60783-59-7; **19**, 98945-37-0; **20**, 98945-38-1; **21**, 98945-39-2; **23**, 98945-41-6; **23a**, 98945-43-8; **24**, 98945-42-7; **26**, 98945-44-9; **27**, 98945-45-0; **29**, 98945-47-2; **31**, 98945-46-1; MeOH, 67-56-1; EtOH, 64-17-5; $ClCH_2CH_2OH$, 107-07-3; $HOCH_2CH_2OH$, 107-21-1; $HO(CH_2)_5OH$, 111-29-5; $HOCH_2CH(OH)CH_2OH$, 56-81-5; 2,2-dichloroethanol, 598-38-9; 2,2,2-tricholoroethanol, 115-20-8; glycolic acid, 79-14-1; ethyl glycolate, 623-50-7; 2,4-diamino-6-methoxy-5-nitrosopyrimidine, 98143-11-4; benzil, 134-81-6.

α,α-Dimethoxy-*o*-xylylene (5-(Dimethoxymethylene)-6-methylene-1,3-cyclohexadiene): Formation by 1,4-Elimination and Electrocyclic Routes and Reactions

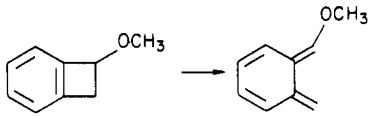
Randall J. Moss, Russell O. White, and Bruce Rickborn*

Department of Chemistry, University of California, Santa Barbara, California 93106

Received May 20, 1985

The title reactive intermediate **4**, which features an unprecedented (*Z*)-alkoxy substituent, is generated in two independent ways. The ortho ester **5** undergoes 1,4-elimination on treatment with lithium diisopropylamide, at convenient rates in the temperature range 50–70 °C. In the absence of added dienophile, **4** generated in this manner forms a spiro [2 + 4] dimer and a [4 + 4] dimer, both involving bonding between the two unsubstituted methylene groups. Diels–Alder adducts of **4** with norbornene (NB), norbornadiene, and cyclopentene are described. The ketal **8** formed from **4** and NB undergoes further 1,4-elimination, generating a new *o*-xylylene which in turn adds a second NB to yield the novel bis-adduct **11**. Thermal opening of α,α-dimethoxybenzocyclobutene (**6**) is also used to generate **4**. Rate constants for this reaction were determined over the temperature range 132–168 °C, through the use of *N*-phenylmaleimide, which efficiently traps the intermediate, thereby preventing reclosure to **6** and other decomposition reactions. The E_a for this electrocyclic opening is 33.6 kcal/mol; comparative data from the literature are discussed. In the absence of a dienophile, **4** generated in this way recloses to **6** as its major reaction pathway but also undergoes an unusual rearrangement to form methyl *o*-ethylbenzoate (**26**). The overall rate of this reaction is ca. one-tenth that of the opening of **6** to **4** and restricts the range of dienophiles which can be used to trap **4** generated from **6**. For example, even at the lowest temperature (132 °C) needed to observe electrocyclic opening, and in the presence of a very large excess of NB, competitive cycloadduct formation and rearrangement to **26** are observed. Flash vacuum pyrolysis of **6** was also briefly examined.

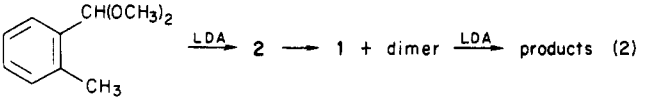
The elegant work of Sammes and colleagues[1] demonstrated that the thermal conversion of α-methoxybenzocyclobutene (**1**, name is common usage; IUPAC rules require the "dihydro" designation) to α-methoxy-*o*-xylylene (**2**) occurs with exclusive formation of the *E* isomer as shown in eq 1. The methoxy substituent of **1** causes a



(1)

1 2

remarkable (ca. 9 kcal/mol) lowering of the activation energy for this ring-opening reaction, compared with the unsubstituted case.[1] The methoxy system also differs from the unsubstituted material in that **2** closes readily to reform **1** under conditions where *o*-xylylene, at its steady-state concentration, undergoes preferential (second-order) dimerization and polymerization. The activation parameters for the reactions of **2** are unknown, whereas the temperature-dependent behavior of *o*-xylylene can be appreciated by consideration of these parameters as determined by Roth and co-workers.[2] We have recently shown[3] that the acetal **3** on treatment with lithium diisopropylamide (LDA) also affords **2** in high yield, and arguments were presented supporting the view that this process also forms the *E* isomer as the sole trappable (Diels–Alder) intermediate. In qualitative agreement with Sammes' observation, conversion of **2** to **1** was also demonstrated, although dimer of **2** was also formed (eq 2).



(2)

3

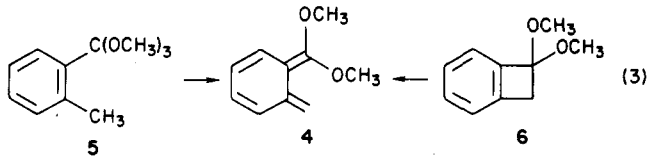
Very recently Kirmse, Rondan, and Houk[4] have described the effects of substituents on the formally analogous (to eq 1) cyclobutene–butadiene rearrangement; a 3-methoxy substituent lowers the activation barrier here also by ca. 9 kcal/mol and forms exclusively the (*E*)-vinyl ether (outward rotation of the alkoxy group). When an alkoxy group is constrained by orbital symmetry effects to move inward (as in *cis*-3,4-dimethoxycyclobutene), appreciable destabilization of the transition state results. Although net rate enhancement was observed for this material, the geometrically very similar 3,3-dimethoxycyclobutene undergoes rearrangement at a rate comparable to, or slightly slower than, that of the unsubstituted parent olefin.[5]

α,α-Dimethoxy-*o*-xylylene (**4**) is an especially intriguing material in this context, since it is the simplest representative of an unknown class of *o*-xylylenes, in which one alkoxy group must, in the planar structure, assume the *Z* geometry. We envisioned approaching **4** in the two ways

(1) Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 409.
(2) Roth, W. R.; Scholz, B. P. *Chem. Ber.* **1981**, *114*, 3741. Roth, W. R.; Biermann, M.; Dekker, H.; Jochems, R.; Mosselman, C.; Hermann, H. *Ibid.* **1978**, *111*, 3892.
(3) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 3694.
(4) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.
(5) We thank Professor Kirmse for providing the data on 3,3-dimethoxycyclobutene (E_a = 32.8 kcal/mol; log *A* = 13.7) and permission to quote these unpublished results.

0022-3263/85/1950-5132$01.50/0

illustrated in eq 3, i.e., by LDA-induced 1,4-elimination



5 4 6 (3)

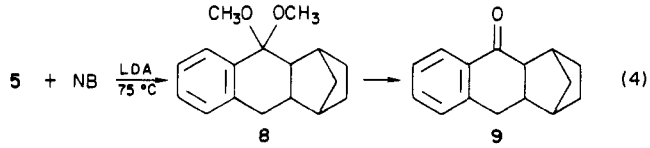
of the ortho ester **5** and thermal rearrangement of the benzocyclobutenone dimethyl ketal **6**. Fortunately, a synthesis of **5** (which resists classical ortho ester preparative methods) was reported[6] shortly before this work was initiated. The ketal **6** was prepared by condensation of benzyne with 1,1-dimethoxyethylene as described by Stevens,[7] with some modifications to facilitate the reaction.

Results and Discussion

(a) Base-Induced Reactions. Evidence for the formation of reactive intermediates, absent low-temperature isolation or direct spectroscopic observation, is necessarily indirect and often is inferred from the production of an isolable product. Diels–Alder reactions are traditionally used to probe the formation of *o*-xylylenes, and we have used this method to examine the 1,4-elimination of methyl *o*-methylbenzyl ether (**7**) (which gives the parent *o*-xylylene)[8] and the acetal **3**[3] and in the present study of the ortho ester **5**. Before discussing these results, it is instructive to consider the relative rates of the base-induced eliminations of the three substrates. It was previously found[3] that the ether **7** is more reactive than the acetal **3**, and one might have anticipated continuation of this trend leading to even slower reaction for the ortho ester. However, competition kinetics demonstrate that **5** is more reactive than either **3** or **7**. The relative rates have the values: $k(5) = 6$; $k(7) = 4$; $k(3) = 1$. The reason for this unusual order is not apparent. Perhaps the most informative aspect of these data is that the reactivities differ by such small factors. This suggests that similar mechanisms are involved in all three reactions and shows that there is no major stabilization of the transition state for the elimination by the (*E*)-methoxy group in the acetal or destabilization by the (*Z*)-methoxy group in the ortho ester reaction, in contrast to the very large effects discussed above for the thermal rearrangements.

Typical carbonyl-containing dienophiles are not amenable to use with strong bases, and we therefore turned to simple olefins as prospective trapping agents. Among these, norbornene (NB) has proven especially effective, giving high yields of cycloadducts with both *o*-xylylene[8] and **2**.[3] The base-induced reaction of **5** in the presence of excess NB was therefore an early focus of this study.

Evidence for the formation of **4** was obtained through the isolation and characterization of the cycloadduct ketal **8** (eq 4). The yields of **8** from several reactions were



8 9 (4)

variable and never exceeded 65%. It was necessary to control the relative amount of LDA employed to ca. 1.5–2 equiv to attain these levels. Lower amounts led to incomplete reaction with recovery of sizeable amounts of **5**, while a greater excess of base caused lower yields of **8**, indicative of further reaction as anticipated by analogy with the earlier study[3] of the acetal **3**. Additional yield diminishing features are the formation of dimer of **4** and possible ring closure of **4** to **6**, leading to other base-sensitive materials; these aspects are discussed in greater detail below.

Table I. LDA-Induced Reactions of 5 with Norbornene

method[a]	LDA, equiv	time, h	% 5 recd	yield of 8, %
A	1.4	3.0	14	28
A	2.8	0.5	<1	24
A	2.8	3.0	<1	19
B	1.4	5.0[b]	25	59
B	2.0	6.5[b]	2	56

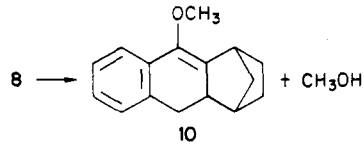
[a] Method A: addition of **5** to refluxing solution of LDA and NB. Method B: the base was added via syringe pump to the refluxing solution of **5** and NB. [b] Total time, including 0.5-h reflux after syringe pump addition completed.

Furthermore, and in contrast to earlier work with the ether and acetal systems, the mode of addition of reagents significantly affected the yield of **8**. The best results were obtained when LDA was added slowly (via syringe pump) to a refluxing (hexane) solution of **5** and NB, as shown in Table I. Since the overall rate-determining step (regardless of procedure) must be the 1,4-elimination, this suggests that the presence of excess LDA is detrimental because of reaction of the base with the reactive intermediate. Although basic products were not examined in this study, this view is supported by several observations, including the isolation of an LDA-incorporated product in the earlier work with **3**.

The ketal **8** was very susceptible to hydrolysis and elimination and did not survive attempted silical gel chromatography. Partial hydrolysis and elimination also occurred on neutral and basic alumina, although it was possible using deactivated neutral alumina to isolate sufficient **8** for further examination. Since **8** also decomposed on attempted VPC analysis, yields were determined by subjecting crude product mixtures to acid-catalyzed hydrolysis, whereby **8** was converted to ketone **9**, which was stable to both column and VPC conditions. The structure of **9** was established by alternative synthesis, involving simple PDC oxidation of the corresponding alcohol, both epimers of which were available from earlier work.[3]

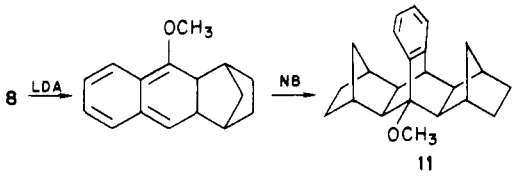
The ketal **8** exhibited unusual NMR features. The methoxy groups are of course chemically distinct and absorb at significantly different frequencies. However, these absorptions at 25 °C were observed as very broad singlets, and this feature was much more pronounced at 300 MHz than at 60 MHz, showing that it was rooted in chemical shifts rather than long-range couplings. Variable-temperature NMR was used to probe the cause; at −60 °C the methoxy peaks appeared as two sharp singlets, and other features of the spectrum were simplified and in keeping with the proposed structure of **8**. Decoupled spectra were also consistent with this structure and allowed complete specification of all signals. Reasoning that the room-temperature broadening was due to an (acid-catalyzed) methoxy exchange process, which in the limit might make the two groups equivalent, the sample was heated. This treatment, however, resulted in the appearance of two new sharp methoxy singlets, attributed to elimination of methanol and the formation of the vinyl ether **10** (eq 5). This process was also observed when **8** in $CDCl_3$ was treated with trifluoroacetic acid at room temperature; a rapid reaction occurred leading to a mixture of **9** and **10**. Since the trace of acid normally found in chlorinated

(6) Sakai, S.; Fujinami, T.; Kosogi, K.; Matsnaga, K. *Chem. Lett.* **1976**, 891.
(7) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2393.
(8) Tuschka, T.; Naito, K.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 70.



solvents ($CDCl_3$) seemed a likely source of catalyst for both the broadening and elimination, a sample of 8 in C_6D_6 was examined. Broadened methoxy peaks were observed in this solvent at room temperature also, and elimination to 10 likewise occurred as the temperature was increased, although more slowly than in $CDCl_3$. Addition of triethylamine (in either solvent) caused no change in the shape of the spectrum, and addition of CD_3OD (to the $CDCl_3$ solution containing triethylamine) likewise caused no change in shape or intensity of absorptions. These observations rule out methoxy group exchange as the cause of the broadening. The alternative explanation is an unusually slow interconversion of conformers, and models suggest that inversion of the center ring boat-like forms may have a substantial barrier due to interaction of a methoxy group with the peri aromatic hydrogen and the bridgehead hydrogen of the norbornyl group. The sharp low-temperature spectrum (with only two methoxy absorptions) must then be attributed to a single conformer; while it is possible that the minor conformer is insoluble at −60 °C, this was not visually evident, and the failure to detect other contributors remains an unanswered feature.

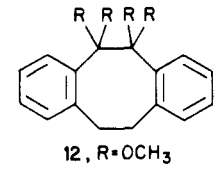
The ketal 8 is a substrate for further base-induced 1,4-elimination, as confirmed by the isolation of the interesting bis(norbornene) adduct 11, which must arise as shown in eq 6. The formation of 11 has precedent in the reaction

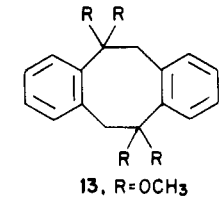


of acetal 3 with norbornene, from which the demethoxy analogue of this structure was isolated,[3] and presumably involves the loss of the methoxy group which is trans to the norbornyl group in 8. The structure of 11 is based on symmetry features as shown by its ^{13}C NMR spectrum (16 lines) and the characteristic upfield shift of the methylene bridge protons, which lie in the shielding region of the aromatic ring. Evidence supporting the proposed route to 11 was obtained by treating an isolated sample of 8 with LDA and excess norbornene.

Although trapping of the *o*-xylylene 4 by excess NB is a fairly efficient process, even under these conditions some dimer is formed, along with some insoluble presumably polymeric material. In the absence of NB, the dimer is formed in modest yield (13% isolated when a mixture of reactants was refluxed) and was readily separated from other materials by evaporation of the ether extracts and precipitation of the crude dimer with hexane, in which it has very low solubility (this may account for it surviving the basic conditions under which it is formed.) A similar yield was obtained when the reaction was carried out at 50 °C, with slow addition of the LDA to the ortho ester in hexane solution.

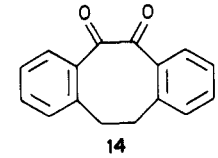
This dimer is clearly a formal [4 + 4] adduct and has analogy in the reaction of unsubstituted *o*-xylylene. Two structures may be written, the "head-to-head" 12 and "head-to-tail" 13. Although the planar structures shown stress the symmetry features of these materials, models indicate that a significant barrier is introduced by the four methoxy groups for chair or tub conformational inter-

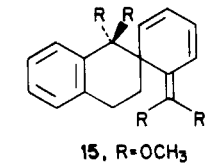




conversions. The room-temperature 300-MHz ^1H NMR spectrum in fact contained two equal area very broad methoxy absorptions, and the (two) benzylic proton absorptions were similarly broadened. At −1 °C, the spectrum exhibits two sharp methoxy peaks, and the benzylic protons appeared as a complex AA′BB′ array, as expected for a conformer of 12 having C_2 (chair) or C_s (tub) symmetry, but not for 13 barring unanticipated long-range coupling. Warming the $CDCl_3$ solution of 12 to 76 °C caused coalescence of the two methoxy peaks to a very broad absorption centered at the midpoint, and this process was reversible. The barrier, $\Delta G^{\ddagger}$(349 K), for interconversion of conformers resulting in time-average equivalent methoxy groups is estimated to be ca. 23–24 kcal/mol.

The head-to-head structure 12 of this dimer was additionally confirmed by conversion to the known dione 14.[9]





No indication of formation of the alternative [4 + 4] dimer 13 was found. Interestingly, the major product formed in the base-induced reaction of 5 (in the absence of added dienophile) is the novel [2 + 4] dimer 15. Surprisingly, it proved possible to isolate this material in nearly pure form by rapid workup and chromatography on low activity alumina. The structure of 15 is based on its NMR features, which include four distinct (sharp) methoxy peaks, four vinyl proton absorptions, and the four distinct and mutually spin-coupled protons of the ethano linkage. The latter feature establishes the regiochemistry of the cycloaddition, i.e., the unsubstituted methylene double bond functions as the dienophile, and bonding of the two unsubstituted termini occurs, in analogy to the formation of 12. As expected, 15 was unstable and decomposed even at −10 °C over a period of days. The product(s) of this decomposition have not been identified, but NMR analysis indicates that little if any rearrangement to 12 has occurred.

The preferred formation of [2 + 4] dimer parallels the observations of Errede on the low-temperature behavior of the parent unsubstituted *o*-xylylene, where it was also shown that the spiro dimer was unstable and polymerized by both radical and acid-catalyzed processes.[10]

Dimers 15 (23–30%) and 12 (10–15%) account for roughly half of the 5 used in these experiments. Much of the remainder appears to be polymeric or oligomeric material lost in the workup. Only one other substance, isolated in 1% yield, was obtained by chromatography. This compounds appears (MS, NMR) to be 1-methoxy-3-methylnaphthalene. Although its origin is unclear, it presumably incorporates the three-carbon fragment from LDA, perhaps via imine–enamine formation, cycloaddition, and subsequent eliminations.

(9) Leonard, N. J.; Kresge, A. J.; Oki, M. *J. Am. Chem. Soc.* **1955**, *77*, 5078.
(10) Errede, L. A. *J. Am. Chem. Soc.* **1961**, *83*, 949.

We were particularly interested in the question of cyclization of dimethoxy-o-xylylene **4** to dimethoxybenzocyclobutene **6**; i.e., whether this process occurred at a reasonable rate at the temperature of the base-induced reactions (70–75 °C), in competition with obviously fast but second-order processes such as Diels–Alder reactions and dimer formation. As shown in a later section, closure of **4** to **6** at this temperature would be effectively irreversible. Thus, the formation of dimers **12** and **15** is *prima facie* evidence that the reaction (**4** → **6**) is not the exclusive pathway for loss of this reactive intermediate. It should again be noted that closure is the dominant reaction of (*E*)-α-methoxy-o-xylylene (at slightly higher temperature[1]), whereas unsubstituted o-xylylene gives no detectable benzocyclobutene when generated at 75 °C.[8]

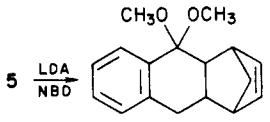
The ability to detect **6** (if formed) depends upon its reactivity toward LDA. A competition kinetics experiment involving 1 equiv each of ortho ester **5**, benzocyclobutene **6**, and LDA showed that **6** is significantly more reactive than **5** (second-order $k(6)/k(5) = 7 \pm 1$). Presumably **6** undergoes elimination to give the benzocyclobutadiene **16** as a reactive intermediate (eq 7). In our earlier work with

(7)

16

the acetal **3**, it was possible to demonstrate the formation of α-methoxybenzocyclobutene and its subsequent elimination, by trapping the resultant benzocyclobutadiene with 1,3-diphenylisobenzofuran. An attempt to do the analogous experiment with **6** was inconclusive, possibly because cycloaddition is less favorable with **16** or because the cycloadduct once formed undergoes further reaction. Since this approach was not promising, an effort was made to detect **6** directly by capillary VPC, in the reaction mixture obtained when **5** was treated with 0.3 equiv of LDA; a very small peak (ca. 0.1% compared to the residual **5**) with the retention time of **6** was observed. Attempts to verify this structure by GC/MS were thwarted by the small amount of this material in the mixture. Thus it is not clear if *any* measurable amount of cyclization of **4** to **6** occurs under the base-induced reaction conditions.

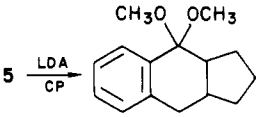
Other dienophiles that have served as trapping agents for o-xylylenes formed in strongly basic conditions are norbornadiene (NBD) and cyclopentene (CP),[3,8] and the study of **5** was extended to encompass these materials. The LDA-induced reaction of **5** in the presence of excess NBD gave the expected adduct **17** (eq 8), which was isolated in 60% yield by chromatography on deactivated alumina. The variable-temperature NMR features of **17** were similar to those described above for the NB adduct.[11] The structural relationship was confirmed by catalytic reduction of **17**, which resulted in not only reduction of the double bond but also hydrolysis of the ketal function, giving rise to the previously described ketone **9**. Attempts to isolate or detect products of further elimination of **17** were not successful, even though it was established that **17** did react with excess strong base.[12]



(8)

17

Cyclopentene (CP) is not as efficient as the bicyclic olefins in trapping the o-xylylenes examined in earlier work,[3,8] and this feature is also evident in the reaction of **5**. Cycloadduct **18** was obtained in 37% yield (eq 9).

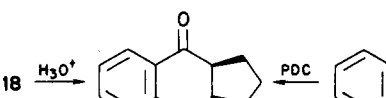


(9)

18

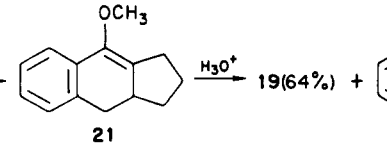
Again, a comparison with the results obtained from the acetal **3** is interesting; with this substrate, only the cis cycloadduct was formed. Various arguments support the view that this material is formed by specific endo cycloaddition to (*E*)-α-methoxy-o-xylylene and that the *E* isomer is formed predominantly or exclusively in this elimination.[3] The reaction with CP contrasts with that of, e.g., norbornene, which exhibits little endo/exo selectivity (although reaction occurs exclusively to the exo face of the dienophile.) Parallel behavior is exhibited by these two dienophiles with isobenzofuran, which can serve as a model for a (*Z*)-alkoxy-o-xylylene (neglecting its status as a Hückel aromatic). Although the symmetry introduced by the *gem*-dimethoxy group masks the stereochemical evidence obtained in reactions of **3**, the similar yields of CP cycloadducts obtained with the three o-xylylenes examined in this and earlier work support the view that no major new barrier to cycloaddition is introduced by the (*Z*)-methoxy group of **4**; i.e., it is likely that **18** is also formed by endo cycloaddition.

The adduct **18** exhibited the (normal) expected ^{1}H NMR spectrum at room temperature, i.e., two sharp methoxy absorptions. Additional proof of structure was obtained by rapid hydrolysis (THF, aqueous acid, 10 min, 25 °C) to the cis ketone[13] **19**, which was identical with material prepared by PDC oxidation of the alcohol **20**, which in turn had been prepared by an independent route as described[3] earlier (eq 10). Like the other ketals described in this work, **18** was unstable to chromatography on activity I alumina; such treatment provided the enol ether **21**. Hydrolysis of **21**, which was significantly slower (requiring 2 h at reflux for completion) than the conversion of **18** to **19**, gave a mixture consisting of **19** (64%) and **22** (36 ± 3%), as outlined in eq 11. This same mixture ratio of



(10)

19 **20**



(11)

21 **22(36%)**

(11) The bridge methylene protons of **17** appear as an AB q at −35 °C, at which temperature two sharp methoxy absorptions are also seen. At room temperature the methoxy peaks are broadened and somewhat shifted, while the methylene protons have merged to a broad singlet. Interestingly, the singlet is centered *downfield* of the center point of the low-temperature AB q, suggesting that the preferred low-temperature form is the "nonextended" boat in which the methylene protons would experience the shielding effect of the aromatic ring. This would be anticipated if the steric interaction of the methylene bridge and "axial" methoxy group were significant. A precipitate was observed at the lower temperature in this instance, which may explain why only a single conformer is seen.

(12) A dark ether-insoluble material was formed from **17** and excess base. We had anticipated that 1-methoxynaphthalene might be formed by elimination followed by retro-Diels–Alder loss of cyclopentadiene,[3] but this known material was clearly absent in the NMR spectrum of the crude product.

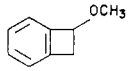
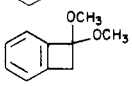
(13) This ketone, of unspecified composition as formed in a Friedel–Crafts cyclization reaction, has been reported by: Van den Heuvel, C. G.; Nibbering, N. M. M. *Org. Mass Spectrom.* **1978**, *13*, 584.

Table II. Rate Constants for Electrocyclic Opening of 6[a]

T,[b] °C	NPM, equiv	$10^6 k_1$, s^{-1}
132	1.0	2.2 ± 0.2
144	1.0	6.0 ± 0.7
144	0.5	5.8 ± 0.4
144	5.0	6.5 ± 0.5
155.5	1.0	18.4 ± 1.7
168	1.0	65 ± 3

[a] Rates were followed by VPC analysis, using *n*-tetradecane as the internal standard. The error limits on the rate constants were determined graphically to reflect the greatest deviation in point scatter. [b] The bath solvents used at reflux were in order of increasing temperature chlorobenzene, *o*-xylene, bromobenzene, and *tert*-butylbenzene.

Table III. Activation Energies for Electrocyclic Opening

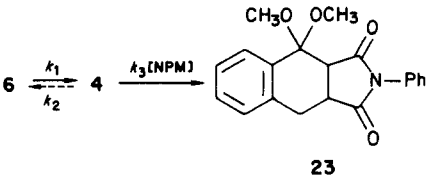
	E_a, kcal/mol		E_a, kcal/mol
	39.9[a]		32.5[d]
	31.3[b]		23.5[d]
	33.6[c]		32.8[e]
			28.6[d]

[a] From ref 2. [b] Determined from the rate constants given in ref 1. [c] This work; the log *A* for this reaction is 12.4. The corresponding $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values are 32.8 kcal/mol and −4.3 cal/(mol deg), respectively. [d] As given in ref 4. [e] See ref 5.

19/22 was obtained when pure **19** was epimerized by treatment with dilute methoxide in methanol; the ratio was unchanged after 18 h (25 °C), indicating that it represents the equilibrium position. Similar cis/trans equilibrium ratios have been reported for 1-hydrindanone (75/25)[14] and 4-hydrindanone (76/24),[15] both at higher temperatures.

Overall, it is concluded that the base-induced 1,4-elimination of **5** closely parallels the reactions of the ether **7** and the acetal **3** studied earlier. This work establishes that the base-induced reaction is capable of forming an *o*-xylylene containing a (previously unknown) (*Z*)-alkoxy function.

(b) Thermal Reactions of 6. The activation parameters for electrocyclic opening of **6** to **4** are of particular interest, for reasons outlined in the introduction. In order to measure the pertinent rate constant, it was necessary to use a dienophile of sufficient reactivity to preclude the back reaction, closure of **4** to **6**. This approach was used by Sammes in his study of the thermal opening of α-methoxybenzocyclobutene, with maleic anhydride as the dienophile. Since the ketal **6** is sensitive to acid (invariably present or formed in maleic anhydride reactions), we examined the use of *N*-phenylmaleimide (NPM), and this proved suitable. Rates were determined over the temperature range 132–168 °C by using this dienophile. The reactions were carried out in *tert*-butylbenzene solvent, in small sealed tubes immersed in a refluxing solvent to maintain the desired temperature. The extent of reaction was followed by VPC analysis, using an internal standard, monitoring the loss of ketal **6** (and concomitant disappearance of NPM.) Good first-order behavior was observed, with data points taken over 1 or more half-lives. Variation in the initial concentration of NPM from 0.5 to 5 equiv/mol of **6** was examined in the mid-temperature region and had no effect on the rate constant, showing that the cycloaddition step is not rate-determining. Separate experiments established that the expected cycloadduct **23** is formed in high yield. When **6** was heated in the absence of NPM, it decomposed (see discussion below) at an appreciable rate, but significantly slower than in the presence of NPM; therefore, the primary mode of reaction of **4** in the absence of a trapping agent, at the temperatures employed here, is electrocyclic closure to reform **6**. Thus these conditions meet the requirement $k_3[\text{NPM}] >> k_2 >> k_1$ (eq 12) and afford the rate constant of interest (k_1). These

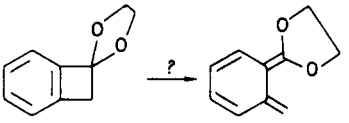


(12)

23

data are given in Table II. The derived activation parameters for this process are displayed in Table III, along with comparative data from the literature for the benzocyclobutene and cyclobutene series.

We had anticipated that **6** might have a much higher activation enthalpy than the value determined experimentally, based in part on Kirmse's results with alkoxy-substituted cyclobutenes[4,5] and particularly on Sammes' brief mention[1] of the ethylene ketal analogue of **6**, compound **24**. It was reported that attempts to trap an intermediate *o*-xylylene from this system with maleic anhydride or dimethyl acetylenedicarboxylate (DMAD) at temperatures up to 131 °C caused no loss of the ketal, while at 140 °C decomposition of the ketal, of undetermined nature, was observed in the presence of DMAD. As already noted, the acidic properties of maleic anhydride make it less than ideal for use with a ketal, and our experiences with **6** and DMAD indicate that the latter is not a satisfactory dienophile at the temperatures required for ring opening, in part at least because of the known self-condensation of this reagent.[12] It remains to be seen if a different dienophile, e.g., NPM, would effect the desired trapping of **25** or if there is a fundamental difference in the reactions of **24** (**25**) compared to **6** (**4**).



(13)

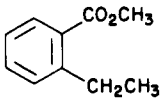
24 **25**

The E_a for ring opening of **6** (33.6 kcal/mol) indicates that the transition state has retained roughly two-thirds of the 9 kcal/mol (ΔE_a) stabilization energy associated with the (developing) (*E*)-methoxy group; i.e., this effect overshadows the negative influence of the (developing) (*Z*)-methoxy group. The parallel ΔE_a values seen in comparing the benzocyclobutene and cyclobutene systems (Table III) diverge for the *gem*-dimethoxy cases, for reasons which are not understood. Interestingly, the ΔE_a for **6** resembles that found by Kirmse et al.[4] for *cis*-3,4-dimethoxycyclobutene (see Table III), suggesting that the 3,3-dimethoxycyclobutene system is anomalous. Comparative data are not available for the analogous *cis*-dimethoxybenzocyclobutene; Sammes and co-workers[1] reported that no adduct was obtained from this compound and maleic anhydride even at 140 °C, although "general decomposition" occurred at this and higher temperatures. Since it is not known if this decomposition reflects electrocyclic opening, it is not possible to estimate the perti-

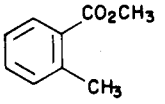
(14) House, H. O.; Rasmussen, G. H. *J. Org. Chem.* **1963**, *28*, 31.
(15) Lo Cicero, B.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914.
(16) Kauer, J. C.; Simmons, H. E. *J. Org. Chem.* **1968**, *33*, 2720.

nent activation energy of this substrate from these observations.

When the ketal **6** is heated alone or in solution without added dienophile, it decomposes yielding as the major product methyl *o*-ethylbenzoate (**26**), accompanied by varied but generally lesser amounts of methyl *o*-methylbenzoate (**27**). Although we have no direct evidence on



26



27

the mechanism of formation of either product, **26** may arise via **4** by an apparently unprecedented [1,5]-methyl shift from oxygen to carbon. Several pathways to **27** may be envisioned, but attempts to clarify its origins have not been conclusive. The ratio of **26**/**27** ranged from ca. one to ten under various solution/temperature conditions. Two kinetic runs were made at 168 °C in *tert*-butylbenzene and *p*-cymene, which gave ratios (**26**/**27**) of 3 ± 0.5 and 1.9 ± 0.1, respectively. These ratios did not change systematically over 4 half-lives, as might have been expected if **27** were formed, for example, by a process involving adventitious water or other minor impurity. Although the amount of **27** formed in *p*-cymene did increase (relative to the ratio found in *tert*-butylbenzene), the change is not dramatic as might have been anticipated if this material were formed by a hydrogen abstraction free radical process.

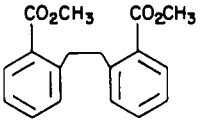
The rates of loss of **6** in the two solvents were similar, and interestingly, only a factor of 10 slower than the reaction in the presence of NPM at the same temperature. Assuming that formation of **26** involves a first-order reaction of **4** (as seems likely), the electrocyclic closure to **6** is favored over this isomerization to **26** by at most a few kilocalories per mole. This has important consequences in the choice of reaction conditions and dienophiles which will be suitable for cycloadduct formation with this system.

This point was evident in attempts to prepare a cycloadduct from **4** (generated by the thermal reaction of **6**) which had already been isolated from **4** generated by the base-induced reaction of **5**. We felt that it was important to establish this common link to further the argument that the same intermediate (**4**) is involved in both processes. Success was finally achieved by using a very large excess of norbornene (the same 5 M solution of NB in hexane as used in the base-induced reactions was employed) and operating at the lowest temperature (132 °C) at which the NPM reaction could be conveniently followed. The reaction was carried out in small sealed tubes immersed in a refluxing chlorobenzene bath and was slower ($k = 1.2 \times 10^{-6}$ s^{-1}) than in the presence of NPM at this temperature by approximately a factor of 2. Of particular significance, the NB cycloadduct ketal **8** was detected by capillary VPC and confirmed by GC/MS (comparison of the EI cracking pattern with that of an authentic sample of **8**).[17] A peak was also found for the *o*-ethyl ester **26**, and again this structure was confirmed by GC/MS. Thus the isomerization of **4** to **26** is competitive with the cycloaddition of **4** to NB at this temperature, in spite of the overwhelmingly large concentration of NB employed. Although not corrected for response factors, the (flame ionization) peak areas for **8**/**26** were in a ratio of ca. 70/30, showing that significant amounts of both were present.

The formation of **8** in this thermal reaction establishes the common link to the base-induced procedure and supports the view that the same intermediate (**4**) is involved in both processes. These results also provide a nice practical illustration of the importance of temperature when first-order processes compete with second-order reactions which may have low activation enthalpies but are subject to large negative activation entropies (e.g., Diels–Alder and dimer-forming reactions).[18] Successful synthetic applications thus require either an especially low activation enthalpy (implicit in the NPM reaction) or diminishing the importance of the entropy term, either by the use of an intramolecular trap or by lowering the temperature of the reaction. It is the latter which gives the base-induced reactions an advantage; the lower temperatures used in the 1,4-elimination allow the isolation of cycloadducts with dienophiles as poorly activated as cyclopentene, whereas the activation energy for electrocyclic opening of **6** requires a higher reaction temperature which in turn makes the bimolecular trapping reactions disfavored for all but the best dienophiles.

In contrast to the reaction of **6**, the thermal opening of α-methoxybenzocyclobutene provides a very efficient route to the cycloadduct with cyclopentene, at temperatures around 100 °C.[3] This difference can be explained partly by the lower temperature needed for opening of the monomethoxy derivative, but perhaps more importantly, the α-methoxy-*o*-xylylene has a built-in protective device—its primary mode of reaction is reclosure to the benzocyclobutene. This pathway is also favored when **4** is generated thermally but is not as effective in protecting the substrate because of the competing rearrangement to **26** which has only a slightly higher activation energy.

Finally, we have briefly examined the flash vacuum pyrolysis of **6**, through a packed quartz tube at ca. 500 °C. A small amount of solid was formed near the exit of the pyrolysis chamber, which proved to be the known[19] diester **28** (ca. 4% obtained after recrystallization from ligroin.)



28

The cold trap contained 60% of a mixture which was taken up in CH_2Cl_2 and analyzed by capillary VPC. The major constituent (ca. 85%) was the ester **26**, with most of the remainder being **28**. A peak corresponding to **27** was also observed, but accounted for less than 2% of the mixture.

Although the mechanism of formation of **28** is unknown, it is interesting to note that this structure follows the "head-to-head" regiochemistry found in the [4 + 4] dimer isolated from the base-induced reactions of **5** and also evident in the spiro dimer formed under those conditions.

Experimental Section

Proton NMR spectra were obtained on a Varian EM-360, CFT-20 (80 MHz), or Nicolet NT-300 instrument, in $CDCl_3$ solvent; ^{13}C NMR spectra were recorded on the latter two instruments. IR spectra were recorded on a P-E 283 spectrophotometer, and MS data were obtained on either a VG ZAB-2F or a VG 70-250 spectrometer. An HP 5790A VPC was used with the latter for GC/MS. Melting points (uncorrected) were obtained in open capillary tubes on a Mel-temp apparatus. Combustion analyses were performed by Galbraith Laboratories, Knoxville, TN.

Analytical VPC for the base-induced reactions was done on an HP 5880 instrument, with a 2 m × 3.2 mm 20% SE-30 column,

(17) The ketal **8** remains intact under the capillary VPC and the GC/MS conditions used, in contrast to its behavior in attempted preparative VPC, which caused decomposition to the enol ether.

(18) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; 2nd ed.; Harper and Row: New York, 1981; p 848.
(19) Bergmann, E. D.; Pelchowicz, Z. *J. Am. Chem. Soc.* **1953**, *75*, 4281.

TC detector, and *n*-tetradecane as the internal standard. Yields are corrected for differences in thermal conductivity. For the kinetic determinations of reactions of **6**, an HP 5830A instrument with flame ionization detection and a 25 m × 0.2 mm HP Ultra II column were employed.

Diisopropylamine was distilled from CaH_2 and stored under N_2 with 3A molecular sieves. Olefins (except norbornene which was used as received and *N*-phenylmaleimide which was recrystallized from hexanes), *tert*-butylbenzene, *p*-cymene, and hexanes were distilled from CaH_2 prior to use. *n*-Butyllithium in hexane was titrated periodically with 2-butanol and phenanthroline. LDA was prepared by dropwise addition of the amine to *n*-butyllithium in hexane at 0 °C. All reactions were carried out under N_2.

Based-induced reactions of **5** were carried out, unless otherwise specified, by slow syringe pump addition (6–7 h) of an LDA solution (consisting of LDA dissolved in 10.0 mL of the reaction solvent) to **5** in 40.0 mL of the olefin alone, hexane alone, or 5 M olefin/hexane (with NB and NBD) at reflux. When the addition was complete, the mixture was refluxed for an additional short period, cooled, and then quenched with an equal volume of water. After several extractions with ether (ca. 150-mL total) the combined organic phase was washed with brine, dried (K_2CO_3), and evaporated. The resulting residue was triturated with hexane to remove **12** prior to further purification and analysis.

Where indicated, yields of cycloadduct were determined by first hydrolyzing a small portion of the above residue (5% H_2SO_4, THF, 10 min, $NaHCO_3$ neutralization, and ether workup) followed by VPC analysis. In this way, ketal products were analyzed as the corresponding ketones and **5** as methyl *o*-toluate.

1-Methyl-2-(trimethoxymethyl)benzene (5). Following the literature procedure[6] **5** was prepared from methyl 2-methylbenzenecarbodithioate[20] in 91% yield: bp 99 °C (8 torr) (lit.[6] 103–104 °C (15 torr)): ^{1}H NMR δ 2.4 (s, 3 H), 3.0 (s, 9 H, methoxy), 7.2 (m, 3 H, aromatic), 7.7 (m, 1 H, aromatic).

Benzocyclobutenone Dimethyl Ketal (6).[7] Methyllithium (66 mmol) in ether was added dropwise, over a period of 1 h, to a refluxing ether solution of 10.5 g of 1-bromo-2-chlorobenzene and 7.26 g of 1,1-dimethoxyethylene. The latter was prepared from chloroacetaldehyde dimethyl acetal following a procedure described for the bromide.[21] This modification (chloride instead of bromide) resulted in a higher yield of the olefin.

When the addition was complete, the solution was cooled, quenched with water, and extracted with ether. The combined ether phase was dried (K_2CO_3) and evaporated. Spinning-band distillation of the residue gave 4.83 g (54%) of **6**, bp 60–62 °C (0.5 torr). In addition to **6**, a small amount of *o*-chlorotoluene (0.72 g, 10%) was obtained.

Base-Induced Reaction of 5. (a) Without Added Dienophile. A mixture of 254 mg of **5** and 1.5 equiv of LDA was refluxed in hexane (50 mL) for 1 h, cooled, quenched with water, and extracted with ether. After drying (K_2CO_3) and evaporation, the residue was triturated with hexane to give 22 mg (13% based on consumed **5**) of **12** as tan needles. Recrystallization from hexane/$CHCl_3$ gave colorless needles: mp 243.5–244.7 °C; ^{1}H NMR (−1 °C) δ 2.79 (s, 6 H, methoxy), 2.84 (BB′ of AA′BB′ q, 2 H, benzylic), 3.21 (AA′ of AA′BB′ q, 2 H, benzylic), 3.56 (s, 6 H, methoxy), 7.08 (dd, 2 H, *J* = 7 and 2 Hz, aromatic), 7.21 (m, 4 H, aromatic), 7.71 (dd, 2 H, *J* = 7 and 2 Hz, aromatic);MS-CI, calcd for $C_{20}H_{25}O_4$ *m/e* 329.1752, found *m/e* 329.1761. Anal. Calcd: C, 73.13; H, 7.38. Found: C, 72.89; H, 7.38.

By preparative VPC of the residue, 1-methoxy-3-methylnaphthalene (present in ca. 1%) was obtained as a colorless solid: ^{1}H NMR δ 2.52 (s, 3 H, CH_3), 4.01 (s, 3 H, methoxy), 6.68 (br s, 1 H, aromatic), 7.23 (br s, 1 H, aromatic), 7.4 (m, 2 H, aromatic); MS-CI, *m/e* (relative intensity) 173 (P + 1, 100), 172 (81).

(b) With Norbornene. From 556 mg of **5**, 2.0 equiv of LDA in norbornene/hexane, 0.5-h additional reflux, was obtained 8.1 mg of tan solid dimer **12**. VPC indicated 2% of recovered **5** and 55% yield of **8**. Chromatography of the residue on WN-3 alumina, activity grade III (100% Skelly-solv), gave, as partially separated mixtures (NMR), 383 mg (52%) of ketal **8** and 84 mg (9.3%) of 2:1 adduct **11**.

8: pale yellow liquid; ^{1}H NMR (−60 °C) δ 0.35 (br d, 1 H, *J* = 9 Hz, syn methylene bridge), 0.56 (br d, 1 H, *J* = 10 Hz, anti methylene bridge), 1.23 (m, 2 H, endo ethylene bridge), 1.44 (m, 2 H, exo ethylene bridge), 2.01 (m, 2 H, bridgehead), 2.21 (dd apparent t, 1 H, *J* = ca. 9 and 8 Hz, distal ring fusion), 2.36 (d, 1 H, *J* = 9 Hz, proximal ring fusion), 2.54 (d, 1 H, *J* = 15 Hz, cis benzylic), 2.81 (s, 3 H, methoxy), 3.03 (AB q, 1 H, *J* = 15 and 8 Hz, trans benzylic), 3.42 (s, 3 H, methoxy), 7.12 (m, 1 H, aromatic), 7.25 (m, 2 H, aromatic), 7.61 (d, 1 H, *J* = 7 Hz, aromatic); ^{13}C NMR (C_6D_6, 25 °C) δ 31.45, 32.09, 34.97, 36.15, 39.95, 43.63, 45.73, 49.05, 49.80, 51.00, 101.77, 126.82, 127.85, 128.81, 129.43, 138.41, 140.97; MS, calcd for $C_{17}H_{22}O_2$ *m/e* 258.1620, found *m/e* 258.1635.

Chromatography of 110 mg of a mixture of **8** and **11** along with other minor components on silica gel (10% ether in Skelly-solv) followed by PLC (silica gel, 10% CH_2Cl_2 in Skelly-solv) gave 3.6 mg of 1-methoxy-3-methylnaphthalene and 25.5 mg of colorless crystalline **11**: mp 125–126.5 °C; ^{1}H NMR δ −0.45 (dt, 2 H, *J* = 10 and 2 Hz, syn methylene bridge), 0.22 (d, 2 H, *J* = 10 Hz, anti methylene bridge), 1.08 (m, 4 H, endo ethylene bridge), 1.34 (m, 4 H, exo ethylene bridge), 1.81 (br s, 2 H, distal bridgehead), 1.95 (m, 4 H, proximal bridgehead and distal ring fusion), 2.08 (d, 2 H, *J* = 9 Hz, proximal ring fusion), 2.83 (br s, 1 H, benzylic), 3.44 (s, 3 H, methoxy), 6.95 (dd, 1 H, *J* = 7 and 1 Hz, aromatic), 7.15 (dt, 1 H, *J* = 7 and 1 Hz, aromatic), 7.23 (dt, 1 H, *J* = 7 and 1 Hz, aromatic), 7.36 (dd, 1 H, *J* = 7 and 1 Hz, aromatic); ^{13}C NMR δ 30.96, 31.25, 33.68, 36.24, 40.75, 42.05, 47.88, 48.95, 50.08, 78.63, 121.63, 123.88, 126.08, 126.33, 139.22, 141.24; MS, calcd for $C_{23}H_{28}O$ *m/e* 320.2140, found *m/e* 320.2123. Anal. Calcd: C, 86.20; H, 8.81. Found: C, 86.25; H, 8.81.

In an similar experiment, the residue (after trituration with hexane) was chromatographed on basic alumina to give 136 mg (23%) of the vinyl ether **10** and 205 mg (38%) of ketone **9**.

9: colorless crystalline solid after sublimation: mp 66–66.5 °C; ^{1}H NMR δ 1.14 (dt, 1 H, *J* = 10 and 1 Hz, syn methylene bridge), 1.33 (m, 3 H, anti methylene bridge and endo ethylene bridge), 1.64 (m, 2 H, exo ethylene bridge), 2.18 (br s, 1 H, distal bridgehead), 2.45 (m, 3 H, proximal bridgehead and ring fusion), 2.97 (m, 2 H, benzylic), 7.17 (br d, 1 H, *J* = 7.5 Hz, aromatic), 7.27 (br t, 1 H, *J* = 7.5 Hz, aromatic), 7.43 (dt, 1 H, *J* = 7.5 and 1 Hz, aromatic), 7.68 (dd, 1 H, *J* = 7.5 and 1 Hz, aromatic); ^{13}C NMR δ 201.07, 142.00, 134.97, 132.83, 127.83, 126.59, 126.08, 54.96, 43.64, 40.79, 40.43, 35.12, 32.01, 29.40, 29.07; IR (KBr) 2950 and 2870, 1679, 1599 cm^{-1}; MS, calcd for $C_{15}H_{16}O$ *m/e* 212.1200, found *m/e* 212.1211. Anal. Calcd: C, 84.84; H, 7.60. Found: C, 85.06; H, 7.57.

10: colorless liquid after preparative VPC: ^{1}H NMR δ 1.30–1.85 (m, 6 H, norbornyl), 2.14 (br s, 1 H, distal bridgehead), 2.35 (dd, 1 H, *J* = 14 and 6 Hz, benzylic), 2.54 (m, 2 H, benzylic and ring fusion), 3.24 (br s, 1 H, proximal bridgehead), 3.74 (s, 3 H, methoxy), 6.95–7.25 (m, 3 H, aromatic), 7.32 (d, 1 H, *J* = 7 Hz, aromatic); MS, calcd for $C_{16}H_{18}O$ *m/e* 226.1358, found *m/e* 226.1351.

(b) With Nornornadiene. ^{1}H NMR and VPC analysis of the reaction mixture obtained by treatment of 510 mg of **5** with 1.5 equiv of LDA in 5 M NBD/hexane (0.5-h additional reflux) indicated ca. 8% recoverd **5** and ca. 60% yield of the ketal **17**. Chromatography of the residue on activity grade III, neutral alumina (100% Skelly-solv to 5% ether in Skelly-solv) gave two major fractions. The first consisted of (by NMR) 39 mg of **17** and 12 mg of 1-methoxy-3-methylnaphthalene. The major fraction (401 mg) was a pale yellow liquid, and the NMR showed this to be **17** of >95% purity (overall yield of **17**, 66%): ^{1}H NMR (−36 °C) δ 0.52 and 0.76 (AB q, 2 H, methylene bridge), 2.14 (dd apparent t, 1 H, *J* = 8 and 8 Hz, distal ring fusion), 2.31 (br d, 1 H, *J* = 8 Hz, proximal ring fusion), 2.53 (br s, 1 H, bridgehead), 2.62 (m, 2 H, benzylic and bridgehead), 2.82 (s, 3 H, methoxy), 3.22 (dd, 1 H, *J* = 11 and 8 Hz, benzylic), 3.45 (s, 3 H, methoxy), 6.24 (br s, 2 H, vinyl), 7.20 (m, 3 H, aromatic), 7.64 (d, 1 H, *J* = 6 Hz, aromatic); MS-CI, *m/e* (relative intensity) 257 (P + 1, 3), 159 (100).

(c) With Cyclopentene. From 504 mg of **5**, 1.5 equiv of LDA, in cyclopentene (2-h additional reflux), was obtained 31 mg of the dimer **12**. VPC and NMR analysis indicated that greater than

(20) Meijer, J.; Vermeer, P.; Brandsma, L. *Recl. Trav. Chem. Pays-Bas* **1973**, *92*, 601. Meyer, R.; Scheithauer, S.; Kunz, D. *Chem. Ber.* **1966**, *99*, 1393. Rullkotter, J.; Budzikiewicz, H. *Org. Mass Spectrom.* **1976**, *11*, 44.

(21) Corey, E. J.; Bass, J. P.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

95% of **5** had been consumed and that the major components consisted of the ketal **18** (37% yield) and the spiro dimer **15** (ca. 123 mg). Chromatography of a portion (384 mg) of the residue on neutral alumina, activity grade I (5% ether in Skelly-solv), gave two fractions. The first (23.6 mg) contained a 95:5 mixture of **18** to **21** as a colorless viscous liquid. **18**: ^{1}H NMR δ 0.7–1.9 (5 sep m, 6 H, propano bridge), 2.36 (apparent d, 1 H, J = 14 Hz, proximal ring fusion), 2.60 (m, 1 H, distal ring fusion), 2.83 (s over dd, 4 H, methoxy and benzylic), 3.05 (dd, 1 H, J = 14 and 7 Hz, benzylic), 3.39 (s, 3 H, methoxy), 7.11 (m, 1 H, aromatic), 7.21 (m, 2 H, aromatic), 7.65 (m, 1 H aromatic); MS, calcd for $C_{14}H_{16}O$ (P – methanol) m/e 200.1202, found m/e 200.1188.

The second fraction contained 52.1 mg of the vinyl ether **21** as a colorless semisolid: ^{1}H NMR δ 1.35, 1.59, 1.93, and 2.10 (4 sep m, 4 H, propano bridge), 2.50 (m, 2 H), 2.67 (m, 2 H), 2.86 (dd, 1 H, J = 14 and 6 Hz, benzylic), 3.70 (s, 3 H, methoxy), 7.11 (m, 2 H, aromatic), 7.19 (m, 1 H, aromatic), 7.34 (br d, 1 H, J = 8 Hz, aromatic); MS, calcd for $C_{14}H_{16}O$ m/e 200.1201, found m/e 200.1202.

Chromatography of the remaining residue (239.6 mg) on neutral alumina, activity grade III (100% Skelly-solv to 10% ether in Skelly-solv), gave 67.1 mg of **18** as a pale yellow liquid, and 47.8 mg of the spiro dimer **15** also as a pale yellow liquid. **15**: ^{1}H NMR δ 1.78 (ddd apparent dt, 1 H, J = 13, 5, and 5 Hz, methylene), 2.13 (ddd, 1 H, J = 13, 11, and 5 Hz, methylene), 2.57 (ddd apparent dt, 1 H, J = 15, 5, and 5 Hz, benzylic), 2.76 (ddd, 1 H, J = 15, 11, and 5 Hz, benzylic), 2.92 (s, 3 H, methoxy), 3.02 (s, 3 H, methoxy), 3.06 (s, 3 H, methoxy), 3.49 (s, 3 H, methoxy), 5.54 (ddd, 1 H, J = 10, 5, and 1 Hz, vinyl), 5.74 (ddd, 1 H, J = 10, 5, and 1 Hz, vinyl), 5.84 (d, 1 H, J = 10 Hz, vinyl), 6.32 (d, 1 H, J = 10 Hz, vinyl), 7.1 (m, 3 H, aromatic), 7.6 (m, 1 H, aromatic).

Treatment of 8 with TFA. A mixture of 36 mg (0.14 mmol) of **8** and 2.0 μL (0.028 mmol) of trifluoroacetic acid (TFA) in 0.6 mL of $CDCl_3$ was stirred with 4A molecular sieves for 2 h at 25 °C and then poured into saturated $NaHCO_3$. The mixture was extracted five times with 5.0-mL portions of ether and the combined organic phase washed with brine and dried over K_2CO_3. Evaporation and chromatography of the residue (silica gel, 5% ether in Skelly-solv) gave 9.8 mg (31%) of the vinyl ether **10** as a colorless liquid and 15.9 mg (54%) of the ketone **9**.

Alternative Synthesis of 9. To 13.9 mg (0.065 mmol) of an epimeric mixture of alcohols[3] in 0.7 mL of CH_2Cl_2 was added 34.8 mg (0.1 mmol) of PDC. After being stirred at 25 °C for 18 h, the mixture was taken up in ether and filtered. Evaporation of the solvent followed by PLC (silica gel, 30% ether in Skelly-solv) gave 10.6 g (77%) of colorless crystalline **9**, mp (after sublimation) 64.0–65.5 °C. The NMR, IR, and MS spectra are identical with those obtained for **9** from hydrolysis of **8**.

Hydrogenation of 17. The ketal **17** (98 mg) in ethanol was treated with Adams' catalyst and 1 atm H_2 pressure. After the theoretical amount of H_2 was consumed, the reaction was stopped and the mixture filtered and evaporated. Chromatography of the residue on silica gel (5% ether in Skelly-solv) gave 40 mg (49%) of the ketone **9**. In addition to this, 9 mg of the corresponding alcohol[3] was obtained.

In a separate experiment, 44.3 mg of **17** was hydrolyzed (THF, aqueous acid, 30 min) and following the typical workup gave 35.4 mg (98%) of the corresponding ketone: ^{1}H NMR δ 1.2 (br s, 2 H, methylene bridge), 2.2 (m, 2 H), 2.7 (m, 2 H), 3.0 (m, 1 H, benzylic), 3.3 (m, 1 H, benzylic), 6.2 (m, 2 H, vinyl), 7.2 (m, 3 H, aromatic), 7.7 (m, 1 H, aromatic); IR (neat): 3060, 2940, 1670, 1600, 1455, 750, 720 cm^{-1}.

The material was hydrogenated, without further purification, as described above. The ^{1}H NMR of the residue indicated a mixture of **9** and the alcohol (58:42) obtained in quantitative yield.

Hydrolysis of Ketal 18. Treatment of 23.6 mg of **18** with 0.5 mL of 5% aqueous H_2SO_4 in 3.0 mL of THF for 10 min followed by neutralization with saturated $NaHCO_3$ and ether workup gave after chromatography (silica gel, 5% ether in Skelly-solv) 16.3 mg (86%) of the ketone **19** as a colorless liquid: ^{1}H NMR δ 1.45, 1.73, 1.83, 2.05 (4 sep m, 6 H, propano bridge), 2.70 (m, 1 H, distal ring fusion), 2.84 (dd over m, 2 H, J = 16 and 8 Hz, benzylic and proximal ring fusion), 3.00 (dd, 1 H, J = 16 and 6 Hz, benzylic), 7.22 (d, 1 H, J = 8 Hz, aromatic), 7.30 (dd apparent dt, 1 H, J = ca. 8 and 1 Hz, aromatic), 7.47 (ddd apparent dt, 1 H, J = ca. 8 and 1 Hz, aromatic), 7.98 (dd, 1 H, J = 8 and 1 Hz, aromatic); IR ($CDCl_3$) 2950, 1670, 1605 cm^{-1}. Anal. Calcd: C, 83.86; H, 7.46. Found: C, 84.02; H, 7.39.

Hydrolysis of the Vinyl Ether 21. Treatment of 24 mg of **21** as above for 2 h at reflux gave after chromatography 3.0 mg of pure **22** as a colorless solid (mp 62–63 °C), 2.0 mg of pure **19** as a colorless liquid, and 18 mg of a mixture of the two epimers (overall yield 77%, ratio of cis to trans of 1.8:1).

22: ^{1}H NMR δ 1.50 (m, 1 H, propano bridge), 1.6–2.2 (m, 7 H, propano bridge and distal ring fusion), 2.43 (ddd, 1 H, J = 13, 11, and 8 Hz, proximal ring fusion), 2.83 (dd, 1 H, J = 16 and 11 Hz, benzylic), 3.21 (dd, 1 H, J = 16 and 4 Hz, benzylic), 7.30 (m, 2 H, aromatic), 7.46 (ddd apparent dt, 1 H, J = 7 and 1 Hz, aromatic), 8.04 (dd, 1 H, J = 8 and 1 Hz, aromatic); MS, calcd for $C_{13}H_{14}O$ m/e 186.1044, found m/e 186.1037.

Alternative Synthesis of 19. A mixture of 0.7 mg of the alcohol **20**[3] and 2.3 mg (1.6 equiv) of PDC in 0.5 mL of CH_2Cl_2 was stirred at 25 °C for 2.75 h. After filtration and evaporation, the residue was chromatographed (silica gel, 10% ether in Skelly-solv) to give **19** in quantitative yield.

Reaction of 6 with NPM. A mixture of 160 mg of **6** and 172 mg of NPM in 10.0 mL of *tert*-butylbenzene (sealed tube) was heated at 170 °C for 2.5 days. The tube was opened and the solvent evaporated. After trituration of the residue with hot hexane, the hexane-soluble material was chromatographed on silica gel (20% ether in Skelly-solv) to give 214 mg (65%) of **23**: colorless crystals from hexane; mp 109.8–110.6 °C; ^{1}H NMR δ 2.91 (s, 3 H, methoxy), 3.21 (dd, 1 H, J = 14 and 2 Hz, benzylic), 3.33 (dd, 1 H, J = 14 and 7 Hz, benzylic), 3.52 (ddd, 1 H, J = 9, 7 and 2 Hz, ring fusion), 3.68 (s, 3 H, methoxy), 3.87 (d, 1 H, J = 9 Hz, ring fusion), 6.78 (m, 2 H, aromatic), 7.20 (m, 1 H, aromatic), 7.25–7.35 (m, 5 H, aromatic), 7.72 (m, 1 H, aromatic); ^{13}C NMR δ 27.8, 38.0, 44.5, 47.1, 47.6, 97.5, 124.7, 125.0, 125.2, 126.6, 126.7, 127.1, 127.5, 130.2, 132.6, 133.0, 171.3, 176.3; IR (KBr) 1779, 1708 cm^{-1}. Anal. Calcd: C, 71.20; H, 5.68. Found: C, 71.17; H, 5.67.

Flash Vacuum Pyrolysis of 6. The ketal **6** (228 mg) was vaporized onto a packed quartz tube at 500 °C and 0.1 torr. A solid material, which had collected on the outlet tube, was scraped off and recrystallized from ligroin to give 8.8 mg of **28**, mp 104–105 °C (lit.[19] mp 103 °C). The remaining material, collected in the dry ice trap, was dissolved in CH_2Cl_2 and examined by VPC. This was found to consist mainly of the ester **26** and the diester **28**. The solvent was evaporated to give 134 mg of a yellow liquid, and the NMR of this confirmed the presence of **26** and **28**. After further evaporation (to remove the ester **26**) 20 mg of the diester **28** was obtained as a yellow crystalline solid: ^{1}H NMR δ 3.2 (s, 4 H, benzylic), 3.83 (s, 6 H, methoxy), 7.0–7.5 (m, 6 H, aromatic), 7.7–8.0 (m, 2 H, aromatic); MS-CI, m/e (relative intensity) 299 (P + 1, 7.3), 267 (P – methanol, 100).

26: ^{1}H NMR δ 1.3 (t, 3 H, J = 7 Hz), 3.0 (q, 2 H, J = 7 Hz), 3.9 (s, 3 H, methoxy), 7.1–7.5 (m, 3 H, aromatic), 7.7–8.0 (m, 1 H, aromatic).

Acknowledgment. Financial support by the University of California Cancer Research Coordinating Committee is gratefully acknowledged. Dr. Hugh Webb provided expert assistance with MS and GC/MS data collection. We wish particularly to acknowledge the helpful correspondence provided by Professor Wolfgang Kirmse (Ruhr-Universität Bochum).

Registry No. **4**, 99097-98-0; **5**, 60743-19-3; **6**, 81447-53-2; **8**, 99097-99-1; **9**, 99098-00-7; **9**-ol (isomer 1), 91548-30-0; **9**-ol (isomer 2), 91466-80-7; **10**, 99098-01-8; **11**, 99098-02-9; **12**, 99098-03-0; **15**, 99098-04-1; **17**, 99098-05-2; **18**, 99098-06-3; **19**, 70071-90-8; **20**, 91466-82-9; **21**, 99098-07-4; **22**, 99098-08-5; **23**, 99098-09-6; NBD, 121-46-0; norbornene, 498-66-8; cyclopentene, 142-29-0.