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Unexpected *Z*-stereoselectivity in the Ramberg–Bäcklund reaction of diarylsulfones leading to *cis*-stilbenes: the effect of aryl substituents and application in the synthesis of the integrastatin nucleus

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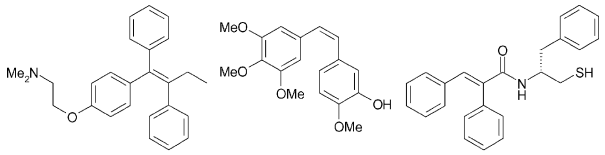
With certain substituent patterns, benzyl benzyl sulfone systems have been found to give unexpectedly high *Z*-stereoselectivity (up to $E:Z = 1:16$) in the Meyers variant of the Ramberg–Bäcklund reaction. A range of sulfones, bearing various aryl substituents, were explored to rationalize this unprecedented selectivity for *Z*-stilbene systems. This high level of double bond stereocontrol has also been utilized in the synthesis of integrastatin nucleus, the core of two highly bioactive anti-HIV compounds.

Introduction

Stilbene systems are found throughout nature and are present in many man-made, biologically active compounds, the most recognizable of which is the widely prescribed drug Tamoxifen® **1** (Fig. 1), used for the treatment of breast cancer.[1] Other interesting examples include combretastatin A-4 **2**, an anti-tumour compound,[2] and *N*-(1-mercaptomethyl-2-phenylethyl)-2,3-diphenylacrylamide **3**, which has been found to inhibit the endothelin converting enzyme (ECE), an enzyme involved in vascoconstriction.[3] All three of these molecules are based on *cis*-stilbenes.



1 2 3

Fig. 1 Tamoxifen® **1**, combretastatin **2** and *E*-*N*(*R*)-(1-mercaptomethyl-2-phenylethyl)-2,3-diphenylacrylamide **3**.

During investigations into the synthesis of the HIV-1 integrase-inhibiting integrastatin natural products (**4** and **5**, Fig. 2),[4] we found that sulfone **6** underwent the Ramberg–Bäcklund reaction (RBR), using Meyers' conditions,[5] to give the key olefin intermediate **7** in good yield and in a 1 : 1 ratio of *E* and *Z*-isomers (Scheme 1).

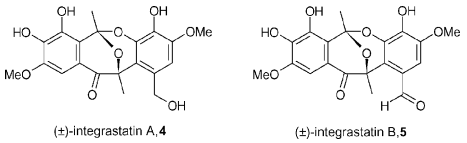
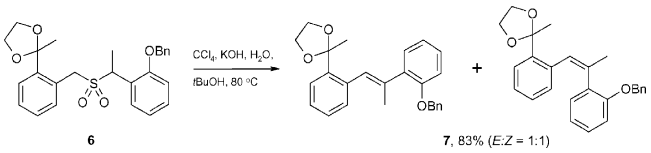
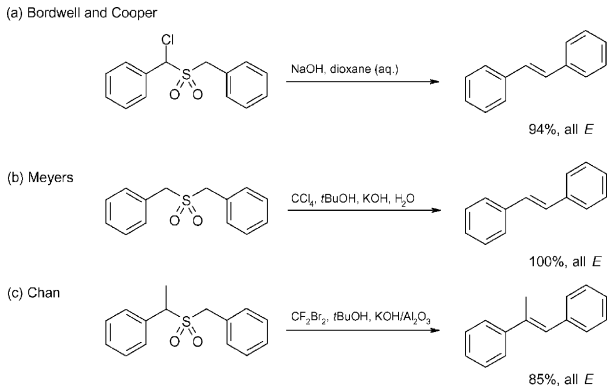


Fig. 2 The integrastatins.



Scheme 1 Exposure of sulfone **6** to Meyers' conditions.

At first glance this reaction seemed unremarkable, but a comparison with literature stilbene syntheses highlighted two major discrepancies. The first of these was the fact that any *cis*-product had been formed in a RBR synthesis. In general, benzyl benzyl sulfone systems undergo the RBR to afford solely *trans*-stilbene products, as has been shown by Bordwell and Cooper (Scheme 2(a)),[6] Neureiter,[7] Meyers *et al.* (Scheme 2(b)),[5] and more recently, Chan *et al.* (Scheme 2(c)).[8]



Scheme 2 Previous benzyl benzyl sulfone RBR studies.

Although it is widely accepted that in the course of the reaction the *cis*-episulfone intermediate **9** is formed preferentially (Scheme 3), deuterium-labelling experiments by Tokura *et al.*[9] have shown that phenyl substituents are sufficiently anion-stabilizing to ensure a fast epimerization of the episulfone thus affording exclusively the *trans*-stilbene product (also Scheme 3).

The second unexpected factor in our findings was that KOH–*t*BuOH was employed as the base system, a method that has been shown, even in aliphatic systems, to promote the epimerization of the intermediate episulfone to give the *trans*-products. In-depth base *vs.* selectivity studies by both Neureiter[7] and Scholz and Burtscher[10] have highlighted this property, and it has been used to great effect in aliphatic systems (where the *cis*-products, *e.g.* **12**, usually predominate) as shown in Scheme 4.

The "high" *Z*-selectivity that had been observed with sulfone **6** was consequently of great interest, and further work was undertaken to try to rationalize this result.

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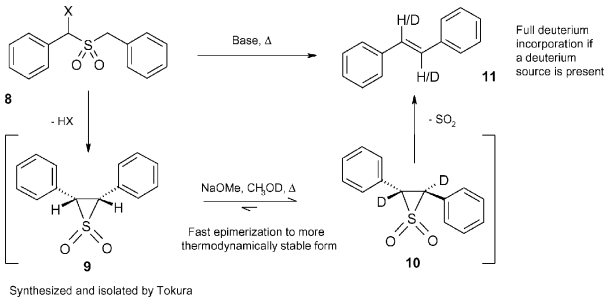
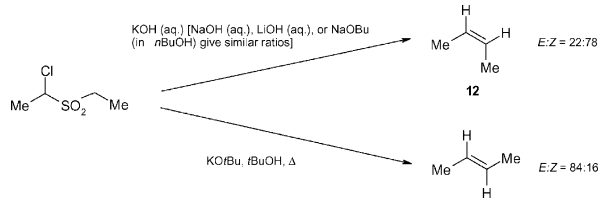


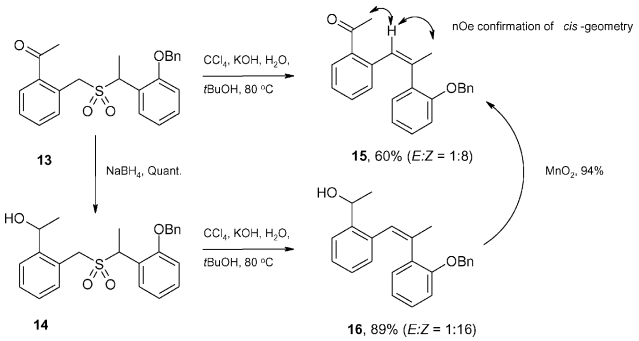
Scheme 3 Reaction pathway of the RBR in stilbene systems.



Scheme 4 Treatment of α-chloroethyl ethyl sulfone with different bases.[7]

Results and discussion

In the published examples of RBR-formed stilbene systems, most possessed unsubstituted aryl groups. It was decided, therefore, to investigate the effect of altering the ketal group in sulfone system **6**, and to this end ketone **13** and alcohol **14** were synthesized and exposed to the same RBR conditions (Scheme 5).



Scheme 5 RBR of sulfones **13** and **14**.

Surprisingly, these sulfones produced even larger proportions of the *cis*-stilbene products, affording the olefins **15** and **16** in 1 : 8 and 1 : 16 $E : Z$ ratios, respectively. The absolute stereochemistry of the olefin double bond was confirmed through NOE analysis of **15**. To our knowledge, this observed *cis*-selectivity is the largest of any reported for the synthesis of stilbenes by the RBR.[11]

Initial theories as to the reason for this *cis*-preference centered on the electronics of the aromatic rings. One suggestion was that the sulfones might be undergoing π-stacking to minimize the interaction between the surfaces of the molecules with the solvent molecules, and thus directing a *cis*-alignment from the beginning (Fig. 3).

To investigate this theory further, a range of sulfones were synthesized (**20** and **27–33**, Scheme 6) through coupling of benzyl halides **21–23** with thiols **18** and **24–26** using the standard procedures outlined in Scheme 6. Of the coupling partners, compounds **22**, **23** and **26** were commercially available, whilst compounds **21** and **25** were synthesized *via* literature procedures.[12,13] Novel thiols **18** and **24** were prepared by treating the known compounds, 1-(2-benzyloxyphenyl)-ethanol (**17**)[14] and 1-(2-methoxyphenyl)-ethanol[15] respectively, with Lawesson's reagent.

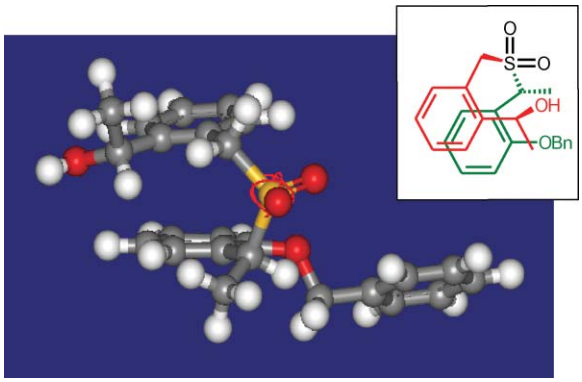


Fig. 3 Proposed π-stacking for sulfone **14**.

These sulfones were then treated with potassium hydroxide and carbon tetrachloride in aqueous *tert*-butanol under standard Meyers conditions. The stereochemical outcomes of these reactions are shown in Table 1.

Table 1 suggests that the observed selectivity is not solely due to π-stacking. Comparison of sulfones **27** and **29** (entries [iv] and [vii]) with sulfones **28** and **30** (entries [v] and [viii]) shows a much higher selectivity for the *cis*-isomer when the hydroxyethyl moiety is present. If, indeed, π-stacking was the reason for the *cis*-selectivity, then it should be expected that the sulfones with the most powerful electron withdrawing group (the nitro group) would afford the *cis*-olefins in the greatest proportions, providing an electron donating group is also present on the opposing aromatic ring. This is not the case, and the only nitro-containing sulfone to give any appreciable amount of the *cis*-isomer is sulfone **28** (entry [v]), with a ratio of $E : Z = 1 : 1$.

When there are only two substituents present on the sulfone, and disubstituted stilbenes are formed (entries [vii]–[xi]), the effect of the hydroxyethyl group is again apparent, with the sulfones bearing this group (**29** and **31**) the only systems to afford any of the *cis*-olefin product. The other three sulfones, **30**, **32** and **33**, yield solely the *trans*-isomer of the corresponding olefin, as would be expected from the literature studies.

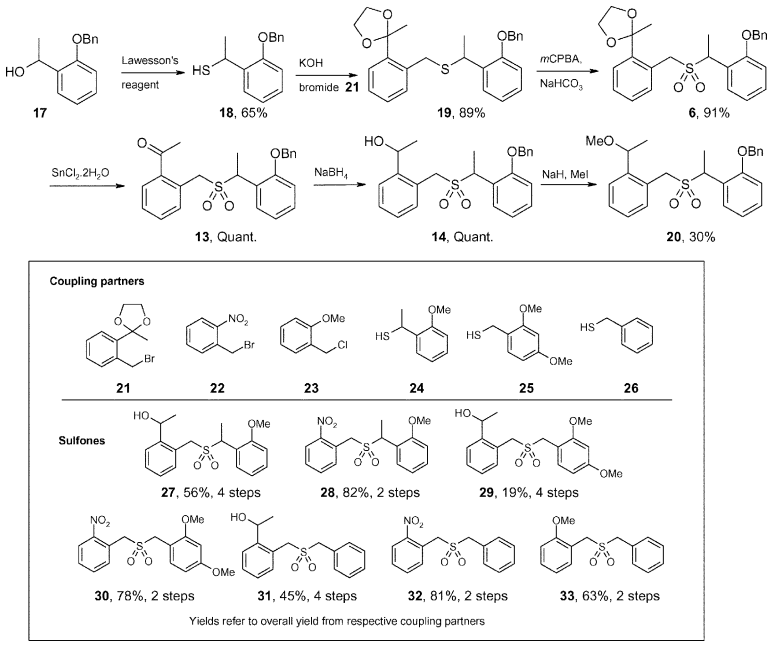
Furthermore, comparison of entries [vii] and [ix] shows equal selectivity for the *cis*-product ($E : Z = 2 : 3$) from sulfones **29** and **31**. These results highlight the apparent unimportance of the methoxy substituents of the second aryl ring.

This apparent reliance on the hydroxyethyl group for the high *cis*-selectivities suggests a revised mechanism for the RBR in our stilbene systems:

Assuming that the formation of the *cis*-episulfone is favoured in our systems, as is predicted,[5–10] then both the acidity of the benzylic protons and the strength of the base should favour fast epimerization to the *trans*-isomer. We propose that the observed *cis*-selectivity in these studies is due to an intramolecular base-promoted extrusion of SO_2, which is taking place before full epimerization of the intermediate episulfone **42** occurs, therefore retaining the *cis*-configuration in the product. This process would proceed by way of a 5-*exo*-*tet* ring breaking process to give **43**,[16] which would then break down to afford *Z*-**16** (Scheme 7).

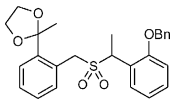
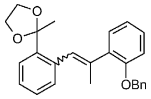
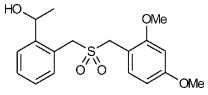
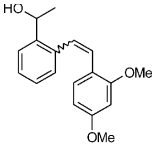
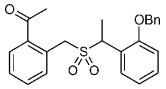
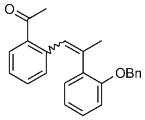
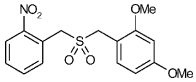
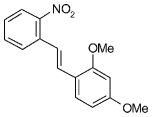
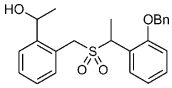
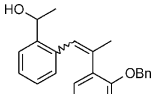
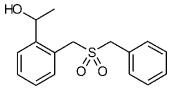
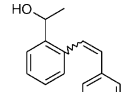
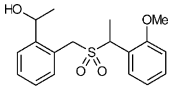
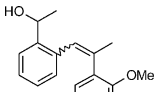
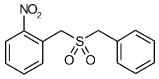
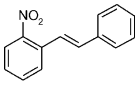
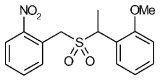
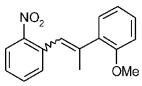
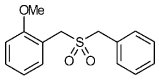
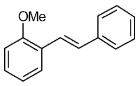
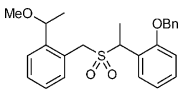
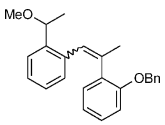
This proposed mechanism can now be used to explain all of the observed results. The highest proportion of *cis*-product is consistently seen when the free hydroxyethyl group is present. The reduction in selectivity when forming disubstituted, as opposed to trisubstituted olefins, is likely to be a statistical effect, due to the presence of twice as many epimerisable protons in the intermediate episulfone, leading to a higher proportion of *trans*-product.

The high *Z*-stereoselectivity apparent when the methyl ketone functionality is present (sulfone **13**, entry [ii]) can be explained by considering the enolate form of the ketone, which it is presumed will be present in some quantity under the highly basic reaction conditions to effect the SO_2 extrusion process. This can also go through a five-membered transition state (analogous to **14**),

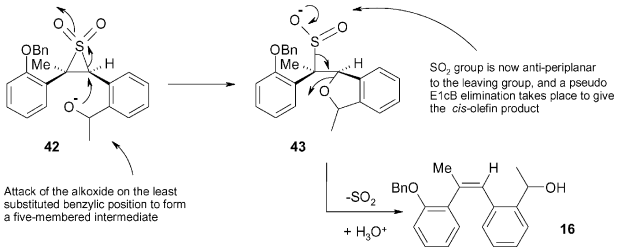


Scheme 6 Synthetic route to the sulfones.

Table 1 Results of the RBR experiments using KOH–aq. *t*BuOH in CCl_4

	Sulfone	Alkene[a]		Sulfone	Alkene[a]
[i]	 **6**	 **7**, 83%, *E*:*Z* = 50:50[b]	[vii]	 **29**	 **37**, 84%, *E*:*Z* = 40:60[b]
[ii]	 **13**	 **15**, 60%, *E*:*Z* = 10:90	[viii]	 **30**	 **38**, 47%, All *E*
[iii]	 **14**	 **16**, 89%, *E*:*Z* = 5:95	[ix]	 **31**	 **39**, 87%, *E*:*Z* = 40:60
[iv]	 **27**	 **34**, 59%, *E*:*Z* = 10:90	[x]	 **32**	 **40**, 32%, All *E*
[v]	 **28**	 **35**, 36%, *E*:*Z* = 50:50	[xi]	 **33**	 **41**, 80%, All *E*
[vi]	 **20**	 **36**, 90%, *E*:*Z* = 30:70			

[a] *E* : *Z* ratios quoted as percentage composition of total yield, to the nearest 5%, from ^{1}H-NMR spectra. [b] Ratios calculated from isolated isomers.



Scheme 7 Proposed intramolecular base-promoted SO_2 extrusion from episulfone **42**.

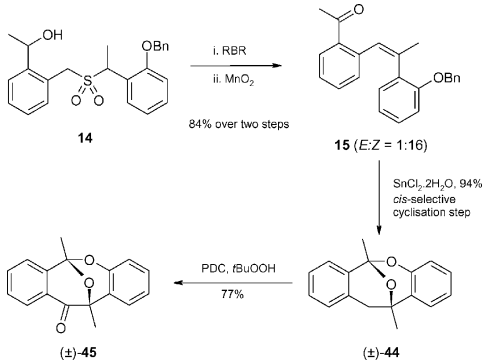
selectively affording the *cis*-product, in only a slightly lower proportion than **14**.

The reasonable *Z*-stereoselectivity showed with sulfones **6** and **20** (entries [i] and [vi]) can also be explained by this theory, with the oxygen lone pairs on the *ortho*-alkoxy substituent (rather than a formal anion) responsible for the intramolecular extrusion. The higher selectivity observed with **20** over **6** is possibly due to the reduced steric hindrance of the methyl ether compared to the ketal group.

The only other example in which the *cis*-product is observed is a nitro-example where an α-methyl group is also present (entry [v]). It is thought that the *cis*-selectivity in this case may be due to nitro-group involvement in sulfur dioxide extrusion.

Exploiting the selectivity in synthesis

The importance of this work has been highlighted in the synthesis of the integrastatin nucleus **45** (Scheme 8). We demonstrated that only the *cis*-isomer **15** undergoes a Lewis acid-promoted cyclisation, which is thought to proceed by using the olefin double bond to hold the starting olefin in the reactive conformation (impossible with the *trans*-isomer), to give tetracycle **44** (confirmed by X-ray crystallography[17]). Various benzylic oxidation trials on this tetracycle have shown that by utilization of a PDC–*t*BuOOH complex formed on Celite® at low temperature, the integrastain nucleus **45** can be formed in a yield of 61% from the sulfone **14**.[17]



Scheme 8 Synthesis of the integrastatin nucleus.

The structure of the integrastatin nucleus has been further ascertained through X-ray analysis of the crystalline product (Fig. 4).

Conclusions

Through investigations into various benzyl sulfone systems, we have been able to demonstrate a remarkable *cis*-selectivity in the Ramberg–Bäcklund reaction leading to disubstituted and particularly trisubstituted stilbenes. The *Z*-stereochemistries attained are the highest yet recorded in the literature for stilbenes (up to a 95% composition of the *cis*-isomer has been observed), and have been achieved through manipulation of aryl groups remote from the central sulfone system.

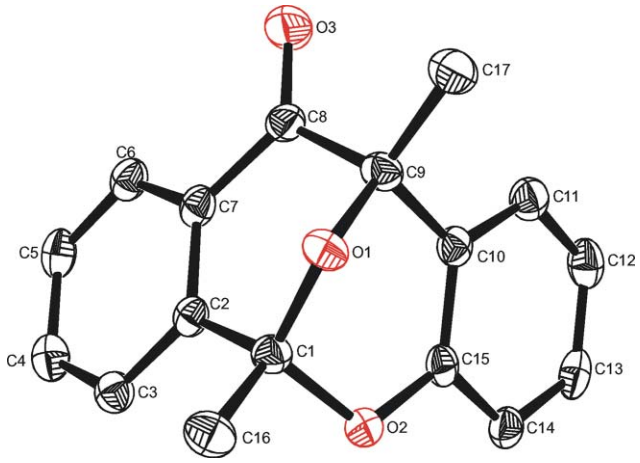


Fig. 4 ORTEP drawing of integrastatin nucleus **45** (50% probability thermal ellipsoids).[18]

These results extend the scope of the RBR in synthetic chemistry, as shown by the synthesis of the integrastatin nucleus **45**.

Experimental

(±)-1-(2-Benzyloxyphenyl)-ethanethiol, 18 and (±)-1-(2-methoxyphenyl)-ethanethiol, 24

(a) To a stirred solution of 1-(2-benzyloxyphenyl)-ethanol (4.36 g, 19.0 mmol) in dichloromethane (300 mL) under nitrogen was added Lawesson's reagent (4.64 g, 11.0 mmol). The reaction mixture was stirred at room temperature for 28 hours and the solvent was then removed *in vacuo* to give a yellow gum (6.20 g). Purification by flash chromatography, eluting with 9 : 1 petroleum ether–ethyl acetate, afforded the *title compound* **18** (3.00 g, 65%) as a pale yellow oil; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.44; ν_{max} (neat)/cm^{-1} 2968, 2560 (SH), 1241; δ_H ($CDCl_3$, 270 MHz) 1.67 (3 H, d, *J* 7.0 Hz, CH_3), 2.15 (1 H, d, *J* 6.2 Hz, SH), 4.69 (1 H, dq, *J* 7.0, 6.2 Hz, CH), 5.14 (2 H, s, CH_2), 6.94–6.97 (2 H, m, 2 ArH), 7.18–7.44 (7 H, m, 7 ArH); δ_C ($CDCl_3$, 67.9 MHz) 24.6 (CH_3), 31.8 (CH), 70.3 (CH_2), 112.1 (ArH), 121.3 (ArH), 126.5 (ArH), 127.4 (2 ArH), 128.1 (2 ArH), 128.8 (2 ArH), 137.2 (C), 155.2 (C)—1 quaternary carbon signal not observed; *m*/*z* (CI) 262 (MNH_4^+, 25%), 211 (100); [Found MNH_4^+, 262.1268 (error = 0.8 ppm). $C_{15}H_{16}OS$ requires: MNH_4^+, 262.1266].

(b) Thiol **24** was prepared in an identical procedure to that for **18** and isolated in a 58% yield as a colourless oil; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.47; ν_{max} (neat)/cm^{-1} 2965, 1491, 1244, 753; δ_H ($CDCl_3$, 400 MHz) 1.65 (3 H, d, *J* 6.8 Hz, CH_3), 2.12 (1 H, d, *J* 6.0 Hz, SH), 3.87 (3 H, s, OCH_3), 4.61 (1 H, dq, CH), 6.87 (1 H, d, *J* 7.6 Hz, ArH), 6.96 (1 H, dd, *J* 7.6, 7.2 Hz, ArH), 7.18–7.21 (1 H, m, ArH), 7.40 (1 H, d, *J* 7.6 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 24.9 (CH_3), 31.9 (CH), 55.8 (OCH_3), 111.0 (ArH), 121.2 (ArH), 126.6 (ArH), 128.3 (ArH), 134.5 (C), 156.3 (Ar(C)O); *m*/*z* (CI) 186 (MNH_4^+, 24%), 135 (100); [Found MNH_4^+, 186.0950 (error = 1.2 ppm). $C_9H_{12}OS$ requires: MNH_4^+, 186.0953].

(±)-2-{2-[1-(2-Benzyloxyphenyl)-ethylsulfanylmethyl]-phenyl}-2-methyl-[1,3]dioxolane, 19

To a stirred solution of **18** (3.06 g, 12.5 mmol) in ethanol (60 mL) was added powdered potassium hydroxide (0.74 g, 13.2 mmol). The resultant mixture was cooled to 0 °C and a solution of **21** (3.39 g, 13.2 mmol) in ethanol (40 mL) added dropwise over 10 minutes. The reaction was allowed to warm to room temperature and stirred for 18 hours. The solvent was then removed *in vacuo* and the residue extracted with dichloromethane, washing with water and saturated sodium chloride solution, before drying over magnesium sulfate. Filtration and removal of the solvent

in vacuo gave a clear gum. Purification by flash chromatography, eluting with 19 : 1 petroleum ether–ethyl acetate, afforded the *title compound* **19** (4.67 g, 89%) as a clear oil; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.31; ν_{max} (neat)/cm^{-1} 2970, 1450, 1239, 1038; δ_H ($CDCl_3$, 400 MHz) 1.56 (3 H, d, *J* 7.0 Hz, CH_3), 1.62 (3 H, s, CH_3), 3.68–3.71 (2 H, m, 2 CH), 3.90 (2 H, s, CH_2), 3.93–3.96 (2 H, m, 2 CH), 4.72 (1 H, q, *J* 7.0 Hz, CH), 5.10 (2 H, s, CH_2), 6.95 (1 H, d, *J* 6.2 Hz, ArH), 7.02 (1 H, dd, *J* 7.7, 7.7 Hz, ArH), 7.10–7.12 (2 H, m, 2 ArH), 7.22–7.26 (2 H, m, 2 ArH), 7.30–7.45 (5 H, m, 5 ArH), 7.51 (1 H, d, *J* 7.6 Hz, ArH), 7.59 (1 H, d, *J* 7.6 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 22.0 (CH_3), 27.6 (CH_3), 33.5 (CH_2), 37.2 (CH), 64.3 (2 CH_2), 70.4 (CH_2), 109.3 (C), 112.0 (ArH), 121.4 (ArH), 126.5 (ArH), 126.7 (ArH), 127.4 (2 ArH), 127.9 (ArH), 128.0 (ArH), 128.1 (ArH), 128.2 (ArH), 128.7 (2 ArH), 131.6 (ArH), 132.8 (C), 136.4 (C), 140.5 (C), 155.9 (Ar(C)O)—1 quaternary carbon signal not observed; *m*/*z* (CI) 421 (MH^+, 100%); [Found MH^+, 421.1837 (error = 0.1 ppm). $C_{26}H_{28}O_3S$ requires: MH^+, 421.1837].

(±)-2-{2-[1-(2-Benzyloxyphenyl)-ethanesulfonylmethyl]-phenyl}-2-methyl-[1,3]dioxolane, 6

To a stirred solution of **19** (1.14 g, 2.7 mmol) and sodium hydrogen carbonate (0.94 g, 10.2 mmol) in dichloromethane (30 mL) and water (5 mL) at 0 °C, was added *meta*-chloroperbenzoic acid (1.40 g, 8.1 mmol). The reaction mixture was allowed to stir for a further 30 minutes at 0 °C, then warmed to room temperature and stirred for 16 hours. Saturated sodium metabisulfite solution was then added and the organic layer extracted with dichloromethane, washing with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, before drying over sodium sulfate. Filtration and removal of the solvent *in vacuo* and purification by flash chromatography, eluting with 3 : 1 petroleum ether–ethyl acetate, afforded the *title compound* **6** (1.11 g, 91%) as a white solid; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.15; mp 137–140 °C; (Found C, 69.3; H, 6.3. $C_{26}H_{28}O_5S$ requires: C, 69.0; H, 6.2%); ν_{max} (nujol)/cm^{-1} 2725, 1297, 1043; δ_H ($CDCl_3$, 400 MHz) 1.42 (3 H, s, CH_3), 1.75 (3 H, d, *J* 6.6 Hz, CH_3), 3.67–3.70 (2 H, m, 2 CH), 3.81–3.83 (2 H, m, 2 CH), 4.55 (2 H, d, *J* 7.6 Hz, CH_2), 5.11 (1 H, q, *J* 6.6 Hz, CH), 5.14 (2 H, d, *J* 6.4 Hz, CH_2), 7.04–7.07 (2 H, m, 2 ArH), 7.23–7.27 (2 H, m, 2 ArH), 7.34–7.47 (5 H, m, 5 ArH), 7.56 (2 H, d, *J* 7.8 Hz, 2 ArH), 7.64 (2 H, d, *J* 7.8 Hz, 2 ArH); δ_C ($CDCl_3$, 67.9 MHz) 13.5 (CH_3), 28.0 (CH_3), 53.0 (CH_2), 55.6 (CH), 64.3 (2 CH_2), 70.8 (CH_2), 108.9 (C), 112.2 (ArH), 121.7 (ArH), 123.7 (C), 125.1 (C), 126.9 (ArH), 127.7 (2 ArH), 128.2 (ArH), 128.4 (ArH), 128.5 (ArH), 128.9 (3 ArH), 129.9 (ArH), 130.1 (ArH), 132.7 (C), 143.0 (C), 156.2 (Ar(C)O); *m*/*z* (CI) 453 (MH^+, 25%), 211 (100); [Found MH^+, 453.1737 (error = 0.2 ppm). $C_{26}H_{28}O_5S$ requires: MH^+, 453.173].

(±)-1-{2-[1-(2-Benzyloxyphenyl)ethanesulfonylmethyl]-phenyl}-ethanone, 13

To a stirred solution of **6** (1.30 g, 2.9 mmol) in dichloromethane (30 mL) was added tin(II) chloride dihydrate (1.30 g, 5.8 mmol) and the reaction stirred for 8 hours. The reaction mixture was then filtered through Celite® and the solvent removed *in vacuo* to give a colourless gum. Purification by flash chromatography, eluting with 3 : 2 petroleum ether–ethyl acetate, afforded the *title compound* **13** (1.18 g, 100%) as a colourless oil; R_F [petroleum ether–ethyl acetate (2 : 1)] 0.23; ν_{max} (neat)/cm^{-1} 1734, 1693 (CO), 1312 (SO_2), 1133 (SO_2); δ_H ($CDCl_3$, 400 MHz) 1.71 (3 H, d, *J* 7.0 Hz, CH_3), 2.56 (3 H, s, CH_3), 4.44 (1 H, d, *J* 12.9 Hz, CH_2), 4.68 (1 H, d, *J* 12.9 Hz, CH_2), 5.03 (1 H, q, *J* 7.0 Hz, CH), 5.11 (1 H, d, *J* 11.6 Hz, CH_2), 5.21 (1 H, d, *J* 11.6 Hz, CH_2), 7.04–7.09 (2 H, m, 2 ArH), 7.22–7.25 (1 H, m, ArH), 7.32–7.50 (8 H, m, 8 ArH), 7.60–7.63 (2 H, m, 2 ArH); δ_C ($CDCl_3$, 100 MHz) 13.5 (CH_3), 29.3 (CH_3), 52.2 (CH_2), 55.4 (CH), 70.8 (CH_2), 112.3 (ArH), 121.7 (ArH), 123.2 (C), 125.1 (C), 127.6 (2 ArH), 128.2 (ArH), 128.5 (2 ArH), 128.8 (2 ArH), 129.4 (ArH), 130.0 (ArH), 131.0 (ArH), 133.7 (ArH), 136.4 (C), 140.5 (C), 156.1 (Ar(C)O), 202.5 (ketone); *m*/*z* (CI) 426 (MNH_4^+, 60%), 228 (95), 211 (100); [Found MNH_4^+, 426.1742 (error = 0.6 ppm). $C_{24}H_{24}O_4S$ requires: MNH_4^+, 262.1266].

(±)-1-{2-[1-(2-Benzyloxyphenyl)ethanesulfonylmethyl]-phenyl}-ethanol, 14

To a stirred solution of **13** (1.17 g, 2.9 mmol) in ethanol (15 mL) at room temperature was added sodium borohydride (0.22 g, 5.8 mmol). The reaction was stirred at room temperature for 6 hours. The solvent was then removed *in vacuo* and the residue extracted with ethyl acetate, washing with water and brine and drying over sodium sulfate. Filtration and removal of the solvent *in vacuo* afforded a 1 : 1 mixture of diastereomers of the *title compound* **14** (1.15 g, 98%) as a colourless gum; R_F [petroleum ether–ethyl acetate (1 : 1)] 0.26; ν_{max} (neat)/cm^{-1} 3490 (OH), 1734, 1245; δ_H ($CDCl_3$, 400 MHz) 1.33 (3 H, d, *J* 6.4 Hz, CH_3), 1.38 (3 H, d, *J* 6.4 Hz, CH_3), 1.76 (6 H, m, 2 CH_3), 2.77 (2 H, brs, 2 OH), 4.05 (1 H, d, *J* 13.6 Hz, CH_2), 4.12 (1 H, d, *J* 13.6 Hz, CH_2), 4.23 (1 H, d, *J* 13.6 Hz, CH_2), 4.33 (1 H, d, *J* 13.6 Hz, CH_2), 4.71 (1 H, q, *J* 6.4 Hz, CH), 4.82 (1 H, q, *J* 6.4 Hz, CH), 5.06–5.19 (6 H, m, 2 CH_2), 7.07–7.18 (8 H, m, 8 ArH), 7.34–7.50 (16 H, m, 16 ArH), 7.62 (1 H, d, *J* 8.0 Hz, ArH), 7.64 (1 H, d, *J* 8.0 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 13.6 (CH_3), 14.9 (CH_3), 22.7 (CH_3), 23.1 (CH_3), 51.3 (2 CH_2), 55.4 (2 CH), 71.4 (2 CH_2), 74.3 (CH), 74.4 (CH), 112.4 (2 ArH), 122.1 (2 ArH), 124.3 (2 C), 126.4 (2 ArH), 127.4 (2 ArH), 127.5 (2 ArH), 127.8 (4 ArH), 128.7 (6 ArH), 128.8 (2 ArH), 129.8 (2 C), 130.3 (2 ArH), 132.4 (2 ArH), 135.3 (2 C), 143.4 (2 C), 156.4 (2 Ar(C)O); *m*/*z* (CI) 428 (MNH_4^+, 6%), 211 (100); [Found MNH_4^+, 428.1896 (error = 0.1 ppm). $C_{24}H_{26}O_4S$ requires: MNH_4^+, 428.1896].

(±)-1-(2-Benzyloxyphenyl)-ethylsulfonylmethyl-[2-(1-methoxy-ethyl)]-phenyl, 20

To a stirred solution of **14** (0.28 g, 0.7 mmol) in THF (8 mL) at 0 °C under nitrogen was added sodium hydride (60% w/w in mineral oil, 0.03 g, 0.8 mmol). The reaction was stirred for 30 minutes at 0 °C before addition of methyl iodide (50 µL, 0.8 mmol). The mixture was then warmed to room temperature and allowed to stir for 3 hours. The solvent was removed *in vacuo*, and the residue extracted with ethyl acetate, washing with water and brine and drying over magnesium sulfate. Filtration and removal of the solvent *in vacuo* gave a yellow oil (0.21 g). Purification by flash chromatography, eluting with 3 : 1 petroleum ether–ethyl acetate, afforded a 1 : 1 mixture of diastereomers of the *title compound* **20** (0.09 g, 30%) as a yellow oil; R_F [petroleum ether–ethyl acetate (1 : 1)] 0.43; ν_{max} (neat)/cm^{-1} 2977, 1600, 1312, 1134 (SO_2); δ_H ($CDCl_3$, 400 MHz) 1.18 (3 H, d, *J* 6.4 Hz, CH_3), 1.26 (3 H, d, *J* 6.4 Hz, CH_3), 1.76 (6 H, d, *J* 7.0 Hz, 2 CH_3), 3.05 (3 H, s, OCH_3), 3.09 (3 H, s, OCH_3), 4.03 (1 H, d, *J* 6.7 Hz, CH_2), 4.06 (1 H, d, *J* 6.7 Hz, CH_2), 4.10 (1 H, d, *J* 6.7 Hz, CH_2), 4.14 (1 H, d, *J* 6.7 Hz, CH_2), 4.26 (1 H, q, *J* 6.4 Hz, CH), 4.36 (1 H, q, *J* 6.4 Hz, CH), 5.05–5.14 (6 H, m, 2 CH_2; 2 CH), 7.06–7.19 (8 H, m, 8 ArH), 7.31–7.48 (16 H, m, 16 ArH), 7.66 (2 H, d, *J* 6.8 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 13.2 (CH_3), 14.3 (CH_3), 22.6 (CH_3), 23.0 (CH_3), 52.3 (2 CH_2), 55.3 (CH), 55.4 (CH), 56.4 (2 OCH_3), 71.0 (2 CH_2), 75.4 (CH), 75.5 (CH), 112.3 (2 ArH), 122.0 (2 ArH), 124.3 (2 C), 126.3 (2 ArH), 127.4 (2 ArH), 127.5 (2 ArH), 127.7 (4 ArH), 128.6 (6 ArH), 128.9 (2 ArH), 129.8 (2 C), 130.3 (2 ArH), 132.4 (2 ArH), 136.3 (2 C), 144.2 (2 C), 156.0 (2 Ar(C)O); *m*/*z* (CI) 442 (MNH_4^+, 100%); [Found MNH_4^+, 442.2055 (error = 0.3 ppm). $C_{25}H_{28}O_4S$ requires: MNH_4^+, 442.2052].

In a similar manner to the procedures described above sulfones **27–33** were prepared.

(±)-1-{2-[1-(2-Methoxyphenyl)-ethanesulfonylmethyl]-phenyl}-ethanol, 27

Isolated as a 1 : 1 mixture of diastereomers in an overall yield of 56% (4 steps) as a creamy white oil; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.08; ν_{max} (neat)/cm^{-1} 3355 (OH), 1265, 739; δ_H ($CDCl_3$, 400 MHz) 1.36 (3 H, d, *J* 6.4 Hz, CH_3), 1.47 (3 H, d, *J* 6.4 Hz, CH_3), 1.76 (6 H, 2 d, *J* 7.7 Hz, 2 CH_3), 2.82 (1 H, s, OH), 2.91 (1 H, s, OH), 3.89 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 4.11 (2 H, m, CH_2), 4.29 (1 H, d, *J* 13.4 Hz, CH_2), 4.36 (1 H, d, *J* 13.4 Hz, CH_2), 4.75 (1 H, q, *J* 6.4 Hz, CH), 4.97 (1 H, q, *J* 6.4 Hz, CH), 5.04–5.07 (2 H, m, 2 CH), 6.94–6.97 (2 H, m, ArH), 7.08–7.26 (6 H, m, 6 ArH), 7.37–7.41 (4 H, m, 4 ArH), 7.50–7.53 (2 H, m, 2 ArH), 7.60 (1 H, d, *J* 7.6 Hz, ArH), 7.65 (1 H, d, *J* 7.6 Hz, ArH); *m*/*z* (CI) 352 (MNH_4^+, 3.5%), 152 (45), 135 (100); [Found MNH_4^+, 352.1583 (error = 1.3 ppm). $C_{18}H_{22}O_4S$ requires: MNH_4^+, 352.1578].

Due to the complex nature of the diastereomeric mixture, it proved impossible to fully assign the ^{13}C-NMR spectrum.

1-(2-Methoxyphenyl)-ethylsulfonylmethyl-(2-nitro)-phenyl, 28

Isolated in an overall yield of 82% (2 steps) as a white solid; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.19; mp 155–158 °C; ν_{max} (nujol)/cm^{-1} 1461, 1377 (SO_2), 1115; δ_H ($CDCl_3$, 400 MHz) 1.73 (3 H, d, J 7.2 Hz, CH_3), 3.92 (3 H, s, OCH_3), 4.35 (1 H, d, *J* 13.3 Hz, CH_2), 4.83 (1 H, d, *J* 13.3 Hz, CH_2), 5.06 (1 H, q, *J* 7.2 Hz, CH), 6.96 (1 H, d, *J* 8.0 Hz, ArH), 7.07 (1 H, dd, *J* 8.0, 8.0 Hz, ArH), 7.35–7.38 (2 H, m, 2 ArH), 7.53–7.55 (3 H, m, 3 ArH), 8.03 (1 H, d, *J* 8.0 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 13.4 (CH_3), 53.0 (CH_2), 56.1 (OCH_3), 56.3 (CH), 111.1 (ArH), 122.0 (ArH), 127.7 (C), 122.8 (C), 126.0 (ArH), 129.8 (ArH), 130.1 (ArH), 130.7 (ArH), 133.4 (ArH), 134.4 (ArH), 150.3 (Ar(C)NO_2), 157.0 (Ar(C)O); *m*/*z* (CI) 353 (MNH_4^+, 3.5%), 135 (100); [Found MNH_4^+, 353.1176 (error = 1.3 ppm). $C_{16}H_{17}NO_5S$ requires: MNH_4^+, 353.1171].

(±)-1-[2-(2,4-Dimethoxyphenylmethanesulfonylmethyl)-phenyl]-ethanol, 29

Isolated in an overall yield of 19% (4 steps) as a white solid; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.12; mp 101–104 °C; δ_H ($CDCl_3$, 400 MHz) 1.45 (3 H, d, *J* 6.4 Hz, CH_3), 2.96 (1 H, s, OH), 3.85 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.33–4.39 (4 H, m, 2 CH_2), 4.96 (1 H, q, *J* 6.4 Hz, CH), 6.53 (1 H, s, ArH), 6.57 (1 H, d, *J* 8.0 Hz, ArH), 7.23–7.27 (2 H, m, 2 ArH), 7.37–7.41 (2 H, m, 2 ArH), 7.53 (1 H, d, *J* 8.0 Hz, ArH); this compound was immediately subjected to the RBR due to problems with stability.

(2,4-Dimethoxy)-phenylmethanesulfonylmethyl-(2-nitro)-phenyl, 30

Isolated in an overall yield of 78% (2 steps) as an orange glass; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.16; mp 119–122 °C; ν_{max} (nujol)/cm^{-1} 1613, 1348 (SO_2), 1157 (SO_2); δ_H ($CDCl_3$, 400 MHz) 3.84 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 4.38 (2 H, s, CH_2), 4.71 (2 H, s, CH_2), 6.53–6.57 (2 H, m, 2 ArH), 7.34 (1 H, d, *J* 8.4 Hz, ArH), 7.49–7.60 (3 H, m, 3 ArH), 8.06 (1 H, d, *J* 7.6 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 54.0 (CH_2), 54.8 (CH_2), 55.9 (OCH_3), 56.1 (OCH_3), 99.3 (ArH), 105.7 (ArH), 108.8 (C), 122.7 (C), 126.0 (ArH), 130.2 (ArH), 133.5 (ArH), 133.8 (ArH), 134.5 (ArH) 150.5 (Ar(C)NO_2), 158.8 (Ar(C)O), 162.3 (Ar(C)O); *m*/*z* (CI) 369 (MNH_4^+, 15%), 151 (100); [Found MNH_4^+, 369.1125 (error = 1.3 ppm). $C_{16}H_{17}NO_6S$ requires: MNH_4^+, 369.1120].

(±)-1-(2-Phenylmethanesulfonylmethylphenyl)-ethanol, 31

Isolated in an overall yield of 45% (4 steps) as a clear gum; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.15; ν_{max} (neat)/cm^{-1} 3320 (OH), 1122; δ_H ($CDCl_3$, 400 MHz) 1.46 (3 H, d, *J* 6.4 Hz, CH_3), 2.80 (1 H, s, OH), 4.31 (2 H, s, CH_2), 4.37 (2 H, d, *J* 5.6 Hz, CH_2), 4.99 (1 H, q, *J* 6.4 Hz, CH), 7.25–7.28 (2 H, m, 2 ArH), 7.40–7.44 (6 H, m, 6 ArH), 7.56 (1 H, d, *J* 7.6 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 23.8 (CH_3), 54.9 (CH_2), 59.8 (CH_2), 67.2 (CH), 123.9 (C), 127.6 (ArH), 127.9 (C), 128.2 (ArH), 129.5 (2 ArH), 129.6 (ArH), 130.2 (ArH), 131.2 (2 ArH), 132.9 (ArH), 146.2 (C); *m*/*z* (CI) 308 (MNH_4^+, 5%), 273 (100); [Found MNH_4^+, 308.1325 (error = 1.6 ppm). $C_{16}H_{18}O_3S$ requires: MNH_4^+, 308.1320].

(2-Nitro)-phenylmethanesulfonylmethylphenyl, 32

Isolated in an overall yield of 81% (2 steps) as a white solid; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.30; mp 132–135 °C; ν_{max} (nujol)/cm^{-1} 1460, 1308 (SO_2), 1121 (SO_2); δ_H ($CDCl_3$, 400 MHz) 4.32 (2 H, s, CH_2), 4.72 (2 H, s, CH_2), 7.40–7.48 (5 H, m, 5 ArH), 7.54–7.57 (3 H, m, 3 ArH), 8.09 (1 H, d, *J* 8.0 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 54.8 (CH_2), 60.7 (CH_2), 122.7 (C), 126.2 (ArH), 127.5 (C), 129.5 (2 ArH), 129.7 (ArH), 130.6 (ArH), 131.2 (2 ArH), 133.9 (ArH), 134.6 (ArH)–Ar(C)NO_2 signal not observed; *m*/*z* (CI) 309 (MNH_4^+, 20%), 262 (60), 108 (100); [Found MNH_4^+, 309.0908 (error = 0.3 ppm). $C_{14}H_{13}NO_4S$ requires: MNH_4^+, 309.0909].

(2-Methoxy)-phenylmethanesulfonylmethylphenyl, 33

Isolated in an overall yield of 63% (2 steps) as a white solid; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.26; mp 92–95 °C; ν_{max} (nujol)/cm^{-1} 1461, 1303 (SO_2), 1157 (SO_2); δ_H ($CDCl_3$, 400 MHz) 3.88 (3 H, s, OCH_3), 4.12 (2 H, s, CH_2), 4.36 (2 H, s, CH_2), 6.95 (1 H, d, *J* 8.4 Hz ArH), 7.02 (1 H, dd, *J* 7.6, 7.6 Hz, ArH), 7.34–7.39 (6 H, m, 6 ArH), 7.44 (1 H, d, *J* 7.6 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 53.5 (CH_2), 56.0 (OCH_3), 58.3 (CH_2), 111.4 (ArH), 117.0 (C), 121.6 (ArH), 127.6 (C), 129.1 (2 ArH), 129.2 (ArH), 131.0 (ArH), 131.5 (2 ArH), 133.1 (ArH), 157.8 (Ar(C)O); *m*/*z* (CI) 294 (MNH_4^+, 6%), 277 (MH^+, 2), 121 (100); [Found MNH_4^+, 294.1163 (error = 0.2 ppm). $C_{15}H_{16}O_3S$ requires: MNH_4^+, 294.1164].

Representative RBR procedure

2-{2-[2-(2-Benzyloxyphenyl)-propenyl]-phenyl}-2-methyl-[1,3]-dioxolane, 7. To a stirred solution of **6** (0.28 g, 0.6 mmol) in carbon tetrachloride (4 mL), *tert*-butanol (4 mL) and water (0.7 mL), was added powdered potassium hydroxide (0.74 g, 13.0 mmol). The reaction mixture was then heated at 80 °C for 14 hours. The solvent was then removed *in vacuo* and the residue extracted with ethyl acetate, washing with water and saturated sodium chloride solution and drying over magnesium sulfate. Filtration and removal of the solvent *in vacuo* gave a brown oil (0.25 g). Purification by flash chromatography, eluting with 14 : 1 petroleum ether–ethyl acetate, afforded a 1 : 1 mixture of *Z* and *E* isomers of the *title compound* **7** (0.20 g, 83%) as a colourless oil. These isomers were separated using preparative HPLC (MeCN–AcOH, mixed gradient solvent system);

Z-**7**: R_F [petroleum ether–ethyl acetate (4 : 1)] 0.48; ν_{max} (neat)/cm^{-1} 2886, 1596, 1039; δ_H ($CDCl_3$, 400 MHz) 1.59 (3 H, s, CH_3), 1.97 (3 H, s, CH_3), 3.63–3.65 (2 H, m, 2 CH), 3.90–3.92 (2 H, m, 2 CH), 5.05 (2 H, s, CH_2), 6.89–6.94 (2 H, m, 2 ArH), 6.90 (1 H, s, vinyl CH), 7.16–7.37 (10 H, m, 10 ArH), 7.51 (1 H, d, *J* 8.0 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 19.0 (CH_3), 26.6 (CH_3), 64.4 (2 CH_2), 70.6 (CH_2), 109.7 (C), 112.8 (ArH), 121.4 (ArH), 126.3 (ArH), 126.9 (ArH), 127.6 (2 ArH), 127.9 (ArH), 128.1 (ArH), 128.8 (2 ArH), 130.1 (ArH), 130.4 (vinyl CH), 131.7 (ArH), 135.8 (C), 136.6 (C), 136.7 (C), 137.8 (C), 141.1 (C), 156.4 (Ar(C)O)—1 ArH signal not observed; *m*/*z* (CI) 387 (MH^+, 90%), 325 (100); [Found MH^+, 387.1959 (error = 0.4 ppm). $C_{26}H_{26}O_3$ requires: MH^+, 387.1960].

E-**7**: R_F [petroleum ether–ethyl acetate (4 : 1)] 0.48; ν_{max} (neat)/cm^{-1} 2886, 1237, 1040; δ_H ($CDCl_3$, 400 MHz) 1.70 (3 H, s, CH_3), 2.18 (3 H, s, CH_3), 3.703.73 (2 H, m, 2 CH), 3.96–3.99 (2 H, m, 2 CH), 5.02 (2 H, s, CH_2), 6.68 (1 H, dd, *J* 8.0, 8.0 Hz, ArH), 6.74–6.79 (4 H, m, 4 ArH), 6.94–6.97 (1 H, m, ArH), 7.03

(1 H, dd, *J* 8.0, 8.0 Hz, ArH), 7.12 (1 H, brs, vinyl CH), 7.20–7.25 (5 H, m, 5 ArH), 7.41 (1 H, d, *J* 7.6 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 26.4 (CH_3), 26.9 (CH_3), 64.6 (2 CH_2), 70.1 (CH_2), 109.9 (C), 112.5 (ArH), 121.2 (ArH), 125.7 (ArH), 126.2 (vinyl CH), 127.3 (2 ArH), 127.5 (ArH), 127.6 (ArH), 128.0 (ArH), 128.2 (ArH), 128.9 (2 ArH), 130.4 (ArH), 131.4 (ArH), 132.3 (C), 136.4 (C), 136.6 (C), 137.8 (C), 140.2 (C), 156.4 (Ar(C)O); *m*/*z* (CI) 387 (MH^+, 100%), 325 (85); [Found MH^+, 387.1968 (error = 2.1 ppm). $C_{26}H_{26}O_3$ requires: MH^+, 387.1960].

In a similar manner to the procedure described above, olefins **15** (see later for corresponding data), **16** and **34–41** were prepared.

***Z*-(±)-2-{2-[2-(2-Benzyloxyphenyl)-propenyl]-phenyl}-ethanol, 16.** Isolated as a 1 : 16 mixture of *E* : *Z*-isomers (inseparable), in an 89% yield, as a yellow oil; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.25; ν_{max} (neat)/cm^{-1} 3400 (OH), 2857, 1447; δ_H ($CDCl_3$, 400 MHz) 1.36 (3 H, d, *J* 5.6 Hz, CH_3), 1.83 (1 H, brs, OH), 2.01 (3 H, s, CH_3), 5.08 (1 H, q, *J* 5.6 Hz, CH), 5.12 (2 H, s, CH_2), 6.63 (1 H, brs, vinyl CH), 7.01–7.04 (2 H, m, 2 ArH), 7.26–7.45 (10 H, m, 10 ArH), 7.55 (1 H, d, *J* 7.2 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 18.9 (CH_3), 29.8 (CH_3), 67.4 (CH), 70.4 (CH_2), 112.4 (ArH), 121.1 (ArH), 124.6 (ArH), 126.9 (ArH), 127.4 (ArH), 127.5 (2 ArH), 127.7 (ArH), 128.0 (ArH), 128.4 (ArH), 128.6 (2 ArH), 129.6 (C), 129.8 (ArH), 134.6 (C), 135.6 (C), 137.3 (C), 138.4 (vinyl CH), 144.3 (C), 155.9 (Ar(C)O); *m*/*z* (CI) 344 ([M − H_2O]NH_4^+, 20%), 327 ([M − H_2O]$^+$, 100); [Found [M − H_2O]NH_4^+, 344.2004 (error = 3.2 ppm). $C_{24}H_{24}O_2$ requires: [M − H_2O]NH_4^+, 344.2014].

***Z*-(±)-2-{2-[2-(2-Methoxyphenyl)-propenyl]-phenyl}-ethanol, 34.** Isolated as a 1 : 9 mixture of *E* : *Z*-isomers (inseparable), in a 59% yield, as a colourless oil; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.23; ν_{max} (neat)/cm^{-1} 3398 (OH), 2971, 1489, 1251; δ_H ($CDCl_3$, 400 MHz) 1.49 (3 H, d, *J* 7.6 Hz, CH_3), 1.99 (3 H, s, CH_3), 2.28 (1 H, s, OH), 3.86 (3 H, s, OCH_3), 5.13 (1 H, q, *J* 7.6 Hz, CH), 6.63 (1 H, brs, vinyl CH), 6.95 (3 H, m, 3 ArH), 7.25–7.31 (4 H, m, 4 ArH), 7.54 (1 H, d, *J* 8.0 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 19.1 (CH_3), 23.9 (CH_3), 55.9 (OCH_3), 67.9 (CH), 111.4 (ArH), 121.0 (ArH), 125.0 (ArH), 127.1 (vinyl CH), 127.2 (ArH), 127.6 (ArH), 128.7 (ArH), 129.6 (ArH), 130.2 (ArH), 134.4 (C), 136.1 (C), 138.5 (C), 144.4 (C), 157.0 (Ar(C)O); *m*/*z* (EI) 268 (M^+, 1%), 135 (100); [Found M^+, 268.1466 (error = 0.9 ppm). $C_{18}H_{20}O_2$ requires: M^+, 268.1463].

2-(2-Methoxyphenyl)-1-(2-nitrophenyl)-propene, 35. Isolated as a 1 : 1 mixture of *E* : *Z*-isomers (inseparable), in a 36% yield, as a bright yellow oil; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.45; ν_{max} (neat)/cm^{-1} 2959, 1523, 1346, 752; δ_H ($CDCl_3$, 400 MHz) 2.05 (3 H, s, CH_3), 2.22 (3 H, s, CH_3), 3.68 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 6.75–6.98 (7 H, m, 7 ArH), 7.13–7.16 (2 H, m, 2 ArH), 7.30–7.38 (3 H, m, 3 ArH), 7.54–7.59 (2 H, m, 2 ArH), 7.83–7.85 (1 H, m, 1 ArH), 8.02 (1 H, d, *J* 8.0 Hz); *m*/*z* (CI) 287 (MNH_4^+, 100%), 270 (MH^+, 45), 238 (65); [Found MH^+, 270.1130 (error = 0.1 ppm). $C_{16}H_{15}NO_3$ requires: MH^+, 270.1130].

Due to the complex nature of the isomeric mixture, it proved impossible to fully assign the ^{13}C-NMR spectrum.

(±)-2-(2-Benzyloxyphenyl)-1-[2-(1-methoxyethyl)phenyl]-propene, 36. Isolated as a 3 : 7 mixture of *E* : *Z*-isomers (inseparable), in a 90% yield, as a clear gum; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.48; ν_{max} (neat)/cm^{-1} 3064, 2975, 1447, 1224; δ_H ($CDCl_3$, 400 MHz) 1.34 (3 H, d, *J* 6.4 Hz, *Z*-CH_3), 1.39 (3 H, d, *J* 6.4 Hz, *E*-CH_3), 2.03 (3 H, s, *Z*-CH_3), 2.27 (3 H, s, *E*-CH_3), 3.16 (3 H, s, *Z*-OCH_3), 3.21 (3 H, s, *E*-OCH_3), 4.59 (1 H, q, *J* 6.4 Hz, *Z*-CH), 4.69 (1 H, q, *J* 6.4 Hz, *E*-CH), 5.13 (CH_2 signal for both isomers), 6.61 (1 H, brs, *Z*-CH), 6.68 (1 H, brs, *E*-CH), remaining aromatic (ArH) signals at 6.74, 6.85, 7.01, 7.13 and 7.22–7.50 all multiplets (m)—unable to define *E*/*Z* or integrals; *m*/*z* (CI) 327 ([MH − MeOH]$^+$, 100%); [Found [MH − MeOH]$^+$, 327.1746 (error = 0.8 ppm). $C_{25}H_{26}O_2$ requires: [MH − MeOH]$^+$, 327.1749].

Due to the complex nature of the isomeric mixture, it proved impossible to fully assign the ^{13}C-NMR spectrum.

(±)-1-{2-[2-(2,4-Dimethoxyphenyl)-vinyl]-phenyl}-ethanol, 37. Isolated as a 2 : 3 mixture of *E* : *Z*-isomers (separable), in an 84% combined yield, both as clear oils;

Z-**37**: R_F [petroleum ether–ethyl acetate (4 : 1)] 0.45; ν_{max} (neat)/cm^{-1} 3412 (OH), 2967, 1608; δ_H ($CDCl_3$, 400 MHz) 1.43 (3 H, d, *J* 6.4 Hz, CH_3), 1.85 (1 H, brs, OH), 3.73 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 5.15 (1 H, q, *J* 6.4 Hz, CH), 6.18 (1 H, d, *J* 8.8 Hz, ArH), 6.40 (1 H, s, ArH), 6.66 (1 H, d, *J* 12.0 Hz, vinyl CH), 6.78 (2 H, m, 1 ArH and 1 vinyl CH), 7.08–7.13 (2 H, m, ArH), 7.22–7.25 (1 H, m, ArH), 7.53 (1 H, d, *J* 7.6 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 24.2 (CH_3), 55.7 (OCH_3), 55.8 (OCH_3), 67.5 (CH), 98.7 (ArH), 104.5 (ArH), 118.7 (C), 125.3 (ArH), 126.3 (vinyl CH), 126.9 (vinyl CH), 127.5 (ArH), 127.8 (ArH), 129.8 (ArH), 130.7 (ArH), 136.3 (C), 143.7 (C), 158.7 (Ar(C)O), 160.6 (Ar(C)O); *m*/*z* (CI) 285 (MH^+, 15%) 267 (100), 151 (25); [Found MH^+, 285.1488 (error = 0.9 ppm). $C_{18}H_{20}O_3$ requires: MH^+, 285.1491].

E-**37**: R_F [petroleum ether–ethyl acetate (4 : 1)] 0.41; ν_{max} (neat)/cm^{-1} 3412 (OH), 2968, 1608; δ_H ($CDCl_3$, 400 MHz) 1.51 (3 H, d, *J* 6.4 Hz, CH_3), 1.86 (1 H, brs, OH), 3.83 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.31 (1 H, q, *J* 6.4 Hz, CH), 6.47 (1 H, s, ArH), 6.52 (1 H, d, *J* 8.4 Hz, ArH), 7.22–7.27 (3 H, m 2 ArH and 1 vinyl CH), 7.34 (1 H, d, *J* 16.4 Hz, vinyl CH), 7.49 (1 H, d, *J* 8.4 Hz, ArH), 7.51–7.54 (1 H, m, ArH), 7.58–7.61 (1 H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 24.7 (CH_3), 55.8 (OCH_3), 55.9 (OCH_3), 67.5 (CH), 99.0 (ArH), 105.4 (ArH), 120.1 (C), 124.3 (vinyl CH), 125.1 (ArH), 126.3 (vinyl CH), 126.4 (ArH), 127.8 (ArH), 127.9 (ArH), 128.0 (ArH), 136.3 (C), 143.1 (C), 158.5 (Ar(C)O), 161.0 (Ar(C)O); *m*/*z* (CI) 285 (MH^+, 10%), 267 (100), 151 (20); [Found MH^+, 285.1491 (error = 0.1 ppm). $C_{18}H_{20}O_3$ requires: MH^+, 285.1491].

***E*-1-(2,4-Dimethoxyphenyl)-2-(2-nitrophenyl)-ethene, 38.** Isolated as exclusively the *E*-isomer, in a 47% yield, as an orange glass; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.37; mp 94–97 °C; ν_{max} (nujol)/cm^{-1} 1514, 1461, 1160; δ_H ($CDCl_3$, 400 MHz) 3.85 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 6.47 (1 H, s, ArH), 6.53 (1 H, d, *J* 8.0 Hz, ArH), 7.35 (1 H, t, *J* 8.4 Hz, ArH), 7.39 (1 H, d, *J* 16.2 Hz, vinyl CH), 7.51–7.55 (3 H, m, 2 ArH and 1 vinyl CH), 7.80 (1 H, d, *J* 7.6 Hz, ArH), 7.91 (1 H, d, *J* 7.6 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 55.8 (OCH_3), 55.9 (OCH_3), 98.9 (ArH), 105.5 (ArH), 119.1 (C), 121.7 (vinyl CH), 125.0 (ArH), 127.5 (ArH), 128.3 (vinyl CH), 128.6 (ArH), 129.1 (ArH), 133.2 (ArH), 134.3 (C), 148.3 (Ar(C)NO_2), 158.9 (Ar(C)O), 161.7 (Ar(C)O); *m*/*z* (EI) 285 (M^+, 75%), 165 (90), 149 (100); [Found M^+, 285.1006 (error = 1.8 ppm). $C_{16}H_{15}NO_4$ requires: M^+, 285.1001].

(±)-1-(2-Styrylphenyl)-ethanol, 39. Isolated as a 2 : 3 mixture of *E* : *Z*-isomers (inseparable), in an 83% yield, as a clear oil; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.38; ν_{max} (neat)/cm^{-1} 3356 (OH), 2973, 1446, 1072; δ_H ($CDCl_3$, 400 MHz) 1.41 (3 H, d, *J* 6.4 Hz, *Z*-CH_3), 1.51 (3 H, d, *J* 6.4 Hz, *E*-CH_3), 1.77 (1 H, brs, *Z*-OH), 1.92 (1 H, brs, *E*-OH), 5.12 (1 H, q, *J* 6.4 Hz, *Z*-CH), 5.29 (1 H, q, *J* 6.4 Hz, *E*-CH), 6.63 (1 H, d, *J* 12.2 Hz, *Z*-vinyl CH), 6.73 (1 H, d, *J* 12.2 Hz, *Z*-vinyl CH), 6.97 (1 H, d, *J* 16.0 Hz, *E*-vinyl CH), 7.46 (1 H, d, *J* 16.0 Hz, *E*-vinyl CH), remaining aromatic (ArH) signals at 7.05, 7.13, 7.25–7.38 and 7.49–7.59 all multiplets (m)—unable to define *E*/*Z* or integrals; *m*/*z* (EI) 224 (M^+, 10%), 133 (55), 91 (100); [Found M^+, 224.1202 (error = 0.2 ppm). $C_{16}H_{16}O$ requires: M^+, 224.1201].

Due to the complex nature of the isomeric mixture, it proved impossible to fully assign the ^{13}C-NMR spectrum.

***E*-1-(2-Nitrophenyl)-2-phenylethene, 40.** Isolated as exclusively the *E*-isomer, in a 32% yield, as a yellow gum; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.52; δ_H ($CDCl_3$, 400 MHz) 7.08 (1 H, d, *J* 16.0 Hz, vinyl CH), 7.31–7.42 (4 H, m, 3 ArH and

1 vinyl CH), 7.53–7.62 (4 H, m, 4 ArH), 7.76 (1 H, d, *J* 8.0 Hz, ArH), 7.96 (1 H, d, *J* 8.0 Hz, ArH).

Data consistent with literature.[19]

***E*-1-(2-Methoxyphenyl)-2-phenylethene, 41.** Isolated as exclusively the *E*-isomer, in an 80% yield, as a white solid; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.58; mp 54–56 °C (lit.[19] 56–59 °C); δ_H ($CDCl_3$, 400 MHz) 3.89 (3 H, s, OCH_3), 6.90 (1 H, d, *J* 8.0 Hz, ArH), 6.97 (1 H, t, *J* 7.6 Hz, ArH), 7.10 (1 H, d, *J* 16.8 Hz, vinyl CH), 7.22–7.25 (2 H, m, 2 ArH), 7.35 (2 H, dd, *J* 7.2, 7.2 Hz, 2 ArH), 7.48 (1 H, d, *J* 16.8 Hz, vinyl CH), 7.53 (2 H, dd, *J* 7.2, 7.2 Hz, 2 ArH), 7.60 (1 H, d, *J* 7.6 Hz, ArH).

Data consistent with literature.[20]

***Z*-2-{2-[2-(2-Benzyloxyphenyl)-propenyl]-phenyl}-ethanone, 15 *via* MnO_2 oxidation of 16.** To a stirred solution of **16** (0.42 g, 1.22 mmol) in dichloromethane (20 mL) was added manganese(IV) dioxide (1.04 g, 12.2 mmol) and the reaction mixture heated at reflux. After 16 hours a further portion of manganese(IV) dioxide (1.04 g, 12.2 mmol) was added and heating continued for 4 hours. Filtration through Celite®, washing with dichloromethane, and subsequent removal of solvent *in vacuo* afforded the *title compound* **15** (0.39 g, 94%) as a yellow gum; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.39; ν_{max} (neat)/cm^{-1} 2922, 1682 (CO), 1254; δ_H ($CDCl_3$, 400 MHz) 1.96 (3 H, s, CH_3), 2.45 (3 H, s, CH_3), 5.04 (2 H, s, CH_2), 6.71 (1 H, s, vinyl CH), 6.88–6.91 (2 H, m, 2 ArH), 7.18–7.40 (10 H, m, 10 ArH), 7.60 (1 H, d, *J* 7.6 Hz); δ_C ($CDCl_3$, 100 MHz) 19.1 (CH_3), 30.5 (CH_3), 70.8 (CH_2), 112.9 (ArH), 121.5 (ArH), 127.1 (ArH), 127.7 (2 ArH), 128.3 (CH), 128.9 (2 ArH), 129.0 (ArH), 129.3 (ArH), 129.5 (C), 130.0 (ArH), 131.3 (ArH), 131.4 (ArH), 135.1 (C), 137.6 (C), 137.9 (C), 138.5 (C), 139.3 (C), 156.4 (Ar(C)O), 202.8 (ketone)—1 ArH signal not observed; *m*/*z* (CI) 343 (MH^+, 100%); [Found MH^+, 343.1699 (error = 0.3 ppm). $C_{24}H_{22}O_2$ requires: MH^+, 343.1698].

(±)-1,9-Dimethyl-16,17-dioxa-tetracyclo[7,7,1,$0^{2,7}$,$0^{10,15}$]heptadeca-2,4,6,10,12,14-hexaene, 44. To a stirred solution of **15** (16 : 1 *Z* : *E*, 0.55 g, 1.6 mmol) in dichloromethane (40 mL) was added tin(II) chloride (3.63 g, 16.1 mmol). The reaction was allowed to stir at room temperature for 2 days, filtered through Celite®, and the solvent removed *in vacuo* to give an orange oil (0.520 g). Purification by flash chromatography, eluting with 9 : 1 petroleum ether–ethyl acetate, afforded the *title compound* **44** (0.38 g, 94%) as a white solid; R_F [Petroleum ether–ethyl acetate (4 : 1)] 0.42; mp 112–114 °C; ν_{max} (nujol)/cm^{-1} 1115, 901; δ_H ($CDCl_3$, 400 MHz) 1.74 (3 H, s, CH_3), 1.96 (3 H, s, CH_3), 2.92 (1 H, d, *J* 16.0 Hz, CH_2), 3.27 (1 H, d, *J* 16.0 Hz, CH_2), 6.68 (1 H, d, *J* 8.0 Hz, ArH), 6.82 (1 H, dd, *J* 7.6, 7.6 Hz, ArH), 6.99–7.07 (3 H, m, 3 ArH), 7.14–7.26 (2 H, m, 2 ArH), 7.43 (1 H, d, *J* 8.0 Hz, ArH); δ_C ($CDCl_3$, 100 MHz) 26.6 (CH_3), 27.6 (CH_3), 43.0 (CH_2), 73.1 (C), 97.6 (C), 116.8 (ArH), 120.7 (ArH), 124.6 (ArH), 125.7 (ArH), 126.7 (ArH), 128.1 (ArH), 128.2 (2 ArH), 133.2 (C), 135.8 (C), 140.8 (C), 151.0 (Ar(C)O); *m*/*z* (CI) 253 (MH^+, 100%); [Found MH^+, 253.1234 (error = 2.1 ppm). $C_{17}H_{16}O_2$ requires: MH^+, 253.1228].

CCDC reference number 219622. See http://www.rsc.org/suppdata/ob/b4/b418426b/ for crystallographic data in .cif or other electronic format.

(±)-1,9-Dimethyl-16,17-dioxa-tetracyclo[7,7,1,$0^{2,7}$,$0^{10,15}$]heptadeca-2,4,6,10,12,14-hexaen-8-one, 45. To a stirred solution of **44** (0.03 g, 0.12 mmol), PDC (0.260 g, 0.70 mmol) and Celite® (0.20 g) in benzene (3.5 mL) at 6–10 °C under nitrogen, was added TBHP (5.5 M in decane, 0.13 mL, 0.7 mmol). The reaction mixture was stirred below 10 °C for 4 days, with further addition of TBHP (2 × 0.13 mL) after 36 h and 72 h. The mixture was then filtered through a pad of Celite®, washing with ethyl acetate, and the solvent removed *in vacuo* to give a yellow gum (0.050 g). Purification by flash chromatography, eluting with 15 : 1 petroleum ether–ethyl acetate, afforded unreacted **44** (0.014 g, 47% recovered) together with the *title compound* **45** (0.013 g, 41%–77% based on recovered starting material) as white crystals; R_F [petroleum ether–ethyl acetate (4 : 1)] 0.40; mp 145–148 °C; ν_{max} (nujol)/cm^{-1} 1704, 916; δ_H ($CDCl_3$, 400 MHz) 1.86 (3 H, s, CH_3), 2.04 (3 H, s, CH_3), 6.76 (1 H, d, *J* 8.0 Hz, ArH), 6.90 (1 H, dd, *J* 7.6, 7.6 Hz, ArH), 7.12–7.17 (2 H, m, 2 ArH), 7.41 (1 H, dd, *J* 7.6, 7.6 Hz, ArH), 7.52 (1 H, dd, *J* 7.7, 7.7 Hz, ArH), 7.63 (1 H, dd, *J* 7.7, 7.7 Hz, ArH), 7.97 (1 H, d, *J* 7.7 Hz, ArH); δ_C (CD_3CN:$CDCl_3$ 1:1, 100 MHz) 19.6 (CH_3), 25.9 (CH_3), 77.1 (C), 96.3 (C), 116.3 (ArH), 120.7 (C), 121.1 (ArH), 124.7 (ArH), 125.1 (2 ArH), 126.7 (C), 128.8 (ArH), 129.2 (ArH), 134.3 (ArH), 139.7 (C), 149.6 (Ar(C)O), 192.9 (ketone); *m*/*z* (CI) 267 (MH^+, 100%); [Found MH^+, 267.1022 (error = 0.2 ppm). $C_{17}H_{14}O_3$ requires: MH^+, 267.1021].

CCDC reference number 257403. See http://www.rsc.org/suppdata/ob/b4/b418426b/ for crystallographic data in .cif or other electronic format.

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