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A new class of acyclic 2-alkyl-1,2-diaryl (*E*)-olefins as selective cyclooxygenase-2 (COX-2) inhibitors

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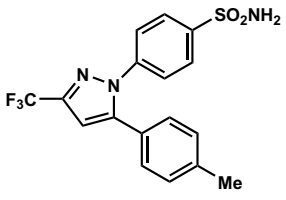
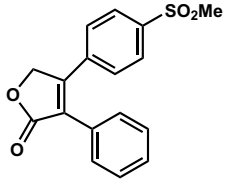
Abstract—A new class of (*E*)-2-alkyl-2-(4-methanesulfonylphenyl)-1-phenylethenes were designed for evaluation as selective cyclooxygense-2 (COX-2) inhibitors. The target olefins were synthesized, via a Takeda olefination reaction, followed by oxidation of the respective thiomethyl olefinic intermediate. In vitro COX-1/COX-2 inhibition studies identified (*E*)-2-(4-methanesulfonylphenyl)-1-phenyloct-1-ene (**8d**) as a potent (IC_{50} = 0.77 μM) and selective (Selectivity Index > 130) COX-2 inhibitor.

Sir John Vane's discovery that nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin and indomethacin inhibit the biosynthesis of prostaglandins significantly enhanced our understanding regarding the mechanism of action of NSAIDs.[1–4] The recent discovery of the second isoform of COX (COX-2) led to the successful development of selective COX-2 inhibitors such as celecoxib (**1**) and rofecoxib (**2**) that exhibit efficient antiinflammatory–analgesic activities with reduced gastrointestinal side effects.[5,6] In addition, selective COX-2 inhibitors may have useful therapeutic indications for the prophylactic treatment of a wide variety of cancers and neurodegenerative disorders.[7–9]

The majority of selective COX-2 inhibitors belong to a class of diarylheterocycles that possess vicinal diaryl moieties attached to a central heterocyclic ring scaffold in conjunction with a COX-2 pharmacophore such as a *para*-SO_2NH_2, or a *para*-SO_2Me, substituent on one of the phenyl rings.[10] Recent studies have shown that compounds possessing a *trans*-stilbenoid system exhibit COX inhibitory activity. In this regard resveratrol (**3**) is a naturally occurring acyclic *trans*-olefin that exhibits COX-1 selectivity.[11] In addition, Kim and co-workers have shown that compounds possessing a *trans*-stilbene template such as 4-methoxystilbene analogues (**4**) inhibit COX-2 mediated production of prostaglandins (PGE_2).[12] As a part of our ongoing program to design novel selective COX-2 inhibitors, we describe herein the synthesis and biological evaluation of a new class of acyclic 2-alkyl-1,2-diaryl (*E*)-olefins possessing a *p*-SO_2Me COX-2 pharmacophore on the C-2 phenyl ring.



Celecoxib (1)



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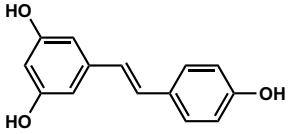
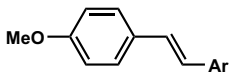


Resveratrol (3)



Ar = 2-Furyl, 3-furyl, 3-thienyl

4-Methoxystilbenes (4)

The olefinic intermediates **7** (R^1 = Et, *n*-propyl, *n*-hexyl, *n*-heptyl; R^2 = H, Me) were generated in situ using a Takeda olefination reaction[13] by $Cp_2Ti[P(OEt)_3]_2$ promoted reductive cross coupling of a carbonyl compound **5** (R^1 = Et, *n*-propyl, *n*-hexyl, *n*-heptyl)[14] with a

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thioacetal **6** (R^2 = H, Me)[15,16] with a good (*E*)-selectivity that was determined after oxidation to the respective $MeSO_2$ olefinic product **8** (R^1 = Et, *n*-propyl, *n*-hexyl, *n*-heptyl; R^2 = H, Me) (**8a**–**e**, *E*:*Z* range of 9.0:1 to 9.7:1). Fractional recrystallizations (two or three) of the crude (*E*)- and (*Z*)-isomeric mixtures using EtOH (95%, w/v) furnished exclusively the desired (*E*)-olefins **8a**–**e** (Scheme 1).[17]

The structure of the (*E*)-olefinic products **8a**–**e** were consistent with their ^{1}H NMR spectral and microanalytical data. The absolute stereochemistry of (***E***)-**8a** (R^1 = Et, R^2 = H) was unambiguously confirmed by a single crystal X-ray analysis (Fig. 1).[18]

It has been proposed that the Takeda olefination reaction proceeds via an elimination of $Cp_2Ti{=}O$ from the oxatitanacyclobutane species (**9**) in the transition state, which originates from the reaction of a carbonyl compound with a titanocene carbene complex (ArCH-$TiCp_2$). The carbene complex is generated via desulfurizative titanation of a thioacetal [$ArCH(SPh)_2$] by a transient low-valent titanium $Cp_2Ti[P(OEt)_3]_2$, which is formed by reductive dechlorination of Cp_2TiCl_2 with Mg in the presence of $P(OEt)_3$.[13] Although the mechanism for (*E*)-stereocontrol in this olefination reaction is still unclear, steric hindrance appears to be an important factor that affects (*E*)-stereocontrol due to the preferential formation of a sterically favoured oxatitanacyclobutane species (**9a**) in which the bulkier (4-methanesulfanylphenyl) and smaller (H) substituents are *cis* to each other in the transition state. On the other hand, formation of the (*Z*)-olefin would involve a sterically disfavoured oxatitanacyclobutane species (**9b**), having two bulky substituents (an unsubstituted phenyl ring and a 4-methanesulfanylphenyl ring) on the same side in the transition state (Fig. 2).

In vitro COX-1/COX-2 enzyme immunoassay data (Table 1) showed that (***E***)-**8a** (R^1 = Et, R^2 = H) was a weak COX-2 inhibitor (COX-2 IC_{50} = 8.0 μM; COX-1 IC_{50} > 100 μM; COX-2 selectivity index > 13). Incorporation of a *p*-methyl substituent on the C-1 phenyl ring in (***E***)-**8b** (R^1 = Et, R^2 = Me) reduced COX-2 inhibitory potency (IC_{50} = 31 μM). However, (***E***)-**8b** showed excellent COX-1 inhibitory potency (COX-1 IC_{50} = 0.03 μM).

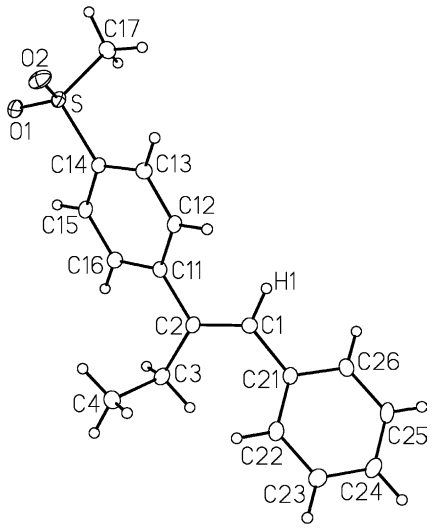


Figure 1. X-ray crystal structure of (*E*)-2-(4-methanesulfonylphenyl)-1-phenylbut-1-ene (**8a**).

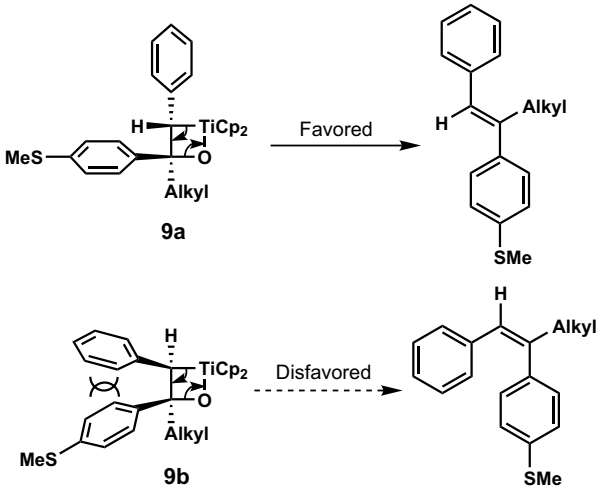
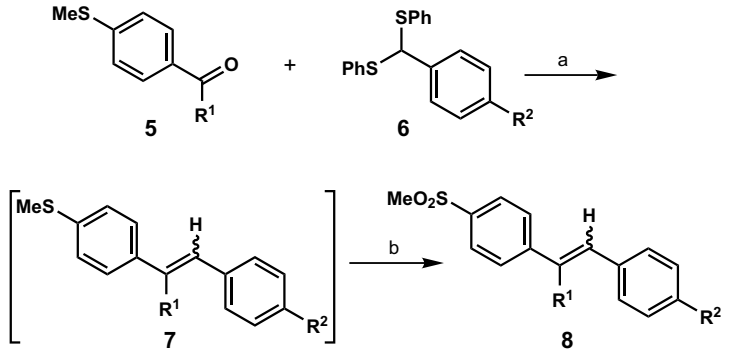


Figure 2. Proposed mechanism for (*E*)-stereoselection involving oxatitanacyclobutane complex (**9**) in the transition state of the olefination reaction.

Increasing the alkyl chain length from Et to *n*-propyl, as in (***E***)-**8c** (R^1 = *n*-propyl, R^2 = H) resulted in a moderate



Scheme 1. Reagents and conditions: (a) Cp_2TiCl_2, molecular sieves 4 A, Mg, $P(OEt)_3$, THF, 25 °C, 15 h; (b) Oxone® (potassium peroxymonosulfate), MeOH, THF, H_2O, 25 °C, 15 h.

Table 1. In vitro COX inhibition assay data for (*E*)-olefins **8a–e**

Compd	R^1	R^2	COX-1 IC_{50} (μM)[a]	COX-2 IC_{50} (μM)[a]	COX-2 SI[b]
(***E***)-**8a**	Et	H	>100	8.0	>13
(***E***)-**8b**	Et	Me	0.03	31.0	—
(***E***)-**8c**	*n*-C_3H_7	H	>100	3.1	>32
(***E***)-**8d**	*n*-C_6H_{13}	H	>100	0.77	>130
(***E***)-**8e**	*n*-C_7H_{15}	H	>100	10.0	>10
Celecoxib	—	—	33.1	0.07	472
Rofecoxib	—	—	>100	0.50	>200

[a] Values are means of two determinations acquired using an ovine COX-1/COX-2 assay kit (Catalog No. 560101, 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}).

increase in COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 3.1 μM; COX-2 selectivity index > 32). As the alkyl chain length was increased, COX-2 inhibitory potency and selectivity increased substantially with (***E***)-**8d** (R^1 = *n*-hexyl, R^2 = H) exhibiting the best combination of COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.77 μM; COX-2 selectivity index > 130), compared to the reference drug rofecoxib (COX-2 IC_{50} = 0.5 μM; COX-1 IC_{50} > 100 μM; COX-2 selectivity index > 200). A further increase in alkyl chain length provided (***E***)-**8e** (R^1 = *n*-heptyl, R^2 = H) that showed a dramatic reduction in COX-2 inhibitory potency (COX-2 IC_{50} = 10 μM) and selectivity (COX-2 selectivity index > 10) since it was 20-fold less potent and selective than rofecoxib.

A molecular modelling (docking)[14] study using the most stable ligand–enzyme complex of **8d** in the COX-2 active site (Fig. 3) showed that the olefinic C=C orientates the C-2 *p*-$MeSO_2$-phenyl substituent in the vicinity of the secondary pocket amino acid residues such that one of the oxygen-atoms of the SO_2Me group undergoes a hydrogen bonding interaction with the backbone N*H* of Ile[517] (distance = 2.33 Å), and N*H* of Gln[192] (distance = 3.33 Å). The other *O*-atom of the SO_2Me moiety is about 3.70 Å from the N*H* of His[90] with the *S*-atom of SO_2Me group inserted about 1.32 Å inside the entrance to the COX-2 secondary pocket (Val[523]).

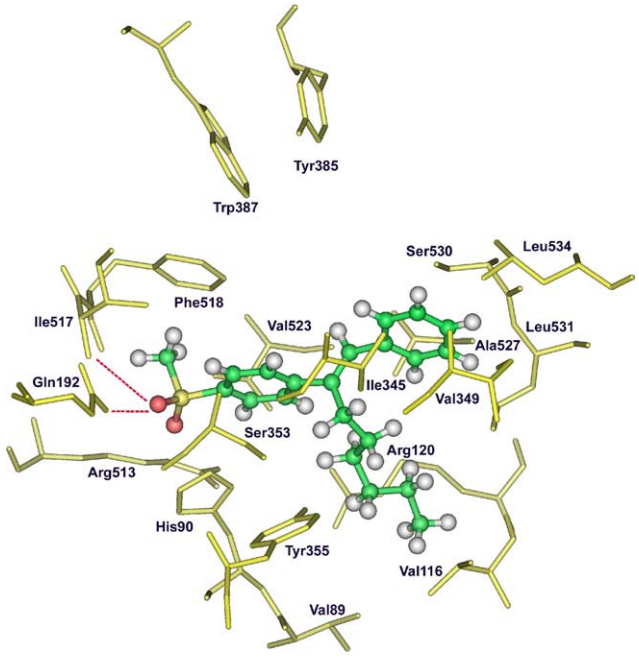


Figure 3. Docking of (***E***)-**8d** in the active site of murine COX-2. Hydrogen atoms of the amino acid residues are not shown for clarity.

The olefinic C=C is interacting with Gly[526] and Ala[527] and the C-1 unsubstituted phenyl ring was orientated towards a region comprised of Ser[530], Leu[531], Leu[534], Val[349] and Ile[345]. The distance between the centre of the C-1 unsubstituted ring and the OH of Ser[530] is about 4.5 Å. The C-2 *n*-hexyl chain of (***E***)-**8d** is orientated towards the mouth of the COX-2 binding site (Arg[120] and Tyr[355]) undergoing hydrophobic interactions with Val[89] and Val[116] (distance < 5 Å). The distance between the olefinic C-2 atom and the OH of Tyr[355] is about 5.0 Å. In this regard, Llorens and co-workers have shown the importance of perturbation of the hydrogen bonding network involving Arg[120], Glu[524] and Tyr[355] at the mouth of the channel by different ligands and their effect on COX inhibition.[19] It is significant to note that the orientation of the lipophilic C-2 *n*-hexyl chain towards the mouth of the COX-2 binding site, has the potential to disrupt the hydrogen bonding network (between His[90], Tyr[355], Arg[120] and Glu[524]). This initial study shows that appropriately substituted acyclic diaryl (*E*)-olefins (**8**) interact favourably within the COX-2 binding site.

In conclusion, this study indicates that (i) the Takeda olefination reaction can be optimized to synthesize acyclic 2-alkyl-1,2-diaryl olefins (**8**) with excellent (*E*)-stereoselectivity, (ii) acyclic diaryl olefins, possessing a *trans*-stilbenoid template [(*E*)-stereochemistry], exhibit selective COX-2 inhibition when a 4-methanesulfonylphenyl substituent is incorporated at the C-2 position, and (iii) COX-2 inhibitory potency and selectivity is dependent upon C-2 alkyl substituent chain length with compound **8d** (R^1 = *n*-hexyl) exhibiting the best combination of COX-2 inhibitory potency and selectivity.

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17. Synthesis (*E*)-2-(4-methanesulfonylphenyl)-1-phenyl-2-alkyl-1-enes (**8**). General procedure $P(OEt)_3$ (3.59 g, 21.6 mmol) was added slowly to a stirred suspension of Cp_2TiCl_2 (2.69 g, 10.8 mmol), powdered molecular sieves 4 A (0.7 g) and Mg turnings (0.29 g, 12 mmol) in dry THF (10 mL), under Ar at 25 °C. After the addition was complete, the reaction mixture was stirred for 3 h at 25 °C. A solution of thioacetal (**6**, R^2 = H, Me; 3.3 mmol) in THF (4 mL) was added to the low-valent titanium reagent at 25 °C. After stirring for 10 min, a solution of the carbonyl compound (**5**, R^1 = Et, *n*-propyl, *n*-hexyl, *n*-heptyl; 3 mmol) in THF (4 mL) was added drop wise to the reaction mixture that was then stirred for 15 h at 25 °C. Aqueous NaOH solution (10 mL of 1 M) was added to the reaction mixture that was stirred vigorously for 5 min. The dispersed insoluble materials present in the reaction mixture were removed by vacuum filtration through a pad of Celite 545. The organic layer was separated and the aqueous layer was extracted with ether (3×10 mL). The combined organic fractions were washed with water (10 mL), and the organic fraction was dried (Na_2SO_4). Removal of the solvent in vacuo afforded the respective 4-methanesulfanylphenyl olefinic intermediate (**7**, R^1 = Et, *n*-propyl, *n*-hexyl, *n*-heptyl, R^2 = H, Me). The intermediate **7** was dissolved in THF–MeOH (1:1, v/v) (10 mL) and a solution of Oxone® (potassium peroxymonosulfate) (4.06 g, 6.6 mmol) in water (20 mL) was added drop wise at 0 °C with stirring. The reaction was allowed to proceed for 15 h at 25 °C, the solvent was removed in vacuo, and water (20 mL) was added to the residue. Extraction with EtOAc (3×30 mL), drying the organic fraction (Na_2SO_4) and removal of the solvent in vacuo gave a residue from which the 4-methanesulfonylphenyl (*E*)- and (*Z*)-olefinic products were separated (**8**, R^1 = Et, *n*-propyl, *n*-hexyl, *n*-heptyl, R^2 = H, Me) using a silica gel flash column chromatography (*n*-hexane–EtOAc, 3:1 v/v). Subsequent fractional recrystallizations (two or three) of this (*E*):(*Z*) mixture of olefins (**8**) from EtOH (95%, w/v) afforded the respective (*E*)-olefin product **8a**–**e** exclusively in 60–65% overall yield. The physical, spectroscopic and microanalytical data for the (*E*)-olefin **8d** is listed below.
(*E*)-2-(4-Methanesulfonylphenyl)-1-phenyloct-1-ene (**8d**). Yield, 65%; white crystals; mp 130–132 °C; IR (film): 1153, 1318 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 7.3 Hz, CH_2CH_3), 1.15–1.45 [m, 8H, $(CH_2)_4$], 2.72 (t, 2H, J = 7.0 Hz, CH_2–C=C), 3.09 (s, 3H, SO_2CH_3), 6.77 (s, 1H, C=CH), 7.35–7.45 (m, 5H, phenyl hydrogens), 7.64 (d, 2H, J = 8.5 Hz, 4-methanesulfonylphenyl H-2, H-6), 7.94 (d, 2H, J = 8.5 Hz, 4-methanesulfonylphenyl H-3, H-5). Anal. Calcd for $C_{21}H_{26}O_2S$: C, 73.64; H, 7.65. Found: C, 73.49; H, 7.39.
18. Crystal data for (*E*)-2-(4-methanesulfonylphenyl)-1-phenylbut-1-ene (**8a**). Molecular formula: $C_{17}H_{18}O_2S$, formula weight: 286.37, crystal system: monoclinic, space group: $P2_1/c$ (No. 14) with unit cell dimensions a = 18.094 (3) Å, b = 8.8478 (15) Å, c = 9.2677 (15) Å, β = 99.418 (3)°, V = 1463.7 (4) $Å^3$, Z = 4, ρ_{calcd} = 1.300 g cm^{-3}, μ = 0.220 mm^{-1}. A crystal fragment of approximate dimensions $0.58 \times 0.52 \times 0.02$ mm^3 was mounted in a non-specific orientation on a Bruker PLATFORM/SMART 1000 CCD diffractometer. All intensity measurements were performed using Mo Kα radiation (λ = 0.71073 Å) with a graphite crystal incident beam monochromator. The intensity data were collected at −80° using ω scans (0.3° scans, 20 s exposures). A total of 2994 independent reflections were collected to a maximum 2θ limit at 52.84°. The structure was solved by direct methods. Refinement of atomic parameters was carried out by using full-matrix least-squares on F^2 (SHELXL-93), giving final agreement factors (R indices) of $R_1(F)$ = 0.0566 (on 1987 data with $I \geqslant 2s(I)$) and $wR_2(F^2)$ = 0.1531 (on all 2994 data). Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 242132. Copies of the data can be obtained free of charge by application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: 44-0-1223-336033 or, e-mail: deposit@ccdc.cam.ac.uk or, http://www.ccdc.cam.uk).
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