A Facile One-Pot Conversion of Acetates of the Baylis−Hillman Adducts to [*E*]-α-Methylcinnamic Acids

Deevi Basavaiah,* Marimganti Krishnamacharyulu, Rachakonda Suguna Hyma, Pakala K. S. Sarma, and Nagaswamy Kumaragurubaran

School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

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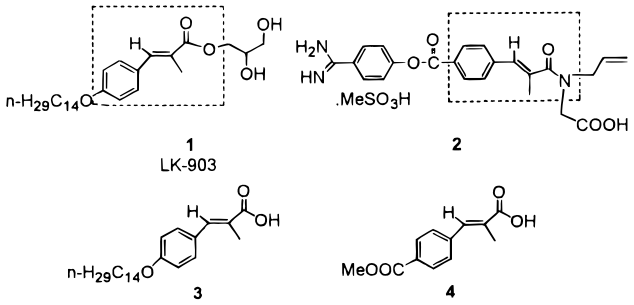
A simple and convenient stereoselective synthesis of [*E*]-α-methylcinnamic acids via the nucleophilic addition of hydride ion from sodium borohydride to methyl 3-acetoxy-3-aryl-2-methylenepropanoates followed by hydrolysis and crystallization is described. Efficacy of this methodology in the synthesis of [*E*]-*p*-(myristyloxy)-α-methylcinnamic acid, an active hypolipidemic agent, and [*E*]-*p*-(carbomethoxy)-α-methylcinnamic acid, a valuable synthon for an orally active serine protease inhibitor, is also demonstrated.

α-Methylcinnamic acid moiety is an important and central structural unit present in various biologically active molecules.[1,2] For example, 1-[*p*-(myristyloxy)-α-methylcinnamoyl]glycerol (LK-903) (**1**) is a very active hypolipidemic agent.[1] *N*-Allyl-*N*-[4-{(4-amidinophenoxy)-



carbonyl}-α-methylcinnamoyl]glycine methanesulfonate (**2**) and its analogues are potent orally active serine protease inhibitors.[2] Also [*E*]-2-methyl-3-(4-(myristyloxy)-phenyl)prop-2-enoic acid (**3**)[1] itself shows good hypolipidemic activity. [*E*]-2-Methyl-3-(4-carbomethoxyphenyl)-prop-2-enoic acid (**4**) is a valuable synthon for the synthesis of serine protease inhibitor **2**.[3] Therefore, development of a simple and efficient methodology for the stereoselective synthesis of [*E*]-α-methylcinnamic acids and their derivatives is an interesting problem in organic synthesis.[4] The Baylis−Hillman reaction is a versatile carbon−carbon bond forming reaction that provides multifunctional molecules which have been successfully used in various stereoselective transformations.[5] In continuation of our interest in the Baylis−Hillman reaction,[6] we herein report a convenient and simple synthesis of [*E*]-α-methylcinnamic acids via the reaction of sodium borohydride with methyl 3-acetoxy-3-aryl-2-methylenepropanoates followed by hydrolysis and crystallization.

Hoffmann and Rabe used Superhydride ($LiBEt_3H$) for the conversion of methyl 3-acetoxy-2-methylenealkanoates into methyl [2*E*]-2-methylalk-2-enoates.[7] However, the utility of sodium borohydride (which is readily available and cheap) as a source of hydride nucleophile in the stereoselective nucleophilic addition of hydride to the acetates of Baylis−Hillman adducts has not been reported so far in the literature. We have therefore examined the possible application of $NaBH_4$ as a source of hydride nucleophile (Scheme 1).

Accordingly, we have first treated methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**5a**) with $NaBH_4$ under a variety of conditions. The best results were obtained when a solution of **5a** in anhydrous *tert*-butyl alcohol was treated with $NaBH_4$ for 15 min at room temperature. The resulting methyl 2-methyl-3-phenylprop-2-enoate (**6a**) was obtained in 95% [*E*]-selectivity as evidenced by ^{1}H NMR spectral analysis of the crude product after the usual workup.[8] Subsequent hydrolysis of this crude product **6a** with KOH/MeOH for 2 h at room temperature has provided [2*E*]-2-methyl-3-phenylprop-2-enoic acid (**7a**) after crystallization from EtOAc/hexane (1:1) in 74% overall yield (based on the acetate **5a**) and in 100% [*E*]-isomeric purity as evidenced by ^{1}H NMR spectral analysis (procedure A in Experimental Section). Encouraged by this observation, we have synthesized a variety of [*E*]-3-aryl-2-methylprop-2-enoic acids (**7b**−**f**) without isolating the cinnamic ester intermediate from methyl

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(8) In the ^{1}H NMR spectrum of the crude product (**6a**), a peak at δ 7.68 was assigned to the olefinic proton of the [*E*]-isomer and a very minor peak (≈ 5%) at δ 6.70 was assigned to the olefinic proton of the [*Z*]-isomer. Also a doublet observed at δ 1.14 with very low intensity indicates presumably the presence of the saturated ester in very small amounts (≈ 2%).

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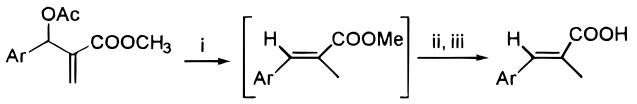
Scheme 1



5a-f **6a-f** 93-98% [E] **7a-f** 100% [E] 70-75% (over all)

Ar = phenyl, *p*-tolyl, *p*-chlorophenyl, *p*-isopropylphenyl 2,4-dichlorophenyl, naphth-1-yl

i) $NaBH_4$, *t*-butanol, 15 min, rt ii) KOH/MeOH, 2h, rt iii) crystallization

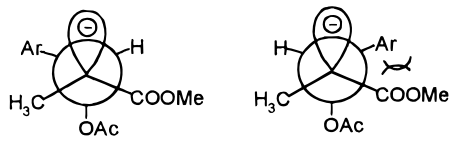
Table 1: Synthesis of [*E*]-α-Methylcinnamic Acids[a–c]

acetate	Ar	[*E*]-α-methylcinnamic acid	yield (%)[d]
5a	phenyl	**7a**	74
5b	*p*-tolyl	**7b**	72
5c	*p*-chlorophenyl	**7c**	73
5d	*p*-isopropylphenyl	**7d**	70
5e	2,4-dichlorophenyl	**7e**	75
5f	naphth-1-yl	**7f**	74

[a] All reactions were carried out on a 5 mM scale of the acetate with $NaBH_4$ (5 mM) at room temperature for 15 min in anhydrous *tert*-butyl alcohol,[9] hydrolysis of the resulting crude esters **6a**–**f** was carried out with KOH/MeOH at room temperature for 2 h, and the crude acids (procedures A and B in the Experimental Section) were crystallized from EtOAc/hexane (1:1). [b] All molecules were obtained as crystalline solids, and satisfactory spectral [IR, ^{1}H NMR, ^{13}C NMR] data and elemental analyses were obtained for all compounds. The [*E*]-stereochemistry was assigned on the basis of chemical shift value of vinylic proton in ^{1}H NMR spectra. ^{1}H NMR and ^{13}C NMR spectral analyses indicate the absence of any [*Z*]-isomer. [c] All these molecules **7a**–**f** are known in the literature. Melting points of these compounds are in agreement with literature values.[10] [d] Overall isolated yield of the pure [*E*]-acids based on acetates **5a**–**f**.

3-acetoxy-3-aryl-2-methylenepropanoates (**5b**–**f**) in 100% [*E*]-isomeric purity and in good yields following a similar protocol (Scheme 1, Table 1). We have also developed a one-pot synthesis of α-methylcinnamic acids in comparable yields even without isolating the crude esters **6a**–**f**, i.e., by directly treating the reaction mixtures of esters (**6a**–**f**) with KOH/MeOH (procedure B in Experimental Section).

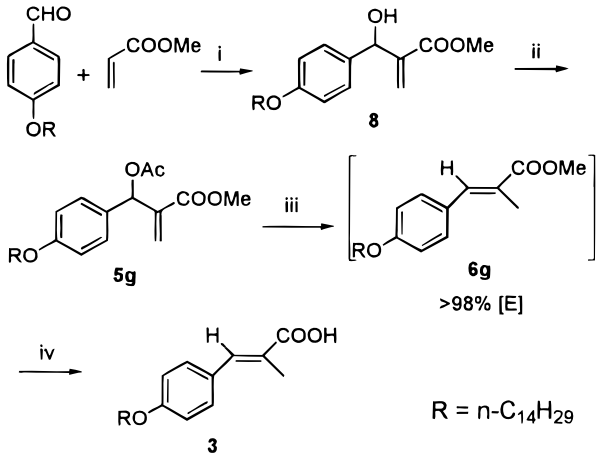
The [*E*]-selectivity in the reaction of the acetates **5a**–**f** with sodium borohydride can be possibly explained by considering the transition state models **I** and **II**. The transition state **I** is more favored than **II** since the COOMe group is bigger than the methyl group.



I favored **II** unfavored

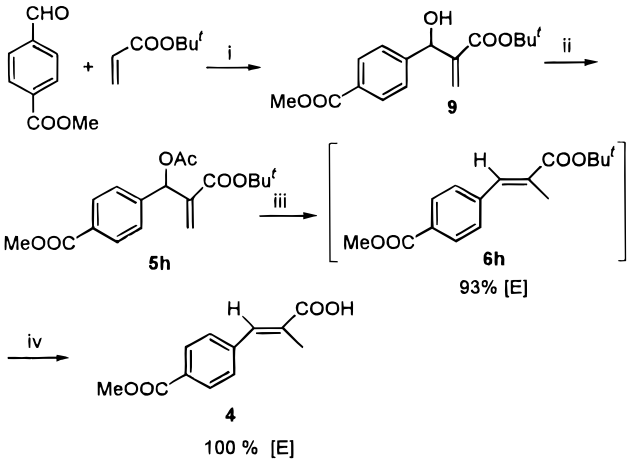
The efficacy of this methodology has been demonstrated by the synthesis of the hypolipidemic agent [*E*]-2-methyl-3-(4-myristyloxy)phenylprop-2-enoic acid (**3**) starting from 4-(myristyloxy)benzaldehyde (Scheme 2). Conversion of **3** into its monoglyceride ester, LK-903 (**1**), has already been reported by Watanabe et al.[1] Similarly [*E*]-2-methyl-3-(4-(methoxycarbonyl)phenyl)prop-2-enoic acid (**4**), an important synthon for an orally active serine protease inhibitor drug (**2**), was also synthesized starting from 4-(methoxycarbonyl)benzaldehyde (Scheme 3).

Scheme 2



i) DABCO, 20 days, 71% ii) AcCl, pyridine, 88% iii) $NaBH_4$, *t*-BuOH, 15 min, rt iv) KOH/MeOH, 2 h, rt, crystallization, 75% (from **5g**).

Scheme 3



i) DABCO, 6 days, 72% ii) AcCl, pyridine, 95% iii) $NaBH_4$, *t*-BuOH, 15 min, rt iv) CF_3COOH, anisole, 2 h, rt, crystallization, 63% (from **5h)**

This protocol describes, for the first time, the utility of the easily available and inexpensive reagent sodium borohydride as a source of hydride nucleophile for the nucleophilic addition to the acetates of the Baylis–Hillman adducts, thus providing a convenient new methodology for the synthesis of [*E*]-3-aryl-2-methylprop-2-enoic acids. We are presently investigating the application of this methodology in the synthesis of some other important biologically active molecules.

Experimental Section

All the required Baylis–Hillman products were obtained by the reaction of the corresponding aldehydes with methyl acrylate in the presence of a catalytic amount of DABCO according to the literature procedure.[11] The acetates of the Baylis–Hillman adducts, i.e., methyl 3-acetoxy-3-aryl-2-methylenepropanoates (**5a**–**f**), were obtained by the treatment

of the corresponding Baylis−Hillman adducts with acetyl chloride in the presence of pyridine at room temperature.

Methyl 3-Hydroxy-2-methylene-3-(4-(tetradecyloxy)-phenyl)propanoate (8). A mixture of 4-(tetradecyloxy)-benzaldehyde (3.18 g, 10 mM), methyl acrylate (1.72 g, 20 mM), and DABCO (0.224 g, 2 mM) was allowed to stand at room temperature for 20 days. The reaction mixture was diluted with ether, washed successively with 2 N hydrochloric acid, water, and a saturated aqueous sodium bicarbonate solution, and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography (5% EtOAc in hexanes) provided **8** as white solid.: yield 1.14 g (71% based on 1.92 g of the recovered *p*-(tetradecyloxy)benzaldehyde, i.e., 40% reaction); mp 72 °C; ^{1}H NMR δ 0.89 (dist. t, 3H), 1.15−1.88 (m, 24H), 2.86 (d, 1H, J = 5.2 Hz), 3.72 (s, 3H), 3.94 (t, 2H, J = 6.6 Hz), 5.53 (d, 1H, J = 5.0 Hz), 5.85 (s, 1H), 6.32 (s, 1H), 6.87 (d, 2H, J = 8.2 Hz), 7.28 (d, 2H, J = 8.2 Hz); ^{13}C NMR δ 14.07, 22.69, 26.11, 29.37, 29.69, 31.95, 51.77, 68.14, 72.72, 114.52, 125.25, 127.92, 133.49, 142.59, 158.94, 166.80; IR (KBr) 3364, 1724 cm^{-1}.

***tert*-Butyl 3-Hydroxy-2-methylene-3-(4-(methoxycarbonyl)phenyl)propanoate (9).** This compound was prepared from 4-(methoxycarbonyl)benzaldehyde (1.64 g, 10 mM) and *tert*-butyl acrylate (1.538 g, 12 mM) in the presence of DABCO (0.224 g, 2 mM) by following a procedure similar to that of **8**. **9:** reaction time 7 days; yield 2.10 g (72%); mp 68−70 °C; ^{1}H NMR δ 1.40 (s, 9H), 3.28 (m, 1H), 3.91 (s, 3H), 5.53 (d, 1H, J = 6.2 Hz), 5.71 (s, 1H), 6.27 (s, 1H), 7.45 (d, 2H, J = 8.0 Hz), 8.02 (d, 2H, J = 8.0 Hz); ^{13}C NMR δ 27.91, 52.03, 73.05, 81.84, 125.61, 126.51, 129.34, 129.60, 143.02, 146.93, 165.37, 166.92; IR (KBr) 3304, 1716 cm^{-1}.

Methyl 3-Acetoxy-2-methylene-3-(4-(tetradecyloxy)-phenyl)propanoate (5g). To a solution of **8** (0.808 g, 2 mM) and pyridine (0.316 g, 4 mM) in dry dichloromethane at 0 °C was added acetyl chloride (0.314 g, 4 mM) slowly, and the solution was stirred at room temperature for 1 h. The reaction mixture was taken up in ether and washed successively with a 2 N HCl solution, water, and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography (2% EtOAc in hexanes) provided the pure acetate **5g**: yield 0.788 g (88%); mp 59 °C; ^{1}H NMR δ 0.88 (dist. t, 3H), 1.12−1.87 (m, 24H), 2.09 (s, 3H), 3.70 (s, 3H), 3.93 (t, 2H, J = 6.7 Hz), 5.87 (s, 1H), 6.37 (s, 1H), 6.63 (s, 1H), 6.85 (d, 2H, J = 8.6 Hz), 7.28 (d, 2H, J = 8.6 Hz); ^{13}C NMR δ 14.07, 21.04, 22.67, 26.06, 29.37, 29.66, 31.92, 51.85, 68.00, 72.91, 114.42, 124.97, 129.09, 129.64, 139.96, 159.29, 165.44, 169.32; IR (KBr) 1741, 1716 cm^{-1}.

***tert*-Butyl 3-Acetoxy-2-methylene-3-(4-(methoxycarbonyl)phenyl)propanoate (5h).** This compound was obtained as a viscous liquid by the reaction of *tert*-butyl 3-hydroxy-2-methylene-3-(4-(methoxycarbonyl)phenyl)propanoate (**9**) (1.46 g, 5 mM) with acetyl chloride (0.785 g, 10 mM) in the presence of pyridine (0.95 g, 12 mM) in dichlormethane following a procedure similar to that of **5g**. **5h**: yield 1.58 g (95%); ^{1}H NMR δ 1.37 (s, 9H), 2.11 (s, 3H), 3.91 (s, 3H), 5.76 (s, 1H), 6.35 (s, 1H), 6.68 (s, 1H), 7.44 (d, 2H, J = 8.4 Hz), 8.01 (d, 2H, J = 8.0 Hz); ^{13}C NMR δ 20.95, 27.85, 52.06, 72.80, 81.66, 125.34, 127.66, 129.64, 129.99, 140.59, 143.12, 163.86, 166.62, 169.25; IR (neat) 1740, 1724 cm^{-1}.

[*E*]-2-Methyl-3-phenylprop-2-enoic Acid (7a) (Procedure A). To a solution of methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**5a)** (1.17 g, 5 mM) in anhydrous *tert*-butyl alcohol (5 mL) was added $NaBH_4$ (0.19 g, 5 mM), and the solution was stirred at room temperature for 15 min. *tert*-Butyl alcohol was distilled off under reduced pressure, and the residue was diluted with water and extracted with ether. The ether layer was dried over anhydrous Na_2SO_4 and concentrated.[8] The crude product was treated with 85% KOH (1.00 g) in methanol (5 mL) at room temperature for 2 h. The methanol was removed under reduced pressure, the residue was diluted with water, acidified with dilute HCl, and extracted with ether, and the combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated, and the crude acid obtained was crystallized from ethyl acetate and hexanes (1:1) to provide the acid **7a** as colorless crystals: yield 0.599 g (74%); mp 81−83 °C {lit.[10] mp 80−81 °C }; ^{1}H NMR δ 2.14 (s, 3H), 7.25−7.62 (m, 5H), 7.83 (s, 1H), 11.35 (b, 1H); ^{13}C NMR δ 13.70, 127.68, 128.47, 128.72, 129.88, 135.67, 141.17, 174.61; IR (KBr) 3350−2660, 1666, 1620 cm^{-1}. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.21. Found: C, 73.85; H, 6.21.

Procedure B (Procedure for One-Pot Synthesis of 7a). To a stirred solution of **5a** (1.17 g, 5 mM) in *tert*-butyl alcohol (5 mL) was added $NaBH_4$ (0.19 g, 5 mM) at room temperature. After 15 min, 85% KOH (1.00 g) in methanol (5 mL) was added and the stirring was continued for 2 h at room temperature. Usual workup (as mentioned above) followed by crystallization from ethyl acetate and hexanes (1:1) afforded the pure acid **7a** as colorless crystals: yield 0.615 g (76%).

Compounds **7b**−**f** and **3** were synthesized according to both the procedures A and B and the yields were comparable.

[*E*]-2-Methyl-3-(4-methylphenyl)prop-2-enoic Acid (7b): yield 72%; mp 165−167 °C {lit.[10] mp 168−169 °C}; ^{1}H NMR δ 2.16 (s, 3H), 2.39 (s, 3H), 7.23 (d, 2H, J = 7.6 Hz), 7.36 (d, 2H, J = 7.6 Hz), 7.81(s, 1H); ^{13}C NMR δ 13.75, 21.35, 126.62, 129.19, 129.96, 132.81, 138.94, 141.13, 174.28; IR (KBr) 3350−2600, 1667, 1630 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.62; H, 6.89.

[*E*]-3-(4-Chlorophenyl)-2-methylprop-2-enoic Acid (7c): yield 73%; mp 168−169 °C {lit.[10] mp 166−167 °C}; ^{1}H NMR δ 2.12 (d, 3H, J = 1.4 Hz), 7.24−7.50 (m, 4H), 7.76 (s, 1H); ^{13}C NMR δ 13.81, 128.24, 128.84, 131.15, 134.10, 134.82, 139.80, 173.69; IR (KBr) 3300−2600, 1672, 1625 cm^{-1}. Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 61.42; H, 4.59.

[*E*]-2-Methyl-3-(4-isopropylphenyl)prop-2-enoic Acid (7d): yield 70%; mp 89−90 °C {lit.[10] mp 89−90 °C}; ^{1}H NMR δ 1.27 (d, 6H, J = 6.8 Hz), 2.16 (s, 3H), 2.92 (m, 1H), 7.27 (d, 2H, J = 8.0 Hz), 7.39 (d, 2H, J = 8.0 Hz), 7.81(s, 1H); ^{13}C NMR δ 13.76, 23.82, 34.03, 126.58, 126.71, 130.15, 133.23, 141.18, 149.85, 174.72; IR (KBr) 3260−2650, 1678, 1622 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.85; H, 7.92.

[*E*]-3-(2,4-Dichlorophenyl)-2-methylprop-2-enoic Acid (7e): yield 75%; mp 143 °C {lit.[10] mp 146−147 °C}; ^{1}H NMR δ 2.01 (d, 3H, J = 1.5 Hz), 7.29 (m, 2H), 7.47 (s, 1H), 7.85 (s, 1H); ^{13}C NMR δ 13.80, 127.02, 129.76, 130.43, 131.20, 132.76, 135.18, 137.08, 173.44; IR (KBr) 3350−2600, 1703, 1635 cm^{-1}. Anal. Calcd for $C_{10}H_8Cl_2O_2$: C, 51.98; H, 3.49. Found: C, 51.62; H, 3.48.

[*E*]-3-(Naphth-1-yl)-2-methylprop-2-enoic Acid (7f): yield 74%; mp 153 °C {lit.[10] mp 155−156°C}; ^{1}H NMR δ 1.97 (d, 3H, J = 1.5 Hz), 7.31−8.00 (m, 7H), 8.31 (s, 1H); ^{13}C NMR δ 14.01, 124.66, 125.17, 126.25, 126.57, 126.81, 128.64, 128.99, 129.97, 131.58, 132.87, 133.58, 139.83, 174.10; IR (KBr) 3200−2650, 1684, 1618 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.69. Found: C, 78.92; H, 5.70.

[*E*]-3-(4-(Tetradecyloxy)phenyl)-2-methylprop-2-enoic Acid (3). This reaction was carried out on a 1 mM scale on the acetate **5g** with 1 mM of $NaBH_4$. **3**: yield 75%; mp 90 °C {lit.[1] mp 90−91 °C}; ^{1}H NMR δ 0.87 (dist. t, 3H), 1.13−1.88 (m, 24H), 2.17 (s, 3H), 4.00 (t, 2H, J = 6.5 Hz), 6.93 (d, 2H, J = 8.2 Hz), 7.41 (d, 2H, J = 8.2 Hz), 7.78 (s, 1H); ^{13}C NMR δ 13.83, 14.17, 22.77, 26.13, 29.32, 29.46, 29.76, 32.02, 68.25, 114.62, 125.10, 128.15, 131.84, 140.99, 159.80, 174.49; IR ($CHCl_3$) 3610−2640, 1682, 1602 cm^{-1}; MS m/z 374 (M^+). Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.00; H, 10.25.

[*E*]-3-(4-(Methoxycarbonyl)phenyl)-2-methylprop-2-enoic Acid (4). A solution of crude *tert*-butyl 2-methyl-3-(4-(methoxycarbonyl)phenyl)prop-2-enoate (**6h)** [obtained by the

(9) The ^{1}H NMR spectrum of the crude products (**6a**−**f**) indicated the presence of 2−7% [*Z*]-isomer.

(10) Gensler, W. J.; Berman, E. *J. Am. Chem. Soc.* **1958**, *80*, 4949.
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treatment of *tert*-butyl 3-acetoxy-3-(4-(methoxycarbonyl)phenyl)-2-methylenepropanoate (**5h**) (0.334 g, 1 mM) with sodium borohydride (0.038 g, 1 mM) following the procedure A] in anisole (5 mL) was treated with trifluoroacetic acid (0.57 g, 5 mM) at room temperature for 2 h. Anisole was distilled off under reduced pressure, and the reaction mixture was diluted with ether and washed with saturated aqueous K_2CO_3 and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated, and the crude product was crystallized from ethyl acetate and hexanes (1:1) to afford pure acid **4** as a white crystalline solid: yield 0.138 g (63%); mp 136−137 °C; ^{1}H NMR δ 2.15 (s, 3H), 3.94 (s, 3H), 7.49 (d, 2H, J = 8.3 Hz), 7.83 (s, 1H), 8.08 (d, 2H, J = 7.9 Hz); ^{13}C NMR δ 13.83, 52.22, 129.70, 130.10, 139.80, 140.14, 166.64, 173.72; IR (KBr) 3180−2620, 1728, 1678 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.42; H, 5.46.

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Supporting Information Available: ^{13}C NMR spectra of the compounds **7a**−**f**, **3**, and **4** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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