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PAPER

Stereoselective synthesis of hydroxy stilbenoids and styrenes by atom-efficient olefination with thiophthalides†

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The synthesis of stilbenoids and styryl carboxylic acids is accomplished with high *E*-stereoselectivity by olefination of aldehydes with thiophthalides under basic conditions. The olefination is highly atom-efficient as it only loses elemental sulfur during the reaction. This olefination, in conjunction with retro Kolbe–Schmitt reaction, allows facile synthesis of *E*-hydroxystilbenoids with minimal employment of protecting groups. This study also discloses two important findings: formation of i) 4-methylsulfanyl isocoumarins and ii) an 2-arylindenone.

Introduction

Hydroxystilbenes and stilbenoids are a well-known class of natural products, and occur in a wide variety of structures.[1] Many members of this class display beneficial biological activities. The activities encompass therapeutic potential in cancers,[2] cardiovascular diseases,[3] viral infections,[4] diabetes,[5] Alzheimer's disease,[6] dementia[7] and also radical scavenging activity.[8] Hydroxystilbenoids, resveratrol[9] (Res **1**) (Fig. 1), piceatannol[10] (**2**) and oxyresveratrol[11] (**3**) have gained prominence as synthetic targets due to their remarkable physiological activities. The stilbenoids and styryl acids are also found as structural motifs in many other important bioactive natural products (Fig. 1) namely, pyriculol[12] (*e.g.* **4**), resorcyclic acid lactones[13] (RALs, *e.g.* **5**), hydroxy flavonoids,[14] chromones,[15] and varitriols[16] (*e.g.* **6**). *Trans*-stilbenoids also form the backbones of organic probes[17] for cation sensing, photovoltaic solar cells,[18] light emitting diodes[19] (LEDs), organogels[20] and recognition probes[21] of disaccharides. Additionally, they serve as the precursors for 3,4-dihydroisocoumarins,[22] substituted phthalides[23] and oligoresveratrols.[24]

Commercially, Res (**1**) is produced from the roots of *Polygonum cuspidatum*, a Chinese plant used in folk medicine. Nevertheless, the large scale production from the natural sources is not viable due to low yield.[25] Consequently, the synthesis of stilbenoids has generated a great deal of interest among researchers and a large number of synthetic methods are reported in the literature. Traditionally, the strategies rely upon i) Wittig[26] ii) Horner–Wadsworth–Emmons[27] (HWE) iii) Heck[28] iv) Ramberg–Bäcklund[29] v) Julia[30] vi) Wittig–Heck[31] and vii) Perkin[32] reactions *etc.* The majority of them suffer from low *E*-stereoselectivity and atom economy. High *E*-stereoselectivity can be achieved by the use of olefin cross metathesis[33] reaction but formation of the homoproducts is a serious impediment. The application of the Wittig, HWE or Heck reaction necessitates protection of the active hydrogens throughout a synthesis. Phenolic groups are almost always protected, because of their susceptibility to oxidation.[34] These issues have been recently addressed by the McNulty group[35] and the Wittig reaction has been modified to render it more adaptable for the hydroxystilbenoids.

However, efficient and *trans*-selective olefinations remain to be innovated. This necessity prompted us to initiate a thorough reinvestigation of our preliminary report on an uncommon olefination.[36] Toluates (*e.g.* **7** Scheme 1), which can be converted readily to thiophthalides[37] (*e.g.* **8**) in two steps, were found to react with aromatic and aliphatic aldehydes **9** to give *trans*-stilbenoids and styryl acids **11** respectively. The reaction was proposed

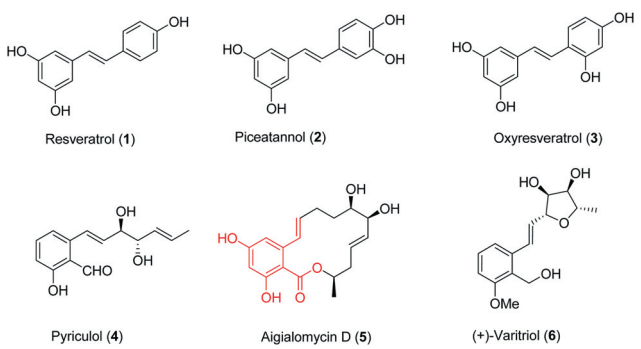

Fig. 1 Stilbenoids and styryl acids decorated natural products.

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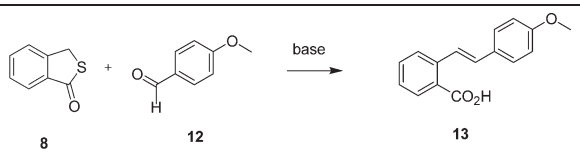
†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C spectra of synthesized compounds. CCDC 855857 and 855858. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/c2ob06991a

Scheme 1 Mechanism of the olefination with thiophthalides.[36]

Table 1 Base screening studies in the olefination with aromatic aldehydes



Entry	Substrates	Base (2 equiv)–solvent	Product[a]	% yield
1	**8** and **12**	LTB–THF	(*E*)-**13**	75
2	**8** and **12**	KTB–THF	(*E*)-**13**	58
3	**8** and **12**	NaH–DMF	(*E*)-**13**	45
4	**8** and **12**	LDA–THF	(*E*)-**13**	92
5	**8** and **12**	LiHMDS–THF	(*E*)-**13**	46
6	**8** and **12**	KHMDS–THF	(*E*)-**13**	10
7	**8** and **12**	$NaNH_2$–THF	(*E*)-**13**	72

[a] The *Z*-isomers could be not detected.

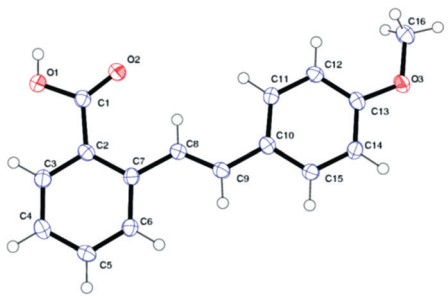


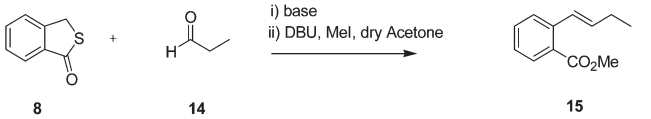
Fig. 2 ORTEP view of the acid **13**.

to proceed through the formation of episulfide intermediates **10** followed by *in situ* extrusion of elemental sulfur. But the promise of the olefination as a synthetic method was seriously impeded by low yields (30–55%). In this article, we report significant improvement of the yields by appropriate choice of bases, and demonstrate the scope and usefulness of the olefination in conjunction with retro Kolbe–Schmitt reaction in the synthesis of natural stilbenoids.

Results and discussion

This work began with optimization study of the reaction of parent thiophthalide **8** with *p*-anisaldehyde **12**. The results are summarized in Table 1. The structure of product **13** was confirmed by X-ray structure analysis (Fig. 2). As revealed, LDA appeared to be the most effective base, giving the product **13** in 92% yield, remarkably better than our earlier report[36] on similar reactions. The outcome with $NaNH_2$, which is cheaper than the lithium bases, is also encouraging. It is also noteworthy

Table 2 Base screening studies on olefination with aliphatic aldehydes



Entry	Substrates	Base (2 equiv)–solvent	Product[b]	% yield[a]
1	**8** and **14**	LTB –THF	(*E*)-**15**	45[c]
2	**8** and **14**	KTB–THF	(*E*)-**15**	35
3	**8** and **14**	NaH–DMF	(*E*)-**15**	Intractable
4	**8** and **14**	LDA–THF	(*E*)-**15**	10
5	**8** and **14**	LiHMDS–THF	(*E*)-**15**	Intractable
6	**8** and **14**	KHMDS–THF	(*E*)-**15**	Intractable
7	**8** and **14**	$NaNH_2$–THF	(*E*)-**15**	22

[a] The yields refer to that over two steps: olefination and methyl esterification. [b] The *Z*-isomers could not be detected. [c] The reaction product was accompanied by 26% of isocoumarin **16**.

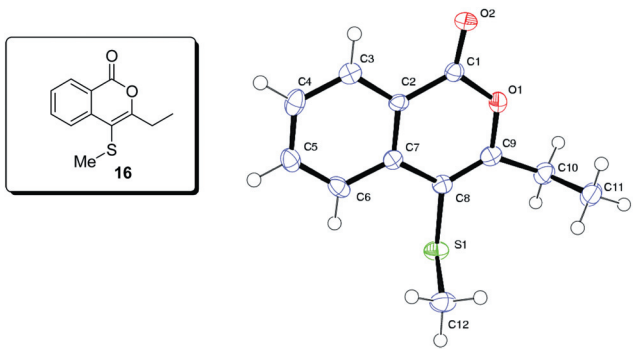


Fig. 3 Structure and ORTEP view of isocoumarin **16**.

that the olefination is highly stereoselective and furnished only the *E*-isomer **13**. The screening study (Table 2) of the bases was carried out with propionaldehyde **14** as a model aliphatic aldehyde. Due to the difficulty in purification of the resulting acid, the reaction mixture was treated with DBU–CH_3I[38] and the corresponding methyl ester was isolated and characterized. The yield of the product **15** was not significant, the highest being observed with lithium *tert*-butoxide (LTB). It may be noted that under Julia olefination conditions compound **15** is formed as an inseparable 1 : 1 mixture of *E* and *Z* isomers.[39a] Evidently, the efficiency of the olefination with propionaldehyde is inferior to that with aromatic aldehydes under similar conditions.

This is partly because of an interesting yet competing and unprecedented side reaction leading to the isocoumarin **16** (Fig. 3), the structure of which was confirmed by the X-ray crystallographic analysis.

Following the optimization studies, we explored the scope of the olefination for selected aliphatic, aromatic aldehydes and ketones as shown in Table 3. With butyraldehyde **17** (Table 3), the yield of the olefination product **18** was slightly higher. The corresponding isocoumarin product (*cf.* **16**) was not formed. The reaction of citronellal **19**, furnished two products, the desired styryl ester **20** and isocoumarin **21** in significant yields. As a model study on the synthesis of varitriol (**6**), ribosyl aldehyde **22**,[39b] prepared in four steps from D-glucose was condensed

Table 3 Substrate scope of the olefination with thiophthalides

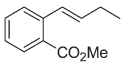
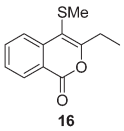
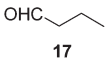
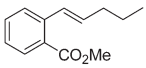
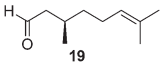
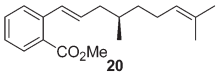
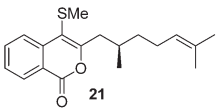
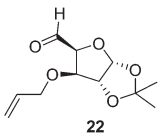
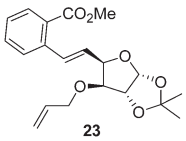
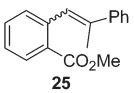
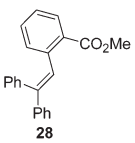
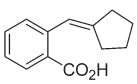
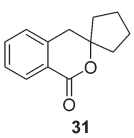
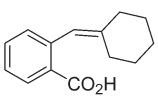
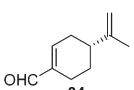
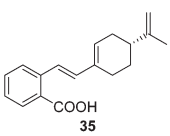
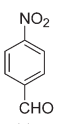
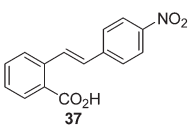
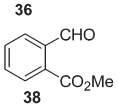
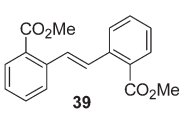
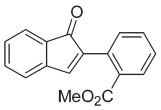
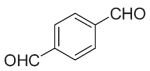
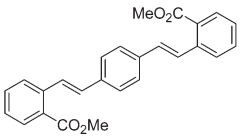
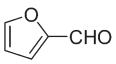
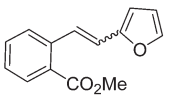
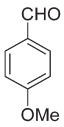
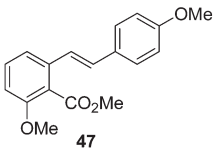
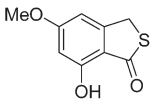
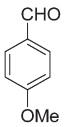
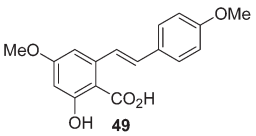
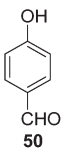
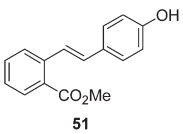
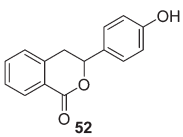
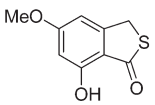
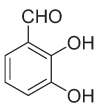
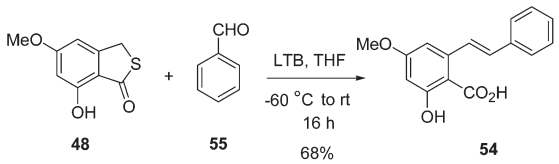
Entry	Donor	Acceptor[a]	Product	% yield
1	**8**	 **14**	 **15**	45[b]
			 **16**	26[b]
2	**8**	 **17**	 **18**	56[b]
3	**8**	 **19**	 **20**	35[b]
			 **21**	29[b]
4	**8**	 **22**	 **23**	73[b]
5	**8**	 **24**	 **25**	68[b]
6	**8**	 **27**	 **28**	72[b]
7	**8**	 **29**	 **30**	62[b]
			 **31**	62[b]
8	**8**	 **33**	 **32**	38[b]
9	**8**	 **34**	 **35**	71[b]
10	**8**	 **36**	 **37**	67[c]
11	**8**	 **38**	 **39**	25[c]

Table 3 *(Contd.)*

Entry	Donor	Acceptor[a]	Product	% yield
	8		 **40**	52[c]
12	**8**	 **41**	 **42**	73[c]
13	**8**	 **43**	 **44**	67[b]
14	 **45**	 **46**	 **47**	65[c]
15	 **48**	 **46**	 **49**	68[d]
16	**8**	 **50**	 **51**	35[d]
			 **52**	42[d]
17	 **48**	 **53**		Intractable

[a] Unless otherwise stated, all the reactions were carried out using 1.2 equiv of acceptor. [b] Two equiv of LTB were used. [c] Two equiv of LDA were used. [d] Four equiv of LTB were used.

with thiophthalide **8** in the presence of LTB. The outcome was sugar appended styryl ester **23**. The reaction of acetophenone **24** with thiophthalide **8** under the specified reaction conditions gave a mixture of products, from which the desired stilbenoids **25** were obtained in 68% yield as an inseparable mixture of the two geometrical isomers as indicated by the ^{1}H NMR spectrum. Since the reaction mixture was contaminated with a small amount of the episulfides **26** (*vide* Scheme 5), a modified set of reaction conditions was employed for the olefination of benzophenone **27**. In the case of benzophenone **27**, the reaction mixture was refluxed with trimethyl phosphite[40] in toluene for desulfurization of the episulfide intermediate prior to esterification (DBU–MeI in acetone) and the corresponding styryl ester **28** was obtained in 72% yield. Similar reaction with cyclopentanone **29** afforded corresponding styryl acid **30** in 62% yield (Table 3). Since it was susceptible to lactonization on standing, it was only characterized by its NMR spectral data. Instead, the dihydroisocoumarin derivative **31** was fully characterized by analyzing NMR spectral and HRMS data. In contrast, the styryl acid **32**, obtained by condensation of thiophthalide **8** with cyclohexanone **33**, could be isolated and characterized as it was. In order to delineate the reactivity of an α,β-unsaturated aldehyde, perillaldehyde **34** was reacted with parent thiophthalide **8** in the presence of LTB. Olefination product **35** was the sole product and isolated in 71% yield. For the olefination of aromatic aldehydes, LDA was used since it appeared to give higher yields of



Scheme 2 Synthesis of 3-hydroxy-5-methoxystilbene-2-carboxylic acid **54**.

the products (Table 1). The reaction of *p*-nitrobenzaldehyde **36** with thiophthalide **8** expectedly provided styryl acid **37** as the single isomer in 67% yield. With methyl 2-formylbenzoate **38**, the reaction of the thiophthalide **8** was somewhat unexpected. 2-Arylindenone **40** was unusually formed as the major product (52% yield) along with the expected diester **39** (25% yield). The speculative mechanism for the formation of 2-arylindenone **40** is depicted in Scheme 7. In order to test the feasibility of double olefination, terephthaldehyde **41** was reacted with the parent thiophthalide **8** in the similar manner as before. The expected diolefination product **42** was obtained as the only product in 73% yield. The reaction of furfural **43** in the presence of LTB was not stereoselective. It provided an inseparable mixture of geometrical isomers **44** (combined yield of 67%). In addition, a substantial amount of 2-furoic acid was obtained.

In view of the wide occurrence of phenolic–OH groups in natural stilbenoids, the reactivity of methoxy substituted thiophthalide **45** was examined. Its reaction with *p*-methoxybenzaldehyde **46** smoothly furnished styryl ester **47** in 65% yield. To develop the potential of this method as a protecting-group-free[41] olefination technique, OH-unprotected thiophthalide[42] **48** was reacted with *p*-anisaldehyde **46** (Table 3) in the presence of LTB as base and the corresponding hydroxystilbenoid **49** obtained in 68% yield. In the similar vein, OH-unprotected aldehyde *i.e.* *p*-hydroxybenzaldehyde **50** was also subjected to the olefination. The expected hydroxystilbenoid **51** was obtained in 35% yield along with the dihydroisocoumarin derivative **52** (42%), which probably formed during acidic work-up. In order to accomplish a protecting group free synthesis of pholidotol-*C*,[43] we attempted to condense thiophthalide **48** with 2,3-dihydroxybenzaldehyde **53**. However, no definitive product formed with either LTB or LDA.

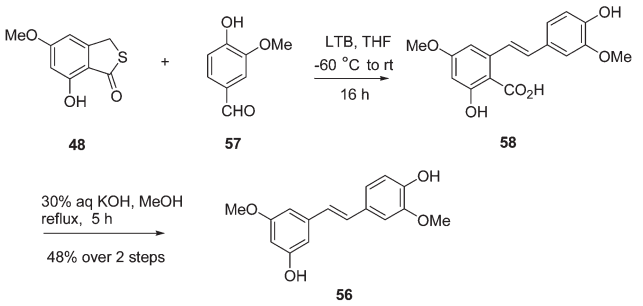
Synthesis of 3-hydroxy-5-methoxystilbene-2-carboxylic acid (54)

Hydroxystilbenoid **54**[44] was isolated from methanolic extracts of pigeonpea (*Cajanus cajan Millsp.*) leaves and it was shown to inhibit lettuce radicle elongation.

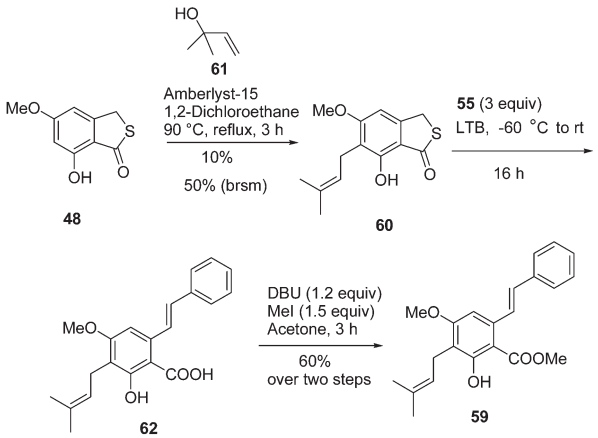
For the synthesis of stilbene acid **54**, hydroxythiophthalide **48** was submitted to reaction with benzaldehyde **55** (4 equiv) under the conditions given in Scheme 2. The desired styryl acid **54** was produced in 68% yield. It is worth noting that protection of the phenolic-OH in **48** was not necessary.

Synthesis of 3′,4-dihydroxy-3,5′-dimethoxystilbene (56)

In extending the scope of the olefination, decarboxylation of stilbene acids was explored under retro-Kolbe–Schmitt conditions.[45] We decided to synthesize 3′,4-dihydroxy-3,5′-dimethoxystilbene **56**, isolated from the legume *Cassia didymobotrya*.[46] The reaction of thiophthalide **48** with vanillin **57** (Scheme 3) in the presence of LTB furnished styryl acid **58** along with unreacted starting materials **48** and **57**. After preliminary chromatography, the crude acid **58** was dissolved in minimum volume of methanol and refluxed with 30% aq KOH for 5 h to effect the retro Kolbe–Schmitt reaction. The hydroxystilbene **56** was obtained in 48% yield.



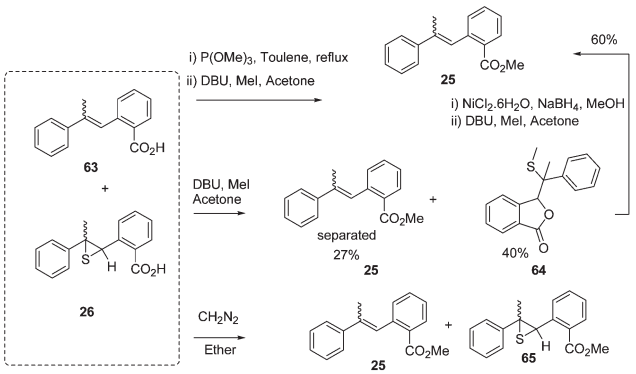
Scheme 3 Synthesis of 3′,4-dihydroxy-3,5′-dimethoxystilbene **56**.



Scheme 4 Synthesis of methyl ester of cajaninstilbene acid **59**.

Synthesis of methyl cajaninstilbene carboxylate (59)

Cajaninstilbene acid[47a] was isolated from the methanol extract of the pod surfaces of *Cajanus cajan* and reported to show strong antioxidant activity,[47b] equivalent to that of resveratrol. Retrosynthesis of **59** revealed the requirement of the prenylated thiophthalide **60**. We attempted its preparation by *ortho*-selective prenylation of 5-methoxy-7-hydroxythiophthalide **48** with 1,1-dimethylallyl alcohol **61** in 1,2-dichloroethane (Scheme 4) in presence of different Lewis acids. The results were not encouraging although prenylation[48] of β-naphthol are reported to proceed with excellent yields and regioselectivity. The Lewis acids $Sc(OTf)_3$, $SnCl_4{\cdot}5H_2O$, ZnI_2, $Cu(OTf)_2$ and Amberlyst-15 were chosen in line with a previous study.[48] All the reactions were carried out with 1 mmol of the thiophthalide **48**, 1.2 mmol of the alcohol **61** and 20 mol% of the catalyst. In the case of Amberlyst-15 under reflux, the conversion was maximum (20%).



Scheme 5 Trapping of episulfide **26**.

The starting thiophthalide was recovered and based on its recovery the yield of **60** was about 50%. Use of increased proportion of the alcohol, loading of the catalyst, heating the reaction mixture at 120 °C in a pressure tube or even heating the thiophthalide **48** in the neat alcohol **61** was of no avail in increasing the yield of the reaction. Reaction of the prenylated thiophthalide **60** with excess benzaldehyde **55** (3 equiv) in the presence of excess LTB (Scheme 4) resulted in the formation of the acid **62**. DBU promoted methylation of the crude acid **62** furnished methyl ester of cajaninstilbene acid **59** in good yield.

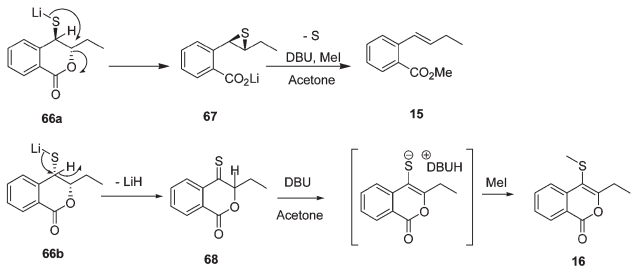
Mechanistic study

A) Trapping of episulfide 26

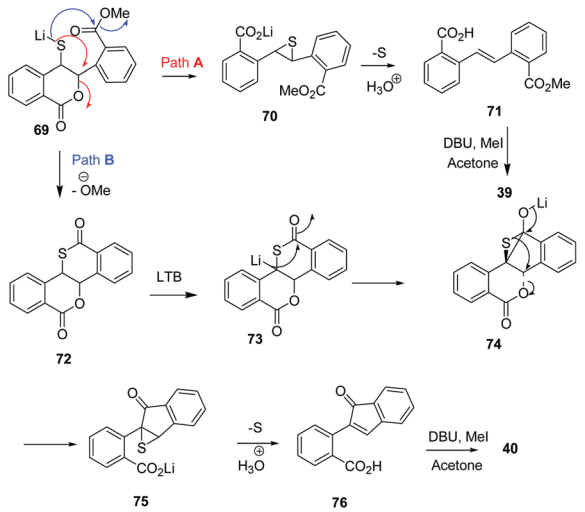
In order to provide an acceptable evidence for the proposed episulfide intermediate **26**, the reaction between thiophthalide **8** and acetophenone **24** was chosen (Table 3). The ^{1}H NMR study of the reaction mixture indicated the formation of both **63** and **26**. Two singlets[40] at δ 4.74 and 4.71 were diagnostic of the two isomers of the latter. Attempts for the isolation of **26** were without success. It is to be noted that isolable episulfides are rare in the literature. Refluxing the reaction mixture in toluene in the presence of trimethyl phosphite ensured sulfur extrusion. For derivatization, the mixture was submitted to methylation with DBU–CH_3I in acetone. Quite unexpectedly, the reaction furnished phthalide **64** (Scheme 5) in 40% yield, besides the ester **25** in 27% yield. Formation of **64** indirectly proved the formation of **26**. Treatment of **64** with $NiCl_2$–$NaBH_4$[49] followed by DBU–CH_3I in acetone afforded the ester **25** in 60% yield. Treatment of the mixture with diazomethane in ether furnished two inseparable esters **25** and **65**. Two singlets at δ 4.83 and 4.80 in the ^{1}H NMR spectrum indicated the presence of two thiirane esters (mixture of *cis* and *trans* isomer of **65**).

B) Formation of the isocoumarin co-products

The formation of isocoumarin **16** is unprecedented and tentatively formulated as in Scheme 6. It is proposed that both dihydroisocoumarins **66a** and **66b** are formed in appreciable amounts. The intermediate **66a**, in which S^- and lactone 'O' are *trans* to each other collapses to the desired **15** derivative *via* the episulfide intermediate **67**. The energy minimized structure



Scheme 6 Mechanism of formation of the isocoumarin **16**.



Scheme 7 Proposed mechanism for the formation of 2-arylindenone **40**.

(using ORCA software) of the *syn* analogue **66b** indicates that the dihedral angle between the S–C–C and C–C–O planes is about 55°, which is inadequate for intramolecular lactone ring opening to furnish the episulfide (*cf.* **10**). However, for the proposed elimination of LiH leading to **68**, the dihedral angle between Li–S–C and S–C–H of 180° is achievable by single bond rotation. Treatment with DBU–MeI in acetone results in the formation of isocoumarin derivative **16** (Scheme 6). The usual *anti* diastereomer **66a** possesses a dihedral angle of about 171° between the planes S–C–C and C–C–O. It suits intramolecular lactone opening resulting in the formation of the episulfide intermediate **67**.

C) Formation of 2-arylindenone 40

The intermediate **69** formed during the course of the reaction might have followed intramolecular cyclization path-A and path-B (Scheme 7). The thiirane intermediate **70** formed in path-A undergoes desulfurization to give styryl acid **71**, which after *O*-methylation furnishes the diester **39**. The path-B provides thiolactone **72** which undergoes LTB mediated lateral lithiation to result in lithio species **73**. This intermediate **73** then undergoes intramolecular nucleophilic rearrangement through **74** to give episulfide intermediate **75**. Sulfur extrusion from **75** followed by acidic work-up yields the acid **76**. This was characterized as its ester derivative **40**. The structure of this unusual **40** was established by analysis of NMR spectral data.

Conclusions

The olefination of aldehydes with thiophthalides for the synthesis of stilbenoids and styryl carboxylic acids is found to be highly stereoselective and atom-efficient. It is shown to proceed through episulfide intermediates followed by sulfur extrusion. Protection of labile phenolic hydroxyl groups could be avoided during some synthesis. The olefination is applied in the synthesis of three natural hydroxystilbenoids. This study also discloses that the carboxylic acid group *ortho* to the phenolic OH group undergoes retro Kolbe–Schmitt reaction. The unusual formations of isocoumarin and indenone could be further elaborated.

Experimental section

Typical olefination procedure with LTB (Method A)

A solution of thiophthalide (1 mmol) in dry THF (5 mL) was added to a suspension of LTB (2 mmol) in dry THF (10 mL) at −60 °C under an inert atmosphere. The resulting solution was stirred at −60 °C for 30 min after which a solution of an aldehyde or ketone (1.2 mmol) in dry THF (5 mL) was added to it. The cooling bath was removed after about 30 min at −60 °C and the reaction mixture was brought to room temperature and further stirred for 12–16 h. The reaction was then quenched with 6 N HCl and THF removed under reduced pressure. The residue was then extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na_2SO_4) and concentrated to provide the crude product. This was then purified by column chromatography on silica gel or by crystallization or by subjecting to methylation (DBU–CH_3I) followed by column chromatography on silica gel.

Typical olefination procedure with LDA (Method B)

LDA (2 mmol) was prepared by adding *n*-BuLi (2 mmol, 1.6 M in hexane) to a solution of diisopropylamine (2 mmol) in THF (10 mL) at −78 °C under an inert atmosphere. After 30 min at −78 °C, an appropriate thiophthalide (1 mmol) in THF (5 mL) was added dropwise over 10 min. The reaction mixture was stirred at −78 °C for 30 min and then a solution of appropriate aldehyde (1.2 mmol) in THF (5 mL) was added dropwise over 15 min at −78 °C. The reaction mixture was further stirred at −78 °C for 30 min and then allowed to warm at room temperature and stirred for 12–16 h. The crude product was then purified by column chromatography on silica gel, or by crystallization or by directly subjecting to esterification and then it was purified by column chromatography on silica gel.

Typical esterification procedure with DBU

DBU (2 mmol) was added to a stirred solution of a crude acid (1 mmol) in dry acetone (5 mL) at rt and the reaction was stirred for 15 min. Iodomethane (5 mmol) was added to the mixture over a period of 5–10 min, and stirring was continued for 3–4 h at rt. The reaction mixture was concentrated and diluted with ethyl acetate (50 mL). The resulting solution was washed successively with water (10 mL), saturated aqueous solution of sodium thiosulfate (5 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel to afford the corresponding pure ester.

2-[2-(4-Methoxy-phenyl)-vinyl]benzoic acid[50] (13)

^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 12.97 (brs, 1H), 7.82–7.74 (m, 3H), 7.55–7.47 (m, 3H), 7.33 (t, 1H, J = 7.6 Hz), 7.11 (d, 1H, J = 16.4 Hz), 6.95 (d, 1H, J = 8.4 Hz), 3.80 (s, 3H); ^{13}C NMR (100 MHz, [D_6]-DMSO): δ = 169.2, 159.7, 138.6, 132.3, 130.8, 136.3, 130.0, 128.4, 127.4, 126.8, 125.2, 114.7, 55.5.

Methyl 2-but-1-enylbenzoate (15)[39a]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, 1H, J = 7.6 Hz), 7.54 (d, 1H, J = 8 Hz), 7.43 (t, 1H, J = 7.2 Hz), 7.25 (t, 1H, J = 7.2 Hz), 7.13 (d, 1H, J = 15.6 Hz), 6.20–6.16 (m, 1H), 3.90 (s, 3H), 2.32–2.19 (m, 2H), 1.13–1.09 (t, 3H, ^3J = 7.6); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 139.9, 135.7, 132.1, 130.5, 128.3, 127.6, 127.4, 126.6, 52.2, 26.5, 13.8.

3-Ethyl-4-methylsulfanylisochromen-1-one (16)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 3.05–3.0 (m, 2H), 2.26 (s, 3H), 1.31 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 162.1, 148.0, 145.3, 140.0, 128.0, 125.0, 120.7, 109.4, 26.2, 19.2, 12.7; IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1727, 1606, 1461, 1409, 1180, 1072, 765, 692; HRMS (ESI+): required for $C_{12}H_{14}O_2S^+$ ([MH]$^+$) m/z = 221.0636, found m/z = 221.0630.

Methyl 2-pent-1-enylbenzoate (18)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 16.6 Hz, 1H), 6.18–6.10 (m, 1H), 3.89 (s, 3H), 2.23 (q, J = 7.2 Hz, J = 10 Hz, 2H), 1.57–1.48 (m, 2H), 0.97 (t, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 149.8, 144.0, 142.0, 140.4, 128.7, 128.3, 127.4, 126.6, 52.2, 35.4, 22.6, 14.9; HRMS (ESI+): required for $C_{13}H_{16}O_2Na^+$ ([M + Na]$^+$) m/z = 227.1048, found m/z = 227.1041.

Methyl 2-(4,8-dimethylnona-1,7-dienyl)benzoate (20)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, J = 1.6 Hz, J = 8 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.46–7.42 (m, 1H), 7.27–7.23 (m, 1H), 7.11 (d, J = 15.6 Hz, 1H), 6.15–6.08 (m, 1H), 5.12–5.09 (m, 1H), 3.89 (s, 3H), 2.31–1.97 (m, 4H), 1.69 (s, 3H), 1.68 (s, 3H), 1.46–1.38 (m, 1H), 1.25–1.16 (m, 2H), 0.95 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 139.7, 132.6, 131.9, 131.2, 130.3, 129.7, 128.2, 127.3, 126.5, 124.8, 52.0, 40.6, 36.8, 32.9, 25.7, 25.6, 19.5, 17.7; HRMS (ESI+): required for $C_{19}H_{26}O_2Na^+$ ([M + Na]$^+$) m/z = 309.1830, found m/z = 309.1823.

3-(2,6-Dimethylhept-5-enyl)-4-methylsulfanylisochromen-1-one (21)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 5.08 (t, J = 6.8 Hz, 1H), 2.97–2.81 (m, 2H), 2.23 (s, 3H), 2.12–1.96 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.47–1.38 (m, 1H), 1.33–1.24 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 161.9, 147.7, 145.1, 141.5, 129.8, 127.8, 124.9, 124.3, 120.5, 110.6, 39.5, 36.8, 31.8, 25.7, 25.5, 19.3, 18.7, 17.7; HRMS (ESI+): required for $C_{19}H_{24}O_2SNa^+$ ([M + Na]$^+$) m/z = 339.1495, found m/z = 339.1495.

Methyl 2-[2-(6-allyloxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-vinyl]benzoate (23)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.54 (d, J = 16.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 6.25 (dd, J = 8 Hz, 16 Hz, 1H), 5.98 (d, J = 3.6 Hz, 1H), 5.88–5.81 (m, 1H), 5.27 (d, J = 17.2 Hz, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.84 (dd, J = 2.8 Hz, 8 Hz, 1H), 4.62 (d, J = 3.6 Hz, 1H), 4.14–4.01 (m, 2H), 3.92–3.89 (m, 4H), 1.55 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 138.3, 134.0, 132.7, 132.2, 130.4, 128.6, 127.6, 127.5, 126.4, 117.3, 111.5, 104.9, 83.9, 83.1, 81.5, 71.3, 52.1, 26.8, 26.2; HRMS (ESI+): required for $C_{20}H_{25}O_6$ ([M + H]$^+$) m/z = 361.1651, found m/z = 361.1648.

Methyl 2-(2-phenylpropenyl)benzoate (25)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.6 Hz, *trans*-isomer), 7.88 (d, J = 7.6 Hz, *cis*-isomer), 7.62 (d, J = 7.6 Hz, *trans*-isomer), 7.53 (t, J = 7.6 Hz, *trans*-isomer), 7.47–7.29 (m, *cis* and *trans* isomer), 7.17–7.09 (m, *cis* and *trans* isomer), 6.98 (s, *cis* isomer), 6.87 (d, J = 6.8 Hz, *cis* isomer), 3.92 (s, *cis* isomer), 3.90 (s, *trans* isomer), 2.29 (s, *cis* isomer), 2.13 (s, *trans* isomer); ^{13}C NMR (100 MHz, $CDCl_3$): (mixture of *cis* and *trans*) δ = 167.9, 143.7, 140.2, 136.2, 132.6, 132.2, 131.8, 131.3, 130.8, 129.7, 128.9, 128.5, 127.7, 127.4, 126.8, 126.2, 52.2, 17.3; HRMS (ESI+): required for $C_{17}H_{16}O_2Na^+$ ([M + Na]$^+$) m/z = 275.1048, found m/z = 275.1053.

Methyl 2-(2,2-diphenylvinyl)benzoate[51] (28)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, 1H, J = 2.4), 7.43 (s, 1H), 7.37–7.28 (m, 5H), 7.20–7.13 (m, 5H), 7.10–7.08 (m, 2H), 6.96–6.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.79, 143.13, 143.06, 139.98, 139.76, 131.62, 131.33, 131.01, 130.17, 129.88, 128.18, 128.16, 128.03, 127.86, 127.56, 127.14, 126.44, 52.09.

2-(Cyclopentylidenemethyl)benzoic acid (30)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.5 (d, J = 7.4 Hz, 1H), 7.53–7.47 (m, 2H), 7.34–7.27 (m, 1H), 7.0 (brs, 1H), 2.57–2.46 (m, 4H), 1.75 (brs, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.8, 148.3, 141.1, 142.5, 141.3, 140.0, 127.7, 125.9, 119.8, 35.1, 31.1, 30.0, 25.7.

Spiro[3*H*-2-benzopyran-3,1′-cyclopentan]-1(4*H*)-one[52] (31)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 3.09 (s, 2H), 2.02–1.92 (m, 4H), 1.68–1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 148.8, 143.5, 140.0, 127.6, 127.4, 125.2, 91.4, 38.5, 37.6, 23.8; HRMS (ESI+): required for $C_{13}H_{15}O_2^+$ ([M + H]$^+$) m/z = 203.1072, found m/z = 203.1067.

2-(Cyclohexylidenemethyl)benzoic acid (32)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 8 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 6.66 (s, 1H), 2.32 (t, J = 6 Hz, 2H), 2.19 (t, J = 5.6 Hz, 2H), 1.74–1.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 142.8, 140.5, 142.2, 141.4, 141.1, 128.3, 126.1, 121.5, 37.4, 29.7, 28.5, 27.9, 26.6; HRMS (ESI+): required for $C_{14}H_{17}O_2^+$ ([M + H]$^+$) m/z = 217.1229, found m/z = 217.1226.

2-[2-(4-Isopropenylcyclohex-1-yl)vinyl]benzoic acid (35)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 16 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 16 Hz, 1H), 5.96 (s, 1H), 4.75 (s, 2H), 2.53–2.48 (m, 1H), 2.35–2.12 (m, 4H), 1.98–1.94 (m, 1H), 1.76 (s, 3 H), 1.61–1.50 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.5, 149.7, 140.8, 136.1, 135.2, 133.0, 132.4, 131.6, 131.2, 127.0, 126.6, 124.1, 108.9, 41.2, 31.7, 27.5, 25.1, 20.9; HRMS (ESI+): required for $C_{18}H_{20}O_2Na^+$ ([M + Na]$^+$) m/z = 291.1361, found m/z = 291.1357.

2-[2-(2-Nitrophenyl)vinyl]benzoic acid (37)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, J = 7.6 Hz, 1H), 8.05–7.99 (m, 2H), 7.85 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 2H), 7.52–7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 148.2, 149.8, 143.7, 143.5, 143.4, 143.0, 141.9, 129.1, 128.5, 128.4, 127.5, 126.9, 125.0 (one signal is perhaps overlapped); HRMS (ESI+): required for $C_{15}H_{11}NO_4Na^+$ ([M + Na]$^+$) m/z = 292.0586, found m/z = 292.0582.

Dimethyl bis-2,2′-(1,2-ethenediyl)benzoate[53] (39)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, 1H, J = 8 Hz), 7.88 (s, 1H), 7.82 (d, 1H, J = 8 Hz), 7.53 (t, 1H, J = 7.4 Hz), 7.33 (t, 1H, J = 7.2 Hz), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 139.7, 132.5, 130.8, 130.4, 128.7, 127.8, 127.5, 52.3.

Methyl 2-(1-oxo-1*H*-inden-2-yl)benzoate (40)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1H), 8.07 (d, J = 8 Hz, 2H), 7.86 (d, J = 8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.63–7.59 (m, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 193.6, 167.0, 144.0, 147.5, 143.8, 143.5, 143.1, 142.5, 141.1, 140.2, 129.2, 129.0, 128.4, 124.8, 123.5, 121.4, 52.3; IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2950, 1698, 1689, 1479, 1268, 1079, 952, 885, 757, 700; HRMS (ESI+): required for $C_{17}H_{12}O_3^+$ ($[M]^+$) *m/z* = 264.0786, found *m/z* = 264.0776.

Dimethyl 2,2′-(1,4-phenylenedi-2,1-ethenediyl)bisbenzoate (42)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 16.4 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.55 (s, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 16 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 149.2, 147.1, 142.2, 141.1, 140.8, 128.6, 127.4, 127.2, 126.9, 52.2 (perhaps one signal is overlapped); HRMS (ESI+): required for $C_{26}H_{22}O_4Na^+$ ($[M + Na]^+$) *m/z* = 421.1416, found *m/z* = 421.1408.

Methyl 2-(furan-2-yl-vinyl)benzoate[39a] (44)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8 Hz, *cis* isomer), 7.91–7.84 (m, c*is* and *trans* isomer), 7.65 (d, *J* = 7.6 Hz, *trans* isomer), 7.56–7.42 (m, *cis* and *trans* isomer), 7.38–7.28 (m, *cis* and *trans*), 7.20 (s, *cis* isomer), 6.90 (d, *J* = 12.4 Hz, *cis* isomer), 6.83 (d, *J* = 16.4 Hz, *trans* isomer), 6.46–6.40 (m, *cis* and *trans* isomer), 6.23 (d, *J* = 1.6 Hz, *cis* isomer), 5.92 (d, *J* = 3.2 Hz, *cis* isomer), 3.93 (s, *trans* isomer), 3.85 (s, *cis* isomer); ^{13}C NMR (100 MHz, $CDCl_3$): mixture of *cis* and *trans* δ = 167.8, 153.2, 142.4, 141.4, 139.5, 138.6, 132.0, 131.8, 130.0, 130.6, 130.4, 128.6, 128.0, 127.2, 127.0, 126.4, 125.5, 114.1, 117.7, 117.6, 111.5, 111.0, 109.5, 109.1, 52.1, 51.9.

Methyl 2-methoxy-6-[2-(4-methoxyphenyl)ethenyl]benzoate (47)

^{1}H NMR: (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.8 Hz, 2H), 7.35–7.28 (m, 2H), 7.04 (d, *J* = 16 Hz, 1H), 6.93–6.88 (m, 3H), 6.81 (d, *J* = 8 Hz, 1H), 3.96 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 169.8, 166.7, 146.6, 141.5, 140.6, 129.9, 128.2, 122.8, 122.7, 117.6, 114.3, 109.6, 56.1, 55.4, 52.6; HRMS (ESI+): required for ($[M + Na]^+$) *m/z* = 321.1103, found *m/z* = 321.1101.

2-Hydroxy-4-methoxy-6-[2-(4-methoxyphenyl)vinyl]benzoic acid (49)

m.p. = 162 °C–168 °C; ^{1}H NMR (400 MHz, [D_6]-acetone): δ = 7.83 (d, *J* = 16 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 16 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, [D_6]-acetone): δ = 174.2, 167.0, 165.6, 161.0, 144.9, 141.8, 141.5, 129.3, 128.6, 116.3, 107.8, 104.8, 101.1, 56.3, 56.0; HRMS (ESI+): required for $C_{17}H_{17}O_5^+$ ($[M + H]^+$) *m/z* = 301.1076 found *m/z* = 301.1073.

Methyl [2-(4-hydroxyphenyl)vinyl]benzoate (51)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 16 Hz, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 16 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 168.6, 166.0, 149.8, 142.4, 141.3, 140.8, 140.3, 128.5, 128.2, 127.0, 126.9, 125.2, 116.8, 52.5; IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3355, 1702, 1600, 1438, 1241, 1078, 966, 819, 651; HRMS (ESI+): required for $C_{16}H_{14}O_3Na$ ($[M + Na]^+$) *m/z* = 277.0841, found *m/z* = 277.0838.

3-(4-Hydroxyphenyl)isochroman-1-one (52)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.34–7.28 (m, 4H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.50 (dd, *J* = 2.8 Hz, *J* = 12 Hz, 1H), 3.36 (dd, *J* = 12.4 Hz, *J* = 16.4 Hz, 1H), 3.12 (dd, *J* = 2.8 Hz, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 156.8, 139.4, 134.3, 130.5, 130.0, 128.2, 128.1, 127.7, 125.0, 116.3, 80.5, 35.3; IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3303, 1693, 1602, 1282, 831; HRMS (ESI+): required for $C_{16}H_{15}O_3^+$ ($[M + H]^+$) *m/z* = 255.1021, found *m/z* = 255.1019.

2-Hydroxy-4-methoxy-6-styrylbenzoic acid (54)

^{1}H NMR: (200 MHz, $CDCl_3$): δ = 12.47 (s, 1H), 7.93 (d, *J* = 16 Hz, 1H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.40–7.26 (m, 3H), 6.82 (d, *J* = 16 Hz, 1H), 6.65 (d, *J* = 2.6 Hz, 1H), 6.43 (d, *J* = 2.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7, 165.6, 163.9, 143.2, 137.4, 130.5, 130.2, 128.6, 127.6, 126.7, 107.1, 104.2, 100.2, 55.4.

3′,4-Dihydroxy-3,5′-dimethoxystilbene (56)

^{1}H NMR (400 MHz, [D_6]-acetone): δ = 8.38 (s, 1H), 7.76 (s, 1H), 7.23 (d, *J* = 1.6 Hz, 1H), 7.09 (d, *J* = 16 Hz, 1H), 7.04–6.95 (m, 2H), 6.82 (d, *J* = 8 Hz, 1H), 6.64 (s, 2H), 6.32 (t, *J* = 2 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, [D_6]-acetone): δ = 162.4, 159.9, 148.9, 147.9, 141.2, 130.7, 130.1, 127.2, 121.6, 116.3, 110.4, 107.0, 104.2, 101.7, 56.6, 55.8.

7-Hydroxy-5-methoxy-6-(3-methylbut-2-enyl)-3*H*-benzo[*c*]thiophen-1-one (60)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.47 (s, 1H), 6.39 (s, 1H), 5.03 (t, *J* = 5.8 Hz, 1H), 4.26 (s, 2H), 3.86 (s, 3H), 3.27 (d, *J* = 6.8 Hz, 2H), 1.76 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.8, 163.8, 156.7, 146.4, 132.6, 121.3, 119.5, 114.3, 97.8, 56.4, 34.2, 25.9, 24.4, 18.0; HRMS (ESI+): required for $C_{14}H_{16}O_3SNa^+$ ($[M + Na]^+$) *m/z* = 287.0718, found *m/z* = 287.0711.

Methyl 2-hydroxy-4-methoxy-3-(3-methylbut-2-enyl)-6-styrylbenzoate (59)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.04 (s, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.01 (t, *J* = 7.2 Hz, 2H), 6.94–6.90 (m, 2H), 6.10 (s, 1H), 5.95 (d, *J* = 16.4 Hz, 1H), 4.72 (t, *J* = 6.8 Hz, 1H), 3.51 (s, 3H), 3.45 (s, 3H), 2.97 (d, *J* = 6.4 Hz, 2H), 1.32 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2, 162.9, 162.8, 141.2, 137.9, 131.8, 131.1, 128.9, 128.5, 127.6, 126.4, 123.8,

121.8, 104.8, 98.4, 55.9, 52.4, 26.3, 26.0, 18.4; IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1698, 1589, 1479, 1268, 1079, 952, 887, 757; HRMS (ESI+): required for $C_{22}H_{25}O_4^+$ ([M + H]$^+$) *m/z* = 353.1747, found *m/z* = 353.1748.

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