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Benzo[*e*]isobenzofuran. Formation and Reactions of the Parent and Alkoxy-Substituted Derivatives

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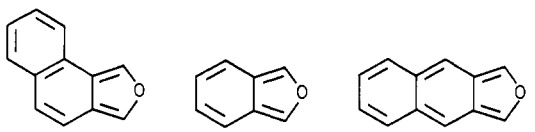
Benzo[*e*]isobenzofuran (**1**) is formed by base-induced 1,4-elimination of either acetal **9** or **11** and may be isolated in high yield as a crystalline solid. Cycloaddition reactions of preformed **1** have been carried out with various dienophiles. These reactions may also be accomplished by heating the acetals in the presence of dienophiles and acid catalyst, where **1** is generated as an intermediate. The cycloaddition reaction of **1** and maleic anhydride is found to be reversible at higher temperature (slow at 60 °C). Unsymmetrical dienophiles react with **1** to give equal amounts of regioisomers, and evidence points to lack of regioselectivity under both kinetically controlled and equilibrating conditions. The acetals **9** and **11** are shown to interconvert with acid catalyst at 140 °C, where **1** is an intermediate of greater stability than the acetals; the equilibrium K for **9** ⇌ **11** is approximately unity. Various acid-catalyzed cycloaddition reactions of ortho esters **8** and **10**, yielding polysubstituted phenanthrene derivatives, are described.

Wege has recently reported[1] the synthesis of benzo[*e*]-isobenzofuran (**1**, naphtho[1,2-c]furan) by pyrolysis[2] of the corresponding (dihydro)naphthyne–furan derivative and found that it is qualitatively more stable than the parent isobenzofuran **2**. Our work in this area began with a novel

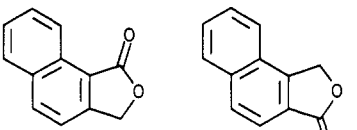


1 **2** **3**

1,4-elimination procedure[3] leading to **2** and its 1-alkoxy analogue,[4] and we have recently extended this approach to the linearly annulated benzo[*f*]isobenzofuran **3**.[5] As anticipated, **3** appears to be more reactive than **2**; while **3** has only been intercepted as a reactive intermediate, **2** is moderately stable in neutral solution. It was of interest to apply this methodology[3,4] to prospective precursors of **1** and its alkoxy derivatives, in order to examine reactivity and regioselectivity features of this dissymmetric isomer of **3**. In this paper we report the formation of the precursor acetals and ortho esters, the preparation of **1** by base-induced elimination of acetals, and the acid-catalyzed equilibration, via **1**, of these regioisomeric acetals. In addition, various cycloadditions with preformed **1** and acid-catalyzed reactions of both acetals and ortho esters are described.

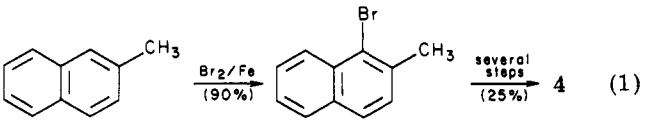
Results and Discussion

(a) Preparation of Precursors. The lactones **4** and **5** were needed as starting materials for the corresponding



4 **5**

acetals and ortho esters. Both are known compounds, and for the preparation of **4** the literature procedure,[6,7] with minor modifications, was followed with commercial 2-methylnaphthalene as shown in eq 1. The literature ap-



(1)

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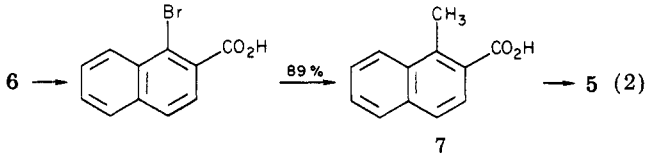
proaches[7,8] to lactone **5** were less attractive and led to the consideration of alternative routes to 1-methyl-2-naphthoic

(1) Stringer, M. B.; Wege, D. *Tetrahedron Lett.* **1980**, *21*, 3831.
(2) Wiersum, U. E.; Mijs, W. J. *Chem. Commun.* **1972**, 347. Wiersum, U. E. *Aldrichimica Acta* **1981**, *14* (3), 53.
(3) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061.
(4) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 2734.
(5) Mir-Mohamed-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 2237.
(6) Adams, R.; Binder, L. O. *J. Am. Chem. Soc.* **1941**, *63*, 2773.
(7) Brewster, J. H.; Fusco, A. M. *J. Org. Chem.* **1963**, *28*, 501.
(8) Gribble, G. W.; Holubowitch, E. J.; Venuti, M. C. *Tetrahedron Lett.* **1977**, 2857.

0022-3263/83/1948-3869$01.50/0

acid. This material has been made by "abnormal" addition of the Grignard reagent from 1-(chloromethyl)naphthalene to ethyl chloroformate followed by hydrolysis.[9] This procedure involves the usual difficulties of preparing a benzylic Grignard reagent, and for this and reasons of yield a better method was desirable. The low-temperature metal–halogen exchange reaction first studied by Gilman[10,11] and extended by Parham[12] offered interesting possibilities. Although 1-bromonaphthalene readily undergoes the exchange[10] reaction at this peri position, it was not clear what to expect with the further influence of a substituent at the 2-position. The bromide **6** was first converted to 1-bromo-2-naphthoic acid[13] (eq 2), and it was



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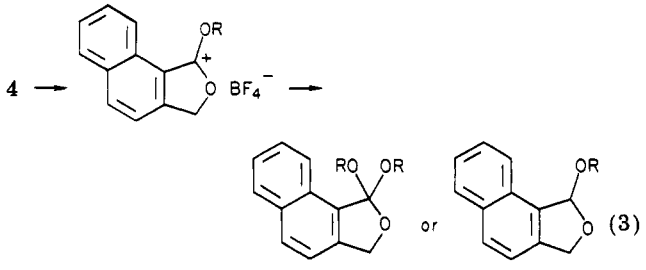
found that it cleanly gives metal–halogen exchange at −90 °C; however, we were unable to isolate useful yields of addition products with either formaldehyde or methyl chloromethyl ether as electrophiles. It appeared that when *n*-butyllithium was used for the exchange, some coupling product with the resultant bromobutane occurred. This observation led us to examine the use of methyllithium followed by excess methyl iodide, and indeed this gives excellent yields of 1-methyl-2-naphthoic acid (**7**). Subsequent conversion of **7** to lactone **5** was accomplished with minor modifications of literature procedures.[7]

Alkylation of **4** and **5** was accomplished by using dialkoxycarbenium tetrafluoroborates[14] as described for a related lactone[5] (eq 3 and 4). Conversion to ortho esters **8** and **10** followed Meerwein's method.[15] The preparation of acetals **9** and **11** was best done by using a reductive procedure recently developed in this laboratory.[16] In general we found it most convenient to prepare the ethoxy derivatives and convert these to methoxy analogues as needed by acid-catalyzed exchange with methanol. The dimethoxy ortho esters are especially prone to reconversion to lactone through hydrolysis or methanolysis.

(b) Base-Induced Formation of 1. Several small-scale reactions were carried out with acetal **9E** (**9**, R = Et) and **11M** (**11**, R = Me) by using various solvents (hexane, ether, THF) and strong bases. Rapid elimination occurred (mild exotherm) in all cases. The extent of reaction was followed by ^{1}H NMR by observing the loss of the acetal methine proton (ca. 6.6 ppm) and the formation of the complex multiplet aromatic pattern (7.0–8.3 ppm) characteristic of **1**.[17] We initially used lithium diisopropylamide, but found



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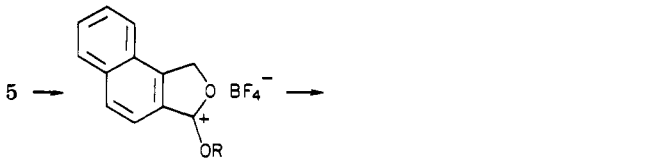


10 11

that n-butyllithium in hexane also functioned well for the elimination, perhaps due to the presence of other "carrier" bases. Methyllithium in ether with a small amount of diisopropylamine cleanly effected the formation of **1**.[18]

As noted by Wege,[1] **1** is sufficiently stable for isolation and handling, although material left for several days at room temperature darkened and appeared to polymerize, as suggested by the development of a broad featureless absorption in the aromatic region of the NMR spectrum. When **1** is prepared by the 1,4-elimination procedure, it is obtained as an off-white viscous oil or semisolid (melting point depression by traces of solvent or other impurities). Wege has found that pure **1** isolated by the flash vacuum pyrolysis method has a melting point of 61–63 °C. We have isolated **1** as a colorless solid (mp 62–64 °C) by chromatography on basic alumina using pentane (2% ether) elution. Samples of **1** in $CDCl_3$ solution in capped NMR tubes showed no change over several days.

The relative reactivities of acetals **9E** and **11E** were examined by treating an equimolar mixture with approximately 0.5 equiv of base (CH_3Li with catalytic *i*-Pr_2NH). The resulting mixture was examined by NMR; **11E** may be somewhat more reactive than **9E**, but the difference is not large or clearly beyond NMR integration error. Further addition of CH_3Li converted this mixture to **1** in essentially quantitative yield.

Solutions of preformed **1** were treated at room temperature with the dienophiles (in order of reactivity) dimethyl acetylenedicarboxylate (DMAD), α-acetoxyacrylonitrile (AAN), 2-butenolide (BL), and norbornene (NB). No reaction with NB was observed over a period of 3 days. This observation is in keeping with the relatively slow room-temperature reaction of the parent isobenzofuran **2** with NB[5] and reflects the greater stability of **1** compared to **2**.

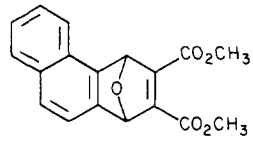
(9) Gilman, H.; Kirby, J. E. *J. Am. Chem. Soc.* **1929**, *51*, 3475.
(10) Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1940**, *62*, 2327. This paper contains a useful discussion of the relative rates of exchange (ArX + RLi) vs. coupling (ArLi + RX) and paved the way for the widespread use of this procedure.
(11) Jones, R. G.; Gilman, H. "Organic Reactions"; Wiley: New York, 1951; Vol. VI, Chapter 7. Methyllithium in ether was reported to be ineffective for exchange with 1-bromonaphthalene, with *n*-propyllithium the reagent of choice for this substrate. Since the exchange process efficiency was based on the yield of acid after treatment with CO_2, it may be that facile coupling with CH_3Br was responsible for this conclusion.
(12) Parham, W. E.; Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1978**, *43*, 1606 and earlier references cited therein.
(13) Stetter, H.; Siehnhold, E. *Chem. Ber.* **1955**, *88*, 1223. Cirigottis, K. A.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1974**, *27*, 2209.
(14) Borch, R. F. *J. Org. Chem.* **1969**, *34*, 627.
(15) Meerwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060.
(16) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1982**, *47*, 5391.
(17) Professor Wege kindly provided a copy of his ^{1}H NMR spectrum of **1** (see ref 1).
(18) We have recently found that this is a useful way of generating isobenzofuran itself from the corresponding acetal, thus avoiding the need to remove stoichiometric amounts of amine from the resulting solution. The use of methyllithium allows gasometric measurement of the extent of reaction. Excess base has been shown to generate 1-lithioisobenzofuran, which can be usefully employed in formation of derivatives.[19] While this lithiation presents no problems in cases where the isobenzofuran solution is stable enough for water washing, use of excess base is undesirable for certain applications and can easily be avoided.
(19) Unpublished work with S. Crump.

Table I. Interconversion of Acetals at 140 °C[a]

starting acetal	time, h	product distribution, % 9M[b]	11M[b]	1[b]	starting matl
9E	0.5	20		trace	80
	4.5	38	33	29	
11E	0.5		53	20	27
	4.5	32	41	27	

[a] Reactions were carried out in sealed tubes in chlorobenzene as the solvent by using 0.42 M acetal, 0.1 equiv of mesitoic acid, and 8.0 equiv of methanol. [b] These percentages were determined by ^{1}H NMR of vacuum evaporated residues (in $CDCl_3$).

Addition of a solution of 1 to diluted DMAD gave rapid formation of the cycloadduct **12**, which was isolated as a pure crystalline solid.



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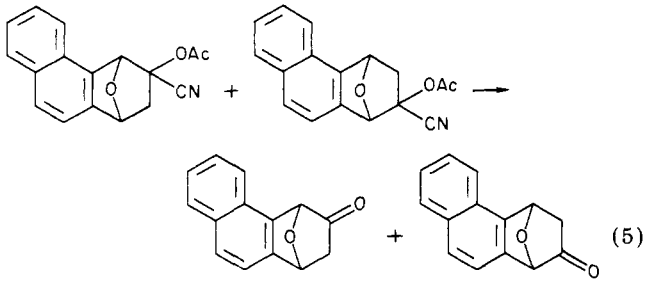
The reactions with the unsymmetrical dienophiles AAN and BL were of particular interest for examining regioselectivity associated with the inherent dissymmetry of **1**. The reaction with BL proved to be rather slow, requiring 100 h for consumption of **1**, as judged by disappearance of its approximate singlet (1 H) at 8.3 ppm. The yield of cycloadducts was estimated from residual BL to be ≥60%. The mixture showed a very complex spectrum presumably due to a mixture of regio- and stereoisomers. Major absorptions appeared at the chemical shifts expected on the basis of comparison with isolated exo and endo BL cycloadducts of **2**[20] and **3**;[5] both of the latter reactions exhibit slight exo/endo selectivity, and similar behavior was anticipated for the reaction of **1**. It was not possible to determine regioselectivity from the complex mixture obtained in this small-scale reaction; we return to this question in a later section.

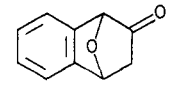
The reaction with ca. 1 equiv of AAN was complete within 24 h at room temperature. The complexity due to stereoisomers (exo/endo) was removed in this system by treating the crude cycloadduct with sodium methoxide in methanol, leading to regioisomeric ketones **13** and **14** (eq 5). NMR analysis of the crude product mixture showed



(5)

13 **14**

that the ketones were formed in equal (50 ± 3%) amounts. This mixture exhibited an interesting pattern in the proton NMR spectrum for the bridgehead benzylic hydrogens, consisting of doublets at 6.24 and 5.90 ppm and singlets at 5.54 and 5.22 ppm. The doublets are due to spin coupling of the bridgehead proton β to the carbonyl group with the adjacent exo methylene proton, and it is of interest that for both **13** and **14** the proton β to the carbonyl is significantly deshielded relative to the α bridgehead proton. This mixture was chromatographed on silica gel, and although only slight separation of **13** and **14** occurred, it was sufficient to show that the outer peaks (at 6.24 and 5.22 ppm) are associated with one isomer (**14**) and conversely that the inner doublet and singlet are due to isomeric ketone **13**. The assignment of structure is based in part on comparison with the NMR spectrum of the simpler analogue **15**, which shows the α-proton singlet at 4.88 ppm



15

and the β-proton doublet at 5.56 ppm.[21] While all of these signals in **13** and **14** are shifted downfield by the effect of the additional aromatic ring (compared to **15**), one expects the α proton of **14** to be more like that of **15**; similarly, the β proton of **14** and the α proton of **13** should experience the strongest deshielding effect of benzannulation, and these are found approximately 0.3 ppm downfield of the analogous signals for the other isomer.

The observation that the AAN cycloaddition with **1** is essentially devoid of regioselectivity is tempered by the modest yield (18%) of ketones **13** and **14** isolated after chromatography. However, results discussed below for the acid-catalyzed cycloaddition reactions of acetals reinforce the conclusion that these reactions occur with negligible regioselectivity.

These results demonstrate that the base-induced 1,4-elimination process for acetals **9** and **11** is a viable route to isolable **1** and that **1** exhibits moderate reactivity in cycloaddition reactions at room temperature. While rates have not been measured, **1** is clearly more reactive than furan and less reactive than isobenzofuran **2**, much as expected. Further evidence of the relative stability of **1** is presented in the next section.

(c) Acid-Catalyzed Reactions of Acetals. The utility of acetals as precursors to Diels–Alder adducts of isobenzofurans was considerably extended by the observation that these materials can be used directly with dienophiles in an acid-catalyzed process.[3-5] We have recently demonstrated that isobenzofuran **2** is indeed an intermediate under these conditions by examining the pattern of deuterium incorporation in the residual acetals from reactions carried out in the presence of CH_3OD.[5] The acetals used in the present study offered a more direct way of exploring this question, since, depending upon the relative stabilities of the various species generated, one might expect to observe interconversion of **9** and **11** if **1** is formed as an intermediate under acid-catalyzed conditions. On the basis of our earlier work with the lower homologue precursor of **2**, we chose to examine the ethyl derivatives **9E** and **11E** in the presence of excess (8 equiv) of methanol in chlorobenzene as the solvent at 140 °C (sealed tubes). Samples were examined after 0.5 and 4.5 h, after starting with pure regioisomer in each case. The results are displayed in Table I.

Several interesting observations emerge from these data: (1) the 4.5-h results show that **9** and **11** are interconverted, via **1**; (2) the acetals **9M** and **11M** are of approximately equal energy; (3) benzo[e]isobenzofuran (**1**) is in fact a product of greater thermodynamic stability than the ace-

(20) Makhlouf, M. A. Dissertation, University of California at Santa Barbara, 1982.

(21) Unpublished work with M. L. Chase.

tals at this temperature (4) the 0.5-h data show that transacetalization (Me for Et) occurs more rapidly than regioisomerism; (5) the differences in the 0.5-h data for **9E** and **11E** suggest that the latter is more reactive.

On expansion of these points, the interconversion of **9** and **11** was anticipated on the basis of our earlier work,[5] but the position of equilibrium between these isomers (K = ca. 1) was not predictable. It appears that the acetal functionality is easily accommodated in **9**; i.e., there is no significant added steric interaction in **9** due to the alkoxy group and the peri proton introduced by angular benzannulation.

It is clear that **1** has appreciable stability in the presence of excess alcohol and acid catalyst. Note that the dissociation of the acetal to **1** plus ROH is entropically favored, and the equilibrium position in the absence of added alcohol (8 equiv used in these experiments) would by mass action quite strongly favor the formation of **1** at 140 °C. Two additional experiments were carried out to verify this point. When a sample of **9M** with 0.1 equiv of mesitoic acid was refluxed for 3.5 h in chlorobenzene (131 °C, under N_2) and then vacuum evaporated, the NMR spectrum was devoid of methoxy signals and showed a broad absorption in the aromatic region presumably due to oligomerization of **1**. Repetition of this experiment with **9E** in a sealed tube (140 °C for 4.3 h) gave, after evaporation, evidence for the presence of **1** (substantial peak at 8.2 ppm) with very little acetal remaining. It seems clear that **1** is indeed more stable thermodynamically than the acetals at this temperature, although its reactivity toward acid-catalyzed or radical-induced polymerization diminishes the utility of this approach for the isolation of **1**.

The short reaction time results in Table I indicate that transacetalization with retention of the starting regioisomer structure occurs more rapidly than the interconversion of **9** and **11** and also more rapidly than formation of **1**. We assume that transacetalization takes place by an acid-catalyzed S_N1 process that retains the furan ring; it follows that the elimination step from the intermediate carbocation, rather than formation of this cation, is rate determining for both **9** and **11** going to **1**. The 0.5-h data for **9** and **11** (Table I) suggest that the latter is more reactive for both transacetalization and elimination. Attempts to substantiate this point by entering the equilibrium with preformed **1** were, however, inconclusive. Thus, a sample of **1** with 8.0 equiv of methanol and 0.1 equiv of mesitoic acid was heated in chlorobenzene (sealed tube) for 0.5 h at 140 °C. The NMR spectrum of the residue after evaporation showed broadened aromatic and benzylic region absorptions, too large in comparison to the methoxy singlet to be accommodated by only **9** plus **11** and implying significant oligomerization. A sealed NMR tube containing $CDCl_3$ solvent, mesitoic acid catalyst, and a ratio of methanol/**1** of 16:1 gave no measurable reaction in 24 h at 22 °C. At 100 °C loss of **1** appeared to be complete when examined after 50 min, with **9M** and **11M** being formed in essentially equal amounts. While this shows that **1** can indeed serve as a precursor to the acetals, this ratio of products likely does not reflect the relative rates of formation of the two intermediate carbocations, because of the unknown but presumably large extent of further equilibration. Because of the many variables involved and the problem of oligomerization, no additional efforts were made to ascertain the regioselectivity of protonation of **1** under these conditions.

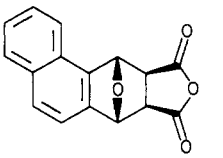
Since it was possible to convert ethyl to methyl acetal in refluxing methanol (acid catalyst) without regioisomerization (or incorporation of deuterium when CH_3OD was used), it was hoped that these conditions might be useful for examination of kinetically controlled protonation of **1**. However, an attempt to use this medium was thwarted by the low solubility of **1**; heating did not effect dissolution but caused oligomerization.

Acid-catalyzed cycloaddition reactions of the acetals were carried out in refluxing chlorobenzene by using 0.1 equiv of mesitoic acid and a slight excess of dienophile. The reaction with AAN and **9E** (34 h) gave a residue on evaporation which was directly treated with sodium methoxide/methanol, yielding 43% of the isomeric ketones **13** and **14**, again in equal amounts by NMR integration; 17% of **9E** was recovered. While the question of cycloaddition reversibility was not addressed directly, the fact that the same ratio is generated in the room-temperature reaction with preformed **1** reinforces the conclusion that negligible kinetic regioselectivity is involved.

This sequence was repeated with **11E**; in this case no acetal remained (by NMR) after 2 h, and the subsequent methanolysis gave 87% of chromatographed **13** plus **14**, once again in equal amounts. The difference in reactivity between **9E** and **11E** reflects the relative ease of formation of **1** from the two isomers, as discussed earlier.

The reactions of both **9E** and **11E** with DMAD were complete within 1 h when ethyldiisopropylammonium tetrafluoroborate[5] was used as the catalyst, with adduct **12** produced in moderate yield from both reactions. Use of mesitoic acid as a catalyst with **11E** gave a slower reaction (28 h), with **12** being isolated in 71% yield.

Consumption of acetal **9E** with 1 equiv of maleic anhydride (MA) in refluxing chlorobenzene was complete in less than 2.5 h. No additional catalyst is required for this reaction, in agreement with earlier observations.[3] When the mixture cooled, a solid precipitated (64%) which proved to be essentially pure exo adduct **16**.



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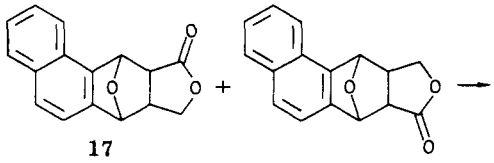
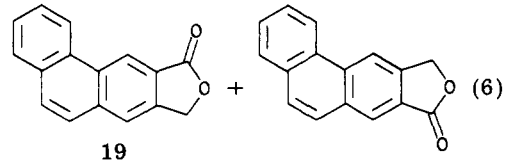
Examination of the mother liquor after evaporation indicated that it contained mainly exo-**16**, with no evidence for appreciable endo isomer. This result differed from those reported earlier for isobenzofurans **2** and **3**, both of which exhibited little exo/endo selectivity with MA when generated in the same manner from the corresponding acetals. To examine the question of reversibility of the cycloaddition, we carried out a reaction with preformed **1**, which was added slowly to a solution of MA in $CDCl_3$ at room temperature. The NMR spectrum taken a few minutes after the addition showed that the reaction was complete, with the exo/endo isomers being formed in a ratio of ca. 55:45. This solution was then refluxed (61 °C) for several days, with intermittent examination by NMR, and the ratio was observed to change slowly to favor *exo*-**16**. The large exo selectivity found in the higher temperature (131 °C) reaction thus reflects reversibility of the cycloaddition reaction and the expected greater stability of the exo isomer. This behavior is reminiscent of the Diels–Alder reactions of furan itself, where reversibility is especially facile, and the different behavior of **1** compared to **2** and **3** is presumably related to the greater stability of **1** being reflected in the activation energy for reversal.

The reactions of **9E** and **11E** with BL were followed by NMR and showed interesting differences. The **11E** re-

action was complete in ca. 3 h and gave a complex spectrum resembling that of the room-temperature reaction with preformed 1. The slower reacting **9E** (16 h) spectrum was initially also complex but gradually simplified with continued heating. The final spectrum was consistent with products having exo structures, and this is attributed to reversibility as discussed for the MA reaction. In order to simplify the regioselectivity question, we treated the mixture of cycloadducts **17** and **18** with $TiCl_4$ followed by triethylamine to obtain aromatized lactones **19** and **20** (eq 6). The 60-MHz spectrum of this mixture exhibited a



17 18

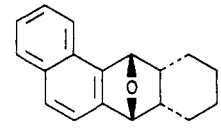


19 20 (6)

broad peak in the benzylic methylene region, which was resolved on a 300-MHz instrument into two sharp singlets of equal area. Chromatography of this mixture did not effect separation of **19** and **20**. The same 1:1 ratio of these products was obtained from the reactions of both **9E** and **11E**. Since different extents of equilibration were appearent in these two reactions, the results imply that the cycloaddition of 1 and BL involves neither kinetic nor thermodynamic regioselectivity.

It is possible that similar equilibration has occurred in the reactions of AAN and the acetals; if so, one may conclude that these reactions also lack thermodynamic regioselectivity.

In order to test the limits of reactivity of 1 with poor dienophiles, we carried out a sealed-tube reaction of **9E**, mesitoic acid catalyst, and cyclohexene (4 equiv) in chlorobenzene solvent. The residue was examined after 100 h at 140 °C and showed a peak at 8.2 ppm, implying the presence of 1. Cycloadduct **21** was produced in low yield;

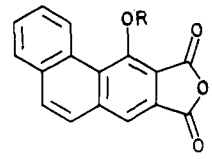


21

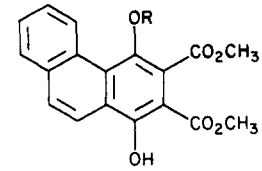
this material is characterized as the endo product by the appearance of two doublets (J = 4 Hz) at 5.27 and 5.67 ppm. The absence of exo adduct is inferred from the lack of singlets expected for the benzylic protons of this structure. The preference for endo cycloaddition of cyclohexene parallels its behavior with isobenzofuran **2**,[5] and the absence of exo product implies that this cycloaddition is not significantly reversible under the conditions employed.

(d) Reactions of Ortho Esters. Only acid-catalyzed reactions of ortho esters **8** and **10** were examined. A common side product was the lactone (**4** or **5**), which may be formed in several ways as demonstrated with the linearly benzannulated precursor.[5] The cycloadditions were carried out in refluxing chlorobenzene by using a slight excess of dienophile and 0.1 equiv of mesitoic acid. Sufficient time was allowed to convert the initially formed ketal adducts to their aromatized derivatives, when this process was feasible.

Treatment of **8M** with MA afforded 20% of purified phenanthrene derivative **22**. The reaction of this ortho ester and DMAD gave 40% of **23**.



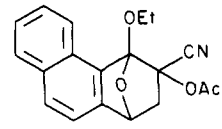
22, R = Me
24, R = Et



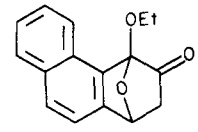
23, R = Me
25, R = Et

Similar yields of isolated products were obtained with the analogous ethyl ortho ester **8E**. Thus MA gave **24** (20%) and DMAD gave **25** (47%).

The reaction of **8E** with AAN gave crude product **26** which was directly converted to the ketone **27**, isolated in



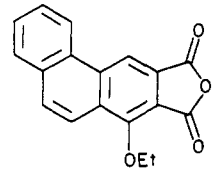
26



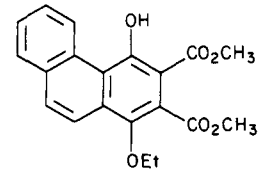
27

good overall yield as an oil, by methoxide/methanol treatment. The NMR spectra of both **26** and **27** support the regiochemistry shown, as expected on the basis of results obtained with the simpler ortho ester precursor of 1-alkoxyisobenzofuran.[4]

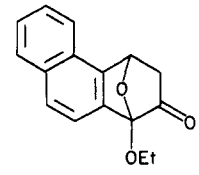
Reaction of the ortho ester **10E** with MA gave 56% of aromatized product **28** in 1.2 h. Use of DMAD and acid



28



29



30

catalyst afforded **29** in excellent yield after 2.3 h. The crude cycloadduct from **10E** and AAN (2.5 h) was directly converted to keto ketal **30** by methoxide/methanol treatment in high overall yield. Again the NMR spectra of both the AAN adduct and **30** indicate that the regioisomer shown is formed exclusively.

These reactions illustrate the utility of the ortho ester functionality in generating polysubstituted aromatics, as demonstrated earlier by MacLean[22] and in our work[4] with the simpler ortho ester derived from phthalide. While this sequence is successful with the angularly annulated compounds **8** and **10**, we have shown that alternative reaction pathways preclude these applications for the linearly benzannulated ortho ester.[5] These observations again

(22) Contreras, L.; Slemon, C. E.; MacLean, D. B. *Tetrahedron Lett.* 1978, 4237. Contreras, L.; MacLean, D. B. *Can. J. Chem.* 1980, *58*, 2573, 2580. Contreras, L.; MacLean, D. B.; Faggiani, R.; Lock, C. J. L. *Ibid.* 1981, *59*, 1247.

reflect the relative ease of formation (greater stability) of benzo[e]isobenzofuran compared to the linearly fused benzo[f]isobenzofuran.

Experimental Section

Proton NMR spectra were recorded on a Varian T-60 with $CDCl_3$ as the solvent unless otherwise specified; 300-MHz spectra were obtained on a Nicolet NT-300 instrument. Melting points (uncorrected) were determined in open capillary tubes on a Mel-Temp apparatus. IR spectra were obtained on a PE 283 and mass spectral data on a VG Micromass ZAB-2F instrument. Combustion analyses were done by Galbraith Laboratories, Knoxville, TN. The 2-methylnaphthalene was purchased from Aldrich Chemical Co.

3(1*H*)-Benzo[*e*]isobenzofuranone (4). The procedure of Adams and Binder[6] was used to prepare 1-bromo-2-methylnaphthalene [bp 140–146 °C (7 torr)] in 90% yield; conversion to 2-methyl-1-naphthoic acid followed the literature procedure,[6] giving 57% of recrystallized ($CHCl_3$–hexane) material: mp 124–126 °C; NMR δ 2.65 (s, 3 H), 7.2–8.3 (m, 6 H). The methyl ester[23] [bp 120–122 °C (0.8 torr)] was prepared via the acid chloride using methanol/pyridine: NMR δ 2.38 (s, 3 H), 3.85 (s, 3 H), 6.95–7.95 (m, 6 H). Bromination was effected with NBS (1.1 equiv) in refluxing CCl_4 by using benzoyl peroxide catalyst; on cooling, lactone **4** precipitated (small amount)[24] and was separated from succinimide by water washing. The remaining CCl_4 solution contained methyl 2-(bromomethyl)-1-naphthoate [NMR (CCl_4) δ 3.98 (s, 3 H), 4.55 (s, 2 H), 6.95–8.0 (m, 6 H)] along with a small amount of unreacted starting material. This crude product was refluxed for several hours in aqueous 5% NaOH. After being cooled and acidified with 10% HCl, the mixture was extracted with CH_2Cl_2, dried, and evaporated to give a solid residue; recrystallization from $CHCl_3$–hexane gave **4**: mp 154–156 °C (lit.[7] mp 154.5–156 °C); NMR δ 5.32 (s, 2 H), 7.35–8.2 (m, 5 H), 8.85–9.10 (m, 1 H). The overall yield from 2-methylnaphthalene was 25%.[25]

1(3*H*)-Benzo[*e*]isobenzofuranone (5). In a 2-L three-necked flask, a mixture of 146 g (0.66 mol) of 1-bromo-2-methylnaphthalene, 1 g of benzoyl peroxide, and 600 mL of CCl_4 was brought to reflux, while 131 g (0.66 mol) of NBS was added in portions over 1 h. The stirred mixture was heated an additional 7 h, cooled, washed with 150 mL of 10% NaOH followed by water, and dried over K_2CO_3. Rotary evaporation gave 195 g (98%) of a liquid which crystallized on standing, mp 107–109 °C; the NMR of this material [δ 4.73 (s, 2 H), 7.2–8.3 (m, 6 H)] indicated that it was nearly pure 1-bromo-2-(bromomethyl)naphthalene (less than 5% starting material), and it was used without further purification. The entire sample was taken up in 500 mL of glacial acetic acid, and 217 g (2.6 m) of NaOAc was added. After the mixture had been refluxed for 10 h, most of the solvent was removed by distillation by using a water aspirator. The residue was taken up in CH_2Cl_2, washed several times with water and bicarbonate solution, dried over $MgSO_4$, and evaporated. The residue was distilled [bp 171–173 °C (2.5 torr)] to give 132 g (80%) of 1-bromo-2-(acetoxymethyl)naphthalene, which slowly crystallized on standing: mp 97–103 °C; NMR δ 2.1 (s, 3 H), 5.3 (s, 2 H), 7.2–8.4 (m, 6 H). Saponification was effected in 300 mL of 10g methanolic KOH solution (exothermic, 2 h) followed by dilution in water and ether extraction. Drying (K_2CO_3) and evaporation gave a white solid in quantitative yield. Recrystallization from aqueous methanol afforded 74 g (66%) of 1-bromo-2-(hydroxymethyl)naphthalene: mp 101–102 °C; NMR (CCl_4) δ 4.6 (br s, OH, shifts on dilution), 4.85 (s, 2 H), 7.2–8.4 (m, 6 H).

A portion (20 g 0.08 mol) of this alcohol was dissolved in DMF and treated with 105 g (0.28 mol) of pyridinium dichromate.[28] After 24 h, 5% HCl was added, and the mixture was extracted with ether; the ethereal phase was in turn extracted with 10% NaOH, and the aqueous phase was acidified to pH 1 and extracted again with ether. After the mixture was dried ($MgSO_4$) and the solvent evaporated, crude acid was obtained in 65% yield. Recrystallization from benzene gave 1-bromo-2-naphthoic acid: 58%; mp 191–194 °C (lit.[12] mp 191 °C); NMR ($CDCl_3$–acetone-d_6) δ 7.4–8.0 (m, 5 H), 8.2–8.5 (m, 1 H).

An oven-dried 500-mL flask was fitted with a dropping funnel, N_2 bubbler, low-temperature thermometer, and magnetic stirrer. The 1-bromo-2-naphthoic acid (18.0 g, 0.07 mol) was taken up in 200 mL of anhydrous ether with enough dry THF to effect solution and cooled to −95 °C in a bath of ether–liquid N_2. Methyllithium in ether (103 mL, 0.14 mole) was added slowly, maintaining the temperature below −92 °C, with subsequent stirring for 0.75 h at this temperature. Methyl iodide (10 mL, 0.14 mol) was then added, and the stirred solution was allowed to come to room temperature overnight. The product was extracted into 5% NaOH, which was in turn acidified to pH 1; the resulting precipitate was taken up in ether, dried over $MgSO_4$, and evaporated to give 10.0 g (77%) of colorless solid [mp 175–177 °C (lit.[9] mp 174 °C)], essentially pure 1-methyl-2-naphthoic acid: NMR δ 3.03 (s, 3 H), 7.45–8.35 (m, 6 H).

The photochemical bromination of this material in CCl_4 was effected by using a sunlamp while slowly adding 9.0 g (3 mL, 0.054 mol) of Br_2 in CCl_4, with a total reaction time of 6 h. When the mixture cooled, 12.8 g (90%) of a yellow solid precipitated: mp 210 °C dec., NMR (acetone-d_6) δ 5.65 (s, 2 H), 7.4–8.6 (m, 6 H). This 1-(bromomethyl)-2-naphthoic acid was dissolved in 200 mL of 5% KOH and refluxed for 12 h. Cooling, acidification, and extraction with CH_2Cl_2 followed by drying and evaporation gave lactone **5**: 5.5 g (62%); mp 116–117 °C (lit. mp 116.5–117,[7] 120–120.5 °C[8]); NMR δ 5.52 (s, 2 H), 7.4–8.1 (m, 6 H).

3-Ethoxy-1,3-dihydrobenzo[*e*]isobenzofuran (9E). Diethoxycarbenium tetrafluoroborate was prepared by adding 1.33 equiv of distilled $BF_3{\cdot}Et_2O$ to triethyl orthoformate (32 mmol) in dry CH_2Cl_2 and pumping off the volatiles to give an oily residue. This was taken up in 11 mL of CH_2Cl_2, and then 5.3 g (29 mmol) of lactone **4** in 40 mL of CH_2Cl_2 was added. After the mixture was stirred at 22 °C for 3 h, 15 mL of CCl_4 was added, and the mixture was cooled to −10 °C, causing the formation of colorless crystals. These were collected, and an additional crop was obtained by adding 15 mL more of CCl_4 and again cooling and filtering. The combined solid weighed 8.1 g (94%): NMR (CD_3NO_2) δ 1.83 (t, 3 H, J = 7 Hz), 5.40 (q, 2 H, J = 7 Hz), 6.37 (s, 2 H), 7.9–8.7 (m, 6 H).

To an ice-cooled solution of $NaBH_4$ (17.4 mmol) and pyridine (13.2 mmol) in 16 mL of dry DMF was added 3.95 g (13.2 mmol) of this ethylated salt in portions over 0.2 h, and the mixture was stirred an additional 1.5 h before addition of excess water. The mixture was extracted several times with pentane, dried over K_2CO_3, and evaporated to give 2.12 g (75%) of pale yellow oil, essentially pure **9E** by NMR. Chromatography on basic alumina with pentane/ether (9:1) gave 1.52 g of pure **9E** as a colorless oil: NMR δ 1.26 (t, 3 H, J = 7 Hz), 3.72 (q, 2 H, J = 7 Hz), 4.93–5.46 (*ABX* pattern, 2 H, downfield proton coupled, J = 2.5 Hz, to the acetal proton), 6.64 (d, 1 H, J = 2.5 Hz), 7.25–8.04 (m, 6 H). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.57; H, 6.60.

3-Methoxy-1,3-dihydrobenzo[*e*]isobenzofuran (9M). Quantitative conversion of **9E** to **9M** was effected by refluxing in methanol containing a trace of acetic acid for 3 h. Chromatography on basic alumina with pentane/ether (9:1) gave pure **9M** as a colorless oil: NMR δ 3.43 (s, 3 H), 5.00–5.53 (*ABX* pattern, 2 H, downfield proton coupled to acetal proton, J = 2.5 Hz), 6.65 (d, 1 H, J = 2.5 Hz), 7.38–8.03 (m, 6 H); MS, calcd for $C_{13}H_{12}O_2$ m/z 200.0837, found 200.0841.

1-Ethoxy-1,3-dihydrobenzo[*e*]isobenzofuran (11E). Ethylation of lactone **5** (1.1 g, 6.0 mmol) was accomplished as

(23) Meyer, F.; Sieglitz, A. *Chem. Ber.* **1922**, *55*, 1851. These authors were the first to note that 2-methyl-1-naphthoic acid does not undergo Fischer esterification.

(24) Brewster and Fusco[7] prepared lactone **4** by heating the analogous ethyl ester at 150–160 °C for 2 h, where formation is accompanied by evolution of bromoethane. These authors noted that the isomer which served as a precursor to lactone **5** does not give analogous thermal reaction.

(25) This lactone is also reported as the exclusive product from $NaBH_4$ or $LiAlH_4$ reduction of 1,2-naphthalic anhydride;[26] the latter is available by a multistep procedure given in ref 27.

(26) Nose, A.; Kudo, T. Yakugaku Zasshi **1975**, *95*, 1390.

(27) Hershberg, E. B.; Fieser, L. F. "Organic Syntheses"; Wiley: New York, 1943; Collect Vol. II, p 423.

(28) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

described above. Since addition of CCl_4 gave an oil, the volatiles were removed in vacuo, and the residue, taken up in 20 mL of CH_2Cl_2, was used directly in the reduction step. Dropwise addition to a cold solution of $NaBH_4$ (10.2 mmol) in 8 mL of dry DMF (no pyridine used) was followed by stirring for 0.5 h and then addition of excess water. Extraction with CH_2Cl_2, drying, and evaporation gave 1.57 g of yellow oil, mainly **11E** by NMR. Chromatography gave pure **11E** (59%) as a colorless oil which slowly crystallized: mp 47.5–49 °C; NMR δ 1.25 (t, 3 H, J = 7 Hz), 3.70 (q, 2 H, J = 7 Hz), 5.17–5.65 (*ABX* pattern, 2 H, downfield proton coupled to acetal proton, J = 2.5 Hz), 6.37 (d, 1 H, J = 2.5 Hz), 7.25–7.90 (m, 6 H). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.24; H, 6.58.

1-Methoxy-1,3-dihydrobenzo[e]isobenzofuran (11M). Conversion of **11E** to **11M** was done as described for the regioisomer **9M**. Pure **11M** was obtained as a colorless oil: NMR δ 3.40 (s, 3 H), 5.15–5.66 (*ABX* pattern, 2 H, downfield proton coupled as before, J = 2.5 Hz), 6.30 (d, 1 H, J = 2.5 Hz), 7.12–7.90 (m, 6 H). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.70; H, 6.11.

Benzo[e]isobenzofuran (1). This general procedure is appropriate for any of the acetals **9E**, **9M**, **11E**, or **11M**. A sample of acetal (0.66 mmol) in 1.5 mL of ether was cooled to 0 °C, 10 μL of diisopropylamine was added, and this was followed by 0.7 mL of 1.55 M CH_3Li in ether (1.1 mmol). After being stirred for 0.3 h, the mixture was taken up in water, extracted with ether, dried (K_2CO_3), and evaporated to give a pale yellow semisolid (95%, by NMR essentially pure **1**). Chromatography on basic alumina with 4% ether in pentane gave colorless crystals: mp 62–64 °C; NMR (300 MHz, CCl_4/CD_2Cl_2) δ 7.07–7.26 (AB q, 2 H, central ring protons, J = 10 Hz, downfield proton further coupled, J = 0.9 Hz), 7.35–7.45 (m, 2 H), 7.57–7.66 (m, 1 H), 7.91–7.96 (m, 2 H, includes one furan proton as d, J = 1.5 Hz), 8.27 (dd, "bay region" furan proton, J = 1.5, 0.9 Hz).

Acid-Catalyzed Reactions of Acetals. The general conditions used are described in the text; variations and analytical data are given below.

(a) DMAD Adduct 12. This product was isolated by chromatography on silica gel by using graded pentane–CH_2Cl_2 elution, with recrystallization from hexane: mp 107–108 °C; NMR (300 MHz) δ 3.77 (s, 3 H), 3.79 (s, 3 H), 6.14 (d, 1 H, J = 1.3 Hz), 6.53 (d, 1 H, J = 1.3 Hz), 7.35–7.95 (m, 6 H); MS, m/z (relative intensity) 310 (21), 250 (22), 168 (100). Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.58; H, 4.64.

(b) Methanolyzed AAN Adducts 13 and 14. Purified 1:1 mixtures of ketones **13** and **14** were obtained by chromatography on silica gel with pentane/CH_2Cl_2 (50/50); no separation of isomers was effected, as shown by NMR before and after chromatography. The mixture was isolated as a colorless oil. The pertinent NMR signals for assignment are described in the text: MS, calcd for $C_{14}H_{10}O_2$ m/z 210.0680, found 210.0693.

(c) MA Adduct 16. Recyrstallization from $CHCl_3$/hexane gave pure *exo*-**16**: mp 214–215 °C; NMR (acetone-d_6) δ 3.37 (s, 2 H), 5.95 (s, 1 H), 6.28 (s, 1 H), 7.38–8.00 (m. 6 H). Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 71.97; H, 3.85.

A room-temperature reaction with preformed **1** gave in addition to *exo*-**16** the endo isomer, identified by NMR only: δ 4.0–4.2 (complex m, 2 H) and presumed doublets which fall partially under the benzylic proton singlets of the exo isomer. Refluxing for 6 days in $CDCl_3$ caused disappearance of the endo absorptions and enhancement of the exo signals.

(d) BL Adducts after $TiCl_4$ Treatment (19 + 20). The general procedure, applied to several samples of either crude or column chromatographed BL cycloadducts, is illustrated. The adduct was dissolved in CH_2Cl_2 and 3 molar equiv of $TiCl_4$ added. The red-brown solution was stirred for 0.5 h, and then 3 equiv of Et_3N was added. After 1 h the mixture was taken up in water and extracted into CH_2Cl_2, which was dried and rotary evaporated. No separation of **19** and **20** occurred on chromatography, which gave a pale yellow solid residue: NMR (300 MHz) δ 5.45 and 5.49 (equal area singlets, total integral 2 H), 7.61–7.98 (m, 5 H), 8.41 (s, 0.5 H), 8.69 (m, 2 H), 9.19 (s, 0.5 H); MS, calcd for $C_{16}H_{10}O_2$ m/z 234.0681, found 234.0703.

(e) Cyclohexene Adduct 21. Chromatography (silica gel, ether) gave a low yield of oil, identified as *endo*-**21**: NMR δ 1.05–1.60 (m, 8 H), 2.20–2.55 (m, 2 H), 5.27 (d, 1 H, J = 4 Hz), 5.67 (d, 1 H, J = 4 Hz), 7.10–7.82 (m, 6 H); MS (CI), calcd for $C_{18}H_{19}O$ (P + H) m/z 251.1436, found 251.1409.

3,3-Dimethoxy-1,3-dihydrobenzo[e]isobenzofuran (8M). Dimethoxycarbenium tetrafluoroborate was prepared as described above for the ethyl analogue by using trimethyl orthoformate. A 20% excess was used to alkylate lactone **4**, and this product was added to excess sodium methoxide in methanol. After 4 h (shorter reaction times results in lower yields of ortho ester and regeneration of lactone; low solubility of the carbenium ion salt appears to be responsible) water was added, and the product was taken up in ether, dried (K_2CO_3), and evaporated. An off-white solid was obtained (85%) which by NMR [δ 3.30 (s, 6 H), 5.20 (s, 2 H), 7.35–8.35 (m, 6 H)] was mostly the desired **8M**, contaminated with a small amount of **4**. Attempts to recrystallize this material resulted in conversion to **4**; the nearly pure material was used in the cycloaddition reactions.

3,3-Diethoxy-1,3-dihydrobenzo[e]isobenzofuran (8E). The ethylated salt from **4** was stirred with excess sodium ethoxide/ethanol for 6 h. A workup as above gave 91% of nearly pure **8E** as a colorless oil: NMR δ 1.10 (t, 6 H, J = 7 Hz), 2.93–3.82 (complex m due to diastereotopic protons, 4 H), 5.13 (s, 2 H), 7.3–8.4 (m, 6 H); MS, Calcd: (for P – C_2H_5O base peak) m/z 213.0914, found 213.0913.

Attempted crystallization of this material also resulted in conversion to **4**, and so it was used as obtained (less than 10% **4** as a contaminant).

1,1-Diethoxy-1,3-dihydrobenzo[e]isobenzofuran (10E). The salt from **5** was treated for 21 h with ethoxide/ethanol to give crude product in excellent yield as a yellow oil which was nearly pure by NMR. Chromatography on basic alumina with pentane containing a trace of Et_3N gave pure **10E** as a colorless oil: NMR δ 1.71 (t, 6 H, J = 7 Hz), 3.20–3.80 (complex m, 4 H, diastereotopic protons), 5.41 (s, 2 H), 7.39–7.98 (m, 6 H). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.34; H, 6.85.

Acid-Catalyzed Ortho Ester Reactions. (a) 8M with MA 22. Crude product precipitated from the chlorobenzene solution on cooling, after refluxing for 24 h (20% yield). Recrystallization from $CHCl_3$ gave pure **22** as yellow needles: mp 247–249 °C; NMR δ 4.36 (s, 3 H), 7.70–8.53 (m, 7 H); IR (KBr) 1828, 1764 cm^{-1}; MS, calcd for $C_{17}H_{10}O_4$ m/z 278.0576, found 278.0575.

The mother liquor was examined by NMR, which indicated the formation of a major amount of lactone **4**.

(b) 8E with MA 24. Identical conditions gave aromatized adduct again in 20% yield. Recrystallization ($CHCl_3$) gave pure **24**: mp 222.5–224 °C; NMR δ 1.62 (t, 3 H, J = 7 Hz), 4.56 (q, 2 H, J = 7 Hz), 7.68–8.38 (m, 7 H); MS, m/z (relative intensity) 292 (73), 264 (25), 192 (100), 163 (58). Anal. Calcd for $C_{18}H_{12}O_4$: C, 73.97; H, 4.14. Found: C, 73.69; H, 4.13.

Evaporation of the mother liquor gave a residue which was largely **4**.

(c) 10E with MA 28. The reaction appeared to be complete after 1.2 h of refluxing, at which point the solvent was evaporated to give a yellow solid residue. Recrystallization from $CHCl_3$/hexane gave **28**: 56% yield; mp 183–184.5 °C dec; NMR δ 1.57 (t, 3 H, J = 7 Hz), 4.79 (q, 2 H, J = 7 Hz), 7.67–8.85 (m, 7 H). Anal. Calcd for $C_{18}H_{12}O_4$: C, 73.97; H, 4.14. Found: C, 73.77; H, 4.33.

(d) 8M with DMAD (23). Glacial acetic acid (0.1 equiv) was used as the catalyst. After refluxing for 65 h, the chlorobenzene was vacuum evaporated to give a yellow orange solid, mostly **23** by NMR. Two recrystallizations from methanol gave pure **23**: 40%; pale yellow plates; mp 146.5–147 °C (phase change at 141 °C; on remelting, the higher melting point only is obsrved). NMR δ 3.77 (s, 3 H), 3.96 (s, 3 H), 3.99 (s, 3 H), 7.47–8.42 (m, 5 H), 9.32–9.47 (m, 1 H), 11.9 (s, OH). MS, calcd for $C_{19}H_{16}O_6$ m/z 340.0947, found 340.0945.

(e) 8E with DMAD 25. Two recrystallizations from methanol/water gave 47% of pure **25** as dense straw-colored crystals: mp 153–155 °C; NMR δ 1.44 (t, 3 H, J = 7 Hz), 3.93 (q, 2 H, J = 7 Hz), 3.99 (s, 3 H), 4.02 (s, 3 H), 7.55–8.42 (m, 5 H), 9.37–9.57 (m, 1 H), 11.9 (s, OH); MS, m/z (relative intensity) 354 (96), 322 (100), 294 (80), 293 (89), 262 (41), 234 (58). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.54; H, 5.31.

(f) 10E with DMAD 29. After 2.3 h reflux, the **10E** was consumed, but the product appeared (NMR) to be a mixture of the initially formed cycloadduct and the aromatized derivative.

Heating was continued an additional 42 h, after which the solvent was evaporated to give a dark oily residue, mainly **29** by NMR. Chromatography gave essentially pure material (93%), which was twice recrystallized from hexane to give pale yellow **29**: mp 106.5–107.5 °C; NMR δ 1.46 (t, 3 H, J = 7 Hz), 3.97 (s, 6 H), 4.07 (q, 2 H, J = 7 Hz), 7.59–7.96 (m, 5 H), 9.78–9.91 (m, 1 H), 13.1 (s, OH). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.65; H, 5.36.

(g) 10E with AAN 30. This mesitoic acid catalyzed addition was complete within 2.5 h. Chromatography of the residue from vacuum evaporation gave crude product in good yield as a nearly colorless oil. Methoxide/methanol treatment (3.5 h, 22 °C) gave a yellow oil (78%) which was mainly the anticipated product. Chromatography afforded 40% of **30** as a colorless oil: mp, slightly below room temperaturef NMR (300 MHz) δ 1.41 (t, 3 H, J = 7 Hz), 2.09 (d, 1 H, J = 16.5 Hz), 2.82 (dd, 1 H, J = 16.5, 5.1 Hz), 4.03 (q, 2 H, J = 7 Hz), 6.06 (d, 1 H, J = 5.1 Hz), 7.60–7.97 (m, 6 H). MS (CI), calcd for $C_{16}H_{15}O_3$(P + H) m/z 255.1021, found 255.1039.

(h) 8E with AAN 27. The reaction with regioisomer **8E** and AAN was also complete within 2.5 h. The NMR of the crude product suggested that it was largely a single isomer (stereo and regio) of **26**, with pertinent absorptions at δ 1.76 (d, 1 H, J = 13.5 Hz), 3.32 (dd, 1 H, J = 13.5, 5.4 Hz), 3.92 (q, 2 H, J = 7 Hz), and 5.4 (d, 1 H, J = 5.4 Hz). Conversion by methoxide/methanol treatment gave crude **27**: NMR δ 1.43 (t, 3 H, J = 7 Hz), 2.05 (d, 1 H, J = 16.5 Hz), 2.71 (dd, 1 H, J = 16.5, 4.8 Hz), 5.65 (d, 1 H, J = 4.8 Hz), 7.10–8.30 (m, 6 H). This material decomposed on standing in $CDCl_3$ solution overnight and was not further analyzed. The conclusion that no regioisomeric keto ketal is formed is based on the absence of a benzylic proton singlet anticipated for this structure and the good correlation of integrals for absorptions due to **27**.

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Registry No. **1**, 232-74-6; **4**, 5657-01-2; **5**, 4781-04-8; **6**, 2586-62-1; **7**, 4488-44-2; **8E**, 87262-71-3; **8M**, 87262-72-4; **9E**, 87262-73-5; **9M**, 87262-74-6; **10E**, 87262-75-7; **11E**, 87262-76-8; **11M**, 87262-77-9; **12**, 87262-78-0; **13**, 87262-79-1; **14**, 87262-80-4; *exo*-**16**, 87262-81-5; *endo*-**16**, 87332-56-7; **19**, 87262-82-6; **20**, 87262-83-7; *endo*-**21**, 87262-84-8; **22**, 87262-85-9; **23**, 87262-86-0; **24**, 87262-87-1; **25**, 87262-88-2; **26**, 87262-89-3; **27**, 87262-90-6; **28**, 87262-91-7; **29**, 87262-92-8; **30**, 87262-93-9; DMAD, 762-42-5; AAN, 3061-65-2; MA, 108-31-6; BL, 497-23-4; methyl 2-methyl-1-naphthoate, 56020-58-7; 2-methyl-1-naphthoic acid, 1575-96-8; 2-methyl-1-naphthalenecarbonyl chloride, 10008-12-5; methyl 2-(bromomethyl)-1-naphthoate, 2417-76-7; 2-methylnaphthalene, 91-57-6; 1-bromo-2-(bromomethyl)naphthalene, 37763-43-2; 1-bromo-2-(acetoxymethyl)naphthalene, 87262-94-0; 1-bromo-2-(hydroxymethyl)naphthalene, 76635-70-6; 1-bromo-2-naphthoic acid, 20717-79-7; 1-(bromomethyl)-2-naphthoic acid, 87262-95-1; diethoxycarbenium tetrafluoroborate, 1478-41-7; 3-ethoxy-1,3-dihydrobenzo[*e*]isobenzofuran-3-ium tetrafluoroborate, 87262-97-3; cyclohexene, 110-83-8; dimethoxycarbenium tetrafluoroborate, 18346-68-4.

Ketal Claisen Rearrangements of Simple Aliphatic Ketals[1]

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The ketal Claisen rearrangement has been studied with eight simple unsymmetrical ketals in order to establish the regioselectivity associated with the transformation. Three different allylic alcohols were examined. Carbon–carbon bond formation on the more highly substituted branch of the parent ketone generally predominated over substitution on the less highly substituted branch. However, additional substituents on the α or β carbons of the ketal lower the selectivity substantially. Extensive β substitution can completely reverse the normal selectivity. The reaction is relatively insensitive to the concentration of the weak acid catalyst. The yields range between 27% and 84%, and the products have been characterized. A model that accounts for the observations is also described.

The Claisen rearrangement is a very general and powerful synthetic tool.[2] The enolate Claisen rearrangement,[3] the ortho ester Claisen rearrangement,[4] and the amide acetal Claisen rearrangement[5] have provided synthetic chemists with convenient methods for exploiting this historically important pathway to γ,δ-unsaturated carbonyl compounds.

Stereochemical studies have also played an important part in this development. The early work of Perrin,[6] Faulkner,[7] and Johnson[8] demonstrated that Claisen rearrangements could be used to generate trans-disubstituted and E-trisubstituted double bonds. Additionally, the olefinic geometries control the relative stereochemistry of

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