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Efficient Syntheses of 2-(3',5'-Difluorophenyl)-3-(4'-methylsulfonylphenyl)-cyclopent-2-enone, a Potent COX-2 Inhibitor

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Abstract: 2-(3',5'-Difluorophenyl)-3-(4'-methylsulfonylphenyl)cyclopent-2-enone **(1)** displays high selectivity and potency against COX-2. Three efficient syntheses of this diarylcyclopentenone are described. The first approach employs a Suzuki coupling reaction as the key step while the second synthesis features an intramolecular Friedel-Crafts acylation. The third, and preferred route to this compound involves a sequential malonate alkylation and acylation and ring-closure sequence.

Keywords: COX-II inhibitor; Synthesis; Suzuki coupling; Acylation; Alkylation

Introduction

Cyclooxygenase (COX) catalyzes the first step in arachidonic acid metabolism.[1] Two isoforms of the membrane protein COX are known:[2] COX-1 is responsible for the physiological production of prostaglandins; COX-2 is responsible for the elevated production of prostaglandins during inflammation. Most traditional non-steroidal anti-inflammatory drugs (NSAID's) inhibit both COX-1 and COX-2 with little specificity, leading to serious side effects such as gastric lesions and renal toxicity.[3] The identification of a COX-2-selective inhibitor,

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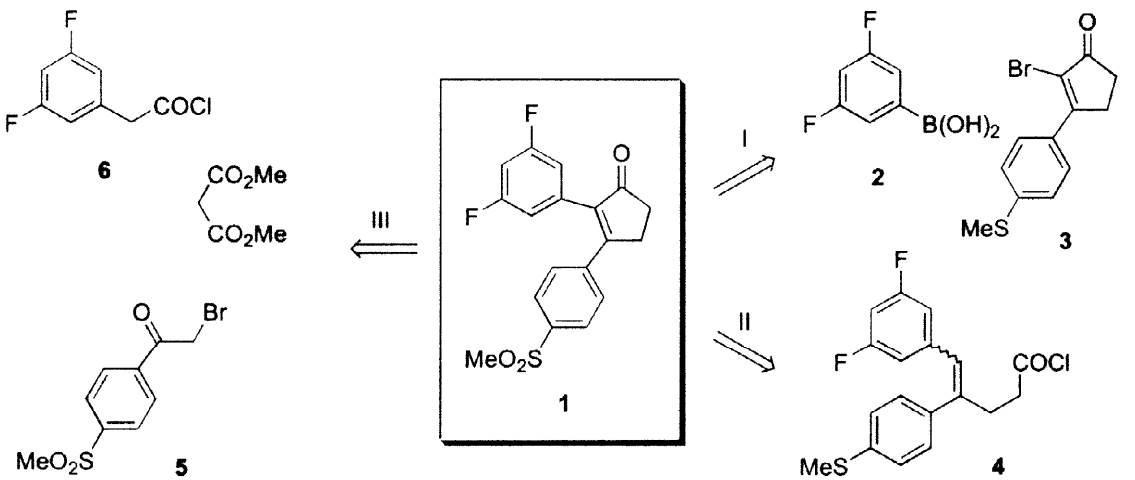
therefore, should offer potent anti-inflammatory activity *in vivo* with minimal side effects.[4] As a class, 2,3-diarylcyclopentenones have shown selectivity and potency as COX-2 inhibitors. Within this class, 2-(3',5'-difluorophenyl)-3-(4'-methylsulfonylphenyl)cyclopent-2-enone (**1**) has shown both high selectivity and potency for COX-2. With this compound as representative of the synthetic challenges associated with this class of inhibitors, we initiated studies aimed at defining practical syntheses of this target. As a result, three uniquely different approaches emerged from our studies (Scheme 1), all of which could be applied to the general synthesis of 2,3-diarylcyclopentenones. The first approach involves a Suzuki coupling reaction as the key step, while the second route features a modified Shapiro reaction and intramolecular Friedel-Crafts acylation as the principal steps. The third route employs a simple malonate alkylation and acylation sequence, followed by a classical ring closure and decarboxylation.

Scheme 1



Results and Discussion

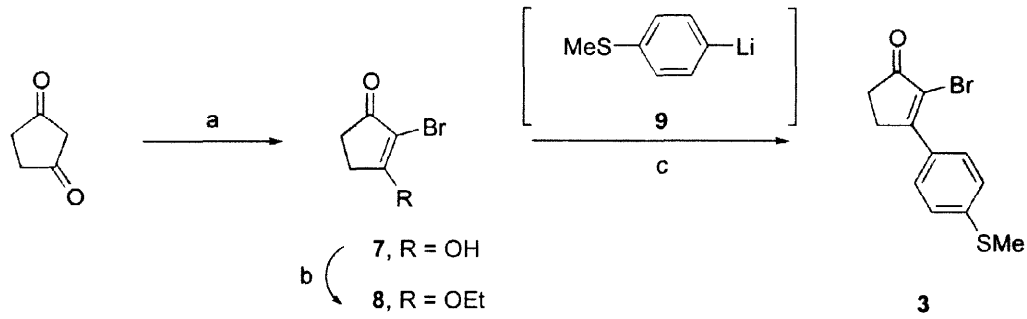
Suzuki Coupling Route

The first synthesis of 2-(3',5'-difluorophenyl)-3-(4'-methylsulfonylphenyl)cyclopent-2-enone (**1**) is based on a Suzuki coupling reaction between the boronic acid **2** and the bromoenone **3** as shown in Scheme 1. Bromoenone **3** was readily prepared in three steps from 1,3-cyclopentanedione (Scheme 2). Bromination of 1,3-cyclopentanedione was best run using NBS and aqueous potassium bicarbonate as base.[6] In this reaction no overbromination was detected even in the presence of excess NBS, and the product **7** was obtained in high yield (87%) by direct crystallization from the reaction mixture (upon acidification to pH 3). Conversion of the bromodione **7** to the ethyl vinyl ether **8** was accomplished in high yield (87%) using 1 mol% 10-

camphorsulfonic acid (CSA) in EtOH-toluene with water removal *via* Soxhlet trap packed with 4 Å molecular sieves. At reaction completion the mixture was concentrated, to remove ethanol, and the solution of **8** in toluene was carried on to the next step after aqueous work-up and drying.

Lithiation of 4-bromothioanisole was carried out using *n*-BuLi in THF below -55 °C to give aryllithium **9**. While **9** undergoes alkylation with BuBr slowly at this temperature (1-2% per hour) this decomposition process is more significant at higher temperature. Thus, reaction of **9** with **8** was carried out at -50 °C to -40 °C, and then the reaction was quenched with aqueous H_2SO_4, to give the product **3** cleanly. The highly pure (>99% pure) bromoenone **3** was isolated by crystallization from toluene-heptane in 84% yield (73% from **7**).

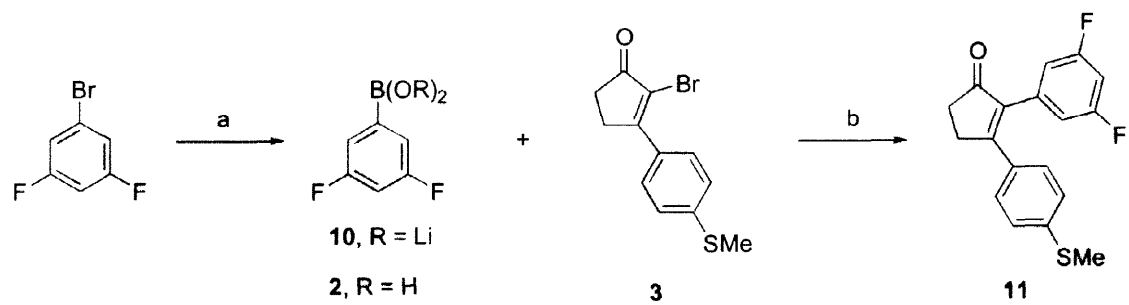
Scheme 2



Conditions: a) 1. NBS, $KHCO_3$, 2. H_3O^+; b) EtOH-Toluene, 1%CSA; c) THF, -50 to -40 °C

The boronic acid **2** was prepared, in the usual manner, by metal-halogen exchange of 1,3-difluorobromobenzene with *n*-BuLi at low temperature to give 1,3-difluorophenyl lithium which was trapped with triisopropyl borate (Scheme 3). This reaction was initially carried out at -90 °C in diethyl ether, which was considered impractical. It was found that the reaction proceeded equally well in diethoxymethane at -78 °C to give the boronic acid **2** in 72-75% yield. Conveniently, addition of water to the reaction mixture followed by separation of the organic layer (containing impurities) provided an aqueous solution of the pure boronic acid (HPLC: 99% pure) as its lithium salt **10**. The solution of boronate salt **10** was directly used in the Suzuki coupling step without further isolation or purification (*vide infra*).

Scheme 3



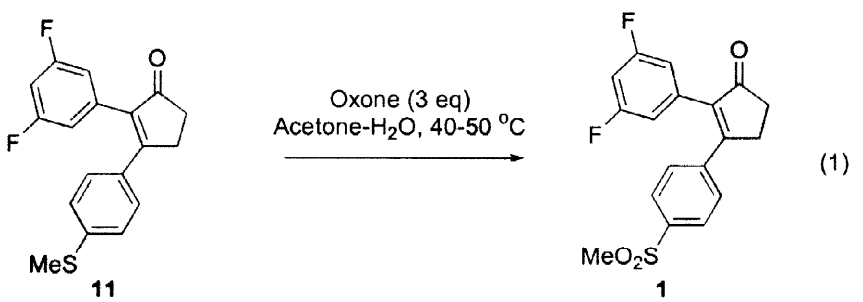
Conditions: a) 1. n-BuLi, $B(OiPr)_3$, $(EtO)_2CH_2$, 2. H_2O or H_3O^+; b) $PdCl_2(PPh_3)_2$, Toluene-H_2O

A study of the Suzuki coupling of bromoenone **3** with boronic acid **2** was conducted (Table 1).[5] As anticipated, the efficiency of this reaction was highly dependent on the catalyst. For instance it was found that $Pd(OAc)_2$-PPh_3 was inactive, while $PdCl_2(PPh_3)_2$ was a highly effective catalyst. Use of amine bases instead of inorganic bases such as Na_2CO_3 resulted in lower yield, partially due to the debromination (reduction) of the bromoenone **3**. Although the coupling reaction was effective in several solvents such as THF, *t*-BuOMe, and $(EtO)_2CH_2$, toluene was preferred since the product is more soluble in this solvent, allowing the reaction to be run at a reasonable concentration (0.3*M*). The optimal catalyst loading is 1 mol%, which results in complete reaction within approx. 5 h. Use of 0.5 mol% of the catalyst is possible, but provides complete reaction in approx. 14 h. Finally, the reaction proceeded equally well using the crude boronate salt **10**, and therefore isolation and purification of the boronic acid is not necessary.

Table 1. Suzuki Coupling Reaction Conditions

Entry	Solvent	Catalyst	Base	Isolated Yield of **11**
1	*i*-PrOH-H_2O	$Pd_2(dba)_3$	*i*-Pr_2NH	74%
2	Toluene-H_2O	$PdCl_2(PPh_3)_2$	Na_2CO_3	85-93%
3	*t*-BuOMe-H_2O	$PdCl_2(PPh_3)_2$	Na_2CO_3	88%
4	$(EtO)_2CH_2$-H_2O	$PdCl_2(PPh_3)_2$	Na_2CO_3	87%

It was found that the crude product **11**, isolated by crystallization from the reaction mixture, was contaminated with significant quantities of Pd (~1000 ppm) which was a serious concern unless it was efficiently removed *en route* to final drug product. Fortunately, the level of residual Pd could be significantly reduced by the treatment of the reaction mixture with a combination of *n*-Bu_3P and Darco KB prior to product crystallization.[7] While treatment of the reaction mixture with 10 mol% *n*-Bu_3P alone reduced the residual Pd to 90-125 ppm, a combination of Darco KB and 10 mol% *n*-Bu_3P reduced the residual Pd to 15-45 ppm. It is likely that soluble Pd complexes are sequestered by *n*-Bu_3P and subsequently removed during the crystallization while insoluble Pd residue is further removed by the Darco treatment and filtration.



(1)

Conversion of sulfide **11** to sulfone **1** was accomplished in a simple, clean, and efficient manner using Oxone (equation 1).[8] Thus, treatment of the sulfide **11** with Oxone (3 eq) in acetone-H_2O (90:10) at 40-45 °C

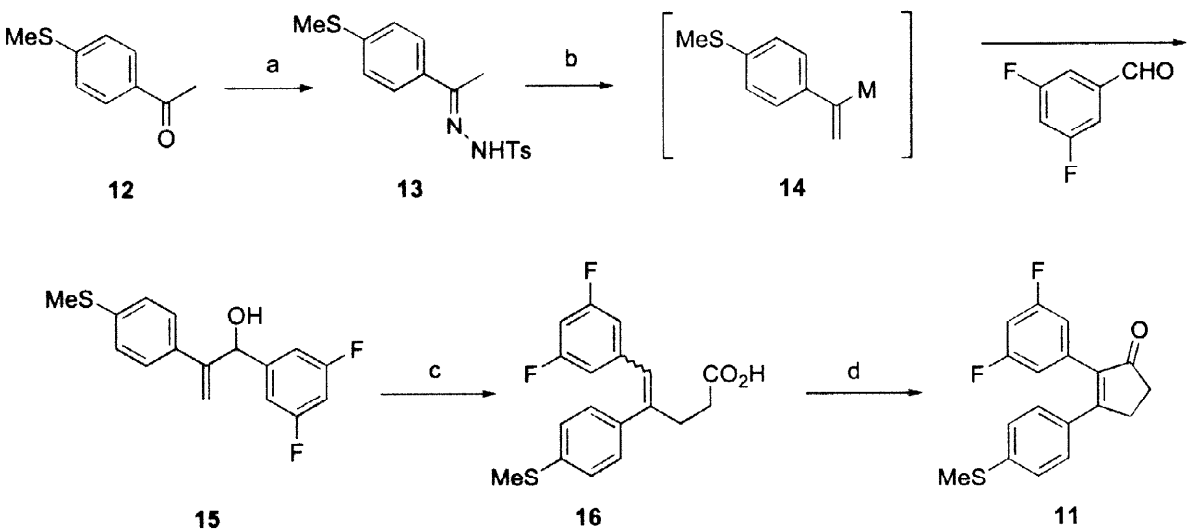
resulted in full conversion to sulfone **1** in 5-6 h. It was found that water was essential for this reaction as without it, or with less water (eg. 5%), the reaction proceeded sluggishly. The reaction mixture was filtered to remove inorganics (sulfate salts) and then water was added to the filtrate at 25 °C to crystallize the product. This procedure is productive, high yielding (95%) and provides 2-(3',5'-difluorophenyl)-3-(4'-methylsulfonylphenyl)cyclopent-2-enone (**1**) in excellent purity (HPLC: >99% pure). Interestingly, the product obtained from this oxidation reaction is essentially free of Pd, even if the sulfide **11** is contaminated with high levels of Pd. For example, use of sulfide **11** contaminated with >900 ppm of Pd (not treated with Bu_3P and Darco KB), provided **1** with <2 ppm residual Pd. It is speculated that Pd complexes are oxidized by Oxone, and are either removed during filtration of salts or are present in the mother liquors upon product crystallization.

This efficient, chromatography-free synthesis of **1** proceeds in an overall yield of 56% in six steps from 1,3-cyclopentanedione. This approach should be readily applicable to the general synthesis of diaryl cyclopentenones simply by variation of the boronic acid and bromoenone fragments in the Suzuki coupling.

Shapiro Reaction Route

The route described above has several drawbacks. In particular, 1,3-cyclopentanedione is expensive and not available in large quantities. Also, there are two steps require low temperature conditions which are not ideal for large scale synthesis. Thus, we examined alternative routes to diaryl cyclopentenone **1** in search of a more practical process. As depicted in Scheme 4, an alternative synthesis was developed involving Shapiro reaction,[9] Claisen rearrangement[10] and intramolecular Friedel-Crafts reaction[11] to give the penultimate intermediate **11**, which could be converted to the target molecule **1** using Oxone as described previously.

Scheme 4

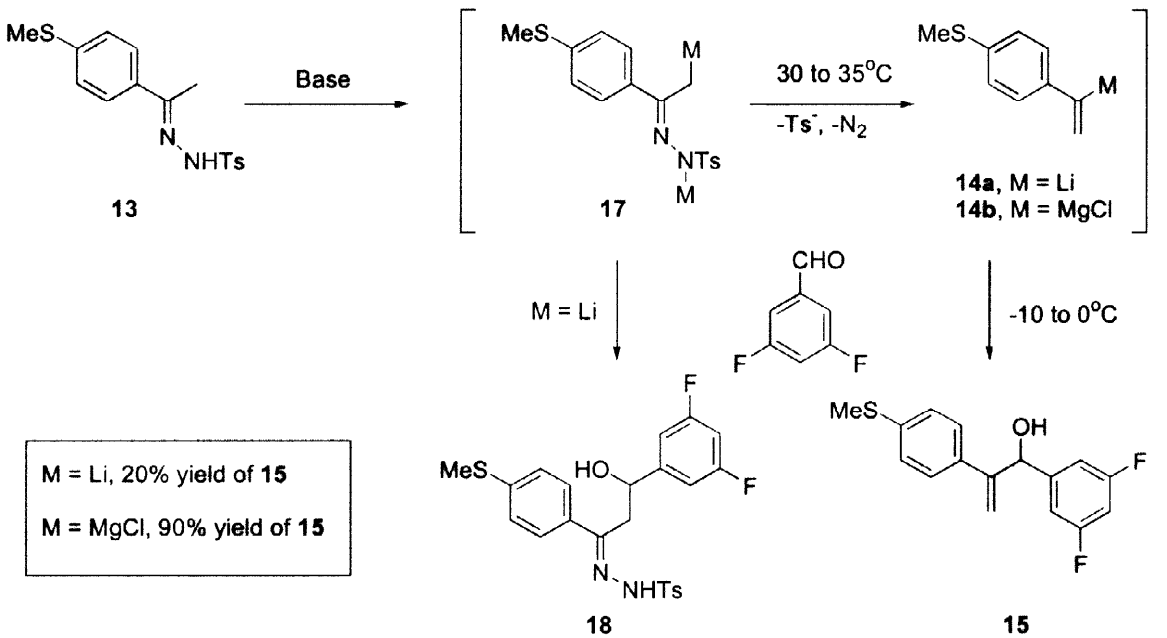


Conditions: a)$TsNHNH_2$, cat. PPTS, CH_3CN, o-dichlorobenzene; b) i-PrMgCl, THF-Toluene; c) 1. $CH_3C(OEt)_3$,10mol% $(CH_3)_3CCO_2H$, Toluene, reflux; 2. NaOH, THF, reflux; d) $AlCl_3$, $(COCl)_2$, CH_2Cl_2

This synthesis employs 4-methylthioacetophenone **12** as a commercially available, inexpensive starting material.[12] A solution of compound **12** in a mixture of *o*-dichlorobenzene and acetonitrile was treated with $TsNHNH_2$ in the presence of 10 mol% pyridinium *p*-toluenesulfonate (PPTS) at 70 °C for 3h. At reaction completion acetonitrile was removed *in vacuo* and *i*-PrOH was added to crystallize the product. In this manner, tosyl hydrazone **13** was obtained in 92% isolated yield and 99.5 % purity (HPLC).

Initial attempts to convert tosyl hydrazone **13** into the allylic alcohol **15** utilized standard Shapiro reaction conditions (Scheme 5).[9] Hydrazone **13** was reacted with 2 equiv. *n*-BuLi at -10 to 0 °C to generate the dianion **17** (M = Li). Upon warming to 30-35 °C, fragmentation of dianion **17** with elimination of Ts^- and N_2 was expected to provide the corresponding vinyl lithium **14a** (M = Li). Although approx. 90% of the hydrazone was consumed in this reaction, the yield of the vinyllithium **14** (based on yield of olefin **19**) was only 25%. Not surprisingly, quenching the vinyl lithium **14** with 3,5-difluorobenzaldehyde provided only 20% yield of the desired allylic alcohol **15**. Interestingly, the reaction of dianion **17** with 3,5-difluorobenzaldehyde provided the addition product **18** in 95% yield. This implied that the elimination step to form the vinyllithium **14a** from dianion **17** was problematic, presumably due to the instability of **14a** (M = Li) at elevated temperatures. Fortunately, the reaction could be greatly improved by simply changing the metal from Li to MgCl.

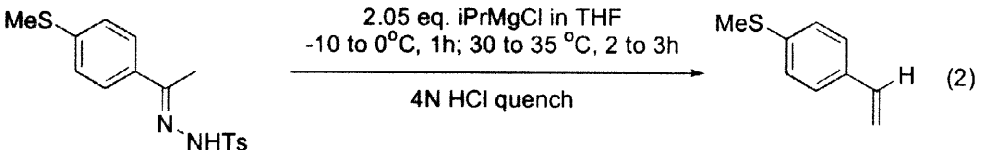
Scheme 5



As summarized in Table 2, the optimal conditions for formation of the Grignard reagent **14b** involve reaction of the hydrazone **13** with *i*-PrMgCl in THF or Toluene-THF at 35 °C in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA). Under these conditions conversion of **13** to Grignard reagent **14b** was complete within 3h. Subsequent reaction with 3,5-difluorobenzaldehyde at -10 °C provided allylic alcohol **15**

in 90% yield as THF-toluene solution which was taken directly into the next step. The greatly improved result obtained using this modification of the Shapiro reaction was rationalized in terms of greater stability of the vinyl Grignard reagent **14b** (M = MgCl) compared to the vinyl lithium species **14a**. A preliminary literature search indicated that this is the first example of the use of a Grignard reagent as base in the Shapiro reaction, and it is expected that it may also be useful in other systems.[9]

Table 2. Selected modified Shapiro reaction conditions



13 **19**

Entry	TMEDA	Solvent	Conversion	LC Yield of **19**
1	1.0 eq.	THF	>97%	80%
2	-	THF	>97%	74%
3	**2.0 eq.**	**THF**	**>97%**	**96%**
4	**2.0 eq.**	**Toluene**	**>97%**	**95%**
4	-	Toluene	>97%	36%
5*	1.0 eq.	$MeOCH_2CH_2OMe$	34%	10 to 20%
6*	-	$MeOCH_2CH_2OMe$	30%	<10%

* Required warming to 60 °C for elimination of N_2 and Ts^-.

As shown in Scheme 4, Claisen rearrangement of the allylic alcohol **15** was affected under standard conditions[10] (2 equiv. $CH_3C(OEt)_3$, 10 mol% $(CH_3)_3CCO_2H$, toluene, reflux, 18 h) to give the rearranged ester (HPLC: *Z*:*E* = 92:8) in 90% yield. Both *E* and *Z* isomers could be separated by column chromatography and characterized by NOE difference experiments. However, product isolation was not necessary, and the isomeric mixture was carried on directly to the next step. The crude product was hydrolyzed using NaOH in aqueous THF at 60 °C for 3 h. After acidification and extraction into *i*-PrOAc, carboxylic acid **16** was crystallized from *i*-PrOAc-hexane and was obtained in 67% yield (over three steps from hydrazone **13**). The *Z*:*E* ratio in the isolated solid **16** was 98.7:1.3, with most of the *E*- isomer remaining in the mother liquors. Although both *Z*- and *E*- isomers could be converted to cyclopentenone **11** in the Friedel-Crafts reaction, purification of the carboxylic acid prior to ring closure is preferred based on final product purity.

The cyclopentenone ring of **1** was formed *via* an intramolecular Friedel-Crafts reaction.[11] This transformation was briefly investigated using the acid **16** directly (under strongly acidic conditions) but no useful conditions were identified. Conversely, the intramolecular Friedel-Crafts reaction *via* the corresponding acid chloride derived from **16** was quite efficient. Thus, the acid **16** was converted into the corresponding acid

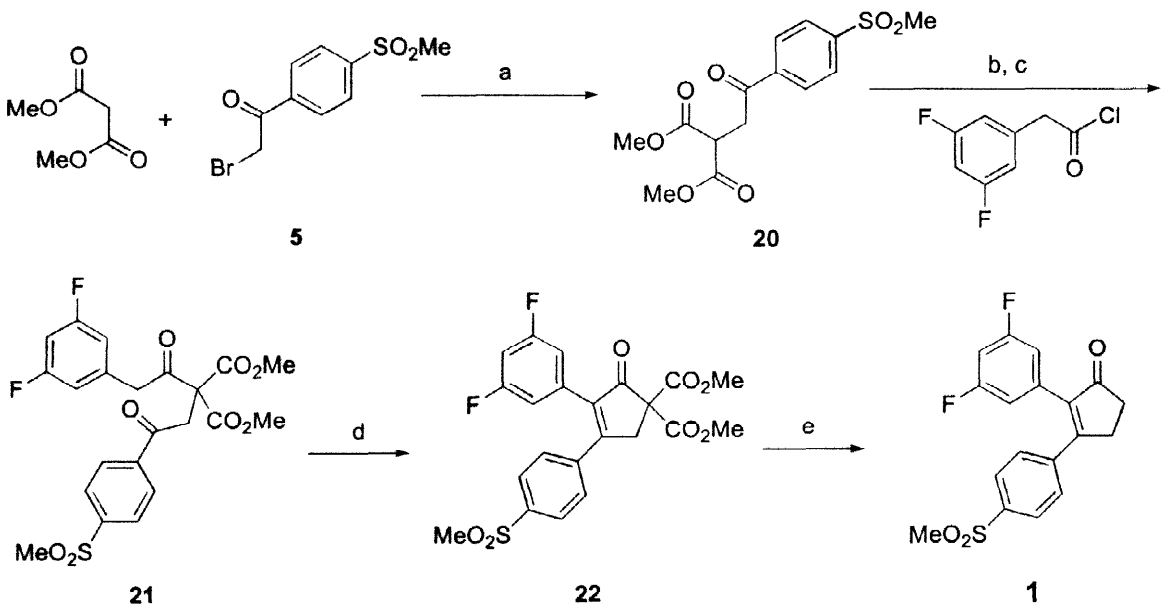
chloride **4** ($(COCl)_2$, CH_2Cl_2, 25 °C) which was then added to a slurry of $AlCl_3$ in CH_2Cl_2 at -5 to 0 °C. After aqueous workup, the ring closed product **11** was isolated in 90% yield by crystallization from toluene-heptane. The synthesis was completed using Oxone as described previously to provide **1** in 99.5% purity (HPLC).

This efficient, chromatography-free synthesis of **1** proceeds in an overall yield of 54% in six steps from 4-methylthioacetophenone **12**. This route employs readily available raw materials, avoids the use of low temperatures and heavy metals, and should be applicable to the general synthesis of diarylcyclopentenones simply by variation of the acetophenone and aryl aldehyde fragments in the Shapiro reaction.

Malonate Alkylation-Acylation Route

The third route to compound **1** is based on sequential malonate alkylation-acylation followed by ring-closure and decarboxylation (Scheme 6).

Scheme 6



Conditions: a) K_2CO_3, Acetone, 45 °C; b) $MgBr_2{\cdot}OEt_2$, Pyridine, MeCN/THF, 0 °C; c) -35 to -25 °C, 1h; d) 0.2 eq. Et_3N, RT, 2h; e) 3*M* H_2SO_4, HOAc, 90 °C, 10h

The synthesis began with the alkylation of dimethyl malonate with the commercially available bromosulfone **5**.[13] Initial screening of reaction conditions for the malonate alkylation reaction focused on minimization of the bis-alkylation product.[14] Obviously, for each mole of bis alkylated product formed, there was wastage of two moles of bromosulfone **5**, which presented problems in terms of efficiency and product purification. The ratio of mono:bis alkylated products and the efficiency of this reaction was found to be dependent on solvent, base, temperature, mode of addition and the amount of dimethyl malonate.[14] Some of

these reactions were summarized in Table 3. The optimal conditions were found to be 8 equiv. malonate, K_2CO_3, acetone, 45 °C, and slow addition of bromosulfone **5**. The ratio of mono:bis alkylation was 96:4 in solution, and the product **20** was isolated in 80% yield (>99.5:0.5, mono:bis) after aqueous workup and crystallization from *i*-PrOAc.

Table 3. Mono/Bis-alkylation Ratio

Malonate (eq)	Solvent	Base	Temp °C	Mono/Bis	Isolated yield of **20**
2	DMF	NaOMe	0	1:1	30%
2	DMF	NaOMe	-60	2:1	55%
2	acetone	K_2CO_3	45	82:18	--
6	acetone	K_2CO_3	60	85:15	--
6	acetone	K_2CO_3	60 (Slow addition)	94:6	--
8	acetone	K_2CO_3	45 (Slow addition)	96:4	80%

Acylation of compound **20** using 3,5-difluorophenylacetyl chloride turned out to be non-trivial. The construction of quaternary centers in this manner is not widely precedented in the literature.[15] In our case the situation is not straightforward since the product **21**, once formed, tends to undergo rapid intramolecular condensation, providing complex mixtures of acylation and ring closed products. Our efforts concentrated on the development of a mild and well controlled acylation procedure. It was planned that the ring closure would be effected in a separate step although, in principle, it should be possible to carry out the acylation and ring closure in one-pot.

Table 4. Optimization of Acylation

Base	Solvent	Temperature	Conversion
NaH	THF	-30 °C	60%
NaH	THF	-70 °C	75%
$Et_3N/MgBr_2OEt_2$	MeCN	-30 °C to 0 °C	80%
$Pyr/MgBr_2OEt_2$	MeCN/THF	-30 °C	95%

A solution to our acylation problem was uncovered by modification of the Rathke method.[16] Using the standard procedure ($MgCl_2$, Et_3N, MeCN) low conversion was obtained possibly due to the heterogeneous nature of the reaction mixture. Alternative Mg salts were explored for this reaction, and it was found that $MgBr_2{\cdot}Et_2O$ (pyridine as base) provided a homogeneous reaction mixture and that the acylation reaction provided **21** cleanly. The optimal procedure for this acylation involved preparation of the Mg enolate, using

$MgBr_2 \cdot Et_2O$-Pyridine in a mixture of MeCN and THF at 0 °C, followed by reaction with 3,5-difluorophenylacetyl chloride **6** at -30 °C. THF was used as co-solvent to prevent acetonitrile from freezing. Under these conditions, the reaction proceeded to >95% conversion with minimal side reactions (Table 4). After workup (aq. HCl), the crude product **21** was taken directly on to the next step, as a solution in mainly *t*-butylmethylether.

The conversion of **21** to the cyclized product **22** was readily effected under basic conditions. The crude product from the acylation reaction was treated directly with 0.2 equiv. of Et_3N at 25 °C for 2 h, to give complete conversion to **22**. After workup (aq. HCl), the product was crystallized from *i*-PrOAc-heptane to give **22** in 80% isolated yield and excellent purity (HPLC: >99%) over the two steps.

Several conditions were screened for the conversion of **22** into diarylcyclopentenone **1**. Under basic conditions (eg. aq. NaOH) rapid monodecarboxylation occurred, as expected. The second decarboxylation, to give **1**, was sluggish and provided many side products (mainly those due to ring opening). Interestingly, it was found that decarboxylation could be affected quite cleanly under acidic conditions. Treatment of compound **22** with 3*M* H_2SO_4-HOAc at 90 °C for 10 h, resulted in complete conversion to 2-(3',5'-difluorophenyl)-3-(4'-methylsulfonylphenyl)cyclopent-2-enone (**1**), which was crystallized, in 95% yield and 99.8% purity (HPLC), after cooling to 25 °C and addition of water.

This efficient synthesis of **1** proceeds in an overall yield of 60% in four steps from bromosulfone **5**. This route employs readily available raw materials, avoids the use of low temperatures and heavy metals, and should be readily applicable to the general synthesis of diarylcyclopentenone simply by variation of the bromo acetophenone and arylacetic acid fragments in the malonate alkylation-acylation sequence.

Conclusion

In summary, three practical and efficient syntheses of 2-(3',5'-difluorophenyl)-3-(4'-methylsulfonylphenyl)cyclopent-2-enone (**1**) have been developed, which provide the final product in high overall yield (>55%) and excellent purity (HPLC: >99.5%). Taken together, these different synthetic approaches should allow for the rapid construction of an essentially unlimited array of functionalized diaryl cyclopentenones. In terms of a practical, economical, large scale process for the synthesis of compound **1**, each of the routes are considered suitable. However, the malonate route is particularly attractive since it is the most productive (fewest steps), all raw materials are available and inexpensive, and the use of heavy metals is avoided.

Experimental

General. Melting points are uncorrected. ^{1}H, ^{13}C NMR spectra were collected at 400 and 100 MHz, respectively. All reactions were run under nitrogen and all reagents were plant grade unless otherwise noted. Combustion analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Analytical reversed-phase high-performance liquid chromatography (HPLC) assay: Zorbox RX C-8 column (4.6 x 250 mm) with mobile phase MeCN: 0.1% H_3PO_4 in H2O and UV detection at 220 nm.

2-Bromo-1,3-cyclopentandione (7) To a slurry of 1,3-cyclopentandione (2.68 Kg, 27.3 mol) in 20 L of water at room temperature was added a solution of $KHCO_3$ (3.0 Kg, 30.05 mol) in 20 L of water over 1 h. CO_2 was evolved during the addition of $KHCO_3$ and the reaction mixture became a brown homogenous solution. To the solution at room temperature, NBS (5.4 Kg, 30.05 mol) was added in portions at such a rate to control the temperature below 30 °C (ca. 1 h). The brown solution was aged for another 90 min and ca. 3.4 L of aqueous 10 *N* H_2SO_4 was added until pH = 2. During the acid quench, a yellow solid precipitated. The slurry was stirred for 30 min, and the solid was collected by filtration and washed with water (2x4 L). The product was dried under vacuum for 48 h to give 4.21 Kg (87% yield) of 2-bromo-1,3-cyclopentandione (**7**). Its physical and spectroscopic properties were identical to the reported data.[6]

2-Bromo-3-ethoxyl-2-cyclopenten-1-one (8) Under nitrogen atmosphere, a solution of 2.5 Kg (13.0 mol) of 2-bromo-1,3-cyclopentandione (**7**) and 32.8 g (0.13 mol) of 10-camphorsulfonic acid in 12.5 L of ethanol and 12.5 L of toluene was heated under reflux for 24 h, with water removal using a 5 L Soxhlet extractor filled with 4 Å molecular sieves. The reaction solution was concentrated under reduced pressure to ca. 6 L, followed by addition of 14 L of toluene. The organic phase was washed, sequentially, with 4 L of half-saturated $KHCO_3$, and 2 L of water. The organic phase was concentrated under reduced pressure to ca. 10 L (HPLC assay: 87% yield) and directly used for next step. Chromatography of a small sample on silica gel column provided analytically pure 2-bromo-3-ethoxyl-2-cyclopenten-1-one (**8**). Its physical and spectroscopic properties were identical to the reported data.[6]

2-Bromo-3-(4'-methylthiophenyl)-2-cyclopenten-1-one (3) To a solution of 4-bromothioanisole (31.9 g, 157 mmol, 1.15 eq.) in THF (480 mL) at -70 °C was added *n*-BuLi (1.6 M in hexanes, 94 mL, 150.4 mmol, 1.1 eq.) over 30 min to give a heavy slurry. The slurry was aged for 1 h at -60 to -70 °C and then a solution of bromoether (**8**) in toluene (28 g, 137 mmol in 140 mL) was added over 45 min., keeping the reaction temperature at <-40 °C. The mixture was aged 30 min at -40 to -50 °C and then 4*N* H_2SO_4 (200 mL) was added (temperature rose to 0 °C during addition) to form a slurry, which dissolved to form two clear phases upon warming to 25 °C. The layers were separated, the aqueous layer was extracted with toluene (80 mL) and the

combined organics were washed with 5% $NaHCO_3$ (100 mL) and H_2O (100 mL). The organic layer was vacuum concentrated to 100 mL, diluted with toluene (200 mL) and re-concentrated to 150 mL. Hexanes (150 mL) was added to the slurry and the mixture was stirred at 25 °C for 1 h. The product was filtered, washed with 1:1 toluene:hexanes (50 mL), and then dried *in vacuo* at 25 °C, to give 32.45 g (84% yield, HPLC: 99% pure) of 2-bromoenone **3** as pale yellow solid: mp 120 °C. IR (KBr): 1703, 1595, 1571 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 11.1 Hz, 2 H), 7.32 (d, J = 11.1 Hz, 2 H), 3.07(m, 2 H), 2.68 (m, 2 H), 2.54 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4, 166.1, 143.4, 130.0, 128.1, 125.3, 120.6, 32.3, 30.3, 14.9. Anal. Calcd. for $C_{12}H_{11}BrOS$: C, 50.90; H, 3.92. Found: C, 51.13; H, 3.88.

3,5-Diflurophenyl boronic acid lithium salt (10) To a solution of 1-bromo-3,5-difluorobenzene (40g, 207 mmol) in $(EtO)_2CH_2$ (400 mL) at -78 °C was added *n*-BuLi (1.6 *M* in hexane, 130 mL, 207 mmol) dropwise, keeping the temperature below -70 °C. The mixture was aged at -78 °C for 30 min to give a white slurry. Triisopropyl borate (41 g, 218 mmol) was added dropwise and the mixture was warmed to 0 °C and quenched with 200 mL of water. The aqueous layer was separated and used directly in the next step (HPLC assay: 70% yield). 20 mL of the aqueous solution was treated with 4 mL 3 *N* HCl to precipitate the boronic acid as white solid: mp 250 °C (dec.). IR (KBr): 1571 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.42 (m, 2H), 7.20 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8 (dd, J_{CF} = 252, 10 Hz), 143.6, 115.9 (dd, J_{CF} = 20, 10 Hz), 105.3 (t, J_{CF} = 25 Hz).

2-(3',5'-Difluorophenyl)-3-(4'-methylthiophenyl)cyclopent-2-en-1-one (11) A mixture of aqueous boronic acid solution (1.5 Kg assayed, 9.48 mol) from the above step, Na_2CO_3 (1.67 Kg, 15.7 mol), bromide **3** (2.25 Kg, 7.9 mol) in toluene (30 L) was degassed three times with N_2/vacuum. Catalyst $PdCl_2(PPh_3)_2$ (55.3 g, 78 mmol) was added to the mixture. The whole mixture was degassed twice and heated under reflux for 5-6 h to complete the reaction. The reaction mixture was cooled to room temperature and n-Bu_3P (200 mL) was added. The organic layer was separated and treated with Darco KB (120 g) at room temperature for 10h. The mixture was filtered and wet cake was washed with toluene (5 L). The filtrate and wash were combined, concentrated, and crystallized from toluene-heptane (1:2, 12 L). The resultant slurry was filtered and the wet cake was washed with toluene-heptane (1:4, 5L), heptane (3L) and dried to give 2.35 Kg (93% yield) of the product as pale tan solid: mp 128-129 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (m, 2H), 7.17 (m, 2H), 6.78 (m, 3H), 3.05 (m, 2H), 2.71 (m, 2H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.2, 168.8, 163.0 (dd, J_{CF} = 252, 10 Hz), 142.6, 137.2, 135.9 (t, J_{CF} = 10 Hz), 132.1, 128.4, 125.6, 112.5 (d, J_{CF} = 20 Hz), 103.4 (t, J_{CF} = 25 Hz), 34.7, 29.4, 14.9. Anal. Calcd. For $C_{18}H_{14}OSF_2$: C, 68.34; H, 4.46. Found: C, 68.37; H, 4.43.

2-(3',5'-Difluorophenyl)-3-(4'-(methylsulfonyl)phenyl)cyclopent-2-en-1-one (1) A mixture of sulfide **11** (2.14 Kg, 6.76 mol) in acetone (34 L), Oxone (49.5% $KHSO_5$, 6.24 Kg, 20.3 mol) and water (3.4 L) was heated at 40

°C with stirring for 4-5 h. The reaction mixture was filtered to remove inorganics. The solid was washed with acetone (2x10 L). The combined filtrate and wash were concentrated to about 20 L to give a slurry. Water (40 L) was slowly added to the slurry over 2 h, and the mixture was stirred at room temperature for another 2-3 h. The slurry was filtered and the wet solid was washed with water (25 L) and dried by vacuum under nitrogen to give 2.23 Kg (94.7% yield) of product **1** as white solid: mp 154-155 °C. IR (KBr): 1690, 1590, 1310, 1280, 1130 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (m, 2H), 7.50 (m, 2H), 6.79 (m, 1H), 6.72 (m, 2H), 3.09 (m, 2 H), 3.08 (s, 3 H), 2.77 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6, 166.9, 162.9 (dd, J_{CF} =252, 20 Hz), 141.5, 140.4, 139.6, 134.3 (t, J = 10 Hz), 128.7, 127.6, 112.2 (dd, J_{CF} =20, 10 Hz), 103.8 (t, J_{CF} = 25 Hz), 44.1, 34.6, 29.7. *m/z* 348, 333, 270, 239, 227, 127, 115, 63, 15. Anal. Calcd. For $C_{18}H_{14}O_3SF_2$: C, 62.06; H, 4.05. Found: C, 62.03; H, 3.97.

(1-Aza-2-(4'-methylthiophenyl)prop-1-enyl)((4'-methylphenyl)sulfonyl)amine (13) To a solution of 4-methylthioacetophenone (**12**) (135 g, 0.812 mol) and pyridinium *p*-toluenesulfonate (20 g, 0.081 mol) in 1.3 L of *o*-dichlorobenzene and 1.0 L of MeCN at room temperature was added $TsNHNH_2$ (136.6 g, 0.773 mol). The reaction mixture was heated to 70 °C for 3 h. MeCN was completely removed in vacuum. 400 mL of 2-propanol was added and the slurry was aged at room temperature for 1 h. The white solid was collected by filtration and washed with 2-propanol (4x100 mL). The product was dried in a vacuum oven under N_2 atmosphere overnight to give 237 g (92% yield) of tosyl hydrazone **13** as white solid: mp 159 °C. IR (KBr): 3238, 1600, 1400, 1342 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (br s, 1 H), 7.92 (d, J = 7.7 Hz, 2 H), 7.57 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 7.62 Hz, 2 H), 7.18 (d, J = 8.0 Hz, 2 H), 2.48 (s, 3 H), 2.41 (s, 3 H), 2.16 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 144.1, 141.0, 135.3, 133.6, 129.5, 128.1, 126.6, 125.6, 21.5, 15.2, 13.4. Anal. Calcd. for $C_{16}H_{18}N_2O_2S_2$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.47. H, 5.46. N, 8.72.

1-(3',5'-Difluorophenyl)-2-(4'-methylthiophenyl)prop-2-en-1-ol (15) To a mixture of tosyl hydrazone **13** (120 g, 0.36 mol) in dry toluene (1080 mL) at -10 °C was added *N,N,N',N'*-tetramethylethylenediamine (120 mL). *i*-PrMgCl (375 mL) was added at such a rate to keep the reaction temperature at -10 °C. The reaction solution was aged at -10 °C for 30 min, warmed to 0 °C and aged at 0 °C for 30 min and at 30 to 35 °C for 2 h. When the temperature reached to approx. 20 °C, N_2 started to evolve and the color of the solution gradually turned brown. The reaction solution was cooled to -10 °C followed by the dropwise addition (40 min.) of a solution of 46.4 g (0.33 mol) of 3,5-difluorobenzaldehyde in toluene (50 mL). The reaction mixture was aged at -10 °C for 30 min. followed by the addition of aqueous 5*N* HCl (390 mL) at -10 to 0 °C. The mixture was aged at room temperature for 15 min. and the organic layer was separated, sequentially washed with water (200 mL), saturated aqueous $NaHCO_3$ (2x200 mL) and water (200 mL). The resulting solution of product **15** in toluene (HPLC assay: 90% yield) was concentrated to ca. 800 mL and directly used for next step. Chromatography of a

small sample on a silica gel column (EtOAc/hexane = 1:4) provided alcohol **15** as an oil: IR (film): 3400, 1629, 1596 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 2 H), 7.16 (m, 2 H), 6.95 (m, 2 H), 6.68 (m, 1 H), 5.65 (s, 1 H), 5.55 (s, 1 H), 5.42 (s, 1 H), 2.47 (s, 3 H), 2.05 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (dd, J_{CF} = 250, 10 Hz), 148.9, 145.9 (t, J_{CF} = 10 Hz), 138.6, 134.9, 127.4, 126.3, 114.8, 109.6 (dd, J_{CF} = 20, 10 Hz), 103.0 (t, J_{CF} = 25 Hz), 75.3, 15.5.

5-(3',5'-Difluorophenyl)-4-(4'-methylthiophenyl)pent-4-enoic acid(16) A solution of the alcohol **15** (86 g, 0.29 mol), pivalic acid (3.0 g, 0.029 mol) and triethyl orthoacetate (95.4 g, 0.588 mol) in toluene (800 mL) was heated at 100-104 °C for 18 h. The reaction results in the generation of EtOH, which was removed as it was formed by distillation. The crude rearranged ester (HPLC assay: *Z*:*E* = 92:8, 90% yield) was then concentrated and dissolved in THF (800 mL) followed by addition of a solution of NaOH (35.3 g, 0.88 mol) in 300 mL of water. The reaction solution was warmed to 60 °C for 3 h and was cooled to room temperature. Aqueous 5*N* HCl (200 mL) was added dropwise to the reaction mixture. The organic layer was separated, washed with water (2x200 mL), and concentrated. The crude product was dissolved in *i*-PrOAc (60 mL) at 50 °C. Hexane (540 mL) was added over 1 h. The slurry was cooled to 20 °C and stirred at the same temperature for 30 min. The off-white solid was collected by filtration and was washed with *i*-PrOAc-hexane (5:95, 100 mL). The wet cake was dried *in vacuo* under a N_2 atmosphere at room temperature overnight to afford 75.5 g (69% overall yield from **13**) of the acid **16** (*Z*:*E* ratio in the isolated solid **16** is 98.7:1.3).

Chromatography of a small sample of the rearranged esters on a silica gel column (EtOAc/hexane = 1:9) provided the *cis* and *trans* ethyl esters as an oil. For ethyl ester of **16** (*cis*): IR (film): 1732, 1617, 1585 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.4 Hz, 2 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.53 (m, 1 H), 6.44 (m, 2 H), 6.39 (s, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 2.80 (dt, *J* = 1.0, 7.4 Hz, 2 H), 2.50 (s, 3 H), 2.39 (t, *J* = 7.4 Hz, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 162.6 (dd, J_{CF} = 240, 10 Hz), 143.5, 140.3 (t, J_{CF} = 10 Hz), 138.3, 135.7, 128.8, 126.7, 125.3, 111.6 (dd, J_{CF} = 20, 10 Hz), 101.8 (t, J_{CF} = 25 Hz), 60.4, 35.6, 32.8, 15.6, 14.2. For ethyl ester of **16** (*trans*): ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 6.85 (m, 2 H), 6.72 (m, 1 H), 6.62 (s, 1 H), 4.08 (q, *J* = 7.1 Hz, 2 H), 3.02 (t, *J* = 7.8 Hz, 2 H), 2.50 (s, 3 H), 2.37 (t, *J* = 7.8 Hz, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

Recrystalization of a small sample of the above isolated acid **16** from *i*-PrOAc/hexane (5:95) provided pure *cis* acid **16** (*cis*): mp 104 °C. IR (KBr): 3035, 1709, 1625, 1589, 1439 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, br, 1 H), 7.21 (d, *J* = 8.2Hz, 2 H), 7.05 (d, *J* = 8.2 Hz, 2 H), 6.52 (m, 1 H), 6.45 (m, 2 H), 6.41 (s, 1 H), 2.82 (t, *J* = 7.3 Hz, 2 H), 2.50 (s, 3 H), 2.45 (t, *J* = 7.3 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 162.6 (dd, J_{CF} = 250, 10 Hz), 143.0, 140.2 (t, J_{CF} = 10 Hz), 138.4, 135.4, 128.8, 126.8, 125.5, 111.7 (dd, J_{CF} = 20, 10 Hz), 101.9 (t, J_{CF} = 20 Hz), 35.2, 32.4, 15.6. Anal. calcd. for $C_{18}H_{16}F_2O_2S$: C, 64.66; H, 4.82. Found: C, 64.67;

H, 4.70.

2-(3',5'-Difluorophenyl)-3-(4'-methylthiophenyl)cyclopent-2-en-1-one (11) To a solution of the acid **16** (19.9 g, 59.51 mmol), DMF (218 mg, 3 mmol) and CH_2Cl_2 (250 mL) at 0 °C was added oxalyl chloride (8.3 g, 65.46 mmol) dropwise over 30 min. The reaction solution was allowed to warm to room temperature and aged for 1 h. The mixture was concentrated under reduced pressure to half of the original volume at 25 °C. The resultant acid chloride solution in CH_2Cl_2 was added to a slurry of $AlCl_3$ (9.1 g, 68.44 mmol) in CH_2Cl_2 (150 mL) at -5 to 0 °C over 30 min. The resulting homogenous reaction solution was aged for 30 min at -5 to 0 °C. The reaction solution was transferred slowly into 100 mL of aqueous 1*N* HCl *via* cannula. During the quench, the solution temperature was maintained below 10 °C by controlling the rate of addition and by external cooling. The mixture was stirred vigorously at room temperature for 1 h. The organic layer was separated and washed with water (2x50 mL). Upon concentration, the product was crystallized from a mixture of toluene (30 mL) and heptane (70 mL). The product was collected by filtration, washed with toluene-heptane (1:4, 100 mL) and dried in a vacuum oven under N_2 atmosphere at room temperature to afford 17.1 g (90% yield) of cyclopentenone **11** as an off-white solid.

Dimethyl 2-(2'-(4'-(methylsulfonyl)phenyl)-2'-oxoethyl)propane-1,3-dioate (20) *A* solution of bromosulfone **5** (14 g, 50.5 mmol) in acetone (110 mL) was added to the mixture of dimethylmalonate (53 g, 401 mmol) and K_2CO_3 (14 g, 101 mmol) at 40-45 °C over 5 h. The mixture was stirred for an additional 1 h at the same temperature and cooled to room temperature followed by the addition of ethyl acetate (100 mL) and water (100 mL). The organic layer was separated and washed sequentially with aqueous 10% monobasic sodium phosphate solution (75 mL) and half-saturated brine (50 mL). The organic solution was concentrated under reduced pressure and *i*-PrOAc (50 mL) was added to the residue to give a slurry. The slurry was stirred at room temperature for 1 h, cooled to -10 °C and aged for another 1 h with stirring. The slurry was filtered and the wet cake was washed with *i*-PrOAc (40 mL) and dried to give the product **20** (13.38 g, 80% yield) as a white crystalline solid: mp 121-122 °C. IR (KBr): 1740, 1720, 1680, 1200, 1150 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 4.08 (t, J = 7.0 Hz, 1 H), 3.77 (s, 6H), 3.64 (d, J = 7.0 Hz, 2 H), 3.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 169.1, 144.6, 139.9, 129.1, 127.9, 53.0, 46.7, 44.3, 38.2. Anal. Calcd. For $C_{14}H_{16}O_7S$: C, 51.21; H, 4.91. Found: C, 51.26; H, 4.74.

Dimethyl-2-(2'-(3',5'-difluorophenyl)acetyl)-2-(2'-(4'-(methylsulfonyl)phenyl)-2'-oxoethyl)propane-1,3-dioate (21) To a solution of 3,5-difluorophenylacetic acid (4.72 g, 27.4 mmol) in CH_2Cl_2 (25 mL) and DMF (75 μL) was added oxalyl chloride (3.77 g, 29.7 mmol) over 20 min at room temperature. The mixture was aged at room temperature for 1 h and the acid chloride **6** was formed. The solution was concentrated to an oil, re-dissolved in THF (10mL) and used directly in the next step.

Magnesium bromide etherate (5.90 g, 22.8 mmol) was added to a solution of compound **20** (7.5 g, 22.8 mmol) in THF (60 mL) and MeCN (60 mL). The reaction mixture was stirred at room temperature for 10-15 min until all solid was dissolved. The solution was then cooled to 0 °C and pyridine (3.8 mL, 47.0 mmol) was added over 2-3 min. The reaction mixture was aged at same temperature for 2-3 h and cooled to -25 to -30 °C. The acid chloride **6** in THF solution was then added *via* cannula over 10 min, while the reaction temperature was kept below -25 °C. The mixture was aged at -25 °C for 1 h and quenched by adding aqueous 1 *N* HCl (32 mL) followed by *t*-butylmethyl ether (40 mL) at -25 to -30 °C. The reaction mixture was allowed to warm to room temperature. The organic layer was separated, washed with water (25 mL) and half-saturated brine (25 mL) and was directly used in the next step. Concentration of a small sample afforded product **21** as an oil: IR (KBr): 1730, 1690, 1600, 1210, 1150 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.3 Hz, 2 H), 8.05 (d, J = 8.3 Hz, 2 H), 6.77 (m, 2H), 6.71 (m, 1H), 4.21 (s, 2H), 3.90 (s, 2H), 3.86 (s, 6H), 3.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 195.0, 166.9, 162.7 (dd, J_{CF} = 252, 10 Hz), 144.5, 139.8, 137.2 (d, J_{CF} = 10 Hz), 129.0, 127.8, 112.7 (dd, J_{CF} = 20, 10 Hz), 102.5 (t, J_{CF} = 30), 68.5, 53.7, 46.5, 44.1, 42.0.

Methyl-3-(3',5'-difluorophenyl)-1-(methoxycarbonyl)-4-(4'-methylsulfonyl)phenyl)-2-oxocyclopent-3-enecarboxylate (22) Triethylamine (0.46 g, 4.56 mmol) was added to the solution (150 mL) of the acylation product **21** (11.0 g, 22.8 mmol) at room temperature. The mixture was stirred at room temperature for 2-3 h and was cooled to 10 °C. The reaction was quenched by the addition of aqueous 0.2 *N* HCl (30 mL) and half saturated brine (50 mL). The organic layer was separated and concentrated, the product was crystallized in 2:1 *i*-PrOAc and heptane to give 8.47 g (80% yield over two steps) of the diester **22** as a white solid: mp 172-173 °C. IR (KBr): 1730, 1590, 1150, 1120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (m, 2H), 7.54 (m, 2H), 6.82 (m, 1H), 6.75 (m, 2H), 3.87 (s, 6H), 3.72 (s, 2H), 3.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 166.6, 165.1, 163.1 (dd, J_{CF} = 252, 10 Hz), 142.4, 139.0, 136.7, 133.2 (t, J_{CF} = 10 Hz), 129.1, 128.0, 112.6 (dd, J_{CF} = 20, 10 Hz), 104.6 (t, J_{CF} = 25 Hz), 65.4, 53.9, 44.3, 39.3. Anal. Calcd. For $C_{22}H_{18}O_7SF_2$: C, 56.89; H, 3.91. Found: C, 56.83; H, 3.94.

2-(3',5'-difluorophenyl)-3-(4'-(methylsulfonyl)phenyl)cyclopent-2-en-1-one (1) A mixture of diester **22** (15 g, 32.3 mmol) in acetic acid (135 mL) and aqueous 3*M* sulfuric acid (15 mL) was heated at 90 °C for 10 h. The mixture was cooled to room temperature followed by addition of water (150 mL) slowly over 2 h to give a slurry. The slurry was filtered and the wet cake was washed with water. The cake was dried to afford compound **1** as a white solid (10.7 g, 95%).

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