catalyst were used, lower yields were formed, presumably due to competing intermolecular displacement.

Table I summarizes the results obtained for a series of biphase lactonizations. In all cases the yields compare favorably with those of conventional homogeneous cyclizations carried out under high dilution conditions;[6] final product concentrations were, however, very high and approached 0.1 M!

The major synthetic attractiveness of the use of solid–liquid phase-transfer catalysis as a high dilution technique is its experimental simplicity (the use of mechanically driven syringes and other slow addition devices are avoided) and the fact that only small quantities of solvent are required. Efforts are now underway to apply this approach to other cyclization processes.

Experimental Section

General Methods. Unless stated otherwise, all reagents and chemicals were obtained commercially and were used without further purification. 6-Bromohexanoic acid (Aldrich), 8-bromooctanoic acid (K & K Laboratories), and 12-bromododecanoic acid (Aldrich) were purified by recrystallization from hexane. Authentic lactones were either obtained commercially or derived from Baeyer–Villiger oxidation of commercially available cycloalkanones. 15-Hydroxypentadecanoic acid lactone and 16-hydroxyhexadecanoic acid lactone were obtained from the Columbia Organic Chem. Co. Toluene and tetrahydrofuran were dried by distillation from sodium and benzophenone under a nitrogen atmosphere. Pyridine and hexane were distilled from calcium hydride. All ^{1}H NMR and IR spectra were recorded with Varian EM 360L and Beckman Acculab 7 spectrometers, respectively; chemical shifts were recorded in δ values (ppm) from internal tetramethylsilane as standard. Product mixtures were analyzed by GLC on a Hewlett-Packard Model 5830 A flame ionization instrument (2 ft × 0.125 in. UCW-982 on Chromosorb W column).

16-Bromohexadecanoic Acid. A mixture of 5.08 g (20 mmol) of 16-hydroxyhexadecanoic acid lactone, 20 mL of 50% aqueous NaOH, 30 mL of benzene, and 0.1 g of tetrabutylammonium hydrogen sulfate was stirred overnight at 70 °C. The mixture was cooled to room temperature, acidified with 3 N HCl, and extracted with chloroform. After the organic layer ($MgSO_4$) was dried the solvent was evaporated in vacuo and the residue was recrystallized from benzene to give 4.6 g (85%) of 16-hydroxyhexadecanoic acid having mp 97–99 °C (lit.[7] mp 94 °C). To a mixture of 16-hydroxyhexadecanoic acid (2.5 g, 9.2 mmol), pyridine (20 mL), and THF (20 mL) was added dropwise a solution of methanesulfonyl chloride (2.0 mL, 25.8 mmol) in 10 mL of pyridine over 0.5 h at 0 °C. The mixture was then stirred for 2 h at room temperature. After solvent evaporation under reduced pressure, the residue was acidified with 3 N HCl in an ice–water bath, extracted with chloroform (3 × 50 mL), washed with water (2 × 100 mL), and dried over $MgSO_4$. The IR spectrum of the crude product exhibited an anhydride band at 1800 cm^{-1}. After solvent evaporation, the crude product was dissolved in 100 mL of THF, and 10 mL of 4 N NaOH was added slowly in an ice–water bath. Further stirring for 0.5 h at room temperature followed by extraction with $CHCl_3$ and recrystallization from acetone gave 1.94 g (61%) of 16-[(methylsulfonyl)oxy]hexadecanoic acid having mp 97–98 °C: IR ($CHCl_3$) 1695 (>C=O), 1350 cm^{-1} (>SO_2); ^{1}H NMR ($CDCl_3$) δ 1.23 (br s, 26 H, CH_2), 2.32 (t, 2 H, CH_2CO), 2.96 (s, 3 H, CH_3), 4.20 (t, 2 H, SO_2CH_2).

A mixture of 16-[(methylsulfonyl)oxy]hexadecanoic acid (0.7 g, 2.0 mmol), KBr (2.4 g, 20 mmol), water (5 mL), toluene (3 mL), and tetrabutylammonium hydrogen sulfate (0.1 g) was stirred at 100 °C for 2 h. The aqueous phase was extracted with toluene and the combined organic phase washed with water. After drying (Na_2SO_4), recrystallization from hexane gave 0.45 g (67%) of 16-bromohexadecanoic acid having mp 70–71 °C (lit.[8] mp 71 °C).

15-Bromopentadecanoic acid was prepared by using similar procedures.

Potassium Salts of ω-Bromocarboxylic Acids. To a solution of 1.0 mmol of a given ω-bromocarboxylic acid dissolved in 10 mL of methanol (in the case of 15-bromopentadecanoic acid and 16-bromohexadecanoic acid, acetone was used as the solvent) was added 0.3 mL of 3.33 N KOH [CH_3OH–H_2O (8:2) used as solvent]. The solvent was then evaporated under reduced pressure and the colorless solid residue dried in vacuo [2 h, 90 °C (0.1 mm)].

Small-Scale Lactonization. Typically, an 8-mL culture tube (Corning no. 9826) equipped with a 2 × 12.7 mm Teflon-coated magnetic stir bar was charged with 31.7 mg (0.1 mmol) of potassium 12-bromododecanoic acid, 1 mL of dry toluene containing 0.05 mmol of *n*-hexadecane (internal standard), plus 0.8 mg of tetrabutylammonium bromide. The mixture was stirred at 90 °C for 3 h. Analysis of the organic layer by GLC indicated a 95% yield of 12-hydroxydodecanoic acid lactone.

12-Hydroxydodecanoic Acid Lactone. A 40-mL culture tube (Corning no. 9825) equipped with a 1 × $^5/_{16}$ in. Teflon-coated magnetic stir bar was charged with 0.317 g (1.0 mmol) of potassium 12-bromododecanoic acid, 10 mL of toluene, and 8 mg of tetrabutylammonium bromide. The mixture was stirred at 90 °C for 3 h, filtered, and concentrated under reduced pressure. Purification by thin-layer chromatography using silica gel (10% ether in hexane) gave 0.188 g (95%) of 12-hydroxydodecanoic acid lactone having an IR spectrum, GLC retention time, and R_f value (0.80) identical with that of an authentic sample.

Registry No. 1, 1643-19-2; $HO_2C(CH_2)_5Br$·K, 83306-55-2; $HO_2C(CH_2)_7Br$·K, 85115-83-9; $HO_2C(CH_2)_{11}Br$·K, 85115-84-0; $HO_2C(CH_2)_{14}Br$·K, 77172-45-3; $HO_2C(CH_2)_{15}Br$·K, 85115-85-1; 6-hydroxyhexanoic acid lactone, 502-44-3; 8-hydroxyoctanoic acid lactone, 5698-29-3; 12-hydroxydodecanoic acid lactone, 947-05-7; 15-hydroxypentadecanoic acid lactone, 106-02-5; 16-hydroxyhexadecanoic acid lactone, 109-29-5; 16-bromohexadecanoic acid, 2536-35-8; 16-[(methylsulfonyl)oxy]hexadecanoic acid, 85115-82-8.

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Synthesis of 4-Hydroxybenzo[*a*]pyrene

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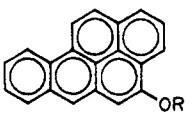
In connection with a program to prepare polycyclic hydrocarbon metabolites of authentic structure as standards for carcinogenesis research,[1] we required a practical synthetic route to 4-hydroxybenzo[*a*]pyrene (**1a**). The



1a: R = H
b: R = Ac

only previously reported synthesis of **1a** involved catalytic dehydrogenation of 4-oxo-4,5,5a,6,6a,7,8,9,10,10a-decahydrobenzo[*a*]pyrene,[2] itself synthetically accessible only via complex multistep synthesis involving troublesome isomer separations and low overall yield.[3] 4-Hydroxybenzo[*a*]pyrene has also been obtained along with 5-hydroxybenzo[*a*]pyrene from dehydration of the 4,5-dihydrodiol of benzo[*a*]pyrene.[4] However, attempts to separate these isomers by chromatography were frustrated

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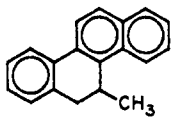
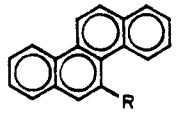
by their tendency to decompose on the columns.

We now report a convenient practical synthesis of **1a**. The approach is based upon the earlier finding that reductive methylation of chrysene with sodium in liquid ammonia followed by treatment with methyl bromide affords 5-methyl-5,6-dihydrochrysene (**2**) in good yield



2



3a: R = CH_3
b: R = CH_2Br
c: R = CH_2CN
d: R = CH_2CONH_2
e: R = CH_2CO_2H

(93%).[5] Dehydrogenation of **2** with trityl fluoroacetate, generated in situ from reaction of trityl alcohol in refluxing trifluoroacetic acid,[6] proceeded smoothly to provide pure 5-methylchrysene (**3a**) (86%). The accompanying triphenylmethane was removed by treatment with sodamide and air (to generate the hydroperoxide) and passage through a column of alumina.[7] The proton NMR spectrum of **3a** matched closely that of authentic 5-methylchrysene prepared by another method and differed markedly from that of 6-methylchrysene.[8] In addition to a methyl singlet at δ 3.25,[9] the NMR spectrum of **3a** revealed three aromatic protons (H_4, H_{10}, and H_{11}) at low field (δ 8.53–9.10) characteristic of 5-substituted chrysene isomers.

Bromination of **3a** with *N*-bromosuccinimide in CCl_4 in the presence of benzoyl peroxide gave 5-(bromomethyl)chrysene (**3b**). Treatment of **3b** with KCN in Me_2SO[10] afforded 5-(cyanomethyl)chrysene (**3c**), which underwent hydrolysis with KOH in aqueous ethylene glycol (40 h) to yield 5-chrysenylacetamide (**3d**) (59%). Acidification of the mother liquor yielded a second product shown to be 5-chrysenylacetic acid (**3e**) (37%). Prolonged hydrolysis of **3d** (86 h) converted it to the free acid. Hydrolysis of **3c** in aqueous diglyme (40 h) gave **3e** directly (55%) along with an insoluble polymer.

Cyclization of **3e** in liquid HF afforded pure **1a** (84%) as a yellow solid, mp 225–227 °C, somewhat higher than reported (lit.[2] mp 195–196 °C). The 270-MHz proton NMR spectra of **1a**, its acetate, and intermediates **3a–e** were entirely consistent with the structural assignments. In particular, the spectrum of **1a** showed no indication of the presence of the keto tautomer, 4-oxo-4,5-dihydrobenzo[*a*]pyrene, contrary to an earlier theoretical prediction[11] that the keto structure might exist preferentially.

Acid-catalyzed deacetoxylation of *cis*-4,5-diacetoxy-4,5-dihydrobenzo[*a*]pyrene[4] with *p*-toluenesulfonic acid in refluxing benzene afforded a mixture of the 4- and 5-phenol acetates in 3:2 ratio. Fractional crystallization followed by chromatography on Florisil gave **1b** and 5-acetoxybenzo[*a*]pyrene in overall yield of 30% and 11%, respectively.

Experimental Section

Methods and Materials. Proton NMR spectra were obtained on Varian T60 and Bruker 270-MHz spectrometers; chemical shifts are reported relative to Me_4Si in $CDCl_3$ unless indicated otherwise. IR spectra were obtained on a Perkin-Elmer Model 137 Infracord spectrophotometer. Tetrahydrofuran (THF), hexane, pyridine, toluene, and dimethyl sulfoxide (Me_2SO) were dried over $LiAlH_4$ and distilled from this reagent; CCl_4 was dried over P_2O_5. Gaseous methyl bromide (Matheson Co.) was purified by passage through a tube of Ascarite. *N*-Bromosuccinimide (NBS) was recrystallized from water and dried over P_2O_5. 5-Methyl-5,6-dihydrochrysene (**2**) was synthesized as previously described.[5] Microanalyses for C and H correct to ±0.3% were obtained for all new compounds.

5-Methylchrysene (3a). A solution of **2** (5.23 g, 21.4 mmol) and triphenylmethane (5.75 g, 23.5 mmol) in 20 mL of trifluoroacetic acid was maintained at reflux for 16 h and then cooled to room temperature, and water was added, followed by solid sodium bicarbonate. Extraction with ether and conventional workup afforded a dark brown residue (10.89 g). This was dissolved in benzene and filtered through a short column of silica gel to yield a light yellow solid (10.61 g). A solution of this solid in THF (100 mL) was added to a solution of $NaNH_2$ generated from reaction of Na metal (506 mg, 22 mmol) in ammonia (150 mL) in the presence of $FeCl_3$ (30 mg).[7] After 30 min, a stream of dry air was introduced, and the deep red solution turned brown. After 10 min, NH_4Cl (20 g) was added and the reaction worked up in the usual way to yield a brown solid, which was then chromatographed on neutral alumina. Elution with hexane gave minor impurities followed by 4.46 g (86%) of **3a** as a colorless solid: mp 117–118 °C (lit.[5,12] mp 117.2–117.8 °C, 117–118 °C; NMR δ 3.25 (s, 3, CH_3),[12] 7.55–8.15 (m, 8, aromatic), 8.53–9.10 (m, 3, H_4, H_{10}, and H_{11}).

5-(Bromomethyl)chrysene (3b). To a solution of **3a** (2.42 g, 10 mmol) in 15 mL of CCl_4 was added NBS (1.78 g, 10 mmol) and dibenzoyl peroxide (90 mg). The resulting heterogeneous solution was refluxed until the NBS was consumed (25 min), then filtered, and evaporated. The residue was partitioned between $CHCl_3$ and water. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by trituration with benzene followed by chromatography on silica gel to yield 2.41 g (75%) of **3b** as a white solid: mp 183–185 °C. Crystallization from CH_2Cl_2–ethanol gave the analytical sample as colorless plates: mp 186.5–187 °C; NMR δ 5.27 (s, 2, benzylic), 7.50–8.15 (m, 8, aromatic), 8.60–9.33 (m, 3, H_4, H_{10}, and H_{11}).

The following variations of the reaction conditions had the indicated effect on yield of **3b**: reaction time 1 h, 28%; no initiator, 50%; UV initiation, 4 h, 30%.

5-(Cyanomethyl)chrysene (3c). Solid **3b** (500 mg, 1.56 mmol) was added over a 10-min period to a rapidly stirred suspension of KCN (100 mg, 1.57 mmol) in Me_2SO (25 mL) at 70 °C. The solution was stirred at 70 °C for an additional 40 min, then cooled, diluted with water, and extracted with ether. The ether extract was washed with dilute HCl and water, dried over $MgSO_4$, and evaporated to afford a solid residue (385 mg). Chromatography of the latter on silica gel gave on elution with benzene–hexane (1:1) an unidentified material (30 mg) followed by **3c** as a light yellow solid (338 mg, 81%); mp 134–136 °C. Crystallization from CH_2Cl_2–hexane afforded **3c** as light yellow plates: mp 137–138 °C; NMR δ 4.40 (s, 2, CH_2), 7.40–8.63 (m, 11, aromatic).

Hydrolysis of 3c. A suspension of **3c** (286 mg, 1 mmol) in a solution of KOH (500 mg) in ethylene glycol (35 mL) and water

(1) This investigation was supported by research contract CP-033385 from the National Cancer Institute, DHHS. Samples of pure 4- and 5-hydroxybenzo[*a*]pyrene were furnished to the Chemical Repository, Illinois Institute of Technology, Research Institute for distribution to qualified investigators.

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(20 mL) was refluxed for 45 h. The reaction mixture was cooled to room temperature, and the resulting precipitate was filtered off, washed with water, and dried over P_2O_5 to afford 167 mg (59%) of **3d** as white solid; mp 250–254 °C. Crystallization from chloroform and recrystallization from chloroform–petroleum ether gave the analytical sample as white needles: mp 254–255 °C; IR (KBr) 3350 and 1650 cm^{-1}.

Acidification of the filtrate with dilute HCl precipitated a white solid, which was filtered, washed with water, and dried over P_2O_5 to yield **3e** (106 mg, 37%); mp 234–236 °C. Crystallization from benzene–hexane gave pure **3e** as light yellow prisms: mp 236 °C; NMR (acetone-d_6) δ 4.20 (s, 2, CH_2), 7.12–7.43 and 7.51–7.82 (m, 8, aromatic), 8.26–8.58 (m, 3, H_4, H_{10}, and H_{11}); IR (KBr) 1680 cm^{-1} (C=O).

A solution of **3c** (110 mg, 0.412 mmol) and NaOH (2 g) in ethylene glycol (20 mL), diglyme (10 mL), and water (10 mL) was refluxed for 40 h. Addition of ice–water and acidification with dilute HCl precipitated **3e** (65 mg, 55%) accompanied by an insoluble polymeric residue.

Hydrolysis of 3d. A suspension of **3d** (65 mg, 0.228 mmol) in a solution of NaOH (100 mg) in ethylene glycol (10 mL) and water (4 mL) was heated at reflux for 86 h. The product was filtered to remove a small amount of an insoluble material and acidified with HCl. Conventional workup furnished **3e** (55 mg, 85%).

4-Hydroxybenzo[*a*]pyrene (1a). A solution of **3e** (83 mg, 0.29 mmol) in anhydrous HF (20 mL) in a Teflon bottle was stirred under N_2 for 15 h. Evaporation of the HF in a stream of N_2 required 2 h. To the resulting greenish yellow residue was added a solution of $NaHCO_3$ (100 mg) in 40 mL of water. This was stirred together for 30 min, then extracted with ether, and worked up in a conventional manner. The crude product was triturated with two 3-mL portions of hexane and then purified by vacuum sublimation at 160–200 °C (0.03 mmHg) to afford pure **1a** (65 mg, 84%) as a yellow solid: mp 225–227 °C dec (lit.[2] mp 195–196 °C); NMR (acetone-d_6) δ 7.46 (s, 1, H_5), 7.73–7.84 (m, 2, $H_{8,9}$), 8.09 (t, 1, J = 8 Hz, H_2), 8.24–8.30 (m, 1, H_3), 8.34–8.46 (m, 3, $H_{6,7,12}$), 8.59 (d, 1, J = 8 Hz, H_1), 9.08–9.20 (m, 1, H_{10}), 9.16 (d, 1, J = 9 Hz, H_{11}), 9.58–9.68 (m, 1, OH); the OH absorption vanished when D_2O was added.

4-Acetoxybenzo[*a*]pyrene (1b). Acetylation of **1a** (53 mg, 0.24 mmol) with acetic anhydride (20 mL) and pyridine (2 mL) at room temperature for 5 h gave after workup and chromatography on Florisil (eluted with benzene) 62 mg (92%) of **1b** as a yellow solid: mp 170–172 °C; NMR δ 2.48 (s, 3, CH_3), 7.77 (s, 1, H_5), 7.79–7.83 (m, 2, $H_{8,9}$), 7.89 (t, 1, J = 8 Hz, H_2), 8.02 (d, 1, J = 8 Hz, H_3), 8.14 (d, 1, J = 8 Hz, H_1), 8.20–8.28 (m, 1, H_7), 8.21 (d, 1, J = 9 Hz, H_{12}), 8.47 (s, 1, H_6), 8.89–8.99 (m, 1, H_{10}), 8.92 (d, 1, J = 9 Hz, H_{11}).

4- and 5-Acetoxybenzo[*a*]pyrene. *cis*-4,5-Diacetoxy-4,5-dihydrobenzo[*a*]pyrene[4] (2.60 g, 7 mmol) was refluxed with *p*-toluenesulfonic acid monohydrate (260 mg) in 100 mL of dry benzene for 4 h under nitrogen. Conventional workup afforded 2.2 g of a foam, which was chromatographed under N_2 on a short column of Florisil. Elution with benzene gave 1.99 g (91%) of 4- and 5-acetoxybenzo[*a*]pyrenes in 3:2 ratio (by NMR). Crystallization from benzene–hexane gave **1b** (264 mg), which recrystallized from CH_2Cl_2–hexane as pale yellow needles: mp 170–172 °C; its NMR spectrum matched that of an authentic sample.

The mother liquor was concentrated to dryness in vacuo, taken up in benzene (25 mL), and chromatographed on a short column of Florisil under N_2. Elution with hexane gave a trace amount of benzo[*a*]pyrene. Elution with hexane–benzene (1:1) gave 62 mg of an unidentified yellow solid followed by 140 mg of 5-acetoxybenzo[*a*]pyrene: NMR δ 2.52 (s, 3, CH_3), 7.72–7.86 (m, 2, $H_{8,9}$), 7.79 (s, 1, H_4), 7.99 (t, 1, J = 8 Hz, H_2), 8.10 (d, 1, J = 8 Hz, H_3), 8.20–8.28 (m, 2, $H_{1,7}$), 8.28 (d, 1, J = 9 Hz, H_{12}), 8.45 (s, 1, H_6), 8.98 (m, 1, H_{10}), 8.99 (d, 1, J = 9 Hz, H_{11}).

Further elution with increasing proportions of benzene in hexane gave fractions rich in the 4-isomer, which were recrystallized to afford an additional 68 mg of **1b**. The overall purification procedure afforded 332 mg (15%) of pure **1b**, 140 mg (6.4%) of the pure 5-isomer, and 1.18 g (54%) of recovered mixed isomers. Repetition of the procedure twice more furnished overall yields of 30% and 11% of the 4- and 5-isomers, respectively.

Hydrolysis of 1b. A solution of **1b** (267 mg, 0.86 mmol) was heated at reflux in glacial acetic acid (15 mL) and concentrated HCl (3 mL) for 100 min. Addition of ice–water followed by extraction with ether and conventional workup furnished crude **1a** (242 mg). Trituration with hexane (5 mL) gave 210 mg (91%) of essentially pure **1a**; the NMR spectrum matched that of the authentic compound. The color and appearance of this compound was dependent upon the mode of purification. While sublimed **1a** was yellow, the recrystallized compound appeared black, but afforded yellow solutions.

Acknowledgment. The 270-MHz NMR spectrometer was funded in part through the University of Chicago Research Center Grant No. CA 14599.

Registry No. **1a**, 37574-48-4; **1b**, 56182-98-0; **2**, 34908-52-6; **3a**, 3697-24-3; **3b**, 85083-61-0; **3c**, 85083-62-1; **3d**, 85083-63-2; **3e**, 85083-64-3; 5-acetoxybenzo[*a*]pyrene, 24027-82-5; *cis*-4,5-diacetoxy-4,5-dihydrobenzo[*a*]pyrene, 56182-92-4.

Calixarenes. 10. Oxacalixarenes

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The base-catalyzed condensation of *p-tert*-butylphenol and paraformaldehyde yields a series of cyclic oligomers[1,2] for which the name "calixarene" has been suggested.[3] Under certain conditions a homologue containing an extra oxygen in the macrocyclic ring, designated as a dihomooxacalix[4]arene (**1**),[1,4] can also be isolated (Chart I). Although ^1H NMR analysis of the crude mixture indicates **1** to be present in significant quantities, its isolation in good yield in pure form is difficult. This note is concerned with an alternate route to **1** as well as the related oxacalixarenes *p-tert*-butyltetrahomodioxacalix[4]arene (**2**) and *p-tert*-butylhexahomotrioxacalix[3]arene (**3**).

The action of aqueous formaldehyde on *p-tert*-butylphenol in the presence of base is reported to yield the bis(hydroxymethyl) monomer **4** under mild conditions and the bis(hydroxymethyl) dimer **5** under more strenuous conditions.[5] When the published details were followed, a difficultly separable mixture of **4** and **5** was produced, but by extending the reaction time to 7 days, **5** could be isolated in pure form (Scheme I). Although **5** is obtained in only ca. 30% yield, the simplicity of the procedure makes it a readily available material. Alternatively, we have prepared **5** by debromination of the previously described *o*-bromo-*o'*-hydroxymethyl dimer **8**[1] followed by hydroxymethylation with aqueous formaldehyde and base. Condensation of **5** with *p-tert*-butylphenol in the presence of a catalytic amount of *p*-toluenesulfonic acid produces the linear tetramer **6** in 82.5% yield. An interesting property of **6** is its propensity to form a 1:2 complex with cyclohexane. The complex, which melts at 105 °C, is stable to heating for 24 h at 55 °C under vacuum but loses cyclohexane at its melting point to give solvent-free **6** melting at 212–213 °C. Treatment of **6** with excess aqueous

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