Regiospecific Synthesis of Heterosubstituted Phenols from 3-Alkoxycarbonyl-3,5-dienoic Acids via Benzannulation Reaction

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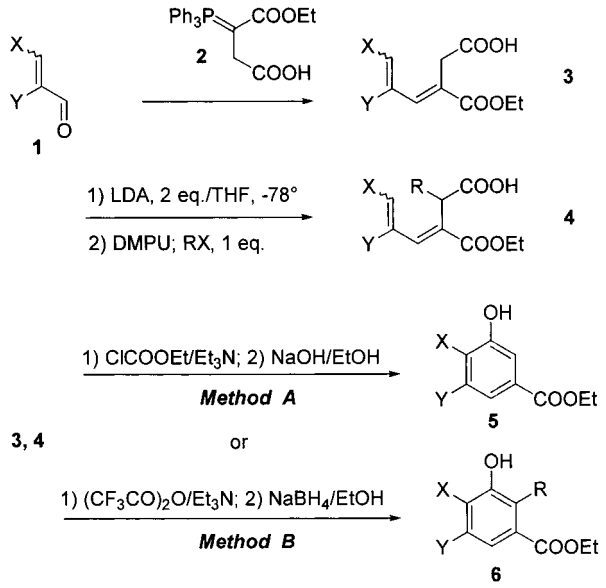
Introduction

The regiospecific preparation of polysubstituted aromatic compounds is one of the challenging problems in organic synthesis. The classic approach is based on aromatic substitution, which introduces a substituent to a preexisting arene. A great variety of synthetic methodologies based on this route have been developed, and the most well-known are electrophilic or nucleophilic substitutions,[1] catalyzed coupling reactions,[2] and metalation−functionalization reactions.[3] The main restriction of this approach lies in the activating or deactivating and orienting effects of the substituents that limit the application of the synthetic methods.

Other approaches that build up the aromatic moiety starting from acyclic precursors[4] have received growing interest since the preparation of highly substituted compounds in only few steps and the avoidance of ortho−meta−para mixtures obtained in conventional aromatic synthesis show several advantages. These general features are common in the most useful benzannulation routes based on Diels−Alder [4 + 2] cycloaddition,[5] transition-metal-catalyzed [2 + 2 + 2] and [4 + 2] cycloaddition,[6] [3 + 3][7] and [4 + 2][8] benzannulation, 1,6-electrocyclic reaction,[9] and Dötz reaction.[10]

Recently, we have developed a method of benzannulation that allows the construction of 4-substituted 3-hydroxybenzoic acid derivatives by mild base-promoted cyclization of substituted 3-alkoxycarbonyl-3,5-hexadienoic acids.[11] The latter process is very flexible, and we have previously shown that it can be used in the preparation of oligoaryls,[11,12] naphthalenes,[13] chiral tetrahydronaphthalenes,[14] ring-fused heterocycles,[15] *C*-arylglycosides,[16] and many natural products of different structure.[17] The introduction of a heterosubstituent into hydroxybenzoic acid derivatives by classical routes usually requires harsh conditions and often does not proceed with high positional selectivity. Otherwise, our benzannulation approach affords regiospecifically the substituted phenols and the mild conditions used allow the introduction of different kinds of heterosubstituents. We report herein the exploitation of this synthetic methodology to obtain 4- and 5-heterosubstituted 3-hydroxybenzoic acid derivatives starting from readily available 2- and 3-heterosubstituted α,β-unsaturated aldehydes.

Scheme 1



X, Y = *hydrogen, aryl, alkyl, halogen, alkoxy, thioaryl, trimethylsilyl*
R = *methyl, allyl*

Results and Discussion

As mentioned above, the design of our synthetic path is based on the preparation of aldehydes **1** followed by their homologation to the related hexadienoic acids **3** and **4** (Scheme 1), which are cyclized to phenols **5** and **6**, respectively. The 2- and 3-heterosubstituted α,β-unsaturated aldehydes **1** were prepared starting from easily available materials and using known methodologies (see the Experimental Section). The synthesis of the 3-alkoxycarbonyl-3,5-hexadienoic acids **3** was performed by means

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(10) (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (b) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187.

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(13) Fuganti, C.; Serra, S. *J. Chem. Res., Synop.* **1998**, 638.

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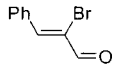
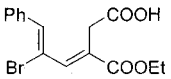
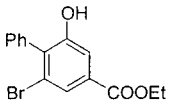
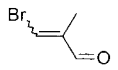
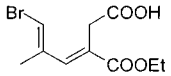
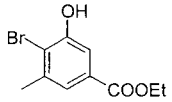
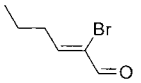
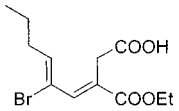
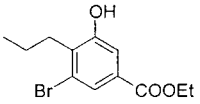
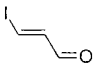
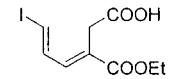
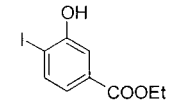
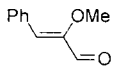
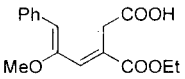
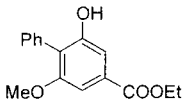
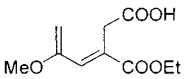
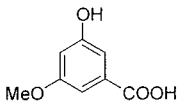
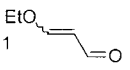
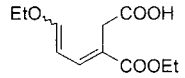
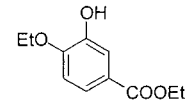
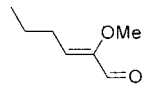
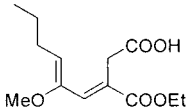
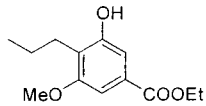
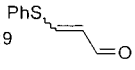
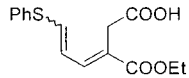
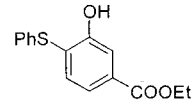
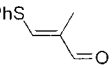
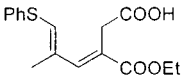
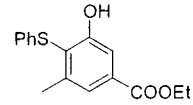
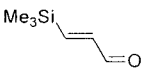
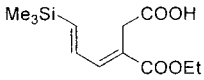
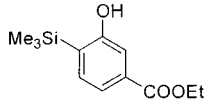
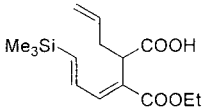
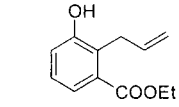
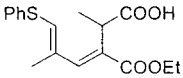
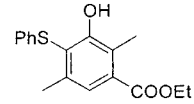
Table 1. Synthesis of Acids 3, 4 and Phenols 5, 6 from Aldehydes 1

Entry	Aldehydes **1**	Wittig conditions and yields[a]	Acids **3** and **4**	Benzannulation conditions[b] and yields[a]	Phenols **5** and **6**
a	**2*Z*** 	50°C, 12h, 70%		**3*E*, 5*Z*** A/ 78%	
b	*E*/*Z* 4:1 	r.t. 3d, 74%		3*E*, 5*E* A/ 89%	
c	2*Z* 	r.t. 4d, 68%		3*E*, 5*Z* A/ 72%	
d	2*E* 	r.t. 3d, 90%		3*E*, 5*E* A/60% B/91%	
e	2*Z* 	50°C, 6h, 88%		3*E*, 5*Z* A/ 88%	
f		r.t. 1d		3*E* A/ 70%[c, d]	
g	*E*/*Z* 4:1 	r.t. 6d, 67%		3*E*, 5*E* and 3*E*, 5*Z* (4:1) A/ 90%	
h	2*Z* 	r.t. 5d, 71%		3*E*, 5*Z* B/ 89%	
i	*E*/*Z* 1:9 	50°C, 6h, 95%		3*E*, 5*E* and 3*E*, 5*Z* (1:9) A/ 70%	
j	2*E* 	r.t. 5d, 75%		3*E*, 5*E* B/ 86%	
k	2*E* 	r.t. 2d, 87%		3*E*, 5*E* A/50% B/60%	
l		alkylation of acid **3k** with CH_2CHCH_2Br, 88%		3*E*, 5*E* B/80%	
m		alkylation of acid **3j** with MeI, 85%		3*E*, 5*E* B/ 95%	

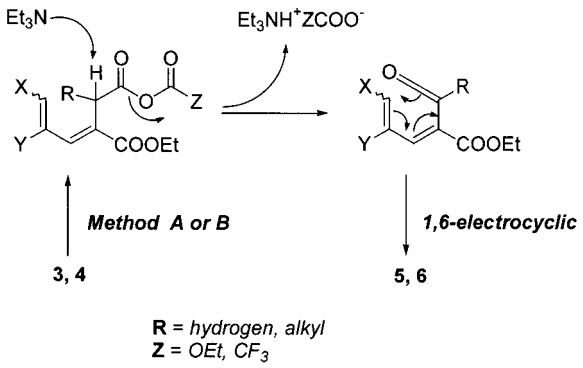
[a] After chromatography and/or crystallization. [b] A and B are the benzannulation methods. [c] Combined yield of the two steps (Wittig and benzannulation). [d] Obtained as benzoic acid derivative by hydrolysis of the related ester.

of a Wittig reaction of aldehydes **1** with triphenyl(α-carbethoxy-β-carboxyethyl)phosphonium ylide **2**.[18] The reaction proceeded smoothly for all substrates (Table 1) and the yield of isolated acid **3** range from 65 to 95% depending either on the steric hindrance in the α position or the presence of electron-withdrawing or electron-releasing substituents. The steric requirements can strongly affect the reaction trend. This was confirmed by further experiment of Wittig reaction of ylide **2** with different α-phenyl-β-alkoxy acroleins and α-iodo-β-alkyl acroleins,[19] which were also unaffected under forcing

(18) (a) For the preparation of this ylide, see: Hudson, R. F.; Chopard, P. A. *Helv. Chim. Acta* **1963**, *46*, 2178. (b) Compounds **3a**,**c**−**f**,**h**,**j**−**k** were prepared starting from isomerically pure aldehydes **1**, and they were obtained as single stereoisomers. Otherwise, the aldehydes **1g**,**i** were available as an *E*/*Z* mixture and their homologation to dienic acids gave compounds **3g**,**i** as a corresponding mixture of two regioisomers (see the Experimental Section). Since the Wittig reaction of the ylide **2** with the aldehydes affords the 3-(*E*)-alkylidenesuccinic acid monomethyl esters in ahighly stereoselective way, we assigned the *E* stereochemistry at the new formed double bonds of the compounds **3**. For previous studies on the stereoselectivity of this reaction, see: Röder, E.; Krauss, H. *Liebigs Ann. Chem.* **1992**, 177. Paquette, L. A.; Schulze, M. M.; Bolin, D. *J. Org. Chem.* **1994**, *59*, 2043.

(19) The reaction of ylide **2** with 2-bromoacrolein, 2,3-dibromoacrolein, and 2-iodoacrolein was also tested, but quick polymerization of the starting aldehydes occurs before the formation of dienic acids.

Scheme 2



conditions. Despite this limitation, a great variety of substituents on the starting aldehydes **1** were tolerated, and also acroleins bearing labile substituents (such as Br, I, and Si) reacted in a straightforward way.

Moreover, to devise a new entry to 2-substituted 3-hydroxybenzoic acids, we examined next the alkylation in the α position[20a] of the acids **3**. We found that the conversion of **3** in the corresponding dianions using 2 equiv of LDA as base in the presence of 4 equiv of DMPU[20b] followed by reaction with methyl iodide or allyl bromide gave the α alkylated acids, without isomerization of the dienic framework.[21] As representative examples we converted acids **3j** and **3k** to the acids **4m** and **4l**, respectively, in good yields and with quite complete regioselectivity.[22] Then, the combination of Wittig reaction by means of ylide **2** with α alkylation of the so-obtained acids was a useful route to dienic acids **3** and **4** that can be easily benzannulated to phenols **5** and **6**, respectively.

This cyclization step was performed by two simple experimental procedures that work under very mild conditions and differ in the use of activating agent. In both procedures, the acids **3** or **4** were treated at room temperature and in THF solution with ethyl chloroformate (method A) or trifluoroacetic anhydride (method B) as activating agents, followed by the addition of an excess of triethylamine. The so-formed mixed anhydrides were unstable in base and were converted in a divinylketene intermediate that cyclized through a 1,6-electrocyclic reaction (Scheme 2) to give phenols **5** or **6**. Since the activating agent and the base were used in excess, a slight amount of carboxyethyl trifluoroacetyl derivatives of the resulting phenols were also formed. These products were easily converted into the suitable phenols in the workup procedure by quick treatment with ethanolic KOH (method A) or by reduction with $NaBH_4$ (method B).

The rates of conversion and the yields of products are dependent on the activating agent and on the nature of the starting acids. When ethyl chloroformate is used, the reaction is very fast (few minutes at 0−20°) and we obtained the phenolic derivatives together with a slight amount (less than 10%)[23] of the diethyl esters of the starting acids. We assume that ethanol, derived from the decomposition of mixed anhydrides, reacts in competitive behavior with the divinylketenes to give the ethyl esters. According to our explanation, the same procedure, performed by using trifluoroacetic anhydride as activating agent and by prolonging the reaction time (2 h), gives the phenolic derivatives in higher yield. Furthermore, in both procedures the conversion of starting acid was quantitative and the resulting phenolic compounds were formed regiospecifically.

The examination of the substitution pattern of the acids **3a**−**j** and **4m** shows the flexibility of the present synthetic approach: phenyl, alkyl, halo, alkoxy, and thiophenyl groups are unaffected to give the related phenols **5a**−**j** and **6m**, respectively, and in high yields. The acids **3k** and **4l** were cyclized to phenols **5k** and **6l** with partial (less than 20% for **k**) and complete (**l**) loss of the trimethylsilyl group. Since the amount of benzannulated phenols indicate a quantitative conversion to the aromatic compounds, these different trends can be explained in term of a low stability of the *o*-trimethylsilyl phenols.[24]

In conclusion, these experiments demonstrate the utility and the flexibility of this benzannulation procedure in the regiospecific synthesis of heterosubstituted phenols. The starting materials are easily available, the experimental procedure is very simple, and the products are obtained in high yields. Moreover, this pathway shows many advantages over the classical routes based on the aromatic substitution, and its claimed versatility allows the preparation of a wide set of 2,4,5-substituted 3-hydroxybenzoic acid derivatives not easily accessible through the available methods.

Experimental Section

General Methods. ^1H NMR spectra were recorded in $CDCl_3$ solution at room temperature, unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^1H). The chemical-shift scale is based on internal tetramethylsilane. IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. Mass spectra were measured on a Finnigan-MAT TSQ 70 spectrometer. Melting points were measured on a Reichert melting point apparatus, equipped with a Reichert microscope, and are uncorrected. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on a silica gel columns.

Aldehydes 1a−k. The aldehydes **1a**−**k** were prepared as follows. (*Z*)-2-bromo-3-phenylpropenal[25] **1a**, (*E*/*Z* 4:1)-2-methyl-3-bromopropenal[26] **1b**, (*Z*)-2-bromohex-2-enal[27] **1c**, (*Z*)-2-methoxy-3-phenylpropenal **1e**, and (*Z*)-2-methoxyhex-2-enal[28] **1h** have been obtained from the corresponding unsaturated aldehydes via a bromination−HBr elimination sequence (aldehydes **1a**−**c**) and a α-methoxylation procedure[28] (aldehydes **1e** and **1h**), respectively. (*E*)-3-Iodopropenal[29] **1d** was obtained by HI addition on propynal. 2-Methoxypropenal[30] **1f** was obtained by Mannich reaction on methoxyacetaldehyde. (*E*/*Z* 4:1)-3-Ethoxy-

(20) (a) For α-alkylation of β,γ-unsaturated acid, see: van der Veen, R. H.; Cerfontain, H. *J. Org. Chem.* **1985**, *50*, 342. (b) We tested also the LDA−HMPA system for this alkylation. The results were comparable, so we preferred the less toxic DMPU as reagent of choice for this reaction.

(21) Alkylation of halogen substituted dienic acids **3a**−**d** afforded only trace of the acids **4a**−**d**. This behavior was probably due to the base-induced elimination of halogen atoms.

(22) The products of γ alkylation were not detected in the reaction mixture whereas α-dialkylated products were formed in slight amount (less than 10%, GC analysis).

(23) Phenol **5d** was obtained together with 20% of diethyl ester of acid **3d**. This different behavior can be explained in term of major steric hindrance around the position 6 of the hexadienoic system.

(24) Other authors noted the instability of *o*-triethylsilylphenols; see ref 8c.

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propenal[31] **1g** was obtained from malonaldehyde bis(diethyl acetal). (*E*/*Z* 1:9)-3-Thiophenylpropenal **1i** and (*E*)-3-trimethylsilylpropenal **1k** were obtained by MnO_2 oxidation of the related allylic alcohol which was prepared by addition of thiophenol[32] on propargylic alcohol and by reduction[33] of 3-trimethylsilyl-2-propyn-1-ol, respectively. (2*E*)-3-thiophenyl-2-methylpropenal (**1j**) was synthesized by addition of sodium thiophenate on aldehyde **1b**.[34]

General Procedure for the Synthesis of 3-Ethoxycarbonyl-3,5-hexadienoic Acids 3. The aldehyde **1** (50 mmol) in toluene (80 mL) was treated with triphenyl(α-carbethoxy-β-carboxyethyl)phosphonium ylide **2** (24.4 g, 60 mmol) and hydroquinone (50 mg, 0.45 mmol) at the temperature indicated and stirred for the necessary period of time (see Table 1). The solvent was removed under reduced pressure, and the residue was purified by chromatography on a silica gel column eluting with the suitable hexane/ethyl acetate mixture to afford pure acid **3**.

(3*E*,5*Z*)-3-(Ethoxycarbonyl)-5-bromo-6-phenyl-3,5-hexadienoic acid (3a): yield 70%; colorless crystals (from hexane/ethyl acetate); mp 82−83 °C; FT-IR (film) 1702, 1618, 1412, 1263, 1230, 1202, 957, 689 cm^{-1}; EI-MS *m*/*z* 339 (M^+, 18), 259 (M^+ − Br, 92), 213 (32), 185 (100), 169 (6), 157 (34), 141 (55), 139 (32), 129 (36), 115 (44); ^1H NMR (250 MHz, $CDCl_3$) δ 7.72−7.63 (2H, m), 7.52 (1H, s), 7.44−7.30 (3H, m), 7.13 (1H, s), 4.28 (2H, q, *J* = 7.1 Hz), 3.71 (2H, s), 1.32 (3H, t, *J* = 7.1 Hz). Anal. Calcd for $C_{15}H_{15}BrO_4$ (339.18): C, 53.12; H, 4.46. Found: C, 53.15; H, 4.45.

(3*E*,5*E*)-3-(Ethoxycarbonyl)-5-methyl-6-bromo-3,5-hexadienoic acid (3b): yield 74%; only the (3*E*,5*E*) isomer was obtained although a 4:1 *E*/*Z* mixture of aldehyde **1b** was employed in the preparation; colorless oil; FT-IR (film) 3090, 1712, 1641, 1260, 1200, 1100, 1027, 767 cm^{-1}; EI-MS *m*/*z* 197 (M^+ − Br, 46), 151 (73), 123 (100), 107 (9), 95 (14), 79 (27); ^1H NMR (250 MHz, $CDCl_3$) δ 7.23 (1H, s), 6.46 (1H, m), 4.25 (2H, q, *J* = 7.1 Hz), 3.51 (2H, s), 1.98 (3H, d, *J* = 0.9 Hz), 1.31 (3H, t, *J* = 7.1 Hz). Anal. Calcd for $C_{10}H_{13}BrO_4$ (277.11): C, 43.34; H, 4.73. Found: C, 43.45; H, 4.70.

(3*E*,5*Z*)-3-(Ethoxycarbonyl)-5-bromo-3,5-nonadienoic acid (3c): yield 68%; colorless oil; FT-IR (film) 1714, 1372, 1271, 1204, 1095, 788, 767 cm^{-1}; EI-MS *m*/*z* 306 (M^+ + 1, 1), 304 (M^+ − 1, 1), 288 (5), 286 (5), 260 (M^+ − OEt, 8), 225 (M^+ − Br, 84), 179 (85), 161 (20), 151 (42), 123 (100), 105 (27); ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (1H, s), 6.13 (1H, dt, *J* = 6.7, 1.2 Hz), 4.25 (2H, q, *J* = 7.1 Hz), 3.61 (2H, s), 2.35−2.20 (2H, m), 1.49 (2H, sext, *J* = 7.5 Hz), 1.31 (3H, t, *J* = 7.1 Hz), 0.96 (3H, t, *J* = 7.5 Hz). Anal. Calcd for $C_{12}H_{17}BrO_4$ (305.16): C, 47.23; H, 5.61. Found: C, 47.45; H, 5.55.

(3*E*,5*E*)-3-(Ethoxycarbonyl)-6-iodo-3,5-hexadienoic acid (3d): yield 90%; pale yellow crystals (from hexane/ethyl acetate); mp 106 °C; FT-IR (film) 1717, 1629, 1414, 1273, 1230, 1082, 972, 956, 768 cm^{-1}; EI-MS *m*/*z* 310 (M^+, 2), 266 (23), 237 (9), 183 (30), 137 (66), 109 (100), 82 (24), 65 (31); ^1H NMR (250 MHz, $CDCl_3$) δ 7.37−7.20 (2H, m), 7.05 (1H, dd, *J* = 12.8, 0.9 Hz), 4.24 (2H, t, *J* = 7.2 Hz), 3.46 (2H, s), 1.30 (3H, t, *J* = 7.2 Hz). Anal. Calcd for $C_9H_{11}IO_4$ (310.09): C, 34.86; H, 3.58. Found: C, 34.80; H, 3.55.

(3*E*,5*Z*)-3-(Ethoxycarbonyl)-5-methoxy-6-phenyl-3,5-hexadienoic acid (3e): yield 88%; colorless crystals (from hexane/ethyl acetate); mp 98−100 °C; FT-IR (film) 1700, 1593, 1244, 1193, 1050, 700 cm^{-1}; EI-MS *m*/*z* 290 (M^+, 5), 259 (M^+ − OMe, 6), 245 (M^+ − OEt,10), 199 (100), 167 (36), 153 (14), 139 (78), 91 (29); ^1H NMR (250 MHz, $CDCl_3$) δ 7.51 (1H, s), 7.38−7.16 (5H, m), 6.10 (1H, s), 4.20 (2H, q, *J* = 7.1 Hz), 3.82 (2H, s), 3.73 (3H, s), 1.24 (3H, t, *J* = 7.1 Hz). Anal. Calcd for $C_{16}H_{18}O_5$ (290.31): C, 66.19; H, 6.25. Found: C, 66.30; H, 6.22.

(3*E*)-3-(Ethoxycarbonyl)-5-methoxy-3,5-hexadienoic acid (3f) and (3*E*,5*E*)-3-(ethoxycarbonyl)-6-ethoxy-3,5-hexadienoic acid (3g): colorless oil. The compounds were transformed into the corresponding phenol immediately after the purification step because of their instability. The compound **3g** was obtained as a 4:1 mixture of (3*E*,5*E*) and (3*E*,5*Z*) isomers as confirmed by GC analysis.

(3*E*,5*Z*)-3-(Ethoxycarbonyl)-5-methoxy-3,5-nonadienoic acid (3h): yield 71%; colorless oil; FT-IR (film) 1709, 1636, 1264, 1203, 1098, 1035 cm^{-1}; EI-MS *m*/*z* 256 (M^+, 4), 238 (8), 225 (15), 210 (41), 199 (57), 181 (67), 167 (54), 153 (71), 139 (73), 109 (100); ^1H NMR (250 MHz, C_6D_6) δ 7.31 (1H, s), 4.98 (1H, t, *J* = 7.7 Hz), 4.04 (2H, q, *J* = 7.2 Hz), 3.93 (2H, s), 3.18 (3H, s), 2.04−1.91 (2H, m), 1.18 (2H, sext, *J* = 7.5 Hz), 0.98 (3H, t, *J* = 7.2 Hz), 0.77 (3H, t, *J* = 7.5 Hz). Anal. Calcd for $C_{13}H_{20}O_5$ (256.29): C, 60.92; H, 7.87. Found: C, 70.11; H, 7.82.

(3*E*,5*E*)-3-(Ethoxycarbonyl)-6-thiophenyl-3,5-hexadienoic acid (3i): yield 95%; colorless oil; FT-IR (film) 1711, 1618, 1558, 1280, 958, 745 cm^{-1}; EI-MS *m*/*z* 292 (M^+, 49), 248 (3), 220 (63), 191 (42), 135 (79), 123 (41), 110 (100), 91 (48); ^1H NMR (250 MHz, $CDCl_3$) δ 7.48−7.28 (5H, m), 7.03−6.84 (2H, m), 6.38 (1H, dd, *J* = 14.7, 11.7 Hz), 4.22 (2H, q, *J* = 7.2 Hz), 3.4 (2H, s), 1.29 (3H, t, *J* = 7.2 Hz). Anal. Calcd for $C_{15}H_{16}O_4S$ (292.35): C, 61.62; H, 5.52. Found: C, 61.45; H, 5.45.

(3*E*,5*E*)-3-(Ethoxycarbonyl)-5-methyl-6-thiophenyl-3,5-hexadienoic acid (3j): yield 75%; colorless crystals (from hexane/ethyl acetate); mp 77 °C; FT-IR (film) 3434, 1702, 1614, 1276, 1199, 1030, 816, 743 cm^{-1}; EI-MS *m*/*z* 306 (M^+, 8), 281 (7), 260 (4), 207 (10), 183 (8), 155 (9), 137 (9), 123 (100), 110 (19), 77 (11); ^1H NMR (250 MHz, $CDCl_3$) δ 7.44−7.22 (6H, m), 6.70 (1H, s), 4.23 (2H, q, *J* = 7.2 Hz), 3.61 (2H, s), 2.04 (3H, s), 1.29 (3H, t, *J* = 7.2 Hz). Anal. Calcd for $C_{16}H_{18}O_4S$ (306.38): C, 62.72; H, 5.92. Found: C, 62.75; H, 5.91.

(3*E*,5*E*)-3-(Ethoxycarbonyl)-6-(trimethylsilyl)-3,5-hexadienoic acid (3k): yield 87%; colorless crystals (from hexane); mp 58 °C; FT-IR (film) 1713, 1629, 1416, 1286, 1207, 990, 859, 841 cm^{-1}; EI-MS *m*/*z* 256 (M^+, 4), 241 (5), 227 (6), 195 (11), 183 (100), 167 (22), 151 (21), 137 (66), 123 (32), 109 (29); ^1H NMR (250 MHz, C_6D_6) δ 7.46 (1H, d, *J* = 10.8 Hz), 6.72 (1H, dd, *J* = 18, 10.8 Hz), 6.09 (1H, dd, *J* = 18, 0.7 Hz), 4.00 (2H, q, *J* = 7.1 Hz), 3.41 (2H, s), 0.96 (3H, t, *J* = 7.1 Hz), −0.02 (9H, s). Anal. Calcd for $C_{12}H_{20}O_4Si$ (256.37): C, 56.22; H, 7.86. Found: C, 56.30; H, 7.85.

General Procedure for the Synthesis of 2-Alkyl-3-ethoxycarbonyl-3,5-hexadienoic Acids 4 from Acids 3. A stirred solution of diisopropylamine (8.8 mL, 63 mmol) in dry THF (90 mL) was cooled to −78 °C and treated with a 10 M solution of *n*-BuLi (6.3 mL) under a static atmosphere of nitrogen. After 15 min, DMPU (14.5 mL, 120 mmol) was added, followed by the dropwise addition of a THF (20 mL) solution of acid **3** (30 mmol). The mixture immediately turned deep red, and the reaction was stirred for another 1 h. Then, the suitable alkylating agent (iodometane or allyl bromide, 30 mmol) was added rapidly and the solution became pale red within 30 min. The temperature was raised to 0 °C, and the mixture was diluted with ether (200 mL) and acidified with an excess of 5% aqueous HCl (150 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 60 mL). The combined organic portions were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column eluting with the suitable hexane/ethyl acetate mixture to afford pure acid **4**.

(3*E*,5*E*)-2-Allyl-3-(ethoxycarbonyl)-6-(trimethylsilyl)-3,5-hexadienoic acid (4l): yield 88%; colorless oil; FT-IR (film) 1713, 1642, 1622, 1570, 1416, 1208, 988, 917, 840 cm^{-1}; EI-MS *m*/*z* 296 (M^+, 6), 255 (3), 235 (5), 223 (46), 209 (14), 177 (19) 149 (21), 133 (26), 105 (30), 75 (100); ^1H NMR (250 MHz, C_6D_6) δ 7.52 (1H, d, *J* = 10.9 Hz), 6.83 (1H, dd, *J* = 18, 10.9 Hz), 6.09 (1H, d, *J* = 18 Hz), 5.78−5.58 (1H, m), 5.05−4.82 (2H, m), 4.00 (2H, q, *J* = 7.2 Hz), 3.85 (1H, dd, *J* = 9, 5.5 Hz), 3.03−2.92 (1H, m), 2.78−2.60 (1H, m), 0.97 (3H, t, *J* = 7.2 Hz), 0.03 (9H, s). Anal. Calcd for $C_{15}H_{24}O_4Si$ (296.43): C, 60.78; H, 8.16. Found: C, 60.95; H, 8.20.

(3*E*,5*E*)-2,5-Dimethyl-3-(ethoxycarbonyl)-6-thiophenyl-3,5-hexadienoic acid (4m): yield 85%; colorless crystals (from hexane/ethyl acetate); mp 82−83 °C; FT-IR (film) 3435, 1714, 1691, 1605, 1275, 1248, 1073, 1022, 810, 750 cm^{-1}; EI-MS *m*/*z* 320 (M^+, 2), 274 (15), 211 (64), 165 (56), 137 (100), 109 (19), 91 (15), 77 (17); ^1H NMR (250 MHz, $CDCl_3$) δ 7.42−7.24 (6H, m), 6.61 (1H, s), 4.20 (2H, q, *J* = 7.2 Hz), 3.97 (1H, q, *J* = 7.1 Hz), 2.05 (3H, s), 1.39 (3H, d, *J* = 7.1 Hz), 1.27 (3H, t, *J* = 7.2 Hz).

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Anal. Calcd for $C_{17}H_{20}O_4S$ (320.4): C, 63.73; H, 6.29. Found: C, 63.54; H, 6.35.

General Procedure for the Benzannulation of Acids 3 and 4 to Phenols 5 and 6. Method A. Ethyl chloroformate (3.8 mL, 40 mmol) was added in one portion to a solution of acid **3** or **4** (20 mmol) in dry THF (40 mL), and then Et_3N (8.4 mL, 60 mmol) was added, keeping the temperature under 20 °C by external cooling. The reaction mixture was stirred for 15 min at room temperature, treated with an excess of 5% aqueous HCl (100 mL), and extracted with ethyl acetate (2 × 100 mL). Concentration of organic phase gave a residue that was treated with ethanolic (100 mL) NaOH (2.4 g, 60 mmol) at room temperature for 15 min.

Method B. TFAA (5.6 mL, 40 mmol) was added in one portion to a solution of acid **3** or **4** (20 mmol) in dry THF (60 mL), and then Et_3N (8.4 mL, 60 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h, acidified with an excess of 5% aqueous HCl (100 mL), and extracted with ethyl acetate (2 × 100 mL). The organic phase was concentrated under reduced pressure and the residue dissolved in ethanol (100 mL). The latter mixture was cooled to 0 °C and treated with $NaBH_4$ (1.52 g, 40 mmol), stirring for 1 h.

Both procedures continue as follows: the reaction was diluted with ethyl acetate (100 mL) and 5% aqueous HCl (100 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 60 mL). The combined organic portions were washed with brine (100 mL), dried, and concentrated under reduced pressure. The so-obtained crude phenol **5** or **6** was purified by chromatography on a silica gel column eluting with the suitable hexane/ethyl acetate mixture.

4-Phenyl-5-bromo-3-hydroxybenzoic acid ethyl ester (5a): method A; yield 78%; colorless crystals (from hexane/ethyl acetate); mp 148−149 °C; FT-IR (film) 3365, 1699, 1416, 1302, 1243, 770, 700 cm^{-1}; EI-MS *m/z* 322 (M^+ + 1, 42), 320 (M^+ − 1, 41), 277 (M^+ − EtOH, 74), 219 (10), 168 (72), 139 (100), 128 (8); ^1H NMR (250 MHz, $CDCl_3$) δ 7.90 (1H, d, J = 1.6 Hz), 7.64 (1H, d, J = 1.6 Hz), 7.56−7.40 (3H, m), 7.34−7.27 (2H, m), 5.64 (1H, s), 4.37 (2H, q, J = 7.1 Hz), 1.39 (3H, t, J = 7.1 Hz). Anal. Calcd for $C_{15}H_{13}BrO_3$ (321.17): C, 56.10; H, 4.08. Found: C, 56.00; H, 4.05.

4-Bromo-5-methyl-3-hydroxybenzoic acid ethyl ester (5b): method A; yield 89%; colorless crystals (from toluene); mp 104−105 °C; FT-IR (film) 3387, 1690, 1592, 1423, 1319, 1265, 770 cm^{-1}; EI-MS *m/z* 260 (M^+ + 1, 46), 258 (M^+ − 1, 47), 245 (M^+ − Me, 12), 243 (M^+ − Me, 13), 232 (38) 230 (39), 215 (98), 213 (100), 187 (21) 185 (22), 77 (23); ^1H NMR (250 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 1.9 Hz), 7.48 (1H, d, J = 1.9 Hz), 5.9−6.2 (1H, bs), 4.37 (2H, q, J = 7.1 Hz), 2.44 (3H, s), 1.39 (3H, t, J = 7.1 Hz). Anal. Calcd for $C_{10}H_{11}BrO_3$ (259.10): C, 46.36; H, 4.28. Found: C, 46.25; H, 4.30.

4-Propyl-5-bromo-3-hydroxybenzoic acid ethyl ester (5c): method A; yield 72%; colorless crystals (from hexane); mp 88 °C; FT-IR (film) 3423, 1698, 1575, 1416, 1290, 1216, 1105, 854 cm^{-1}; EI-MS *m/z* 288 (M^+ + 1, 100), 286 (M^+ − 1, 88), 259 (M^+ − Et, 85), 256 (81), 243 (14), 231 (22), 229 (22), 213 (8), 77 (10); ^1H NMR (250 MHz, $CDCl_3$) δ 7.78 (1H, d, J = 1.5 Hz), 7.58 (1H, d, J = 1.5 Hz), 6.1−6.4 (1H, bs), 4.38 (2H, q, J = 7.2 Hz), 2.84−2.78 (2H, m), 1.61 (2H, sext, J = 7.2 Hz), 1.39 (3H, t, J = 7.2), 1.01 (3H, t, J = 7.2 Hz). Anal. Calcd for $C_{12}H_{15}BrO_3$ (287.15): C, 50.19; H, 5.27. Found: C, 50.05; H, 5.25.

4-Iodo-3-hydroxybenzoic acid ethyl ester (5d): method B; yield 91%; colorless crystals (from toluene); mp 119−120 °C; FT-IR (film) 3384, 1695, 1590, 1419, 1230, 757, 618 cm^{-1}; EI-MS *m/z* 292 (M^+ + 1, 66), 277 (7), 264 (40), 247 (M^+-OEt, 100), 219 (16), 119 (10), 92 (13); ^1H NMR (250 MHz, $CDCl_3$) δ 7.76 (1H, d, J = 8.2 Hz), 7.67 (1H, d, J = 1.9 Hz), 7.33 (1H, dd, J = 8.2, 1.9 Hz), 5.98 (1H, bs), 4.38 (2H, q, J = 7.2 Hz), 1.39 (3H, t, J = 7.2 Hz). Anal. Calcd for $C_9H_9IO_3$ (292.07): C, 37.01; H, 3.11. Found: C, 37.17; H, 3.08.

4-Phenyl-5-methoxy-3-hydroxybenzoic acid ethyl ester (5e): method A; yield 88%; colorless crystals (from hexane/ethyl acetate); mp 118−120 °C; FT-IR (film) 3411, 1699, 1589, 1464, 1320, 1250, 1097, 697 cm^{-1}; EI-MS *m/z* 272 (M^+, 100), 257 (M^+ − Me, 6), 244 (9), 227 (M^+ − OEt, 46), 200 (32), 128 (19); ^1H NMR (250 MHz, $CDCl_3$) δ 7.55−7.32 (6H, m), 7.27−7.22 (1H, m), 4.39 (2H, q, J = 7.1 Hz), 3.93 (1H, s), 3.78 (3H, s), 1.40 (3H, t, J = 7.1 Hz). Anal. Calcd for $C_{16}H_{16}O_4$ (272.30): C, 70.57; H, 5.92. Found: C, 70.41; H, 5.98.

5-Methoxy-3-hydroxybenzoic acid (5f): method A; yield 70%; colorless crystals (from ethanol); mp 199−200 °C; FT-IR (film) 3288, 1694, 1617, 1255, 807, 716 cm^{-1}; EI-MS *m/z* 168 (M^+, 100), 151 (M^+ − OH, 15), 138 (8), 121 (37), 108 (9), 95 (11), 69 (14); ^1H NMR (400 MHz, CD_3COCD_3) δ 9.6 (2H, bs), 7.16 (1H, s), 7.10 (1H, s) 6.66 (1H, t, J = 2.2 Hz), 3.80 (3H, s). Anal. Calcd for $C_8H_8O_4$ (168.15): C, 57.14; H, 4.80. Found: C, 56.96; H, 4.83.

4-Ethoxy-3-hydroxybenzoic acid ethyl ester (5g): method A; yield 90%; colorless crystals (from hexane); mp 81−82 °C; FT-IR (film) 3408, 1695, 1614, 1515, 1304, 1278, 1216, 765 cm^{-1}; EI-MS *m/z* 210 (M^+, 57), 182 (12), 165 (M^+ − OH, 24), 154 (40), 137 (100), 109 (12), 81 (6); ^1H NMR (250 MHz, $CDCl_3$) δ 7.63−7.57 (2H, m), 6.88−6.82 (1H, m), 5.71 (1H, bs), 4.33 (2H, q, J = 7.2 Hz), 4.17 (2H, q, J = 7.2 Hz), 1.47 (3H, t, J = 7.2 Hz), 1.37 (3H, t, J = 7.2 Hz). Anal. Calcd for $C_{11}H_{14}O_4$ (210.23): C, 62.85; H, 6.71. Found: C, 62.70; H, 6.75.

4-Propyl-5-methoxy-3-hydroxybenzoic acid ethyl ester (5h): method B; yield 89%; colorless crystals (from hexane/ethyl acetate); mp 91 °C; FT-IR (film) 3415, 1702, 1596, 1424, 1262, 1131, 772 cm^{-1}; EI-MS *m/z* 238 (M^+, 46), 209 (M^+ − Et, 100), 193 (M^+ − OEt, 18), 181 (14), 163 (14), 151 (13), 125 (9), 77 (7); ^1H NMR (250 MHz, $CDCl_3$) δ 7.29 (1H, d, J = 1.4 Hz), 7.13 (1H, d, J = 1.4 Hz), 5.97 (1H, bs), 4.37 (2H, q, J = 7.2 Hz), 3.85 (3H, s), 2.70−2.60 (2H, m), 1.55 (2H, sext, J = 7.4 Hz), 1.38 (3H, t, J = 7.2 Hz), 0.95 (3H, t, J = 7.4 Hz). Anal. Calcd for $C_{13}H_{18}O_4$ (238.28): C, 65.53; H, 7.61. Found: C, 65.70; H, 7.55.

4-Thiophenyl-3-hydroxybenzoic acid ethyl ester (5i): method A; yield 70%; colorless crystals (from hexane/ethyl acetate); mp 110−111 °C; FT-IR (film) 1716, 1475, 1439, 1250, 749, 692 cm^{-1}; EI-MS *m/z* 274 (M^+,100), 259 (2), 246 (14), 229 ((M^+ − OEt, 48), 201 (6), 173 (9), 140 (7), 129 (5), 115 (4), 95 (5); ^1H NMR (250 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 1.8 Hz), 7.64−7.50 (2H, m), 7.31−7.10 (5H, m), 6.53 (1H, bs), 4.38 (2H, q, J = 7.1 Hz), 1.39 (3H, t, J = 7.1 Hz). Anal. Calcd for $C_{15}H_{14}O_3S$ (274.34): C, 65.67; H, 5.14. Found: C, 65.49; H, 5.19.

4-Thiophenyl-5-methyl-3-hydroxybenzoic acid ethyl ester (5j): method B; yield 86%; colorless crystals (from hexane/ethyl acetate); mp 62 °C; FT-IR (film) 3402, 1695, 1583, 1315, 1247, 1041, 771, 732 cm^{-1}; EI-MS *m/z* 288 (M^+, 100), 273 (M^+ − Me, 3), 260 (7), 243 (M^+ − OEt, 38), 182 (16), 171 (6), 154 (9), 109 (7), 77 (9); ^1H NMR (250 MHz, $CDCl_3$) δ 7.59 (1H, s), 7.56 (1H, s), 7.30−7.10 (3H, m), 7.04−6.97 (2H, m), 6.89 (1H, s), 4.38 (2H, q, J = 7.2 Hz), 2.41 (3H, s), 1.40 (3H, t, J = 7.2 Hz). Anal. Calcd for $C_{16}H_{16}O_3S$ (288.36): C, 66.64; H, 5.59. Found: C, 66.47; H, 5.56.

4-Trimethylsilyl-3-hydroxybenzoic acid ethyl ester (5k): method A; yield 50%; colorless crystals (from hexane); mp 103−104 °C; FT-IR (film) 3351, 1690, 1408, 1300, 1220, 846, 759 cm^{-1}; EI-MS *m/z* 238 (M^+, 25), 223 (M^+ − Me, 100), 222 (63), 195 (40), 177 (60), 149 (51), 135 (15), 119 (6), 105 (9), 91 (10), 75 (15); ^1H NMR (250 MHz, $CDCl_3$) δ 7.59−7.52 (2H, m), 7.42 (1H, d, J = 7.5 Hz), 6.05 (1H, bs), 4.38 (2H, q, J = 7.2 Hz), 1.39 (3H, t, J = 7.2 Hz), 0.32 (9H, s). Anal. Calcd for $C_{12}H_{18}O_3Si$ (238.36): C, 60.47; H, 7.61. Found: C, 60.55; H, 7.67.

2-Allyl-3-hydroxybenzoic acid ethyl ester (6l): method B; yield 80%; colorless crystals (from hexane/ethyl acetate); mp 56−58 °C; FT-IR (film) 3380, 1672, 1583, 1466, 1285, 760 cm^{-1}; EI-MS *m/z* 206 (M^+, 100), 191 (56), 177 (23), 161 (M^+ − OEt, 86), 149 (24), 131 (76), 115 (22), 105 (47), 77 (37); ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 (1H, dd, J = 7.7, 1.2 Hz), 7.18 (1H, t, J = 8 Hz), 6.99 (1H, dd, J = 8, 1.2 Hz), 6.14−5.96 (1H, m), 5.24 (1H, bs), 5.15 (1H, t, J = 1.6 Hz), 5.12−5.06 (1H, m), 4.35 (2H, q, J = 7.2 Hz), 3.76 (2H, dt, J = 5.9, 1.6 Hz), 1.38 (3H, t, J = 7.2 Hz). Anal. Calcd for $C_{12}H_{14}O_3$ (206.24): C, 69.88; H, 6.84. Found: C, 70.05; H, 6.80.

2,5-Dimethyl-4-thiophenyl-3-hydroxybenzoic acid ethyl ester (6m): method B; yield 95%; colorless oil; FT-IR (film) 3396, 1722, 1583, 1479, 1320, 1226, 1056, 738 cm^{-1}; EI-MS *m/z* 302 (M^+, 100), 273 (17), 257 (M^+ − OEt, 36), 228 (12), 196 (7), 168 (7), 123 (5), 91 (6) 77 (5); ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (1H, s), 7.27−7.12 (3H, m), 7.11 (1H, s), 7.04−6.96 (2H, m), 4.38 (2H, t, J = 7.1 Hz), 2.47 (3H, s), 2.35 (3H, s), 1.41 (3H, t, J = 7.1 Hz).

Anal. Calcd for $C_{17}H_{18}O_3S$ (302.39): C, 67.52; H, 6.00. Found: C, 67.70; H, 5.96.

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Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **5a**−**k**, and **6l**,**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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