CH_3$, $R^4 = C_2H_5$; $R^3 = H$, $R^4 = CH_2CH(CH_3)_2$; $R^3 + R^4 = (CH_2)_3$; $R^3 = C_6H_5$, $R^4 = CH_3$; $R^3 = H$, $R^4 = CH_2C(CH_3)_3$]. The Diels–Alder reaction is sensitive to steric hindrance in the 3-vinylindole, and the limits have been fairly well defined. Methyl or ethyl esterification converted the acid products to the more soluble esters, which were then dehydrogenated with chloranil in refluxing *o*-xylene or 3–10% palladium-on-carbon in refluxing *o*-dichlorobenzene to the corresponding carbazole-2-carboxylate esters, thus providing an overall synthesis of carbazoles in three laboratory steps from indole. The mass spectral fragmentations of all the compounds described are interpreted in detail.

The Diels–Alder reaction, followed by a dehydrogenation step or other elimination in situ or at a later time, of 3-vinylindole[2] (**1**) or substituted 3-vinylindoles[3] (such as **5**) with dienophiles has been shown to lead, via tetrahydrocarbazoles (such as **3**) from ethylenic dienophiles (such as **2**) or dihydrocarbazoles (such as **7**) from acetylenic dienophiles (such as **6**), to the corresponding carbazoles (such as **4** or **8**). This reaction has been described as the "vinylindole synthesis of carbazoles".[3a]

The acid-catalyzed condensations of 3-unsubstituted indoles with monofunctional methylene or methyl ketones have been postulated to proceed in many cases through intermediate 3-vinylindoles (3-alkenylindoles),[4] and these have been isolated in some cases where the 3-vinylindoles were sufficiently stable under the reaction conditions. Such cases include the reactions of 2-methylindole with desoxybenzoin (1,2-diphenylethanone) to give 2-methyl-3-(1,2-diphenylethenyl)indole[5] and with the cyclohexanone derivative 3,4,4a,9a-tetrahydro-4,4,4a,9-tetramethyl-9*H*-carbazol-2(1*H*)-one to give 3,4,4a,9a-tetrahydro-4,4,4a,9-tetramethyl-2-(2-methylindol-3-yl)-9*H*-carbazole,[4a] the reactions of 1- and 2-methylindole, 1,2-dimethylindole, and 2-phenylindole with 2-indanone to give the corresponding 3-(1*H*-inden-2-yl)indoles in yields of 69, 94, 85, and 85%, respectively,[3b] and the reactions of 2-substituted indoles with methyl ketones to give the corresponding methylvinylindoles (**9**)[4g] and with a variety of six-membered-ring ketones to give the corresponding 3-cycloalkenylindoles.[4h]

We have now combined the synthesis of 3-vinylindoles from ketones with the vinylindole synthesis of tetrahydrocarbazoles in one flask by using indole (1 equiv) and excess ketone precursor **10** as the solvent, usually at reflux, with maleic acid (**11**, 1 equiv) both as the catalyst for 3-vinylindole formation and as the dienophile for the Diels–Alder reaction. These reactions, which constitute an "in situ vinylindole synthesis of tetrahydrocarbazoles", are accompanied by decarboxylation, giving the corresponding substituted tetrahydro-9*H*-carbazole-2-carboxylic acids **12** in 20–57% yield as the sole crystalline products. These acids were converted to their more soluble methyl or ethyl esters **13** to facilitate NMR characterization and solubility in the refluxing *o*-xylene or *o*-dichlorobenzene

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(2) Noland, W. E.; Sundberg, R. J. *J. Org. Chem.* **1963**, *28*, 884–5.

(3) (a) Noland, W. E.; Kuryla, W. C.; Lange, R. F. *J. Am. Chem. Soc.* **1959**, *81*, 6010–7. (b) Makky, A.-M. M. M.S. Thesis, University of Minnesota, Minneapolis, Minn., July 1961. (c) Campbell, R. W. Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., Aug 1961; *Diss. Abstr.* **1962**, *22*, 3851. (d) Johnson, D. C. Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., Nov 1961; *Ibid.* **1962**, *23*, 834. (e) Weinmann (now Mukherjee), J. M. Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., Jan 1964; *Ibid.* **1964**, *25*, 1588. (f) Zee, S.-H. M.S. Thesis, University of Minnesota, Minneapolis, Minn., April 1964. (g) Johnson, R. A. Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., April 1965; *Ibid.* **1966**, *26*, 5719. (h) Lindberg, S. E. Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., April 1969; *Diss. Abstr. Int. B* **1969**, *30*, 2610–1. (i) Sundberg, R. J. "The Chemistry of Indoles"; Academic Press: New York, 1970; pp 125–7. (j) Remers, W. A. In "Indoles, Part 1"; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Chapter 1, pp 174–5. (k) Hosmane, R. S.; Hiremath, S. P.; Schneller, S. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2450–3. (l) Hiremath, S. P.; Purohit, M. G. *Indian J. Chem.* **1974**, *12*, 493–5. (m) Bergamasco, R.; Porter, Q. N.; Yap, C. *Aust. J. Chem.* **1977**, *30*, 1531–44. (n) Bergamasco, R.; Porter, Q. N.; Yap, C. *Ibid.* **1978**, *31*, 1841–4.

(4) (a) Noland, W. E.; Venkiteswaran, M. R.; Richards, C. G. *J. Org. Chem.* **1961**, *26*, 4241–8. (b) Noland, W. E.; Venkiteswaran, M. R.; Lovald, R. A. *Ibid.* **1961**, *26*, 4249–54. (c) Noland, W. E.; Richards, C. G.; Desai, H. S.; Venkiteswaran, M. R. *Ibid.* **1961**, *26*, 4254–62. (d) Noland, W. E.; Venkiteswaran, M. R. *Ibid.* **1961**, *26*, 4263–9. (e) Reference 3i, pp 47–51. (f) Reference 3j, pp 83–5. (g) Simurdak, R. C. Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., June 1972; *Diss. Abstr. Int. B* **1974**, *34*, 3175–6. (h) Freter, K. *J. Org. Chem.* **1975**, *40*, 2525–9.

(5) Noland, W. E.; Robinson, D. N. *J. Org. Chem.* **1957**, *22*, 1134–5.

0022-3263/79/1944-4402$01.00/0