(c 0.47, EtOH); optical purity 59%. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.18; H, 7.46. (b) (-)-Alcohol **3A**: 30 mg (31% yield); mp 166-167 °C; $[\alpha]^{23}_D$ -122.4° (c 0.465, EtOH); optical purity 81%. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.21; H, 8.58.

Oxidation of 3A with HLADH-NAD$^+$-FMN. The racemic alcohol **3A**[17] (mp 155-160 °C; 101.5 mg, 0.63 mmol), NAD$^+$ (42.7 mg, 0.063 mmol), and FMN (620 mg, 1.25 mmol) were dissolved in 1000 mL of the glycine-NaOH buffer solution. The reaction was initiated by adding HLADH (8 mg) and was allowed to proceed at 20 °C. The GLC monitoring of the process showed 32% oxidation of the substrate alcohol after 52 h of incubation. The reaction was terminated, and workup of the metabolite mixture gave the following materials. (a) (-)-Ketone **3K**: 18 mg (18% yield); mp 162-163 °C; $[\alpha]^{21}_D$ -55.3° (c 0.33, EtOH); optical purity 63%. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.12; H, 7.65. (b) (+)-Alcohol **3A**: 55 mg (54% yield); mp 166-168 °C; $[\alpha]^{21}_D$ +34.6° (c 0.50, EtOH); optical purity 23%. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.41; H, 8.71.

4-C_2-Methanoditwistanone (4K) and 4-C_2-Methanoditwistanol (4A). Reduction of 4K with HLADH-NADH. The racemic ketone **4K**[14] (mp 111-113 °C; 70.0 mg, 0.37 mmol) dissolved in 700 mL of the Sørensen buffer solution was treated with NADH (286 mg, 0.38 mmol) and HLADH (16 mg) at 22 °C. After 70 h when GLC monitoring indicated 43% reduction of the starting material, the incubation was terminated, and workup of the mixture afforded the following metabolites. (a) (+)-4-C_2-Methanoditwistanone (**4K**):[18] 29.4 mg (42% yield); mp 116-118 °C; $[\alpha]^{22}_D$ +206.4° (c 0.265, EtOH); optical purity 81%; CD (c 5.3 × 10^{-4} M, isooctane) $[\Theta]_{291}$ -7.64 × 10^3. Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.96; H, 8.59. (b) (-)-4-C_2-Methanoditwistanol (**4A**):[18] 24.5 mg (35% yield); mp 112-113 °C; $[\alpha]^{22}_D$ -362.4° (c 0.21, EtOH); optical purity 96%. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.07; H, 9.60.

Oxidation of 4A with HLADH-NAD$^+$-FMN. The racemic alcohol **4A**[12] (mp 101-102 °C; 50.6 mg, 0.265 mmol), NAD$^+$ (18.7 mg, 0.0274 mmol), and FMN (272 mg, 0.55 mmol) were dissolved in 600 mL of the glycine-NaOH buffer solution. HLADH (9.7 mg) was added, and the reaction was allowed to proceed at 25 °C until GLC monitoring indicated 40% oxidation of the substrate alcohol (96 h). Workup of the metabolite mixture gave the following materials. (a) (-)-Ketone **4K**: 17 mg (34% yield); mp 111-112.5 °C; $[\alpha]^{27}_D$ -260° (c 0.10, EtOH); optical purity 100%. Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.91; H, 8.54. (b) (+)-Alcohol **4A**: 23 mg (46% yield); mp 111-112.5 °C; $[\alpha]^{27}_D$ +289° (c 0.155, EtOH); optical purity 76%. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.11; H, 9.52.

(18) For the absolute configuration and the absolute rotation of 4-C_2-methanoditwistanone (**4K**) and the corresponding alcohol (**4A**), see ref 12.

Acknowledgment. This research was partially supported by grants from the Ministry of Education, Japan (449015), Yamada Science Foundation, and Suntory Institute for Bioorganic Research to which the authors' thanks are due.

Registry No. (±)-**1A**, 77341-13-0; (-)-(*M*)-**1A**, 71806-64-9; (+)-(*P*)-**1A**, 77341-14-1; (±)-**1K**, 71806-62-7; (+)-(*M*)-**1K**, 71806-63-8; (-)-(*P*)-**1K**, 61826-77-5; (±)-**2A**, 77341-15-2; (-)-(*M*)-**2A**, 77341-16-3; (+)-(*P*)-**2A**, 57287-42-0; (±)-**2K**, 69056-10-6; (-)-(*M*)-**2K**, 69056-11-7; (+)-(*P*)-**2K**, 57287-43-1; (±)-**3A**, 77341-17-4; (-)-(*M*)-**3A**, 61393-99-5; (+)-(*P*)-**3A**, 61473-81-2; (±)-**3K**, 66007-14-5; (-)-(*M*)-**3K**, 61473-76-5; (+)-(*P*)-**3K**, 61473-82-3; (±)-**4A**, 77122-78-2; (-)-(*M*)-**4A**, 77122-79-3; (+)-(*P*)-**4A**, 77079-53-9; (±)-**4K**, 77079-54-0; (-)-(*M*)-**4K**, 77122-07-7; (+)-(*P*)-**4K**, 77341-18-5; (±)-**5A**, 77341-19-6; (±)-**5K**, 71806-61-6; (±)-**6K**, 69009-72-9; (±)-**8A**, 77341-20-9; (±)-**8K**, 73679-80-8.

Metalation of *o*-Halostyrene Oxides. Preparation of Benzocyclobutenols

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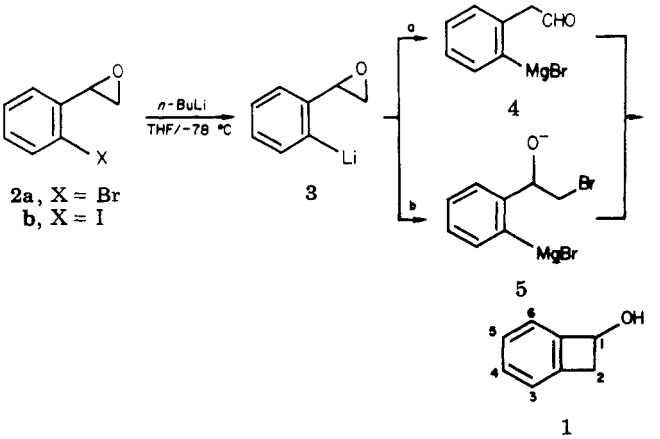
Received October 21, 1980

o-Bromo- and *o*-iodostyrene oxides are converted in fair to good yield to benzocyclobutenols upon treatment with *n*-BuLi and $MgBr_2$ in THF or ether at -78 °C, followed by warming to room temperature. The reaction involves initial halogen-lithium exchange followed either by $MgBr_2$-initiated opening of the epoxide function to a haloalkoxide or rearrangement of the epoxide function to a ketone or aldehyde followed by cyclization. Benzocyclobutenol formation was not successful in the case of *o*-halostilbene oxides.

We recently reported a new route to benzocyclobutenol (**1**) based on *o*-bromo- or *o*-iodostyrene oxide **2** as starting material.[1] This interconversion involved a halogen-lithium exchange between **2** and *n*-butyllithium in THF at -78 °C to generate the lithiated epoxide **3**, followed by either a $MgBr_2$-mediated rearrangement to the metalated phenylacetaldehyde **4** or an opening to the bromoalkoxide **5**, and subsequent cyclization (Scheme I). Several other *o*-halostyrene oxides were also converted into benzocyclobutenols. In some examples, including the conversion of **2** to **1**, both mechanistic pathways occurred simultaneously while in others the rearrangement route was dominant.

Scheme I



Benzocyclobutenes in general[2,3] and benzocyclobutenols (the Chemical Abstracts nomenclature for benzocyclobutenol is bicyclo[4.2.0]octa-1,3,5-trien-7-ol; for convenience the benzocyclobutenol nomenclature together with the numbering shown in structure **1** has been adopted) in particular[4] have been shown to be valuable intermediates

(1) K. L. Dhawan, B. D. Gowland, and T. Durst, *J. Org. Chem.*, **45**, 922 (1980).
(2) W. Oppolzer, *Synthesis*, 793 (1978).
(3) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, H. Matsumoto, and K. Fukumoto, *J. Am. Chem. Soc.*, **99**, 3461 (1977); T. Kametani, H. Matsumoto, H. Nemoto, and K. Fukumoto, *ibid.*, **100**, 6218 (1978).

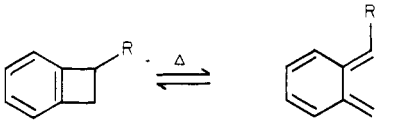
0022-3263/81/1946-2730$01.25/0

Table I. Preparation and Reaction of *o*-Halostyrene Oxides

starting epoxide	prep eq no.	yield, %	product	yield, %
2-bromostyrene oxide	1	82	benzocyclobutanol	83
2-iodostyrene oxide	1	87	benzocyclobutanol	85
2-bromo-α-methylstyrene oxide	1	53	2-methylbenzocyclobutanol	40[a]
2-bromo-*cis*-β-methylstyrene oxide	3	78	2-methylbenzocyclobutanol + 1 methylbenzocyclobutanol	50[c]
2-bromo-*trans*-β-methylstyrene oxide	2	60	1-methylbenzocyclobutanol	35
2-iodo-*trans*-β-methylstyrene oxide	2	73	1-methylbenzocyclobutanol	34
2-bromo-*trans*-β-benzylstyrene oxide	2	57	1-benzylbenzocyclobutanol	40[c]
2-iodo-5-methoxystyrene oxide	1	78	4-methoxybenzocyclobutanol	76
2-bromo-4,5-(methylenedioxy)styrene oxide	1	82	4,5-(methylenedioxy)benzocyclobutanol	75
2-bromo-*trans*-stilbene oxide	1	67	*trans*-stilbene oxide	>70[d]
2-iodo-*trans*-stilbene oxide	2	41	benzyl phenyl ketone	>87[e]

[a] 4:1 trans/cis mixture. [b] 1:1 mixture. [c] Accompanied by 40% of dibenzyl ketone. [d] Reaction in THF. [e] Reaction in ether.

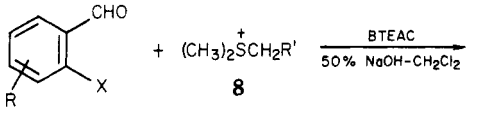
in natural product syntheses since both undergo ring opening to the reactive *o*-quinodimethanes **6** which readily undergo both inter- and intramolecular Diels–Alder reactions. Furthermore, the hydroxyl group in benzocyclobutenols may serve as a valuable entry to other benzocyclobutenones and further transformations thereof or be converted to a leaving group and subsequently displaced by a variety of nucleophiles.



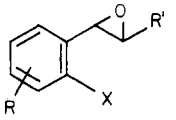
6, R = alkyl or OH

We have therefore investigated the scope of the reactions outlined in Scheme I as a viable route to various benzocyclobutenols and report herein our results.

Preparation of Epoxides. The epoxides used in this study were prepared by the reaction of sulfur ylides, generated from the corresponding sulfonium salts under phase-transfer conditions, with the appropriate carbonyl compound.[5] The combinations of sulfonium salt and carbonyl compound which were most often used are given in eq 1 and 2.

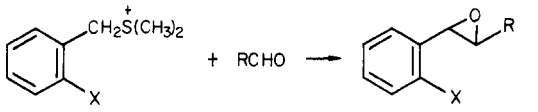


7 **8**



(1)

9, R′ = H or aryl; R = H, OMe, 3,4-OCH_2O

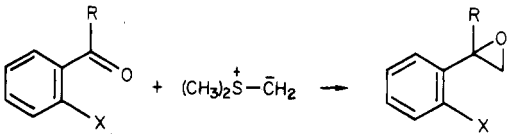


(2)

9, R = alkyl

The reagents shown in eq 1 were most useful in preparing the styrene oxides **9** (R′ = H) or stilbene oxides (R′ = aryl), while the combination shown in eq 2 was used for the preparation of the β-alkylstyrene oxides **9** (R = alkyl). In these reactions, the epoxides were obtained almost exclusively as the trans isomers as determined by the small 1.5–2.0-Hz vicinal epoxide coupling constant in the ^1H NMR spectra.[5]

The α-substituted styrene oxides **10** were prepared according to eq 3, while the *cis*-β-methyl derivative **11** was prepared by epoxidation of the corresponding alkene (eq 4).



(3)

10a, R = CH_3
b, R = C_6H_5

(4)

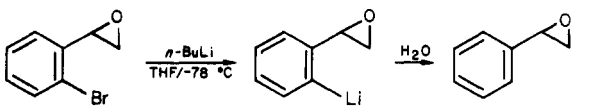
11

Formation of Benzocyclobutanols. Reactions of *o*-bromo- and *o*-iodostyrene oxides were carried out in one of two ways.

Method A. A solution of the epoxide in THF at −78 °C containing 2 equiv of suspended $MgBr_2$[6] was treated with *n*-BuLi for about 10 min. The reaction mixture was then warmed to room temperature and quenched with aqueous NH_4Cl solution.

Method B. *n*-BuLi was added to the epoxide in THF or ether at −78 °C followed within 5 min by 2 equiv of $MgBr_2$.[6] The reaction was then continued as above. The results are recorded in the Table I.

As indicated in our preliminary paper, the first step in these reactions is halogen–metal exchange. This was verified in the case of the epoxide **2** by protonation at low temperature to yield styrene oxide (eq 5). Similarly both the *o*-bromo- and *o*-iodostyrene oxides **9** (X = Br or I, R = Ph) gave *trans*-stilbene oxide via the intermediacy of an ortho-metalated stilbene oxide (**9**, X = Li or MgBr).



(5)

2a **3a**

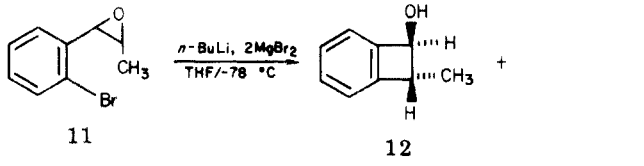
(4) B. J. Arnold, S. M. Mellows, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1266 (1973).

(5) A. Merz and G. Markl, *Angew. Chem., Int. Ed. Engl.*, **12**, 845 (1973); Y. Yano, T. Okonogi, M. Sunaga, and W. Tagagi, *J. Chem. Soc.*, 527 (1973). The use of Cl^- rather than Br^- or I^- as the counterion of the sulfonium salt leads to greatly improved results.

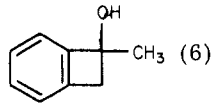
(6) $MgBr_2$ was prepared by reaction of Mg with 1,2-dibromoethane in ether. The lower layer of the two-phase system, 2.5 M in $MgBr_2$, was employed.

Both of the mechanisms for benzocyclobutenol formation shown in Scheme I are operative in some instances. For example, the conversion of **2a** to **4** in THF was shown by deuterium labeling in the β-position of the epoxide to occur via a 2:1 ratio of paths a and b.[1]

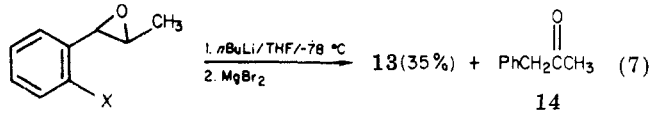
2-Bromo-*cis*-β-methylstyrene oxide (**11**) gave in 50% yield a 1:1 mixture of *trans*-2-methylbenzocyclobutanol (**12**) and 1-methylbenzocyclobutanol (**13**)[7] (eq 6). This



11 12



13

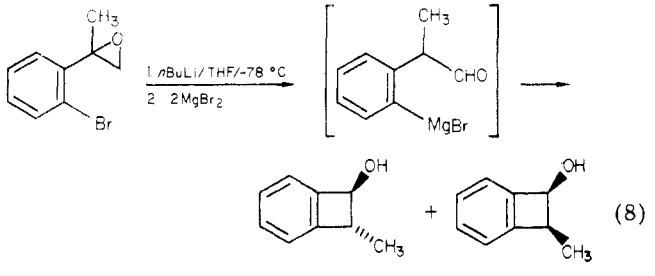


14

result is interpretable in terms of a 1:1 ratio of pathways a and b. In contrast, the *o*-iodo- and *o*-bromo-*trans*-β-methyl derivatives **9** (X = Br, or I, R = CH_3) reacted only via the rearrangement route, affording **13** in a 35% isolated yield. In addition to **13**, a small amount of phenylacetone (**14**), but no **12**, was detected in the NMR spectrum of the crude product. The ketone is presumably formed via an intramolecular enolization of the ortho-metalated phenylacetone followed by subsequent quenching (see eq 7).

Epoxide **9** (X = Br, R = CH_2Ph) behaved similarly and afforded a 1:1 mixture of 1-benzylbenzocyclobutenol (**15**) and dibenzyl ketone (**16**, Scheme II). Intramolecular enolization is apparently more important in this example due to incresed acidity of the benzylic hydrogens in structure **17**.

Not unexpectedly, the α-methyl derivative **10a** reacted exclusively via the rearrangment pathway a and afforded in 40% yield a 4:1 mixture of *trans*- and *cis*-2-methylbenzocyclobutenols (**12** and **18**, eq 8).

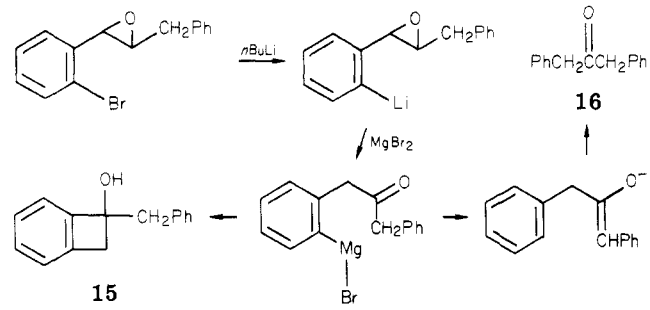


12 18

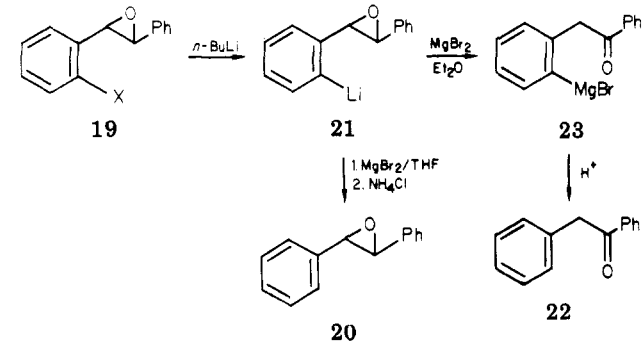
In contrast, no benzocyclobutanol could be obtained from *o*-bromo- or *o*-iodostilbene oxide **19**. When the halogen–metal exchange was carried out in THF at −78 °C followed by $MgBr_2$ addition, warming to 0 °C, and quenching with aqueous NH_4Cl, *trans*-stilbene oxide **20** was obtained in greater than 90% yield (Scheme III). The reluctance of the metalated intermediate **21** to undergo either rearrangement or ring opening of the epoxide is quite surprising. When the solvent was changed from THF to the less basic diethyl ether, benzyl phenyl ketone **22** was obtained in >80% yield, signifying that rearrangement to

(7) L. Horner, P. V. Subramanian, and K. Eibers, *Justus Liebigs Ann. Chem.*, 714, 91 (1968).

Scheme II

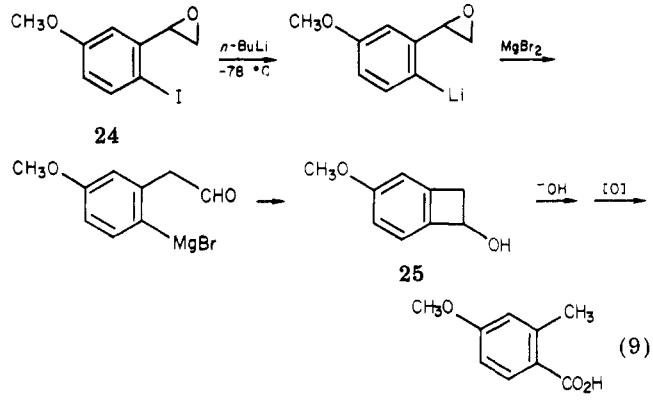


Scheme III



23 had taken place. Cyclization of **23** appears to be unfavorable, and enolization, eventually resulting in the formation of **22**, predominates. Traces of **22** in addition to **20** were also obtained in THF when 4 equiv of $MgBr_2$ was employed.

2-Iodo-5-methoxystyrene oxide (**24**) reacted exclusively via the rearrangement route (eq 9), either in ether or in



THF, to afford 4-methoxybenzocyclobutene (**25**; mp 39–42 °C, 76% yield). Benzocyclobutenol **25**, whose structure proof was reported earlier (see also Experimental Section), should be convertable into 11-oxoestrone by use of methodology stimilar to that of Kametani's estrone methyl ether synthesis.[2a] 2-Bromo-4,5-(methylenedioxy)styrene oxide gave in 75% yield 4,5-(methylenedioxy)benzocyclobutenol, mp 118–120 °C.

Experimental Section

General Methods. NMR spectra were taken on Varian HA-100, T-60, and FT-80 spectrometers in $CDCl_3$ solution with Me_4Si as an internal standard. Infrared spectra were obtained, neat for liquids and as $CHCl_3$ solutions for solids, on a Beckman IR-20A instrument. Melting points (Gallenkamp apparatus) are uncorrected. A typical workup refers to partitioning the reaction products between water and CH_2Cl_2, drying the CH_2Cl_2 layer, and evaporating the solvent. Yields, unless otherwise specified, refer

to isolated yields of chromatographically pure products. The intermediate halo epoxides were generally not analyzed. Their structures followed from the method of synthesis and their NMR spectra.

Preparation of Sulfonium Salts. Trimethylsulfonium chloride was a gift.[8] The corresponding iodide was obtained from Aldrich Chemical Co. The remaining sulfonium salts were prepared as aqueous solutions by heating the corresponding halide with dimethyl sulfide in water. The preparation of benzyldimethylsulfonium chloride is illustrative. Benzyl chloride (63 g, 0.5 mol), dimethyl sulfide (37 g, 0.6 mol), and water (40 mL) were heated to reflux for about 2 h or until essentially one phase had formed. The cooled solution was extracted twice with 25 mL of ether to remove the excess dimethyl sulfide, unreacted benzyl chloride, and any nonsalt products. The aqueous portion was stirred and evacuated by using an aspirator to remove the remaining ether. The salt concentration in the somewhat viscous solution (120 g) was estimated by NMR to be 69%. The yield of benzyldimethylsulfonium chloride was 88%. The solution can be stored at room temperature and is indefinitely stable.

(o-Iodobenzyl)dimethylsulfonium bromide was prepared by heating 23.0 g of o-iodobenzyl bromide, 9 mL of dimethyl sulfide, and 10 mL of H_2O overnight. (o-Bromobenzyl)dimethylsulfonium bromide was similarly prepared.

Epoxidation of Aromatic Aldehydes. General Procedure. 2-Bromostyrene Oxide. 2-Bromobenzaldehyde (Aldrich; 25 g, 0.135 mol), trimethylsulfonium chloride[8] (18.4 g), and 1.25 g of benzyltriethylammonium chloride were suspended in 125 mL of CH_2Cl_2. The solution was stirred and cooled in an ice bath, and 125 mL of 50% NaOH was added dropwise. After the addition was completed, the reddish reaction mixture was allowed to warm to room temperature, stirred for a further 1 h, diluted with 100 mL of water, and extracted three times with 50 mL of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, the solvent was evaporated, and the crude red liquid (26 g) was distilled under vacuum. The yield of 2-bromostyrene oxide was 22 g (82%): clear liquid; bp 94–96 °C (1.3 mm); NMR δ 2.65 (dd, J = 3, 6 Hz, 1 H), 3.20 (dd, J = 4, 6 Hz, 1 H), 4.17 (dd, J = 3, 4 Hz, 1 H), 7.0–7.7 (m, 4 H).

2-Bromo-β,β-dideuteriostyrene Oxide. This compound was prepared in 80% yield by addition of 1.2 g (0.01 mol) of $(CH_3)_3S^+Cl^-$ to a solution prepared from 4.6 g of Na and 18 mL of D_2O. To this solution were added 0.2 g of benzyltriethylammonium chloride and 1.6 g (0.0088 mol) of o-bromobenzaldehyde. The mixture was stirred for 1 h and worked up as usual. The NMR spectrum of the product showed 1.8 atoms of D/molecule at the indicated position.

2-Iodostyrene Oxide. From 20 g (0.086 mol) of 2-iodobenzaldehyde, 0.094 mol of triethylsulfonium chloride, and 1 g of benzyltriethylammonium chloride was obtained 18.5 g (87%) of 2-iodostyrene oxide: bp 90–91 °C (3 mm); NMR δ 2.62 (dd, J = 3, 6 Hz, 1 H), 3.17 (dd, J = 4, 6 Hz, 1 H), 4.00 (dd, J = 3, 6 Hz, 1 H), 6.9–7.5 (m, 3 H), 7.70 (d, J = 7 Hz, 1 H).

2-Iodo-5-methoxystyrene Oxide. 2-Iodo-5-methoxybenzaldehyde [mp 114–115 °C (ether/petroleum ether)] was obtained in 90% yield upon pyridinium chlorochromate oxidation of the corresponding benzyl alcohol [white needles, mp 66–67 °C (ether–petroleum ether)], which in turn had been prepared in 67% yield by iodination of 3-methoxybenzyl alcohol with CF_3CO_2Ag and I_2 in $CHCl_3$.[9]

Treatment of 3.0 g of 2-iodo-5-methoxybenzaldehyde (11.5 mmol) with 1.58 g of trimethylsulfonium chloride (12.7 mmol) under the above phase-transfer conditions afforded, after chromatography on silica gel (hexane–ethyl acetate, 4:1), 2.35 g (78%) of the title epoxide: NMR δ 2.54 (dd, J = 2, 6 Hz, 1 H), 3.06 (dd, J = 6, 4 Hz, 1 H), 3.90 (dd, J = 4, 2 Hz, 1 H), 6.4–6.8 (m, 2 H), 7.65 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_9H_{10}IO_2$: C, 39.15; H, 3.29. Found: C, 39.40; H, 3.17.

2-Bromo-4,5-(methylenedioxy)styrene Oxide. Treatment of 360 mg (1.5 mmol) of 2-bromo-4,5-(methylenedioxy)benzaldehyde[10] with 125 mg (1.6 mmol) of trimethylsulfonium chloride under the usual phase-transfer conditions gave 317 mg (82%) of 2-bromo-4,5-(methylenedioxy)styrene oxide as a clear oil: NMR δ 2.52 (dd, J = 6, 2 Hz, 1 H), 3.05 (dd, J = 6, 4 Hz, 1 H), 4.05 (1 H, dd, J = 4, 2 Hz, 1 H), 5.90 (s, 2 H), 6.60 (s, 1 H), 6.85 (s, 1 H); mass spectrum, m/e 243 (M^+). The compound was sufficiently pure for further use.

2-Bromo-*trans*-β-methylstyrene Oxide. An aqueous solution containing 1.5 mmol of (o-bromobenzyl)dimethylsulfonium bromide was mixed with 660 mg (1.5 mmol) of freshly distilled acetaldehyde and 400 mg of benzyltriethylammonium chloride dissolved in 25 mL of CH_2Cl_2. To this was added dropwise over 10 min 30 mL of 50% NaOH. The solution was stirred for 30 min and worked up. Distillation afforded a 60% yield of epoxide as a colorless liquid: bp 75–78 °C (1 mm); NMR δ 1.48 (d, J = 6.0 Hz, 3 H), 2.7–3.0 (qd, J = 6, 2 Hz, 1 H), 3.85 (d, J = 2.0 Hz), 6.9–7.7 (m, 4 H).

2-Iodo-*trans*-β-methylstyrene Oxide. This compound was prepared in 73% yield in a similar manner to the bromo derivative above. The epoxide, a yellowish oil, was not distilled but used directly as obtained: NMR δ 1.45 (d, J = 6 Hz, 3 H), 2.7–3.0 (qd, J = 6, 2 Hz, 1 H), 3.70 (d, J = 2.0 Hz, 1 H), 6.7–7.9 (m, 4 H).

2-Bromo-α-methylstyrene Oxide. Trimethylsulfonium iodide (2.04 g, 10 mmol) was added to 20 mL of dry THF containing 2.10 mmol of lithium diisopropylamide. The reaction mixture was cooled to −78 °C, 1.87 g (9.5 mmol) of 2-bromoacetophenone was added, and the mixture was then allowed to warm to room temperature. The usual workup gave 2.0 g of a brownish liquid which was purified by silica gel chromatography. The yield of colorless liquid was 1.1 g (56%): NMR δ 1.6 (s, 3 H), 2.73 (d, J = 5, 1 H), 2.93 (d, J = 5 H, 1 H), 7.0–7.6 (m, 4 H).

2-Bromo-*cis*-β-methylstyrene Oxide. 2-Bromo-*cis*-β-methylstyrene was prepared from 2-bromobenzaldehyde and ethylidinetriphenylphosphorane in dry THF at room temperature: NMR δ 1.7–1.85 (m, 3 H), 5.5–6.7 (m, 2 H), 6.85–7.7 (m, 4 H). The CH_3 signal indicated a mixture of isomers.

This material (2.2 g) was epoxidized with 40% peracetic acid in CH_2Cl_2 (overnight). The crude organic product was distilled to give 1.2 g (50%) of epoxide: bp 87–88 °C (0.3 mm); NMR δ 1.01 (d, J = 6 Hz, 3 H), 3.46 (m, 1 H), 4.12 (d, J = 4 Hz, 1 H), 7.0–7.7 (m, 4 H).

2-Bromo-*trans*-β-benzylstyrene Oxide. This epoxide was prepared in 57% yield as a clear liquid [bp 135–138 °C (0.02 mm)] from the reaction of 10 mmol of a 21% aqueous solution of (o-bromobenzyl)dimethylsulfonium bromide and 10 mmol of phenylacetaldehyde under the usual conditions: NMR δ 3.06 (br s, 3 H), 3.96 (br s, 1 H), 6.7–7.7 (m, 9 H).

2-Bromo-*trans*-stilbene Oxide. 2-Bromobenzaldehyde (3.70 g, 20 mmol) and 30 mmol of a 70% solution of benzyldimethylsulfonium chloride were reacted under the usual phase-transfer conditions to afford 6.5 g of crude organic product. This was fractionated to give methyl o-methylbenzyl sulfide [bp 75–80 °C (0.4 mm)] and 4.99 g (91%) of epoxide: bp 162–165 °C (0.4 mm); NMR δ 3.70 (d, J = 2.0 Hz, 1 H), 4.13 (d, J = 2.0 Hz, 1 H), 7.0–8.0 (m, 9 H).

2-Iodo-*trans*-stilbene Oxide. This compound was prepared in the same manner as the 2-bromo derivative above by using 7.0 g of crystalline (o-iodobenzyl)dimethylsulfonium bromide and 2.0 g of benzaldehyde: 41% yield; bp 147 °C (0.2 mm); NMR δ 3.70 (d, J = 2.0 Hz, 1 H), 4.00 (d, J = 2.0 Hz, 1 H), 6.5–8.2 (m, 9 H).

Preparation of Benzocyclobutenols. General Procedures. (A) In THF. The reaction of o-bromostyrene is representative. o-Bromostyrene oxide (0.4 g, 2.0 mmol) and $MgBr_2$ (1.6 mL, 2.5 M in ether) were dissolved in 20 mL of dry THF. The solution was stirred and cooled to −78 °C, during which time the $MgBr_2$ precipitated. The reaction mixture was then treated with 2.2 mol of n-BuLi (hexane solution), kept at −78 °C for up to 20–30 min, and then allowed to warm to room temperature. The usual workup followed by chromatography of the crude product on silica gel (1:2 ethyl acetate–hexane) afforded 200 mg (83%) of benzocyclobutanol, mp 55–56 °C (lit.[11] mp 56–58 °C).

In the case of the interconversion of **2a** to **1** the reaction was carried out a number of times by different workers on scales

(8) Kindly supplied by Dr. M. Rosenberger, Hoffmann-LaRoche Inc., Nutley, NJ. The material was of approximately 85% purity, the remainder being solvent methanol.

(9) D. E. Janssen and C. V. Wilson, "Organic Syntheses", Wiley, New York, 1963, Collect. Vol. IV, p 547.

(10) A. Orr, R. Robinson, and M. Williams, *J. Chem. Soc.*, 946 (1917).

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ranging from 400 mg to 8 g of epoxide. The yield of benzocyclobutenol was generally in the 70–85% range.

In THF with the Order of Addition of $MgBr_2$ and *n*-BuLi Reversed. In these situations the $MgBr_2$ was added within 2–3 min after completion of the *n*-BuLi addition. The yield of benzocyclobutanol from *o*-bromostyrene oxide with this procedure was generally 65–75%.

(C) In Ether. When the reaction was carried out in ether the order of addition was *n*-BuLi followed by $MgBr_2$. In several experiments, *o*-bromostyrene oxide was converted to benzocyclobutenol in 60–70% yield via this method.

Benzocyclobutenol-d_2. *o*-Bromo-β,β-dideuteriostyrene (402 mg, 2 mmol) was reacted with 4 mmol of $MgBr_2$ and 2 mmol of *n*-BuLi in THF as outlined in procedure A. The yield of recrystallized (hexanes) benzocyclobutanol was 150 mg (62%). The NMR spectrum showed a ratio 2:1:1 for the α to β-cis to β-trans hydrogens.

Benzocyclobutenol from *o*-Iodostyrene Oxide. Iodo epoxide **2b** (1.3 g, 5.3 mmol) was dissolved in 30 mL of THF. $MgBr_2$ (10.8 mmol) was added and the solution cooled to −78 °C. The reaction mixture containing the suspended $MgBr_2$ was then treated with 5.8 mmol of *n*-BuLi, kept at −78 °C for 30 min, warmed to 0 °C, and worked up. Chromatography of the crude product gave 0.57 g (85%) of benzocyclobutenol, identical with the material obtained from **2a**.

4-Methoxybenzocyclobutenol. Iodostyrene oxide (**24**; 552 mg, 2.0 mmol) in 10 mL of anhydrous ether at −78 °C was treated first with 2.2 mmol of *n*-BuLi and then with 4 mmol of $MgBr_2$. The reaction mixture was warmed to room temperature and worked up, and the crude product was purified by silica gel chromatography (4:1 hexane–ethyl acetate). The yield of 4-methoxybenzocyclobutanol was 227 mg (76%): white needles; mp 39–42 °C; NMR δ 2.75 (1 H, OH), 2.94 (dd, J = 14.0, 1.0 Hz, 1 H), 3.50 (dd, J = 14.0, 4.5 Hz, 1 H), 3.76 (s, 3 H), 5.15 (dd, J = 4.5, 1 Hz, 1 H), 6.6–7.2 (m, 3 H); ^{13}C NMR δ 41.7, 55.4, 70.0, 108.9, 114.1, 123.6, 139.8, 143,4, 161.1; IR ($CHCl_3$) 3300–3600 cm^{-1} (br). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.71; H, 6.58.

Structure Elucidation. 4-Methoxybenzocyclobutenol was heated with 10 mL of ethanol and 1 mL of 50% NaOH solution for 2 h. Workup afforded an aldehyde (280 mg) which had NMR peaks at δ 2.63 (s, 3 H), 3.86 (s, 3 H), 6.73 (d, J = 2 Hz, 1 H), 6.80 (dd, J = 7, 2 Hz, 1 H), 7.73 (d, J = 7 Hz, 1 H), and 10.08 (s, 1 H). On air oxidation this aldehyde was converted in 4-methoxy-2-methylbenzoic acid, mp 175–177 °C (lit.[12] mp 175–177 °C).

4,5-(Methylenedioxy)benzocyclobutenol was prepared in 75% yield in ether as the reaction solvent: mp 118–120 °C; NMR δ 2.23 (1 H, OH), 2.83 (dd, J = 14.0, 1.0 Hz, 1 H), 3.41 (dd, J = 14.0, 4.5 Hz, 1 H), 5.10 (dd, J = 4.5, 1.0 Hz, 1 H), 5.87 (s, 2 H), 6.61 (s, 1 H), 6.71 (s, 1 H); IR ($CHCl_3$) 3200–3550 cm^{-1} (br); mass spectrum, m/e 164 ($M^{+\cdot}$). Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.49; H, 4.89.

1-Methylbenzocyclobutanol. This product was obtained in 35% and 34% isolated yields from *o*-bromo- and *o*-iodo-*trans*-β-methylstyrene oxide, respectively, by using THF as solvent and procedure B: mp 77–78 °C (lit.[7] mp 79–80 °C); ^{1}H NMR δ 1.63 (s, 3 H), 2.43 (1 H, OH), 3.15 (d, J = 14 Hz, 1 H), 3.32 (d, J = 14 Hz, 1 H), 7.0–7.3 (m, 4 H); ^{13}C NMR δ 25.6, 48.3, 78.2, 120.4, 124.0, 127.2, 129.3, 165.8; mass spectrum, m/e 134 ($M^{+\cdot}$).

1-Benzylbenzocyclobutanol. This product was obtained from 867 mg of 2-bromo-*trans*-β-benzylstyrene oxide by using THF as solvent (procedure B). The crude reaction product was separated by preparative TLC and gave, as the upper band, in 40% yield dibenzyl ketone (identified by comparison of its NMR and IR spectra with those of an authentic sample). The lower band was identified as the desired benzocyclobutenol: yield 40%; colorless oil; ^{1}H NMR 2.67 (1 H, OH), 3.17 (s, 2 H), 3.18 (d, J = 14 Hz, 1 H), 3.50 (d, J = 14 Hz, 1 H), 7.0–7.5 (m, 9 H); ^{13}C NMR δ 45.1, 46.8, 80.2 (nonaromatics); mass spectrum, m/e 210 ($M^{+\cdot}$).

Reactions of 2-Bromo- and 2-Iodo-*trans*-stilbene Oxide. The bromo epoxide (1.1 g, 4 mmol) was dissolved in 20 mL of THF at −78 °C and reacted sequentially with 4 mmol of *n*-BuLi followed by 8 mmol of $MgBr_2$ solution. The reaction mixture was allowed to warm to room temperature and then worked up. The yield of isolated *trans*-stilbene oxide [NMR δ 3.87 (s, 2 H), 7.3 (s, 10 H)] was 543 mg (70%). A similar result was obtained when 2-iodo-*trans*-stilbene oxide was employed.

When the above reaction was carried out on 3 mmol of bromo epoxide in 30 mL of ether with 3 mmol of *t*-BuLi for the halogen–lithium exchange, deoxybenzoin (510 mg, 87%) was obtained after chromatography.

Acknowledgment. The continued financial assistance of NSERC (Canada) is gratefully acknowledged.

Registry No. **1**, 35447-99-5; **1-2,2-d_2**, 77287-55-9; *cis*-**1-1,2-d_2**, 77287-56-0; *trans*-**1-1,2-d_2**, 77287-57-1; **2a**, 71636-51-6; **2a-β,β-d_2**, 72525-55-4; **2b**, 72525-47-4; **7** (X = I; R = 5-OMe), 77287-58-2; **7** (X = I; R = H), 26260-02-6; **7** (X = Br; R = H), 6630-33-7; **7** (X = Br; R = 3,4-OCH_2O), 56008-63-0; **7** (X = R = H), 100-52-7; **8** (R = H) Cl^-, 3086-29-1; **8** (R = C_6H_4-*o*-Br) Br^-, 77287-59-3; **8** (R = H) I^-, 2181-42-2; **8** (R = Ph) Cl^-, 14182-14-0; **8** (R = C_6H_4-*o*-I) Br^-, 77287-60-6; **9** (X = Br; R = 3,4-OCH_2O; R^1 = H), 77287-61-7; *trans*-**9** (X = Br; R = H; R^1 = Me), 77287-62-8; *trans*-**9** (X = I; R = H; R^1 = Me), 77287-63-9; *trans*-**9** (X = Br; R = H; R^1 = CH_2Ph), 77287-64-0; **10a** (X = Br), 71095-28-8; *cis*-**11**, 77287-65-1; **12**, 72525-54-3; **13**, 19164-60-4; **15**, 77287-66-2; **16**, 102-04-5; **18**, 77287-67-3; *trans*-**19** (X = Br), 77287-68-4; *trans*-**19** (X = I), 77287-69-5; *trans*-**20**, 1439-07-2; **22**, 451-40-1; **24**, 72525-51-0; **25**, 72525-53-2; acetaldehyde, 75-07-0; 2-bromoacetophenone, 2142-69-0; 2-bromo-*cis*-β-methylstyrene, 31026-78-5; ethylidinetriphenylphosphorane, 1754-88-7; phenylacetaldehyde, 122-78-1; methyl *o*-methylbenzyl sulfide, 5925-79-1; 4-methoxy-2-methylbenzaldehyde, 52289-54-0; 4-methoxy-2-methylbenzoic acid, 6245-57-4; 4,5-(methylenedioxy)benzocyclobutenol, 77287-70-8.

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1-Methoxyisobenzofuran: Formation from 1,3-Dihydro-1,1-dimethoxyisobenzofuran

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Received December 8, 1980

1-Methoxyisobenzofuran is formed by treatment of 1,3-dihydro-1,1-dimethoxyisobenzofuran with either a trace of acetic acid in refluxing toluene or with LDA at 70 °C. The requirements to obtain Diels–Alder adducts under both sets of conditions are examined, and various products are characterized.

We have recently reported the formation of isobenzofuran **2** from **1** using either strong base conditions (where solutions of **2** may be isolated) or in direct reaction with maleic anhydride, where **2** is implicated as a transient

0022-3263/81/1946-2734$01.25/0