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Article

A Simple and Highly Efficient Preparation of Structurally Diverse Aryl β-diketoacids as HIV-1 Integrase Inhibitors†

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In order to provide a facile and practical access to structurally diverse aryl β-diketoacids, An improved and highly efficient oxalylation method was developed which employed commercially available and cheap reagents. The oxalylation of aryl methyl ketones, the key step to construct the pharmacophore of aryl β-diketoacids, was considerably facilitated by a new combination of dimethyl oxalate as an oxalic source and sodium *tert*-butoxide as a base. A wide variety of aryl β-diketoacids bearing different functional groups can be prepared rapidly in high yields at room temperature with this method, which has significant advantages over the previously reported procedures in a wider application range, much less amount of reagents, pretty higher yields and quite shorter reaction time. The bis-aryldiketoacids **3k** and **3l**, readily prepared by this method, displayed interesting and promising inhibitory activities against HIV-1 integrase and HIV-1 replication in cells.

Keywords oxalylation, sodium *tert*-butoxide, dimethyl oxalate, aryl β-diketoacid, HIV-1 integrase inhibitor, bis-diketoacid

Introduction

Aryl diketoacids (ADK) constitute an interesting class of bioactive structural motif. They were initially reported as effective inhibitors of viral polymerases, in particular hepatitis C virus RNA-dependent RNA polymerase (HCV RdRp), hepatitis B virus polymerase (HBV pol) and reverse transcriptase of human immunodeficiency virus (HIV RT).[1] Recently the diketoacids were discovered as the most promising class of HIV-1 integrase inhibitors.[2,3] HIV-1 integrase (IN) is an essential enzyme for the replication and infection of retroviruses,[4] so IN is an attractive target for antiviral therapy.[5] Among the numerous IN inhibitors identified,[6-8] the most developed are the aryl diketo (ADK) family (Figure 1),[3] among which S-1360 was the first drug as an HIV-1 IN inhibitor to enter clinical trials.[9,10] These findings have fuelled the recent surge of interest in the development of HIV-1 IN inhibitors.[6]

The structure-activity relationship study and further development of ADK-based inhibitors require a ready access to structurally diverse aryl β-diketoacids. However, the conventional methods to synthesize ADK compounds, *i.e.* diethyl oxalate or dimethyl oxalate in the presence of NaH or NaOEt or NaOMe,[11-15] exhibited very low efficiency for the sterically hindered or halogen-substituted aryl ketones, greatly limiting the preparation of various aryl diketoacids needed for the discovery and development of IN inhibitors. Herein we report our newly developed facile and practical oxalylation method, which employs dimethyl oxalate as a convenient oxalic source and sodium *tert*-butoxide as a base to prepare a wide range of aryl diketoacids in high yields (Scheme 1).

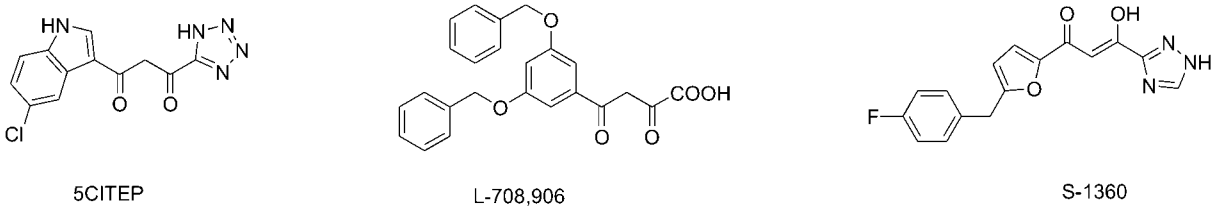

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Figure 1 Reported ADK-based HIV IN inhibitors.

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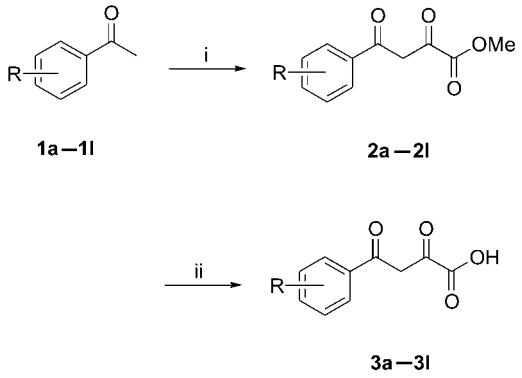
† Dedicated to Professor Chengye Yuan on the occasion of his 80th birthday.

Scheme 1[a]



[a](i) Procedure A: $(CO_2Me)_2$, $NaOCH_3$, THF-DME (1∶1), r.t., ⩾24 h; Procedure B: $(CO_2Me)_2$, NaOBu-*t*, THF-DME (1∶1), r.t., 10 min—1.5 h (except for **1i,** 12 h); (ii) 1 mol/L NaOH, THF-CH_3OH (1∶1), r.t., 1 h.

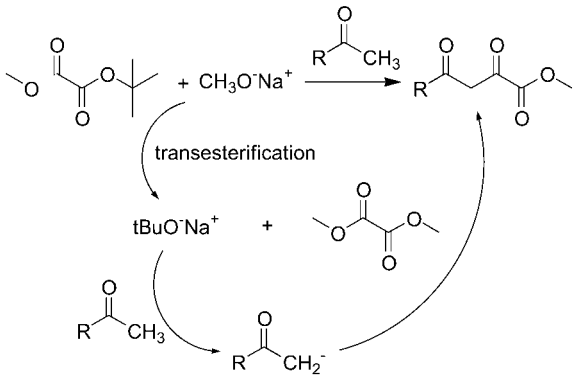
Results and discussion

As part of our program to examine the structural features of the ADK family which are related to IN inhibitory potency and selectivity, we have tried to develop a simple and highly efficient procedure to afford more structurally diverse aryl β-diketoacids conveniently. Recently we reported that *tert*-butyl methyl oxalate instead of conventional dimethyl oxalate in the presence of sodium methoxide was an efficient system to prepare a variety of aryl diketoacids in good to excellent yields at room temperature.[16] However, this methodology is not effective for electron-withdrawing group substituted acetophenones such as 4-nitroacetophenone and 4-trifluoromethylacetophenone. Furthermore, the key oxalylating agent, *tert*-butyl methyl oxalate needs preparing from oxalyl chloride via two-step reaction. So, it is intriguing to optimize the procedure, starting from commercially available and cheap reagents.

Based on the preliminary study on the mechanism of *tert*-butyl methyl oxalate mediated oxalylation with sodium methoxide as a base, we proposed that sodium methoxide might react first with the *tert*-butyl methyl oxalate to generate dimethyl oxalate and sodium *tert*-butoxide in a transesterification, then the resulting sodium *tert*-butoxide would function as a better base in the reaction (Scheme 2).[16] Enlightened by this idea, we supposed that sodium *tert*-butoxide could be used directly as a base to promote the dimethyl oxalate mediated coupling reaction. Interestingly, the new combination of dimethyl oxalate and sodium *tert*-butoxide was found remarkably efficient for the oxalylation of a wide range of aryl methyl ketones, even more efficient than its cognate system of *tert*-butyl methyl oxalate and sodium methoxide. The positive results of the mechanism-based design further proved our proposed mechanism in turn.

As summarized in Table 1, the new combination of dimethyl oxalate/sodium *tert*-butoxide compares

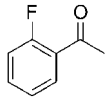
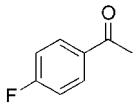
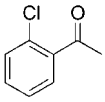
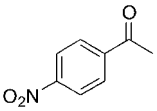
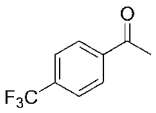
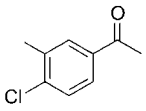
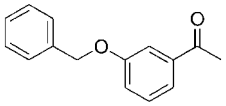
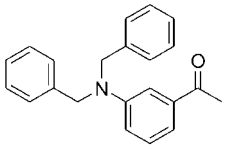
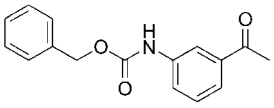
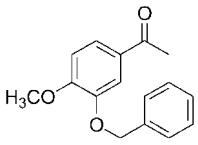
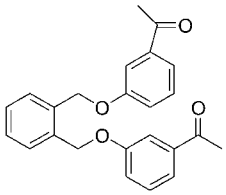
Scheme 2 Proposed mechanism of the oxalylation mediated by *tert*-butyl methyl oxalate and sodium methoxide



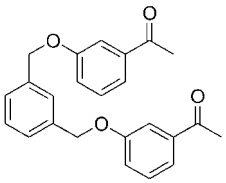
favorably with both the conventional system of dimethyl oxalate/sodium methoxide and our recently reported system of *tert*-butyl methyl oxalate/sodium methoxide for the preparation of various ADK derivatives. A variety of aryl methyl ketones bearing electron-donating or electron-withdrawing groups as well as sterically crowded and bis-(aryl methyl ketone) examples were screened. The coupling of variously substituted acetophenones with dimethyl oxalate in the presence of sodium *tert*-butoxide occurred very efficiently at room temperature, using 1 equiv. of aryl ketone, 2 equiv. of dimethyl oxalate, and 2.5 equiv. of sodium *tert*-butoxide. In the case of using sodium methoxide as a base, the quantity of sodium methoxide was increased to 5 equiv. when dimethyl oxalate was used, whereas the amount of sodium methoxide still required 4 equiv. when *tert*-butyl methyl oxalate was employed as oxalic source. The optimized mixed solvent of THF and DME (1∶1) was used for the standard coupling procedure.

It is clear that, in most cases, shorter time and better yields were achieved for the couplings using sodium *tert*-butoxide, compared with those using sodium methoxide as a base. Halogen (**1a—1c**, **1f**), electron-withdrawing group (**1d—1e**), and electron-donating group (**1g—1l**) substituted acetophenones all exhibited an overwhelming preference for the sodium *tert*-butoxide/dimethyl oxalate system. Especially for the preparation of electron-withdrawing group substituted ADK products, the current combination displayed a unique advantage over its cognate system of *tert*-butyl methyl oxalate and sodium methoxide, the former proceeding rapidly in excellent yields, while the latter just affording low to moderate yields after a longer reaction time. The number and the position of the substituents on the phenyl ring did not affect the efficiency. Even the hindered ketones (**1a**, **1c**, **1k—1l**) did not attenuate the reactivity. Similar to *tert*-butyl methyl oxalate and sodium methoxide method, the new oxalylation system of dimethyl oxalate/sodium *tert*-butoxide showed special advantage in the synthesis of bis-aryl diketoacids (entries 11, 12 in Table 1),which constitute a novel set of ADK-based HIV-1 IN inhibitors.[14,17] The preparation of bis-diketo acid via dimethyl oxalate in the presence of sodium methoxide failed at room temperature, even after 24 h

Table 1 Coupling of aryl methyl ketones with three oxalylation systems

Entry	Aryl ketone		Isolated yield (%) (Reaction time)			Product
			I[a]	II[b]	III[c]	
1		**1a**	44 (24 h)	95 (10 min)	81 (1.0 h)	**2a**
2		**1b**	12 (24 h)	100 (20 min)	97 (1.5 h)	**2b**
3		**1c**	0 (24 h)	NA[d]	92 (10 min)	**2c**
4		**1d**	30 (24 h)	52 (2 h)	98 (10 min)	**2d**
5		**1e**	18 (24 h)	71 (2 h)	94 (10 min)	**2e**
6		**1f**	0 (24 h)	86 (12 h)	93 (0.5 h)	**2f**
7		**1g**	33 (24 h)	78 (2 h)	89 (10 min)	**2g**
8		**1h**	14 (36 h)	76 (2 h)	82 (10 min)[e]	**2h**
9		**1i**	0 (24 h)	92 (3 h)[f]	85 (12 h)	**2i**
10		**1j**	0 (24 h)	NA	97 (10 min)	**2j**
11		**1k**	0[g] (24 h)[h]	94 (0.5 h)[h]	84 (10 min)[h]	**2k**

Continued

Entry	Aryl ketone		Isolated yield (%) (Reaction time)			Product
			I[a]	II[b]	III[c]	
12		**1l**	0 (24 h)	NA	88 (10 min)	**2l**

[a] Dimethyl oxalate/sodium methoxide system. The coupling was performed according to procedure A. [b] *tert*-Butyl methyl oxalate/sodium methoxide system. The data were reported in Ref. 16 and used here as a comparison. [c] Dimethyl oxalate/sodium *tert*-butoxide system. The coupling was carried out according to procedure B. [d] Not available. [e] The isolated yield was obtained with 4 equiv. of NaOMe. [f] The isolated yield was obtained after 3 h stirring at 40 ℃. [g] NaOMe (10.0 equiv.), dimethyl oxalate (5.0 equiv.), toluene-DME-THF (1∶1∶1), 60 ℃ overnight, the isolated yield 50%. [h] 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.

stirring (**1k**, **1l**). Raising the temperature to 60 ℃ in toluene and DME helped the reaction to proceed in moderate yields (50%—60%) after 12 h heating. However, the coupling mediated by sodium *tert*-butoxide (**1k**, **1l**) resulted in high yields (85%—88%) within a very short time (10 min at room temperature usually).

The final aryl diketoacids can be readily obtained from the hydrolysis of the resulting aryl diketoacid methyl ester with 1 mol/L NaOH in MeOH-THF at room temperature. The typical procedure was exampli-fied by the preparation of aryl diketoacid **3k**.

Compared to the recently reported *tert*-butyl methyl oxalate/sodium methoxide method,[16] the dimethyl oxalate/sodium *tert*-butoxide system exhibited an improved efficiency and significant advantages in terms of a wider application range, less amount of reagents and shorter reaction time. Furthermore, the commercially available and cheap reagents employed render this new combination an attractive and practical approach to prepare active ADK-based HIV IN inhibitors in large scale.

Among our synthetic ADK compounds, the bis-aryl diketoacids **3k** and **3l** were chosen to test the HIV-1 IN inhibitory activity. The bioassay was evaluated in an extracellular HIV-1 integrase assay[18] and in a single-cycle replication assay using envelope-deficient HIV-1.[19] The data were summarized in Table 2.[20] Both exhibited interesting and promising inhibitory activity against HIV-1 integrase as well as anti-viral efficiency in HIV-infected cells.

Conclusion

In summary, we developed a facile and efficient procedure to prepare variously substituted aryl diketoacids with a new combination of dimethyl oxalate/sodium *tert*-butoxide. The oxalylation was accomplished in high speed with excellent yields under mild conditions. This methodology is applicable to a wide range of aryl methyl ketones bearing electron-donating or electron-withdrawing groups, or bis-(aryl methyl ketone) examples, thus offering a general method for the preparation of structurally diverse ADK-containing derivatives. The bis-aryldiketoacids **3k** and **3l**, readily prepared by this method, displayed interesting and potent inhibitory activity against HIV-1 integrase and antiviral potency in HIV-infected cells. This highly efficient preparation of aryl β-diketoacids using dimethyl oxalate in the presence of sodium *tert*-butoxide will potentially benefit the development of HIV-1 IN inhibitors.

Experimental

^{1}H NMR spectra were recorded on a Varian 300 MHz or 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Varian Mercury VX 400 MHz spectrometer. Elemental analyses were obtained on a Vario EL analyzer. Melting points (uncorrected) were determined on a Buchi-510 capillary apparatus. IR spectra were recorded on a Bio-Rad FTS-185 spectrophotometer. HRMS (ESI) spectra were obtained on a APEXIII 7.0 TESLA FTMS mass spectrometer. Substituted aryl acetophenones **1a**—**1f** were of commercial grade, and **1g**—**1l** were synthesized according to the literature procedure. The solvents (toluene, THF and DME) were dried over sodium wire and distilled prior to use. Flash column chromatography was performed on silica gel H (10—40 μm) with petroleum ether-ethyl acetate system as eluent.

General procedure for oxalylation of aryl methyl ketone

Procedure A: 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 mol/L aqueous HCl solution and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine

Table 2 Inhibition of HIV-1 integrase catalytic activities and HIV-1 replication in cells by the synthesized bis-aryldiketoacids[20]

Compd	Inhibition of integrase catalytic activities[a]			Antiviral activities[b]	
	3'-Processing $IC_{50}/(\mu mol \cdot L^{-1})$[c]	Strand transfer $IC_{50}/(\mu mol \cdot L^{-1})$[c]	SI[d]	$EC_{50}/(\mu mol \cdot L^{-1})$[e]	$CC_{50}/(\mu mol \cdot L^{-1})$[f]
3k	1.8±0.9	0.3±0.2	6	39±3	>200
3l	7.3±2.3	0.4±0.1	18	>200	>200

[a] Assays were performed with recombinant HIV-1 integrase (0.2 μmol•L^{-1}) preincubated with the inhibitor in reaction buffer at 30 ℃ for 30 min. Then, 20 nmol•L^{-1} of the 5'-end ^{32}P-labeled linear oligonucleotide substrate was added, and incubation was continued for an additional 1 h. For details see Ref. 19. [b] The anti-HIV activity was evaluated in human T cell line CEM-SS infected with HIV-1 as described by Weislow *et al.*[20] [c] IC_{50}: Inhibitory concentration 50% (inhibition of purified integrase). [d] SI: Sensitivity index=IC_{50} 3'−P/IC_{50} ST. [e] EC_{50}: Effective concentration 50% (protection of HIV-1 infected CEM cells). [f] CC_{50}: Cytotoxic concentration 50% (toxicity to uninfected CEM cells).

respectively, dried over Na_2SO_4 and concentrated under vacuum. Purification by silica gel flash chromatography provided the desired product.

Procedure B: To a stirred mixture of *tert*-BuONa (2.5 equiv.) and dimethyl oxalate (2.0 equiv.) in anhydrous THF at 0 ℃ was added dropwise aryl methyl ketone (1.0 equiv.) in DME. The resulting orange-yellow mixture was stirred at room temperature for 1.5 h at most (for **1i**, 12 h). The reaction was quenched with 1.0 mol/L aqueous HCl solution and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine respectively, dried over Na_2SO_4 and concentrated under vacuum. Purification by silica gel flash chromatography provided the desired product.

4-(2-Chlorophenyl)-2-hydroxy-4-oxo-but-2-enoic acid methyl ester (**2c**): White solid. m.p. 80—81 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 6.97 (s, 1H), 7.35—7.39 (m, 1H), 7.42—7.49 (m, 2H), 7.63—7.65 (m, 1H), 14.60 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.54, 166.99, 162.07, 135.52, 132.62, 131.94, 130.79, 130.05, 126.93, 103.05, 53.32; IR (KBr) ν: 3444, 2964, 1726, 1591, 1432, 1274, 1043, 733 cm^{-1}; EI-MS *m/z* (%): 240 (M^+, 0.59), 205 (25.88), 181 (100.0), 139 (30.12); Anal. calcd for $C_{11}H_9ClO_4$: C 54.90, H 3.77; found C 55.12, H 3.88.

4-(3-Benzyloxy-4-methoxy-phenyl)-2-hydroxy-4-oxo-but-2-enoic acid methyl ester (**2j**): Yellow solid. m.p. 149—150 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 3.96 (s, 3H), 5.25 (s, 2H), 6.94 (d, J=8.7 Hz, 1H), 7.03 (s, 1H), 7.30—7.35 (m, 1H), 7.36—7.45 (m, 4H), 7.56 (s, 1H), 7.58 (d, J=2.1 Hz, 1H), 14.65 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.36, 166.49, 162.62, 153.04, 149.51, 135.76, 128.51 (×2), 128.02, 127.02 (×2), 122.52, 112.29, 110.18, 98.03, 70.83, 56.13, 53.16; IR (KBr) ν: 3466, 2947, 1747, 1595, 1514, 1427, 1259, 1003, 771, 748 cm^{-1}; EI-MS *m/z* (%): 342 (M^+, 19.95); 283 (6.05); 91 (100); Anal. calcd for $C_{19}H_{18}O_6$: C 66.66, H 5.30; found C 66.71, H 5.02.

2-Hydroxy-4-(3-{3-[3-(3-hydroxy-3-methoxycarbonylacryloyl)phenoxymethyl]benzyloxy}phenyl)-4-oxo-but-2-enoic acid methyl ester (**2l**): Pale yellow solid. m.p. 145—148 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.95 (s, 6H), 5.16 (s, 4H), 7.06 (s, 2H), 7.21—7.24 (m, 2H), 7.39—7.45 (m, 5H), 7.56 (s, 1H), 7.58—7.61 (m, 4H), 15.20 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.32 (×2), 168.55 (×2), 162.32 (×2), 158.75 (×2), 136.69 (×2), 136.10 (×2), 129.79 (×2), 128.87 (×2), 127.11 (×2), 126.33 (×2), 120.70, 120.62, 113.26 (×2), 98.23 (×2), 69.97 (×2), 53.26 (×2); IR (KBr) ν: 951, 1745, 1605, 1450, 1271, 1211, 1059, 885, 771 cm^{-1}; EI-MS *m/z* (%): 531 (0.1), 374 (14.0), 239 (100.0), 221 (12.0), 163 (28.0), 121 (10.0), 104 (36.0); Anal. calcd for $C_{30}H_{26}O_{10}$: C 65.93, H 4.80; found C 65.76, H 4.78.

2-Hydroxy-4-(3-{2-[3-(3-carboxy-3-hydroxy-bonylacryloyl)phenoxymethyl]benzyloxy}phenyl)-4-oxo-but-2-enoic acid (**3k**): A solution of compound **2k**: (0.164 g, 0.30 mmol) in THF/CH_3OH (1∶1) (4.0 mL) was treated with 1.0 mol/L NaOH (3.0 mL, 3.0 mmol). The reaction mixture was stirred for 1 h at room temperature, then extracted with ether. The water phase was acidified with 2.0 mol/L HCl solution to pH=1—2 and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was recrystallized from petroleum ether/methane dichloride to give compound **3k** as a pale yellow solid (0.109 g, yield 70.0%). m.p. 186—188 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.36 (s, 4H), 7.06 (s, 2H), 7.32—7.35 (m, 2H), 7.39—7.41 (q, J=13.40 Hz, 2H), 7.45—7.49 (m, 2H), 7.55—7.59 (m, 3H), 7.61—7.64 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ: 190.35 (×2), 169.47 (×2), 163.22 (×2), 158.44 (×2), 136.04 (×2), 134.29 (×2), 129.63 (×2), 128.88 (×2), 128.30 (×2), 120.31 (×2), 112.98 (×2), 97.78 (×2), 67.82 (×2); IR (KBr) ν: 3539, 3466, 1701, 1624, 1574, 1290, 1261, 899, 775 cm^{-1}, HR-ESI-MS calcd for $C_{28}H_{22}O_{10}$ $(M+Na)^+$ 541.1111, found 541.1113.

2-Hydroxy-4-(3-{3-[3-(3-carboxy-3-hydroxy-bonylacryloyl)phenoxymethyl]benzyloxy}phenyl)-4-oxo-but-2-enoic acid (**3l**): Compound **3l** was obtained from the hydrolysis of compound **2l** with 1.0 mol/L aqueous NaOH solution (3.2 mL, 3.2 mmol) in THF/CH_3OH (1∶1) (4.0 mL) analogously to compound **3k**. Recrystallization from petroleum ether/methane

dichloride afforded compound **3l** as a pale yellow solid (0.122 g, yield 73.5%). m.p. 188—191 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.23 (s, 4H), 7.09 (s, 2H), 7.33—7.36 (m, 2H), 7.48—7.51 (m, 6H), 7.63—7.68 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 190.33 (×2), 163.51 (×2), 158.65 (×4), 136.50 (×4), 130.27 (×2), 127.93 (×6), 120.42 (×2), 113.12 (×2), 98.28 (×2) 69.21 (×2); IR (KBr) ν: 3533, 2895, 2459, 1685, 1624, 1574, 1286, 1263, 901, 775 cm^{-1}; HR-ESI-MS calcd for $C_{28}H_{22}O_{10}$ $(M+Na)^+$ 541.1111, found 541.1108.

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