

**3-Hexanoyl-2-[9-((*tert*-butyldimethylsilyl)oxy)nonanoyl]-*sn*-glycerophosphatidylcholine (10).** A mixture of 0.2 g (0.6 mmol) of lysocaproyllecithin 9, 0.2 g (0.66 mmol) of 9-[(*tert*-butyldimethylsilyl)oxy]nonanoic acid (8), 0.15 g (0.75 mmol) of dicyclohexylcarbodiimide, and 50 mg (0.4 mmol) of (dimethylamino)pyridine were stirred in 100 mL of chloroform at room temperature under nitrogen for 48 h. The mixture was filtered to remove dicyclohexylurea and concentrated on a rotary evaporator. The residue in a small volume of chloroform was passed through a column of Rextyne I-300. Initially, the column was eluted with chloroform to remove excess 8 and then with 1:1 chloroform-methanol to recover the title product 10. Further purification of 10 was effected by HPLC. The lipid 10, recovered in 60% yield, had a retention time of 5.6 min.

**3-Hexanoyl-2-(9-hydroxynonanoyl)-*sn*-glycerophosphatidylcholine (11).** The above silyloxy lipid 10 (0.3 g, 0.5 mmol) was treated in dioxane solution with trifluoroacetic acid (0.6 mL) and 1 mL of water. After being stirred at room temperature for 1 h, the product was extracted with chloroform. Usual workup gave the desilylated lipid 11 in about 90% yield.

The preparation of 11 was also carried out by directly condensing lysocaproyllecithin 9 (0.6 mmol) with 0.22 g (0.66 mmol) of the hydroxy acid anhydride 13 in the presence of (dimethylamino)pyridine (0.05 g, 0.4 mmol) in chloroform solution at room temperature. The anhydride 13 was earlier made by treating the acid 3 with DCC in dichloromethane solution at room temperature for 5 h. The product 11 could be obtained in only 30% yield after chromatography over silica gel. A solid, mp 89 °C, was also recovered in an earlier fraction eluted with chloroform in ~35% yield and was characterized by its <sup>1</sup>H NMR as 14.

**3-Hexanoyl-2-[9-((chlorodimethylsilyl)oxy)nonanoyl]-*sn*-glycerophosphatidylcholine (12).** The lipid 11 (0.2 g, 0.5 mmol) was dissolved in chloroform and stirred at room temperature under nitrogen with 0.8 g of dichlorodimethylsilane and 0.5 g of pyridine for 24 h. The mixture was filtered to remove pyridine hydrochloride and concentrated in vacuum to yield 0.2 g of residue (65%), which was purified by HPLC. The product 12 had a retention time of 4.2 min: <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm from TMS) 0.21 (s, 6 H), 0.91 (t, 3 H), 1.03-1.63 (br s, 18 H), 2.26 (t, 3 H), 3.48 (br s, 9 H), 3.67-4.25 (br m, 11 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, ppm from TMS) 1.66 (SiCH<sub>3</sub>), 13.55 (CH<sub>3</sub>), 21.85, 24.10, 30.73, 33.71 (11 C, aliphatic), 54.17 (N(CH<sub>3</sub>)<sub>3</sub>), 60.48 (CH<sub>2</sub>O), 60.53 (CH<sub>2</sub>O), 63.75 (CH<sub>2</sub>OSi), 65.47 (CH<sub>2</sub>NMe<sub>3</sub>), 70.43 (CHO), 70.55 (OCH<sub>2</sub>CH<sub>2</sub>NMe<sub>3</sub>), 172.56 and 173.32 (C=O).

**Synthesis of 3-Hexanoyl-2-[12-((chlorodimethylsilyl)oxy)dodecanoyl]-*sn*-glycerophosphatidylcholine (21).** This compound was obtained by a procedure similar to 12. Condensation of the lysocleithin 9 with 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoic acid<sup>23</sup> according to the conditions utilized for making 10, gave 19 in ~75% yield (HPLC retention time, 6.1 min). Product 19 was desilylated to 20 in 90% yield with trifluoroacetic acid and 20 was resilylated with dichlorodimethylsilane (for conditions, see preparation of 12) to yield about 70% of 21 (HPLC retention time, 4.9 min): <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm from TMS) 0.18 (s, 6 H), 0.87 (t, 3 H), 1.04-1.68 (br s, 24 H), 2.32 (t, 4 H), 3.51 (br s, 9 H), 3.60-4.09 (br m, 11 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, ppm from TMS) 1.59 (SiCH<sub>3</sub>), 13.50 (CH<sub>3</sub>), 21.90, 24.05, 29.87, 30.15, 33.18 (14 C, aliphatic), 54.29 (NCH<sub>3</sub>), 60.48 (CH<sub>2</sub>O), 60.60 (CH<sub>2</sub>O), 62.55 (CH<sub>2</sub>OSi), 65.41 (CH<sub>2</sub>NMe<sub>3</sub>), 70.35 (CHO), 70.63 (OCH<sub>2</sub>CH<sub>2</sub>NMe<sub>3</sub>), 173.40, 174.71 (C=O).

**Surface Attachment of 12 and 21.** Oxidized silicon wafers, pretreated according to previously reported procedures,<sup>24</sup> were refluxed with the appropriate chlorosilyl derivative (0.1 g, 0.15 mmol) in dry chloroform (25 mL) and dry pyridine (0.2 mL) in a nitrogen atmosphere for 24 h. The solution was decanted off, and the wafers were washed several times with chloroform and methanol and finally vacuum-dried. For longevity, these lipid-treated wafers were stored under nitrogen in the refrigerator.

**Registry No.** 2, 2553-17-5; 2-ol, 3788-56-5; 4, 34957-73-8; 7, 110774-17-9; 8, 110774-18-0; 9, 58445-96-8; 10, 110774-19-1; 11, 110774-20-4; 12, 110774-23-7; 13, 110774-21-5; 14, 110774-22-6; 18, 77744-42-4; 19, 110774-24-8; 20, 110796-30-0; 21, 110774-25-9.

(24) Yoneyama, H.; Matumoto, N.; Tamura, H. *Langmuir* 1986, 2, 377-380.

## A Convenient Synthesis of Tetrakis(2-bromoethyl)methane<sup>1</sup>

George R. Newkome,\* V. K. Gupta, Rodger W. Griffin,<sup>2a</sup> and Sadao Arai<sup>2b</sup>

Department of Chemistry, University of South Florida, Tampa, Florida 33620

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During our quest to prepare tetradirectional unimolecular cascades,<sup>3</sup> we needed convenient access to symmetrical tetrasubstituted methanes. The obvious derivatives of pentaerythrol such as its tetramesylate or tetrakis(bromomethyl)methane were inert to nucleophilic substitution under normal conditions.<sup>4</sup> It was surmised that the corresponding homologue would circumvent this problem, thus a required high-yield route to tetrakis(2-bromoethyl)methane (1) was devised and is herein reported.

Classically, 1 was prepared by the bromination of tetrakis(2-hydroxyethyl)methane,<sup>5</sup> which was derived from citric acid in eleven steps.<sup>6</sup> Our approach to the synthesis of tetrabromide 1 is shown in Scheme I.

Tetrahydro-4H-pyran-4-one (3), prepared in a two-step process from the readily available 3-chloropropionyl chloride,<sup>7</sup> was treated with excess ammonia in absolute ethanol and 2 mol of ethyl cyanoacetate to give the ammonium salt of the Guareschi imide (4a).<sup>8</sup> The free imide (4b) was easily obtained by acidification of the ammonium salt 4a with concentrated hydrochloric acid. Hydrolysis/decarboxylation of 4a to the *gem*-diacid 5a by treatment with warm sulfuric acid or alkaline conditions caused considerable decomposition due to ring cleavage. Reaction of the salt of 4 with boiling concentrated hydrochloric acid smoothly led to the desired diacid in 65% from salt 4a. Acid 5a was esterified under normal Fischer conditions to give (72%) the diester, which was reduced with LiAlH<sub>4</sub> to generate (82%) diol 6. The <sup>13</sup>C NMR showed two different α (δ 58.1 and 63.5) and β (δ 36.4 and 39.2) carbon atoms, which is supportive of the 4,4-disubstituted pyran 6.

Treatment of diol 6 with KBr in concentrated H<sub>2</sub>SO<sub>4</sub> or with a mixture of HBr (48%) and concentrated H<sub>2</sub>SO<sub>4</sub> gave a mixture of 7 and 1 in poor isolated yield. The reaction of diol 6 with concentrated HCl gave (65%) spiro diether 7 as the major product. Subsequent treatment of this spiro diether with a mixture of HBr and H<sub>2</sub>SO<sub>4</sub> gave the desired tetrabromide 1 via smooth ether cleavage. The direct conversion of diol 6 to tetrabromide 1 was accomplished (57%) by bromination with PBr<sub>3</sub> and HBr (48%). The reaction of 1 and potassium carbonate at 275 °C gave a trace amount of tetravinylmethane.<sup>9</sup>

## Experimental Section

**General Comments.** Melting point data were obtained from

(1) Chemistry of Micelles Series. Part 4. Preceding paper, see: Newkome, G. R.; Baker, G. R.; Saunders, M. J.; Russo, P. S.; Gupta, V. K.; Yao, Z.-q.; Miller, J. E.; Bouillon, K. *J. Chem. Soc., Chem. Commun.* 1986, 752.

(2) (a) Visiting summer scholar from Manatee Community College, Bradenton, FL, 1987; (b) Visiting scholar from the Tokyo Metropolitan University, Tokyo, Japan, 1985-1987.

(3) Newkome, G. R.; Arai, S. 193rd National Meeting of the American Chemical Society, Denver, CO; April 5-10, 1987; ORGN 66.

(4) For example: Buchta, E.; Merck, W. *Justus Liebigs Ann. Chem.* 1966, 694, 1.

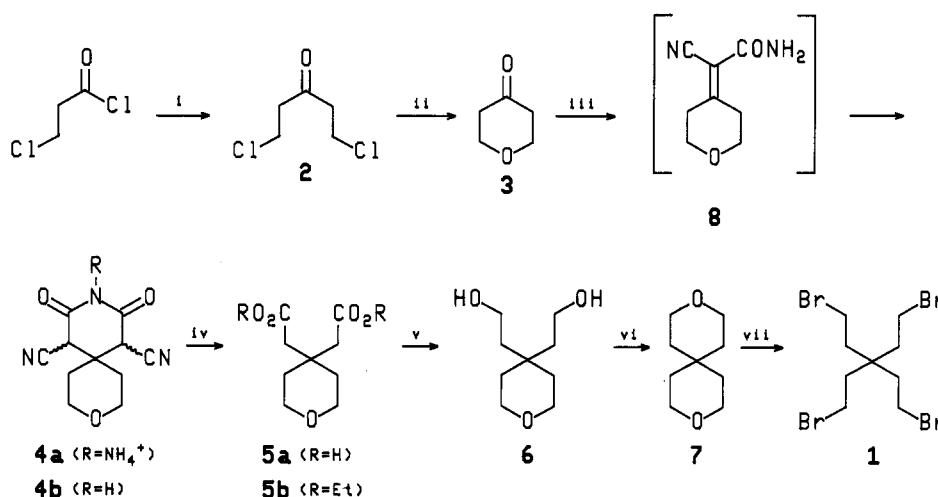
(5) Rice, L. M.; Scott, K. R. *J. Org. Chem.* 1967, 32, 1966.

(6) Ingold, C. K.; Nickolls, L. C. *J. Chem. Soc., Trans.* 1922, 1646.

(7) Owen, G. R.; Reese, C. B. *J. Chem. Soc. C* 1970, 2401. Arentzen, R.; Yan Kui, Y. T.; Reese, C. B. *Synthesis* 1975, 509.

(8) Kon, G. A. R.; Thorpe, J. F. *J. Chem. Soc., Trans.* 1911, 99, 422; 1919, 115, 686.

(9) Berger, J. G.; Stogryn, E. L.; Zimmerman, A. A. *J. Org. Chem.* 1964, 29, 950. Gleiter, R.; Haider, R.; Bischof, P.; Lindner, H.-J. *Chem. Ber.* 1983, 116, 3736.

Scheme I<sup>a</sup>

<sup>a</sup> (i)  $\text{CH}_2=\text{CH}_2$ ,  $\text{AlCl}_3$ , 5–10 °C; (ii)  $\text{H}_3\text{PO}_4$  (85%)/ $\text{NaH}_2\text{PO}_4\cdot\text{H}_2\text{O}$ , 100–103 °C; (iii)  $\text{NH}_3$  (anhydrous)/EtOH,  $\text{CNCH}_2\text{CO}_2\text{Et}$ , –5 °C, then  $\text{HCl}$  (concentrated)/ $\text{H}_2\text{O}$ , 25 °C; (iv)  $\text{HCl}$  (concentrated), reflux, 24 h, then EtOH/ $\text{C}_6\text{H}_6$ / $\text{H}_2\text{SO}_4$ , reflux; (v)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; (vi)  $\text{HCl}$  (concentrated), 95 °C, 2–3 h; (vii)  $\text{HBr}$  (48%)/ $\text{H}_2\text{SO}_4$  (concentrated), 100 °C, 20 h.

samples in capillary tubes with a Gallenkamp melting point apparatus (MFB-595) and are uncorrected. IR spectra were measured on an IBM IR 38 FTIR spectrophotometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR data were recorded on an IBM NR-80 spectrometer and were obtained in  $\text{CDCl}_3$  solutions, except where noted, with  $\text{Me}_4\text{Si}$  as the internal standard. MS data were obtained at 70 eV by Herb Land (LSU) on a Hewlett-Packard Model 5985 GC/MS spectrometer (assignments and relative intensities are reported in brackets).

**Tetrahydro-4H-pyran-4-one (3)** was prepared in a two-step process from 3-chloropropionyl chloride via 1,5-dichloropentan-3-one (2), according to a literature procedure:<sup>7</sup> bp 60–61 °C (15 mm) [lit.<sup>7</sup> bp 58 °C (12 mm)]; IR (neat) 1723 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  2.47 (t,  $\text{CH}_2\text{CO}$ ,  $J = 6$  Hz, 4 H), 3.97 (t,  $\text{CH}_2\text{O}$ ,  $J = 6$  Hz, 4 H);  $^{13}\text{C}$  NMR  $\delta$  41.9 ( $\text{OCH}_2\text{CH}_2$ ), 66.9 ( $\text{OCH}_2$ ), 205.6 ( $\text{C}=\text{O}$ ).

**Spirane 4b.** To a saturated ammonia-ethanol solution, prepared by bubbling anhydrous  $\text{NH}_3$  through absolute EtOH (300 mL) at –5 °C for 3 h, was added a mixture of distilled ethyl cyanoacetate (33.92 g, 0.30 mol) and tetrahydropyran-4-one (3; 15.06 g, 0.15 mol) at –5 °C. The mixture was sealed and maintained at –5 °C for 5 days. The resultant white crystalline precipitate was filtered, washed with dry ether, and air-dried. The solid was shown to be the ammonium salt (4a) of the Guareschini imide: 21.37 g (57%); mp 190.5–191.5 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.61 (m,  $\text{OCH}_2\text{CH}_2$ , 4 H), 3.69 (m,  $\text{OCH}_2$ , 4 H), 3.96 [s,  $\text{CH}(\text{CN})$ , 2 H]; MS,  $m/e$  233 ( $\text{M}^+ - \text{NH}_3$ , 1);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  33.9 ( $\text{OCH}_2\text{CH}_2$ ), 35.0 (quaternary C), 47.2 and 55.7 (CCN), 63.1 ( $\text{OCH}_2$ ), 116.4 and 126.3 (CN), 164.5 ( $\text{C}=\text{O}$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_3$ : C, 52.79; H, 5.64; N, 22.39. Found: C, 52.54; H, 5.63; N, 22.28.

If the ethanol is not saturated with  $\text{NH}_3$  or if there is excess moisture, the yields of the ammonium salt 4a decrease due to the formation of cyano amide 8 as white crystals: mp 152.5–153.5 °C;  $^1\text{H}$  NMR  $\delta$  2.76, 3.21 (2 t,  $\text{OCH}_2\text{CH}_2$ , 2 H each), 3.80, 3.88 (2 t,  $\text{OCH}_2$ , 2 H each); MS,  $m/e$  166 ( $\text{M}^+$ , 13).

**Spirane 4a** (500 mg, 5 mmol) was dissolved in a minimum volume of warm water and concentrated aqueous  $\text{HCl}$  was added until the pH was 3–4. After 10 h at 25 °C, the free dicyano imide 4b was filtered and washed with cold water (5 mL): mp 250 °C (white crystals); 420 mg (90%);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.75 (m,  $\text{OCH}_2\text{CH}_2$ , 4 H), 3.7 (m,  $\text{OCH}_2$ , 4 H), 5.1 (s,  $\text{CH}$ , 2 H), 12.3 (br s,  $\text{NH}$ , 1 H); MS,  $m/e$  233 ( $\text{M}^+$ , 1). Anal. Calcd for  $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3$ : C, 56.65; H, 4.76; N, 18.02. Found: C, 56.45; H, 4.76; N, 17.94.

**4,4-Pyrandiacetic Acid (5a).** A suspension of spirane 4a (50 g, 0.20 mol) in concentrated  $\text{HCl}$  (500 mL) was refluxed for 24 h. The mixture was cooled to 25 °C, and the resulting brown solid was filtered. The solid was washed several times with water. The combined filtrates were concentrated in vacuo to give (65%) diacid 5a as white microcrystals: mp 113–115 °C; IR (KBr) 1711  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ )  $\delta$  1.72 (t,  $\text{OCH}_2\text{CH}_2$ , 4 H), 2.66 (s,  $\text{CH}_2\text{CO}$ , 4 H),

3.76 (t,  $\text{OCH}_2$ , 4 H);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  32.0 (quaternary C), 35.0 ( $\text{OCH}_2\text{CH}_2$ ), 40.2 ( $\text{CH}_2\text{CO}$ ), 62.5 ( $\text{OCH}_2$ ), 172.9 ( $\text{C}=\text{O}$ ).

**Diethyl 4,4-Pyrandiacetate (5b).** A solution of crude diacid 5a, anhydrous EtOH (100 mL), benzene (150 mL), and concentrated  $\text{H}_2\text{SO}_4$  (6 mL) was refluxed for 3 h. The solution was concentrated, water was added, and the mixture was neutralized carefully with saturated aqueous  $\text{NaHCO}_3$ . The product was extracted with  $\text{CHCl}_3$ , dried over anhydrous  $\text{MgSO}_4$ , evaporated in vacuo, and distilled to give the colorless diester 5b: 24.4 g (72%); 47% from 4; bp 103–105 °C (0.5–0.8 mm);  $^1\text{H}$  NMR  $\delta$  1.23 (t,  $\text{CH}_3$ ,  $J = 7$  Hz, 6 H), 1.65 (t,  $\text{OCH}_2\text{CH}_2$ ,  $J = 5.5$  Hz, 4 H), 2.57 (s,  $\text{CH}_2\text{CO}_2$ , 4 H), 3.67 (t,  $\text{OCH}_2$ ,  $J = 5.5$  Hz, 4 H), 4.08 (q,  $\text{CH}_2\text{CH}_3$ ,  $J = 7$  Hz, 4 H);  $^{13}\text{C}$  NMR  $\delta$  13.7 ( $\text{CH}_3$ ), 32.5 (quaternary C), 35.3 ( $\text{OCH}_2\text{CH}_2$ ), 40.3 ( $\text{CH}_2\text{CO}$ ), 59.6 ( $\text{CH}_2\text{CH}_3$ ), 62.8 ( $\text{OCH}_2$ ), 171.0 ( $\text{C}=\text{O}$ ). Anal. Calcd for  $\text{C}_{13}\text{H}_{22}\text{O}_5$ : C, 60.44; H, 8.59. Found: C, 60.39; H, 8.29.

The corresponding methyl ester was prepared in a similar manner: mp 197–197.5 °C (white microcrystals); 220 mg (97%);  $^1\text{H}$  NMR  $\delta$  1.66 (t,  $\text{OCH}_2\text{CH}_2$ , 4 H), 2.63 (s,  $\text{CH}_2\text{CO}$ , 4 H), 3.65 (s,  $\text{CH}_3$ , 6 H), 3.68 (t,  $\text{OCH}_2$ , 4 H).

**4,4-Bis(2-hydroxyethyl)pyran (6).** A solution of ester 5b (2.9 g,  $1.12 \times 10^{-2}$  mol) in anhydrous ether (5 mL) was slowly added to a stirred suspension of  $\text{LiAlH}_4$  (1.07 g,  $2.8 \times 10^{-2}$  mol) in anhydrous ether (40 mL). After being stirred at 25 °C for 30 min, the mixture was refluxed overnight. The reaction was decomposed carefully by adding water, stirred for 4 h, and filtered. The residue was washed with ether ( $4 \times 10$  mL). The combined ethereal extract was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo to give (82%) the desired diol 6, as a colorless oil: 1.6 g;  $^1\text{H}$  NMR  $\delta$  1.49 (t,  $\text{OCH}_2\text{CH}_2$ ,  $J = 5.4$  Hz, 4 H), 1.74 (t,  $\text{CH}_2\text{CH}_2\text{OH}$ ,  $J = 6.8$  Hz, 4 H), 2.5 (br s, OH, 2 H), 3.6 ( $\text{OCH}_2$ ,  $J = 5.4$  Hz, 4 H), 3.73 (t,  $\text{CH}_2\text{OH}$ ,  $J = 6.8$  Hz, 4 H);  $^{13}\text{C}$  NMR  $\delta$  32.0 (quaternary C), 36.4 ( $\text{OCH}_2\text{CH}_2$ ), 3.92 ( $\text{CH}_2\text{CH}_2\text{OH}$ ), 58.1 ( $\text{C}-\text{H}_2\text{OH}$ ), 63.5 ( $\text{OCH}_2\text{CH}_2$ ). Anal. Calcd for  $\text{C}_9\text{H}_{18}\text{O}_3$ : C, 62.04; H, 10.41. Found: C, 61.89; H, 10.35.

**Tetrakis(2-bromoethyl)methane (1). Procedure A. Direct Conversion.** To a stirred solution of diol 6 (3.72 g,  $2.14 \times 10^{-2}$  mol) in  $\text{PBr}_3$  (10 mL) was slowly added 48%  $\text{HBr}$  (2 mL) with cooling. The solution was then warmed at 120 °C for 12 h. After cooling, the mixture was poured into water (200 mL) and neutralized with  $\text{NaHCO}_3$ . The product was extracted with  $\text{CH}_2\text{Cl}_2$ , and the extract was washed with  $\text{H}_2\text{O}$ , dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to give tetrabromide 1, which was recrystallized from absolute EtOH to afford long colorless needles: 5.36 g (57%); mp 181–182 °C (lit.<sup>5</sup> mp 183–184 °C);  $^1\text{H}$  NMR  $\delta$  1.90 (m,  $\text{CH}_2\text{CH}_2\text{Br}$ , 8 H), 3.34 (m,  $\text{CH}_2\text{Br}$ , 8 H);  $^{13}\text{C}$  NMR  $\delta$  25.8 ( $\text{CH}_2\text{Br}$ ), 39.7 ( $\text{CH}_2\text{CH}_2\text{Br}$ ), 43.3 (quaternary C).

**Procedure B. Via 3,9-Dioxospiro[5.5]undecane (7).** A mixture of diol 6 (500 mg, 2.87 mmol) and concentrated  $\text{HCl}$  (2 mL) was refluxed for 2.5 h. After cooling, the mixture was poured

into water (2 mL), carefully neutralized with solid  $\text{NaHCO}_3$ , and extracted with ether. The extract was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo to give spiro diether 7 as an oil: 290 mg (65%); bp 65–66 °C (1.0–1.5 mm) [lit.<sup>5</sup> bp 88–89 °C (4.5 mm)];  $^1\text{H NMR}$   $\delta$  1.55 (t,  $\text{CH}_2\text{CH}_2\text{O}$ ,  $J = 5.5$  Hz, 8 H), 3.66 (t,  $\text{CH}_2\text{O}$ ,  $J = 5.5$  Hz, 8 H).

To a stirred solution of the spiro diether 7 (1.5 g, 0.96 mmol) in 48%  $\text{HBr}$  (10 mL) was added with cooling concentrated  $\text{H}_2\text{SO}_4$  (5 mL). The mixture was warmed at 100 °C for 20 h and then worked up as described above in procedure A to afford pure tetrabromide 1: 2.5 g (59%).

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**Registry No.** 1, 5794-98-9; 3, 29943-42-8; 4a, 110796-52-6; 4b, 4703-71-3; 5a, 110796-49-1; 5b, 110796-53-7; 5b (methyl ester), 110796-54-8; 6, 110796-50-4; 7, 180-47-2; 8, 110796-51-5; ethyl cyanoacetate, 105-56-6.

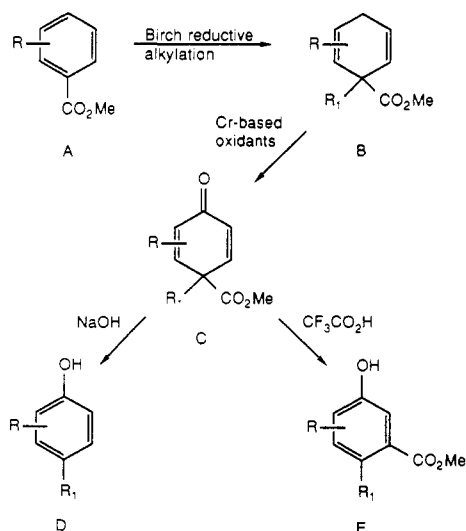
### A Synthetically Useful Conversion of Benzoic Acid Derivatives to 4-Alkylphenols and 4-Alkyl-3-carbalkoxyphenols

Arthur G. Schultz,\* Roger E. Harrington, Mark Macielag, Parag G. Mehta,<sup>1</sup> and Arthur G. Taveras

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

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Substituted phenols play crucial roles in biosynthetic transformations, and they represent important building blocks for organic synthesis. Hence, there is a continuing need for the development of strategies for the preparation of phenolic substrates that are not readily available by conventional aromatic substitution chemistry.<sup>2</sup> This note describes three-step conversions of benzoic acid derivatives A to 4-alkylphenols D and 3-carbalkoxy-4-alkylphenols E. The process combines recently reported methodology used to convert benzoic acid derivatives to 2,5-cyclohexadien-1-ones<sup>3</sup> with familiar rearrangements of dienones to phenols.<sup>4</sup>

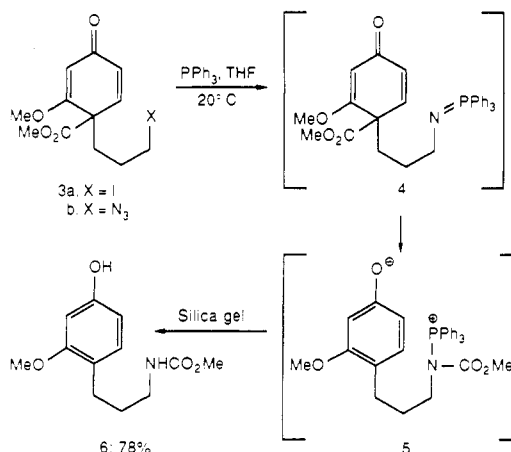


(1) Summer research participant, 1985.

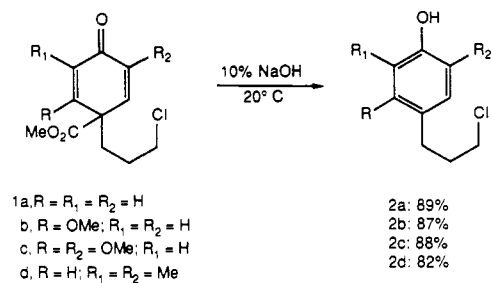
(2) For a recent example, see: Trost, B. M.; Saulnier, M. G. *Tetrahedron Lett.* 1985, 26, 123.

(3) Schultz, A. G.; Lavieri, F. P.; Macielag, M.; Plummer, M. J. *Am. Chem. Soc.* 1987, 109, 3991.

Scheme I



2,5-Cyclohexadien-1-ones 1a–d were prepared from the corresponding benzoic ester by Birch reductive alkylation, followed by allylic oxidation.<sup>3</sup> Brief treatment of 1a–d with aqueous sodium hydroxide solution at room temperature provided the 4-(3-chloropropyl)phenols 2a–d in excellent yields.<sup>5</sup>



An interesting variant of this nucleophile-induced substitution process was discovered from treatment of 4-(3-azidopropyl)-2,5-cyclohexadienone 3b with triphenylphosphine in tetrahydrofuran (THF); after chromatography on silica gel, the phenolic urethane 6 was obtained (Scheme I). This reaction presumably involves intramolecular methoxycarbonyl group transfer in the intermediate phosphine imine 4 to give zwitterion 5, from which hydrolysis to 6 and triphenylphosphine oxide occurs during chromatography on silica gel.

Rearrangements of a series of 4,4-disubstituted 2,5-cyclohexadienones in trifluoroacetic acid to 3,4-disubstituted phenols have shown that the carbomethoxy group migrates in preference to simple alkyl substituents.<sup>6</sup> With the literature conditions, both 1a and 7<sup>7</sup> cleanly underwent dienone–phenol rearrangements to 4-alkyl-3-carbomethoxyphenols 8a and 8b, respectively.

As illustrated in Scheme II, the method is particularly suited to the preparation of highly substituted 3-carbalk-

(4) For reviews of the dienone–phenol rearrangement, see: (a) de Mayo, P. In *Elucidation of Structures by Physical and Chemical Methods*; Bentley, K. W., Ed.; Wiley-Interscience: New York, 1963; p 1106. (b) Collins, C. J.; Eastham, J. F. In *The Chemistry of the Carbonyl Group*; Patai, S., Ed.; Wiley-Interscience: New York, 1966; p 775. (c) Waring, A. J. *Adv. Alicycl. Chem.* 1966, 1, 207. (d) Miller, B. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1969; Vol. 1, p 275.

(5) For the analogous conversion of 4-methyl-4-carbomethoxy-2,5-cyclohexadien-1-one (7; prepared by a Diels–Alder construction) to *p*-cresol, see: Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. J. *Am. Chem. Soc.* 1979, 101, 7001.

(6) Marx, J. N.; Argyle, J. C.; Norman, L. R. *J. Am. Chem. Soc.* 1974, 96, 2121.

(7) The rearrangement of 4-methyl-4-carbomethoxy-2,5-cyclohexadien-1-one to 4-methyl-3-carbomethoxyphenol is reported in ref 6.