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An improved and practical synthesis of 5,5-dimethyl-3-(2-propoxy)-4-(4-methanesulfonylphenyl)-2-(5*H*)-furanone (DFP—a selective inhibitor of cyclooxygenase-2)☆

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Abstract—DFP, a highly selective and potent COX-2 inhibitor, has been synthesized by a modified approach. Three modifications of the existing method enabled us to prepare DFP in good quantity.

1. Introduction

DFP [5,5-dimethyl-3-(2-propoxy)-4-(4-methanesulfonylphenyl)-2(5*H*)-furanone] **1**, one of the most selective cyclooxygenase-2 (COX-2) inhibitors recently discovered by Merck,[1] belongs to the 3,4-disubstituted furanone class of compounds that includes rofecoxib **2**[2] (Fig. 1). DFP has been shown to be a more potent and more selective inhibitor of COX-2 isozyme than rofecoxib. Cyclooxygenase (COX), the first enzyme involved in the biosynthesis of prostaglandins (PGs), prostacyclins and thromboxanes from arachidonic acid, is known to exist in two distinct isoforms,[3a,b] namely COX-1 and COX-2. COX-1 is constitutively expressed in the kidney as well as in the gastrointestinal tract and is responsible for gastric cytoprotection and for platelet aggregation.[3c] Thus interruption of COX-1 activity may lead to gastro-intestinal toxicity such as ulceration, bleeding and perforation. In contrast COX-2 is inducible by pro-inflammatory molecules and plays a major role in the biosynthesis of PGs in inflammatory cells (monocytes and macrophages).[3a,d] The traditional non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2 and thus down regulate the PGs in almost all cells and tissues. This accounts for their anti-inflammatory activity as well as undesired side effects associated with their uses.[3e] However, selective inhibition of COX-2 over COX-1 is beneficial for the treatment of inflammatory diseases with reduced ulcerogenic side effects. In accordance with this hypothesis, like rofecoxib, DFP showed significantly reduced gastrointestinal side effects and has been considered as a potent COX-2 inhibitor for the treatment of chronic pain.

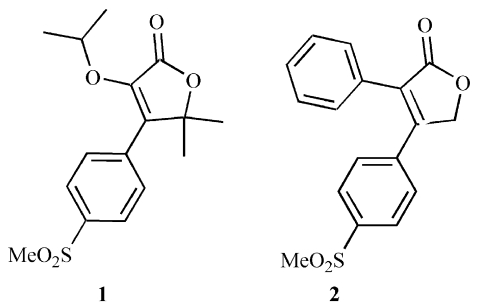
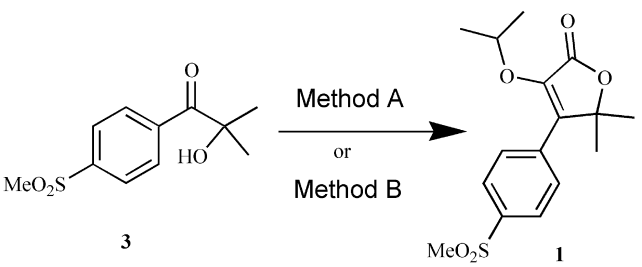


Figure 1. Structure of DFP (**1**) and rofecoxib (**2**).

In continuation with our ongoing project for the development of selective COX-2 inhibitors[4] we were in need of a large quantity of DFP for an in-house experiment. A number of methods have been described in the literature for the synthesis of 3,4-diarylfuranones[4d,e,5] including rofecoxib.[6] However these methods were not suitable for the synthesis of DFP because of its relatively different structural feature,



Scheme 1. Reported synthesis of DFP (Ref. 1): *Reagents and conditions*: method A (a) $ClCOCH_2OAc$, Py; (b) DBU; (c) ^{i}PrI, Ag_2CO_3; method B (a) $^{i}PrOCH_2COOH$, CMC, DMAP; (b) DBU or NaH.

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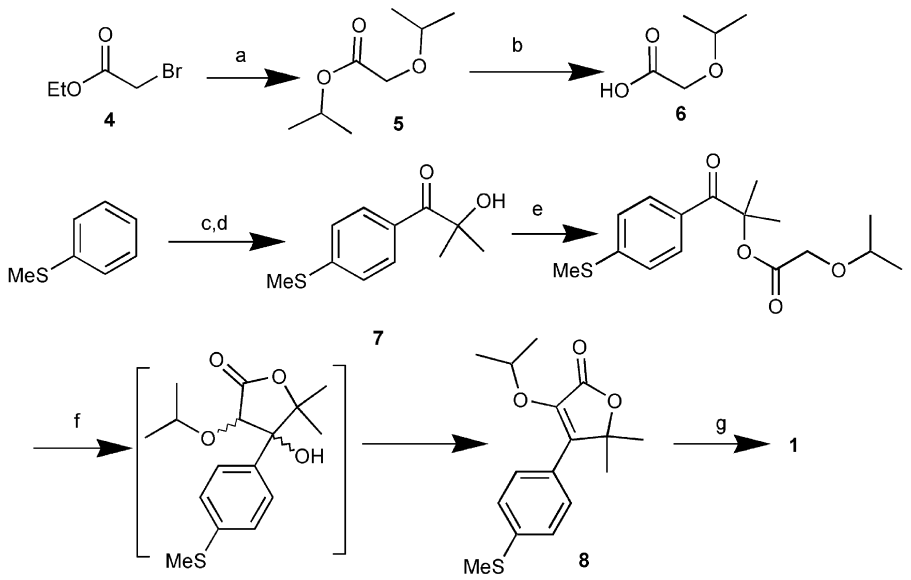
namely the presence of an alkoxy side chain in place of an aryl moiety at the C-3 position of the furanone ring. Thus a different approach was adopted for the synthesis of DFP and its analogues.[1,7] The original synthesis[1] of DFP is illustrated in Scheme 1. The crucial steps for the synthesis of DFP involve coupling of acetoxyacetyl chloride (method A) or 2-alkoxyacetic acid (method B) with the tertiary alcohol **3** followed by base-promoted intramolecular cyclization of the resulting ester. Method B appeared as a better choice for the preparation of DFP on large scale due to (a) availability of the required reagents, (b) it does not involve the use of a moisture sensitive acid chloride. Following method B we, however, failed to prepare DFP in good yield even after several attempts. Due to the presence of base-labile methylsulfonyl ($MeSO_2$-) group[8a,b] the cyclization step led to the formation of a number of unidentified side products along with the partial hydrolysis of ester[8c] thereby decreasing the yield of the desired compound in a small-scale preparation. On the other hand this step was found to be sluggish when applied to the large-scale preparation of DFP. Moreover, preparation of the tertiary alcohol **3** via oxidation of the methylsulfanyl precursor often led to the formation of 4-methylsulfonylbenzoic acid (via cleavage of C–C bond)[8d] as a side product. Therefore, to establish a more convenient method by addressing all these problems we have modified the existing procedure to access an improved and cost-effective method for the synthesis of DFP in 10 g scale. Here, in this paper we wish to present our modified synthesis of DFP using readily available and inexpensive reagents.

2. Results and discussion

Our synthesis of DFP is shown in Scheme 2. We anticipated that the presence of the methylsulfanyl (CH_3S-) group in place of the methylsulfone would favor the base mediated cyclization reaction more efficiently without generating undesired side products. Thus our modifications included (a) coupling of the α-hydroxyacetophenone **7** with 2-isopropoxyacetic acid **6** before oxidation of the methylsulfanyl group, (b) replacement of the coupling reagent CMC [1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate] with less expensive DCC (1,3-dicyclohexylcarbodiimide), (c) conversion of the methylsulfanyl derivative **8** to the sulfone **1** in the last step. We have also established a practical route for the synthesis of 2-isopropoxyacetic acid **6** as shown in Scheme 2.

The reported method[1,9] for the synthesis of 2-isopropoxyacetic acid **6** involves nucleophilic displacement of chlorine from sodium 2-chloroacetate by isopropanol in the presence of sodium hydride. However in our hands sodium 2-chloroacetate participated in a self-condensation reaction to provide a polymeric material when employed under the same reaction conditions. To avoid this side reaction we decided to use the protected acid in the form of its ester. Thus commercially available ethyl-2-bromoacetate **4** reacted smoothly with sodium isopropoxide generated in situ from metallic sodium and isopropanol to afford the corresponding ether **5** in 82% yield. However, **5** was characterized as its isopropyl ester rather than the ethyl one due to the participation of the ethyl ester in a *trans*-esterification reaction during the above conversion. Alkaline hydrolysis of **5** in methanol provided the desired acid **6** in 94% yield. 2-Isopropoxyacetic acid was thus prepared in 77% overall yield.

The other key starting compound α-hydroxyacetophenone **7** was prepared[1] by acylating thioanisole using 2-methylpropionyl chloride in the presence of aluminium chloride followed by hydroxylation[10] at the tertiary center under phase transfer conditions (Scheme 2). In our initial attempt the hydroxylation was carried out according to the procedure described earlier[10d] using a combination of readily available NaOH, KCl and NaOCl at 25°C for 20 h in water. This procedure proved to be less efficient mainly because of formation of the corresponding benzoic acid



Scheme 2. Improved synthesis DFP: *Reagents and conditions*: (a) ^{i}PrOH, Na, reflux, 1 h. (b) 10% NaOH, MeOH, 85°C, 1 h. (c) Isobutyryl chloride, $AlCl_3$, 25°C, 4 h. (d) NaOH, CCl_4–toluene, Aliquat 336, 15–25°C, 22 h. (e) **6**, DCC, DMAP, CH_2Cl_2, 0–25°C, 4 h. (f) DBU, CH_3CN, 80°C, 18 h. (g) Oxone, acetone–H_2O, 25°C, 3 h.

(~45% yield) as a side product. Thus we adopted the same procedure that was used for the synthesis of DFP earlier and the reaction was carried out smoothly using sodium hydroxide and Aliquot 336 in a mixture of carbon tetrachloride and toluene. Hydroxyketone **7** was obtained in 71% yield from thioanisole. Esterification of **7** with 2-isopropoxyacetic acid **6** was initially carried out using CMC and DMAP (dimethylaminopyridine) in dichloromethane. However, low conversion (50%) and the cost of CMC were major concerns of this process. Use of alternative coupling agents such as a combination of DABCO and EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] in toluene was also attempted but only a marginal improvement in yield was observed when compared with the CMC-mediated esterification process. We therefore focused on the use of the cheaper (than CMC) and still effective coupling reagent DCC[11] for the esterification. Experimentally, the reaction was carried out using α-hydroxyacetophenone **7** (1 equiv.), 2-isopropoxyacetic acid **6** (1.4 equiv.), DCC (1.4 equiv.) and DMAP (0.4 equiv.) in dichloromethane at 0–25°C for 3 h. Good conversion was observed and the desired ester was isolated in 75% yield after usual work-up and purification.

The ester thus obtained was then treated with a base to facilitate the intramolecular ring closure. A number of bases including diisopropylamine, NaH and KO^{t}Bu were examined for this purpose and all were found to be effective. However, the duration of the reaction was 3 days in the case of diisopropylamine and although the reaction was much faster with the other two bases, use of a large quantity of moisture-sensitive NaH or KO^{t}Bu was not acceptable for safety reasons. Finally, DBU (1,8-diazabicyclo [5.4.0] undec-7-ene) was used for this reaction. Experimentally the reaction was carried out in acetonitrile at 80°C for 18 h to effect the intramolecular ring closure. After completion the reaction mixture was quenched with 2N HCl in order to neutralize the DBU and to effect the complete dehydration of the intermediate 4-hydroxyfuranone generated during the reaction. This also helped in separating out of the product as a solid from the reaction mixture. Extraction followed by purification of the crude product provided the lactone **8** in 54% yield. Unlike the original procedure[1] (step b of method B, Scheme 1) as mentioned earlier, cyclization proceeded well in this case and no formation of side products was observed. DBU mediated similar type of intramolecular ring closure reaction of phenacyl ester in the presence of aerial oxygen yielded corresponding maleic anhydrides rather than desired furanones.[4b,c] We, however, did not observe formation of any such products when the cyclization was performed in the presence of atmospheric oxygen perhaps due to the absence of methylene hydrogens in the furanone ring of **8**.

Oxidation of **8** was carried out using oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in aqueous acetone to afford the final compound **1** in quantitative yield. No over oxidation of the resulting compound or partial cleavage of C–C bond (as noted during preparation of the tertiary alcohol **3** according to the procedure reported earlier) was observed in this step. The reaction mixture was diluted with water to effect product crystallization and the separated product was isolated by filtration. Purity of **1** was achieved without performing any further purification procedure and was used directly for pharmacological studies. We have used this coupling-cyclization–oxidation reaction sequence to prepare 10 g of DFP and applied this procedure for the large-scale production of **1**. To assess the merit of this new strategy, the synthesis of DFP was carried out according to the reported method as well as the present method simultaneously. The original route via 2-isopropoxyacetic acid (method B, Scheme 1) led to the synthesis of **1** in 23% overall yield from the hydroxyketone **3** whereas the overall yield from **7** was 40% (Scheme 2) according to the present method. Moreover, we have observed remarkable improvement in handling each step while following the new route compared to the earlier one.

All the intermediates synthesized including the final compound were characterized by ^{1}H NMR and IR spectrometry and by Mass spectrometry. Lactone **8** was identified by the appearance of IR absorption at 1752 and 1627 cm^{-1} (characteristic of highly substituted furanone ring) in its IR spectra. The methylsulfanyl moiety of **8**, which appeared at 2.52 ppm, was shifted to 3.07 ppm, a characteristic peak of methylsulfone group attached to an aromatic ring, in the ^{1}H NMR spectra of **1** after the oxidation reaction.

Mechanistically,[4c] the cyclization of ester proceeds through a Dieckmann condensation reaction in the presence of DBU followed by facile dehydration of the resulting 4-hydroxyfuranone leading to the formation of lactone **8**.

3. Conclusion

In conclusion, we have described an improved and efficient method for the synthesis of a selective COX-2 inhibitor DFP that allowed its preparation in large quantities. We also developed a practical method for the synthesis of one of its key starting materials i.e. 2-isopropoxyacetic acid. The formation of a side product during the conversion of the methylsulfanyl group to a methylsulfone was avoided by shifting this oxidation step to the end of the reaction sequence. Distinct advantages of this modified approach over the published procedure are (a) smooth conversion and cleaner reaction product at the crucial ring closure step (b) cost-effectiveness and (c) robustness. The modified method is therefore amenable for large-scale production of DFP. The methodology has been utilized for the synthesis of a similar class of compounds having anti-inflammatory activities.[4a] Further applications of this procedure to more complex systems are under active investigation.

4. Experimental

4.1. General methods

All the solvents used are commercially available. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254; Merck), visualizing with ultraviolet light or Iodine spray. Flash chromatography was performed on silica gel (SRL 230–400 mesh) using distilled petroleum ether (40–60°C), ethyl acetate, dichloromethane, chloroform and methanol. ^{1}H and ^{13}C NMR

spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solution on Varian Gemini 200 and 50 MHz spectrometers respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a Perkin–Elmer 1650 FT-IR spectrometer. UV spectra were recorded on Shimadzu UV 2100S UV–VIS recording spectrophotometer. Melting points were determined using Buchi melting point B-540 apparatus and are uncorrected. Thermal analysis data were generated with the help of Shimadzu DSC-50 detector. MS spectra were obtained on a HP-5989A mass spectrometer. Purity was determined by HPLC (AGIL-AUTO) using the conditions specified in each case: column, mobile phase (range used), flow rate (ranges used), detection wavelength, retention times.

4.1.1. Preparation of isopropyl-2-isopropoxyacetate (5).[12a] Sodium metal (8 g, 0.35 mol) was added portionwise to isopropanol (600 mL) at 25°C with vigorous stirring and the mixture was heated to reflux for 2 h. To this mixture was added ethyl-2-bromoacetate (56.3 g, 0.33 mol) dropwise over 2 h at refluxing temperature. The reaction mixture then cooled to 25°C and stirred for 48 h at the same temperature. Solvent was removed under reduced pressure and the residue was treated with water (400 mL). The aqueous mixture was extracted with ethyl acetate (3×100 mL). The organic layers were collected, washed with cold water (2×100 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the title compound (40 g, 82% yield) as a light brown oil, bp 162–164°C (lit.,[12a] 164.5–166.5°C); ^{1}H NMR ($CDCl_3$) 5.02–5.00 (m, 1H, –OC*H*Me_2), 4.01 (s, 2H, CH_2), 3.65–3.45 (m, 1H, –OC*H*Me_2), 1.26–1.17 (m, 12H, CH_3); IR (KBr, cm^{-1}): 1751 (s, C=O); MS (CI, *i*-Butane): 160 (M^+, 38), 117 (100%).

4.1.2. Preparation of 2-isopropoxyacetic acid (6).[9a] To a solution of isopropyl-2-isopropoxyacetate (40 g, 0.250 mol) in methanol (200 mL) was added an aqueous solution of 10% NaOH slowly with stirring at 25°C. The mixture was then stirred for 1 h at the same temperature and methanol was removed under vacuum. The aqueous mixture was then washed with ethyl acetate (2×75 mL) and then acidified with 2N HCl (100 mL). The mixture was extracted with ethyl acetate (2×100 mL). The organic layers were collected, combined and washed with water (2×100 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to provide the title compound (30 g, 94% yield) as a light yellow oil.[9]; ^{1}H NMR ($CDCl_3$) 8.05 (bs, 1H, OH), 4.01 (s, 2H, CH_2), 3.74–3.59 (m, 1H, –OC*H*Me_2), 1.21 (d, J=6.1 Hz, 6H, CH_3); IR (KBr, cm^{-1}): 3410 (bs), 1734 (s, C=O); MS (CI, *i*-Butane): 118 (M^+, 30), 117 (100%).

4.1.3. Preparation of 2-methyl-1-(4-methylsulfanylphenyl)-1-propanone.[12b] To a suspension of aluminium chloride (63.0 g, 0.48 mol) in dichloromethane (250 mL) was added 2-methylpropanoyl chloride (47 mL, 0.48 mol) dropwise over 15 min at 0°C. The reaction mixture was then stirred at 25°C for 2 h until a clear solution was obtained. A solution of thioanisole (50 g, 0.403 mol) in dichloromethane (200 mL) was added slowly and dropwise over 1.5 h to this mixture at 25°C with vigorous stirring. Stirring was continued for 4 h at 25°C and the mixture was then poured into crushed ice (250 g) and extracted with chloroform (3×200 mL). The combined organic layers were washed with water (3×100 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the title compound (70 g, 89% yield) as a pale yellow solid, mp 45–46°C (lit.,[12b] 44–45°C); ^{1}H NMR ($CDCl_3$) 7.87 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H), 3.54–3.47 (m, 1H, C*H*Me_2), 2.51 (s, 3H, SCH_3), 1.20 (d, J=6.8 Hz, 6H, CH_3); IR (KBr, cm^{-1}): 1677 (s, C=O), 1589 (s); MS (CI, *i*-Butane): 194 (M^+, 100%).

4.1.4. Preparation of 2-hydroxy-2-methyl-1-(4-methylsulfanylphenyl)-1-propanone (7).[12c] To a mixture of 2-methyl-1-(4-methylsulfanylphenyl)-1-propanone (70 g, 0.36 mol), Aliquot 336 (27 mL, 0.06 mol) and carbon tetrachloride (51.5 mL, 0.53 mol) in toluene (100 mL) was added NaOH (31.4 g, 0.786 mol) slowly and portion wise over 30 min. The mixture was then stirred for 2 h at 15°C and 20 h at 25°C. After completion of the reaction the mixture was diluted with water (300 mL), acidified with 2N HCl (100 mL) and extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with water (2×200 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound thus obtained was purified by column chromatography using 10% EtOAc–petroleum ether to provide the title compound (60 g, 80% yield) as colorless oil, bp 148–149°C at 0.1 Torr (lit.,[12c] 150°C at 0.1 Torr); ^{1}H NMR ($CDCl_3$) 7.97 (d, J=8.5 Hz, 2H), 7.27 (d, J=8.6 Hz, 2H), 4.13 (bs, 1H, OH), 2.51 (s, 3H, SCH_3), 1.63 (s, 6H, CH_3); IR (KBr, cm^{-1}): 3447 (bs, OH), 1666 (s, C=O), 1588 (s); MS (CI, *i*-Butane): 210 (M^+, 100%).

4.1.5. Preparation of 1,1-dimethyl-2-(4-methylsulfanylphenyl)-2-oxoethyl-2-isopropoxyacetate. To a mixture of 2-hydroxy-2-methyl-1-(4-methylsulfanylphenyl)-1-propanone (50 g, 0.24 mol), 2-isopropoxyacetic acid (40 g, 0.34 mol), DMAP (11.6 g, 0.09 mol) in dichloromethane (500 mL) was added DCC (70.30 g, 0.34 mol) slowly over 30 min at 0°C with stirring. The mixture was then warmed to 25°C and stirring continued for 3 h. After completion of the reaction the mixture was filtered through celite, the filtrate was collected and concentrated under vacuum. The residue was purified over silica gel using 8% EtOAc–petroleum ether (2 L) to give the required ester (55 g, 75% yield) as a colorless solid, mp 47°C; ^{1}H NMR ($CDCl_3$) 7.91 (d, J=8.3 Hz, 2H), 7.21 (d, J=8.3 Hz, 2H), 3.96 (s, 2H, CH_2), 3.45–3.39 (m, 1H, C*H*Me_2), 2.49 (s, 3H, SCH_3), 1.65 (s, 6H, CH_3), 1.09 (d, J=6.9 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 197.71, 169.86, 145.25, 130.47, 128.99 (2C), 128.86, 124.80, 84.88, 72.49, 65.81, 25.27 (2C), 21.59 (2C), 14.63; IR (KBr, cm^{-1}): 1752 (s, C=O), 1681 (s, C=O), 1593 (s); IR (KBr, cm^{-1}): 1755 (s, O–C=O), 1681 (s, C=O), 1589 (s); MS (CI, *i*-Butane): 310 (M^+, 100%); HRMS Calcd for $C_{16}H_{23}O_4S$ ($M+H^+$): 311.1317. Found: 311.1317.

4.1.6. Preparation of 3-isopropoxy-5,5-dimethyl-4-(4-methylsulfanylphenyl)-2,5-dihydro-2-furanone (8). To a solution of 1,1-dimethyl-2-(4-methylsulfanylphenyl)-2-oxoethyl-2-isopropoxyacetate (40 g, 0.129 mol) in acetonitrile

(250 mL) was added DBU (38.4 ml, 0.258 mol) slowly over 15 min under a nitrogen atmosphere at 25°C. The mixture was stirred for 0.5 h at 25°C and then heated to reflux for 18 h. The mixture was cooled to room temperature, diluted with water (100 mL) and 2N HCl (50 mL) and then extracted with EtOAc (3×100 mL). The organic layers were collected, combined, washed with water (2×100 mL) and dried over anhydrous Na_2SO_4. After removal of solvent under vacuum the crude product was purified by column chromatography over silica gel using 6% EtOAc–petroleum ether (400 ml) to give the desired product (10 g, 54% yield) as a white semisolid; ^{1}H NMR ($CDCl_3$) 7.63 (d, J=8.3 Hz, 2H), 7.28 (d, J=8.3 Hz, 2H), 5.11–5.05 (m, 1H, $CHMe_2$), 2.52 (s, 3H, SCH_3), 1.64 (s, 6H, CH_3), 1.27 (d, J=6.3 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.74, 141.18, 140.09, 139.07, 134.97, 128.17 (2C), 127.05 (2C), 85.91, 73.06, 26.61 (2C), 22.08 (2C), 15.90; IR (KBr, cm^{-1}): 1752 (s, C=O), 1627 (s, C=C), 1593 (s); MS (CI, *i*-Butane): 292 (M^+, 25), 250 (80), 177 (100%); Anal. calcd for $C_{16}H_{20}O_3S$: C, 65.73; H, 6.89. Found: C, 65.70; H, 6.90.

4.1.7. Preparation of 3-isopropoxy-5,5-dimethyl-4-(4-methylsulfonylphenyl)-2,5-dihydro-2-furanone (1). To a solution of 3-isopropoxy-5,5-dimethyl-4-(4-methylsulfanylphenyl)-2,5-dihydro-2-furanone (10 g, 0.034 mol) in acetone (200 mL) was added a solution of oxone (52.60 g, 0.086 mol) in water (200 mL). The reaction mixture was stirred vigorously for 3 h at 25°C. After completion of the reaction the solvent was removed under reduced pressure and water (200 mL) was added. The mixture was then extracted with EtOAc (2×100 mL), organic layers collected, combined, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the title compound (11 g, 99% yield) as an off white powder, mp 126–127°C; ^{1}H NMR ($CDCl_3$) 7.98 (d, J=8.8 Hz, 2H), 7.83 (d, J=8.8 Hz, 2H), 5.28–5.20 (m, 1H), 3.07 (s, 3H), 1.64 (s, 6H), 1.26 (d, J=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.14, 140.78, 140.05, 139.97, 135.37, 128.47 (2C), 127.15 (2C), 82.91, 73.36, 43.93, 26.38 (2C), 22.28 (2C); IR (KBr, cm^{-1}): 1747 (s), 1652 (s), 1595 (s); MS (CI, *i*-Butane): 325 (M^+, 100), 283 (40), 237 (20%). HPLC: 97.56%, Novapak C18 (150 mm), water–acetonitrile (50:50), 1 mL/min, 290 nm, retention time: 4.76 min. Anal. calcd for $C_{16}H_{20}O_5S$: C, 59.24; H, 6.21. Found: C, 59.20; H, 6.22.

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