Isoaromatization of 4-Alkylidene-3-oxo-1-cyclohexene-1-carboxylates. Convenient Synthesis of Methyl 4-Alkyl-3-hydroxybenzoates†

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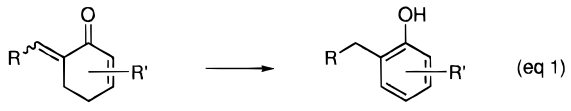
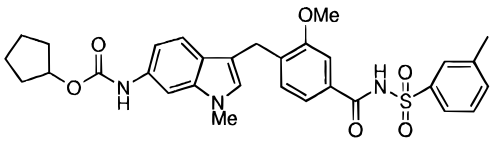
Introduction

While the isoaromatization of 6-alkylidene-2-cyclohexen-1-ones **1** to 2-alkylphenols **2** has been observed in several systems,[1a−f] this transformation, formally a double tautomerization, has rarely been exploited for the synthesis of phenols with defined substitution patterns (eq 1).[2] In connection with our interest in the antiasthmatic



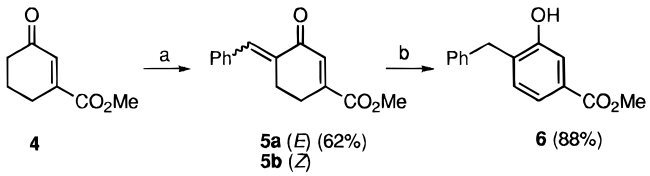
1 **2**



3 (ICI-204,219)

LTD_4 antagonist ICI-204,219 (**3**),[3] a general synthesis of the central 4-alkyl-3-hydroxybenzoate core unit was sought which would allow rapid variation of the alkyl substituent. We wish to report a convenient synthesis of methyl 4-alkyl-3-hydroxybenzoates that employs an isoaromatization reaction of the type depicted in eq 1 as a key step. This strategy complements methods of *o*-phenol alkylation, such as alkylation *via o*-lithiated species[4] and *o*-quinone methides,[5] phenylboronic acid-[6ab] and dichlorophenylborane-mediated condensations with aldehydes,[6c] the Claisen rearrangement,[7a−c] and *o*-alkenylation with 1-alkynes,[8] which could suffer from poor regiocontrol in the case of unsymmetrical phenols and be incompatible with sensitive functionality, especially in cases employing organometallic intermediates.

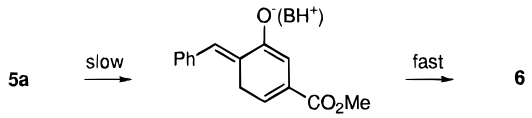
Scheme 1[a]



4 **5a** (*E*) (62%) **5b** (*Z*) **6** (88%)

[a] Key: (a) PhCHO, TsOH, $PhCH_3$, Δ; (b) DBU, $PhCH_3$.

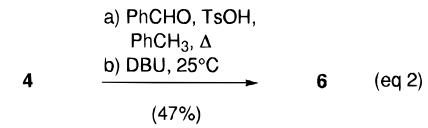
Scheme 2



7a

Results and Discussion

Initial model studies focused on the preparation of methyl 4-benzylidene-3-oxo-1-cyclohexene-1-carboxylate (**5a**,**b**) and its subsequent isoaromatization to methyl 3-hydroxy-4-(phenylmethyl)benzoate (**6**) (Scheme 1). Acid-catalyzed aldol condensation of methyl 3-oxo-1-cyclohexene-1-carboxylate (**4**), prepared on a large scale by oxidation of methyl 1-cyclohexene-1-carboxylate,[9] with benzaldehyde under Dean−Stark conditions in refluxing toluene afforded the *E*-dienone **5a** in 62% yield after chromatography. None of the *Z*-dienone **5b** was isolated, nor any products arising from aldol condensation at the γ-position of the enone, nor phenol **6**. The regiochemistry of this acid-catalyzed aldol condensation paralleled that of the kinetic enolate aldol condensation of 3-alkoxy-2-cyclohexen-1-ones, which also occur at the α′-position.[10] Dienone **5a**, while stable to acidic and neutral media and to a solution of triethylamine, even at elevated temperature, underwent smooth conversion to phenol **6** by treatment with DBU at rt. Two- and one-proton singlets, diagnostic of the dibenzylic methylene and hydroxyl protons of **6**, were observed at δ 4.01 and 5.37 ppm, respectively. That base strength was crucial to the isoaromatization reaction suggests that the rate-limiting step is deprotonation of **5a** to produce enolate **7a**, which then rearranges to **6** (Scheme 2). To demonstrate the convenience of this method for the synthesis of **6**, the sequence was repeated without isolation of **5a** by simply treating the crude aldol mixture with DBU at rt (eq 2). By this "one-pot" procedure, phenol **6** was obtained in 47% overall yield.



Kinetic enolate aldol condensation was next investigated for the preparation of dienones **5a**,**b**, since the

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

‡ To whom correspondence should be addressed concerning the X-ray structures of dienones **5a** and **5b**.

(1) (a) Morris, I. G.; Pinder, A. R. *J. Chem Soc.* **1963**, 1841. (b) Kobayashi, T.; Kumazawa. S.; Kato, T.; Kitahara, Y. *Chem. Lett.* **1975**, 301. (c) Kaiser, R.; Lamparsky, D.; Schudel, P. *J. Agric. Food Chem.* **1975**, *23*, 943. (d) Aizenshtat, Z.; Hausmann, M.; Pickholtz, Y.; Tal, D.; Blum, J. *J. Org. Chem.* **1977**, *42*, 2386. (e) Wiberg, K. B.; Matturro, M. G.; Okarma, P. J.; Jason, M. E.; Dailey, W. P.; Burgmaier, G. J., Bailey, W. F.; Warner, P. *Tetrahedron* **1986**, *42*, 1895. (f) Birch, A. J.; Quartey, J. A. K.; Smith, H. *J. Chem. Soc.* **1952**, 1768.

(2) Reference 1d describes the synthesis of 2,6-dialkyl-, 2,3,6-trialkyl-, and 2,4,6-trialkylphenols by high-temperature, transition metal-catalyzed isoaromatization of the corresponding 2,6-dialkylidenecyclohexanones. All subsituents in the 2- and 6-positions are identical. The reaction was shown to proceed *via* 6-alkylidine-2-cyclohexen-1-one intermediates.

(3) Matassa, V. G.; Maduskuie, T. P., Jr.; Shapiro, H. S.; Hesp, B.; Snyder, D. W.; Aharony, D.; Krell, R. D.; Keith, R. A. *J. Med. Chem.* **1990**, *33*, 1781.

(4) See: Morey, J.; Costa, A.; Deya, P. M.; Suner, G.; Saa, J. M. *J. Org. Chem.* **1990**, *55*, 3902 and references cited therein.

(5) See: Katritzky, A. R.; Zhang, Z.; Lan, X.; Lang, H. *J. Org. Chem.* **1994**, *59*, 1900 and references cited therein.

(6) (a) Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365. (b) Lau, C. K.; Williams, H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Belanger, P. C. *Can. J. Chem.* **1989**, *67*, 1384. (c) Lau, C. K.; Mintz, M.; Bernstein, M. A.; Dufresne, C. *Tetrahedron Lett.* **1993**, *34*, 5527.

(7) (a) Goering, H. L.; Jacobsen, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 3277. (b) Harwood, L. M. *J. Chem. Soc., Chem. Commun.* **1983**, 530. (c) Robertson, D. W.; Lacefield, W. B.; Bloomquist, W.; Pfeifer, W.; Simon, R. L.; Cohen, M. L. *J. Med. Chem.* **1992**, *35*, 310.

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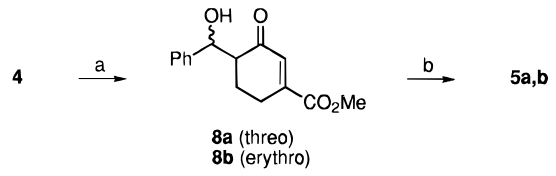
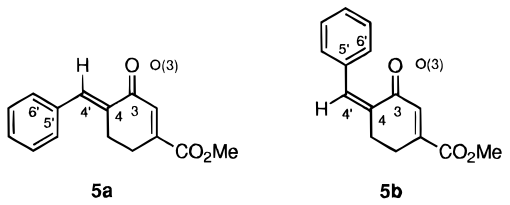
Scheme 3[a]



[a] Key: (a) (i) LHMDS, THF, −78 °C; (ii) PhCHO; (b) MeO_2C-$NSO_2N(Et)_3$, PhH, Δ.



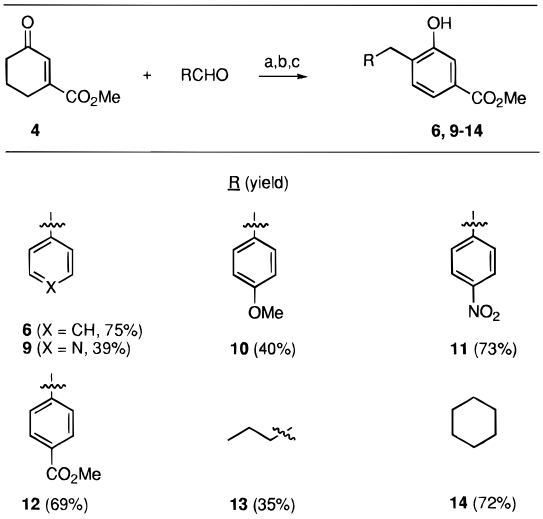
Dihedral Angle

	O(3)-C(3)-C(4)-(C4')	C(4)-C(4')-C(5')-C(6')
5a	7°	26°
5b (form A)	35°	21°
5b (form B)	37°	3°

Figure 1. Key dihedral angles from the X-ray structures of dienones **5a** and **5b**.

thermodynamically controlled, acid-catalyzed condensation proved to be less reliable in the case of less reactive and more volatile aldehydes. Addition of the lithium enolate of **4** to benzaldehyde gave a mixture of diastereomeric aldols **8a**,**b** predominating, as expected,[10] in the threo diastereomer **8a** (Scheme 3). Several methods to effect dehydration of aldols **8a**,**b** to **5a**,**b** were investigated, such as Ac_2O/pyridine, TFAA/TEA, and TFAA/DBU, but only complex mixtures containing unreacted aldols, acylated intermediates, dienones **5a,b**, and phenol **6** were obtained. Treatment of **8a** with Burgess reagent[11] in refluxing benzene, however, led smoothly to a mixture of dienones **5a** and **5b**, respectively, from which the more strained **5b** was isolated for the first time by flash chromatography. Structural assignments of **5a** and **5b** were initially based on NMR, where a 0.9 ppm downfield chemical shift was observed for the deshielded styryl proton of **5a** relative to that of **5b**, and were ultimately confirmed by X-ray crystallography.[12] Key dihedral angles obtained from the X-ray structures of **5a** and **5b** are shown in Figure 1, where it should be noted that **5b** crystallized in two distinct forms (forms A and B) differing mainly in the dihedral angle about the styrene single bond (C(4′)−C(5′)). The additional strain inherent in the *Z*-isomer **5b**, due to the steric interaction between the phenyl group and the ketone carbonyl, was evident in the large dihedral angle about the C(3)−C(4) bond, 35° and 37° for forms A and B, respectively. This compared to 7°, or close to planarity, for the corresponding dihedral angle of the *E*-isomer **5a**. We believe the

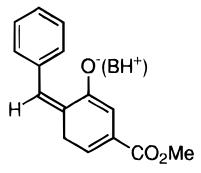
Table 1.[a] **Synthesis of Methyl 4-Alkyl-3-hydroxybenzoates by Sequential Kinetic Enolate Aldol Condensation, Dehydration, and Isoaromatization**



[a] Reaction conditions: (a) (i) LHMDS, THF, −78 °C; (ii) RCHO; (b) $MeO_2CNSO_2N(Et)_3$, PhH, Δ; (c) DBU, $PhCH_3$.

X-ray structure of **5b** represents the first example of a (*Z*)-6-alkylidene-2-cyclohexen-1-one.[13]

With the structures of **5a** and **5b** secure, their relative rate of rearrangement to phenol **6** was studied qualitatively by NMR. Interestingly, in an experiment in which a 50:50 mixture of **5a** and **5b** in $CDCl_3$ was treated with 1.5 equiv of DBU, it was found that at a time point (30 min) where all of **5a** had reacted, half of **5b** remained. On the basis of our mechanism, which postulates that deprotonation of **5a**,**b** is the rate-determining step for the base-catalyzed isoaromatization to **6** (see Scheme 2), the slower rate of reaction for the more strained dienone **5b** can be explained by the fact that the distorted C(3)−C(4) dihedral angle reduces π-overlap of the corresponding enolate **7b** relative to that of **7a**, rendering **5b** less acidic than **5a** and, hence, less reactive. The strain in enolate **7b** could be further compounded by the steric effect of the cation (BH^+).



7b

The kinetic enolate aldol condensation−dehydration−isoaromatization sequence was next repeated without purification of aldol and dienone intermediates in order to demonstrate its utility for the synthesis of 4-alkyl-3-hydroxybenzoates. Using benzaldehyde as the aldehyde component and a 10% excess of the enolate of **4**, phenol **6** was obtained in 75% overall yield after final purification (Table 1). The sequence was then applied successfully to four aromatic and two aliphatic aldehyde substrates, affording the corresponding phenols **9**−**14** in yields ranging from 35 to 73%. Pyridine (**9**), nitro (**11**), and ester (**12**) functionalities were compatible with the

(8) Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1995**, *117*, 1151.
(9) Lange, G. L.; Otulakowski, J. A. *J. Org. Chem.* **1982**, *47*, 5093.
(10) Torii, S.; Inokuchi, T.; Ogawa, H. *Bull. Chem. Soc. Jpn.* **1979,** *52*, 1233.
(11) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(12) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(13) A computer-assisted substructure search of the Cambridge Structural Data Base was performed.

reaction conditions. Lower yields in the case of **10** and **13** were due to incomplete aldol condensation, while high aqueous solubility during workup was responsible for a diminished yield of the pyridyl derivative **9** (see the Experimental Section).

Conclusion

Kinetic enolate aldol condensation of enone **4** with aliphatic and aromatic aldehydes, followed by sequential dehydration and base-catalyzed isoaromatization, was found to be a reliable method for the synthesis of methyl 4-alkyl-3-hydroxybenzoates, which may be elaborated to produce analogs of the LTD_4 antagonist ICI-204,219. This strategy should be applicable to other enones capable of kinetic deprotonation at the α′-position, thus providing access to 2-alkylphenols with various substitution patterns. It may be used as an alternative to other methods of *o*-phenol alkylation, especially in cases that involve sensitive functionality. With certain aldehyde substrates, acid-catalyzed aldol condensation with *in situ* dehydration may be employed, which shortens the overall sequence by one step.

Experimental Section

^{1}H NMR spectra were determined with a 300 MHz spectrometer. Mass spectra (MS) were measured using the electron impact method on a GC/MS instrument. Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory. Melting points are uncorrected and were obtained on open capillaries. All reactions involving oxygen- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. THF was distilled from Na/benzophenone prior to use. Starting aldehydes were purchased commercially and purified by recrystallization or distillation prior to use. Lithium bis(trimethylsilyl)amide solution (1 M THF) and Burgess reagent ([(methoxycarbonyl)sulfamoyl]trimethylammonium hydroxide) were purchased from Aldrich. All other starting materials and reagents were obtained from commercial suppliers and used without purification.

Flash chromatography was performed using silica gel Woelm (32−63 μm) or Baker silica gel (40 μm). Analytical thin-layer chromatography (TLC) was performed with Merck Kiesselgel 60 F_{254} using ultraviolet light for visualization.

Methyl 3-Oxo-1-cyclohexene-1-carboxylate (4). Following the procedure of Lange and Otulakowski,[9] in a 3-L, three-necked flask equipped with a mechanical stirrer was placed a mixture of 400 mL of acetic anhydride and 800 mL of acetic acid. After the mixture was cooled to 0 °C in an ice bath, 160 g (1.60 mol) of CrO_3 was added in portions to the stirring mixture, and when the addition was complete the mixture was allowed to warm to rt. Meanwhile, a solution of 75.0 g (0.535 mol) of methyl 1-cyclohexene-1-carboxylate in 275 mL of benzene was prepared in 3-L, three-necked flask equipped with a mechanical stirrer, addition funnel, and thermometer. This ice-chilled solution was treated with the oxidizing solution dropwise at such a rate that the exotherm did not exceed 15 °C. When the addition was complete, the mixture was allowed to stir for an additional 0.5 h at rt, chilled to 0 °C, and adjusted to pH 9 by the careful addition of 50% aqueous KOH solution (ca. 2 L) while the temperature was maintained below 15 °C. The mixture was diluted with a mixture of 250 mL of benzene and 1 L of ether, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 500 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (1 L) and brine (1 L), dried ($MgSO_4$), and evaporated to 56 g of a yellow oil. The oil was combined with 82 g of additional material prepared identically from 115 g of methyl 1-cyclohexene-1-carboxylate and distilled using a Vigreux column to provide 82.2 g (39%) of **4** as a light yellow oil: bp 70−72 °C/0.15 Torr (lit.[9] bp 95−100 °C/1.6 Torr).

(*E*)-Methyl 4-Benzylidene-3-oxo-1-cyclohexene-1-carboxylate (5a). A mixture of 1.00 g (6.49 mmol) of enone **4**, 0.600 mL (625 mg, 5.90 mmol) of benzaldehyde, 20 mL of toluene, and 20 mg of *p*-TsOH acid was placed in a flask fitted with a soxhlet extractor containing 3 Å molecular sieves in the thimble. The mixture was heated to reflux for 7 h. The solvent was evaporated, and the residue was diluted with 100 mL of EtOAc, washed with saturated $NaHCO_3$ solution (2 × 75 mL), dried ($MgSO_4$), and evaporated to give 1.71 g of an orange oil. Purification by flash chromatography (100 g of silica gel) using a 20% EtOAc−hexane eluant afforded 889 mg (62%) of **5a** as a yellow oil. Crystallization from hexane gave 460 mg of a bright yellow solid: mp 93−94 °C: ^{1}H NMR ($CDCl_3$) δ 2.61 (2 H, dt, J = 2, 7 Hz), 3.04 (2 H, dt, J = 2, 7 Hz), 3.83 (3 H, s), 6.94 (1 H, s), 7.23−7.45 (5 H, m), 7.65 (1 H, s); MS m/z 242 (M^+), 241 (base), 181, 115. Suitable crystals for X-ray analysis were grown by slow evaporation from MeOH. Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.01; H, 5.91.

(*Z*)-Methyl 4-Benzylidene-3-oxo-1-cyclohexene-1-carboxylate (5b). Isolation of Diastereomers 8a and 8b. A 50 mL, three-necked flask equipped with a low-temperature thermometer, N_2 inlet, and septum was charged with 1.95 mL (1.95 mmol) of a 1 M THF solution of LHMDS and 15 mL of THF. The mixture was cooled to −78 °C, and a solution of 300 mg (1.95 mmol) of enone **4** in 2 mL of THF was added dropwise *via* syringe at such a rate that the exotherm did not exceed −65 C. The resulting yellow mixture was allowed to stir for an additional 10 min at −78 °C, and 0.178 mL (185 mg, 1.77 mmol) of benzaldehyde was added dropwise. After being stirred for an additional 1 h at −78 °C, the mixture was quenched by the addition of 6 mL of saturated aqueous NH_4Cl solution and then allowed to warm to rt. The THF was removed by partial evaporation, and the residue was partitioned between 100 mL of EtOAc and water, respectively. The organic layer was separated, dried ($MgSO_4$), and evaporated to 580 mg of a yellow oil, which was purified by flash chromatography (50 g of silica gel, 15 mL fractions) using a 20−40% EtOAc−hexane eluant. Fractions 21−24 were combined and concentrated to give 4 mg of the erythro diastereomer **8b** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.73−2.75 (5 H, m), 2.50 (1 H, d, J = 5 Hz), 3.80 (3 H, s), 4.54 (1 H, br t), 6.75 (1 H, d, J = 2 Hz), 7.24−7.38 (5 H, m). Fractions 27−32 were combined and concentrated to give 136 mg of the threo diastereomer **8a** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.43−1.65 (2 H, m), 2.27−2.68 (3 H, m), 3.80 (3 H, s), 4.37 (1 H, d, J = 2 Hz), 4.83 (1 H, dd, J = 2, 7 Hz), 6.75 (1 H, d, J = 2 Hz), 7.23−7.39 (5 H, m). The mixed fractions were combined and concentrated to give 295 mg of a mixture **8a** and **8b**; total yield = 94%.

A mixture of 135 mg (0.519 mmol) of **8a**, 185 mg (0.779 mmol) of Burgess reagent, and 7 mL of benzene was heated to reflux for 3 h. The mixture was evaporated, and the residue was diluted with 50 mL of EtOAc, washed with saturated aqueous $NaHCO_3$ (2 × 40 mL), dried ($MgSO_4$), and evaporated to 108 mg of a yellow oil, which was separated by flash chromatography (10 g of silica gel, 15 mL fractions) using a toluene eluant. Fractions 42−47 were combined and concentrated to a yellow semisolid, which was triturated in hexane to give 15 mg of dienone **5b** as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.65−2.84 (4 H, m), 3.82 (3 H, s), 6.72 (1 H, s), 6.80 (1 H, s), 7.21−7.32 (3 H, m), 7.42−7.48 (2 H, m). Suitable crystals for X-ray analysis were grown by slow evaporation from EtOAc.

Methyl 3-Hydroxy-4-(phenylmethyl)benzoate (6). Method A: Isoaromatization of Dienone 5a. A solution of 300 mg (1.24 mmol) of **5a** in 5 mL of toluene was treated dropwise with 188 mg (0.185 mL, 1.24 mmol) of DBU, and the resulting mixture was stirred for 3 h at rt. The solvent was evaporated, and the residue was dissolved in 35 mL of EtOAc, washed with aqueous 1 N HCl solution (2 × 50 mL), dried ($MgSO_4$), and evaporated to 333 mg of a light yellow solid, which was triturated in hexane to give 265 mg (88%) of **6** as a white solid, mp 133−135 °C (see method C below for spectral and analytical data).

Method B: Acid-Catalyzed Aldol Condensation/Isoaromatization. A mixture of 0.500 g (3.24 mmol) of enone **4**, 0.300 mL (313 mg, 2.95 mmol) of benzaldehyde, 20 mL of toluene, and 15 mg of *p*-TsOH was heated to reflux in a flask fitted with a soxhlet extractor containing 3 Å molecular sieves in the thimble. After 5 h, TLC analysis indicated that the reaction was 75% complete, so an additional 15 mg of *p*-TsOH was added and reflux was continued for an additional 2 h. The mixture was allowed to cool to rt and then treated dropwise with 0.49 mL

(499 mg, 3.25 mmol) of DBU. After being stirred for 2 h at rt, the dark brown mixture was evaporated, dissolved in 100 mL of EtOAc, washed with aqueous 1 N HCl solution (1 × 75 mL) and saturated aqueous $NaHCO_3$ solution (1 × 75 mL), dried ($MgSO_4$), and evaporated to 927 mg of a yellow oil. Purification by flash chromatography (100 g of silica gel) using a 25% EtOAc−hexane eluant gave 339 mg (47%) of phenol **6** as a yellow solid.

Method C: Kinetic Enolate Aldol Condensation/Dehydration/Isoaromatization. A 100 mL, three-necked flask equipped with a low-temperature thermometer, N_2 inlet, and septum was charged with 3.24 mL (3.24 mmol) of a 1 M THF solution of LHMDS and 30 mL of THF. The mixture was cooled to −78 °C, and a solution of 500 mg (3.24 mmol) of enone **4** in 5 mL of THF was added dropwise *via* syringe at such a rate that the exotherm did not exceed −65 °C. The resulting yellow mixture was allowed to stir for an additional 15 min at −78 °C, and a solution of 0.299 mL (312 mg, 2.95 mmol) of benzaldehyde in 5 mL of THF was added dropwise at such a rate that the exotherm did not exceed −65 °C. After being stirred for 1 h at −78 °C, the mixture was quenched by the addition of 10 mL of saturated aqueous NH_4Cl solution and was then allowed to warm to rt. The THF was removed by partial evaporation, and the residue was partitioned between 50 mL of EtOAc and water, respectively. The organic layer was separated, combined with two 50 mL EtOAc washes of the aqueous layer, dried ($MgSO_4$), and evaporated to give 835 mg (>100%) of aldols **5a**,**b** as a yellow oil.

To a solution of aldols **5a**,**b** above (2.95 mmol) in 60 mL of benzene was added 1.05 g (4.42 mmol) of Burgess reagent, and the resulting mixture was heated to reflux for 2 h. After being cooled to rt, the solvent was evaporated and the residue was concentrated and partitioned between 100 mL of EtOAc and saturated aqueous $NaHCO_3$ solution, respectively. The aqueous layer was removed, and the organic layer was washed with additional saturated aqueous $NaHCO_3$ solution (1 × 50 mL) and brine (1 × 50 mL), dried ($MgSO_4$), and evaporated to give 823 mg (>100%) of a mixture of dienones **5a** and **5b** (ratio = 15:1, NMR).

A solution of dienones **5a**,**b** above (2.95 mmol) in 15 mL of benzene was treated dropwise with 0.661 mL (672 mg, 4.42 mmol) of DBU, and the mixture was stirred for 1.5 h at rt. The mixture was diluted with 50 mL of EtOAc, washed with aqueous 1 N HCl solution (2 × 25 mL) and brine (1 × 25 mL), dried ($MgSO_4$), and evaporated to 715 mg of a yellow solid. Purification by flash chromatography (50 g of silica gel) using a 20% EtOAc−hexane eluant gave 592 mg of a white solid, mp 115−120 °C, which was triturated in ice-cold hexane to afford 535 mg (75%) of **6** as white colorless crystals, mp 131−132 °C: ^{1}H NMR ($CDCl_3$) δ 3.88 (3 H, s), 4.01 (2 H, s), 5.37 (1 H, s), 7.11−7.55 (8 H, m); MS *m*/*z* 242 (M^+), 211, 183 (base), 165. Anal. Calcd for $C_{15}H_{14}O_3$: C,74.36; H, 5.82. Found: C, 74.06; H, 5.80.

Relative Rate of Isoaromatization of Dienones 5a and 5b. In a NMR tube was placed a solution of 20 mg (0.083 mmol) of a 50:50 mixture of dienones **5a** and **5b** in 1 mL of $CDCl_3$. The mixture was treated with 19 μL (19 mg, 0.13 mmol) of DBU at rt, and the progress of the reaction was monitored by ^{1}H NMR by observing the disappearance of the signals for the corresponding vinyl protons (nonaromatic; **5a**, δ 6.94, 7.65; **5b**, δ 6.72, 6.80). After 30 min, the consumption of **5a** was complete, while that of **5b** was 50%.

General Preparation of Methyl 4-Alkyl-3-hydroxybenzoates 9−14. Method C was followed, substituting the appropriate aldehyde for benzaldehyde. All reactions were run starting with 500 mg of enone **4**. Yields of **9**−**14** were based on final purification by flash chromatography in the indicated eluant followed by trituration in the indicated solvent. The yield of **14** was based on purification by flash chromatography only. All reactions were monitored by TLC. A modification of the workup procedure of compound **9** is noted.

Methyl 3-hydroxy-4-[(4-pyridyl)methyl]benzoate (9): 39% yield; chromatography solvent, 5% MeOH−$CHCl_3$. In the Burgess reagent-mediated elimination reaction, which gave 560 mg of crude dienone, an additional 202 mg of crude dienone was obtained by extraction of the combined aqueous layers with $CHCl_3$ (4 × 100 mL), drying ($MgSO_4$), and evaporation. This material and the original 560 mg of crude dienone were subjected to the isoaromatization reaction separately. During workup, the aqueous 1 N HCl wash was replaced by a water wash, and additional crude product was obtained by backwashing the combined aqueous layers with $CHCl_3$, as described above. From the reaction of the original 560 mg of dienone, 378 mg of crude **9** was obtained as a yellow solid after workup, which was purified by flash chromatography and then triturated in ether to afford 255 mg of **9** as light yellow solid, mp 196−197 °C. A second crop (45 mg) was obtained by similar purification of the evaporated mother liquor combined with the material (263 mg) derived from the reaction of the 202 mg of recovered crude dienone (from the aqueous layers), mp 193−194 °C: ^{1}H NMR (DMSO-d_6) δ 3.81 (3 H, s), 3.95 (2 H, s), 7.21 (2 H, d, J = 6 Hz), 7.24 (1 H, d, J = 8 Hz), 7.38 (1 H, dd, J = 2, 8 Hz), 7.45 (1 H, d, J = 2 Hz), 8.44 (2 H, d, J = 6 Hz), 10.02 (1 H, s); MS *m*/*z* 243 (M^+, base), 212, 184. Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39 N, 5.76. Found: C, 68.96; H, 5.34; N, 5.53.

Methyl 3-hydroxy-4-[(4-methoxyphenyl)methyl]benzoate (10): 40% yield; chromatography solvent, 20% EtOAc−hexane. The chromatographed product (374 mg) was triturated in hexane (320 mg), mp 107−109 °C. The analytical sample was prepared by recrystallization from benzene, mp 122.5−123.5 °C: ^{1}H NMR ($CDCl_3$) δ 3.75 (3 H, s), 3.87 (3 H, s), 3.96 (2 H, s), 5.29 (1 H, s), 6.81 (2 H, d, J = 8 Hz), 7.09−7.14 (3 H, m), 7.49 (1 H, s), 7.51 (1 H, d, J = 8 Hz); MS *m*/*z* 272 (M^+), 108 (base). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.35; H, 5.88.

Methyl 3-hydroxy-4-[(4-nitrophenyl)methyl]benzoate (11): 73% yield; chromatography solvent, 25% EtOAc−hexane. The chromatographed product (650 mg) was triturated in ether (448 mg), mp 158.5−159.5 °C. A second crop (168 mg) was obtained by trituration of the concentrated mother liquor in hexane, mp 155−157 °C: ^{1}H NMR ($CDCl_3$) δ 3.88 (3 H, s), 4.01 (2 H, s), 5.48 (1 H, s), 7.14 (1 H, d, J = 8 Hz), 7.35 (2 H, d, J = 8 Hz), 7.54 (1 H, s), 7.55 (1 H, d, J = 8 Hz), 8.11 (2 H, d, J = 8 Hz); MS *m*/*z* 287 (M^+, base), 270, 256, 240, 228, 207, 181, 152. Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.57; H, 4.99; N, 4.80.

Methyl 3-hydroxy-4-[[4-(methoxycarbonyl)phenyl]methyl]benzoate (12): 69% yield; chromatography solvent, 30% EtOAc−hexane. The chromatographed product (640 mg) was triturated in hexane (613 mg), mp 161−162 °C: ^{1}H NMR ($CDCl_3$) δ 3.87 (6 H, s), 4.05 (2 H, s), 5.53 (1 H, s), 7.12 (1 H, d, J = 8 Hz), 7.38 (2 H, d, J = 8 Hz), 7.50 (1 H, s), 7.52 (1 H, d, J = 8 Hz), 7.93 (2 H, d, J = 8 Hz); MS *m*/*z* 300 (M^+), 269, 241 (base). Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.94; H, 5.35.

Methyl 4-butyl-3-hydroxybenzoate (13): 35% yield; chromatography solvent, 20% EtOAc−hexane. The chromatographed product (260 mg) was triturated in hexane (196 mg), mp 80−81 °C. A second crop (37 mg) was obtained by rechromatography of the evaporated mother liquor and impure fractions followed by trituration in ice-cold hexane, mp 81−82 °C: ^{1}H NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 7 Hz), 1.22−1.39 (2 H, m), 1.47−1.62 (2 H, m), 2.64 (2 H, t, J = 7 Hz), 3.87 (3 H, s), 6.58 (1 H, s), 7.14 (1 H, d, J = 8 Hz), 7.49 (1 H, dd, J = 1, 8 Hz), 7.61 (1 H, d, J = 1 Hz); MS *m*/*z* 208 (M^+), 165 (base). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.97; H, 7.58.

Methyl 3-hydroxy-4-(cyclohexylmethyl)benzoate (14): 72% yield; chromatography solvent, 10% ether−toluene. Trituration of the chromatographed product (524 mg), mp 142−144 °C, in hexane provided the analytical sample (308 mg), mp 148−149 °C: ^{1}H NMR ($CDCl_3$) δ 0.81−1.65 (11 H, m), 2.51 (2 H, d, J = 7 Hz), 3.87 (3 H, s), 5.02 (1 H, s), 7.10 (1 H, d, J = 8 Hz), 7.46 (1 H, s), 7.50 (1 H, d, J = 8 Hz); MS *m*/*z* 248 (M^+), 166 (base). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.26; H, 8.48.

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