Lithium dimethylcuprate was prepared as follows. A solution of 1.02 g (2.1 mmol) of $(Bu_2S)_2CuI$[21] in 10 mL of ether was placed in a 15-mL centrifuge tube fitted with a septum cap. The tube was purged with dry nitrogen and cooled to −78 °C. Addition of 2.1 mmol of ethereal MeLi resulted in precipitation of yellow MeCu. The resulting suspension was centrifuged and the supernatant liquid forced out through a Teflon cannula with dry nitrogen. The resulting MeCu was washed several times at −78 °C with 10-mL portions of dry ether to remove lithium halide. Finally, the methylcopper was suspended in 8 mL of dry ether and 2 mmol of halide-free MeLi was added. Warming to 0 °C gave a clear solution of $LiCuMe_2$. Lithium dimethylcuprate was also prepared by using powdered CuI or Me_2SCuBr[22] instead of $(Bu_2S)_2CuI$. The different preparations gave the same results. Also, $LiCuMe_2$ prepared from ethereal MeLi (Ventron, 1:1 LiBr complex) gave the same results as the above halide-free $LiCuMe_2$.

Alkylation of (−)-*cis*-5-Methyl-2-cyclohexenyl Acetate ((−)-*cis*-4-OAc) with Lithium Dimethylcuprate. In a typical experiment 154 mg (1 mmol) of the above (−)-*cis*-4-OAc, $[\alpha]^{25}_D$ −2.7% ($CHCl_3$),[18] was added to 2 mmol of freshly prepared ethereal $LiCuMe_2$ in a centrifuge tube at 0 °C. The mixture was kept at 0 °C for 8 after which 1 mL of water was added. Methane was evolved and a reddish precipitate formed. After centrifuging, the supernatant liquid was decanted and concentrated, and the product (*trans*-5) was isolated by preparative GC (100 ft XF-1150 on Chromosorb W, 60 °C). Isolated yields ranged from 30% and 40%. Analysis by capillary GC (100 ft SE-30, 50 °C) showed the product to be 99.5% *trans*-5 and 0.5% *cis*-5. Capillary GC of the starting (−)-*cis*-4-OAc (300 ft Ucon LB-2000, 80 °C) showed the acetate to be homogeneous except for a trace (~1.0%) of the trans isomers. Results of this and a similar experiment are given in Table I. That the trace amount of *cis*-5 in the product does not contribute to the observed rotation was established as follows. Fractions containing up to 3% *cis*-5 were obtained by preparative GC. Fractions containing 1% and 3% *cis*-5 had rotations within experimental error of each other and the bottom value in Table I.

In a control experiment, 2 mmol of 35% optically pure (−)-*cis*-4-OAc was reacted with 1 mmol of $LiCuMe_2$ as described above. The unreacted acetate was recovered by preparative GC (10 ft FFAP on Chromosorb W, 70 °C). The optical purity of the recovered (−)-*cis*-4-OAc was found to be unchanged (35%) by direct determination with the chiral NMR shift reagent, Eu(hfbc)$_3$.[12] This experiment shows that *cis*-4-OAc retains its optical configuration under conditions of the reaction with $LiCuMe_2$. Thus loss of configuration for the *cis*-4-OAc → *trans*-5 occurs during the reaction.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE 8108535).

Registry No. (−)-*cis*-4-OAc, 85317-77-7; (−)-*cis*-4-OH, 69685-64-9; (+)-*trans*-5, 85317-78-8; (−)-*trans*-5, 69685-66-1; Eu(hfbc)$_3$, 34788-82-4; $(Bu_2S)_2CuI$, 35907-81-4; MeLi, 917-54-4; MeCu, 1184-53-8; lithium dimethylcuprate, 15681-48-8.

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High Dilution via Solid–Liquid Phase-Transfer Catalysis. A Practical Approach to the Synthesis of Macrolides[1]

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Received October 4, 1982

We report herein an extremely simple and effective procedure for preparing macrolides based on the solid–liquid phase-transfer catalysis principle.[2-4] Our method involves the use of tetrabutylammonium bromide (1) to solubilize and activate the conjugate base of ω-bromocarboxylic acids in toluene (Scheme I). When catalytic quantities of 1 are employed, high dilution conditions are simulated and excellent yields of macrolide are readily obtained.[5]

Attempted intramolecular displacement of 1.0 mmol of potassium 12-bromododecanoic acid *suspended* in 10 mL of toluene at 90 °C, in the absence of a phase-transfer catalyst, resulted in no detectable reaction after 3 h. In contrast, a similar mixture containing 8 mg of 1 produced a 95% yield (GLC) of 12-hydroxydodecanoic acid lactone. Upon filtration, solvent removal, and chromatographic purification, a 95% isolated yield of the macrolide was obtained. When higher concentrations of the soluble

Scheme I

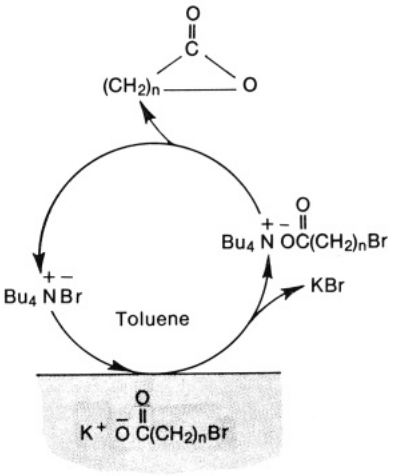
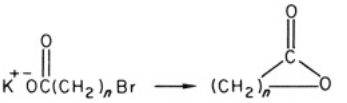


Table I. Biphase Cyclization of ω-Bromocarboxylic Acids[a]



n	ring size	$Bu_4N^+Br^-$, 10^3 M	time, h	yield,[b] %
5	7	2.5	3	92
7	9	1.5	24	26[c]
11	13	2.5	3	95 (95)[d]
		10.0	3	94
		58.0	3	85
		100.0	3	73
14	16	2.5	3	92
15	17	2.5	3	94

[a] Reaction of 0.1 mmol of potassium ω-bromocarboxylic acid suspended in 1.0 mL of anhydrous toluene in the presence of 1 at 90 °C. [b] GLC yield. [c] Yield remained unchanged upon further heating. [d] Isolated yield from a 1.0-mmol-scale reaction.

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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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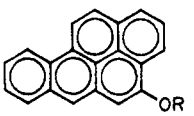
Received July 13, 1982

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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0022-3263/83/1948-1534$01.50/0