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Synthetic Methods

A Weinreb Amide Based Building Block for Convenient Access to β,β-Diarylacroleins: Synthesis of 3-Arylindanones

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Abstract: Towards the synthesis of symmetrical and unsymmetrical β,β-diarylacroleins for assembling diarylmethine fragments present in biologically important molecules, we have developed a new Weinreb amide (WA) based building block, derived from propiolic acid. The WA functionality present in this compound allowed the sequential addition of various arylmagnesium bromide reagents in a controlled manner. The developed methodology for the access to β,β-diarylacroleins has been utilised for the synthesis of biologically important 3-arylindanone molecules.

Introduction

Several compounds of biological and medicinal importance feature a diarylmethine fragment in their structure, wherein the substituted methine carbon centre bears either identical[1] or different[2] aryl groups. For example, fluspirilene **1**, which belongs to the diphenylbutylpiperidines (DPBPs) family, has shown potential as an antagonist of the D_2 receptor and thereby paved way for the development of new cell autophagy inducers.[1b] Peperomin-E **2**, another example with two identical aryl residues on methine carbon, has shown growth inhibitory effects,[1g] whereas other analogues have been identified as anti-inflammatory agents.[1d] (*R*)-Tolterodine **3**, a useful molecule in the treatment of overactive bladder disorders, and competitive muscarinic antagonist, features an diarylmethine fragment, wherein the two aryl residues are different, making the methine carbon a stereogenic centre.[2b] The natural product podophyllotoxin **4**, a potent antimitotic agent that has been known for several decades for a variety of medicinal purposes, also features a diarylmethine fragment in its structure, wherein the two aryl residues are different[2c] (Figure 1). Recently, gallic acid-based 3-aryl-indanone, also displaying a diarylmethine fragment, has been shown to have potent anticancer activity against various human cancer cell lines.[3] Among them, **5** was most promising (IC_{50} = 2.2 μM) against MCF-7, that is, hormone-dependent breast cancer cell line, as it presented no toxicity to human erythrocytes even at higher concentrations (100 μg/mL, 258 μM). Interestingly, the biological activity of isomeric indanone **6** has not been investigated.[4]

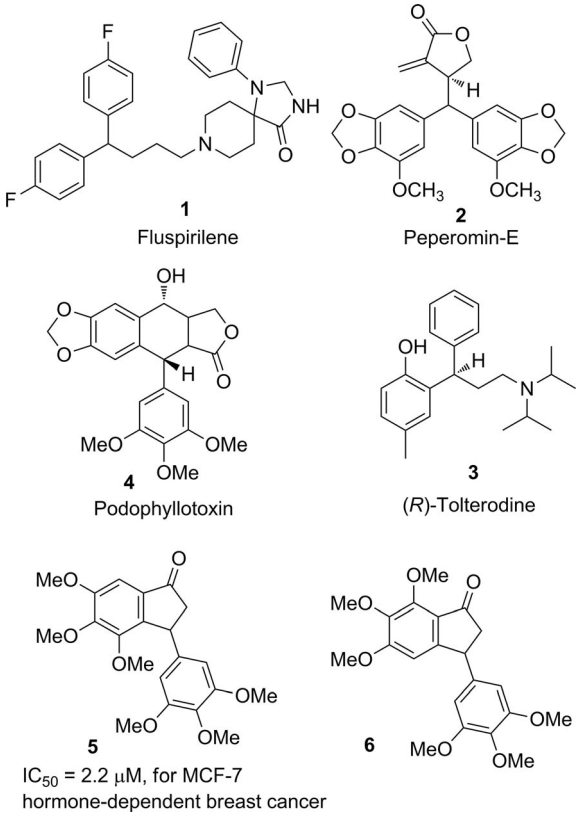

Figure 1. Biologically active molecules with a diarylmethine unit.

Although the use of 3,3-diarylpropanoic acids **7** and 3,3-diarylacrylic acids **8** as building blocks for the assembly of the diarylmethine fragment in synthetic endeavours has been occasionally reported,[5,6] the use of β,β-diarylacroleins **9** as a building block should offer several advantages. The main merit stems from its easier conversion into **8** or **7** and its derivatives, as well as into alcohols, through chemoselective oxidation/reduction protocols. Additionally, the aldehyde functionality allows for carbon chain elongation for further functionalisation and convenient synthesis of value-added products.[7] However, the limited availability of β,β-diarylacroleins **9** due to fewer methods of synthesis presents a great disadvantage, particularly when wide variations of aryl groups at the β-position is

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desired. The different approaches reported so far include (i) Mayer–Schuster rearrangement of propargilic aryl carbinols;[8] (ii) coupling reactions through Heck arylation using a Pd–aryl-urea complex[9a–9c] or Sonogashira-type coupling between aryl boronic acid with ethyl propiolate;[9d] (iii) Wittig directed aldol condensation,[10] and (iv) two-carbon homologation of diaryl ketones with titanium-mediated chemistry, involving use of triethylamine as the source of two carbons[11a] and $ZnBr_2$-mediated homologation of diarylketones using α,α-bis(trimethylsilyl)-*tert*-butylacetaldimine as a source of two carbon atoms.[11b] All these routes have their own limitations; for example, Wittig reactions were found to be successful only with aryl ketones bearing electron-withdrawing groups. Additionally, the formation of product **9** through homologation of aryl ketones requires lower temperature, highly basic reaction medium and long reaction time.[4,7b]

Realising the promise and significance of β,β-diarylacroleins **9** as a valuable building block, we were attracted to design a new synthetic route for its access. The importance of 3-aryl-indanones **10** in general[12] and **5** and **6** in particular provided the additional motivation as synthetic target through β,β-diarylacroleins. In this context, we proposed the hitherto unknown Weinreb amide (WA) based building block **11**, for convenient access to β,β-diarylacroleins **9** (Figure 2). The WA functionality[13] therein would enable easy incorporation of two aryl residues through the use of arylmagnesium bromides as convenient starting substrates. The results of these efforts are presented herein.

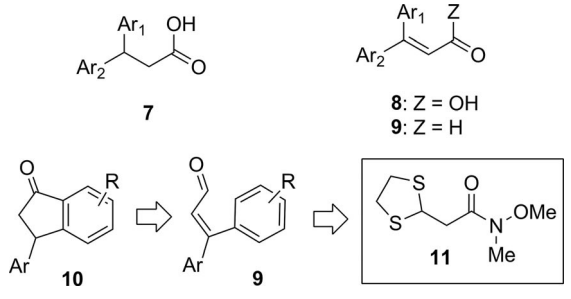
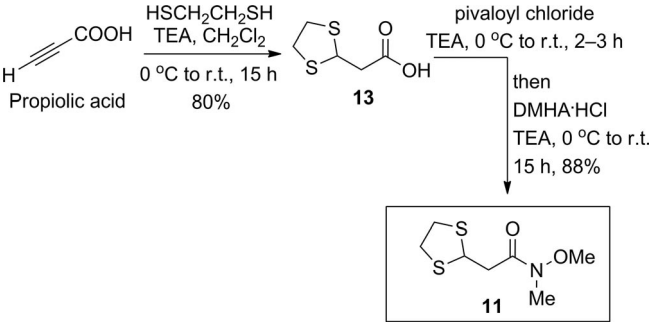


Figure 2. Building block **11** for the synthesis of β,β-diarylacroleins **9** and 3-aryl-indanone **10**.

Results and Discussion

The synthesis of proposed building block **11** in multigram quantities, was achieved by double Michael addition at the terminal carbon of propiolic acid by 1,2-ethanedithiol and triethylamine (TEA) at 0 °C in anhydrous CH_2Cl_2. The reaction produced a white crystalline solid **13** in 80 % yield. Compound **13** was converted into mixed anhydride in situ through the use of pivaloyl chloride and TEA at 0 °C to room temp. and reacted with *N*,*O*-dimethylhydroxylamine, liberated from its hydrochloride salt at 0 °C to room temperature. The reaction was complete in 15 h, furnishing compound **11** in 88 % yield (Scheme 1).

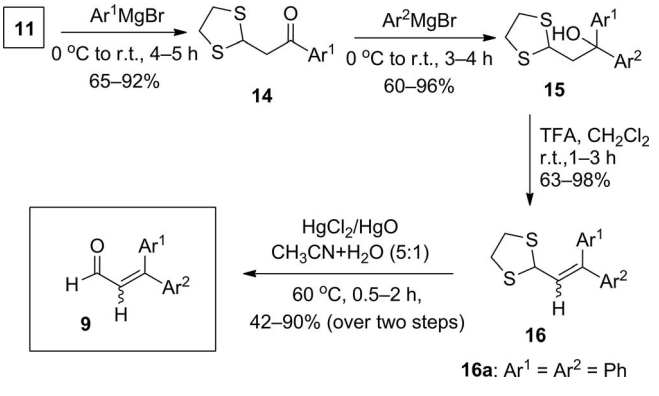


Scheme 1. Synthesis of building block **11**.

The ^1H NMR spectrum of isolated product **11** indicated the mutually coupled α-CH_2 and β-CH proton as a doublet and triplet at δ = 3.00 and 4.90 ppm, respectively, with coupling constant J = 7.2 Hz. Peaks belonging to $NOCH_3$ and NCH_3 were observed as a singlet at δ = 3.68 and 3.18 ppm, respectively. Additionally a multiplet was seen for the $-S(CH_2)_2S-$ moiety in the range 3.26–3.20 ppm.

Further structural support came from ^{13}C NMR spectroscopic analysis, with characteristic signals δ = 171.5 (CO, amide), 61.3 ($-NOCH_3$), and 32.1 ($-NCH_3$) along with other expected signals at 47.9 (CH), 42.6 (CH_2) and 38.5 [$-S(CH_2)_2S-$] ppm. Spectral inferences were also supported by HRMS analysis, which confirmed the presence of mass fragments consistent with the molecular formula of **11** (*m*/*z* calcd. for $C_7H_{14}NO_2S_2$ $[M + H]^+$ 208.0466; found 208.0462).

Building block **11** was then subjected to reaction with various arylmagnesium bromides, in two consecutive steps to furnish arylketones **14** and bibenzylic tertiary alcohols **15** in good yields (Scheme 2, Table 1). For example, arylketone **14a** and tertiary alcohol **15a** were obtained in 91 and 90 % yields, respectively. Facile dehydration with trifluoroacetic acid in anhydrous CH_2Cl_2 afforded **16a** in high yield (87 %). This was evident from the ^1H NMR spectrum, which exhibited mutually coupled doublets (J = 10.4 Hz) at δ = 6.06 ppm (=CH) and 5.04 ppm (-CH). The further unmasking of the aldehyde of **16a** was achieved with $HgCl_2$/HgO in acetonitrile/water (5:1) system at 60 °C, which afforded the β,β-diarylacroleins **9a** with 92 % yield.



Scheme 2. Synthesis of β,β-diarylacroleins **9** from building block **11**.

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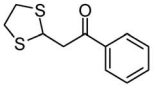
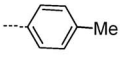
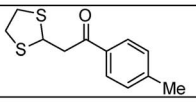
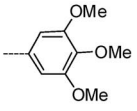
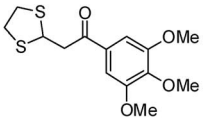
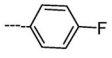
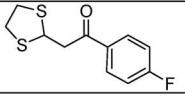
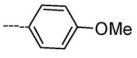
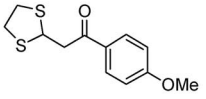
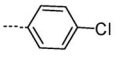
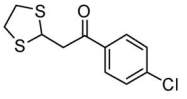
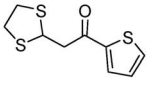
Table 1. Synthesis of arylketones **14**, bibenzylic tertiary alcohols **15** and β,β-diarylacroleins **9** from building block **11**.

Entry	Ar^1	**14** (%)[a]	Ar^2	**15** (%)[a]	**9** (%)[a][b][c]
1		 **14a** (91)	C_6H_5	**15a** (90)	**9a** (80)
			4-CF_3-C_6H_4	**15b** (96)	**9b** (74)
			3,4-$(Cl)_2$-C_6H_3	**15c** (93)	**9c** (71)
			3,5-$(CF_3)_2$-C_6H_3	**15d** (92)	**9d** (62)
			3,5-$(F)_2$-C_6H_3	**15e** (90)	**9e** (73)
			2,4-$(F)_2$-C_6H_3	**15f** (84)	**9f** (72)
			4-Me-C_6H_4	**15g** (86)	**9g** (88)
2		 **14b** (92)	4-Me-C_6H_4	**15h** (81)	**9h** (71)
			3,4-$(OMe)_2$-C_6H_3	**15i** (81)	**9i** (43)
3		 **14c** (65)	3,4,5-$(OMe)_3$-C_6H_2	**15j** (69)	**9j** (42)
			4-Me-C_6H_4	**15k** (74)	**9k** (54)
			4-CF_3-C_6H_4	**15l** (86)	**9l** (57)
4		 **14d** (89)	4-F-C_6H_4	**15m** (79)	**9m** (79)
			4-CF_3-C_6H_4	**15n** (95)	**9n** (67)
5		 **14e** (83)	4-OMe-C_6H_4	**15o** (81)	**9o** (78)
			4-CF_3-C_6H_4	**15p** (76)	**9p** (69)
			3,4-$(Cl)_2$-C_6H_3	**15q** (84)	**9q** (90)
			3,4-$(OMe)_2$-C_6H_3	**15r** (73)	**9r** (53)
6		 **14f** (79)	4-Cl-C_6H_4	**15s** (95)	**9s** (76)
7		 **14g** (74)	3,4-$(Cl)_2$-C_6H_3	**15t** (60)	**9t** (52)

[a] Isolated yield. [b] Yield over two steps. [c] Mixture of geometrical isomers (in case of unsymmetrical aryl rings).

This new route for β,β-diarylacroleins from building block **11** has been generalised, with several examples, **9b**–**t** (Scheme 2, Table 1).

A simple oxidative protocol ($NaClO_2$, NaH_2PO_4•$2H_2O$ in DMSO)[14] on β,β-diarylacroleins **9a**–**s** enabled convenient access to 3,3-diarylacrylic acids **8a**–**s**, whereas the same oxidative procedure followed by reduction (H_2-Pd/C) in ethyl acetate as solvent provided 3,3-diarylpropanoic acids **7a**–**s** in good to excellent yields (Scheme 3, Table 2). Only in the case of substrate **8j** was dichloromethane used as solvent during hydrogenation. Towards the synthesis of 3-aryl-indanones **10** in general and **6** in particular, the initial intramolecular acylation was explored in compounds **7** with chlorosulfonic acid ($ClSO_3H$). For this, **7a** was first treated with neat $ClSO_3H$ according to a reported procedure.[15] However, reaction at 0 °C for 4 h enabled intramolecular acylation and formation of 3-aryl-indanone, in which the 3-aryl moiety had undergone further electrophilic substitution with chlorosulfonyl residue as evident from NMR spectroscopic studies and mass spectroscopic data. Three signals in the ^1H and ^{13}C NMR spectrum [δ = 2.68 (dd, J = 19.2, 4.0 Hz, 1 H), 3.31 (dd, J = 19.2, 8.0 Hz, 1 H), 4.74 (dd, J = 8.4, 4.0 Hz, 1 H) ppm and δ = 204.4 ppm] indicated unambiguously the formation of the indanone ring. The aromatic region from 7.27–8.02 ppm showed one proton less than expected and a region from 124.0–155.9 ppm in the ^{13}C NMR spectrum presented two extra signals. The DEPT spectrum identified the chlorosulfonyl-substi-

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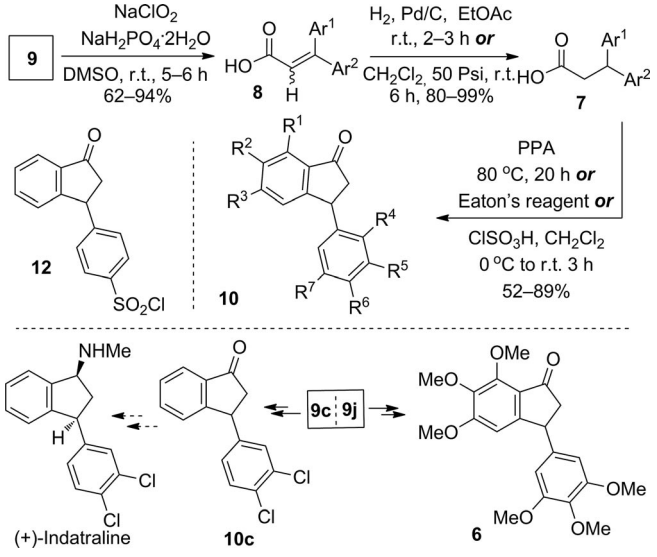
tuted quaternary carbon and the mass data indeed revealed the obtained product as **12**.

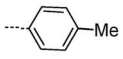
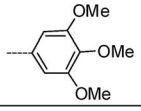
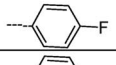
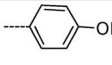
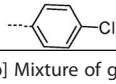


Scheme 3. Synthesis of important 3-arylindanones from β,β-diarylacroleins **9**.

To avoid such undesired substitution by $ClSO_3H$ as solvent with compound **7a**, cyclisation was then explored with either polyphosphoric acid (PPA) or Eaton's reagent[16] (P_2O_5/$MeSO_3H$ in 1:8 by weight) at 70–80 °C. In 18–20 h a clean reaction ensued, giving the desired product **10a** in 82 % yield (Scheme 3). At this stage, it was observed that the formation of indanones **10** from 3,3-diarylpropanoic acid derivatives **7** always occurred through intramolecular cyclisation onto the aryl ring bearing electron-donating groups. The transformation was equally facile with PPA and Eaton's reagent. Only in two substrates, **10i** and **10r**, did the cyclisation occur exclusively with PPA alone (Table 2).

The 3,3-diarylpropanoic acid derivatives **7**, with aryl rings containing electron-withdrawing groups (**7b–f**, **7m** and **7s**), could be readily cyclised with chlorosulfonic acid. For this, the substrates were first dissolved in anhydrous CH_2Cl_2 and then chlorosulfonic acid (15 equiv.) was added slowly at 0 °C and the mixture was stirred for 3 h. Under these new reaction conditions, the corresponding 3-arylindanones **10** were obtained in very good to excellent yield. Substrate **7o** did not form the corresponding 3-arylindanone product under any of these cyclisation protocols (Table 2). With PPA and Eaton's reagent, the compound decomposed to an intractable material, and with chlorosulfonic acid, only chlorosulfonylation of the aromatic ring in compound **7o** occurred. This was evidenced from ^1H NMR spectroscopic analysis of isolated compound for which the disappearance of two protons in the aromatic region was observed along with the presence of two signals in the aliphatic region belonging to CH and CH_2 protons at δ = 4.29 (t, J =

Table 2. Synthesis of 3,3-diarylacrylic acids **8**, 3,3-diarylpropanoic acid **7** and 3-aryl-indanones **10** and **6** from the corresponding β,β-diarylacroleins **9**.

Entry	Ar^1	Ar^2	**8** (%)[a][b]	**7** (%)[a]	3-Aryl-indanone (%)[a]
1		C_6H_5	**8a** (85)	**7a** (94)	R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = H: **10a** (82)[c][d]
		4-CF_3-C_6H_4	**8b** (82)	**7b** (99)	R^1 = R^2 = R^3 = R^4 = R^5 = R^7 = H; R^6 = CF_3: **10b** (83)[e]
		3,4-$(Cl)_2$-C_6H_3	**8c** (94)	**7c** (95)	R^1 = R^2 = R^3 = R^4 = R^7 = H; R^5 = R^6 = Cl: **10c** (80)[e]
		3,5-$(CF_3)_2$-C_6H_3	**8d** (81)	**7d** (99)	R^1 = R^2 = R^3 = R^4 = R^6 = H; R^5 = R^7 = CF_3: **10d** (87)[e]
		3,5-$(F)_2$-C_6H_3	**8e** (80)	**7e** (98)	R^1 = R^2 = R^3 = R^4 = R^6 = H; R^5 = R^7 = F: **10e** (64)[e]
		2,4-$(F)_2$-C_6H_3	**8f** (74)	**7f** (98)	R^1 = R^2 = R^3 = R^5 = R^7 = H; R^4 = R^6 = F: **10f** (52)[e]
2		4-Me-C_6H_4	**8h** (62)	**7h** (98)	R^1 = R^3 = R^4 = R^5 = R^7 = H; R^2 = R^6 = Me: **10h** (66)[c][d]
		3,4-$(OMe)_2$-C_6H_3	**8i** (72)	**7i** (97)	R^1 = R^2 = R^3 = R^4 = R^7 = H; R^5 = R^6 = OMe: **10i** (64)[c]
3		3,4,5-$(OMe)_3$-C_6H_2	**8j** (79)	**7j** (80)	R^1 = R^2 = R^3 = R^5 = R^6 = R^7 = OMe; R^4 = H: **6** (56)[c][d]
		4-Me-C_6H_4	**8k** (69)	**7k** (97)	R^1 = R^2 = R^3 = OMe; R^4 = R^5 = R^7 = H; R^6 = Me: **10k** (70)[d]
4		4-F-C_6H_4	**8m** (88)	**7m** (99)	R^1 = R^3 = R^4 = R^5 = R^7 = H; R^2 = R^6 = F: **10m** (89)[e]
5		4-OMe-C_6H_4	**8o** (89)	**7o** (98)	–
		3,4-$(OMe)_2$-C_6H_3	**8r** (80)	**7r** (94)	R^1 = R^4 = R^5 = R^7 = H; R^2 = R^3 = R^6 = OMe: **10r** (56)[c]
6		4-Cl-C_6H_4	**8s** (83)	**7s** (97)	R^1 = R^3 = R^4 = R^5 = R^7 = H; R^2 = R^6 = Cl: **10s** (79)[e]

[a] Isolated yields. [b] Mixture of geometrical isomers (in case of unsymmetrical aryl rings). [c] Cyclisation procedure A. [d] Cyclisation procedure B. [e] Cyclisation procedure C respectively.

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7.6 Hz, 1 H) and 2.89 (d, J = 7.6 Hz, 2 H) ppm, respectively. The developed method for β,β-diarylacroleins and subsequent conversions has enabled the synthesis of two important racemic indanones, **10c** and **6**, in particular. Racemic **10c**[6e] has been used for the synthesis of important (+)-indatraline, which is a nonselective monoamine transporter inhibitor that is being investigated as medication for the treatment of cocaine addiction,[12b] whereas the latter awaits evaluation as a potential analogue of **5** for anticancer activity.

Conclusions

A new WA based building block **11** has been developed that provides a convenient synthetic route to access β,β-diarylacroleins **9**. Simple functional group interconversions have further enabled convenient access to 3,3-diarylacrylic acids **8** and 3,3-diarylpropanoic acids **7**. The developed methodology has been applied for the synthesis of important 3-arylindanones **10** in general, and isomer **6** of gallic acid based indanone **5**, in particular.

Experimental Section

General Information: All reactions were carried out in oven-dried glassware. Solvents used for column chromatography were LR grade. Thin-layer chromatography was performed on aluminium plates coated with silica gel 60. Visualisation was achieved under UV light or by dipping into 2,4-DNP solution, or by dipping into a solution of cerium(IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in 10 % sulfuric acid (250 mL) followed by charring on a hot plate. Melting points were determined in capillaries and are uncorrected. ^{1}H NMR (400 MHz/500 MHz) and ^{13}C NMR (100 MHz/125 MHz) spectra were recorded in [D]chloroform ($CDCl_3$) or [D_6]DMSO and chemical shifts are given in part per million (ppm). ^{1}H NMR spectra are referenced to $CDCl_3$ (δ =7.26 ppm) and [D_6]DMSO (δ = 2.5 ppm), whereas ^{13}C NMR spectra are referenced to the central line of $CDCl_3$ (δ =77.16 ppm) and [D_6]DMSO (δ = 39.50 ppm). The multiplicity is given as, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, and coupling constants J are reported in Hz. IR spectra were recorded with a JASCO-FT/IR-4100 Spectrometer using NaCl cell. Elemental analysis was determined with a Perkin–Elmer Instruments series II CHNS/O analyser. HRMS were recorded with a MICRO-QTOF mass spectrometer by using the ESI technique at 10 eV.

2-(1,3-Dithiolan-2-yl)acetic Acid (13): To a solution of propiolic acid (4.9 mL, 78.5 mmol) in anhydrous dichloromethane (120 mL), 1,2-ethanedithiol (7.9 mL, 94.2 mmol) and triethylamine (27.4 mL, 196.0 mmol) were added at 0 °C and the reaction mixture was stirred at 0 °C to room temp. for 15 h. Upon completion of the reaction, solvent was evaporated under vacuum and EtOAc (100 mL) was added followed by washing with 10 % aq. HCl solution (30 mL), water (3 × 30 mL) and brine. The organic layer was dried with Na_2SO_4, concentrated and purified by silica gel column chromatography to afford **13**, yield 10.4 g (80 %); colourless crystalline solid; m.p. 96–98 °C; R_f = 0.15 (EtOAc/hexanes, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.82 (t, J = 7.6 Hz, 1 H, C*H*CH_2), 3.30–3.20 [m, 4 H, -S(C*H*$_2$)$_2$S-], 2.91 (d, J = 7.6 Hz, 2 H, C*H*$_2$CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4 (*C*OOH), 47.5 (*C*H), 44.8 (CH_2), 38.7 [-S(CH_2)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1711, 1424, 1287, 931, 770, 669, 646 cm^{-1}. HRMS (ESI): m/z calcd. for $C_5H_8O_2S_2$ + Na^+ [M + Na]$^+$ 186.9863; found 186.9864.

Synthesis of Building Block 2-(1,3-Dithiolan-2-yl)-*N*-methoxy-*N*-methylacetamide (11): To a solution of **13** (5.18 g, 31.5 mmol) in anhydrous dichloromethane (100 mL), pivaloyl chloride (4.3 mL, 34.7 mmol) and triethylamine (9.2 mL, 66.3 mmol) were added at 0 °C and the reaction mixture was stirred at 0 °C to room temp. for up to 3 h. The reaction mixture was kept at 0 °C and solid DMHA·HCl (3.69 g, 37.9 mmol) was added first, followed by the addition of triethylamine (9.2 mL, 66.3 mmol) and the mixture was stirred from 0 °C to room temp. for another 15 h. Upon completion of the reaction as monitored by TLC, dichloromethane (50 mL) was added and the organic layer was washed with 10 % aq. HCl (30 mL), water (3 × 30 mL) and 10 % aq. $NaHCO_3$ (25 mL). The organic layer was separated, dried with anhydrous Na_2SO_4 and purified by silica-gel column chromatography (EtOAc/hexanes, 2:8) to afford **11**, yield 5.81 g (88 %); light-yellow liquid; R_f = 0.31 (EtOAc/hexanes, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (t, J = 7.2 Hz, 1 H, C*H*CH_2), 3.68 (s, 3 H, OC*H*$_3$), 3.26–3.20 [m, 4 H, -S(C*H*$_2$)$_2$S-], 3.18 (s, 3 H, NC*H*$_3$), 3.00 (d, J = 7.2 Hz, 2 H, C*H*$_2$CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5 (*C*O), 61.3 (NO*C*H$_3$), 47.9 (*C*H), 42.6 (*C*H$_2$CO), 38.5 [-S(CH_2)$_2$S-], 32.1 (N*C*H$_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1653, 1461, 1424, 1388, 1276, 1102, 997, 937, 759 cm^{-1}. HRMS (ESI): m/z calcd. for $C_7H_{13}NO_2S_2$ + H^+ [M + H]$^+$ 208.0466; found 208.0462.

Grignard Reagent and Synthesis of Aryl Ketones 14a–b and 14d–g: Grignard reagent was prepared from bromobenzene (7.74 g, 49.2 mmol) and magnesium (1.18 g, 89.2 mmol, activated with iodine) in anhydrous THF (48 mL) at room temperature. Initiation of Grignard reaction was observed within 5–10 min and was exothermic. After complete consumption of magnesium within 50–60 min, the resulting solution was slowly added to a solution of **11** (3.4 g, 16.4 mmol) in THF (15 mL) at 0 °C and stirring was continued for 4–5 h and monitored by TLC. Upon completion of the reaction, saturated aq. NH_4Cl was added cautiously at 0 °C, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated, and purified by silica-gel column chromatography (EtOAc/hexanes, 1:9) to afford phenyl ketone **14a**, yield 3.4 g (91 %); colourless solid; m.p. 68–70 °C; R_f = 0.42 (EtOAc/hexanes, 0.5:9.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.2 Hz, 2 H, Ar*H*), 7.57 (t, J = 7.2 Hz, 1 H, Ar*H*), 7.46 (t, J = 7.6 Hz, 2 H, Ar*H*), 5.01 (t, J = 6.8 Hz, 1 H, C*H*CH_2), 3.57 (d, J = 6.8 Hz, 2 H, C*H*$_2$CO), 3.27–3.23 [m, 4 H, -S(C*H*$_2$)$_2$S-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5 (*C*O), 136.3 (Ar*C*), 133.5 (Ar*C*H), 128.7 (Ar*C*H), 128.2 (Ar*C*H), 49.0 ($CHCH_2$), 47.4 [-S(CH_2)$_2$S-], 38.6 (CH_2CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3062, 2926, 1683, 1597, 1581, 1530, 1447, 1424, 1398, 1348, 1280, 1243, 1182, 1055 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{11}H_{12}OS_2$ + Na^+ [M + Na]$^+$ 247.0227; found 247.0226.

Compound 14b: Yield 1.6 g (92 %); colourless crystalline solid; m.p. 98–100 °C; R_f = 0.56 (EtOAc/hexanes, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.4 Hz, 2 H, Ar*H*), 7.20–7.18 (m, 2 H, Ar*H*), 4.94 (t, J = 6.8 Hz, 1 H, C*H*CH_2), 3.48 (d, J = 6.8 Hz, 2 H, C*H*$_2$), 3.22–3.15 [m, 4 H, -S(C*H*$_2$)$_2$S-], 2.34 (s, 3 H, ArC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0 (*C*O), 144.3 (Ar*C*), 134.0 (Ar*C*), 129.4 (Ar*C*H), 128.3 (Ar*C*H), 48.8 (CH_2), 47.5 ($CHCH_2$), 38.6 [-S(CH_2)$_2$S-], 21.7 (ArC*H*$_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2927, 1679, 1606, 1575, 1527, 1478, 1424, 1347, 1278, 1184, 978, 929, 848 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{12}H_{14}OS_2$ + Na^+ [M + Na]$^+$ 261.0384; found 261.0387.

Preparation of Grignard Reagent and Synthesis of Aryl Ketones 14c: A solution of azeotropically dried (toluene, 3 × 5 mL) 1-bromo-3,4,5-trimethoxybenzene (2.39 g, 9.66 mmol) in anhydrous THF (14 mL) was added to magnesium turnings (0.26 g, 10.8 mmol,

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activated with iodine) following the addition of MeI (0.1 mL, catalytic) under nitrogen and the reaction mixture was kept over a water bath that was heated at 55 °C. The initiation of Grignard reaction was observed within 5–10 min, whereupon the water bath was removed and the mixture was stirred at room temp. After 50–60 min, the resulting off-white reagent solution was slowly added to a solution of **11** (0.50 g, 2.42 mmol) in anhydrous THF (5 mL) at 0 °C and stirring was continued for 4–5 h at room temp. Upon completion of the reaction, saturated aq. NH_4Cl was added cautiously at 0 °C and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, concentrated, and purified over silica gel-column chromatography (EtOAc/hexanes, 2:8) to afford aryl ketone **14c**, yield 0.49 g (65 %); colourless crystalline solid; m.p. 88–90 °C; R_f = 0.37 (EtOAc/hexanes, 0.5:9.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (s, 2 H, Ar*H*), 5.01 (t, *J* = 6.8 Hz, 1 H, C*H*CH_2), 3.91 (s, 9 H, 3 × OCH_3), 3.53 (d, *J* = 6.8 Hz, 2 H, CH_2CO), 3.29–3.23 [m, 4 H, -S(CH_2)$_2$S-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2 (*C*O), 153.2 (Ar*C*), 143.0 (Ar*C*), 131.6 (Ar*C*), 105.7 (Ar*C*H), 61.0 (OCH_3), 56.4 (2 × OCH_3), 48.8 (CH_2CO), 47.6 (*C*HCH_2), 38.7 [-S(CH_2)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1675, 1585, 1507, 1462, 1415, 1507, 1462, 1415, 1350, 1128, 928 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}O_4S_2$ + Na^+ [M + Na]$^+$ 337.0544; found 337.0535.

Compound 14d: Yield 1.58 g (89 %); colourless crystalline solid; m.p. 84–86 °C; R_f = 0.32 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.96 (m, 2 H, Ar*H*), 7.16–7.10 (m, 2 H, Ar*H*), 5.00 (t, *J* = 6.8 Hz, 1 H, C*H*CH_2), 3.54 (d, *J* = 6.8 Hz, 2 H, CH_2), 3.30–3.21 [m, 4 H, -S(CH_2)$_2$S-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.9 (*C*O), 166.0 (d, *J* = 253.6 Hz, Ar*C*F), 132.8 (Ar*C*), 130.8 (Ar*C*H), 115.9 (Ar*C*H), 49.0 (CH_2), 47.4 (*C*HCH_2), 38.7 [-S(CH_2)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1684, 1597, 1508, 1411, 1348, 1156, 984, 837, 684 cm^{-1}. $C_{11}H_{11}FOS_2$ (242.33): calcd. C 54.52, H 4.58; found: C 54.08, H 4.34.

Compound 14e: Yield 1.53 g (83 %); colourless crystalline solid; m.p. 80–82 °C; R_f = 0.38 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.91 (m, 2 H, Ar*H*), 6.93 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 5.01 (t, *J* = 7.2 Hz, 1 H, C*H*CH_2), 3.86 (s, 3 H, ArOCH_3), 3.52 (d, *J* = 7.2 Hz, 2 H, CH_2), 3.30–3.20 [m, 4 H, -S(CH_2)$_2$S-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.9 (*C*O), 163.8 (Ar*C*), 130.5 (Ar*C*H), 129.5 (Ar*C*), 113.9 (Ar*C*H), 55.6 ($ArOCH_3$), 48.6 (CH_2), 47.7 (*C*HCH_2), 38.6 [-S(CH_2)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1674, 1600, 1575, 1512, 1423, 1348, 1260, 1172, 1030, 928, 823 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{12}H_{14}O_2S_2$ + Na^+ [M + Na]$^+$ 277.0333; found 277.0339.

Compound 14f: Yield 1.49 g (79 %); colourless solid; m.p. 86–88 °C; R_f = 0.74 (EtOAc/hexanes, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.43 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.99 (t, *J* = 6.8 Hz, 1 H, C*H*CH_2), 3.53 (d, *J* = 7.2 Hz, 2 H, CH_2), 3.28–3.22 [m, 4 H, -S(CH_2)$_2$S-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2 (*C*O), 140.0 (Ar*C*), 134.7 (Ar*C*), 129.6 (Ar*C*H), 129.1 (Ar*C*H), 49.0 (CH_2), 47.3 (*C*HCH_2), 38.7 [-S(CH_2)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2928, 1684, 1590, 1571, 1424, 1400, 1345, 1279, 1245, 1177 cm^{-1}. $C_{11}H_{11}ClOS_2$ (258.78): calcd. C 51.05, H 4.28; found C 50.73, H 3.95.

Compound 14g: Yield 1.25 g (74 %); brown crystalline solid; m.p. 88–90 °C; R_f = 0.6 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 3.6 Hz, 1 H, Ar*H*), 7.65 (d, *J* = 4.8 Hz, 1 H, Ar*H*), 7.13 (t, *J* = 4.4 Hz, 1 H, Ar*H*), 5.00 (t, *J* = 6.8 Hz, 1 H, C*H*CH_2), 3.48 (d, *J* = 6.8 Hz, 2 H, CH_2), 3.30–3.20 [m, 4 H, -S(CH_2)$_2$S-] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.1 (*C*O), 143.6 (Ar*C*), 134.2 (Ar*C*H), 132.3 (Ar*C*H), 128.3 (Ar*C*H), 49.4 (*C*H), 47.4 (CH_2), 38.7 [-S(CH_2)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2926, 1662, 1516, 1415, 1358, 1275, 1064, 929 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_9H_{10}OS_3$ + K^+ [M + K]$^+$ 268.9531; found 268.9521.

Preparation of Grignard Reagent for the Synthesis of Diaryl Alcohol 15a–i and 15k–t: Grignard reagent was prepared from bromobenzene (2.8 mL, 26.8 mmol) and magnesium (0.64 g, 26.8 mmol, activated with iodine) in anhydrous THF (26 mL) under an inert atmosphere at room temperature. The initiation of Grignard reaction was observed within 5–10 min and, after complete consumption of magnesium within 50–60 min, the resulting solution was slowly added to the solution of compound **14a** (2.0 g, 8.93 mmol) in THF (7 mL) at 0 °C and stirring was continued for 4 h. Upon completion of the reaction, saturated aq. NH_4Cl was added cautiously at 0 °C, the organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated, and purified by silica-gel column chromatography (EtOAc/hexanes, 1:4) to afford alcohol **15a**, yield 2.42 g (90 %); colourless solid; m.p. 126–128 °C; R_f = 0.57 (EtOAc/hexanes, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 7.2 Hz, 4 H, Ar*H*), 7.24 (t, *J* = 7.6 Hz, 4 H, Ar*H*), 7.16 (t, *J* = 7.6 Hz, 2 H, Ar*H*), 4.28 (t, *J* = 6.8 Hz, 1 H, C*H*CH_2), 3.19–3.13 (m, 2 H, -CH_2S-), 3.09–3.02 (m, 2 H, -CH_2S-), 2.82 (d, *J* = 6.4 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1 (Ar*C*), 128.4 (Ar*C*H), 127.2 (Ar*C*H), 126.1 (Ar*C*H), 78.1 (*C*OH), 50.1 [-S(CH_2)$_2$S], 48.9 (*C*HCH_2), 38.2 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3416, 1599, 1523, 1494, 1445, 1425, 1059, 1031, 1010 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{17}H_{18}OS_2$ + Na^+ [M + Na]$^+$ 325.0697; found 325.0707.

Compound 15b: Yield 1.24 g (96 %); colourless solid; m.p. 84–86 °C; R_f = 0.38 (EtOAc/hexanes, 0.5:9.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.53 (m, 4 H, Ar*H*), 7.42–7.39 (m, 2 H, Ar*H*), 7.35–7.31 (m, 2 H, Ar*H*), 7.27–7.23 (m, 1 H, Ar*H*), 4.32 (t, *J* = 6.8 Hz, 1 H, C*H*CH_2), 3.61 (s, 1 H, OH), 3.29–3.21 (m, 2 H, -CH_2S-), 3.19–3.12 (m, 2 H, -CH_2S-), 2.89 (dd, *J* = 6.4, 2.4 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1 (Ar*C*), 145.5 (Ar*C*), 129.2 (Ar*C*), 128.7 (Ar*C*H), 127.6 (Ar*C*H), 126.5 (Ar*C*H), 126.0 (Ar*C*H), 125.4 (q, *J* = 3.6 Hz, Ar*C*H), 78.0 (*C*OH), 50.0 (CH_2), 48.6 (*C*HCH_2), 38.3 (CH_2), 38.2 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3417, 2929, 1618, 1523, 1494, 1444, 1411, 1326, 1168, 1126, 1068, 1013, 928 cm^{-1}. $C_{18}H_{17}F_3OS_2$ (370.45): calcd. C 58.36, H 4.63; found C 58.73, H 4.16.

Compound 15c: Yield 2.48 g (93 %); colourless solid; m.p. 126–128 °C; R_f = 0.63 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 1.6 Hz, 1 H, Ar*H*), 7.51 (d, *J* = 8.8 Hz, 1 H, Ar*H*), 7.45 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.38 (dd, *J* = 8.4, 1.6 Hz, 1 H, Ar*H*), 7.29 (t, *J* = 7.6 Hz, 2 H, Ar*H*), 7.20 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 6.04 (s, 1 H, O*H*), 4.35 (t, *J* = 6.0 Hz, 1 H, C*H*CH_2), 3.18–3.10 (m, 2 H, -CH_2S-), 3.03–2.96 (m, 2 H, -CH_2S-), 2.94–2.85 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2 (Ar*C*), 146.6 (Ar*C*), 130.4 (Ar*C*), 129.9 (Ar*C*), 128.9 (Ar*C*H), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 126.7 (Ar*C*H), 126.6 (Ar*C*H), 125.7 (Ar*C*H), 75.5 (*C*OH), 48.45 (*C*H), 48.41 (CH_2), 38.0 (CH_2), 37.6 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3408, 2928, 1522, 1495, 1470, 1443, 1425, 1379, 1028, 929, 669, 625 cm^{-1}. $C_{17}H_{16}Cl_2OS_2$ (371.34): calcd. C 54.98, H 4.34; found C 55.16, H 4.04.

Compound 15d: Yield 1.43 g (92 %); colourless crystalline solid; m.p. 62–64 °C; R_f = 0.40 (EtOAc/hexanes, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 2 H, Ar*H*), 7.75 (s, 1 H, Ar*H*), 7.44–7.41 (m, 2 H, Ar*H*), 7.39–7.36 (m, 2 H, Ar*H*), 7.31–7.27 (m, 1 H, Ar*H*), 4.34 (dd, *J* = 8.0, 6.0 Hz, 1 H, C*H*CH_2), 3.93 (s, 1 H, OH), 3.32–3.22 (m, 2 H, -CH_2S-), 3.20–3.12 (m, 2 H, -CH_2S-), 2.97 (dd, *J* = 14.8, 5.6 Hz, 1 H, C$H_a$$H_b$), 2.79 (dd, *J* = 14.8, 8.0 Hz, 1 H, C$H_a$$H_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1 (Ar*C*), 144.3 (Ar*C*), 131.6 (q, *J* = 33.0 Hz, Ar*C*H), 129.0 (Ar*C*H), 128.0 (Ar*C*H), 126.3 (Ar*C*H), 125.9 (Ar*C*H), 123.5 (q, *J* = 271.0 Hz, ArCF_3), 121.37 (Ar*C*H), 121.33 (Ar*C*H), 121.2 (Ar*C*H), 77.8 (*C*OH), 50.1 (CH_2), 48.4 (*C*HCH_2), 38.3 [-S(CH_2)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3410, 3064, 2931, 1375, 1352, 1279, 1174, 1139, 900, 844, 769, 707, 682 cm^{-1}. $C_{19}H_{16}F_6OS_2$ (438.44): calcd. C 52.05, H 3.68; found C 52.19, H 3.68.

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Compound 15e: Yield 1.09 g (90 %); colourless crystalline solid; m.p. 100–102 °C; R_f = 0.33 (EtOAc/hexanes, 0.5:0.95). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.39 (m, 2 H, Ar*H*), 7.36–7.32 (m, 2 H, Ar*H*), 7.28–7.24 (m, 1 H, Ar*H*), 6.99–6.93 (m, 2 H, Ar*H*), 6.69–6.63 (m, 1 H, Ar*H*), 4.33 (t, *J* = 6.4 Hz, 1 H, C*H*CH$_2$), 3.67 (br. s, 1 H, O*H*), 3.27–3.21 (m, 2 H, CH_2S-), 3.19–3.12 (m, 2 H, CH_2S-), 2.85 (dd, *J* = 14.8, 6.8 Hz, 1 H, CH_aH$_b$), 2.07 (dd, *J* = 14.8, 6.8 Hz, 1 H, CH_aH$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1 (d, *J* = 247.0 Hz, ArCF), 163.0 (d, *J* = 247.0 Hz, ArCF), 150.58 (Ar*C*), 150.5 (Ar*C*), 145.0 (Ar*C*), 128.7 (Ar*C*H), 127.7 (Ar*C*H), 125.9 (Ar*C*H), 109.3 (dd, *J* = 18.0, 7.0 Hz, Ar*C*H), 102.6 (t, *J* = 25.0 Hz, Ar*C*H), 77.8 (*C*OH), 49.9 (*C*H$_2$), 48.5 (*C*HCH$_2$), 38.3 (*C*H$_2$S-), 38.2 (*C*H$_2$S-) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3407, 2928, 1623, 1597, 1494, 1449, 1434, 1361, 1301, 1117, 1032, 984, 857, 768 cm^{-1}. $C_{17}H_{16}F_2OS_2$ (338.43): calcd. C 60.33, H 4.77; found C 60.61, H 4.27.

Compound 15f: Yield 1.02 g (84 %); colourless crystalline solid; m.p. 100–102 °C; R_f = 0.32 (EtOAc/hexanes, 0.5:0.95). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.39 (m, 2 H, Ar*H*), 7.36–7.32 (m, 2 H, Ar*H*), 7.28–7.25 (m, 1 H, Ar*H*), 6.98–6.93 (m, 2 H, Ar*H*), 6.69–6.63 (m, 1 H, Ar*H*), 4.33 (t, *J* = 6.8 Hz, 1 H, C*H*CH$_2$), 3.66 (s, 1 H, O*H*), 3.29–3.21 (m, 2 H, CH_2S-), 3.19–3.12 (m, 2 H, CH_2S-), 2.85 (dd, *J* = 14.8, 6.8 Hz, 1 H, CH_aH$_b$), 2.79 (dd, *J* = 14.4, 6.8 Hz, 1 H, CH_aH$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.09 (d, *J* = 247.0 Hz, ArCF), 163.03 (d, *J* = 247.0 Hz, ArCF), 150.59 (Ar*C*), 150.51 (Ar*C*), 150.4 (Ar*C*), 145.0 (Ar*C*), 128.7 (Ar*C*H), 127.7 (Ar*C*H), 125.9 (Ar*C*H), 109.3 (dd, *J* = 19.0, 7.0 Hz, Ar*C*H), 102.6 (t, *J* = 25.0 Hz, Ar*C*H), 77.8 (*C*OH), 50.0 (*C*H$_2$), 48.5 (*C*HCH$_2$), 38.3 (*C*H$_2$S-), 38.2 (*C*H$_2$S-) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3410, 3089, 3061, 2929, 1623, 1597, 1494, 1449, 1434, 1363, 1301, 1117, 984, 856 cm^{-1}. $C_{17}H_{16}F_2OS_2$ (338.43): calcd. C 60.33, H 4.77; found C 60.70, H 4.19.

Compound 15g: Yield 0.305 g (86 %); colourless solid; m.p. 130–132 °C; R_f = 0.21 (EtOAc/hexanes, 0.5:0.95). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2 H, Ar*H*), 7.32–7.28 (m, 4 H, Ar*H*), 7.24–7.20 (m, 1 H, Ar*H*), 7.12 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.35 (t, *J* = 6.6 Hz, 1 H, C*H*CH$_2$), 3.33 (s, 1 H, O*H*), 3.27–3.20 (m, 2 H, -CH_2S-), 3.16–3.09 (m, 2 H, -CH_2S-), 2.88 (d, *J* = 6.6 Hz, 2 H, CH_2), 2.31 (s, 3 H, ArCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3 (Ar*C*), 143.2 (Ar*C*), 136.8 (Ar*C*), 129.1 (Ar*C*H), 128.4 (Ar*C*H), 127.1 (Ar*C*H), 126.09 (Ar*C*H), 126.04 (Ar*C*H), 78.0 (*C*OH), 50.1 (*C*H$_2$), 49.0 (*C*HCH$_2$), 38.2 [-S(*C*H$_2$)$_2$S-], 21.1 (ArCH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3416, 2925, 1512, 1494, 1444, 1425, 1064, 1010, 816, 701, 669, 618 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}OS_2$ + Na$^+$ [M + Na]$^+$ 339.0853; found 339.0851. $C_{18}H_{20}OS_2$ (316.48): calcd. C 68.31, H 6.37; found C 68.24, H 6.33.

Preparation of Grignard Reagent for the Synthesis of Diaryl Alcohol 15j: The synthetic procedure used for the preparation of aryl ketone **14c** was used, which furnished alcohol **15j**, yield 0.77 g (69 %); colourless gummy solid; R_f = 0.53 (EtOAc/hexanes, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (s, 4 H, Ar*H*), 4.36 (t, *J* = 6.4 Hz, 1 H, C*H*), 3.84 (s, 6 H, 2 × ArOCH_3), 3.83 (s, 12 H, 4 × ArOCH_3), 3.58 (s, 1 H, O*H*), 3.30–3.24 (m, 2 H, -CH_2S-), 3.21–3.16 (m, 2 H, -CH_2S-), 2.80 (d, *J* = 6.4 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (Ar*C*), 141.5 (Ar*C*), 137.3 (Ar*C*), 103.8 (Ar*C*H), 78.5 (*C*OH), 60.9 (2 × ArOCH$_3$), 56.4 (4 × ArOCH$_3$), 50.4 (*C*H$_2$), 49.0 (*C*H), 38.3 [-S(*C*H$_2$)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3417, 2965, 2938, 2835, 1591, 1506, 1459, 1415, 1324, 1130, 1003, 924, 844, 767 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{23}H_{30}O_7S_2$ + Na$^+$ [M + Na]$^+$ 505.1331; found 505.1337.

General Procedure for the Synthesis of Alkene 16: To a solution of **15a** (0.78 g, 2.58 mmol) in anhydrous dichloromethane (8 mL), trifluoroacetic acid (0.4 mL, 5.16 mmol) was added and the reaction mixture was heated to reflux. The progress of the reaction was monitored by TLC and, upon complete consumption of starting material, additional dichloromethane (10 mL) was added and the mixture was neutralised with saturated aq. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated and purified by silica-gel column chromatography (EtOAc/hexanes, 2:8) to afford **16a**, yield 0.64 g (87 %); colourless solid; m.p. 70–72 °C; R_f = 0.71 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 3 H, Ar*H*), 7.28–7.24 (m, 3 H, Ar*H*), 7.19–7.12 (m, 3 H, Ar*H*), 6.06 (d, *J* = 10.4 Hz, 1 H, =C*H*), 5.04 (d, *J* = 10.8 Hz, 1 H, C*H*), 3.34–3.27 (m, 2 H, -CH_2S-), 3.17 (m, 2 H, -CH_2S-) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1 (Ar*C*), 141.4 (Ar*C*), 138.6 (Ar*C*), 130.1 (*C*H), 128.5 (*C*H), 128.2 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 51.2 (*C*H), 40.0 [-S(*C*H$_2$)$_2$S-] ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2978, 2925, 1521, 1493, 1432, 1037, 928, 876, 618 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{17}H_{16}S_2$ + H$^+$ [M + H]$^+$ 285.0772; found 285.0760.

General Procedure for the Synthesis of β,β-Diarylacroleins 9 from Compound 16: To a solution of **16a** (0.64 g, 2.24 mmol) in CH_3CN/H_2O (10 mL, 5:1), HgO (0.58 g, 2.69 mmol) was added followed by $HgCl_2$ (1.52 g, 5.61 mmol) and the reaction mixture was stirred and heated at 60 °C. Upon complete consumption of starting material within 2 h (ca. 30 min for substrates bearing trimethoxylated aryl groups) as revealed by TLC, the reaction mixture was filtered through Celite to remove solid residues and washed with EtOAc (3 × 3 mL). The filtrate was concentrated, EtOAc (10 mL) was added and the mixture was washed with satd. aq. $NaHCO_3$ (3 × 3 mL) followed by 10 % aq. solution of KI (3 × 3 mL). The organic layer was dried with anhydrous Na_2SO_4, concentrated and purified by silica-gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford **9a**.[17] Yield 0.43 g (92 %); viscous semisolid; R_f = 0.63 (EtOAc/hexanes, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.45 (d, *J* = 8.4 Hz, C*H*O), 7.42–7.31 (m, 5 H, Ar*H*), 7.30–7.22 (m, 5 H, Ar*H*), 6.52 (d, *J* = 8.0 Hz, 1 H, =C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6 (*C*HO), 162.4 (Ar*C*), 139.8 (Ar*C*), 136.7 (Ar*C*), 130.8 (*C*H), 130.6 (*C*H), 129.5 (*C*H), 128.8 (*C*H), 128.7 (*C*H), 128.4 (*C*H), 127.4 (*C*H) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2926, 2857, 1662, 1591, 1569, 1446, 1387, 1344, 1156, 1128, 928 cm^{-1}.

Compound 9b: Yield 0.37 g (74 %, over two steps); yellowish gummy solid; R_f = 0.51 (EtOAc/hexanes, 1:9); mixture of geometrical isomer (ca. 1.1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (d, *J* = 8.0 Hz, minor C*H*O), 9.49 (d, *J* = 8.0 Hz, 1 H, major C*H*O), 7.73 (d, *J* = 8.0 Hz, 2 H, major Ar*H*), 7.63 (d, *J* = 8.0 Hz, minor Ar*H*), 7.53–7.43 (m, 8 H, Ar*H*), 7.42–7.37 (m, 2 H, Ar*H*), 7.34–7.28 (m, 4 H, Ar*H*), 6.66 (d, *J* = 8.0 Hz, 1 H, major =C*H*), 6.60 (d, *J* = 7.6 Hz, minor = C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1 (*C*HO), 192.6 (*C*HO), 160.48, 160.41, 143.4, 140.5, 138.9, 136.0, 131.07, 131.01, 130.8, 130.02, 129.07, 129.01, 128.77, 128.74, 128.6, 128.0, 125.8, 125.76, 125.73, 125.69, 125.64, 125.60, 125.57, 125.53 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2929, 2853, 1724, 1700, 1668, 1614, 1574, 1511, 1447, 1411, 1325, 1277 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{16}H_{11}OF_3$ + H$^+$ [M + H]$^+$ 277.0840; found 277.0836.

Compound 9c: Yield 1.15 g (71 %, over two steps); yellow viscous liquid; R_f = 0.50 (EtOAc/hexanes, 1:9); mixture of geometrical isomer (ca. 1.1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 8.0 Hz, minor C*H*O), 9.51 (d, *J* = 8.4 Hz, 1 H, major C*H*O), 7.56–7.44 (m, 6 H, Ar*H*), 7.42–7.38 (m, 2 H, Ar*H*), 7.34–7.32 (m, 2 H, Ar*H*), 7.29–7.27 (m, 2 H, Ar*H*), 7.21–7.16 (m, 2 H, Ar*H*), 6.06 (d, *J* = 8.0 Hz, 1 H, major =C*H*), 6.54 (d, *J* = 8.0 Hz, minor =C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1 (*C*HO), 192.5 (*C*HO), 159.5 (*C*), 159.4 (*C*), 139.9 (*C*), 138.8 (*C*), 136.7 (*C*), 135.7 (*C*), 134.8 (*C*), 134.1 (*C*), 133.28 (*C*), 133.20 (*C*), 132.3 (*C*H), 131.0 (*C*H), 130.78 (*C*H), 130.75 (*C*H), 130.6 (*C*H), 130.4 (*C*H), 130.1 (*C*H), 130.0 (*C*H), 129.0 (*C*H), 128.8 (*C*H), 128.6 (*C*H), 128.1 (*C*H), 128.0 (*C*H), 127.7 (*C*H) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2393, 1725,

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1694, 1665, 1598, 1584, 1550, 1492, 1469, 1447, 1383, 1285, 1247, 1157, 1130, 1030 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{15}H_{10}OCl_2 + H^+$ $[M + H]^+$ 277.0187; found 277.0174.

Compound 9d: Yield 0.3 g (62 %, over two steps); yellow gummy solid; R_f = 0.56 (EtOAc/hexanes, 1:9); mixture of geometrical isomer (ca. 1.1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, *J* = 7.6 Hz, minor C*H*O), 9.46 (d, *J* = 8.0 Hz, 1 H, major C*H*O), 8.02 (s, 1 H, Ar*H*), 7.93 (s, 1 H, Ar*H*), 7.78 (s, 4 H, Ar*H*), 7.58–7.47 (m, 4 H, Ar*H*), 7.46–7.41 (m, 2 H, Ar*H*), 7.31–7.29 (m, 4 H, Ar*H*), 6.73 (d, *J* = 8.0 Hz, 1 H, =C*H*), 6.61 (d, *J* = 7.6 Hz, 1 H, =C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.6 (C*H*O), 191.5 (C*H*O), 158.5, 158.3, 142.3, 139.0, 138.2, 135.1, 132.6, 132.5, 132.26, 132.20, 131.4, 130.7, 130.5, 130.4, 129.5, 129.3, 129.1, 128.7, 128.53, 128.50, 128.46, 124.41, 123.89, 123.85, 123.45, 123.42, 123.3, 121.7, 121.6 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1727, 1671, 1613, 1379, 1215, 1185, 1143, 1109, 904 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{17}H_{10}OF_6 + H^+$ $[M + H]^+$ 345.0714; found 345.0699.

Compound 9e: Yield 0.51 g (73 %, over two steps); yellow gummy solid; R_f = 0.50 (EtOAc/hexanes, 1:9); mixture of geometrical isomer (ca. 1.5:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.54 (t, *J* = 8.4 Hz, 1.6 H, C*H*O), 7.51–7.45 (m, 3 H, Ar*H*), 7.44–7.38 (m, 2 H, Ar*H*), 7.35–7.32 (m, 2 H, Ar*H*), 7.30–7.28 (m, 1 H, Ar*H*), 6.97–6.92 (m, 1 H, Ar*H*), 6.90–6.84 (m, 4 H, Ar*H*), 6.61 (d, *J* = 8.0 Hz, 1 H, major =C*H*), 6.54 (d, *J* = 7.6 Hz, minor =C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0 (C*H*O), 192.4 (C*H*O), 164.3 (*C*), 164.2 (*C*), 164.1 (*C*), 161.7 (*C*), 161.6 (*C*), 159.2 (*C*), 139.9 (*C*), 138.4 (*C*), 135.5 (*C*), 131.1 (CH), 130.7 (CH), 130.0 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 113.9 (CH), 113.8 (CH), 113.7 (CH), 113.6 (CH), 111.79 (CH), 111.7 (CH), 111.6 (CH), 111.5 (CH), 105.9 (CH), 105.7 (CH), 105.4 (CH), 105.2 (CH), 105.0 (CH), 104.7 (CH) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1723, 1701, 1667, 1620, 1593, 1512, 1435, 1349, 1325, 1122 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{15}H_{10}OF_2 + H^+$ $[M + H]^+$ 245.0778; found 245.0785.

Compound 9f: Yield 0.44 g (72 %, over two steps); yellowish viscous liquid; R_f = 0.27 (EtOAc/hexanes, 0.5:0.95); mixture of geometrical isomers (ca. 1.5:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.54 (t, *J* = 8.4 Hz, major and minor C*H*O), 7.51–7.38 (m, 5 H, Ar*H*), 7.35–7.27 (m, 3 H, Ar*H*), 6.97–6.92 (m, 1 H, Ar*H*), 6.90–6.84 (m, 4 H, Ar*H*), 6.61 (d, *J* = 8.0 Hz, 1 H, major =C*H*), 6.54 (d, *J* = 8.0 Hz, minor =C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0 (C*H*O), 192.4 (C*H*O), 164.4, 164.2, 164.1, 161.9, 161.7, 161.6, 159.2, 139.9, 138.4, 135.5, 131.1, 130.7, 130.0, 129.0, 128.8, 128.5, 128.4, 127.9, 113.9, 113.8, 113.77, 113.70, 111.79, 111.72, 111.6, 111.5, 105.9, 105.7, 105.4, 105.2, 105.0, 104.7 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2851, 1669, 1620, 1590, 1434, 1390, 1354, 1122, 991, 928, 880, 855, 668 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{15}H_{10}OF_2 + H^+$ $[M + H]^+$ 245.0778; found 245.0784.

Compound 9g: Yield 0.1 g (88 %, over two steps); viscous yellow liquid; R_f = 0.32 (EtOAc/hexanes, 0.5:0.95); mixture of geometrical isomer (ca. 1.2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.46 (d, *J* = 8.0 Hz, minor C*H*O), 9.42 (d, *J* = 8.0 Hz, major 1 H, C*H*O), 7.40–7.31 (m, 4 H, Ar*H*), 7.29–7.28 (m, 3 H, Ar*H*), 7.23–7.21 (m, 2 H, Ar*H*), 7.18–7.16 (m, 4 H, Ar*H*), 7.12–7.09 (m, 4 H, Ar*H*), 6.51 (d, *J* = 8.0 Hz, 1 H, major = C*H*), 6.48 (d, *J* = 8.0 Hz, minor =C*H*), 2.35 (s, minor $ArCH_3$), 2.30 (s, major 3 H, $ArCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7 (C*H*O), 162.6 (*C*), 162.4 (*C*), 141.2 (*C*), 140.1 (*C*), 139.8 (*C*), 136.9 (*C*), 133.9 (*C*), 130.9 (CH), 130.8 (CH), 130.5 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 127.2 (CH), 126.6 (CH), 21.5 ($ArCH_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3046, 3005, 1659, 1590, 1575, 1509, 1452, 1445, 1388, 1342, 1248, 1240 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{16}H_{14}O + H^+$ $[M + H]^+$ 223.1123; found 223.1128.

Compound 9j: Yield 0.264 g (42 %, over two steps); yellow solid; m.p. 124–126 °C; R_f = 0.58 (EtOAc/hexanes, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.55 (d, *J* = 7.8 Hz, 1 H, C*H*O), 6.61 (s, 2 H, Ar*H*), 6.53 (s, 2 H, Ar*H*), 6.52 (d, *J* = 8.2 Hz, 1 H, =C*H*), 3.93 (s, 3 H, $ArOCH_3$), 3.90 (s, 3 H, $ArOCH_3$), 3.84 (s, 6 H, $2 \times ArOCH_3$), 3.81 (s, 6 H, $2 \times ArOCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.5 (CHO), 162.1 (*C*), 153.3 (*C*), 153.1 (*C*), 140.6 (*C*), 139.3 (*C*), 134.8 (*C*), 132.0 (*C*), 126.8 (*C*), 108.4 (CH), 106.4 (CH), 61.2 ($ArOCH_3$), 61.1 ($ArOCH_3$), 56.4 ($ArOCH_3$), 56.4 ($ArOCH_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2966, 2939, 2840, 1655, 1580, 1505, 1463, 1431, 1414, 1360, 1327, 1239, 1186, 1169, 1129 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{21}H_{24}O_7 + H^+$ $[M + H]^+$ 389.1600; found 389.1581.

General Procedure for Synthesis of 3,3-Diarylacrylic Acid 8: Oxidation of acroleins **9** were performed by using a reported procedure[14] with some modifications. Compound **9m** (0.50 g, 2.05 mmol) was dissolved in dimethyl sulfoxide (15 mL) and aq. $NaH_2PO_4 \cdot 2H_2O$ (0.1 mL, 80 mg, 0.51 mmol) was added, followed by aq. $NaClO_2$ (3.6 mL, 0.45 g, 4.93 mmol) slowly over a period of 3 h and the mixture was stirred for 6 h at room temp. After complete consumption of starting material as revealed by TLC, the reaction medium was acidified with aq. 20 % HCl to pH ca. 2–3 and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were collected, dried with anhydrous Na_2SO_4, concentrated and purified by silica-gel column chromatography (EtOAc/hexanes, 6:4) to give **8m**, yield 0.47 g (88 %); colourless crystalline solid;[5b] R_f = 0.28 (EtOAc/hexanes, 2:8). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 2 H, Ar*H*), 7.11–7.07 (m, 2 H, Ar*H*), 7.00–6.92 (m, 4 H, Ar*H*), 6.16 (s, 1 H, =C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (*C*OOH), 165.2 (*C*), 164.3 (*C*), 162.7 (*C*), 161.8 (*C*), 157.2 (*C*), 136.9 (*C*), 136.8 (*C*), 134.16 (*C*), 134.13 (*C*), 131.38 (*C*H), 131.30 (*C*H), 130.6 (*C*H), 130.5 (*C*H), 116.4 (*C*H), 115.8 (*C*H), 115.6 (*C*H), 115.3 (*C*H), 115.1 (*C*H) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2926, 2854, 1701, 1671, 1602, 1526, 1447, 1379, 1326, 1280, 1182, 1140 cm^{-1}.

General Procedure for the Preparation of 3,3-Diarylpropanoic Acid 7: To a solution of **8a** (0.74 g, 3.32 mmol) in ethyl acetate (15 mL), 10 % Pd/C (0.18 g, 0.16 mmol), was added and the mixture was stirred at room temp. under a H_2 balloon (for compound **8i**, **8j** and **8k**, a H_2 pressure of 50–60 psi was required for up to 6–8 h) and within 3–4 h the reaction was complete. The reaction mixture was filtered through Celite, washed with EtOAc (3 × 3 mL) and concentrated under reduced pressure to afford **7a**, which was pure enough to be carried forward without any further purification for the next step, yield 0.71 g (94 %); colourless solid;[18] m.p. 140–142 °C; R_f = 0.3 (EtOAc/hexanes, 2:8). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.15 (m, 5 H, Ar*H*), 7.13–7.09 (m, 5 H, Ar*H*), 4.44 (t, *J* = 8.0 Hz, 1 H, $CHCH_2$), 3.00 (d, *J* = 8.0 Hz, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4 (*C*OOH), 143.3 (Ar*C*), 128.7 (Ar*C*H), 127.7 (Ar*C*H), 126.7 (Ar*C*H), 46.7 (*C*H), 40.4 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3064, 1711, 1494, 1450, 1420, 928, 702 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{15}H_{14}O_2 + Na^+$ $[M + Na]^+$ 249.0891; found 249.0898.

General Procedure for the Synthesis of 3-Aryl Indanones

Procedure (A): Cyclisation with Polyphosphoric Acid (PPA): Compound **7a** (0.17 g) was heated with PPA to 90 °C and, after 18–20 h, the progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with ice cold satd. aq. $NaHCO_3$ and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated and purified over silica-gel column chromatography to afford **10a**, yield 0.132 g (82 %); colourless solid;[19] m.p. 64–68 °C; R_f = 0.68 (EtOAc/hexanes, 2:8). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.58–7.54 (m, 1 H, Ar*H*), 7.42–7.39 (m, 1 H, Ar*H*), 7.32–7.21 (m, 4 H, Ar*H*), 7.13–7.11 (m, 2 H, Ar*H*), 4.57 (dd, *J* = 8.0, 4.0 Hz, 1 H, $CHCH_2$), 3.22 (dd, *J* = 19.2, 8.4 Hz, 1 H, CH_aH_bCO), 2.68 (dd, *J* = 19.2, 3.6 Hz, 1 H, CH_aH_bCO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.0 (*C*O), 158.0 (Ar*C*), 143.7 (Ar*C*), 136.8 (Ar*C*), 129.0

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(ArCH), 127.9 (ArCH), 127.7 (ArCH), 126.9 (ArCH), 123.5 (ArCH), 46.9 (CH_2CO), 44.5 ($CHCH_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3064, 2924, 1713, 1602, 1494, 1463, 1454, 1405, 1317, 1289, 1264, 1235, 1092 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{15}H_{12}O + H^+$ $[M + H]^+$ 209.0966; found 209.0977.

Procedure (B): Cyclisation with Eaton's reagent: Eaton's reagent was formed by using the reported procedure.[15] Compound **7k** (0.05 g, 0.15 mmol) was dissolved in Eaton's reagent (ca. 2 mL) and heated to 85–90 °C. After 7–8 h the progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with water and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with 10 % aq. $NaHCO_3$ (3 mL) and the organic layer was dried with anhydrous Na_2SO_4, concentrated and purified over silica-gel column chromatography (EtOAc/hexanes, 2:8) to afford **10k**, yield 33 mg (70 %); yellowish gummy solid; R_f = 0.68 (EtOAc/hexanes, 2:8). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.96–6.94 (m, 2 H, Ar*H*), 6.32 (s, 1 H, Ar*H*), 4.30 (dd, *J* = 8.4, 4.0 Hz, 1 H, C*H*CH_2), 4.01 (s, 3 H, ArOCH_3), 3.78 (s, 3 H, ArOCH_3), 3.72 (s, 3 H, ArOCH_3), 3.07 (dd, *J* = 18.8, 8.4 Hz, 1 H, C$H_a$$H_b$CO), 2.53 (dd, *J* = 18.8, 4.0 Hz, 1 H, CH$_a$$H_b$CO), 2.26 (s, 3 H, ArC$H_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.1 (*C*O), 160.0 (Ar*C*), 156.2 (Ar*C*), 151.1 (Ar*C*), 141.0 (Ar*C*), 140.7 (Ar*C*), 136.7 (Ar*C*), 129.6 (Ar*C*H), 127.5 (Ar*C*H), 122.8 (Ar*C*), 103.9 (Ar*C*H), 62.1 (ArO*C*H_3), 61.4 (ArO*C*H_3), 56.4 (ArO*C*H_3), 47.9 (CH_2CO), 43.9 ($CHCH_2$), 21.1 (Ar*C*H_3) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2968, 2939, 1697, 1590, 1512, 1481, 1467, 1460, 1431, 1415, 1337, 1314, 1257, 1445, 1091 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{19}H_{20}O_4 + H^+$ $[M + H]^+$ 313.1440; found 313.1449.

Compound 6: Yield 56 mg (56 %); yellow solid; m.p. 100–102 °C; R_f = 0.65 (EtOAc/hexanes, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.42 (s, 1 H, Ar*H*), 6.30 (s, 2 H, Ar*H*), 4.48 (dd, *J* = 8.0, 4.0 Hz, 1 H, C*H*CH_2), 4.08 (s, 3 H, ArOCH_3), 3.85 (s, 3 H, ArOCH_3), 3.82 (s, 6 H, 2 × ArOCH_3), 3.79 (s, 6 H, 2 × ArOCH_3), 3.13 (dd, *J* = 18.8, 8.0 Hz, 1 H, C$H_a$$H_b$CO), 2.62 (dd, *J* = 18.8, 4.0 Hz, 1 H, CH$_a$$H_b$CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9 (*C*O), 160.1 (Ar*C*), 155.7 (Ar*C*), 153.6 (Ar*C*), 151.1 (Ar*C*), 141.1 (Ar*C*), 139.4 (Ar*C*), 136.9 (Ar*C*), 122.8 (Ar*C*), 104.6 (2 × Ar*C*H), 103.8 (Ar*C*H), 62.0 (ArO*C*H_3), 61.4 (ArO*C*H_3), 60.9 (ArO*C*H_3), 56.4 (ArO*C*H_3), 56.3 (2 × ArO*C*H_3), 47.7 (CH_2CO), 44.6 ($CHCH_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2927, 2855, 1698, 1590, 1508, 1481, 1463, 1418, 1337, 1259, 1144, 1130, 1092, 1008 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{21}H_{24}O_7 + H^+$ $[M + H]^+$ 389.1600; found 389.1584.

Procedure (C): Cyclisation with $ClSO_3H$: To a solution of **7c** (0.34 g, 1.14 mmol) in anhydrous dichloromethane (10 mL), $ClSO_3H$ (1.6 mL 17.1 mmol) was added at 0 °C under an inert atmosphere and the mixture was stirred at room temp. for up to 3 h. The progress of the reaction was monitored by TLC, upon complete consumption of starting material, the reaction mixture was poured onto ice water and the aqueous layer was extracted with dichloromethane (3 × 10 mL). Combined organic layers were washed with saturated aq. $NaHCO_3$, dried with anhydrous Na_2SO_4, concentrated and purified by silica-gel column chromatography (EtOAc/hexanes, 0.5:9.5) to afford **10c**, yield 0.26 g (80 %); colourless solid;[6e] m.p. 106–108 °C; R_f = 0.68 (EtOAc/hexanes, 2:8). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.62–7.59 (m, 1 H, Ar*H*), 7.45 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 7.38 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.26 (t, *J* = 3.0 Hz, 1 H, Ar*H*), 7.22 (d, *J* = 2.5 Hz, 1 H, Ar*H*), 6.95 (dd, *J* = 8.5, 2.0 Hz, 1 H, Ar*H*), 4.54 (dd, *J* = 8.0, 3.5 Hz, 1 H, C*H*CH_2), 3.23 (dd, *J* = 19.5, 8.5 Hz, 1 H, C$H_a$$H_b$CO), 2.62 (dd, *J* = 19.0, 4.0 Hz, 1 H, CH$_a$$H_b$CO) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.0 (*C*O), 156.6 (Ar*C*), 144.0 (Ar*C*), 136.8 (Ar*C*), 135.5 (Ar*C*H), 133.0 (Ar*C*), 131.2 (Ar*C*), 131.0 (Ar*C*H), 129.7 (Ar*C*H), 128.5 (Ar*C*H), 127.1 (Ar*C*H), 126.8 (Ar*C*H), 123.8 (Ar*C*H), 46.6 (CH_2CO), 43.7 ($CHCH_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2920, 1712, 1602, 1560, 1469, 1395, 1321, 1285, 1273, 1132, 1092, 1032, 934 cm^{-1}. $C_{15}H_{10}Cl_2O$ (277.15): calcd. C 65.01, H 3.64; found C 65.54, H 3.09.

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[1] a) Y. Slutskyy, W. T. Jewella, C. G. Lucerob, *Tetrahedron Lett.* **2013**, *54*, 210–212; b) G. Chen, H. Xia, Y. Cai, D. Ma, J. Yuan, C. Yuan, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 234–239; c) H.-T. Liu, L.-J. Xu, Y. Peng, X. W. Yang, P.-G. Xiao, *Chem. Pharm. Bull.* **2009**, *57*, 405–407; d) C. Tsutsui, Y. Yamada, M. Ando, D. Toyama, J.-I. Wu, L. Wang, S. Taketani, T. Kataoka, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4084–4087; e) S. Liang, Y.-H. Shen, J.-M. Tian, Z.-J. Wu, H.-Z. Jin, W.-D. Zhang, S.-K. Yan, *J. Nat. Prod.* **2008**, *71*, 1902–1905; f) X.-M. Gao, J.-X. Pu, S.-X. Huang, L.-M. Yang, H. Huang, W.-L. Xiao, Y.-T. Zheng, H.-D. Sun, *J. Nat. Prod.* **2008**, *71*, 558–563; g) S. Xu, N. Li, M.-M. Ning, C.-H. Zhou, Q.-R. Yang, M.-W. Wang, *J. Nat. Prod.* **2006**, *69*, 247–250.

[2] a) N. A. Paras, B. Simmons, D. W. C. MacMillan, *Tetrahedron* **2009**, *65*, 3232–3238; b) F. Ulgheri, M. Marchetti, O. Piccolo, *J. Org. Chem.* **2007**, *72*, 6056–6059; c) M. Gordaliza, M. A. Castro, J. M. Miguel Del Corral, A. San Feliciano, *Curr. Pharm. Des.* **2000**, *6*, 1811–1839.

[3] H. O. Saxena, U. Faridi, S. Srivastava, J. K. Kumar, M. P. Darokar, S. Luqman, C. S. Chanotiya, V. Krishna, A. S. Negi, S. P. S. Khanuja, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3914–3918.

[4] For an isolated synthesis of this compound, see: J. G. Taylor, R. d. S. Ribeiro, C. R. D. Correia, *Tetrahedron Lett.* **2011**, *52*, 3861–3864.

[5] a) Y. Li, K. Dong, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 6748–6752; *Angew. Chem.* **2013**, *125*, 6880; b) P. Ghorai, A. Kraus, M. Keller, C. Gotte, P. Igel, E. Schneider, D. Schnell, G. Bernhardt, S. Dove, M. Zabel, S. Elz, R. Seifert, A. Buschauer, *J. Med. Chem.* **2008**, *51*, 7193–7204.

[6] a) P. Prediger, A. R. da Silva, C. R. D. Correia, *Tetrahedron* **2014**, *70*, 3333–3341; b) J. C. Pastre, C. R. D. Correia, *Adv. Synth. Catal.* **2009**, *351*, 1217–1223; c) K. Yoo, H. Kim, J. Yun, *Chem. Eur. J.* **2009**, *15*, 11134–11138; d) F. Song, S. Lu, J. Gunnet, J. Z. Xu, P. Wines, J. Proost, Y. Liang, C. Baumann, J. Lenhard, W. V. Murray, K. T. Demarest, G.-H. Kuo, *J. Med. Chem.* **2007**, *50*, 2807–2817; e) M. Froimowitz, K.-M. Wu, A. Moussa, R. M. Haidar, J. Jurayj, C. George, E. L. Gardner, *J. Med. Chem.* **2000**, *43*, 4981–4992; f) K. P. Boegesoe, *J. Med. Chem.* **1983**, *26*, 935–947.

[7] a) O. Saku, H. Ishida, E. Atsumi, Y. Sugimoto, H. Kodaira, Y. Kato, S. Shirakura, Y. Nakasato, *J. Med. Chem.* **2012**, *55*, 3436–3451; b) R. W. Guthrie, G. L. Kaplan, F. A. Mennona, J. W. Tilley, R. W. Kierstead, J. G. Mullin, R. A. LeMahieu, S. Zawoiski, M. O'Donnell, H. Crowley, B. Yaremko, A. F. Weltont, *J. Med. Chem.* **1989**, *32*, 1820–1835.

[8] a) H. Zheng, M. Lejkowski, D. G. Hall, *Chem. Sci.* **2011**, *2*, 1305–1310; b) J. Garcia-Alvarez, J. Diez, J. Gimeno, C. M. Seifried, *Chem. Commun.* **2011**, *47*, 6470–6472; c) V. Cadierno, J. Francos, J. Gimeno, *Tetrahedron Lett.* **2009**, *50*, 4773–4776; d) N. Marion, P. Carlqvist, R. Gealageas, P. de Frémont. , F. Maseras, S. P. Nolan, *Chem. Eur. J.* **2007**, *13*, 6437–6451.

[9] a) M. R. Smith, J. Y. Kim, M. A. Ciufolini, *Tetrahedron Lett.* **2013**, *54*, 2042–2045; b) M. R. Smith, Y. J. Jang, J. Y. Kim, M. A. Ciufolini, *Tetrahedron* **2013**, *69*, 10139–10151; c) E. Mieczynska, A. Gniewek, I. Pryjomska-Ray, A. M. Trzeciak, H. Grabowska, M. Zawadzki, *Appl. Catal. A* **2011**, *393*, 195–205; d) C. Ebner, A. Pfaltz, *Tetrahedron* **2011**, *67*, 10287–10290.

[10] A. Nudelman, F. Braun, E. Karoly, *J. Org. Chem.* **1978**, *43*, 3788–3789.

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[11] a) P. Bharathi, M. Periasamy, *Org. Lett.* **1999**, *1*, 857–859; b) M. Bellassoued, A. Majidi, *J. Org. Chem.* **1993**, *58*, 2517–2522.
[12] For papers highlighting the importance and synthesis of 3-aryl-indanones, see: a) S. H. Lee, S. J. Park, I. S. Kim, Y. H. Jung, *Tetrahedron* **2013**, *69*, 1877–1880; b) J. G. Taylor, C. R. D. Correia, *J. Org. Chem.* **2011**, *76*, 857–869; c) H. M. L. Davies, T. M. Gregg, *Tetrahedron Lett.* **2002**, *43*, 4951–4953.
[13] For reviews on the applications of Weinreb amides, see: a) S. Balasubramaniam, I. S. Aidhen, *Synthesis* **2008**, 3707–3738; b) J. Singh, N. Satyamurthi, I. S. Aidhen, *J. Prakt. Chem.* **2000**, *342*, 340–347; c) M. Mentzel, H. M. R. Hoffmann, *J. Prakt. Chem.* **1997**, *339*, 517–524.
[14] E. Dalcanale, M. Fernando, *J. Org. Chem.* **1986**, *51*, 567–569.
[15] A. K. Sharma, A. V. Subramani, C. B. Gorman, *Tetrahedron* **2007**, *63*, 389–395.
[16] P. E. Eaton, G. R. Carlson, J. T. Lee, *J. Org. Chem.* **1973**, *38*, 4071–4073.
[17] A. L. Gottumukkala, J. F. Teichert, D. Heijnen, N. Eisink, S. Dijk, C. Ferrer, A. Hoogenband, A. J. Minnaard, *J. Org. Chem.* **2011**, *76*, 3498–3501.
[18] M. P. Cooke Jr., *J. Org. Chem.* **1987**, *52*, 5729–5733.
[19] S. Chassaing, M. Kumarraja, P. Pale, J. Sommer, *Org. Lett.* **2007**, *9*, 3889–3892.

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