evaporation of the solvent. Twenty milliliters of water and 20 mL of dichloromethane were added, followed by 2.0 g (13 mmol) of sodium perborate tetrahydrate at 0 °C and stirring 1.5 h at 20-25 °C. Bulb-to-bulb distillation yielded 1.073 g of material judged by ^1H NMR analysis to contain 1.03 g (65% yield) of ethyl 4-formylpentanoate and the remainder was ethyl levulinate. This sample was used directly for analysis: ^1H NMR ($CDCl_3$) δ 1.11 (d, 3, $CHCH_3$), 1.25 (t, 3, CH_2CH_3), 1.6-2.2 (m, 3, $CHCH_2$), 2.35 (t, 2, CH_2CH_2CO), 4.10 (q, 2, CH_3CH_2O), 9.60 (d, $J \sim 1$ Hz, 1, CHO). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 61.05; H, 8.78.

Reaction of Benzoyl Chloride with 2. To a suspension of 11.5 mmol of **2** prepared by the usual method was added 1.12 g (8 mmol) of benzoyl chloride at -78 °C. After stirring 1 h at -78 °C the mixture was allowed to warm to 0 °C and then was treated with 35 mL of 5 M hydrochloric acid, extracted with 30 mL of dichloromethane, and converted to the 2,4-dinitrophenylhydrazone of acetophenone, 1.83 g (76%).

Reaction of Methyl Benzoate with 2. The solvent was removed under vacuum at 20 °C from 22 mmol of **2** that had been prepared in the usual manner, 30 mL of cyclohexane was added followed by 2.19 g (16 mmol) of methyl benzoate, and the mixture was refluxed for 15 h. Workup as described in the preceding paragraph yielded 3.56 g (74%) of acetophenone 2,4-dinitrophenylhydrazone.

Bis(1-hydroxy-1-octyl) Peroxide (4). A solution of 0.576 g of octanal with 1.1 g of boric acid and 2.8 g of sodium tetraborate decahydrate in 15 mL of water and 35 mL of 30% hydrogen peroxide was stirred for 3 h at 20 °C followed by extraction with ether and recrystallization from ether to yield 0.594 g of **4**: mp 68-70 °C (lit.[13] mp 72 °C); ^1H NMR (Me_2SO-d_6) δ 0.87 and 1.27 (m, n-C_7H_{15}), 5.13 (m, CH(OH)O), 6.2 (br, OH), and 9.87 (m, CHO, integral suggests 20% dissociation to free aldehyde); IR (Nujol) 3300-3400 cm^{-1} (vs, OH), no aldehyde C=O. Anal. Calcd for $C_{16}H_{34}O_4$: C, 66.17; H, 11.79; O, 22.03. Found: C, 66.25; H, 11.73; O, 22.06.

Oxidations of 2-Phenylpropene-1-boronic Acid. The usual procedure was followed on a 10-mmol scale with acetophenone (1.23 g), until after the solvent was evaporated. The crude boronic ester was then analyzed by NMR and shown to contain no more than 1% residual acetophenone. Oxidation in the usual manner with hydrogen peroxide and sodium carbonate as buffer followed by extraction and distillation of the product yielded 0.97 g of material estimated to contain about 40 mol % acetophenone and 60 mol % α-phenylpropionaldehyde by NMR analysis. Further tests were carried out on 0.08-g samples of recrystallized 2-phenylpropene-1-boronic acid in 1 mL of deuteriochloroform with 2.5 mL of the aqueous phase. The solution was stirred with 0.1 g of sodium hydroxide and 0.08 g of sodium perborate tetrahydrate for 5 min. NMR analysis of the deuteriochloroform phase indicated about 1 mol % acetophenone in the resulting α-phenylpropionaldehyde solution. Use of 0.21 g of sodium hydroxide, 0.10 g of sodium tetraborate decahydrate, and 0.10 mL of 30% hydrogen peroxide led to 3 mol % acetophenone. Use of 0.18 g of sodium hydroxide and 0.10 mL of 30% hydrogen peroxide led to 4 mol % acetophenone.

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Registry No. **1**, 59278-44-3; **2**, 57404-82-7; **4**, 57335-83-8; **5**, 72659-45-1; **6**, 72659-46-2; butanal, 123-72-8; heptanal, 111-71-7; octanal, 124-13-0; 4-penten-1-al, 2100-17-6; benzaldehyde, 100-52-7; acetone, 67-64-1; cyclohexanone, 108-94-1; pentanal, 630-19-3; nonanal, 124-19-6; 5-hexen-1-al, 764-59-0; phenylacetaldehyde, 122-78-1; isobutyraldehyde, 78-84-2; cyclohexanecarboxaldehyde, 2043-61-0; $CH_3CH_2COCH_2CH_3$, 96-22-0; $C_6H_5COCH_3$, 98-86-2; $(CH_3)_2C{=}CHCOCH_3$, 141-79-7; $EtO_2CCH_2CH_2COCH_3$, 539-88-8; $(CH_3CH_2)_2CHCHO$, 97-96-1; $C_6H_5CH(CH_3)CHO$, 93-53-8; $(CH_3)_2C{=}CHCH(CH_3)CHO$, 14690-10-9; $EtO_2CCH_2CH_2CH(CH_3)CHO$, 57404-75-8; benzoin, 119-53-9; tetrahydropyranylbenzoin, 51706-34-4; ethyl 2-formylpropionate, 27772-62-9; ethyl pyruvate, 617-35-6; ethyl 4-formylpentanoate, 57404-75-8; ethyl levalinate, 539-88-8; benzoyl chloride, 98-88-4; acetophenone 2,4-dinitrophenylhydrazone, 2074-04-6; methyl benzoate, 93-58-3.

Phase-Transfer Synthesis of Monoalkyl Ethers of Oligoethylene Glycols

Thomas Gibson

Miami Valley Laboratories, The Procter & Gamble Co., Cincinnati, Ohio 45247

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The effects of catalyst, temperature, solvent, and reagent ratios on the phase-transfer-catalyzed Williamson ether synthesis of monoalkyl ethers of oligoethylene glycols have been studied. A convenient method has been developed which gives reproducibily high yields of pure monoethers in the presence of aqueous sodium hydroxide.

Monoalkyl ethers of oligoethylene glycols (1) (eq 1) are

$$RX + HO(CH_2CH_2O)_nH \rightarrow \underset{1}{RO(CH_2CH_2O)_nH} + \underset{2}{RO(CH_2CH_2O)_nR} \quad (1)$$

useful nonionic surfactants. They have been prepared on a laboratory scale by the Williamson ether synthesis, in which the alkoxide is formed in excess glycol using sodium metal or sodium hydride. Reaction with alkylating agents gives variable amounts of dialkylation product (**2**) which can be minimized but not entirely suppressed by the use of a large excess of glycol. On a large scale the reaction requires handling large amounts of sodium or its hydride, and the product is sometimes contaminated with lower ethoxylogues. In our hands, the reaction also gave low (30-60%) yields, and we therefore looked for ways to improve the process.

The application of phase-transfer methodology to the Williamson ether synthesis has been described.[1-5] Freedman has developed a method for the efficient preparation of asymmetrical ethers using 50% aqueous sodium hydroxide as the base and tetrabutylammonium bisulfate as the phase-transfer catalyst.[5] Under the most favorable conditions developed, which involve the use of excess alkyl halide in tetrahydrofuran, tetraethylene glycol is efficiently dialkylated to give **2** in >90% yield.[5]

Initial work using Freedman's conditions, in the presence of a 2- to 10-fold excess of glycol, was moderately successful. Yields varied widely, however, depending on conditions employed, so we decided to concentrate our efforts on a single system in order to untangle the roles

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Table I. Effect of Glycol/Halide Ratio on Alkylation of Diethylene Glycol with Butyl Chloride[a]

expt	glycol halide	solvent	% dialkylation	% monoalkylation
1	0.25	none	97	
2	1.0	none	70	9
3	5.0	none	13	38
4	10.0	none		40
5	1.0	benzene	10	6
6	5.0	benzene	2	8
7	10.0	benzene		8

[a] 60 °C, 4 h, NaOH/halide = 5, TBAB/halide = 0.1.

Table II. Effect of Solvent and Catalyst on Yield of Monoalkylation Product[a]

solvent	catalyst	$Bu(OCH_2CH_2)_2OH$ yield, %
none	none	69
none	TBAB[b]	63
benzene	none	17
benzene	TBAB[b]	26
THF	none	30
THF	TBAB[b]	47

[a] 60 °C, 16 h, BuCl:E_2:NaOH = 1:10:5. [b] Tetrabutylammonium bisulfate, 0.1.

of the numerous variables involved. The system chosen was the reaction of butyl chloride with diethylene glycol because of the ease of analysis by gas chromatography of the trimethylsilyl ethers.

Butyl Chloride/Diethylene Glycol Studies. Table I summarizes data on the yields of mono- and dialkylates as a function of glycol/butyl chloride ratios. In these experiments, tetrabutylammonium bisulfate (TBAB) was used as catalyst. The data show that when the glycol/halide ratio exceeds approximately 5:1, dialkylation is almost completely suppressed. The reaction proceeds at a lower rate when benzene is used as a diluent for the organic phase. As reported by Freedman,[5] dialkylation is very efficient when an excess of halide is used (experiment 1). The rate of the reaction is severely retarded as the ratio increases.

The combined effects of solvent and presence of catalyst were investigated at 60 °C with diethylene glycol to butyl chloride to sodium hydroxide in 10:1:5 ratio. The yields of monoalkylation product after 16 h are summarized in Table II. Yields are based on butyl chloride and are given for distilled product, since contamination with dialkylate is negligible. A number of useful conclusions can be reached by examination of the results: (1) the highest rates are achieved in the absence of solvent; (2) the presence of catalyst has little effect on yield of monoalkylate in the absence of solvent; (3) reaction is faster in THF than in benzene, and (4) when added solvent is used, the reaction proceeds at a somewhat higher rate when catalyst is present.

Table III shows the effect of changing the amount of NaOH present. As the mole ratio of base to halide approaches the stoichiometric value of 1, the yield of monoalkylation product obtained in 16 h at 60 °C drops to about 40%; still, no dialkylation occurs. Carrying out the reactions at higher temperature and for longer periods of time gives good yields, even when the amount of glycol is reduced to 2 molar equiv. Small amounts of dialkylate are produced when a 2:1 glycol/butyl chloride ratio is used. Use of butyl bromide in place of butyl chloride had no obvious effect on the outcome of the reaction.

Table III. Effects of Reagent Ratios on Alkylation of Diethylene Glycol with Butyl Chloride

glycol/halide	time, h	NaOH/halide	temp, °C	% dialkylation	% monoalkylation
10	16	5	60		69
10	16	2	60		55
10	16	1	60		37
10	24	1	100		70
5	24	1	100		59
2	24	1	100	5	65
2	24	1	100	6	62[a]

[a] Butyl bromide.

Table IV.[a] Effects of Chain Length of Alkyl Halide and Glycol

alkyl halide	glycol	glycol/halide	% monoalkylation	% dialkylation
butyl chloride	diethylene	2	65	5
butyl chloride	diethylene	10	70	
butyl chloride	tetraethylene	2	64	10
decyl chloride	diethylene	2	44	20
decyl chloride	diethylene	10	80	
decyl chloride	tetraethylene	2	59	26
decyl chloride	tetraethylene	10	85	
decyl bromide	diethylene	2	21	63
decyl bromide	diethylene	10	79	
decyl bromide	tetraethylene	2	42	48
decyl bromide	tetraethylene	3	64	26
decyl bromide	tetraethylene	10	88	
docosyl bromide	tetraethylene	2	38	39
docosyl bromide[b]	hexaethylene	10	80	

[a] Reactions carried out at 100 °C for 24 h. NaOH:halide = 1. [b] TBAB catalyst used in THF at reflux, 70 h.

Scaling the butyl chloride reaction up to 1 mol (based on butyl chloride) did not alter the yields, except that about 5% of butyl alcohol was obtained. Thus, only minor amounts of hydrolysis were occurring. No attempt was made to detect the formation of butenes in these reactions.

In summary, reaction of butyl chloride with diethylene glycol is best carried out at 100 °C for 24 h without solvent or catalyst, in the presence of 5–10 equiv of glycol and 1 equiv of sodium hydroxide. Under these conditions the yield of monoalkylation product is maximized, dialkylation is negligible, and no appreciable amounts of side products are formed from decomposition of reagents or products. The reaction appears to be complete in 12–16 h, as determined by titration of residual base, but is generally carried to 24 h in order to ensure completion.

Long-Chain Glycol Monoethers. With the method well optimized for the butyl chloride/diethylene glycol system, we turned to the synthesis of longer-chain compounds. Several experiments were carried out, summarized in Table IV, from which several conclusions are apparent. The product ratio proved to be dependent on the alkyl

Table V. Alkylation of Butyl Alcohol and Diethylene Glycol with Butyl Chloride[a]

alcohol	catalyst	yield of alkylation product, %
diethylene glycol	none	25
butyl alcohol	none	5
butyl alcohol	TBAB[b]	38

[a] Alcohol:halide:NaOH = 2:1:1, 60 °C, 18 h. [b] 10 mol %.

chain length, the glycol, and the halide. It is apparent that each system has a unique set of optimum conditions which must be determined empirically. The reaction of alkyl bromides with 2 equiv of glycol gave predominately dialkylation, regardless of the chain length of the glycol or the bromide, when the alkyl group is C_{10} or longer (cf. C_4 reagent in Table III). Reactions carried out with alkyl bromides require a large excess of glycol to provide a high mono/di ratio. In general, however, excellent yields of pure monoether can be obtained from any combination of glycol and halide in the presence of 10 equiv of glycol and 1 equiv of base at 100 °C for 24 h. When the alkyl halide used is a solid, it is more convenient to carry out the reaction in THF with a quaternary salt catalyst. For example, the monodocosyl ether of hexaethylene glycol was obtained from docosyl bromide in 80% yield in the presence of 10 equiv of glycol in the presence of TBAB. The use of quaternary salts suffers from the disadvantage that contamination of product with tertiary amines occurs as a result of Hoffman elimination and their use should be avoided if possible.

The fact that the reaction rate is not altered by the presence of phase-transfer catalyst suggests that the glycol itself functions also as a phase-transfer catalyst, a hypothesis for which there is a growing amount of evidence in the literature. Recent reports, which support this hypothesis, have shown that polyethylene glycol dimethyl ethers and related acyclic polyethers solubilize inorganic salts in organic solvents and do function as catalysts in phase-transer reactions.[6-11] Sieger and Vögtle have recently isolated stable alkaline earth complexes of a number of oligoethylene glycols.[11]

Alternatively, the reaction could be occurring in the aqueous glycol phase or at the interface. The alkyl halides appear to have very low solubility in the aqueous glycol. However, if the reaction were occurring predominantely in the aqueous glycol phase, the formation of substantial amounts of alcohol might be expected. We observed approximately 5% of butyl alcohol formation when butyl chloride was reacted with 2 equiv of glycol and 1 equiv of base. Under these conditions, the ratio of aqueous hydroxyl to glycol hydroxyl is 1:1.25, and it would appear likely that more displacement by hydroxide would occur than that observed if the reaction were taking place in the aqueous glycol. In order to determine whether displacement by alkoxide occurs in the aqueous phase, we carried out the alkylation of a water-soluble alcohol, butyl alcohol, with butyl chloride. Under conditions which gave 25% yield of monoether with diethylene glycol (Table V), only 5% of dibutyl ether was formed from butyl alcohol, showing that little displacement of any kind was occurring in the aqueous layer. Addition of 10 mol % of tetrabutylammonium bisulfate raised the yield of butyl ether to 38%, showing that the reaction is susceptible to phase-transfer catalysis.

The reaction could be taking place at the interface, but the likelihood of this is small, since the result is independent of stirring rate. The rate of formation of monoalkyl ether was the same whether stirring was performed by slow swirling with a magnetic stirring bar or by high-speed turbulent agitation in a Morton flask with a paddle.

In general, reaction of any primary alkyl halide (chloride or bromide) with a slight excess of 50% aqueous sodium hydroxide and 5–10 equiv of glycol at 100 °C for 24 h will provide 70–90% yields of monoalkylation product.[12] No observable byproducts are formed, and the excess glycol can be easily recovered by distillation or partitioning. The ease of handling reagents and the reproducible high yields make this the method of choice for preparing these compounds.

Experimental Section

General Procedure. The following general procedure is applicable to the preparation of any alkyl ethoxylate. A mixture of 50% aqueous sodium hydroxide and glycol is heated for about 0.5 h in an oil bath at the temperature at which the reaction is to be performed. The mixture is stirred magnetically while a stream of argon flushes air from the system. Alkyl halide is added and the reaction allowed to proceed for the desired time. After cooling, the mixture is diluted with water, extracted exhaustively with ether, dried over $MgSO_4$, filtered, and stripped on a rotary evaporator.

Product Analysis. Final workup and analysis procedures differed depending on the system involved. All products were identified by comparison of their properties with those of authentic samples, either purchased or prepared by the traditional method with Na to generate the alkoxide.

A. Butyl Chloride/Diethylene Glycol. Distillation of the crude product gave a single fraction, bp 50–70 °C (0.3 mm), composed of monoalkylate, dialkylate, and occasionally small amounts of diethylene glycol. The alkylation products were isolated by gas chromatography, identified by mass spectral and NMR analysis, and used to derive a quantitative gas chromatographic analysis method. Standard mixtures of the two components, along with hexadecane as internal standard, were treated with excess Regisil (Regis Chemical Co.), to convert the monoether to its trimethylsilyl derivative. Curves were drawn relating composition of the mixture to peak areas (determined by multiplying peak height times retention time). A good straight line resulted for the monoether. The calibration line for the diether showed substantial curvature, probably due to tailing of the peak. Yields were determined from the equations of the calibration curves determined by the least-squares method. Analyses were performed on a 5 ft × 0.25 in. stainless steel column packed with 20% SE-30 on firebrick at 166 °C, flow rate 60 mL/min. All reactions and analyses were performed at least in duplicate to give the results in the tables.

B. Butyl Chloride/Tetraethylene Glycol. The crude product was dissolved in 3:1 methanol/water (v/v) solution and extracted three times with pentane. The combined pentane extracts gave pure diether uncontaminated with monoether. The aqueous methanol solution was distilled to give pure monoether, bp 110 °C (40 μm), identified by comparison with an authentic sample.

C. Decyl Chloride/Diethylene Glycol. The crude product was distilled through a short Vigreux column to give complete separation into a volatile fraction containing traces of 1-decene, decyl halide, and decanol and a pure monoether fraction, bp 105–110 °C (50 μm). The residue contained only diether, as

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(12) Note Added in Proof: Subsequent work has shown that with alkyl bromides, reaction is complete in 1 h.

determined by gas chromatography.

D. Decyl Chloride/Tetraethylene Glycol. Solvent extraction as described for butyl chloride/tetraethylene glycol gave clean separation of monoether and diether and decyl halide. Distillation gave pure monoether, bp 155–165 °C (30 μm).

E. Docosyl Bromide/Tetraethylene Glycol. The crude product from reaction of 0.05 mol of $C_{22}H_{45}Br$ with 0.10 mol of tetraethylene glycol was dissolved in CH_2Cl_2, and an aliquot was chromatographed on 100–200 mesh silica gel. Elution with $CHCl_3$ gave a mixture of docosyl bromide and docosene in about 10% yield. The next compound eluted was docosyl ether, formed in about 10% yield, identified tentatively by NMR and IR spectra. Next was eluted the diether, mp 69–70 °C (ether), 39% yield; identified by IR, NMR, and mass spectra. Anal. Calcd for $C_{52}H_{106}O_5$: C, 77.0; H, 13.2. Found: C, 77.3; H, 13.0. Elution with 70/30 $CHCl_3$/MeOH gave the monoether: mp 59–60 °C (hexane); 38% yield; IR ν_{max} 3480 and 1120 cm^{-1} (melt); ^{1}H NMR τ 6.33 (18 H, m), 8.70 (40 H, s), and 9.13 (3 H, t). Field ionization mass spectrometry showed a molecular ion at m/e 502 ± 1. Anal. Calcd for $C_{30}H_{62}O_5$: C, 71.7; H, 12.4. Found: C, 71.6; H, 12.6.

F. Docosyl Bromide/Hexaethylene Glycol. Reaction of $C_{22}H_{45}Br$ (0.11 mol), hexaethylene glycol (1.1 mol), 50% NaOH (0.56 mol), and Bu_4NHSO_4 (0.01 mol) in THF (250 mL) was carried out for 48 h at reflux. An additional 0.005 mol of catalyst was added and the reaction continued for 22 h. After the solution was cooled, extraction with ether and crystallization from ether gave 51.6 g of the monoether, mp 38–42 °C (80%). Further recrystallization gave mp 57–8 °C; IR ν_{max} 3460 and 1115 cm^{-1} (neat melt); ^{1}H NMR τ 6.32 (24 H, m), 6.54 (2 H, t, J = 6.5 Hz), 8.73 (40 H, m), and 9.12 (3 H, t). Chemical ionization mass spectrometry showed an $(M + 1)^+$ ion at m/e 592. Anal. Calcd for $C_{34}H_{70}O_7$: C, 69.1; H, 11.9. Found: C, 69.7; H, 11.9.

Registry No. Butyl chloride, 109-69-3; diethylene glycol, 111-46-6; diethylene glycol monobutyl ether, 112-34-5; diethylene glycol dibutyl ether, 112-73-2; tetraethylene glycol, 112-60-7; tetraethylene glycol monobutyl ether, 1559-34-8; tetraethylene glycol dibutyl ether, 112-98-1; decyl chloride, 1002-69-3; diethylene glycol monodecyl ether, 23238-41-7; diethylene glycol didecyl ether, 72659-41-7; tetraethylene glycol monodecyl ether, 5703-94-6; tetraethylene glycol didecyl ether, 51750-96-0; decyl bromide, 112-29-8; docosyl bromide, 6938-66-5; tetraethylene glycol monodocosyl ether, 72659-42-8; tetraethylene glycol didocosyl ether, 72659-43-9; hexaethylene glycol, 2615-15-8; hexaethylene glycol monodocosyl ether, 72659-44-0; butyl bromide, 109-65-9; butyl alcohol, 71-36-3.

Studies on the Synthesis of Substituted Phenanthrenoids

Andrew R. Leed, Susan D. Boettger, and Bruce Ganem*[1]

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853

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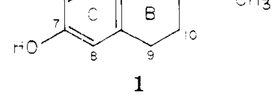
Highly regioselective reactions for the construction of polysubstituted benzenes **18**, **19**, **20**, **22**, **24**, and **44–47** are described, including some remarkable site-selective halogenations. These have been employed in the synthesis of halo-, nitro-, amino-, and urethane-substituted stilbenes **37**, **38**, and **51–56**. Ideas for thermal as well as photochemical cyclizations are presented and explored. Stilbene **54** led to the formation of phenanthrenes **57**, **58**, and **62**; likewise **55** furnished two new tricyclics, **60** and **61**, whereas irradiation of **52** in *tert*-butyl alcohol captured solvent to produce phenanthrenes **63** and **64**. Strategies for the total synthesis of juncusol (**1**), a cytotoxic phytoalexin, are considered.

Of the many defense mechanisms employed by plant populations against pathogens and herbivores, the induced phytoalexin response is an area of active investigation among ecologists and biochemists. Phytoalexins are specific antifungal agents which materialize in appreciable quantities postinfection, and are often present in low levels within the living cells of healthy plants.[2]

A large fraction of the known phytoalexin structures falls in the class of alkyl- and hydroxyl-substituted 9,10-dihydrophenanthrenes, one representative of which is juncusol (**1**), a cytotoxic constituent of the estuarine marsh plant *Juncus roemerianus*.[3] Although a considerable body of preparative phenanthrene chemistry has been developed[4] which pertains to the synthesis of these natural products, the particular nature and degree of functionalization in structures like **1** pose a considerable challenge to existing methodology and have renewed interest in alternative approaches to such polycyclic dihydroaromatics.



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Two independent syntheses of juncusol have recently been published,[5,6] and a full experimental account of the first[5b] describes the unexpected complexity of some classical methods when applied to **1**. In view of these disclosures we wish now to report our own work in this area which focuses first on the matter of polyfunctional benzene construction and then on the design of new phenanthrene-forming cyclizations.

Stilbene Photocyclization. The retrosynthetic analysis of juncusol shown in Scheme I suggested that the C5 vinyl substituent might be introduced late in the synthesis at the stage of a 9,10-dihydrophenanthrene by means of a metal–halogen exchange on bromide **5**. Addition of acetaldehyde to aryllithium **4** would furnish alcohol **3**, ultimately destined for dehydration. Since selective reduction of the 9,10 double bond in phenanthrenes is generally feasible,[7] we felt that phenanthrene **6** might be an attractive synthetic intermediate which, in turn, would be

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