Tetrahedron Vol. 43, No. 9, pp. 2005 to 2011, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

ACID CATALYSIS OF THE RETRO-DIELS ALDER REACTION. FORMATION AND ELECTROPHILIC REACTIVITY OF 2-METHYLENE-1,3-CYCLOPENTANEDIONE.

William H. Bunnelle*
Department of Chemistry, University of Missouri, Columbia, Missouri 65211

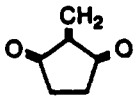
W. Randall Shangraw
Department of Chemistry, College of William and Mary, Williamsburg, Virginia 23185

(*Received in USA* 9 *March* 1987)

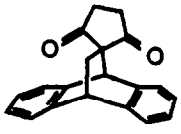
Abstract: The acid mediated decomposition of the Diels-Alder adduct of 1,3-cyclopentanedione with anthracene was studied. An extremely facile, acid catalyzed retro-Diels-Alder fragmentation produces 2-methylene-1,3-cyclopentanedione, which undergoes twofold electrophilic substitution on the cognate anthracene nucleus.

The retro-Diels Alder reaction is widely used for the preparation of reactive alkenes. Since the cycloreversion is generally endothermic with a substantial activation enthalpy, high temperature conditions are typically employed. Recently, there has been much interest in cycloreversions which take place at low temperatures: several anion-accelerated versions have been reported[1], and a study of substituent effects on the rate of fragmentation has appeared.[2] Although dramatic rate enhancement of the Diels-Alder cycloaddition by acid catalysis is well known[3], similar use of acid (as implied by microscopic reversibility) to accelerate the cycloreversion has not been common.

Our interest in the unusual reactivity of 2-alkylidene-1,3-cyclopentanediones[4] has led us to consider the utility of the retro-Diels Alder reaction for the generation and spectroscopic characterization of these elusive intermediates. Thus, 2-methylene-1,3-



1



2

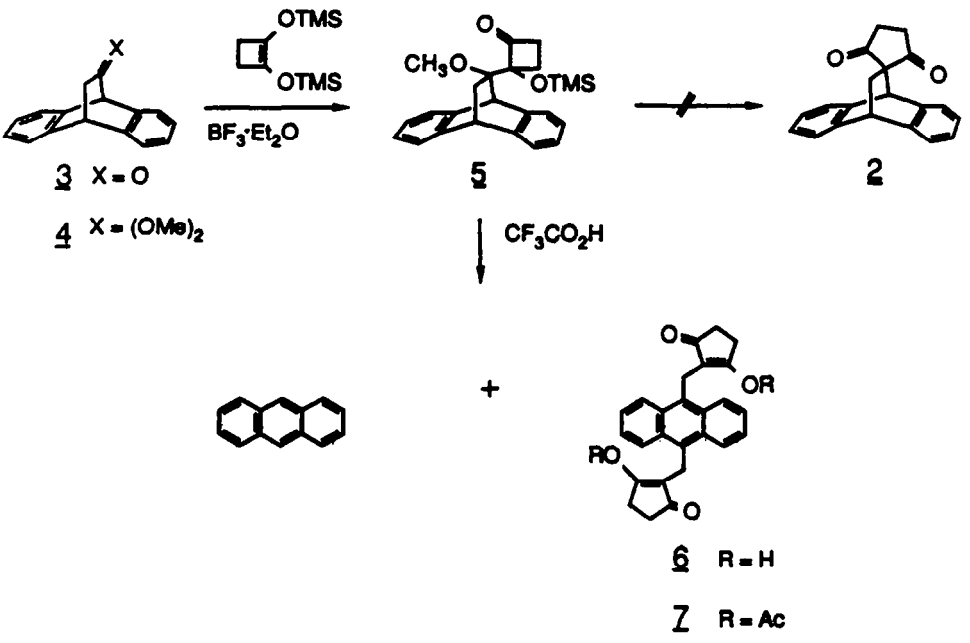
cyclopentanedione (1), parent of this class, would be accessible from the anthracene adduct 2. In our attempts to prepare 2, we encountered an extraordinarily facile rearrangement, which we have now shown to involve the acid mediated retro-Diels-Alder fragmentation of 2. We report here the results of this study.

The synthesis of 2 was planned to follow the spiroannelation method of Kuwajima, et al.[5] (Scheme I). Thus, the known ketone 3 was easily converted to the dimethyl ketal 4. Condensation of 4 with 1,2-bis(trimethylsilyloxy)cyclobutene in the presence of $BF_3 \cdot Et_2O$ led to the desired cyclobutane 5 in 62% yield. Interestingly, spectroscopic analysis (^1H and ^{13}C NMR) indicate that 5 was formed as a single diastereomer, though the stereochemical assignment was not attempted.

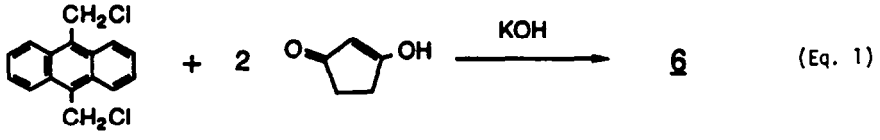
With cyclobutane 5 in hand, the crucial pinacol-type ring expansion to the desired target 2 was attempted. With refluxing trifluoroacetic acid, 5 was immediately converted to an equimolar mixture of anthracene and the 9,10-disubstituted anthracene 6. At room temperature, disappearance of 5 took about 2 hours, but once again only anthracene and 6 were obtained. None of the desired spirodiketone 2 could be isolated. Other acid catalysts were investigated with similar results. Suffice it to say that conditions which caused reaction of 5 invariably gave 6 instead of 2.

The structure of 6 could not be assigned directly, owing to its extreme insolubility in

Scheme I



common organic solvents which prevented complete spectroscopic characterization. The IR spectrum of 6 in the solid state showed bands (1550, 1385 cm^{-1}) attributable to enolized 1,3-cyclopentanedione. We have found that these insoluble compounds can be easily converted to the corresponding enol acetates[4b], which are well-behaved, soluble species. Treatment of 6 with acetic anhydride and triethylamine effected conversion to the bis(enol acetate) 7, obtained as feathery crystals from ethyl acetate. Spectral and analytical data for 7 were fully in accord with the assigned structure, but it is worth noting here the unusual upfield chemical shift (1.0 ppm) for the acetate methyl protons in the NMR of 7. We attribute this to a favored conformation of 7 in which the pendant cyclopentyl rings are tilted out of the anthracene plane, in an orientation which places the acetate groups in the shielding region above and below the aromatic π-system. Confirmation of the structural assignment for 7 (and hence, 6) was obtained by independent synthesis (Eq. 1). Reaction of

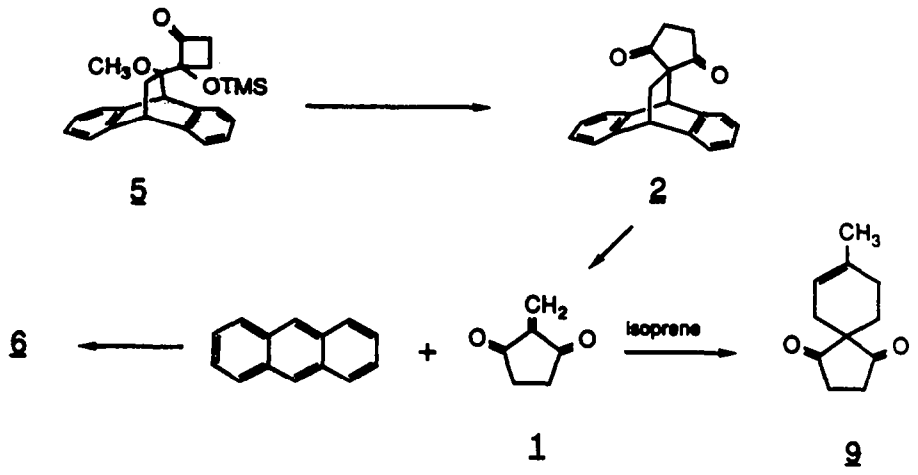


(Eq. 1)

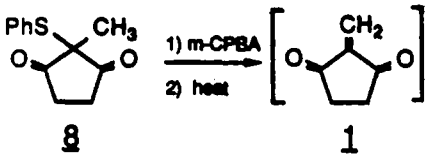
1,3-cyclopentanedione with 9,10-bis(chloromethyl)anthracene was carried out in aqueous base, conditions known to favor C-alkylation of the β-diketone.[6] The major product, after acetylation, was 7, identical in all respects to that described above.

The formation of 6 from 5 is most easily rationalized as follows (Scheme II). As expected, pinacolic rearrangement of 5 occurs to give 2, but this spirodiketone is not stable. Instead, retro-Diels Alder fragmentation produces 2-methylene-1,3-cyclopentanedione (1) and anthracene. Two fold electrophilic substitution[7] of 1 on the cognate anthracene nucleus leads to 6, and the overall stoichiometry of the process provides for a molar equivalent of anthracene.

Scheme II



Several experiments support this mechanism. That 1 is a reasonable precursor to 6 was tested by independent generation of 1 in the presence of anthracene. Thus, m-CPBA oxidation of 2-methyl-2-phenylthio-1,3-cyclopentanedione (8), followed by heating with excess anthracene provides 6 as the major product (Eq. 2). The oxidative elimination of 8 is known[4]

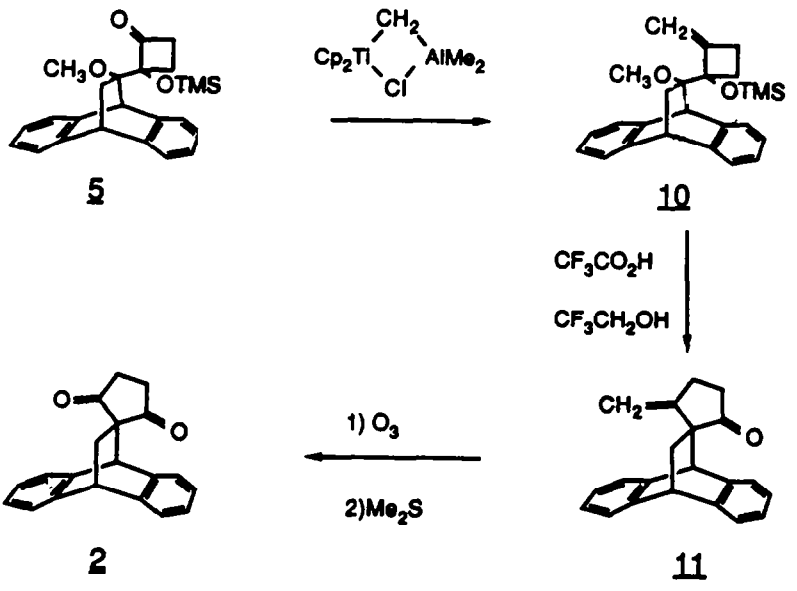


anthracene → 6 (Eq. 2)

to produce 1 as an intermediate; the reactivity of this ene-dione toward anthracene is remarkable. When the sulfoxide from 8 was heated in benzene, no products of electrophilic aromatic substitution were obtained. Likewise, the rearrangement of 5 was carried out with p-toluenesulfonic acid in refluxing benzene. Under these conditions, 7 was isolated in >90% yield after acetylation; there was no evidence for the reaction of 1 with the benzene solvent. On the other hand, repetition of this reaction in benzene-isoprene (1:2 v/v) as the solvent allowed isolation of the spirodiketone 9 in 60% yield (Scheme II). This result indicates clearly that ene-dione 1 is produced free in the conversion of 5 to 6 under these conditions. Isoprene is known to trap 1 efficiently giving the Diels-Alder adduct 9[4].

These experiments are strong confirmation of the latter part of the pathway outlined in Scheme II. Less secure, however, was the postulated decomposition of 2 (formed by rearrangement of 5) to give anthracene and ene-dione 1. There was no reason to expect such instability for 2 at the temperatures of these experiments--similar anthracene adducts are well known and require high temperatures for thermal decomposition.[8] Instead, it seemed likely that the exceptionally facile fragmentation of 2 was an acid-catalyzed retro-Diels Alder process. Acceleration of the Diels Alder cycloaddition by acid catalysis is, of course, well known.[3] According to the principle of microscopic reversibility, a similar effect on the reverse reaction is expected. This phenomenon is not well-established, probably due to the fact that that reaction energetics overwhelmingly favor the adduct at equilibrium. In the case at hand, an unfavorable equilibrium between 2 and 1 is driven by the rapid consumption of 1 to give 6. To test the notion that the fragmentation of 2 to 1 was catalyzed by acid, it was necessary to isolate adduct 2. Since all our attempts at acid mediated rearrangement of 5 led only to 6, we sought a route which would permit the generation of 2 under mild non-acidic conditions. The plan is outlined in Scheme III.

Scheme III



5 10 2 11

Methylenation of 5 was best accomplished with the Tebbe reagent,[9] which provided 10 in 82% yield after chromatography. Pinacolic ring expansion of 10 proceeded with clean migration of the vinyl group[5], smoothly providing the spiroannelated cyclopentanone 11 in 75% yield. Interestingly, we observed no tendency for retro-Diels Alder fragmentation of 11 under the acidic conditions of the pinacolic rearrangement. Conversion of 11 to 2 was accomplished in high yield by ozonolysis, followed by work-up with dimethyl sulfide. The structure of 2 followed clearly from spectroscopic data. A sample of 2 was stable for several weeks at room temperature, but proved highly sensitive to acids. For example, chromatography on silica gel invariably caused partial decomposition of 2, leading to anthracene as a readily identifiable product. More dramatically, addition of a drop of trifluoroacetic acid to an NMR sample of 2 in $CDCl_3$ resulted in rapid (<5 minutes) and complete conversion to a 1:1 mixture of anthracene and 6, demonstrating quite convincingly the powerful acid catalysis on the retro-Diels Alder fragmentation of 2.

Finally, the reaction of 1 with anthracene demonstrates the exceptional electrophilicity of the ene-dione system, and extends the known reactivity of these elusive compounds. Furthermore, the successful synthesis of 2 should allow preparation of 1 under non-nucleophilic (pyrolytic) conditions, permitting characterization of the parent ene-dione chromophore. These studies are in progress.

Experimental

Melting points were determined on a Fisher-Johns hot stage and are uncorrected. IR spectra were recorded on a Nicolet 20DXB spectrometer; significant absorbances are reported in cm^{-1}. ^{1}HNMR spectra of solutions in $CDCl_3$ were recorded on a JEOL FX90Q spectrometer at 90 MHz; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. ^{13}CNMR spectra were obtained on the same instrument at 22.5 MHz; chemical shifts are referenced to the central line of the $CDCl_3$ triplet at 77.0 ppm. Multiplicities were determined by off-resonance decoupling experiments. Microanalyses were performed by MicAnal, Tucson, Arizona.

Reactions were generally carried out under an atmosphere of dry nitrogen. The

concentration of organic solvents (in vacuo) refers to the removal of volatiles on a rotary evaporator at aspirator pressure.

Flash chromatography was performed with Merck Kieselgel 60 (230-400 mesh). Thin layer chromatography was carried out using precoated silica plates supplied by E. Merck. Methylene chloride was distilled from P_2O_5, and tetrahydrofuran was freshly distilled from a blue solution of sodium benzophenone ketyl. Boron trifluoride etherate was vaccum distilled from CaH_2.

9,10-Dihydro-11,11-dimethoxy-9,10-ethanoanthracene (4).

A mixture of ketone 3 (5.92 g), methanol (120 ml), trimethyl orthoformate (30 ml) and p-toluenesulfonic acid (50 mg) was stirred at reflux for 10 hrs. The reaction mixture was neutralized with solid potassium carbonate, and the volatiles removed in vacuo. The residue was partitioned between water and methylene chloride (100 ml). The organic phase was dried ($MgSO_4$), and concentrated. Crystallation from hexane gave 6.11 g (80%) of 4: mp 116-118°C; IR ν 1095 cm^{-1}: ^1H NMR δ 7.4-7.0 (8H,m), 4.50(1H,s), 4.25(1H,t,J=3.5Hz), 3.25(6H,s), 1.95 ppm (2H,d,J=3.5Hz).

9,10-Dihydro-11-methoxy-11-(2-oxo-1-trimethylsilyloxycyclobutyl)-9,10-ethanoanthracene (5).

A three-necked, round bottom flask equipped with stir, bar, septum inlet, addition funnel, and thermometer was charged with a solution of ketal 4 (1.10 g, 4.14 mmol) in methylene chloride (25 ml). The solution was cooled at -65°C as $BF_3 \cdot Et_2O$ (510 µl, 4.14 mmol) was added via syringe. The cold, cloudly yellow mixture was stirred for 10 minutes more. A solution of 1,2-bis(trimethylsilyloxy)cyclobutene (1.20g, 5.22 mmol) in methylene chloride (10 ml) was added dropwise over 1½ hour, and the reaction mixture was stirred at -65°C for an additional 2 hours. Saturated aqueous sodium bicarbonate (30 ml) was added, and the organic layer separated. The aqueous phase was extracted with methylene chloride (10 ml), and the combined organic phase dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (10% EtOAc/pet ether eluent), followed by crystallization from heptane (990 mg, 62%). mp 115-117°C; IRν 1780 cm^{-1}; ^1H NMR δ 7.5-7.0(8H,m), 4.87 (1H,s), 4.31(1H,t,J=3Hz), 3.08(3H,s), 2.75(2H,m), 2.06(2H,d,J=3Hz), 1.65(2H,m), 0.14ppm 9H,s); ^{13}CNMR δ 210.1(s), 144.6(2), 143.7(s), 141.7(s), 140.6(s), 126.1(d), 125.9(d), 125.8(d), 125.7(d), 125.6(d), 123.9(d), 123.1(d), 98.6(s), 83.8(s), 52.7(q), 49.9(d), 44.4(d), 42.0(t), 35.8(t), 25.6(t), 1.5ppm(q), one aromatic C not resolved.

9,10-Bis(2,5-dioxocyclopentylmethyl)antracene(6).

Cyclobutanone 4 (55 mg, 0.14 mmol) was heated to reflux in trifluoroacetic acid (5 ml) for 15 minutes. A precipitate formed rapidly. The mixture was cooled, and the volatiles removed in vacuo. The solid material was triturated with methylene chloride which gave a soluble fraction identified as anthracene (NMR, TLC). The insoluble material (6) was characterized by IR (KBr) ν 3700-3200, 1550, 1385 cm^{-1}.

9,10-Bis(2-acetoxy-5-oxacyclopent-1-enylmethyl)anthracene (7).

The crude solid 6 was suspended in methylene chloride (5 ml). Acetic anhydride (200 µl) and triethyl amine (300 µl) were added, and the mixture stirred at room temperature for 1 hr. The resulting solution was concentrated, then diluted with methylene chloride and washed successively with 10% H_2SO_4 and 10% Na_2CO_3. The organic phase was dried over $MgSO_4$, concentrated, and crystallized from ethyl acetate as delicate feathery crystals (30 mg, 89%). m.p. 254-256°C IR ν 1770, 1695, 1650 cm^{-1}; ^1HNMR δ 8.20, 7.45 (8H, AA'BB'pattern), 4.45 (4H, br s), 2.60 (8H, m), 1.00(6H, s); ^{13}C NMR δ 205.1(s), 177.4(s), 166.0(s), 130.0(s), 129.8(s), 128.7(s), 125.5(d), 125.3(d), 34.1(t), 27.1(t), 21.3(t), 19.4(q); Anal. Calcd for $C_{30}H_{26}O_6$: C, 74.68; H, 5.43. Found: C, 74.78; H, 5.48.

Reaction of 9,10-bis(chloromethyl)anthracene with 1,3-cyclopentanedione. Synthesis of 4.

A suspension of 9,10-bis(chloromethyl)anthracene[10] (275 mg, 1 mmol), 1,3-cyclopentanedione (196 mg, 2 mmol) and KI (300 mg, 2 mmol) in 0.4 M aqueous KOH (5 ml) was stirred at 100°C for 6 hr. The mixture was acidified with 1M HCl(10 ml) and the solid filtered and washed with acetone. The crude solid, which contained unreacted starting

material, was acetylated as above. The diacetate was purified by flash chromatography (10% ethyl acetate-methylene chloride) followed by crystallization from ethyl acetate. Yield: 168 mg (35%).

9,10-Dihydro-11-methoxy-11-(2-methylene-1-trimethylsilyloxycyclobutyl)-9,10-ethanoanthracene (10).

A solution of cyclobutanone 5 (108 mg, 0.27 mmol) in dry THF (2 ml) was stirred at 0°C as a solution of the Tebbe reagent (800 µl, 0.6 M in toluene, 0.48 mmol) was added via syringe. The red mixture was stirred for 2 hours at 0°C, then quenched with 10 drops of saturated sodium bicarbonate. The orange mixture was filtered through a pad of Celite® and a short column of Florisil® with a methylene chloride rinse. The solvents were removed in vacuo, and the residue purified by flash chromatography (50-50 methylene chloride-pet ether eluent) to give 89 mg (82%) of 10. A sample was crystallized from heptane: mp 105-106°C; IR ν 1123, 843 cm^{-1}; ^1H NMR δ 7.6-7.1 (8H, m), 5.19(1H,t,J=3Hz), 5.02(1H,s), 4.90(1H,t,J=3Hz), 4.25(1H,t,J-3Hz), 3.31(3H,s), 2.5-2.0(2H,m), 1.93(1H,dd,J=13,3Hz), 1.70(1H,dd,J=13,3Hz), 1.6-0.7(2H,m), 0.20ppm(9H,s); ^{13}CNMR δ 153.1(s), 144.9(s), 144.0(s), 142.0(s), 141.1(s), 125.8(d), 125.6(d), 125.3(d), 123.1(d), 122.8(d), 111.3(t), 86.5(s), 84.4(s), 52.8(q), 48.0(d), 44.7(d), 38.8(t), 32.1(t), 25.1(t), 2.1ppm(q). 3 aromatic C's not resolved.

9',10'-Dihydro-5-methylenespiro[cyclopentane-1,11'-[9,10]ethanoanthracen]-2-one (11).

Trifluoroacetic acid (200 µl, 2.6 mmol) was added to a stirred solution of 10 (54 mg, 0.14 mmol) in methylene chloride (1 ml) and 2,2,2-trifluoroethanol (4.5 ml) at room temperature. After 2 hours, the pale purple solution was concentrated, and the residue partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography (50-50 hexane-methylene chloride eluent) to provide 30 mg (75%) of 11: mp (x heptane) 133-134°C; IR ν 1740, 878 cm^{-1}; ^1H NMR δ 7.4-7.0 (8H,m), 4.68 (1H, br s), 4.40(1H,t,J=3Hz), 4.08(1H,s), 3.69(1H,br s), 2.9-2.0(4H,m), 2.17(1H,dd,J=13,3Hz), 1.65ppm(1H,dd,J=13,3Hz); ^{13}C NMR δ 215.4, 150.3, 143.8, 143.5, 139.6, 138.6, 126.5, 126.2, 126.1, 125.6, 125.2, 124.9, 123.1, 123.0, 109.3, 59.8, 51.9, 44.4, 36.9, 35.2, 26.4 ppm.

9',10'-Dihydrospiro[cyclopentane-1,11'-[9,10]ethanoanthracene-2,5-dione 2.

A solution of 11 (10 mg, 0.035 mmol) in methylenechloride (6 ml) was cooled to -60°C. A stream of ozone in oxygen (~5%) was bubbled through the solution until a blue color developed, then the excess ozone was removed with oxygen purge. Dimethyl sulfide (200 µl) was added, and the mixture was allowed to warm to room temperature. After 10 hours, the solution was washed with saturated NaCl (3 ml), dried over $MgSO_4$, and concentrated in vacuo. Purification by preparative TLC (10% ethyl acetate in methylene chloride) gave 2 (10 mg), contaminated with traces of anthracene. 2: IR ν 1722cm^{-1}; ^1H NMR δ 7.5-7.0(8H,m), 4.48(1H,t,J=2.6Hz), 4.38(1H,s), 3.15 and 2.65(4H,AA'BB'), 1.90ppm(2H,d,J=2.6Hz); ^{13}C NMR δ 210.0, 143.7, 136.9, 127.2, 125.8, 124.7, 123.5, 64.9, 52.2, 43.8, 34.3, 32.2 ppm.

Acknowledgement: We thank the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work.

References

1. (a) W. Neukam and W. Grimme, Tetrahedron Lett., 2201 (1978).
   (b) O. Papies and W. Grimme, Tetrahedron Lett., 21, 2799 (1980).
   (c) T.V. RajanBabu, D.F. Eaton, and T. Fukunaga, J. Org. Chem., 48, 652 (1983).
   (d) S. Knapp, R.M. Ornaf, and K.E. Rodriques, J. Am. Chem. Soc., 105, 5494 (1983).
2. P. Nanjappan and A. W. Czarnik, J. Org. Chem., 51, 2851 (1986).
3. Pioneering studies on the Lewis acid catalysis of the Diels-Alder reaction:
   (a) P. Yates and P. Eaton, J. Am. Chem. Soc., 82, 4436 (1960).
   (b) G.I. Fray and R. Robinson, J. Am. Chem. Soc., 83, 249 (1961).
   Proton acid catalysis of the Diels-Alder reaction:
   (c) G.A. Olah, D. Meidar, and A.P. Fung, Synthesis, 270 (1979) and references therein.
4. (a) P.E. Eaton and W.H. Bunnelle, Tetrahedron Lett., 25, 23 (1984).
   (b) P.E. Eaton, W.H. Bunnelle, and P. Engel, Can. J. Chem., 62, 2612 (1984).
5. J. Shimada, K. Hashimoto, B.H. Kim, E. Nakamura, and I. Kuwajima, J. Am. Chem. Soc., 106, 1759 (1984).
6. H. Schick, H. Schwarz, A. Finger, and S. Schwarz, Tetrahedron, 38, 1279 (1982).
7. Interestingly, no 1:1 adduct was observed under these conditions. Apparently, initial alkylation activates the anthracene nucleus toward further reaction, and only 2:1 adduct is isolated. Quantitative data pertaining to the activating effect in 9-alkylanthracenes does not seem to be available, but such a two-fold alkylation has precedence: C. Price, Org. React., 3, 1 (1946), and references therein.
8. M. Kodpinid, T. Siwapinyoyos, and Y. Thebtaranonth, J. Am. Chem. Soc., 106, 4862 (1984).
9. S.H. Pine, R.J. Pettit, G.D. Geib, S.G. Cruz, C.H. Gallego, T. Tijerina, and R.D. Pine, J. Org. Chem., 50, 1212 (1985).
10. M.W. Miller, R.W. Amidon, and P.O. Tawney, J. Am. Chem. Soc., 77, 2845 (1955).