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First and mild synthesis of fluorene-9-malonic acid and some substituted derivatives via the intramolecular hydroarylation of 2-phenylbenzylidenemalonic acids

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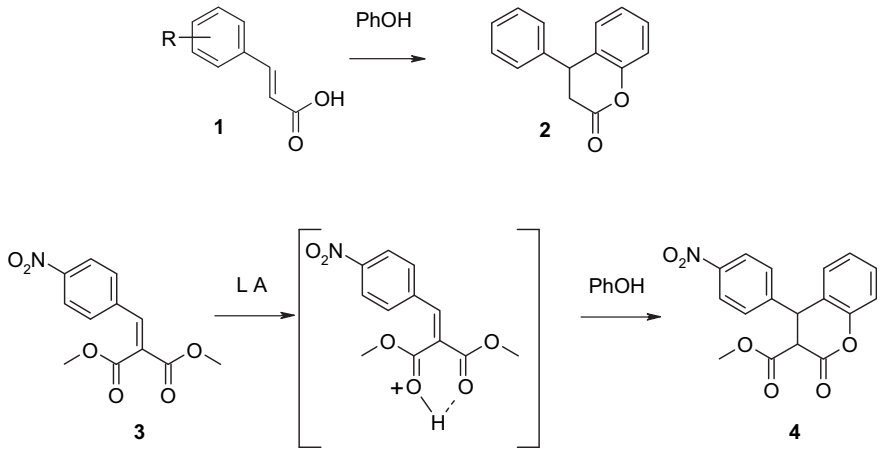
ABSTRACT

Hitherto unknown fluorene-9-malonic acid and some substituted derivatives were easily synthesized in very mild conditions through the intramolecular hydroarylation of 2-phenylbenzylidenemalonic acids issued from the corresponding biphenylcarboxaldehydes.

1. Introduction

Recently, hydroarylation of cinnamic acids **1** was reported as an efficient method to synthesize benzhydrylacetic acid derivatives.[1] Using phenol, this reaction was also widely used for the synthesis of dihydrocoumarin derivatives **2** with potential biological interest (Scheme 1).[2–13] However, such hydroarylations need highly acidic media and are generally limited to electron-rich starting materials. It was however very recently demonstrated that electron-deficient benzylidene-malonic esters, such as *p*-NO_2 derivative **3** can be involved with phenol in a Lewis acid-catalyzed hydroarylation–lactonization sequence to lead more easily to methyl oxochromancarboxylates **4**.[14] In this case, hydroarylation is facilitated by the activating part played by the pendant carboxyl



Scheme 1. Literature hydroarylation of cinnamic acids **1** and benzylidene-malonic esters **3**.

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group, liable to stabilize the protonated intermediate via an intramolecular hydrogen bond.

We imagined adapting this method to achieve the intramolecular hydroarylation of 2-phenylbenzylidenemalonic acids **5** in order to perform the synthesis of unknown fluorene-9-malonic acids **6** (Fig. 1).

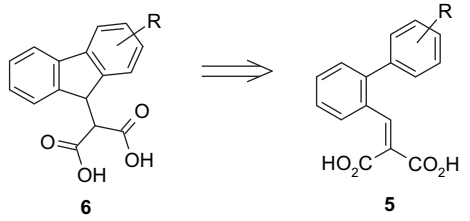


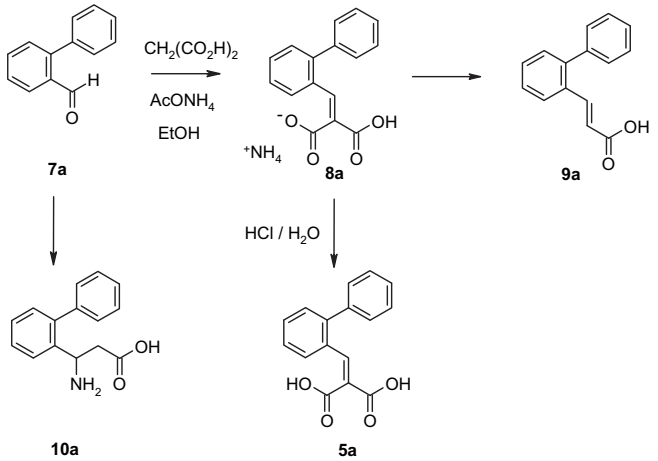
Fig. 1. Retrosynthetic acess to fluorene-9-malonic acids **6**.

Fluorene-9-malonic acid **6a** (R=H) had not been hitherto reported and its unique 1-carboxy-substituted derivative, previously described, was obtained through irradiation of 3-hydroxyfluoranthene-1-carboxylic acid.[15] Nevertheless, we consider this system as potentially interesting particularly because of its analogy with indane-1-malonic acid whose structure was recently designed as a useful scaffold for the synthesis of some PPAR ligands.[16] For this reason, we undertook the synthesis of **6a** and we propose herein an easy and extending pathway to lead to various substituted fluorene-9-malonic acids **6**.

2. Results and discussion

The synthesis of 2-phenylbenzylidenemalonic acid **5a** was performed according to a Rodionow procedure,[17] we use extensively to prepare beta-amino beta-arylpropionic acids from arylaldehydes with considerable interest as building-blocks in medicinal chemistry.[18] Applied to commercially available 2-phenylbenzaldehyde **7a**, the use of malonic acid and ammonium acetate in refluxing ethanol for 6 h did not lead to the expected aminoacid 2-phenyl-beta-homophenylalanine **10a**, whose only traces were recovered, but to a precipitate of the mono ammonium salt of 2-phenyl-benzylidenemalonic acid **8a**, which was formed in 29% yield concomitantly with the decarboxylated phenylcinnamic acid **9a** remaining in solution (Scheme 2).

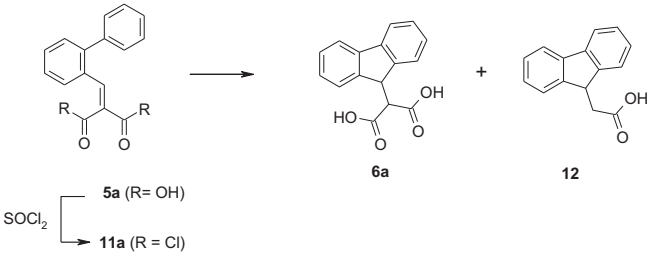
Reducing the time of the reaction to 30 min allowed however to improve the yield for the synthesis of **8a** (58%), whose treatment with aqueous hydrochloric acid gave the diacid **5a**.



Scheme 2. Rodionow–Jonhson synthesis of 2-phenylbenzylidene-malonic acid **5a** and 2-phenylcinnamic acid **9a**.

Acyl chloride **11a**, quantitatively obtained under treatment of **5a** in refluxed $SOCl_2$, was first used to achieve the synthesis of **6a**. Reaction of **11a** with 1.1 equiv of $AlCl_3$ in refluxing CH_2Cl_2 led after 1.5 h to the synthesis of the expected fluorenemalonic acid **6a** in 50% conversion rate (Table 1, entry 1). Prolonging the reaction time in these conditions did not allow the total conversion into **6a**. The latter however took place using 2.2 equiv of the Lewis acid at room temperature (entry 2). Nevertheless, activation through an acyl chloride species appeared not necessary since the application of the same treatment, starting this time directly from the diacid **5a**, led to the same result (entry 3).

Table 1
Cyclization conditions for the synthesis of compounds **6a** and **12**



Entry	Start Mat	Reagent	Solvent	Temp	Time (h)	Conversion rate (%)	
						6a	**12**
1	**11a**	$AlCl_3$ 1.129 equiv	CH_2Cl_2	rflx	1.5	50	0
2	**11a**	$AlCl_3$ 1.1 equiv	CH_2Cl_2	rt	12	100	0
3	**5a**	$AlCl_3$ 2.2 equiv	CH_2Cl_2	rt	12	100	0
4	**5a**	BF_3, Et_2O 2.2 equiv	Et_2O	rt	12	100	0
5	**5a**	TFA 70 equiv	CH_2Cl_2	rt	19	100	0
6	**5a**	TFA 70 equiv	CH_2Cl_2	60 °C[a]	5	100	0
7	**5a**	TFA/TFA_2O 70 equiv/70 equiv	CH_2Cl_2	60 °C[a]	8.5	0	100
8	**5a**	TFA_2O 70 equiv	CH_2Cl_2	60 °C[a]	24	0	0

[a] Sealed tube.

Replacing $AlCl_3$ by $BF_3.Et_2O$ in Et_2O or by TFA in CH_2Cl_2 at room temperature yielded also the complete formation of **6a** after 12 and 19 h, respectively (entries 4 and 5). Heating the trifluoracetic reaction mixture at 60 °C allowed the decrease of the reaction time from 19 h to 5 h (entry 6).

On the other hand, the use of a mixture in equal part of TFA and TFA_2O led to the total decarboxylation of **6a** into fluorene-9-acetic acid **12** (entry 7)[19] for which this sequence constitutes a novel synthesis method. Finally, the treatment of **6a** in pure TFA_2O led only to the degradation of the formed products (entry 8).

During all these attempts, none of the cyclized compounds, belonging to indanone and dibenzocycloheptenone series and potentially issued from the intramolecular acylation of one of the two phenyl rings by one of the two carboxylic acid groups of **5a** or **11a**, were observed.

Concerning the isolation of fluorene-9-malonic acid **6a**, the best results were obtained under treatment with $BF_3 \cdot Et_2O$, then quenching the reaction with MeOH and evaporating the reaction mixture under vacuum in order to eliminate borane derivatives (entry 4). In these conditions, the process yielded **6a** in quantitative yield. Its structure was deduced from 2D NMR experiments but also according to its X-ray resolution (Fig. 2).[20]

The activating part played by the pendant carboxylic acid group of **5a** and **11a** was finally assessed through performing this sequence starting from 2-phenylcinnamic acid **9a**, which did not lead in these conditions to fluorene-9-acetic acid **12**. This role is also in agreement with the similar formation of a 2-cyano-2-(fluoren-9-yl)acetic acid by cyclization of a 2-cyano-3-(biphenyl-2-yl)propenoic acid.[21]

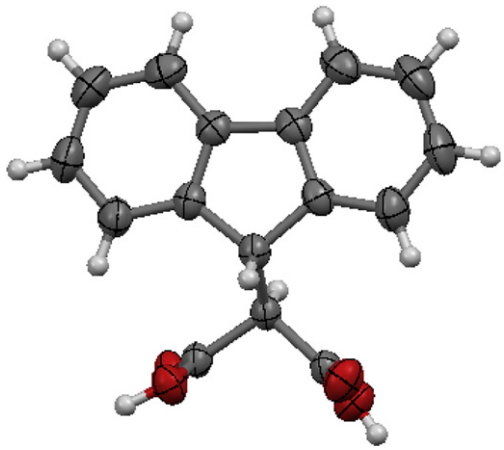


Fig. 2. X-ray structure of fluorene-9-malonic acid **6a**.

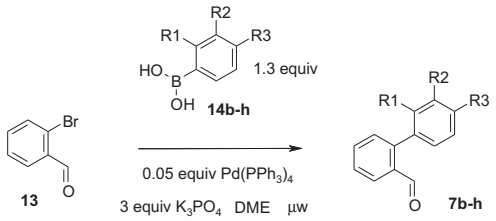
In order to study the scope and limitations of this method, we undertook its applications starting from variously substituted 2-phenylbenzaldehydes **7b**–**h**. Most of them (**7b**–**f**,**h**) were already described in literature,[22–27] but 2-(4-*tert*-butyl-phenyl)benzaldehyde **7g** was unknown. We synthesized all these starting materials according to a microwave promoted Suzuki–Miyaura cross coupling reaction involving 2-bromo-benzaldehyde **13** and substituted phenylboronic acids **14b**–**h** with $Pd(PPh_3)_4$ as catalyst in DME and an aqueous solution of K_3PO_4 as a base. Under these conditions, 2-phenylbenzaldehydes **7b**–**h** were isolated with yields ranging from 39 to 81% (Table 2).

Under treatment with malonic acid and ammonium acetate in refluxing ethanol, 2-phenylbenzaldehydes **7b**–**h** gave, after displacement of the ammonium salts by hydrochloric acid, the 2-phenylbenzylidenemalonic acids **5b**–**h** in low to moderate global yields (Steps 1+2; Table 3).

The procedure selected for the synthesis of **6a** was then applied to **5b**–**h**. Treatment of the latter with $BF_3 \cdot Et_2O$ in Et_2O at room temperature gave contrasted results (Step 3; Table 3).

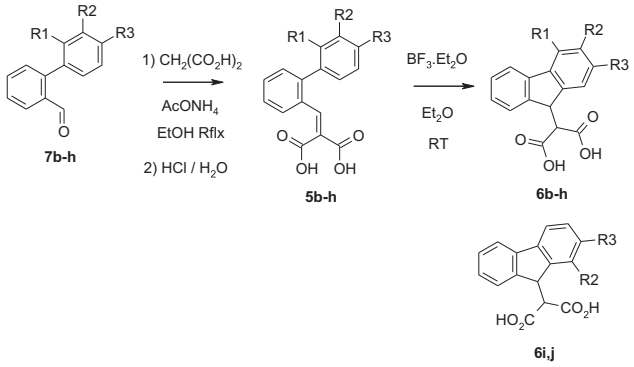
Compounds **5e**–**h**, bearing on their phenyl ring various electron-donating groups able to promote the aromatic electrophilic substitution, were easily and completely cyclized into the novel 2-substituted fluorene-9-malonic acids **6e**–**h**, after a reaction time ranging from 15 to 20 h. They were isolated in a similar manner as described for **6a**.

Table 2
Suzuki–Miyaura cross coupling conditions for the synthesis of compounds **7b**–**h**



Compound	R1	R2	R3	Temp (°C)	P (bars)	µw (W)	Time (h)	Yield (%)
7b	NO_2	H	H	150	5	270	1.5	39
7c	H	CF_3	H	150	6	40	1.5	48
7d	H	Cl	H	150	5	60	1.5	74
7e	H	H	CH_3	150	6	60	1.5	42
7f	H	H	OCH_3	137	4	290	2	81
7g	H	H	$C(CH_3)_3$	150	6	60	1.5	39
7h	CH_3	H	CH_3	150	6	300	1.5	65

Table 3
Reaction conditions for the synthesis of compounds **5b**–**h** and **6b**–**j**



R1	R2	R3	Steps 1+2			Step 3		
			Compound	Rflx Time (min)	Yield (%)	Compoud	Time (h)	Yield (%)
NO_2	H	H	**5b**	30	39	**6b**	15	20
H	CF_3	H	**5c**	30	22	**6c**/**6i**	15	50/20
H	Cl	H	**5d**	15	43	**6d**/**6j**	15	50/50
H	H	CH_3	**5e**	45	16	**6e**	20	quant.
H	H	OCH_3	**5f**	30	30	**6f**	15	quant.
H	H	$C(CH_3)_3$	**5g**	45	25	**6g**	15	quant.
CH_3	H	CH_3	**5h**	30	10	**6h**	15	quant.

Even **5c** and **5d**, substituted by electron-withdrawing groups, lend themselves in these conditions to the cyclization reaction. However in these cases, not only the expected fluorene derivatives **6c** and **6d** were synthesized, but also compounds **6i** and **6j** issued from the cyclisation on the second *ortho* position of the starting materials. Disappointingly, these isomers could not be separated from the reaction mixture.

Only, the deactivated *o*-NO_2 derivative **5b**, appeared less reactive towards this procedure, since it gave in only 20% yield the corresponding fluorenemalonic acid **6b**, which could not be separated from the starting material.

3. Conclusions

In conclusion, we have developed an easy and efficient synthesis in very mild conditions of some novel fluorene-9-malonic acids from 2-bromobenzaldehydes. The sequence involves Suzuki–Miyaura cross coupling with various phenylboronic acids, followed by a Rodionow–Johnson reaction and a subsequent intramolecular hydroarylation of the 2-phenylbenzylidenemalonic acids obtained. Five unknown fluorene-9-malonic acids were thus isolated. They constitute useful scaffolds for medicinal chemistry. The application of this sequence to heterocyclic analogs is furthermore currently under investigation.

4. Experimental section

4.1. General methods

All commercial solvents and reagents were used as-received. The microwave reactions were performed using a Biotage Initiator Microwave oven; temperatures were measured with an IR-sensor and reaction times given as hold times. Flash chromatography was realized on a spot 2 apparatus; column: EVF SiO_2; eluent: cyclohexane/methylene chloride, or cyclohexane/ethylacetate. Melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra were recorded on KBr discs; only selected absorbances were quoted. LC/MS (ESI) analyses were

realized as separating module using the following gradient: A (95%)/B (5%) to A (5%)/B (95%) in 10 min; this ratio was hold during 3 min before return to initial conditions in 1 min. Initial conditions were then maintained for 5 min (A: H_2O, B: CH_3CN; each containing HCOOH: 0.1%; Column: C18 MSC118/2.1_50 mm). MS detection was performed by positive or negative ESI. High Resolution Mass Spectra were performed at 70 eV by electronic impact (HRMS-EI) or by negative electrospray ionization (HRMS-ESI). ^1H and ^{13}C NMR spectra were recorded, respectively, at 400 and 100 MHz or at 500 and 125 MHz, using $CDCl_3$, DMSO-d_6 or CD_3OD as solvents. Chemical shifts δ are reported in parts per million with the solvent resonance as the internal standard; coupling constants J are given in Hertz. Crystal structure determination: data were collected at 296 K with graphite-monochromatized Mo Kα radiation on a diffractometer equipped with a CCD area detector. The crystal structure was solved by direct methods using SHELX97 package. All non-hydrogen atoms were refined anisotropically. All H atoms were calculated and fixed on the heavy atoms in the ideal geometry.

4.2. Synthesis of biphenyl-carbaldehydes

Biphenyl-2-carbaldehyde **7a** was bought from chemical suppliers; all other aldehydes (**7b**–**h**) were obtained as followed: To a degassed solution of 1 equiv of 2-bromobenzaldehyde in DME were added 1.3 equiv of boronic species, 3 equiv of $K_3PO_4 \cdot H_2O$ and 0.05 equiv of $Pd(PPh_3)_4$; the suspension was heated under microwaves irradiation. The resulting mixture was filtrated (washed with Et_2O) and evaporated to dryness under vacuum pressure. The crude product was then purified by flash chromatography.

4.2.1. 2′-Nitrobiphenyl-2-carbaldehyde ***7b***[26]. Starting from 2-bromobenzaldehyde (3 mmol, 555 mg, 351 μl) and 2-(nitrophenyl)boronic acid (3.9 mmol, 651 mg), under the following conditions (1 h 30 min; 150 °C; 5 bar; 270 W), **7b** was obtained as a clear yellow solid (263 mg, 39%); mp 72–73 °C; IR (KBr) ν (cm^{-1}) 3433 (OH), 2923, 2852, 1692 (CO), 1522–1344 (Ph–NO_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H, C*H*O), 8.13 (d, 1H, J_{ortho}=7.8 Hz, H3′), 8.01 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.65 (m, 4H), 7.36 (d, 1H, J_{ortho}=7.8 Hz), 7.26 (m, 1H *under svt residual peak*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1 (*C*HO), 148.6 (C2′), 140.3 (C1), 134.0 ($C_{quat.}$), 133.7 (CH), 133.6 ($C_{quat.}$), 132.7 (CH), 132.4 (CH), 130.1 (CH), 129.8 (CH), 129.1 (CH), 128.7 (CH), 124.5 (C3′); LC–MS t_R=10.7 min, [ESI^-] m/z [M–H]$^-$ 226.

4.2.2. 3′-(Trifluoromethyl)biphenyl-2-carbaldehyde ***7c***[22]. Starting from 2-bromobenzaldehyde (1 mmol, 185 mg, 117 μl) and [3-(trifluoromethyl)phenyl]boronic acid (1.3 mmol, 242 mg), under the following conditions (1 h 30 min; 150 °C; 6 bar; 40 W), **7c** was obtained as a clear oil (119 mg, 48%); IR (KBr) ν (cm^{-1}) 3434, 3067, 2926, 2852, 2753, 1696 (CO), 1598, 1335, 1167–1126–1074 (CF_3), 765; ^1H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H, C*H*O), 8.06 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.73–7.52 (m, 7H), 7.44 (d, 1H, J_{ortho}=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5 (s, *C*HO), 143.0 (s, C1), 137.7 (s, C2), 132.8 (s, CH), 132.6 (s, C1′), 132.4 (s, CH), 129.8 (s, CH), 127.8 (s, CH), 127.5 (s, CH), 127.1 (s, CH), 125.8 (d, $^1J_{CF}$=240.2 Hz, *C*F_3), 125.4 (d, $^3J_{CF}$=5.8 Hz, C2′or C4′), 123.9 (d, $^3J_{CF}$=7.4 Hz, C2′or C4′); LC–MS t_R=12 min, [ESI^+] m/z [M+H+CH_3CN]$^+$ 292, [M+H]$^+$ 251.

4.2.3. 3′-Chlorobiphenyl-2-carbaldehyde ***7d***[21]. Starting from 2-bromobenzaldehyde (1 mmol, 185 mg, 117 μl) and 3-(chlorophenyl) boronic acid (1.3 mmol, 202 mg), under the following conditions (1 h 30 min; 150 °C; 5 bar; 60 W), **7d** was obtained as a yellowish oil (160 mg, 74%); IR (KBr) ν (cm^{-1}); 3432, 3061, 2852, 2752, 1694 (CO), 1596, 1196, 764; ^1H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H, C*H*O), 8.04 (dd, 1H, J_{ortho}=7.8 Hz J_{meta}=1.9 Hz, H3), 7.65 (td, 1H, J_{ortho}=7.8 Hz, J_{meta}=1.9 Hz, H5), 7.53 (t, 1H, J_{ortho}=7.8 Hz, H4), 7.43–7.38 (m, 4H), 7.25 (m *under svt residual peak*, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (*C*HO), 144.3 (C1), 139.6 ($C_{quat.}$), 134.5 ($C_{quat.}$), 133.7 (CH), 133.6 ($C_{quat.}$), 130.6 (CH), 129.9 (CH), 129.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH); LC–MS t_R=12 min, [ESI^+] m/z [M+H+CH_3CN]$^+$ 258, [M+H]$^+$ 217.

4.2.4. 4′-Methylbiphenyl-2-carbaldehyde ***7e***[23]. Starting from 2-bromobenzaldehyde (1 mmol, 185 mg, 117 μl) and 4-(methylphenyl) boronic acid (1.3 mmol, 177 mg), under the following conditions (1 h 30 min; 150 °C; 6 bar; 60 W), **7e** was obtained as a clear oil (82 mg, 42%); IR (KBr) ν (cm^{-1}) 3436 (OH), 3024, 2922, 2846, 2748, 1691 (CO), 1596, 1254, 1193, 823, 763; ^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H, C*H*O), 8.01 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.63 (t, 1H, J_{ortho}=7.8 Hz), 7.48 (t, 1H, J_{ortho}=7.8 Hz), 7.44 (d, 1H, J_{ortho}=7.8 Hz), 7.28 (bs, 4H) 2.43 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6 (*C*HO), 147.6 (C1), 138.0 ($C_{quat.}$), 133.7 ($C_{quat.}$), 133.5 (CH), 132.4 ($C_{quat.}$), 130.8 (CH), 130.0 (or C3′,C5′), 129.1 (C3′,C5′or C2′,C6′), 127.5 (2CH), 21.2 (*C*H_3); LC–MS t_R=11 min, [ESI^+] m/z [M+CH_3CN]$^+$ 238 [M+H]$^+$ 197.

4.2.5. 4′-Methoxybiphenyl-2-carbaldehyde ***7f***[25]. Starting from 2-bromobenzaldehyde (3 mmol, 555 mg, 351 μl) and 4-(methoxyphenyl)boronic acid (3.9 mmol, 593 mg), under the following conditions (2 h 00 min; 137 °C; 4 bar; 290 W), **7f** was obtained as a clear yellow solid (515 mg, 81%). Spectral data (^1H, ^{13}C NMR, IR, MS) are in agreement with those found in the literature.

4.2.6. 4′-tert-Butylphenyl-2-carbaldehyde ***7g***. Starting from 2-bromobenzaldehyde (2 mmol, 370 mg, 235 μl) and 4-(*tert*-butylphenyl)boronic acid (2.6 mmol, 463 mg), under the following conditions (1 h 30 min; 150 °C; 6 bar; 60 W), **7g** was obtained as a clear oil (420 mg, 88%); IR (KBr) ν (cm^{-1}) 3430 (OH), 2959, 2920, 2855, 1691 (CO), 1596, 1472, 1389, 1256, 1194, 836, 767; ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H, C*H*O), 8.02 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.63 (t, 1H, J_{ortho}=7.8 Hz), 7.50–7.45 (m, 4H), 7.32 (d, 2H, J_{ortho}=7.8 Hz), 1.36 (s, 9H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8 (CHO), 151.2 ($C_{quat.}$), 146.0 (C1), 134.7($C_{quat.}$), 133.8 ($C_{quat.}$), 133.5 (CH), 130.8 (CH), 129.9 (2CH), 127.5 (2CH), 125.4 (2CH), 34.7 (*C*$(CH_3)_3$), 31.3 (3C, *C*H_3); LC–MS t_R=13.5 min, [ESI^+] m/z [M+H] $^+$ 239; HRESIMS [M+Na]$^+$ 261.1252 (calcd for $C_{17}H_{18}ONa$ 261.12499).

4.2.7. 2′-4′-Dimethylphenyl-2-carbaldehyde ***7h***[24]. Starting from 2-bromobenzaldehyde (3 mmol, 555 mg, 351 μl) and (2-4-dimethylphenyl)boronic acid (3.9 mmol, 585 mg), under the following conditions (1 h 30 min; 150 °C; 6 bar; 300 W), **7h** was obtained as a yellow clear oil (412 mg, 65%); IR (KBr) ν (cm^{-1}) 3433 (OH), 2922, 2850, 1695 (CO), 1622, 1597, 1447, 1255, 826, 766; ^1H NMR (400 MHz, $CDCl_3$) δ* 9.76 (s, 1H, C*H*O), 8.01 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.62 (t, 1H, J_{ortho}=7.8 Hz, H5), 7.48 (t, 1H, J_{ortho}=7.8 Hz, H4), 7.29 (d, 1H, J_{ortho}=7.8 Hz, H6), 7.12 (s, 1H, H3′), 7.08 (br s, 2H, H5′&H6′), 2.39 (s, 3H, C*H*$_3$), 2.07 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ* 192.5 (CHO), 145.8 (C1), 138.0 (C4′), 135.9 (C2′), 134.5 (C1′), 133.9 (C2), 133.7 (C5), 130.9 (C6), 130.8 (C3′), 130.2 (C6′), 127.6 (C4), 127.0 (C3), 126.4 (C5′), 21.1 (C4′–*C*H_3), 20.2 (C2′–*C*H_3); LC–MS t_R=12.5 min, [ESI^+] m/z [M+H]$^+$ 211.*Assignments according to 2D experiments (HMBC, HMQC).

4.3. Synthesis of *ortho*phenylbenzylidene malonic acids

All malonic acids where obtained as followed. Previous substituted biphenyl-carbaldehydes **7b**–**j** were refluxed in EtOH for 15 min–60 min with 1 equiv of malonic acid and 2 equiv of ammonium acetate. The resulting mixture was cooled to room temperature and stirred for 30 min.

4.3.1. Purification. Conditions A: The formed precipitate was filtered, suspended in water and then acidified with HCl 1 M. The resulting precipitate was dried, washed with water, to give the

corresponding malonic acid; the filtrate was also extracted with CH_2Cl_2 or Et_2O; the organic phase was filtered and dried with anhydrous $MgSO_4$ and evaporated under reduced pressure until dryness to give the same pure substituted malonic acid.

Conditions B: To the mixture was added the same volume of HCl 1 M; after 1 h stirring, EtOH was evaporated, and the resulting aqueous phase was extracted three times with Et_2O; after drying over anhydrous $MgSO_4$, the combined organic phases were evaporated to dryness under vacuum and the resulting crude extract was suspended into a saturated aqueous $NaHCO_3$ solution. The obtained aqueous phase was washed twice with CH_2Cl_2 and then gently acidified with aqueous HCl 6 M; the resulting precipitate was filtered washed with H_2O and dried to give the corresponding malonic acid. The filtrate was also extracted with CH_2Cl_2 or Et_2O; the organic phase was filtered and dried with anhydrous $MgSO_4$ and evaporated under reduced pressure until dryness to give the same pure substituted malonic acid, improving yields of about 20%.

4.3.2. (Biphenyl-2-ylmethylidene)propanedioic acid ***5a***. Starting from (1,1′-biphenyl)-carbaldehyde (**7a**, Sigma) (3 mmol, 546 mg, 483 μl), **5a** was obtained after 30 min refluxing time (conditions A), as a colourless powder (402 mg, 50%); mp 190–191 °C; IR (KBr) ν (cm^{-1}) 3430 (OH), 2927, 2585, 1755 (CO), 1683 (CO), 1424, 1274, 1244; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (br s, 2H, O*H*), 7.58 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.53–7.42 (m, 6H), 7.34–7.31 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7 (*C*O_2H), 165.0 (*C*O_2H), 141.8 (C1), 139.4 ($C_{quat.}$), 139.2 ($C_{quat.}$), 131.5 ($C_{quat.}$), 130.1 (CH), 130.0 (CH), 129.5 (2CH, C2′, C6′or C3′, C5′), 129.4 (CH), 128.5 (2CH, C2′, C6′or C3′, C5′), 128.1 (CH), 127.9 (CH), 127.7 (CH); LC–MS t_R=10.1 min, [ESI$^-$] *m*/*z* [M–H]$^-$ 267, [M–H–CO_2]$^-$ 223; HREIMS [M$^+$] *m*/*z* 268.0723 (calcd for $C_{16}H_{12}O_4$ 268.0735).

4.3.3. [(2′-Nitrobiphenyl-2-yl)methylidene]propanedioic acid ***5b***. Starting from **7b** (1.16 mmol, 263 mg), **5b** was obtained after 30 min refluxing time (conditions A), as a pale yellow solid (131 mg, 39%); mp 216–217 °C; IR (KBr) ν (cm^{-1}) 3401, 3062, 2929, 2659, 2544, 1749 (CO), 1681 (CO), 1531, 1437–1360 (NO_2), 1306, 1184; ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, 1H, J_{ortho}=10.4 Hz, H3′), 7.74–7.62 (m, 3H), 7.44–7.40 (m, 3H), 7.34 (s, 1H, C*H*=C(CO_2H)$_2$), 7.20 (q, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.9 (*C*O_2H), 166.6 (*C*O_2H), 150.5 (C2′), 140.8 (*C*H=C(CO_2H)$_2$), 139.9 ($C_{quat.}$), 135.6 ($C_{quat.}$), 134.2 (CH), 133.7 (CH), 133.6 ($C_{quat.}$), 130.9 (CH), 130.6 ($C_{quat.}$), 130.5 (CH), 129.9 (CH), 129.5 (CH), 129.2 (CH), 125.3 (CH); LC–MS t_R=9.8 min, [ESI$^-$] *m*/*z* [M–H]$^-$ 312. HRESIMS [M–H] *m*/*z* 312.0515 (calcd for $C_{16}H_{10}NO_6$ 312.05081).

4.3.4. {[3′-(Trifluoromethyl)biphenyl-2-yl]methylidene}propanedioic acid ***5c***. Starting from **7c** (0.45 mmol, 112 mg), **5c** was obtained after 30 min refluxing time (conditions A), as a colourless solid (33 mg, 22%); mp 170–171 °C; IR (KBr) ν (cm^{-1}) 3323 (OH), 3074, 2653, 2546, 1750 (CO), 1680 (CO), 1620, 1431, 1335–1303–1257 (CF_3), 1166, 1115; ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (dd, 1H, J_{ortho}=7.8 Hz, J_{meta}=1.9 Hz, H3), 7.67–7.62 (m, 4H), 7.52 (t, 1H, J_{ortho}=7.8 Hz), 7.47–7.42 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.0 (s, *C*O_2H), 166.7 (s, *C*O_2H), 142.5 (s, $C_{quat.}$), 142.2 (s, $C_{quat.}$), 142.0 (s, $C_{quat.}$), 134.5 (s, CH), 133.5 (s, $C_{quat.}$), 131.8 (d, $^2J_{CF}$=32 Hz, C3′), 131.4 (s, CH′), 131.0 (s, CH), 130.3 (s, CH), 129.6 (s, CH), 129.3 (s, CH), 127.4 (d, $^3J_{CF}$=3.3 Hz, C2′ or C4′), 125.5 (d, $^3J_{CF}$=3.3 Hz, C2′ or C4′), 125.5 (d, $^1J_{CF}$=269 Hz, *C*F_3); LC–MS t_R=9.7 min, [ESI$^+$] *m*/*z* [M+H]$^+$ 337. HRESIMS [M–H] *m*/*z* 335.0537 (calcd for $C_{17}H_{10}F_3O_4$ 335.05367).

4.3.5. [(3′-Chlorobiphenyl-2-yl)methylidene]propanedioic acid ***5d***. Starting from **7d** (0.74 mmol, 160 mg), **5d** was obtained after 15 min refluxing time (conditions A), as a colourless powder (96 mg, 43%); mp 191–192 °C; IR (KBr) ν (cm^{-1}) 3435 (OH), 2927, 2586, 1757 (CO), 1684 (CO), 1594, 1424, 1256, 761; ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.50–7.47 (m, 2H), 7.43–7.40 (m, 4H), 7.30 (dt, 1H, J_{ortho}=7.8 Hz, J_{meta}=1.9 Hz, H6′); ^{13}C NMR (100 MHz, CD_3OD) δ 170.1 (*C*O_2H), 166.7 (*C*O_2H), 143.2 (C1), 142.6 (*C*H=C(CO_2H)$_2$), 142.3 ($C_{quat.}$), 135.3 ($C_{quat.}$), 133.3 ($C_{quat.}$), 131.3 (CH), 131.0 (CH), 130.9 (CH), 130.5 (CH), 130.1 ($C_{quat.}$), 129.5 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH); LC–MS t_R=11.0 min, [ESI$^-$] *m*/*z* [M–H]$^-$ 303–301, [M–H–CO_2]$^-$ 259–257. HRESIMS [M–H] *m*/*z* 301.0273 (calcd for $C_{16}H_{10}ClO_4$ 301.02731).

4.3.6. [(4′-Methylbiphenyl-2-yl)methylidene]propanedioic acid ***5e***. Starting from **7e** (0.37 mmol, 82 mg), **5e** was obtained after 45 min refluxing time (conditions A), as a colourless solid (16 mg, 16%); mp 196–197 °C; IR (KBr) ν (cm^{-1}) 3436 (OH), 3151, 3024, 2926, 2852, 1720 (CO), 1683 (CO), 1616, 1380, 1273, 819, 755; ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.53 (s, 1H, C*H*=C(CO_2H)$_2$), 7.45 (t, 1H, J_{ortho}=7.8 Hz, H5), 7.40 (d, J_{ortho}=7.8 Hz, H6), 7.34 (t, 1H, J_{ortho}=7.8 Hz, H4), 7.25 (br s, 4H, H2′, H3′, H5′, H6′), 2.39 (s, 3H, *C*H_3); ^{13}C NMR (100 MHz, CD_3OD) δ 170.4 (*C*O_2H), 167.0 (*C*O_2H), 144.1 (C1), 143.4 (*C*H=C(CO_2H)$_2$), 143.4 (C2), 138.9 (C1′ or C4′), 138.3 (C1′ or C4′), 133.2 (*C*(CO_2H)$_2$), 131.2 (C5), 131.0 (C6), 130.7 (C2′, C6′), 130.0 (C3′, C5′), 129.4 (C3), 128.3 (C4), 21.2 (*C*H_3); LC–MS t_R=10.7 min, [ESI$^-$] *m*/*z* [M–H]$^-$ 281, [M–H–CO_2]$^-$ 237. HRESIMS [M–H] *m*/*z* 281.0818 (calcd for $C_{17}H_{13}O_4$ 281.08193). *Assignments according to 2D experiments (COSY, HMQC).

4.3.7. [(4′-Methoxybiphenyl-2-yl)methylidene]propanedioic acid ***5f***. Starting from **7f** (2.3 mmol, 490 mg), **5f** was obtained after 30 min refluxing time (conditions A), as a colourless solid (221 mg, 32%); mp 175–176 °C; IR (KBr) ν (cm^{-1}) 3427 (OH), 3084, 2924, 2846, 1740 (CO), 1672 (CO), 1608, 1478, 1270, 1242, 827, 761; ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.56 (s, 1H, C*H*=C(CO_2H)$_2$), 7.46 (t, 1H, J_{ortho}=7.8 Hz H4 or H5), 7.41 (d, 1H, J_{ortho}=7.8 Hz, H6), 7.35 (t, 1H, J_{ortho}=7.8 Hz, H4 or H5), 7.30 (d, 2H, J_{ortho}=8.8 Hz, H2′, H6′or H3′, H5′), 7.01 (d, 2H, J_{ortho}=8.8 Hz, H3′, H5′ or H2′, H6′), 3.84 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz, CD_3OD) δ 170.5 (*C*O_2H), 167.1 (*C*O_2H), 161.0 (C4′), 143.8 (C1), 143.6 (*C*H=C(CO_2H)$_2$), 133.4 ($C_{quat.}$), 133.1 ($C_{quat.}$), 132.0 (C2′, C6′), 131.2 (CH), 131.0 (CH), 129.5 (CH), 129.1 ($C_{quat.}$), 128.1 (CH), 114.8 (C3′, C5′), 55.8 (O*C*H$_3$); LC–MS t_R=10.1 min, [ESI$^-$] *m*/*z* [M–H]$^-$ 297, [M–H–CO_2]$^-$ 253. HRESIMS [M–H] *m*/*z* 297.0768 (calcd for $C_{17}H_{13}O_5$ 297.07685).

4.3.8. [(4′-tert-Butylbiphenyl-2-yl)methylidene]propanedioic acid ***5g***. Starting from **7g** (1.76 mmol, 420 mg), **5g** was obtained after 45 min refluxing time (conditions B), as a colourless solid (145 mg, 25%); mp 90–91 °C; IR (KBr) ν (cm^{-1}) 3430 (OH), 2961, 2925, 2851, 1711 (CO), 1693 (CO), 1620, 1479, 1264, 1198, 834, 764; ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.58 (s, 1H, C*H*=C(CO_2H)$_2$), 7.50–7.41 (m, 4H), 7.37–7.30 (m, 3H), 1.36 (s, 9H, *C*H_3); ^{13}C NMR (100 MHz, CD_3OD) δ 170.6 (*C*O_2H), 167.3 (*C*O_2H), 162.5 ($C_{quat.}$), 152.0 ($C_{quat.}$), 143.9 ($C_{quat.}$), 143.7 (*C*H=C(CO_2H)$_2$), 138.3 ($C_{quat.}$), 133.3 ($C_{quat.}$), 131.1 (C5), 131.0 (C6), 130.6 (C2′, C6′or C3′, C5′), 129.6 (C3), 128.3 (C4), 126.3 (C3′, C5′ or C2′, C6′), 35.5 (*C*(CH_3)$_3$), 31.7 (3C, *C*H_3); LC–MS t_R=11.7 min, [ESI$^-$] *m*/*z* [M–H]$^-$ 323, [M–H–CO_2]$^-$ 279. HRESIMS [M–H] *m*/*z* 323.1289 (calcd for $C_{20}H_{19}O_4$ 323.12888).

4.3.9. [(2′,4′-Dimethylbiphenyl-2-yl)methylidene]propanedioic acid ***5h***. Starting from **7h** (1.95 mmol, 410 mg), **5h** was obtained after 30 min refluxing time (conditions B), as a clear oil (57 mg, 10%); IR (KBr) ν (cm^{-1}) 3434 (OH), 2926, 2855, 1733 (CO), 1698 (CO), 1633, 1428, 1258, 1057; ^{1}H NMR (400 MHz, CD_3OD) δ 7.68 (d, 1H, J_{ortho}=7.8 Hz, H3), 7.44 (t, 1H, J_{ortho}=7.8 Hz), 7.35 (t, 1H, J_{ortho}=7.8 Hz), 7.33 (s, 1H, C*H*=C(CO_2H)$_2$), 7.22 (d, 1H, J_{ortho}=7.8 Hz), 7.10 (s, 1H, H3′), 7.05 (d, 1H, J_{ortho}=7.8 Hz), 6.98 (d, 1H, J_{ortho}=7.8 Hz), 2.35 (s, 3H, C*H*$_3$), 2.02 (s, 3H, *C*H_3); ^{13}C NMR (100 MHz, CD_3OD) δ 170.4 (*C*O_2H), 167.3 (*C*O_2H), 144.5 (C1), 141.8 (*C*H=C(CO_2H)$_2$), 138.9 ($C_{quat.}$), 137.9 ($C_{quat.}$),

137.2 ($C_{quat.}$), 133.7 ($C_{quat.}$), 131.8 (CH), 131.4 (CH), 131.0 (CH), 130.7 (CH), 129.2 ($C_{quat.}$), 128.9 (CH), 128.4 (CH), 127.4 (CH), 21.2 (CH_3), 20.1 (CH_3); LC–MS t_R=10.8 min, [ESI$^-$] m/z [M–H]$^-$ 295, [M–H–CO_2]$^-$ 251. HRESIMS [M–H] m/z 295.0976 (calcd for $C_{18}H_{15}O_4$ 295.09758).

4.4. Synthesis of fluorene-9-malonic acids

All fluorene derivatives were obtained as followed: previous benzylidene-malonic acids were stirred in Et_2O with 2.2 equiv of $BF_3 \cdot Et_2O$ at room temperature during 15 h (20 h for **6e**). The reaction was then quenched with MeOH and the medium was evaporated under vacuum to dryness to eliminate borane derivatives.

4.4.1. 9H-Fluoren-9-ylpropanedioic acid ***6a***. Starting from **5a** (0.17 mmol, 45 mg), **6a** was obtained as a colourless powder (45 mg, quant.); mp 190–191 °C; IR (KBr) ν (cm^{-1}) 3431(OH), 2923, 1729 (CO), 1707 (CO), 1449, 1206, 743; ^{1}H NMR (400 MHz, DMSO-d_6) δ* 12.80 (br s, O*H*), 7.84 (d, 2H, J_{ortho}=7.8 Hz, H4, H5), 7.59 (d, 2H, J_{ortho}=7.8 Hz, H1, H8), 7.36 (t, 2H, J_{ortho}=7.8 Hz, H3, H6), 7,28 (t, 2H, J_{ortho}=7.8 Hz, H2, H7), 4.51 (d, 1H, J=5.9 Hz, H9), 3.94 (d, 1H, J=5.9 Hz, $H_{aliph.}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6 (2C, CO_2H), 144.2 (C8a, C9a), 140.7 (C4a, C4b), 127.4 (C3, C6), 126.9 (C2, C7), 124.9 (C1, C8), 119.9 (C4, C5), 54.7 ($CH_{aliph.}$), 53.2 (C9); LC–MS t_R=9.8 min, [ESI$^-$] m/z [M–H]$^-$ 267, [M–H–CO_2]$^-$ 223; HREIMS m/z 268.07395 (calcd for $C_{16}H_{12}O_4$ 268.07354). HREIMS [M–H] m/z 268.07395 (calcd for $C_{16}H_{12}O_4$ 268.07354). *Assignments according to 2D experiments (HMQC, HMBC).

4.4.2. (2-Methyl-9H-fluoren-9-yl)propanedioic acid ***6e***. Starting from **5e** (0.04 mmol, 11 mg), **6e** was obtained as a colourless powder (10 mg, quant.); mp 220–221 °C; IR (KBr) ν (cm^{-1}) 3420 (OH), 2920, 2855, 1714 (CO), 1696 (CO), 1633, 1415, 1083; ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 (d, 1H, J_{ortho}=7.8 Hz), 7.60 (d, 1H, J_{ortho}=7.8 Hz), 7.51 (d, 1H, J_{ortho}=7.8 Hz), 7.36 (s, 1H, H1), 7.29 (t, 1H, J_{ortho}=7.8 Hz,), 7.18 (d, 1H, J_{ortho}=7.8 Hz), 7.16 (t, 1H, J_{ortho}=7.8 Hz), 4.52 (d, 1H, ^3J=6.8 Hz, H9), 3.70 (d, 1H, ^3J=6.8 Hz, C$H_{aliph.}$), 2.34 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 171.7 (CO_2H), 145.7 ($C_{quat.}$), 145.3 ($C_{quat.}$), 142.6 ($C_{quat.}$), 139.9 ($C_{quat.}$), 138.0 ($C_{quat.}$), 129.5 (CH), 128.6 (CH), 127.5 (CH), 126.6 (CH), 126.0 (CH), 120.5 (CH), 120.4 (CH), 56.9 ($CH_{aliph.}$), 47.2 ($CH_{aliph.}$), 21.7 (CH_3); LC–MS t_R=10.4 min, [ESI$^-$] m/z [M–H]$^-$ 281, [M–H–CO_2]$^-$ 237. HRESIMS [M–H] m/z 281.0819 (calcd for $C_{17}H_{13}O_4$ 281.08193).

4.4.3. (2-Methoxy-9H-fluoren-9-yl)propanedioic acid ***6f***. Starting from **5f** (0.17 mmol, 50 mg), **6f** was obtained as a colourless powder (48 mg, quant.); mp 204–205 °C; IR (KBr) ν (cm^{-1}) 3418 (OH), 3009, 2923, 2849, 1713 (CO), 1689 (CO), 1633, 1467, 1259, 1084; ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, 2H, J_{ortho}=7.8 Hz), 7.53 (d, 1H, J_{ortho}=7.8 Hz), 7.32 (t, 1H, J_{ortho}=7.8 Hz), 7.20–7.16 (m, 2H), 6.94 (dd, 1H, J_{ortho}=7.8 Hz, J_{meta}=1.9 Hz), 4.57 (d, 1H, J=6.8 Hz, H9), 3.83 (s, 3H, OCH_3), 3.75 (d, 1H, J=6.8 Hz, C$H_{aliph.}$); ^{13}C NMR (100 MHz, CD_3OD) δ 171.7 (2C, CO_2H), 161.0 ($C_{quat.}$), 147.2 (2C, $C_{quat.}$), 145.0 ($C_{quat.}$), 142.5 ($C_{quat.}$), 135.4 ($C_{quat.}$), 128.7 (CH), 126.8 (CH), 125.8 (CH), 121.5 (CH), 119.9 (CH), 114.8 (CH), 111.8 (CH), 57.0 ($CH_{aliph.}$), 55.9 (OCH_3), 47.3 (C9); LC–MS t_R=9.8 min, [ESI$^-$] m/z [M–H]$^-$ 297, [M–H–CO_2]$^-$ 253, [M–H–$(CO_2)_2$]$^-$ 209. HRESIMS [M–H] m/z 297.0768 (calcd for $C_{17}H_{13}O_5$ 297.07685).

4.4.4. (2-tert-Butyl-9H-fluoren-9-yl)propanedioic acid ***6g***. Starting from **5g** (0.15 mmol, 48 mg), **6g** was obtained as a colourless powder (48 mg, quant.); mp 100–101 °C; IR (KBr) ν (cm^{-1}) 3433 (OH), 2925, 1733 (CO), 1704 (CO), 1631, 1455, 1413, 1189, 1084; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 1H, J_{ortho}=7.8 Hz), 7.68–7.67 (m, 2H), 7.55 (d, 1H, J_{ortho}=7.8 Hz), 7.42 (d, 1H, J_{ortho}=7.8 Hz), 7.34 (t, 1H, J_{ortho}=7.8 Hz), 7.22 (t, 1H, J_{ortho}=7.8 Hz), 4.59 (d, 1H, J=6.8 Hz, H9), 3.62 (d, 1H, J=6.8 Hz, C$H_{aliph.}$), 1.34 (s, 9H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 171.7 (2C, CO_2H), 151.5 ($C_{quat.}$), 145.6 ($C_{quat.}$), 145.1 ($C_{quat.}$), 142.5 ($C_{quat.}$), 139.8 ($C_{quat.}$), 128.7 (CH), 127.6 (CH), 125.9 (CH), 123.1 (CH), 120.6 (CH), 120.3 (CH), 57.3 ($CH_{aliph.}$), 47.4 (C9), 35.7 ($C(CH_3)_3$), 31.9 (3C, CH_3); LC–MS t_R=11.4 min, [ESI$^-$] m/z [M–H]$^-$ 323, [M–H–CO_2]$^-$ 279. HRESIMS [M–H] m/z 323.1292 (calcd for $C_{20}H_{19}O_4$ 323.12888).

4.4.5. (2,4-Dimethyl-9H-fluoren-9-yl)propanedioic acid ***6h***. Starting from **5h** (0.15 mmol, 45 mg), **6h** was obtained as a colourless powder (43 mg, quant.); mp 190–191 °C; IR (KBr) ν (cm^{-1}) 3422 (OH), 2923, 2852, 1744 (CO), 1708 (CO), 1635, 1123, 1083, 1062; ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (d, 1H, J_{ortho}=7.8 Hz), 7.57 (d, 1H, J_{ortho}=7.8 Hz), 7.34 (t, 1H, J_{ortho}=7.8 Hz), 7.24 (s, 1H), 7.21 (t, 1H, J_{ortho}=7.8 Hz), 6.96 (s, 1H), 4.53 (d, 1H, J=5.8 Hz, H9), 3.77 (d, 1H, J=5.8 Hz, $CH_{aliph.}$), 2.62 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 171.9 (CO_2H), 171.7 (CO_2H), 146.1 ($C_{quat.}$), 145.6 ($C_{quat.}$), 143.5 ($C_{quat.}$), 137.7 ($C_{quat.}$), 137.7 ($C_{quat.}$), 133.7 ($C_{quat.}$), 131.8 (CH), 128.5 (CH), 128.5 (CH), 126.8 (CH), 125.8 (CH), 124.0 (CH), 123.6 (CH), 57.1 ($CH_{aliph.}$), 47.0 (C9), 21.5 (CH_3), 21.1 (CH_3); LC–MS t_R=11.8 min, [ESI$^-$] m/z [M–H]$^-$ 295, [M–H–CO_2]$^-$ 251. HRESIMS [M–H] m/z 295.0975 (calcd for $C_{18}H_{15}O_4$ 295.09758).

4.5. Synthesis 9*H*-fluoren-9-ylacetic acid 12

o-Phenylbenzylidene malonic acid **5a** (0.35 mmol, 100 mg) was stirred at 60 °C in CH_2Cl_2 (5 mL) in a sealed tube with 70 equiv of TFA (24.5 mmol, 1.9 mL) and 70 equiv of TFAA (24.5 mmol, 3.4 mL) during 8.5 h. After evaporation under vacuum, the crude material was purified by flash chromatography (CH_2Cl_2/MeOH, 100→80/0→20) to give a colourless solid (47 mg, 60%). Spectral data (^{1}H NMR) are in agreement with those found in the literature.[19]

Supplementary data

^{1}H and ^{13}C NMR spectra are available as Supplementary data. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.026. These data include MOL files and InChIKeys of the most important compounds described in this article.

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