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Highly Efficient Preparation of Aryl β-Diketo Acids with *tert*-Butyl Methyl Oxalate

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Received June 26, 2003

Abstract: An improved and efficient oxalylation of aryl methyl ketones was accomplished with *tert*-butyl methyl oxalate. This is the key step in constructing the pharmacophore of aryl β-diketo acids, which represent a promising new class of HIV-1 integrase inhibitors. Structurally diverse aryl β-diketo acids, including bisdiketo acids, can be prepared rapidly in impressive yields under mild conditions with this method. Advantages over conventional methods with dimethyl (or diethyl) oxalate were observed in both yield and reaction time.

HIV-1 integrase (IN), one of three constitutive viral enzymes required for replication, has emerged as an attractive target for chemotherapeutic intervention in the treatment of AIDS.[1] Integrase catalyzes the insertion of the proviral DNA into the genome of the host cell, which includes three biochemical steps: assembly of proviral DNA on integrase, endonucleolytic processing of the proviral DNA (termed 3′-processing), and strand transfer of the proviral DNA to host cell DNA (termed strand transfer). Although a large number of IN inhibitors have been described, most lack antiviral efficiency in cell culture.[2] Recently, however, a promising new class of inhibitors has emerged, which contain aryl β-diketo (ADK) functionality. These are typified by 5CITEP[3] and L-708,906[4] (Figure 1). ADK-based inhibitors exhibit selective inhibition of strand transfer reactions in extracellular recombinant IN assays and provide potent antiviral effects against HIV-infected cells.[4,5] The discovery of aryl diketo acid derivatives as bona fide inhibitors of integrase and the recent news[6] of Phase II clinical trials with S-1360 are major findings fueling the recent surge of interest in the development of integrase inhibitors.[7]

Aryl diketo acid motifs are among the most promising IN inhibitors currently known, and the 1,3-diketo acid functionality is essential for the enzyme inhibitory activity of these inhibitors.[8] As part of a program to examine the structural features of the ADK family as they relate to IN inhibitory potency and selectivity, we have developed a highly efficient procedure to afford more structurally diverse aryl β-diketo acids conveniently. Herein we would like to report our recent finding on the oxalylation of various acetophenones using *tert*-butyl methyl oxalate under mild conditions.

In general, the synthesis of 4-aryl-4-oxo-2-hydroxy-2-butenoic acids was achieved by the oxalylation of the corresponding aryl ketones in the presence of base, followed by either alkaline or acidic hydrolysis (Scheme 1).[9−12] Literature methods show that the oxalylation of aryl ketones **1** affords the stable intermediate **2**, utilizing either diethyl oxalate or dimethyl oxalate as the oxalic source in the presence of NaH, NaOEt, or NaOMe. The yields are quoted in a wide range of 40−95%, which depends on the structure of the substrate and the reaction conditions (base, solvent, reaction temperature, and time).[9,12,13] Attempts to reproduce these procedures gave inconsistent results with much lower yields, especially for hindered aryl ketones and halide-substituted aryl ketones. So the current diethyl (or dimethyl) oxalate method has limitations in the preparation of various aryl diketo acids needed for SAR study and further development of the inhibitors.

To improve the efficiency of building up the 2,4-dioxobutanoyl functionality on a variety of aryl rings, we introduced a *tert*-butyl group into the oxalylation reagent. Thus *tert*-butyl methyl oxalate and di-*tert*-butyl oxalate were examined in comparison with dimethyl oxalate. Appropriately aryl-substituted acetophenones were treated

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10.1021/jo034903x CCC: $25.00
Published on Web 08/27/2003

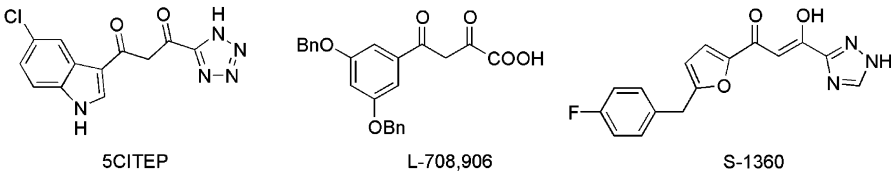
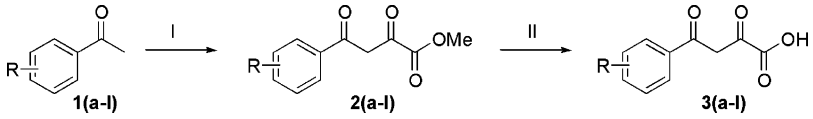


FIGURE 1. Structure of the representative ADK based IN inhibitors.

SCHEME 1[a]



[a] Reagents and conditions: (I) (Condition A) *t*-BuOOCCOOMe, $NaOCH_3$, THF−DME (1:1), rt, ≤2 h (for **1f**, 12 h; for **1i**, 40 °C, 3 h); (Condition B) $(CO_2Me)_2$, $NaOCH_3$, THF−DME (1:1), rt, ≥24 h. (II) 1 N NaOH, THF−CH_3OH (1:1), rt, 1 h.

with the three oxalating agents, respectively, and *tert*-butyl methyl oxalate in the presence of sodium methoxide was the most effective method in preparing a wide range of aryl diketo acids bearing different functional groups (see Table 1).

The coupling of variously substituted acetophenones with *tert*-butyl methyl oxalate[14] occurred efficiently at room temperature, using 1 equiv of aryl ketone, 2 equiv of *tert*-butyl methyl oxalate, and 4 equiv of sodium methoxide. In the same examples with dimethyl oxalate, the quantity of sodium methoxide was increased to 5 equiv to achieve a reasonable yield. The optimized mixed solvent of THF and DME (1:1) was used for the standard coupling procedure. A range of aryl methyl ketones bearing electron-donating and electron-withdrawing groups, as well as sterically crowded and bis(aryl methyl ketones), were screened. The results are shown in Table 1.

In all cases, far shorter times and much better yields were achieved for the couplings with *tert*-butyl methyl oxalate, compared with those using dimethyl oxalate as oxalic source. Halide- and electron-donating group substituted acetophenones (**1a**−**c**,**f**,**g**−**l**) exhibited an overwhelming preference for *tert*-butyl methyl oxalate over dimethyl oxalate in the condensation. The bulky substituents on the aryl (**1g**−**j**) or the hindered ketones (**1k**,**l**) did not retard the inclination. Noteworthily, *tert*-butyl methyl oxalate showed special advantage in the preparation of bis-aryl diketo acids (entries 11 and 12 in Table 1), which constitute a novel set of ADK analogues displaying enhanced inhibitory activity against HIV-1 integrase.[12,15] The preparation of bis-diketo acid via dimethyl oxalate failed at room temperature, even after 24 h of stirring (**1k**,**l**). Raising the temperature to 60 °C in toluene and DME helped the reaction to proceed in moderate yields (50−65%) after 12 h of heating. To our surprise, when *tert*-butyl methyl oxalate was used, impressive yields (85−100%) of these coupling reactions were obtained within a short time (1 h at room temperature usually). For the electron-withdrawing group substituted aryl methyl ketones (**1d**,**e**), the reactivity difference between the dimethyl oxalate and *tert*-butyl methyl oxalate stays significant. The only example of a low yield with *tert*-butyl methyl oxalate occurred with 4-nitroacetophenone (**1e**), which gave the desired ADK product in a yield of 52%.

Literature-reported coupling reactions involving mono-*tert*-butyl oxalate usually produced the corresponding 2,4-dioxo-butanoic acid *tert*-butyl ester.[16,17] This gave us the initial idea to use *tert*-butyl methyl oxalate as the oxalylation agent. We expected the resulting 4-aryl-4-oxo-2-hydroxy-2-butenoic acid *tert*-butyl ester could be converted into the corresponding acids under mild acidic conditions. However, in our case, the coupling of aryl substituted acetophenone with *tert*-butyl methyl oxalate provided unusual 4-aryl-2,4-dioxo-butanoic acid methyl ester with impressive speed and yield. The unexpected results provided us with a practical and facile access to the aryl β-diketo units.

The reactivity of di-*tert* butyl oxalate[18] was also investigated. However, 4-fluoroacetophenone (**1b**) did not react with di-*tert* butyl oxalate in the presence of 4 equiv of sodium methoxide either at room temperature or at 60 °C for 12 h. When the base was changed to sodium *tert*-butoxide (1.05 equiv), the coupling of 4-fluoroacetophenone (**1b**, 1.0 equiv) with di-*tert* butyl oxalate (1.05 equiv) occurred immediately at room temperature to give the corresponding diketo acid *tert*-butyl ester (**4b**) in an isolated yield of 58%. Heating at 60 °C did not improve the yield.

Inspired by the encouraging results with sodium *tert*-butoxide as a base, we explored the possible mechanism

(14) *tert*-Butyl methyl oxalate was prepared from oxalyl chloride in an overall yield of 87%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 3.85 (s, 3H). For synthesis references see: (a) Bucher, G.; Halupka, M.; Kolano, C.; Schade, O.; Sander, W. *Eur. J. Org. Chem.* **2001**, *3*, 545−552. (b) Cox, R. J.; Wang, P. S. H. *J. Chem. Soc., Perkin Trans. 1* **2001**, *17*, 2022−2341.

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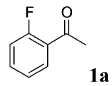
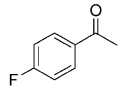
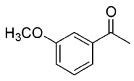
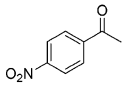
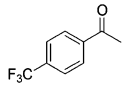
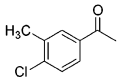
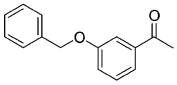
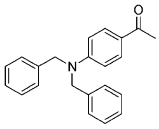
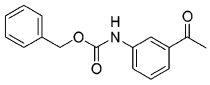
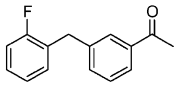
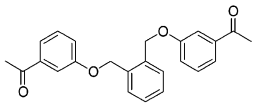
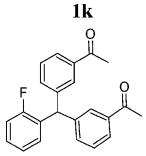
(17) For ethanedioic acid 1,1-dimethylethyl ethyl ester involved coupling reaction, see: (a) Kelly, T. R.; et al. *Tetrahedron Lett.* **1973**, 3501−3504. (b) Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 2725−2727. (c) Carpino, L. A. *J. Org. Chem.* **1964**, *29*, 2820−2824. (d) Pirrung, M. C.; Han, H.; Chen, J. *J. Org. Chem.* **1996**, *61*, 4527−4531.

(18) Di-*tert*-butyl oxalate was prepared in an isolated yield of 75% [mp 68−69 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 18H)] according to the literature: Karabatsos, G. J.; Corbett, J. M.; Krumel, K. L. *J. Org. Chem.* **1965**, *30*, 689−693.

TABLE 1. Coupling of Aryl Methyl Ketones with *tert*-Butyl Methyl Oxalate or Dimethyl Oxalate in the Presence of Sodium Methoxide

Entry	Aryl ketone	Isolated yield (%) / (Reaction time)	
		tert-Butyl methyl oxalate [a]	Dimethyl oxalate [b]
1	 **1a**	95 / (10 min)	44 / (24 h)
2	 **1b**	100 / (20 min)	12 / (24 h)
3	 **1c**	97 / (2 h)	57 / (24 h)
4	 **1d**	52 / (2 h)	30 / (24 h)
5	 **1e**	71 / (2 h)	18 / (24 h)
6	 **1f**	86 / (12 h)	0 / (36 h)
7	 **1g**	78 / (2 h)	33 / (24 h)
8	 **1h**	76 / (2 h)	14 / (36 h)
9	 **1i**	92[c] / (3 h)	0 / (24 h)
10	 **1j**	88 / (2 h)	Trace[d] / (24 h)
11	 **1k**	94[e] / (0.5 h)	0 / (24 h)
12	 **1l**	85[e] / (1 h)	0[f] / (24 h)

[a] The coupling was performed according to procedure A. [b] The coupling was performed according to procedure B. [c] The isolated yield was obtained after 3 h of stirring at 40 °C. [d] NaOMe (5 equiv), dimethyl oxalate (2.5 equiv), toluene−DME (1:1), 60 °C overnight; the isolated yield of the desired diketo product is 65%. [e] The coupling of bis-aryl methyl ketones was performed in toluene−DME−THF (1:1:1) due to solubility, and the quantity of the reagents was adjusted proportionally with the number of ketones. [f] NaOMe (10.0 equiv), dimethyl oxalate (5.0 equiv), toluene−DME−THF (1:1:1), 60 °C overnight; the isolated yield of the desired diketo product is 50%.

of the coupling reaction involving *tert*-butyl methyl oxalate. It seems unlikely that the enolate of acetophenone would attack a much bulkier *tert*-butyl ester faster than a methyl ester. So, we speculated that sodium methoxide might react first with the *tert*-butyl methyl oxalate to generate dimethyl oxalate and *tert*-butoxide in a transesterification. Then the resulting *tert*-butoxide functions as a better base in the reaction. The hypothesis was partially proved by a successful coupling of 2-fluoroacetophenone (**1a**, 1 equiv) with dimethyl oxalate (2 equiv) in the presence of sodium *tert*-butoxide (2 equiv), giving the desired diketo acid methyl ester in an isolated yield of 80% after 1 h of stirring at room temperature.

In summary, we developed an efficient and convenient procedure to prepare various aryl diketo acids. The coupling of substituted aryl methyl ketones with *tert*-butyl methyl oxalate in the presence of sodium methoxide can be accomplished rapidly in impressive yields under mild conditions. This methodology is applicable to a wide range of aryl methyl ketones bearing electron-donating and electron-withdrawing groups as well as bis(aryl methyl ketones) examples. This highly efficient preparation of aryl β-diketo acids with *tert*-butyl methyl oxalate will potentially benefit the development of HIV-1 integrase inhibitors.

Experimental Section

Oxalylation of Aryl Methyl Ketone. Procedure A. To a stirred solution of $NaOCH_3$ (4.0 equiv) in anhydrous THF at room temperature was added dropwise the mixture of *tert*-butyl methyl oxalate (2.0 equiv) and aryl methyl ketone (1.0 equiv) in DME. The resulting orange-yellow mixture was stirred at room temperature for 2 h at most. The reaction was quenched by the addition of 1.0 N aqueous HCl and subjected to an extractive workup (CH_2Cl_2). The solvent was removed under vacuum and the residue was purified by silica gel chromatography to afford the desired diketo product.

Procedure B. To a stirred solution of $NaOCH_3$ (5.0 equiv) in anhydrous THF at room temperature was added dropwise the mixture of dimethyl oxalate (2.0 equiv) and aryl methyl ketone (1.0 equiv) in DME. The resulting orange-yellow mixture was stirred at room temperature for 24 h at least. The reaction was quenched with 1.0 N aqueous HCl and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, respectively, dried over Na_2SO_4, and concentrated under vacuum. Purification by silica gel flash chromatography provided the desired product.

4-(2-Fluorophenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2a): Mp 122−123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.06 (s, 1H), 7.18 (d, 1H, J = 6.6 Hz), 7.21 (d, 1H, J = 8.1 Hz), 8.03 (dd, 1H, J = 5.1, 2.4 Hz), 8.06 (dd, 1H, J = 5.4, 2.4 Hz), 15.25 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.11, 168.02, 165.62 (d), 161.98, 130.77, 130.15, 130.05, 115.83, 115.61, 97.56, 53.00. EI-MS m/z 224 (M^+). IR (film) 2968, 1737, 1596, 1509, 1442, 1283, 1236 cm^{-1}. Anal. Calcd for $C_{11}H_9FO_4$: C 58.93, H 4.05. Found: C 59.15, H 4.00.

4-(4-Fluorophenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2b):[19] Mp 120−121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.06 (s, 1H), 7.18 (dt, 1H, J = 8.4, 1.0 Hz), 7.21 (dt, 1H, J = 8.4, 1.5 Hz), 8.03 (dd, 1H, J = 5.7, 1.8 Hz), 8.06 (dd, 1H, J = 5.1, 2.1 Hz) (an enol proton is not shown in the spectrum). EI-MS m/z 224 (M^+). IR (film) 2968, 1736, 1596,

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1508, 1442, 1236 cm^{-1}. Anal. Calcd for $C_{11}H_9FO_4$: C 58.93, H 4.05. Found: C 58.93, H 4.05.

4-(4-Fluorophenyl)-4-oxo-2-hydroxy-2-butenoic acid *tert*-butyl ester (4b): Mp 64−66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 6.95 (s, 1H), 7.16 (dt, 1H, J = 8.6, 2.7 Hz), 7.18 (dt, 1H, J = 8.7, 2.8 Hz), 7.99 (dd, 1H, J = 5.0, 2.8 Hz), 8.02 (dd, 1H, J = 4.9, 2.9 Hz), 15.25 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.97, 170.57, 165.79 (d), 160.79, 131.23, 130.30, 130.21, 116.06, 115.84, 97.13, 83.83, 27.97 (×3). EI-MS m/z 266 (M^+).

4-(3-Methoxyphenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2c): Mp 86.5−87.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 3.96 (s, 3H), 7.08 (s, 1H), 7.17 (dt, 1H, J = 8.1, 1.5 Hz), 7.43 (dt, 1H, J = 1.0, 7.5 Hz), 7.52 (dd, 1H, J = 1.2, 1.5 Hz), 7.58 (dd, 1H, J = 7.5, 0.9 Hz) (an enol proton is not shown in the spectrum). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.22, 168.17, 162.05, 159.42, 135.77, 129.39, 120.02, 119.81, 111.78, 97.96, 55.21, 52.96. EI-MS m/z 236 (M^+). IR (film) 2959, 1735, 1585, 1492, 1272, 1214, 772 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_5$: C 61.01, H 5.12. Found: C 61.07, H 4.92.

4-(4-Nitrophenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2d):[20] Mp 144−146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.12 (s, 1H), 8.17 (dd, 2H, J = 8.1, 1.5 Hz), 8.37 (dd, 2H, J = 8.4, 1.8 Hz) (an enol proton is not shown in the spectrum). EI-MS m/z 251 (M^+). IR (film) 3118, 2966, 1752, 1605, 1521, 1349, 1109 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_6$: C 52.60, H 3.61, N 5.58. Found: C 52.95, H 3.80, N 5.30.

4-(4-Trifluoromethylphenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2e): Mp 101−103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.11 (s, 1H), 7.78 (d, 2H, J = 8.7 Hz), 8.11 (d, 2H, J = 8.7 Hz), 15.10 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.89, 170.25, 161.67, 137.20, 134.39 (q), 127.66 (×2), 125.44, 125.41, 124.32, 97.69, 53.09. EI-MS m/z 274 (M^+). IR (film) 3106, 2959, 1734, 1623, 1438 cm^{-1}. Anal. Calcd for $C_{12}H_9F_3O_4$: C 52.56, H 3.31. Found: C 53.00, H 3.31.

4-(3-Methyl-4-chlorophenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2f): Mp 99−101 °C. Mixture of two enols in $CDCl_3$, with a ratio of ca. 2:1 by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.95 (s, 3H), 7.03 and 7.04 (s, 1H), 7.36 and 7.47 (d, 1H, J = 8.2 Hz), 7.74 and 7.77 (d, 1H, J = 8.2 Hz), 7.86 and 7.97 (d, 1H, J = 1.8 Hz), 15.18 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.32, 168.75, 162.13, 140.17, 136.66, 132.90, 129.85, 129.33, 126.22, 97.72, 53.13, 20.11. The isomer: δ 189.03, 168.75, 162.13, 142.30, 134.50, 133.77, 131.01, 128.12, 125.61, 97.72, 53.13, 20.43. EI-MS m/z:254 (M^+). IR (film) 1762, 1751, 1722, 1618, 1432, 1273, 1120, 774 cm^{-1}. Anal. Calcd for $C_{12}H_{11}ClO_4$: C 56.84, H 4.22. Found: C 56.59, H 4.35.

4-(3-Benzyloxyphenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2g): Mp 70−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 5.14 (s, 2H), 7.08 (s, 1H), 7.21−7.25 (m, 2H), 7.34−7.47 (m, 6H), 7.59−7.61 (m, 2H), 15.22 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.13, 168.21, 162.05, 158.58, 135.81 (×2), 129.49, 128.21 (×2), 127.74, 127.09 (×2), 120.46, 120.26, 112.99, 97.98, 69.95, 52.97. EI-MS m/z 312 (M^+). IR (film) 3119, 2949, 1731, 1723, 1624, 1578, 1261 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_5$: C 69.22, H 5.16. Found: C 69.18, H 5.19.

4-(4-*N*,*N*-Dibenzylaminophenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2h): Mp 101−102 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.69 (s, 4H), 6.92 (s, 1H), 7.22−7.27 (m, 10H), 7.31−7.34 (m, 3H), 7.37 (s, 1H) (an enol proton is not shown in the spectrum). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.29, 167.85, 162.32, 148.99, 137.42, 135.52 (×2), 129.33, 128.47 (×4), 126.85 (×2), 126.29 (×4), 117.65, 116.23, 110.72, 98.27, 54.28 (×2), 53.02. EI-MS m/z 401 (M^+). IR (film) 3040, 1729, 1595, 1495, 1270 cm^{-1}. Anal. Calcd for $C_{25}H_{23}NO_4$: C 74.79, H 5.77, N 3.49. Found: C 74.70, H 5.81, N 3.31.

4-(3-Benzyloxycarbonylaminophenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2i): Mp 142−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 5.23 (s, 2H), 6.95 (br, 1H), 7.05 (s, 1H), 7.33−7.46 (m, 6H), 7.68 (d, 1H, J = 8.0 Hz), 7.72 (d, 1H, J = 7.5 Hz), 7.97 (s, 1H), 15.20 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + d_6-DMSO) δ 190.00, 168.20, 161.63, 153.04, 139.32, 135.51 (×2), 134.54, 128.64, 127.84 (×2), 127.63 (×2), 123.22, 121.29, 116.96, 97.64, 66.10, 52.66. EI-MS m/z 355 (M^+). IR (film) 3352, 1745, 1726, 1545, 1494, 1311, 1224, 1050 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_6$: C 64.22, H 4.82, N 3.94. Found: C 63.93, H 4.71, N 3.79.

4-(3-(2-Fluorobenzyl)phenyl)-4-oxo-2-hydroxy-2-butenoic acid methyl ester (2j):[10] Mp 58−59 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 4.07 (s, 3H), 7.05 (s, 1H), 7.03−7.10 (m, 2H), 7.15 (dt, 1H, J = 7.4, 1.8 Hz), 7.22 (m, 1H), 7.40−7.47 (m, 2H), 7.84 (dt, 1H, J = 7.4, 1.6 Hz), 7.87 (s, 1H), 15.20 (br, 1H). EI-MS m/z 314 (M^+). IR (film) 3121, 1726, 1625, 1585, 1266, 1235 cm^{-1}.

2-Hydroxy-4-(3-{2-[3-(3-hydroxy-3-methoxycarbonylacryloyl)phenoxymethyl]-benzyloxy}phenyl)-4-oxo-but-2-enoic acid methyl ester (2k): Mp 131−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 6H), 5.26 (s, 4H), 7.03 (s, 2H), 7.19 (dt, 2H, J = 8.4, 1.9 Hz), 7.36−7.43 (m, 4H), 7.52−7.56 (m, 4H), 7.58 (s, 2H), 15.19 (br, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 190.09 (×2), 168.47 (×2), 162.02 (×2), 158.68 (×2), 135.78 (×2), 135.02 (×2), 130.31 (×2), 128.98 (×2), 128.18 (×2), 120.91 (×2), 120.82 (×2), 113.45 (×2), 98.36 (×2), 67.67 (×2), 53.07 (×2). IR (film) 3111, 2952, 1734, 1594, 1436, 1283 cm^{-1}.

4-(3-{(2-Fluoro-phenyl)-[3-(3-hydroxy-3-methoxycarbonylacryloyl)phenyl]-methyl}phenyl)-2-hydroxy-4-oxo-but-2-enoic acid methyl ester (2l): Mp 56−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 6H), 5.97 (s, 1H), 6.89 (dt, 1H, J = 1.6, 7.8 Hz), 7.01 (s, 2H), 7.06−7.12 (m, 2H), 7.26−7.32 (m, 2H), 7.34 (d, 2H, J = 8.0 Hz), 7.47 (dd, 2H, J = 7.9, 7.6 Hz), 7.78 (s, 2H), 7.89 (d, 2H, J = 7.79 Hz), 15.20 (br, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 189.41 (×2), 167.87 (×2), 161.66 (×2), 159.67 (d), 142.64 (×2), 135.98, 134.49 (×2), 134.28 (×2), 130.22, 129.29 (×2), 129.00, 127.77 (×2), 126.45 (×2), 124.38, 115.49 (d), 98.09 (×2), 53.06 (×2), 48.40. IR (film) 2954, 1736, 1602, 1488, 1436, 1273 cm^{-1}. EI-MS m/z 518 (M^+). HRMS (EI) calcd for $C_{29}H_{23}FO_8$ (M^+) 518.1385, found 518.1337.

Acknowledgment. This work was supported by grants from the Shanghai Municipal Committee of Science and Technology (02QB14056), the Chinese Academy of Sciences (KSCX1-SW-11), and the Ministry of Personnel of China.

Supporting Information Available: ^{1}H NMR spectra for **2c**,**f**,**h**,**i**,**k**,**l** and **4b**; ^{13}C NMR spectra for **2a**,**c**,**e**,**f**,**h**,**i**,**k**,**l**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034903X

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