ratio of enol ether to 3-methoxyheptene was 1:1. Additional purification was not attempted.

Preparation of 1-Methoxy-1,3-bis(phenylthio)propane. To (*E*)-1-methoxy-3-(phenylthio)propene (0.30 g, 1.67 mmol) in 5 mL of methylene chloride was added thiophenol (0.35 mL, 3.4 mmol). Then methansulfonic acid (0.04 mL, 0.6 mmol) was added dropwise. The solution was stirred for 2 h in an ice bath at 0 °C. After stirring, the solution was quenched with an excess of triethylamine (0.09 mL, 0.63 mmol). The methylene chloride was then removed by rotatory evaporation and 15 mL of ether was added. The solution was then washed sequentially with 15 mL of water, 15 mL of 10% NaOH (twice), and 15 mL of brine. The ether solution was dried over calcium chloride, filtered, and reduced by rotatory evaporation. Kugelrohr distillation (201 °C/3 mm) gave 0.281 g of a clear thick oil (58%): ^{1}H NMR (CCl_4, δ) 7.17 (m, 10 H, 2 PhS), 4.70 (t, J = 6 Hz, 1 H, $CHOCH_3$) 3.4 (s, 3 H, $CHOCH_3$), 2.64 (t, J = 8 Hz, 2 H, $C_6H_5SCH_2$), 1.87 (q, J = 6 Hz, 2 H, SCH_2CH_2); IR (neat, cm^{-1}) 1587, 1470 (Ph), 1433 (CH_3), 1099 (C-O), 739, 690 (SPh). Anal. Calcd for $C_{16}H_{18}S_2O$: C, 66.16; H, 6.26. Found: C, 65.83; H, 6.05.

Preparation of 1,1-Dimethoxy-3-(phenylthio)propane. To (*E*)-1-methoxy-3-(phenylthio)propene (0.30 g, 1.67 mmol) in 25 mL of methanol was added methanesulfonic acid (0.04 mL, 0.6 mmol) dropwise. The solution was stirred for 21 h and then quenched with triethylamine (0.09 mL, 0.63 mmol). Methanol was then removed by rotatory evaporation and 20 mL of ether was added. The ether solution was washed twice with 20 mL of water and then dried over calcium chloride and filtered. The ether was removed by rotatory evaporation. Kugelrohr distillation (120 °C/3 mm) gave 0.289 g of clear oil (81%): ^{1}H NMR (CCl_4, δ) 7.23 (m, 5 H, C_6H_5S), 4.40 [t, J = 6 Hz, 1 H, $CH(OCH_3)_2$], 3.23 [s, 6 H, $CH(OCH_3)_2$], 2.87 (t, J = 8 Hz, 2 H, $C_6H_5SCH_2$-), 1.90 (dt, J = 6, 8 Hz, 2 H, $-SCH_2CH_2-$); IR (neat, cm^{-1}) 1587, 1477 (Ph), 2439 (CH_3), 1122, 1071 (C—O), 739, 690 (SPh). Anal. Calcd for $C_{11}H_{16}SO_2$: C, 62.22; H, 7.61. Found: C, 62.44; H, 7.33.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the UNO Committee on Research for partial support of this research.

1-Methoxyisobenzofuran from Base-Induced and Acid-Catalyzed Reactions of 1,3-Dihydro-1,3-dimethoxyisobenzofuran

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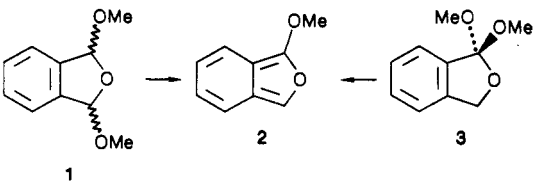
Received July 7, 1986

The title bis acetal (1) has been used in both acid-catalyzed and strong base induced procedures to generate 1-methoxyisobenzofuran (2). The acid-catalyzed reaction is not synthetically useful, since it requires forcing conditions and gives cycloadduct only with very reactive dienophiles (e.g., maleic anhydride). However, the $LiNR_2$-induced 1,4-elimination reaction of 1 yields isolable solutions of 2. This process is strongly solvent-dependent, being more rapid in THF than in diethyl ether, and very slow in hexane. The elimination exhibits syn selectivity in ether solvent, allowing the recovery of unreacted 1 enriched in the cis isomer. However, cis 1 also undergoes base-induced elimination to form 2, showing that an anti elimination pathway, although not favored, is energetically accessible. The utility of the base-induced method was demonstrated by the formation of the 3-lithiated derivative of 2, which was in turn converted to 1-methoxy-3-(trimethylsilyl)isobenzofuran. This derivative gave cycloadducts upon treatment with the dienophiles *N*-methylmaleimide and benzyne, the latter generated by dehydrohalogenation of bromobenzene.

Ortho esters such as **3** are useful precursors of 1-alkoxyisobenzofurans (e.g. **2**), in both acid-catalyzed[2,3] and base-induced[3,4] procedures. The 1-alkoxyisobenzofurans are generated as reactive intermediates under acidic conditions, while the base-induced method allows the preparation of solutions of **2** which have at least modest stability at ambient temperature.[5]

We were interested in exploring possible complementary approaches to **2** from the bis acetal **1**. In this paper we describe both acid-catalyzed and $LiNR_2$-induced reactions of **1**, which show that the conversion to **2** can occur. The acid-catalyzed reaction, although of mechanistic interest, appears to have little synthetic value. The base-induced procedure is more useful and also exhibits solvent-dependent stereoselectivity in the 1,4-elimination under certain conditions.



1 2 3 (1)

Results and Discussion

(a) Preparation of 1 and Identification of Stereoisomers. The substrate **1** was prepared by treatment of *o*-phthalaldehyde in methanol with an acid catalyst. This procedure resulted in the formation of the cyclic bis-acetal **1** along with a small amount of the less volatile acyclic bis-acetal, easily separated by vacuum distillation. The desired product **1** is a mixture of cis(meso) and trans (±) isomers **1c** and **1t**, as shown by the ^{1}H NMR spectrum, which exhibited distinctive singlets at 6.04 (major) and 6.3 ppm (minor isomer), with other features being very similar

(1) Formerly known as B. Mir-Mohamad-Sadeghy
(2) Contreras, L.; Slemon, C. E.; MacLean, D. B. *Tetrahedron Lett.* **1978**, 4237. See also: Contreras, L.; MacLean, D. B.; Faggiani, R.; Lock, C. J. L. *Can. J. Chem.* **1981**, *59*, 1247.
(3) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 2734.
(4) Mir-Mohamad-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 2237.
(5) Mir-Mohamad-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 1477.

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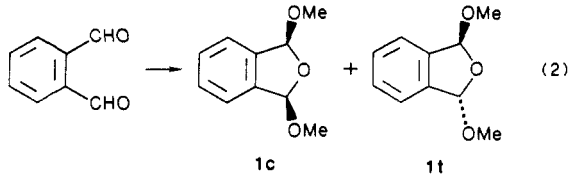
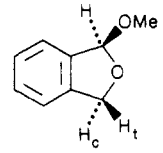


1c 1t

for both compounds. The isomers were formed in a ratio of 65/35 ± 5% in several preparations. Since the conditions used were identical with those we have employed previously for trans-acetalizations of similar compounds, we believe that this ratio reflects the equilibrium position (see below). There does not appear to be an unambiguous method[6] (other than, in principle, X-ray crystallographic analysis or optical isomer resolution) to prove which of the isomers is cis and which trans, although a reasonable assumption allows the conclusion outlined below.

Barfield and co-workers[7] have calculated that the long-range proton coupling constants $J_{2,5}$ for 2,5-dihydrofurans should always be greater for the trans than the cis stereoisomer and have presented spectral data in support of this conclusion. We have verified this point for 1,3-dihydro-1-methoxyisobenzofuran (4) by carrying out



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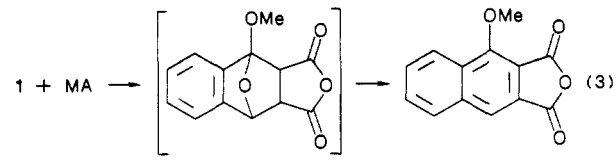
a difference NOE spectroscopy experiment. The benzylic methylene protons of this material are spin coupled to each other with a typical large geminal J value, but only the downfield proton is further split by measurable (2 Hz) long-range coupling to the acetal proton. Presaturation of the methoxy protons caused enhancement of both the acetal proton (6%) and the downfield methylene dd (5%), with no measurable effect on the upfield methylene d. This established that the downfield dd is due to the proton cis to the methoxy group (H_t), and thus that the measurable long-range coupling involves the trans array of protons.

We assume, reinforced by Barfield's conclusion as stated above, that compounds **1c** and **1t** will exhibit coupling behavior in keeping with this result. Because of symmetry this coupling is not observable in the major isotopomers, but the ^{13}C satellites of the ^1H spectrum provided the needed information. Overlapping signals allowed only the detection of the downfield satellite of the downfield isomer (which appeared as a doublet, J = 2 Hz) and the upfield satellite of the upfield isomer (which appeared as a singlet). Thus we conclude that the major isomer is cis (**1c**) and the minor is trans (**1t**).

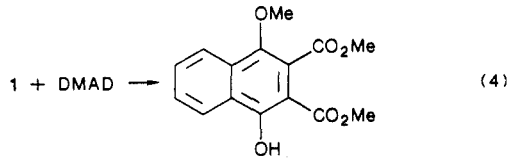
Although it is not clear why the cis isomer is favored, treatment of **1** in ethanol or isopropyl alcohol (but not *tert*-butyl alcohol) with trifluoroacetic acid catalyst at room temperature resulted in the formation of the solvent-derived analogues (1,3-dialkoxy-1,3-dihydroisobenzofurans), with similar (by NMR) ratios of isomers. These observations reinforce the conclusion that the 65/35 cis/trans ratio represents the equilibrium position and also demonstrate that under these conditions, nucleophilic attack of the intermediate carbenium ion occurs more rapidly than elimination to form 1-alkoxyisobenzofuran, since addition of alcohol to the latter would result in the formation of ortho ester.[5]

(b) Acid-Catalyzed Reactions of 1. The bis acetal **1** does undergo elimination to form **2** as an intermediate when heated with an acid catalyst, but the rate is substantially slower than for analogous isobenzofuran formation from either the ortho ester **3** or the mono acetal **4**, as judged by the time/temperature requirements for cycloadduct formation. Under conditions where both **3** and **4** react with in situ dienophiles,[3,4] **1** was recovered essentially unchanged (in amount and cis/trans ratio). However, more forceful conditions (160 °C, 43 h) led to reaction with maleic anhydride (MA). The product **6** was isolated (51%); this material is known[3] to arise by dehydration of the cycloadduct **5** (eq 3).



5 6

The reaction of **1** with dimethyl acetylenedicarboxylate (DMAD) was unsuccessful at lower temperatures with mesitoic acid catalyst, but at 160 °C (100 h), a low yield (19%) of the ring-opened cycloadduct[3] **7** was formed (eq 4). In addition to recovered **1**, a small amount of *o*-



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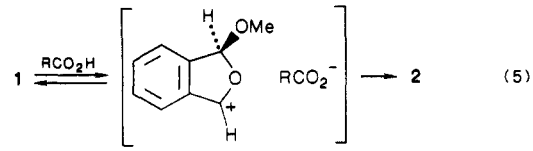
phthalaldehyde was isolated. Because of the thermal instability of DMAD, an effort was made to catalyze the reaction at lower temperature with ethyldiisopropylammonium tetrafluoroborate, but this resulted in an even lower yield.[8]

Cycloadducts were not obtained with other moderately reactive dienophiles which had been successfully applied to reactions of the ortho ester **3**. It appears that the acid-catalyzed reaction of **1** and related bis acetals will have limited utility.

Previous studies[4,9] with mono acetals have established that the cation-forming step is rapid and reversible under typical reaction conditions and the facile trans-acetalization reactions of **1** support the view that this is also true for this bis acetal. Further, the elimination step to form 1-methoxyisobenzofuran (**2**) should be effectively irre-



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(6) We have found this case pedagogically useful to illustrate the inability of chiral shift reagents to distinguish between meso and (±) pairs because both lead to doubled signals, in the meso isomer due to internal diastereomeric site generation, while for the (±) isomer diastereomeric signals arise from *R* and *S* enantiomers, respectively. An exception to this rule occurs when new spin–spin coupling is observed for the meso isomer.

(7) Barfield, M.; Spear, R. J.; Sternhell, S. *J. Am. Chem. Soc.* **1975**, *97*, 5160.

(8) A reaction at 131 °C (93 h) with 10% of this catalyst[4] gave 59% of recovered **1** (cis/trans = 60/40), 41% of *o*-phthalaldehyde, and only 5% of the cycloadduct **7**.

(9) Cornejo, J.; Ghodsi, S.; Johnson, R. D.; Woodling, R.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 3869.

versible, since readdition of methanol to **2** (at lower temperature) leads to the formation of the ortho ester **3** rather than **1**.[5] It appears that the rate-determining step for isobenzofuran formation is the deprotonation of an intermediate carbocation for all three systems, **3**, **4**, and **1** (e.g., the second step of eq 5). The overall rate is depressed when the proton is abstracted from a carbon bearing a methoxy substituent, as in **8**. Similar conditions are required for acid-catalyzed in situ Diels–Alder reactions of **3** and **4**, even though the carbocation generated from **3** must be considerably more stable than that from **4**. Thus, the diminished rate of reaction of **1** compared to **3** or **4** under acid-catalyzed conditions may reflect an electronic effect of the methoxy group which disfavors proton abstraction. The results of base-induced reactions described in the next section tend to support this view.

Finally, it is noted that stereochemical features cannot account for the depressed rate of the acid-catalyzed reaction of **1**, since material recovered from experiments in which **1** had been partially consumed had cis/trans ratios indistinguishable from that of the starting material. This requires that either both cis and trans **1** react with the same overall rate constants or that the isomers are rapidly equilibrated under the reaction conditions.

(c) Base-Induced Reactions of 1. Benzyl methyl ether gives a facile Wittig ether rearrangement reaction when treated with $LiNR_2$.[10] However, when the substrate contains an *o*-methyl group, 1,4-elimination occurs to the exclusion of other processes.[11] Similar conclusions were reached in work with the dimethyl acetals of benzaldehyde and *o*-tolualdehyde.[10] The base-induced reactions of **1** were of special interest in this context, since 1,4-elimination requires proton abstraction from an alkoxy-bearing carbon, a feature shared by the Wittig ether rearrangement. With stereoisomers identified, we were also in a position to examine syn/anti preferences in the elimination reaction.

The lithium diisopropylamide (LDA) induced reaction of **1** exhibited strong solvent dependence, with rates in the order THF > ether > hexane. As in the acid-catalyzed reactions described above, the base-induced reactions of **1** were slower (qualitative observations) than analogous reactions of **3** or **4** in ether or hexane. Again we suggest that this is due to the geminal methoxy group depressing the rate of proton abstraction.

Treatment of **1** in THF at 0 °C with LDA (1 equiv of MeLi, 0.5 equiv of diisopropylamine)[12] caused rapid development of a dark coloration and formation of a precipitate. Quenched after 3 h by addition to aqueous bicarbonate solution and ether, this reaction gave a poor material balance, suggesting that either water soluble or polymeric products had been formed. No unreacted **1** was observed by NMR, nor was a significant amount of phthalide formed. Phthalide is expected from hydrolysis of **2**, and this observation indicates that **2** does not survive under these specific conditions.

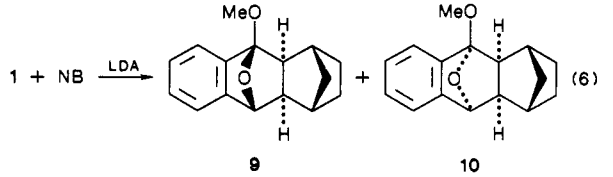
At dry ice/acetone bath temperature in THF solvent, treatment of **1c**/**1t** = 65/35 with 0.1 equiv of amine followed by 2.3 equiv of *n*-butyllithium caused the slow development of an orange color. After 1.5 h, methanol was added and, with warming to ambient temperature, stirring was continued for 12 h. After careful neutral workup, a quantitative combined yield of recovered **1** (75%, cis/trans = 65/35) and ortho ester **3** (25%) was isolated. The latter sensitive material was identified by NMR, through the appearance of characteristic singlets at 3.20 and 4.98 ppm, and enhancement of these peaks when authentic **3** was added to the sample. Since, as noted earlier, it has been demonstrated[5] that methanol will add to **2** to form **3**, this provides evidence that **1** does indeed form **2** upon treatment with LDA. Synthetic applications which reinforce this conclusion are described in the next section. The unchanged cis/trans ratio of the **1** recovered in this experiment suggests that no syn/anti selectivity is associated with the elimination in THF solvent. Possible equilibration of the isomers of **1** under the reaction conditions was ruled out by repeating this experiment, but with a sample of **1c**/**1t** = 85/15 (see below). Again **3** was formed (32%), and the recovered **1** had a ratio (**1c**/**1t** = 80/20) indistinguishable within measurement error from that of the starting material.

The conversion of bis acetal **1** to ortho ester **3** constitutes a novel intramolecular oxidation/reduction process, formally analogous to an intramolecular Cannizzarro reaction.

In ether solvent, the reaction with LDA exhibited selectivity, with **1t** being consumed more rapidly than **1c** (preferred syn elimination). It was relatively easy to obtain recovered **1** enriched in **1c** beyond the equilibrium (ca. 65%) value, but we were unable to press the ratio of **1c**/**1t** beyond 95/5, in spite of several attempts to do so. Presumably this reflects a rate constant ratio, k_{1c}/k_{1t}, of ca. 1/20. In spite of this limitation, material enriched in the cis isomer was useful for determining mechanistic features.

No reaction between **1** and LDA was observed over a period of 12 h in ether at dry ice/acetone bath temperature (cf. THF); treatment with methanol as above gave **1**, unchanged in amount and isomer ratio. In order to observe reaction in this solvent, higher temperatures (0–25 °C) were used. The most selective reaction was obtained at 0 °C. When a 65/35 mixture of **1c**/**1t** was treated with 0.5 equiv of amine and 1.1 equiv of MeLi, with stirring for 1 h prior to bicarbonate workup and vacuum distillation, **1** was obtained in 44% yield, with the ratio of **1c**/**1t** = 95/5. Several similar experiments gave cis-enriched (90 ± 5%) mixtures. When enriched material was resubjected to the basic conditions, at 0 °C or room temperature, some **1** was lost but the ratio of **1c**/**1t** was not enhanced beyond the 95/5 limit, as judged by NMR.

In hexane, no reaction of **1** with LDA occurred even at room temperature. To obtain reaction in this solvent, we resorted to slow addition of LDA (2.5 equiv) to a refluxing (ca. 70 °C) mixture of excess norbornene (NB) and **1** (65/35) in hexane, a technique used earlier with the ortho ester **3**.[3] In two attempts, known cycloadducts[3] **9** and **10** were formed in 58% and 66% combined yields, in ratios of ca. 1/1.[14]



9 **10**

Interestingly, when this experiment was repeated with **1c**/**1t** = 95/5, **9** and **10** were again formed, in good yield (82%, 1/1 ratio by NMR). These reactions show that **1c**

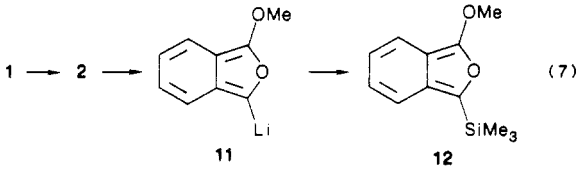
(10) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 3694.
(11) Tuschka, T.; Naito, K.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 70.
(12) Earlier work[13] had demonstrated that in ether solvent, methyllithium alone is not an effective base for causing the 1,4-elimination of **4**, but LDA is an efficient catalyst in the presence of RLi. This allows many base-induced reactions to be carried out with a minimal amount of amine regenerated on workup.
(13) Crump, S. L.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 304.
(14) As shown in earlier work,[3] isomer **10** is very susceptible to hydrolysis; pH 7 buffer was used in the isolation to avoid this complication. The ratio of **9**/**10** is the same as that found when **3** is used as the precursor to **2** under these conditions.[3]

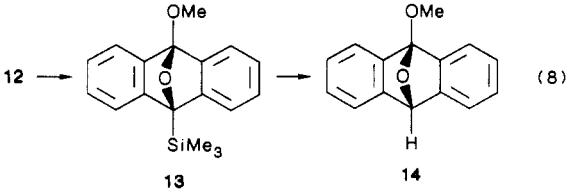
reacts with LDA to form **2**, i.e., a net anti elimination can occur in this solvent also. The question of stereoselectivity was addressed by treating a 65/35 sampling of **1** with 0.5 equiv of LDA. The yield of **9** + **10** was 19% in this instance, and the ratio of isomers of recovered **1** (73%) was 69/31, within measurement uncertainty indistinguishable from the starting mixture. A similar experiment with **1c**/**1t** = 88/12 gave **9** + **10** (21%, 1/1 ratio) and 23% of recovered **1** which had a ratio of 90/10. It therefore appears that, in refluxing hexane, the reaction of **1** with LDA exhibits no measurable stereoselectivity and the isomers of **1** are not interconverted under these conditions.

To summarize, stereoselectivity (preferred syn elimination) was observed in ether, but not in THF or hexane, even though these solvents caused faster and slower rates, respectively. No sign of isomer interconversion was observed in any of the solvents, showing that, if a carbanion intermediate is involved in the elimination, it does not undergo inversion followed by reprotonation. Even in ether, anti elimination is energetically only slightly disfavored compared to the syn process. This behavior parallels that found recently for the LDA-induced elimination reactions of analogues of **1** in which one of the methoxy groups is replaced by a methyl or phenyl substituent (syn elimination favored, but anti elimination also observed[15]).

(d) Some Applications of Base-Induced Reactions. In order to illustrate the utility of the base-induced procedure with **1**, two examples were pursued. The first involves an aryne trapping reaction, which we have shown to be an excellent method for preparing a variety of polycyclic aromatic skeleta.[16] The second example shows that a base-sensitive carbonyl-containing dienophile can be used in conjunction with the base-induced formation of methoxyisobenzofuran.

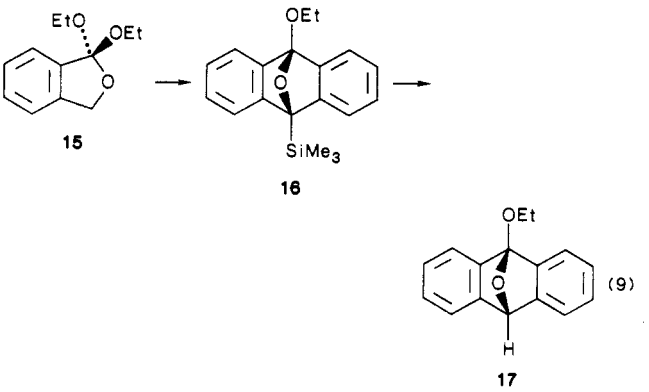
A THF solution of **1** and 0.1 equiv of diisopropylamine was cooled in a dry ice/acetone bath, and 2.3 equiv of *n*-butyllithium was added, with stirring continued for 15 h. These conditions effect both the elimination of **1** to **2** and the further lithiation of **2** to form **11**. To this still cold solutions was added Me_3SiCl. The ^1H NMR spectrum (aromatic region) of this solution indicated complete loss of **1** and the formation of 1-methoxy-3-(trimethylsilyl)-isobenzofuran (**12**), as shown in eq 7. Bromobenzene was added, followed by a freshly prepared solution of lithium tetramethylpiperidide (LTMP) in THF, with warming to room temperature and stirring continued for 15 h. Neutral workup and careful chromatography afforded 81% of crystalline product **13**. This was readily protiodesilylated by treatment with tetrabutylammonium fluoride (TBAF) in THF to give the ketal **14** (eq 8).



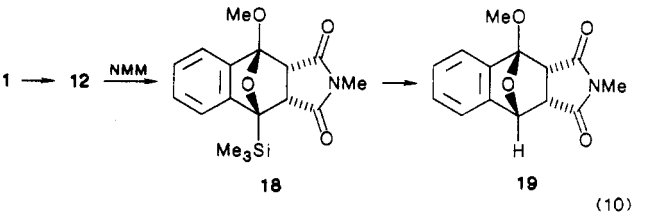


(15) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849.
(16) (a) Crump, S. L.; Netka, J.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 2746. (b) Netka, J.; Crump, S. L.; Rickborn, B. *Ibid.* **1986**, *51*, 1189. (c) Camenzind, R.; Rickborn, B. *Ibid.* **1986**, *51*, 1914. (d) Pollart, D. J.; Rickborn, B. *Ibid.* **1986**, *51*, 3155.

As a partial check on the generality of this chemistry, a similar reaction was carried out with the diethyl ortho ester analogue of **3**, compound **15**. In this instance, a reaction temperature of −5 °C was used, and the Me_3SiCl was added 1 h after the base and **15** were mixed. The bromobenzene/LTMP conditions were the same as in the preceding experiment. The ethyl analogue of **13**, compound **16**, was isolated in 89% yield. Protiodesilylation as before gave **17** (eq 9). The very good yields of these multistep but single-flask procedures are noteworthy.



A somewhat different approach was used to generate 1-methoxy-3-(trimethylsilyl)isobenzofuran (**12**) in the next sequence. We made use of Martin's observation[17] that LTMP and Me_3SiCl are at least moderately compatible (slow to react with each other), by adding a solution of LTMP (4 equiv) to an ice bath cooled ethereal solution of **1** and Me_3SiCl (6 equiv). After stirring for 3 h, *tert*-butyl alcohol was added to destroy residual LTMP.[18] The strong base sensitive dienophile *N*-methylmaleimide (NMM) was then added, and the mixture was stirred overnight at room temperature. Chromatography returned ca. 5% of **1** (>95% cis) and 70% of the cycloadduct **18**.



This product appeared to be a single stereoisomer, and its endo structure was confirmed by protiodesilylation to give **19**, which exhibits a bridgehead proton doublet characteristic of this stereochemistry.[19]

One other generalization is worth making about these base-induced reactions. When the elimination step is relatively slow, such as for reactions of **1** in ether solvent, yields from otherwise rational procedures tend to be low. The same process with the more reactive ortho ester (e.g. **3** or **15**) will give good yields provided that the 1-alkoxy-3-lithioisobenzofuran is not allowed to stand for prolonged periods. It appears that these lithiated species decompose fairly rapidly at ambient temperature. Therefore, one may either use the ortho ester to avoid the longer time required for elimination of **1** or employ the in situ electrophile approach described in connection with eq 10 to avoid the

(17) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.
(18) Reaction with LiO-*t*-Bu may be prevented by the limited solubility of this material.
(19) For unknown reasons, *N*-methylmaleimide reacts with various isobenzofurans with high endo selectivity,[15] unlike *N*-phenylmaleimide or maleic anhydride.

decomposition of materials such as 11. The synthetic utility of isobenzofurans in general and alkoxyisobenzofurans in particular is significantly enhanced by the ability to generate moderately concentrated solutions of these materials, since the successful application of many kinetically second-order processes, e.g., Diels–Alder reactions, is dependent on this variable. Thus the base-induced 1,4-elimination methodology offers a potentially viable alternative to failed or unsatisfactory acid-catalyzed reactions of acetal or ortho ester isobenzofuran precursors.

Experimental Section

General. All reactions were carried out in oven-dried glassware under an inert atmosphere. NMR spectra were recorded in $CDCl_3$ at 300 MHz unless otherwise stated. Solvent purification methods and instruments used in this work have been described previously.[15] Compounds 3,[3] 4,[20] and 15[4] have been described previously. Combustion analyses were performed by MicAnal, Tucson, AZ.

1,3-Dihydro-1,3-dimethoxyisobenzofuran (1). A mixture of 8.5 g (63.4 mmol) of *o*-phthalaldehyde (Aldrich Chemical Co.), 150 mL of methanol, and 0.5 mL of trifluoroacetic acid was stirred at room temperature for 24 h. It was then neutralized by pouring into a 10% Na_2CO_3 solution. The product was extracted into CH_2Cl_2 (3 × 50 mL), and the combined organic phase was washed with brine, dried over K_2CO_3, and rotary evaporated. A stainless steel spinning band column was used to obtain 8.4 g (74%) of 1, bp 74 °C (0.75 torr), with a ratio of 1c/1t = 65/35 (see text): ^1H NMR (proton counts refer to the individual isomer where this distinction could be made) δ 3.39 (s, 6 H, methoxy groups of 1t), 3.41 (s, 6 H, methoxy groups of 1c), 6.04 (s, 2 H, benzylic of major isomer 1c), 6.31 (s, 2 H, benzylic of minor isomer 1t), and 7.38 ppm (br s, 4 H for both isomers); MS calcd for $C_{10}H_{11}O_3$ (P – H) 179.0708, found 179.0703. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.63; H, 6.81.

The pot residue from distillation was examined and appeared to be nearly pure 1,2-bis(dimethoxymethyl)benzene (the open bis acetal of *o*-phthalaldehyde) as judged by ^1H NMR δ 3.30 (s, 12 H), 5.65 (s, 2 H), and 7.35 (s, 4 H) and MS (calcd for $C_{11}H_{15}O_3$ (P – OCH_3) 195.1021, found 195.1015).

Isolation of 95% Purity 1c. To an ice bath cooled solution of 1 (2.0 g, 11 mmol, cis/trans = 65/35) and diisopropylamine (0.8 mL, 5.7 mmol) in 45 mL of ether was added 12 mmol of MeLi in ether. This mixture was stirred for 1 h, at which time direct examination by ^1H NMR indicated loss of essentially all of the trans isomer 1t. Workup involved washing with aqueous bicarbonate solution, drying over K_2CO_3, and vacuum distillation; this gave 837 mg (44%) of material with bp 65 °C (0.5 torr), which by NMR integration consisted of 1c/1t in a ratio of 95/5.

1,3-Diethoxy-1,3-dihydroisobenzofuran.[22] A sample of 1 (312 mg, 1.73 mmol) in 10 mL of absolute ethanol containing a drop of trifluoroacetic acid was stirred at room temperature for 22 h. Isolation as described above for 1 gave crude bis acetal, in a cis/trans ratio of 62/38 (by NMR integration, with assignments based on analogy with 1): ^1H NMR (60 MHz) δ 1.25 (two t, 6 H), 3.7 (m, 4 H), 6.12 (s, 2 H of cis isomer), 6.37 (s, 2 H of trans isomer), and 7.44 ppm (s, 4 H).

1,3-Di-2-propoxy-1,3-dihydroisobenzofuran. A mixture of 0.9 g (6.7 mmol) of *o*-phthalaldehyde, 30 mL of isopropyl alcohol, and 0.3 mL of trifluoroacetic acid was stirred at room temperature for 36 h. Workup as above (with ether extraction) and distillation gave 1.1 g (69%) of product, bp 90 °C (1.0 torr): ^1H NMR δ 1.22 (d, 6 H in trans isomer, J = 6 Hz), 1.28 (d, 6 H in cis isomer, J = 6 Hz), 4.08 (m, 2 H for both isomers), 6.14 (s, 2 H for cis isomer), 6.41 (s, 2 H for trans isomer), and 7.3 ppm (br s, 4 H for both isomers; MS calcd for $C_{14}H_{19}O_3$ (P – H) 235.1334, found 235.1350. The stereochemical assignments are based on analogy to the NMR features of 1; the cis/trans ratio, by integration of the singlets at 6.14 and 6.41 ppm, was 62/38.

Reaction of 1 with Maleic Anhydride. A mixture of 263 mg (1.46 mmol) of 1 and 160 mg (1.63 mmol) of maleic anhydride in 4 mL of *o*-chlorotoluene was refluxed for 43 h. Vacuum evaporation of the solvent followed by recrystallization from toluene/petroleum ether gave 167 mg (51%) of 6, mp 195–196 °C. The mp and NMR spectrum are identical with those of material described previously.[3]

Acid-Catalyzed Reaction of 1 with DMAD. A solution of 338 mg (1.87 mmol) of 1, 250 μL of DMAD (2.03 mmol), and 32 mg (0.19 mmol) of mesitoic acid in 6 mL of *o*-chlorotoluene was refluxed for 100 h. The solvent was removed in vacuo, and a weighed amount of phthalide was added to the residue to serve as a quantitative internal standard for NMR analysis. Identification of 7 (19%) rests on the very characteristic NMR features of this material,[3] particularly the phenolic proton absorption at 11.8 ppm, and three equal area closely spaced methoxy signals. The crude product also contained starting material 1 and a small amount of *o*-phthalaldehyde.

Conversion of 1 to 3. A solution of 463 mg (2.57 mmol) of 1c/1t (65/35) and 70 μL (0.5 mmol) of diisopropylamine in 10 mL of freshly distilled anhydrous THF was cooled in a dry ice/acetone bath. *n*-Butyllithium in hexane (3.8 mL, 5.7 mmol) was added dropwise by syringe. After stirring for 1.5 h, 2 mL of methanol was added (change from orange to colorless); the bath was removed, and stirring was continued for 17 h. The solvent was removed by rotary evaporation, and the residue was taken up in ether and pH 7 buffer. After drying (Na_2SO_4), evaporation gave 460 mg of an oil, which by NMR consisted of 1 and 3 in a ratio of 75/25. The ratio of 1c/1t was identical with that of the starting material. The addition of a small amount of authentic 3[3] to this mixture caused enhancement of the peaks attributed to this material.

LDA-Induced Reaction of 1 with Norbornene; Formation of 9 + 10. An LDA solution was prepared (ice bath) by addition of 5.2 mL of 1.4 M *n*-butyllithium to 0.9 mL of the amine. Additional hexane (5 mL) was added, and this clear solution was drawn into a syringe. It was added via syringe pump (2.5 mL/h) to a refluxing mixture of 1 (533 mg, 2.97 mmol, 1c/1t = 65/35), 5.0 g of norbornene, and 15 mL of hexane. After addition was completed, the cooled mixture was taken up in ether and 5% sodium bicarbonate solution. The usual washing, drying, and evaporation to constant weight gave an oily residue to which weighed phthalide was added as a quantitative standard. Yields of 58% and 66% in two separate experiments were determined by comparison of the phthalide 5.3-ppm integral with those of both 9 and 10 at 5.0 ppm. The identity of these products rests on their characteristic upfield absorptions, as described in earlier work from this laboratory.[3]

9,10-Dihydro-9,10-epoxy-9-methoxy-10-(trimethylsilyl)-anthracene (13). A solution of 1 (453 mg, 2.51 mmol) and 35 μL (0.25 mmol) of diisopropylamine in 10 mL of THF was cooled in a dry ice/acetone bath. *n*-Butyllithium (5.5 mmol, 3.8 mL of hexane solution) was added, and the solution was stirred for 15 h with the bath maintained. To this cold mixture was added a solution of 0.8 mL of Me_3SiCl in 3 mL of THF, and the bath was then removed. After 45 min, an aliquot was removed and examined by NMR, which showed changes in the aromatic region consistent with the loss of starting material and the formation of 1-methoxy-3-(trimethylsily)isobenzofuran (12): ^1H NMR (THF) δ 6.4–6.8 (m, 2 H), 7.0 (d, 1 H), and 7.2 ppm (d, 1 H); the chemical shift values are approximate, based on the observation that the approximate singlet for the aromatic protons of 1 appears at essentially the same position in ether, THF, and $CDCl_3$ solvents.

To this mixture was added 0.79 mL (7.53 mmol) of bromobenzene, followed by a solution of LTMP (3.76 mmol), which had been prepared separately by addition of *n*-butyllithium (in hexane, 2.5 mL) to an ice-cooled mixture of 2,2,6,6-tetramethylpiperidine in 5 mL of THF. The resulting mixture was stirred for 2 h at 0 °C and then 15 h at room temperature. It was then taken up in 200 mL of ether and washed four times with 20-mL portions of cold pH 7 buffer. After drying (K_2CO_3) and evaporation, chromatography on silica gel with 10% ether/hexanes containing 1% of triethylamine gave 81% (600 mg) of 13 as a colorless solid. Recrystallization from petroleum ether gave pure 13: mp 132–133 °C; ^1H NMR δ 0.39 (s, 9 H), 3.79 (s, 3 H), and 6.9–7.4 ppm (m, 8 H); MS calcd and found for $C_{18}H_{20}O_2Si$, 296.1232. Anal. Calcd:

(20) We prefer to prepare 4 by formation of the ethyl analogue[21] followed by trans-acetalization in methanol.

(21) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1982**, *47*, 5391.

(22) Powell, M. R.; Rexford, D. R. *J. Org. Chem.* **1953**, *18*, 810.

C, 72.93; H, 6.80. Found: C, 73.01; H, 6.85.

9,10-Dihydro-9,10-epoxy-9-methoxyanthracene (14). An ice-cooled solution of **13** (300 mg, 1.01 mmol) in 10 mL of THF was treated with 1.1 mmol of TBAF (1.1 mL of 1.0 M in THF). After being stirred for 10 h, the solution was taken up in 100 mL of ether, washed several times with brine, dried, and rotary evaporated to give a quantitative yield of crude but essentially pure **14**, as an oil: ^{1}H NMR δ 3.80 (s, 3 H), 5.97 (s, 1 H), and 6.9–7.4 ppm (m, 8 H); MS calcd for $C_{15}H_{12}O_2$ 224.0837, found 224.0844. No effort was made to purify this product further, because it and related materials (including **13**) were found to be susceptible to air oxidation to anthraquinone.

9,10-Dihydro-9,10-epoxy-9-ethoxy-10-(trimethylsilyl)-anthracene (16). To an ice-bath-cooled solution of 380 mg (1.83 mmol) of **15** and 30 μL (0.21 mmol) of diisopropylamine in 10 mL of THF was added 3.2 mL (4.75 mmol) of *n*-butyllithium in hexane. After 1 h, direct examination of the dark reaction mixture by NMR indicated that all of the **15** had been consumed. A solution of Me_3SiCl (630 μL, 5 mmol) in 3 mL of THF was added dropwise, followed by bromobenzene (0.65 mL, 6.2 mmol) and LTMP (3.1 mmol). The ice bath was removed, and the mixture was stirred for 14 h at room temperature. Workup and chromatographic isolation as described for **13** gave 505 mg (89%) of **16** as an oil: ^{1}H NMR δ 0.39 (s, 9 H), 1.42 (t, 3 H, J = 7 Hz), 4.07 (q, 2 H, J = 7 Hz), and 6.9–7.3 ppm (m, 8 H); MS (chemically induced, methane flow gas) calcd for $C_{19}H_{22}O_2Si$ 310.1388, found 310.1389. In a repetition of this experiment **16** was obtained as a solid, mp 104–106 °C. Anal. Calcd: C, 73.50; H, 7.14. Found: C, 73.84; H, 7.21.

9,10-Dihydro-9,10-epoxy-9-ethoxyanthracene (17). A mixture of 500 mg of **16** (1.6 mmol) and 1.7 mmol of TBAF in 10 mL of THF at 0 °C was stirred for 12 h. Workup as before gave 380 mg (ca. 100%) of essentially pure **17** (oil): ^{1}H NMR δ 1.45 (t, 3 H, J = 7 Hz), 4.10 (q, 2 H, J = 7 Hz), 5.95 (s, 1 H), and 6.9–7.4 ppm (m, 5 H); MS calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0988.

An attempt to chromatograph this product on silica gel with ether/hexanes (1/5) containing 1% triethylamine caused decomposition, with the slow elution of a yellow solid which proved (mp, NMR, MS) to be anthraquinone. The exact mechanism for this oxidation is not known. Other samples of **16** and **17**, on standing exposed to air, have also been observed to oxidize.

4,9-Epoxy-4-methoxy-2-methyl-3a,4,9,9a-tetrahydro-9-(trimethylsilyl)-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (18). To an ice-bath-cooled mixture of 1 (380 mg, 2.1 mmol) and Me_3SiCl (1.8 mL, 13.8 mmol) in 13 mL of ether was added 8.3 mmol of LTMP (prepared by addition of *n*-butyllithium in hexane to the amine in 5 mL of ether, with ice bath cooling). The mixture was stirred for 3 h and then 2.0 mL of *tert*-butyl alcohol was added, followed after 0.5 h by *N*-methylmaleimide (300 mg, 2.6 mmol), with stirring continued overnight. The volatiles were removed by rotary evaporation; the residue was taken up in CH_2Cl_2 (150 mL) and washed with 5% aqueous sodium bicarbonate solution (3 × 20 mL). After drying (K_2CO_3) and evaporation, the residue was chromatographed on 40 g of silica gel using ether/hexanes (1/3) with 1% triethylamine. An early fraction (35 mg) contained (by NMR) essentially pure **1c** contaminated by **18**. Subsequent fractions afforded 483 mg (70%) of crystalline **18**: mp 131–132 °C; ^{1}H NMR δ 0.36 (s, 9 H), 2.24 (s, 3 H), 3.53 (d, 1 H, J = 8 Hz, methine proton adjacent to methoxy), 3.68 (s, 3 H), 3.74 (d, 1 H, J = 8 Hz, methine adjacent to trimethylsilyl group), and 7.1–7.3 ppm (m, 4 H); MS calcd for $C_{17}H_{21}NO_4Si$ 331.1239, found 331.1225. Anal. Calcd: C, 61.61; H, 6.39. Found: C, 61.71; H, 6.33.

4,9-Epoxy-4-methoxy-2-methyl-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (19). A sample of **18** (158 mg, 0.47 mmol) in 5 mL of THF at 0 °C was treated with 0.52 mmol of TBAF. The reaction was complete (TLC) within 0.5 h. Excess ether was added and the organic phase was washed several times with brine, then dried over K_2CO_3, and rotary evaporated to give 119 mg (95%) of nearly pure **19**. Recrystallization from hexane/CH_2Cl_2 gave pure **19**: mp 115–116 °C; ^{1}H NMR δ 2.27 (s, 3 H), 3.57 (d, 1 H, J = 8 Hz), 3.70 (s, 3 H), 3.92 (dd, 1 H, J = 8 and 6 Hz), 5.57 (d, 1 H, J = 6 Hz), and 7.2 ppm (br s, 4 H); MS calcd for $C_{14}H_{13}NO_4$ 259.0844, found 259.0848.

The evidence that this is the endo isomer rests on the bridgehead proton signal at 5.57 ppm appearing as a doublet. A small amount of the exo isomer may have been present in the crude product, but the Diels–Alder reaction to form **18** appears to be >95% endo selective.

Acknowledgment. We thank John Gregson for his early work on the preparation and characterization of **1**, Dan Pollart for carrying out a preparation of **16**, Dr. Hugh Webb for obtaining MS data, and Curt Breneman for his indispensible assistance with NOE experiments. Acknowledgment is made to the donors of Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Regioselectivity of Alkoxyisobenzofuran–Aryne Cycloadditions

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Received September 26, 1986

The cycloaddition reactions of some unsymmetrical arynes with 1-ethoxy-3-(trimethylsilyl)isobenzofuran and a naphtho[1,2-*c*]furan analogue were examined for prospective regioselectivity. The arynes, generated by lithium tetramethylpiperidide induced dehydrohalogenation of the appropriate haloaromatics, were 3-bromo-, 3-chloro-, 3-methoxy-, and 3-methylbenzyne, 3,4-pyridyne, and 1,2-naphthalyne. Regioselectivities ranged from nil (50/50 isomer ratio with 3,4-pyridyne) to modest (ca. 80/20). The products are bridgehead trimethylsilylated ketals, which undergo a novel acid-catalyzed rearrangement to 9-alkoxy-10-[(trimethylsilyl)oxy]anthracenes. These position-differentiated anthracenediol analogues are thought to be formed by ring opening, followed by Brook rearrangement. Isomeric ketal pairs were found to react at different rates, and this selective decomposition was used to isolate one of the cycloadduct isomers from the reaction of 3-bromobenzyne. Lithium–bromine exchange followed by methylation was used to determine its structure, and this information in turn was used to clarify the mechanism of the acid-catalyzed reaction.

The question of selectivity in Diels–Alder reactions of substituted benzynes (arynes) has evoked interest since shortly after the recognition of these reactive intermediates. Various schemes have been employed to explore this matter. For example, the identical ratio of A ring/B ring cycloadducts produced when 1,4-dimethoxyanthracene was treated with benzyne generated in six different ways was used to argue that all six methods gave the same inter-

0022-3263/87/1952-0792$01.50/0