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Triaryl (*Z*)-olefins suitable for radiolabeling with carbon-11 or fluorine-18 radionuclides for positron emission tomography imaging of cyclooxygenase-2 expression in pathological disease

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ABSTRACT

A group of (*Z*)-1,1-diphenyl-2-(4-methylsulfonylphenyl)alk-1-enes were synthesized using methodologies that will allow incorporation of a [^{11}C]OCH_3 substituent at the *para*-position of the C-1 phenyl ring, a [^{11}C]SO_2CH_3 substituent at the *para*-position of the C-2 phenyl ring, a [^{18}F]OCH_2CH_2F substituent at the *para*-position of the C-1 phenyl ring, and a [^{18}F]CH_2CH_2F substituent at the C-2 position of the olefinic bond. The [^{11}C] and [^{18}F] radiotracers are designed as potential radiopharmaceuticals to image cyclooxygenase-2 (COX-2) expression in any organ where COX-2 is upregulated. The COX-1/COX-2 inhibition data acquired suggest that compounds having a [^{11}C]OMe or [^{18}F]OCH_2CH_2F substituent at the *para*-position of the C-1 phenyl ring may be more suitable for imaging COX-2 expression in view of their ability to exclusively inhibit the COX-2 isozyme.

Positron emission tomography (PET) is a valuable medical imaging technique employing compounds labeled with a short-lived positron emitting radioisotope (radiotracer) for quantitative investigations of molecular and cellular transport processes in vivo. In this regard, PET offers exceptional possibilities to study physiology, metabolism, pharmacokinetics and modes of action of novel and established drugs. The most common positron emitters for this purpose include ^{11}C ($t_{1/2}$ = 20.4 min) and ^{18}F ($t_{1/2}$ = 109.6 min). Being bioisosteric with hydrogen, albeit with high electronegativity, ^{18}F is often used to replace hydrogen of otherwise non-fluorinated molecules with minimum effects on biomolecular interactions.[1] The inducible isozyme cyclooxygenase-2 (COX-2) is a relevant target for molecular imaging since low levels of COX-2 are produced during normal cell function in only a few tissues relative to COX-2 over expression that is associated with pathological conditions in a much larger number of organs.[2] COX-2 expression causes a number of undesirable pathophysiological effects that include pain, inflammation, fever, CNS ischemia, and COX-2 upregulation occurs in a variety of malignant tumors.[3–6] Accordingly, selective COX-2 inhibitors have, or may offer, potential for the chemoprevention of various types of cancer such as colon, breast, prostrate, stomach and pancreatic, wherein the over-expression of COX-2 produces COX-2–derived prostaglandins (PGs) that stimulate tumor growth.

A number of radiolabeled compounds have been prepared for use as PET, or SPECT (single photon emission computed tomography), radiotracers to image COX-2 and measure COX-2 over expression. Although [^{11}C]rofecoxib (**1**, see structure in Fig. 1) showed a correlation between [^{11}C]rofecoxib uptake and COX-2 distribution in healthy rats, it's inability to unambiguously detect COX-2 expression in rat inflammation models may have been due to low affinity for the COX-2 isozyme.[7] A [^{18}F] derivative of rofecoxib (**2**) has been synthesized as a potential PET radiotracer.[8] The [^{18}F] derivative of celecoxib (**3**) was synthesized as a potential marker for COX-2 activity.[9] Toyokuni et al. synthesized a [^{18}F]oxazole compound (**4**) as a potential radiotracer to image COX-2.[10] The CH_2F moiety in **4** is metabolically labile. Synthesis of the radioiodinated COX-2 inhibitory potential SPECT radiotracers **5**[11] and **6**[12] have also been reported. Despite recognition of the potential value of COX-2-targeted imaging agents such as **1**–**6**, there is a requirement for continued in vivo investigation using superior agents to establish the clinical utility of this strategy.

A number of general structure–activity relationships (SARs) have emerged for the tricyclic class of selective COX-2 inhibitors, viz: (i) many selective COX-2 inhibitors have two vicinal (adjacent) aryl substituents attached to a five- or six-membered central ring that acts as a scaffold such as benzene, pyridine, thiophene, pyrrole, imidazole, thiazole, cyclopentene, or pyrazole,[13,14] (ii) *para*-substituents on the adjacent aryl rings that provide optimal COX-2 selectivity, potency and oral activity are usually a COX-2 pharmacophore on one ring ($-SO_2Me$, $-SO_2NH_2$) and a F, Me or H substituent on the other aryl ring,[15] (iii) the *para*-position of the COX-2 pharmacophore is critical for COX-2 selectivity since placement at the *meta*-position of the aryl ring may abolish COX-2 activity,[13] (iv) reversing the position, or changing their position on the central ring (regioisomers) of the two aryl moieties (Ar and 4-MeO_2S(or H_2NO_2S)–C_6H_4–) can

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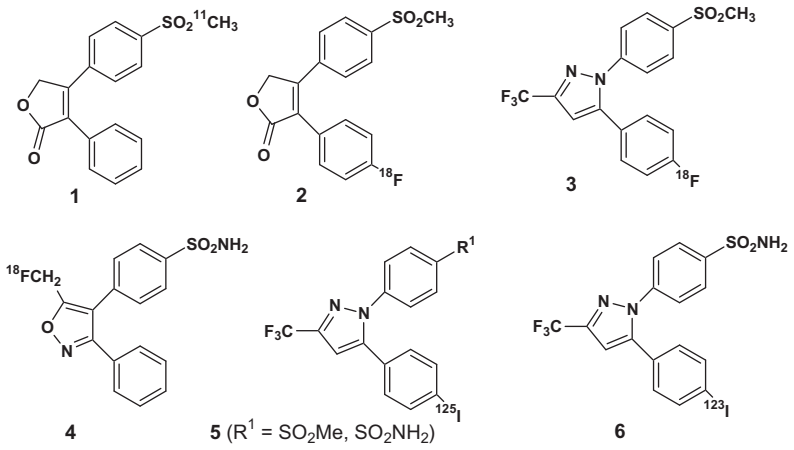


Figure 1. Some examples of selective COX-2 inhibitory compounds designed as PET (**1**–**4**), or SPECT (**5**–**6**), radiotracers.

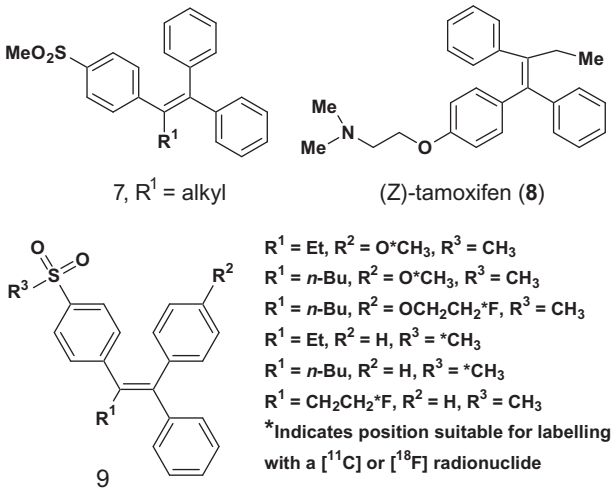
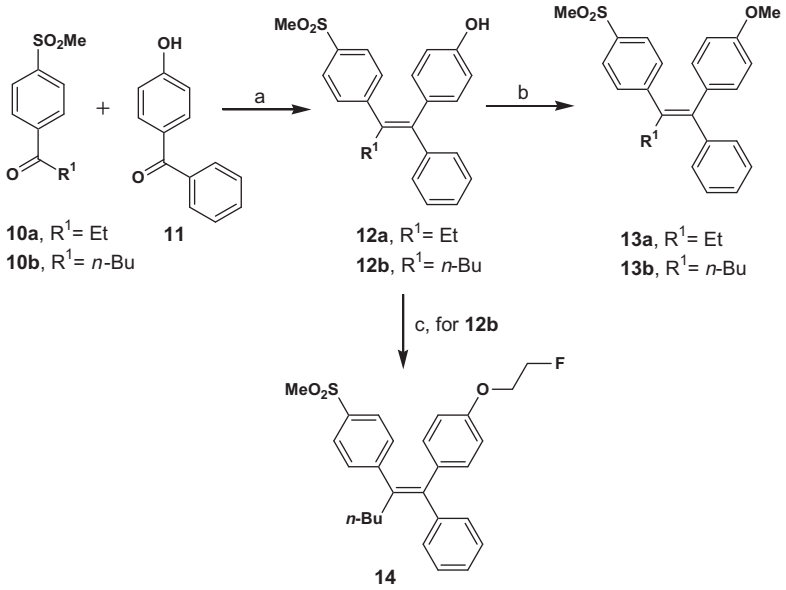


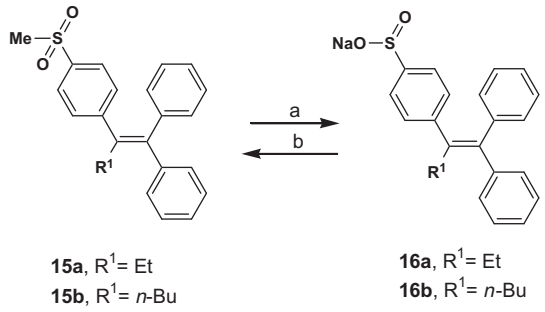
Figure 2. Some examples of tricyclic (*Z*)-olefins that exhibit selective COX-2 inhibitory and anti-inflammatory activities (**7**) and selective estrogen receptor antagonist activity against hormone-responsive breast cancers (**8**), and the putative positions (*) where a [^{11}C]- or [^{18}F]-radionuclide may be incorporated for assessment as imaging agents to target COX-2 expression or estrogen-responsive breast tumors (**9**).

either abolish or enhance COX-2 inhibitory activity,[14] (v) a lipophilic substituent (F, Me) at the *para*-position of one of the aryl rings usually enhances COX-2 inhibitory activity,[15] and a SO_2Me or SO_2NH_2 substituent at the *para*-position of one aryl ring usually provides optimal COX-2 inhibitory potency,[16] (vi) replacement of $-SO_2Me$ by $-SO_2CF_3$, –COMe, $-PO(OH)Me$, $-CO_2H$, $-PO(OH)_2$ or $-SO(=NH)Me$ generally abolishes COX-2 inhibitory activity,[17] (vii) an *ortho*-substituent on an aryl ring, which may distort the active orientation of the two aryl rings, such as 2-MeO–C_6H_4–, may abolish COX-2 inhibitory activity,[16] (viii) potency, selectivity and in vivo efficacy are affected by the substitution pattern on the aryl rings and the position of the COX-2 pharmacophore (SO_2Me, SO_2NH_2) moiety on an aryl ring may be important in preventing oxidative metabolism,[13] and (ix) the lower log *P* for SO_2NH_2 versus SO_2Me might improve absorption and provide a more rapid onset of action.[16]

In an earlier study, we reported a novel group of acyclic triaryl (*Z*)-olefins (**7**, see Fig. 2) that exhibit selective COX-2 inhibitory and anti-inflammatory activities.[18] Furthermore, this group of olefins **7** have a structural relationship to the selective estrogen receptor antagonist (*Z*)-tamoxifen (**8**) that is used to treat hormone-responsive breast cancers.[19] The SARs described in the preceding paragraph were used a guide to select putative positions (*) in the



Scheme 1. Reagents and conditions: (a) Zn, $TiCl_4$, THF, reflux 4.5 h; (b) 5 N NaOH, CH_3I, DMF, 60 °C, 3 min; (c) (i) K_2CO_3, Kryptofix 222, CH_3CN, 50 °C, 15 min; (ii) $TsOCH_2CH_2F$, reflux 10 min.



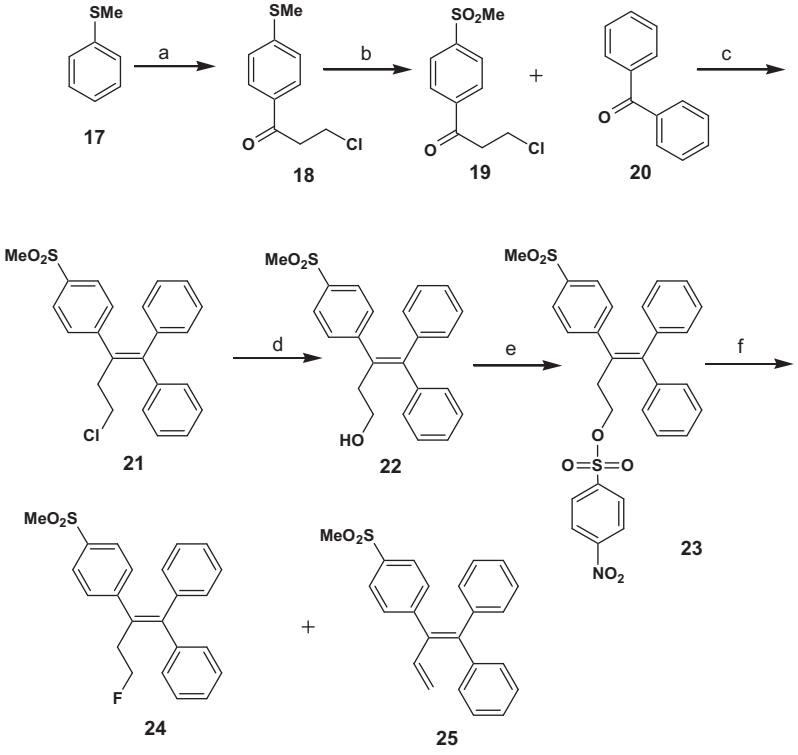
Scheme 2. Reagents and conditions: (a) (i) CH_3MgCl, THF, reflux 2 h; (ii) $(n\text{-}Bu)_3B$, reflux 18 h; (iii) aqueous Na_2CO_3; (b) CH_3I, DMF, 90 °C, 5 min.

tricyclic (*Z*)-olefins (**9**) at which a [^{11}C]- or [^{18}F]-radionuclide could be incorporated for assessment as imaging agents to target COX-2 expression or estrogen-responsive breast tumors in future investigations. We now describe non-radioactive synthetic methodologies that will be applicable to the future radiochemical synthesis of the putative radiopharmaceuticals **9** employing reaction conditions and reagents that employ the corresponding [^{11}C]- or [^{18}F]-reagents.

The (*Z*)-1-(4-hydroxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)alkenes (**12a–b**) were synthesized using a McMurry olefination reaction by Zn–$TiCl_4$ catalzyed reductive cross-coupling of a 4-(methylsufonyl)alkanophenone (**10**, R^1 = Et, *n*-Bu) with 4-hydroxybenzophenone (**11**) in good yields (71–72%) as illustrated in Scheme 1. These cross-coupling reactions of two aryl ketones functionalized by a sulfonyl and hydroxyl substituent proceed in a stereocontrolled manner to afford the target (*Z*)-olefinic products according to the mechanism previously reported.[18,20] The subsequent reaction of the phenols (**12a–b**) with MeI in the presence of 5 N NaOH at 60 °C for 3 min afforded the respective methoxy product (**13a**, R^1 = Et, 36%; **13b**, R^1 = *n*-Bu, 31%). Alternatively, condensation of the phenol **12b** (R^1 = *n*-Bu) with 2-fluoroethyl tosylate ($TsOCH_2CH_2F$) in the presence of K_2CO_3 and Kryptofix 222 with MeCN as solvent at 50 °C with a 15 min reaction time yielded the 2-fluoroethoxyphenyl product **14** in 51% yield. Similar reactions of the phenols (**12a–b**) with [^{11}C]CH_3I, or [^{18}F]$TsOCH_2CH_2F$ will provide a suitable method to synthesize the respective [^{11}C] and [^{18}F] labeled radiopharmaceuticals.

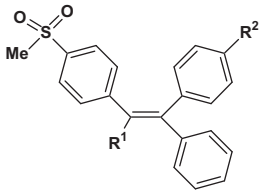
The replacement of natural abundance ^{12}C by ^{11}C in a methylsulfonyl (CH_3SO_2) COX-2 pharmacophore is particularly attractive since the physical chemical, biodistribution and biological properties of the molecule will not be changed. Accordingly, the CH_3SO_2 substituent present in the methylsulfonyl compounds **15a–b** was elaborated to the respective sodium sulfinates (**16a**, R^1 = Et, 50%; **16b**, R^1 = *n*-Bu, 42%) by sequential treatment with the Grignard reagent MeMgCl and then $(n\text{-}Bu)_3B$ using a procedure similar to that reported by de Vries et al.[7] (see Scheme 2). The sodium sulfinates (**16a–b**) are stable readily isolated products that upon treatment with CH_3I in DMF at 90 °C with a 5 min reaction time afford the respective methylsulfonyl compound (**15a**, R^1 = Et, 41%; **15b**, R^1 = *n*-Bu, 49%). Similar reactions of the sodium sulfinates (**16a–b**) with [^{11}C]CH_3I constitute a viable method to synthesize the respective [^{11}C]labeled radiopharmaceuticals.

Access to [^{18}F]radiotracers with a longer radionuclide half-life ($t_{1/2}$ = 109.6 min) is highly relevant since it provides an extended time period, compared to [^{11}C] with a $t_{1/2}$ = 20.4 min, during which optimal imaging can be carried out based on the biodistribution and elimination properties of the radiotracer being investigated. It was therefore of interest to develop a methodology to incorporate a fluorine atom into a C-2 alkyl substituent as illustrated for the 2-fluoroethyl compound **24** in Scheme 3. In this regard, the $AlCl_3$ catalyzed Freidel–Crafts acylation of thioanisole (**17**) with β-chloropropionyl chloride furnished the ketone (**18**, 76%) which was subsequently oxidized to the methylsulfonyl product



Scheme 3. Reagents and conditions: (a) $ClCH_2CH_2COCl$, $AlCl_3$, $CHCl_3$, 25 °C, 1.5 h; (b) oxone (potassium peroxymonosulphate), MeOH, THF, H_2O, 25 °C, 18 h; (c) Zn, $TiCl_4$, THF, reflux 4.5 h; (d) $FeSO_4{\cdot}5H_2O$, DMSO, H_2O, 130 °C, 48 h; (e) 4-nitrobenzenesulphonyl chloride, CH_2Cl_2, 0 °C, 2 h; (f) KF, Kryptofix 222, CH_3CN, 90 °C, 10 min.

Table 1
In vitro COX-1 and COX-2 inhibition data for a group of 1,2-diphenyl-2-(4-methylsulfonylpheny)alkenes **12a–b**, **13a–b**, **14**, **15a–b**, and **24**



Compd	R^1	R^2	IC_{50}[a] (μM)		COX-2 S.I.[b]
			COX-1	COX-2	
12a	Et	OH	>100	>100	—
12b	*n*-Bu	OH	>100	11.8	>8.5
13a	Et	OMe	>100	10.7	>9.3
13b	*n*-Bu	OMe	>100	7.7	>13.0
14	*n*-Bu	OCH_2CH_2F	>100	22.3	>4.5
15a[c]	Et	H	31.6	1.2	26.3
15b	*n*-Bu	H	9.1	2.7	3.4
24	CH_2CH_2F	H	>100	>100	—
Celecoxib			115.9	0.065	1783

[a] The in vitro test compound concentration required to produce 50% inhibition of ovine COX-1 or human recombinant COX-2. The result (IC_{50}, μM) is the mean of two determinations acquired using the enzyme immuno assay kit (Catalog No. 560131, Cayman Chemicals Inc., Ann Arbor, MI, USA) and the deviation from the mean is <10% of the mean value.
[b] In vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).
[c] Data acquired using ovine COX-2 (Catalog No. 56101, Cayman Chemical Inc.).[18]

(**19**, 96%) using potassium peroxymonosulfate (Oxone) as an oxidant (see Scheme 3). The McMurry Zn–$TiCl_4$ catalzyed reductive cross-coupling reaction of the ketone **19** with benzophenone (**20**) afforded the 2-chloroethyl olefin (**21**, 50%), which on subsequent reaction with $FeSO_4{\cdot}5H_2O$ at 130 °C afforded the 2-hydroxyethyl product (**22**, 56%). Reaction of the alcohol **22** with 4-nitrobenzenesulfonyl chloride furnished the 4-nitrobenzenesulfonate (**23**, 63%). Nucleophilic displacement of the 4-nitrobenzenesulfonate moiety present in **23** using KF in Kryptofix 222 at 90 °C with a reaction time of 10 min afforded the target 2-fluoroethyl product **24** in 10% yield. This lower than expected yield is attributed to the fact that the 2-fluoroethyl product **24** undergoes a facile elimination of HF to yield the C-2 vinyl product **25** (60%). Optimization of the reaction conditions employed to minimize the formation of the vinyl product **25** during the synthesis of [^{18}F]labeled **24** did not warrant investigation since the 2-fluoroethyl compound **24** was an inactive inhibitor of the COX-1 and COX-2 isozymes at a test compound concentration of 100 μM.

In vitro COX-1/COX-2 enzyme inhibition studies (see data in Table 1) provided a number of structure–activity relationships (SARs) viz (i) compounds **13a–b** (R^2 = OMe) and **14** ($R^2 = OCH_2CH_2F$) having a substituent at the *para*-position of the C-1 phenyl ring exhibited selective COX-2 inhibitory activity since no inhibition of COX-1 was observed at 100 μM (COX-1 IC_{50} >100 μM), ii) compounds **15a–b** having a R^2 = H substituent, which also inhibited the COX-1 isozyme, were the most potent COX-2 inhibitors, (iii) incorporation of a fluorine atom at the terminal position of a C-2 ethyl substituent abolished both COX-1 and COX-2 inhibitory activity (**24**, $R^1 = CH_2CH_2F$ COX-1 and COX-2 $IC_{50's}$ >100 μM), and (iv) binding affinity data of these putative radiotracers with COX-2 would provide useful information relevant to imaging studies.

In conclusion, (i) synthetic methodologies[21] suitable for the synthesis of the putative [^{11}C] and [^{18}F]labeled radiotracers illustrated in Figure 2 have been developed, and ii) COX-1/COX-2 inhibition data[22] suggest that compounds having a [^{11}C]OMe (**13a–b**) or [^{18}F]OCH_2CH_2F (**14**) R^1 substituent at the *para*-position of the C-1 phenyl ring may be more suitable for imaging COX-2 expression in view of their ability to exclusively inhibit the COX-2 isozyme.

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21. *Experimental procedures and spectral data for compounds* **12a–b**, **13a–b**, **14**, **15a–b**,**16a–b**, **19a–b**, **21–25**. *General*: Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer in $CDCl_3$, CD_3OD, or $CDCl_3$ + CD_3OD with TMS as the internal standard, where *J* (coupling constant) values are estimated in Hertz (Hz). Mass spectra (MS) were recorded on a Water's Micromass ZQ 4000 mass spectrometer using the electrospray (ES) ionization mode. Microanalyses were performed for C, H by the Microanalytical Service Laboratory, Department of Chemistry, University of Alberta and were within ±0.4% of theoretical values. Silica gel column chromatography was performed using Merck Silica Gel 60 ASTM (70–230 mesh). All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. The 4-(methylsulfonyl)alkanophenones (**10a–b**),[18] 2-fluoroethyl *p*-toluenesulphonate[23] and 1,1-diphenyl-2-(4-methylsulfonylphenyl)alkyl-1-enes (**15a–b**)[18] were prepared according to literature procedures. The chemical name for K222 (Kryptofix 222) is 1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane.
General procedure for the synthesis of 1-(4-hydroxyphenyl)-1-phenyl-2-(4-methylsulfonyl-phenyl)alkenes (**12a–b**): Titanium tertrachloride (1.83 mL, 13 mmol) was added dropwise to a stirred suspension of Zn powder (1.7 g, 26.5 mmol) in dry THF (30 mL) under an argon atmosphere at −10 °C, and this mixture was heated at reflux for 2 h to produce the titanium reagent. A cooled suspension of this titanium reagent was added to a solution of the respective 4-(methylsulfonyl)alkanophenone (**10a** or **10b**, 3.3 mmol) and 4-hydroxybenzophenone (**11**, 0.65 g, 3.3 mmol) in THF (65 mL) at 0 °C, and the reaction was allowed to proceed at reflux for 2.5 h. After cooling to 25 °C, the reaction mixture was poured into a 10% aqueous K_2CO_3 solution (100 mL), this mixture was stirred vigorously for 5 min, and the dispersed insoluble material

was removed by vacuum filtration through a Celite 545 pad. The organic fraction was separated, the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic fractions were dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue which was purified by silica gel column chromatography using EtOAc–hexane (2:1, v/v) as eluent followed by recrystallization of the product from EtOAc–hexane. Physical and spectral data for **12a–b** are listed below.

(Z)-1-(4-Hydroxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)but-1-ene (**12a**): Yield, 71%; white crystals; mp 192–193 °C (lit.[18] mp 188–190 °C); IR (film): 3417 (O–H), 2961 (C–H aromatic), 2926 (C–H aliphatic), 1308, 1148 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.50 (q, J = 7.3 Hz, 2H, CH_2CH_3), 3.04 (s, 3H, SO_2CH_3), 4.75 (br s, 1H, OH, exchangeable with D_2O), 6.48 (d, J = 8.5 Hz, 2H, 4-hydroxyphenyl H-3, H-5), 6.71 (d, J = 8.5 Hz, 2H, 4-hydroxyphenyl H-2, H-6), 7.22–7.37 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.75 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 13.3, 28.5, 44.2, 114.4, 126.6, 127.4, 128.0, 129.2, 130.6, 131.8, 133.3, 137.1, 139.5, 140.9, 142.4, 149.2, 155.1; MS m/z (ES^+) 379.1, $C_{23}H_{23}O_3S$ (M+H) requires 379.48.

(Z)-1-(4-Hydroxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)hex-1-ene (**12b**): Yield, 72%; white crystals; mp 171–172 °C; IR (film): 3416 (O–H), 2958 (C–H aromatic), 2921 (C–H aliphatic), 1314, 1146 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.20–1.32 (m, 4H, $(CH_2)_2CH_3$), 2.45 (t, J = 7.3 Hz, 2H, C≡C–CH_2), 3.05 (s, 3H, SO_2CH_3), 4.63 (br s, 1H, OH, exchangeable with D_2O), 6.49 (d, J = 8.5 Hz, 2H, 4-hydroxyphenyl H-3, H-5), 6.70 (d, J = 8.5 Hz, 2H, 4-hydroxyphenyl H-2, H-6), 7.21–7.39 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.74 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.8, 22.8, 31.1, 35.4, 44.5, 114.6, 126.9, 127.6, 128.2, 129.2, 130.6, 132.0, 134.6, 137.6, 138.9, 140.8, 142.8, 149.2, 155.1; MS m/z (ES^+) 407.1, $C_{25}H_{27}O_3S$ (M+H) requires 407.54.

General procedure for the synthesis of 1-(4-methoxyphenyl)-1-phenyl-2-(4-methylsulfonyl-phenyl)alkenes (**13a–b**): Methyl iodide (0.02 mL, 0.3 mmol) was added to a stirred mixture of the respective phenol (**12a** or **12b**, 0.25 mmol) and 5 N NaOH (0.06 mL, 0.3 mmol) in DMF (3 mL) under an argon atmosphere, and this mixture was heated at 70 °C for three minutes. After cooling to 25 °C, crushed ice (20 g) was added, the precipitate that formed was separated and purified by silica gel column chromatography using EtOAc–hexane (2:1, v/v) as eluent, and the product was recrystallized from EtOAc–hexane. Physical and spectral data for **13a–b** are listed below.

(Z)-1-(4-Methoxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)but-1-ene (**13a**): Yield, 36%; white crystals; mp 96–98 °C; IR (film): 2964 (C–H aromatic), 2929 (C–H aliphatic), 1314, 1149 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.50 (q, J = 7.3 Hz, 2H, CH_2CH_3), 3.04 (s, 3H, SO_2CH_3), 3.70 (s, 3H, OCH_3), 6.57 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-3, H-5), 6.76 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-2, H-6), 7.22–7.39 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.75 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.5, 28.8, 44.4, 55.0, 113.1, 126.9, 127.0, 128.2, 129.2, 130.6, 131.8, 134.4, 137.7, 139.4, 140.7, 142.9, 149.0, 158.0; MS m/z (ES^+) 393.2, $C_{24}H_{25}O_3S$ (M+H) requires 393.51. Anal. Calcd for $C_{24}H_{24}O_3S$: C, 73.44; H, 6.16. Found: C, 73.61; H, 6.35.

(Z)-1-(4-Methoxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)hex-1-ene (**13b**): Yield, 31%; white crystals; mp 95–97 °C; IR (film): 2961 (C–H aromatic), 2924 (C–H aliphatic), 1313, 1146 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.23–1.29 (m, 4H, $(CH_2)_2CH_3$), 2.43 (t, J = 7.3 Hz, 2H, C≡C–CH_2), 3.03 (s, 3H, SO_2CH_3), 3.70 (s, 3H, OCH_3), 6.56 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-3, H-5), 6.75 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-2, H-6), 7.21–7.37 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.74 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.8, 22.7, 31.1, 35.4, 44.5, 55.0, 113.1, 127.0, 128.2, 129.2, 130.5, 130.7, 131.8, 134.5, 137.7, 138.3, 140.8, 142.9, 149.3, 158.0; MS m/z (ES^+) 421.2, $C_{26}H_{29}O_3S$ (M+H) requires 421.56. Anal. Calcd for $C_{26}H_{28}O_3S$: C, 74.25; H, 6.71. Found: C, 74.30; H, 6.71.

(Z)-1-[4-(2-Fluoroethoxy)phenyl]-1-phenyl-2-(4-methylsulfonylphenyl)hex-1-ene (**14**): A mixture of (*Z*)-1-(4-hydroxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)hex-1-ene (**12b**, 102 mg, 0.25 mmol), Kryptofix 222 (94 mg, 0.25 mmol) and anhydrous potassium carbonate (38 mg, 0.28 mmol) in acetonitrile (3 mL) was heated at 50 °C for 15 min. 2-Fluoroethyl *p*-toluenesulphonate (55 mg, 0.25 mmol) was added and the mixture was heated under reflux for 10 min. After cooling to 25 °C, the solid was separated by filtration, the filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography using EtOAc–hexane (1:1, v/v) as eluent to give **14** as a white solid; Yield, 51%; mp 48–50 °C; IR (film): 2959 (C–H aromatic), 2928 (C–H aliphatic), 1312, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.79 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.23–1.27 (m, 4H, $(CH_2)_2CH_3$), 2.49 (t, J = 7.3 Hz, 2H, C≡C–CH_2), 3.06 (s, 3H, SO_2CH_3), 4.11 (ddd, J = 28.0, J = 4.3, 4.3 Hz, 2H, OCH_2CH_2F), 4.70 (ddd, J = 48.0, J = 4.3, 4.3 Hz, 2H, OCH_2CH_2F), 6.60 (dd, J = 6.7, 1.8 Hz, 2H, 4-fluoroethoxyphenyl H-3, H-5), 6.77 (dd, J = 6.7, 1.8 Hz, 2H, 4-fluoroethoxyphenyl H-2, H-6), 7.22–7.41 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.75 (dd, J = 6.8, 1.8 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.8, 22.7, 31.1, 35.4, 44.5, 66.8 (d, $^2J_{CCF}$ = 19.7 Hz), 81.8 (d, $^1J_{CF}$ = 171.4 Hz), 113.7, 126.9, 127.0, 128.2, 129.2, 130.5, 131.9, 135.1, 137.7, 138.6, 140.7, 142.8, 149.2, 156.8; MS m/z (ES^+) 453.2, $C_{27}H_{30}FO_3S$ (M+H) requires 453.58. Anal. Calcd for $C_{27}H_{29}FO_3S$: C, 71.65; H, 6.46. Found: C, 71.62; H, 6.58.

General procedure for the synthesis of sodium 4-(1,1-diphenylalk-1-en-2-yl)phenyl sulfinate (**16a–b**): The methyl sulfone (**15a** or **15b**, 1.0 mmol) was dissolved in THF (15 mL) and the solution was cooled in an ice bath. A solution of 3 M MeMgCl (2 mL, 6 mmol) in THF was added and the mixture was heated at reflux for 2 h. After cooling to 25 °C, a solution of 1 M tri-*n*-butylborane in THF (6 mL, 6 mmol) was added, and the mixture was heated at reflux for 21 h. After cooling, the mixture was poured into diethyl ether (250 mL), the precipitate was filtered and then dissolved in THF–H_2O (2:1, v/v; 30 mL), and aqueous Na_2CO_3 was added until the pH was 12. The precipitated magnesium salts were filtered, the filtrate was evaporated to dryness, the residue was extracted with methanol (25 mL), and removal of the methanol in vacuo furnished the respective product **16a** or **16b**. Physical and spectral data for **16a–b** are listed below.

Sodium 4-(1,1-diphenylbut-1-en-2-yl)phenyl sulfinate (**16a**): Yield, 50%; white powder; mp >300 °C; ^1H NMR (CD_3OD): δ 0.89 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.47 (q, J = 7.3 Hz, 2H, CH_2CH_3), 6.85–6.88 (m, 2H, phenyl hydrogens), 6.94–6.97 (m, 3H, phenyl hydrogens), 7.17–7.37 (m, 7H, phenyl hydrogens, phenyl sulfinate H-2, H-6), 7.46 (d, J = 8.5 Hz, 2H, phenyl sulfinate H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.8, 29.9, 124.9, 126.9, 127.8, 128.4, 129.2, 130.3, 130.9, 131.7, 140.9, 142.9, 144.2, 144.7, 144.9, 155.1; MS m/z (ES^+) 393.1, $C_{22}H_{19}Na_2O_2S$ (M+Na) requires 393.44.

Sodium 4-(1,1-diphenylhex-1-en-2-yl)phenyl sulfinate (**16b**); Yield, 42%; white powder; mp >300 °C; ^1H NMR (CD_3OD): δ 0.70 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.09–1.22 (m, 4H, $(CH_2)_2CH_3$), 2.38 (t, J = 7.3 Hz, 2H, C≡C–CH_2), 6.81–6.84 (m, 2H, phenyl hydrogens), 6.89–6.95 (m, 3H, phenyl hydrogens), 7.12–7.32 (m, 7H, phenyl hydrogens, phenyl sulfinate H-2, H-6), 7.41 (d, J = 8.6 Hz, 2H, phenyl sulfinate H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 14.2, 23.8, 32.1, 36.6, 124.8, 126.9, 127.7, 128.5, 129.2, 130.4, 130.8, 131.6, 141.2, 141.8, 144.2, 144.7, 145.2, 155.0; MS m/z (ES^+) 421.1, $C_{24}H_{23}Na_2O_2S$ (M+Na) requires 421.49.

General procedure for preparation of 1,1-diphenyl-2-(4-methylsulphonylphenyl)alk-1-enes (**15a–b**) *from sodium sulfinate salts* (**16a–b**): The sodium sulfinate salt (**16a** or **16b**, 0.25 mmol) was dissolved in DMF (5 mL) and methyl iodide (0.032 μL, 0.5 mmol) was added at 25 °C under argon, and the mixture was heated at 90 °C for 5 min with stirring. Water (5 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were successively washed with water (2 × 15 mL) and brine (15 mL) prior to drying the organic fraction (Na_2SO_4). The solvent was evaporated and the residue obtained was purified by silica gel column chromatography using EtOAc–hexane (1:2, v/v) as eluent to give the respective methyl sulphone **15a** or **15b** as a white powder which recrystallized as white clusters from EtOAc–hexane (yield 41%; mp 120–122 °C; lit.[18] mp 124–126 °C for **15a**; yield 49%; mp 84–86 °C; lit.[18] mp 79–81 °C for **15b**).

β-Chloroethyl p-methylthiophenyl ketone (**18**): 3-Chloropropionyl chloride (1.38 mL, 14.4 mmol) was added dropwise to a stirred suspension of $AlCl_3$ (1.76 g, 13.2 mmol) in chloroform (10 mL). Thioanisole (**17**, 1.38 g, 11.1 mmol) was added at 0 °C and the reaction was allowed to proceed with stirring for 1.5 h at 25 °C. Water (10 mL) was added slowly at 0 °C, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with water (10 mL), dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was recrystallized from CH_2Cl_2–*n*-hexane (1:9, v/v) to afford **18** as pale red crystals in 76% yield; mp 113–115 °C (lit.[24] mp 111–113 °C); IR (film): 2956 (C–H aromatic), 2916 (C–H aliphatic), 1670 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.54 (s, 3H, SCH_3), 3.42 (t, J = 7.3 Hz, 2H, CH_2CH_2Cl), 3.93 (t, J = 7.3 Hz, 2H, CH_2CH_2Cl), 7.28 (d, J = 8.6 Hz, 2H, *m*-phenyl hydrogens), 7.88 (d, J = 8.6 Hz, 2H, *o*-phenyl hydrogens).

β-Chloroethyl p-methylsulphonylphenyl ketone (**19**): A solution of Oxone® (potassium peroxymonosulfate, 4.06 g, 6.6 mmol) in water (20 mL) was added to a stirred solution of β-chloroethyl *p*-methylthiophenyl ketone (**9**, 0.71 g, 3.3 mmol) in THF–MeOH (1:1, v/v; 10 mL) at 0 °C, and the reaction was allowed to proceed with stirring for 18 h at 25 °C. Removal of the solvent in vacuo gave a residue to which water (20 mL) was added. Extraction with EtOAc (3 × 30 mL), washing the combined extracts with water (10 mL), drying the organic fraction (Na_2SO_4), and removal of the solvent in vacuo gave a white solid, which was purified by recrystallization from CH_2Cl_2–*n*-hexane (1:9, v/v) to afford **19** as white crystals in 96% yield; mp 84–86 °C (lit.[24] mp 85–87 °C); IR (film): 2963 (C–H aromatic), 2926 (C–H aliphatic), 1696 (CO), 1314, 1153 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 3.51 (t, J = 6.7 Hz, 2H, CH_2CH_2Cl), 3.95 (t, J = 6.7 Hz, 2H, CH_2CH_2Cl), 8.09 (d, J = 8.6 Hz, 2H, *o*-phenyl hydrogens), 8.15 (d, J = 8.6 Hz, 2H, *p*-phenyl hydrogens).

4-Chloro-1,1-diphenyl-2-(4-methylsulphonylphenyl)but-1-ene (**21**): $TiCl_4$ (1.83 mL, 13 mmol) was added dropwise to a stirred suspension of Zn powder (1.7 g, 26.5 mmol) in dry THF (30 mL) under an argon atmosphere at −10 °C, and this mixture was heated at reflux for 2 h to produce the titanium reagent. A cooled suspension of this titanium reagent was added to a solution of β-chloroethyl *p*-methylsulphonylphenyl ketone (**19**, 0.82 g, 3.3 mmol) and benzophenone (**20**, 0.60 g, 3.3 mmol) in THF (65 mL) at 0 °C, and the reaction was allowed to proceed at reflux for 2.5 h. After cooling to 25 °C, the reaction mixture was poured into a 10% aqueous K_2CO_3 solution (100 mL), this mixture was stirred vigorously for 5 min, and the dispersed insoluble material was removed by vacuum filtration through a Celite 545 pad. The organic fraction was separated, the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic fractions were dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography using EtOAc–hexane (1:1, v/v) as eluent to give **21** as a white solid (0.66 g, 50%); mp 141–143 °C; IR (film): 2962 (C–H aromatic), 2926 (C–H aliphatic), 1312, 1148 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.00 (t, J = 7.3 Hz, 2H, CH_2CH_2Cl), 3.03 (s, 3H, SO_2CH_3), 3.40 (t, J = 7.3 Hz, 2H, CH_2CH_2Cl), 6.85–6.88 (m, 2H, phenyl hydrogens), 7.01–7.06 (m, 3H, phenyl hydrogens), 7.26–

7.42 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.77 (d, J = 8.0 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); MS m/z (ES^+) 397.1, $C_{23}H_{22}ClIO_2S$ (M+H) requires 397.93.

4-Hydroxy-1,1-diphenyl-2-(4-methylsulphonylphenyl)but-1-ene (**22**): A mixture of 4-chloro-1,1-diphenyl-2-(4-methylsulphonylphenyl)but-1-ene (**21**, 397 mg, 1.0 mmol), and $CuSO_4{\cdot}5H_2O$ (250 mg, 1.0 mmol) in H_2O–DMSO (1:3, v/v; 1.4 mL) was heated at 130 °C for 48 hours. After cooling to 25 °C, EtOAc (25 mL) was added, the mixture was washed with H_2O (3 × 10 mL), the organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue obtained was purified by silica gel column chromatography using EtOAc–hexane (2:1, v/v) as eluent to afford **22** as a white solid (212 mg, 56%); mp 164–166 °C; IR (film): 3566–3215 (O–H), 2964 (C–H aromatic), 2928 (C–H aliphatic), 1313, 1151 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.81 (t, J = 7.3 Hz, 2H, CH_2CH_2OH), 3.02 (s, 3H, SO_2CH_3), 3.59 (t, J = 7.3 Hz, 2H, CH_2CH_2OH), 6.85–6.88 (m, 2H, phenyl hydrogens), 7.01–7.05 (m, 3H, phenyl hydrogens), 7.26–7.40 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.73 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); MS m/z (ES^+) 379.1, $C_{23}H_{23}O_3S$ (M+H) requires 379.48.

1,1-Diphenyl-2-(4-methylsulphonylphenyl)-2-(4-nitrophenylsulfonyloxyethyl)eth-1-ene (**23**): A mixture of the alcohol **22** (125 mg, 0.33 mmol), 4-nitrobenzenesulphonyl chloride (81 mg, 0.36 mmol), Et_3N (0.09 mL, 0.66 mmol) and 4-dimethylaminopyridine (8 mg) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 2 h. The mixture was washed with H_2O (5 mL), the organic phase was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue obtained was purified by silica gel column chromatography using EtOAc–hexane (1:1, v/v) as eluent to furnish **23** as a white solid (117 mg, 63%); mp 178–179 °C; IR (film): 2962 (C–H aromatic), 2934 (C–H aliphatic), 1532, 1368 (NO_2), 1350, 1185 (OSO_2), 1312, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.91 (t, J = 6.7 Hz, 3H, CH_2CH_2O), 3.03 (s, 3H, SO_2CH_3), 4.04 (t, J = 6.7 Hz, 3H, CH_2CH_2O), 6.82–6.85 (m, 2H, phenyl hydrogens), 7.03–7.06 (m, 3H, phenyl hydrogens), 7.20–7.40 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.71 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5), 7.95 (dd, J = 8.5, 1.9 Hz, 2H, 4-nitrophenyl H-2, H-6), 8.35 (dd, J = 8.5, 1.9 Hz, 2H, 4-nitrophenyl H-3, H-5); MS m/z (ES^+) 564.1, $C_{29}H_{26}NO_7S$ (M+H) requires 564.64.

4-Fluoro-1,1-diphenyl-2-(4-methylsulphonylphenyl)but-1-ene (**24**) *and 1,1-diphenyl-2-(4-methylsulphonylphenyl)but-1,3-diene* (**25**): A mixture of the 4-nitrophenylsulphonate **23** (130 mg, 0.23 mmol), K222 (87 mg, 0.23 mmol) and KF (13.5 mg, 0.23 mmol) in acetonitrile (5 mL) was heated at 95 °C for 10 min. After cooling to 25 °C, the solid was removed by filtration and discarded, the solvent from the filtrate was removed in vacuo and the residue obtained was purified by silica gel column chromatography using EtOAc–hexane (1:2, v/v) as eluent to give **24** as a white solid (9 mg) and **25** as a yellow solid (50 mg). Physical and spectroscopic data for **24** and **25** are listed below.

4-Fluoro-1,1-diphenyl-2-(4-methylsulphonylphenyl)but-1-ene (**24**): Yield, 10%; white powder; mp 148–150 °C; IR (film): 2962 (C–H aromatic), 2906 (C–H aliphatic), 1314, 1153 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.97 (ddd, J = 22.6, 6.1, 6.1 Hz, 2H, CH_2CH_2F), 3.03 (s, 3H, SO_2CH_3), 4.37 (ddd, J = 47.6, 6.1, 6.1 Hz, 2H, CH_2CH_2F), 6.88–6.89 (m, 2H, phenyl hydrogens), 7.04–7.06 (m, 3H, phenyl hydrogens), 7.27–7.41 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.76 (dd, J = 8.4, 1.8 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 36.4 (d, $^2J_{CCF}$ = 21.8), 44.4, 81.4 (d, $^1J_{CF}$ = 167.0), 126.8, 127.2, 127.3, 127.8, 128.4, 129.4, 130.4, 130.6, 133.2, 138.3, 141.6, 141.8, 144.8, 147.7; MS m/z (ES^+) 381.1, $C_{23}H_{22}FO_2S$ (M+H) requires 381.48. Anal. Calcd for $C_{23}H_{21}FO_2S{\cdot}1/2H_2O$: C, 70.93; H, 5.69. Found: C, 71.02; H, 5.54.

1,1-Diphenyl-2-(4-methylsulphonylphenyl)but-1,3-diene (**25**): Yield, 60%; yellow powder; mp 114–116 °C; IR (film): 3020 (C–H aromatic), 2926 (C–H aliphatic), 1315, 1151 (SO_2) cm^{-1}; ^1H NMR (CD_3OD): δ 3.08 (s, 3H, SO_2CH_3), 4.81 (dd, J_{trans} = 17.5, J_{gem} = 2 Hz, 1H, CH=C*H*H′), 5.20 (dd, J_{cis} = 11.0, J_{gem} = 2 Hz, 1H, CH=CHH′), 6.76 (dd, J_{trans} = 17.5, J_{cis} = 11.0 Hz, 1H, C*H*=CHH′), 6.71–6.80 (m, 2H, phenyl hydrogens), 6.87–6.90 (m, 3H, phenyl hydrogens), 7.02–7.42 (m, 7H, phenyl hydrogens, 4-methylsulfonylphenyl H-2, H-6), 7.79 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5); ^{13}C NMR (CD_3OD): δ 44.3, 118.7, 127.9, 128.7, 128.8, 129.2, 131.7, 131.8, 133.6, 138.7, 138.9, 140.1, 142.8, 143.3, 145.5, 147.7; MS m/z (ES^+) 361.2, $C_{23}H_{21}O_2S$ (M+H) 361.47.

22. *Cyclooxygenase inhibition assays*: The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and human recombinant COX-2 (IC_{50} value, μM) was determined using an enzyme immuno assay (EIA) kit (Catalog no. 560131, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method (Rao, P. N. P.; Amini, M.; Li, H.; Habeeb, A.; Knaus, E. E. *J. Med. Chem.* **2003**, *46*, 4872).
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