Chemistry of micelles series. 4. A convenient synthesis of tetrakis(2-bromoethyl)methane

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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 Rexyne 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-hydroxynonanyl)-*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) and1 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 ^{1}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: ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, ppm from TMS) 1.66 ($SiCH_3$), 13.55 (CH_3), 21.85, 24.10, 30.73, 33.71 (11 C, aliphatic), 54.17 ($N(CH_3)_3$), 60.48 (CH_2O), 60.53 (CH_2O), 63.75 (CH_2OSi), 65.47 (CH_2NMe_3), 70.43 (*C*HO), 70.55 ($OCH_2CH_2NMe_3$), 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 lysolecithin **9** with 12-[(*tert*-butyldimethylsilyl)oxy]dodecanoic acid[23] 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): ^{1}H NMR ($CDCl_3$, 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); ^{13} NMR ($CDCl_3$, ppm from TMS) 1.59 ($SiCH_3$), 13.50 (CH_3), 21.90, 24.05, 29.87, 30.15, 33.18 (14 C, aliphatic) 54.29 (NCH_3), 60.48 (CH_2O), 60.60 (CH_2O), 62.55 (CH_2OSi), 65.41 (CH_2NMe_3), 70.35 (*C*HO), 70.63 ($OCH_2CH_2NMe_3$), 173.40, 174.71 (*C*=O).

Surface Attachment of 12 and 21. Oxidized silicon wafers, pretreated according to previously reported procedures,[24] 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 longivity, 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.

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A Convenient Synthesis of Tetrakis(2-bromoethyl)methane[1]

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During our quest to prepare tetradirectional unimolecular cascades,[3] 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.[4] 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,[5] which was derived from citric acid in eleven steps.[6] Our approach to the synthesis of tetrabromide **1** is shown in Scheme I.

Tetrahydro-4*H*-pyran-4-one (**3**), prepared in a two-step process from the readily available 3-chloropropionyl chloride,[7] was treated with excess ammonia in absolute ethanol and 2 mol of ethyl cyanoacetate to give the ammonium salt of the Guareschi imide (**4a**).[8] 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 $LiAlH_4$ to generate (82%) diol **6**. The ^{13}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_2SO_4 or with a mixture of HBr (48%) and concentrated H_2SO_4 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_2SO_4 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_3 and HBr (48%). The reaction of **1** and potassium carbonate at 275 °C gave a trace amount of tetravinylmethane.[9]

Experimental Section

General Comments. Melting point data were obtained from

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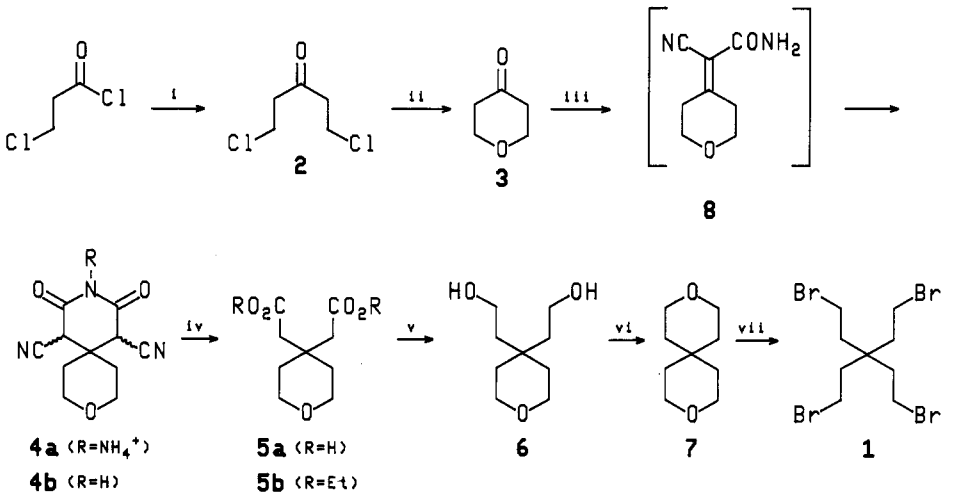
0022-3263/87/1952-5480$01.50/0

Scheme I[a]



[a] (i) $CH_2{=}CH_2$, $AlCl_3$, 5–10 °C; (ii) H_3PO_4 (85%)/$NaH_2PO_4{\cdot}H_2O$, 100–103 °C; (iii) NH_3 (anhydrous)/EtOH, $CNCH_2CO_2Et$, −5 °C, then HCl (concentrated)/H_2O, 25 °C; (iv) HCl (concentrated), reflux, 24 h, then EtOH/C_6H_6/H_2SO_4, reflux; (v) $LiAlH_4$, Et_2O; (vi) HCl (concentrated), 95 °C, 2–3 h; (vii) HBr (48%)/H_2SO_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. ^1H and ^{13}C NMR data were recorded on an IBM NR-80 spectrometer and were obtained in $CDCl_3$ solutions, except where noted, with Me_4Si 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-4*H*-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:[7] bp 60–61 °C (15 mm) [lit.[7] bp 58 °C (12 mm)]; IR (neat) 1723 (C=O) cm^{-1}; ^1H NMR δ 2.47 (t, CH_2CO, J = 6 Hz, 4 H), 3.97 (t, CH_2O, J = 6 Hz, 4 H); ^{13}C NMR δ 41.9 (OCH_2CH_2), 66.9 (OCH_2), 205.6 (C=O).

Spirane 4b. To a saturated ammonia–ethanol solution, prepared by bubbling anhydrous 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 percipitate was filtered, washed with dry ether, and air-dried. The solid was shown to be the ammonium salt (**4a**) of the Guareschi imide: 21.37 g (57%); mp 190.5–191.5 °C; ^1H NMR (DMSO-d_6) δ 1.61 (m, OCH_2CH_2, 4 H), 3.69 (m, OCH_2, 4 H), 3.96 [s, CH(CN), 2 H]; MS, m/e 233 ($M^+ - NH_3$, 1); ^{13}C NMR (DMSO-d_6) δ 33.9 (OCH_2CH_2), 35.0 (quaternary C), 47.2 and 55.7 (CCN), 63.1 (OCH_2), 116.4 and 126.3 (CN), 164.5 (C=O). Anal. Calcd for $C_{11}H_{14}N_4O_3$: 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 NH_3 or if these 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; ^1H NMR δ 2.76, 3.21 (2 t, OCH_2CH_2, 2 H each), 3.80, 3.88 (2 t, OCH_2, 2 H each); MS, m/e 166 (M^+, 13).

Spirane **4a** (500 mg, 5 mmol) was dissolved in a minimum volume of warm water and concentrated aqueous 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%); ^1H NMR (DMSO-d_6) δ 1.75 (m, OCH_2CH_2, 4 H), 3.7 (m, OCH_2, 4 H), 5.1 (s, CH, 2 H), 12.3 (br s, NH, 1 H); MS, m/e 233 (M^+, 1). Anal. Calcd for $C_{11}H_{11}N_3O_3$: 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 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 cm^{-1}; ^1H NMR (D_2O) δ 1.72 (t, OCH_2CH_2, 4 H), 2.66 (s, CH_2CO, 4 H), 3.76 (t, OCH_2, 4 H); ^{13}C NMR (DMSO-d_6) δ 32.0 (quaternary C), 35.0 (OCH_2CH_2), 40.2 (CH_2CO), 62.5 (OCH_2), 172.9 (C=O).

Diethyl 4,4-Pyrandiacetate (5b). A solution of crude diacid **5a**, anhydrous EtOH (100 mL), benzene (150 mL), and concentrated H_2SO_4 (6 mL) was refluxed for 3 h. The solution was concentrated, water was added, and the mixture was neutralized carefully with saturated aqueous $NaHCO_3$. The product was extracted with $CHCl_3$, dried over anhydrous $MgSO_4$, 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); ^1H NMR δ 1.23 (t, CH_3, J = 7 Hz, 6 H), 1.65 (t, OCH_2CH_2, J = 5.5 Hz, 4 H), 2.57 (s, CH_2CO_2, 4 H), 3.67 (t, OCH_2, J = 5.5 Hz, 4 H), 4.08 (q, CH_2CH_3, J = 7 Hz, 4 H); ^{13}C NMR δ 13.7 (CH_3), 32.5 (quaternary C), 35.3 (OCH_2CH_2), 40.3 (CH_2CO), 59.6 (CH_2CH_3), 62.8 (OCH_2), 171.0 (C=O). Anal. Calcd for $C_{13}H_{22}O_5$: 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%); ^1H NMR δ 1.66 (t, OCH_2CH_2, 4 H), 2.63 (s, CH_2CO, 4 H), 3.65 (s, CH_3, 6 H), 3.68 (t, OCH_2, 4 H).

4,4-Bis(2-hydroxyethyl)pyran (6). A solution of ester **5b** (2.9 g, 1.12×10^{-2} mol) in anhydrous ether (5 mL) was slowly added to a stirred suspension of $LiAlH_4$ (1.07 g, 2.8×10^{-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 × 10 mL). The combined ethereal extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give (82%) the desired diol **6**, as a colorless oil: 1.6 g; ^1H NMR δ 1.49 (t, OCH_2CH_2, J = 5.4 Hz, 4 H), 1.74 (t, CH_2CH_2OH, J = 6.8 Hz, 4 H), 2.5 (br s, OH, 2 H), 3.6 (OCH_2, J = 5.4 Hz, 4 H), 3.73 (t, CH_2OH, J = 6.8 Hz, 4 H); ^{13}C NMR δ 32.0 (quaternary C), 36.4 (OCH_2CH_2), 3.92 (CH_2CH_2OH), 58.1 (CH_2OH), 63.5 (OCH_2CH_2). Anal. Calcd for $C_9H_{18}O_3$: 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, 2.14×10^{-2} mol) in PBr_3 (10 mL) was slowly added 48% 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 $NaHCO_3$. The product was extracted with CH_2Cl_2, and the extract was washed with H_2O, dried over anhydrous Na_2SO_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.[5] mp 183–184 °C); ^1H NMR δ 1.90 (m, CH_2CH_2Br, 8 H), 3.34 (m, CH_2Br, 8 H); ^{13}C NMR δ 25.8 (CH_2Br), 39.7 (CH_2CH_2Br), 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 HCl (2 mL) was refluxed for 2.5 h. After cooling, the mixture was poured

into water (2 mL), carefully neutralized with solid $NaHCO_3$, and extracted with ether. The extract was dried over anhydrous Na_2SO_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.[5] bp 88–89 °C (4.5 mm)]; ^1H NMR δ 1.55 (t, CH_2CH_2O, J = 5.5 Hz, 8 H), 3.66 (t, CH_2O, J = 5.5 Hz, 8 H).

To a stirred solution of the spiro diether **7** (1.5 g, 0.96 mmol) in 48% HBr (10 mL) was added with cooling concentrated H_2SO_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

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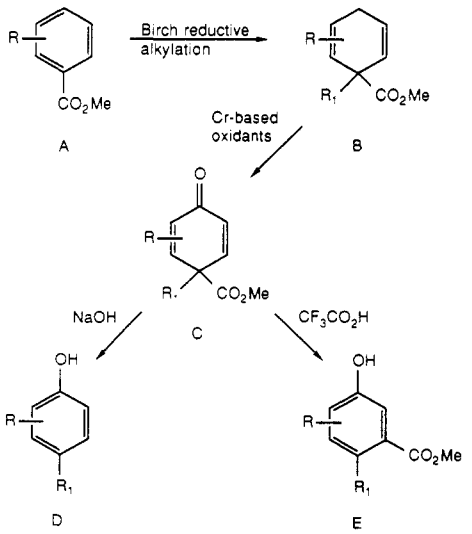
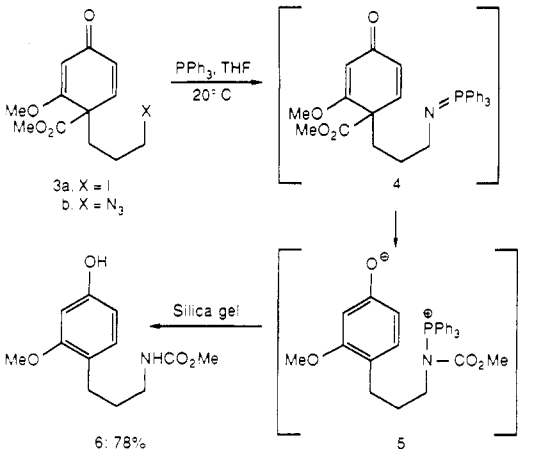
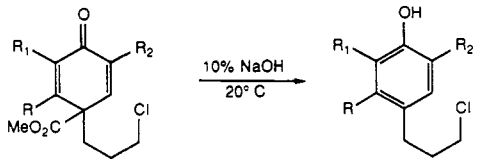
Substituted phenols play crucial roles in biosynthetic transformations, and they represent important building blocks for organic synthesis. Hence, there is a continuing need for the development of strategies for the preparation of phenolic substrates that are not readily available by conventional aromatic substitution chemistry.[2] 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[3] with familiar rearrangements of dienones to phenols.[4]



Scheme I



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



1a, R = R_1 = R_2 = H
b, R = OMe; R_1 = R_2 = H
c, R = R_2 = OMe; R_1 = H
d, R = H; R_1 = R_2 = Me

2a: 89%
2b: 87%
2c: 88%
2d: 82%

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 carbethoxy group migrates in preference to simple alkyl substituents.[6] With the literature conditions, both **1a** and **7**[7] 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-

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0022-3263/87/1952-5482$01.50/0