

# Synthesis of fluorovinylsalicylic acids and their derivatives <sup>☆</sup>

Robert Filler <sup>\*</sup>, Shan Lin, Zhaoxu Zhang

*Department of Chemical and Biological Sciences, Illinois Institute of Technology, Chicago, IL 60616, USA*

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## Abstract

Palladium-catalyzed cross-coupling of iodosalicylic acid derivatives with polyfluorovinyl zinc reagents provided the corresponding fluorovinyl-substituted salicylates. Methyl-5-( $\beta,\beta$ -difluorovinyl) methyl salicylate was prepared by a Wittig reaction of the 5-formyl compound with the strongly nucleophilic ylide,  $[(Et_2N)_3P-CF_2]$ . In one sequence, a fluorine-free benzofuran was obtained, instead of a difluorovinylsalicylate.

*Keywords:* Fluorovinylsalicylic acids; Wittig reaction; Benzofuran

## 1. Introduction

Salicylic acid and its derivatives display a broad range of pharmacological activities. Acetylsalicylic acid and methyl salicylate are used as analgesics, while salicylic acid and some of its derivatives are active against a wide range of pathogenic bacteria, fungi and yeasts [1]. More recently, several isomeric vinylsalicylic acids and their polymers have been shown to exhibit considerable activity as bactericides [2–4]. The monomers can also be co-polymerized with acrylic or methacrylic acid to give various compositions with bioactivity, in some cases, equal to or superior to those of the homopolymers.

Although the incorporation of fluorine in bioactive molecules has been well developed [5], biologically active fluoropolymers have not yet been well studied. In this paper we describe the syntheses of new fluorovinyl salicylic acid derivatives, in preparation for subsequent studies on their polymerization and potential biological activity.

## 2. Results and discussion

In some of the chemistry to be described, we have employed reactions with difluoromethylene phosphoranes and palladium-catalyzed coupling reactions involving polyfluoroalkenyl zinc reagents. We acknowledge the important

contributions in these areas by D.J. Burton and co-workers, which have been of assistance in our studies.

### 2.1. Methyl-2-acetoxy-5- $\alpha,\beta$ -trifluorovinylsalicylate (1)

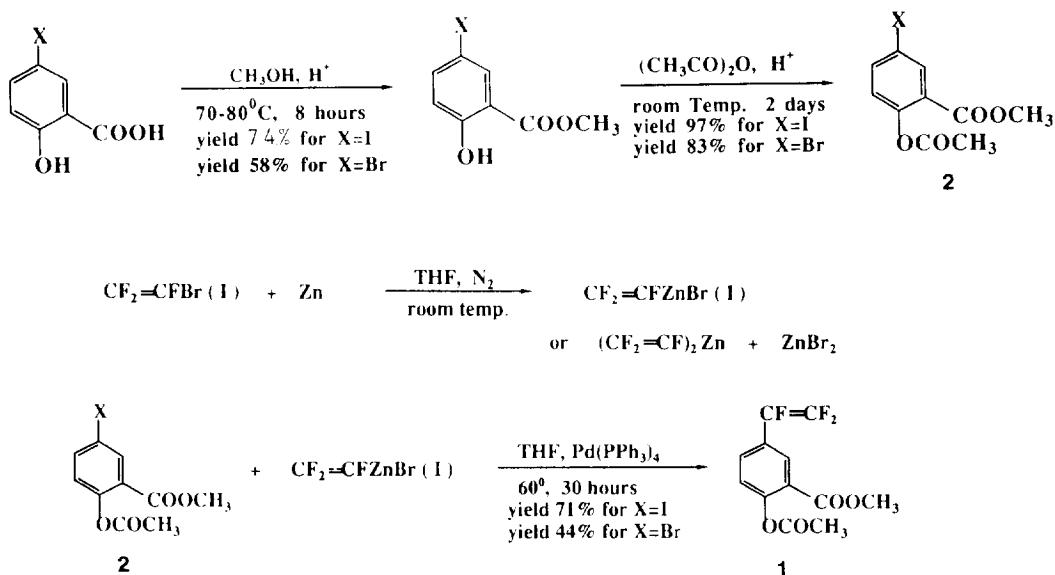
Compound **1** was readily prepared by the sequence shown in Scheme 1. The facile preparation of the 5-halo diester **2** was followed by palladium-catalyzed cross-coupling with the trifluorovinyl zinc reagent, derived from either bromo- or iodotrifluoroethylene. We chose to prepare **2** in order to obviate reaction of the zinc reagent with the active hydrogens of salicylic acid. Moreover, by incorporating the electron-withdrawing carbomethoxy and acetoxy groups, we expected that the coupling reaction would be strongly enhanced, as observed previously [6]. We also anticipated that these protective groups could be easily removed at a later stage.

### 2.2. Methyl-5- $\beta,\beta$ -difluorovinylmethylsalicylate (3)

5-Formylsalicylic acid was converted to its methyl ester. The phenolic hydroxyl was not converted to the acetate because the formyl group could also be attacked by acetic anhydride. Instead, the –OH group was protected as its methyl ether to give **4**. A Wittig reaction of **4** with the ylide,  $[Ph_3P-CF_2]$ , generated from triphenylphosphine and dibromodifluoromethane [7], was unsuccessful in contrast to the behavior of  $[Ph_3P-C\dot{C}H_2]$ , which is very reactive toward aldehydes and ketones. However, electron-releasing groups on phosphorus markedly increase reactivity. Thus, tris(diethylamino) phosphine forms the much more nucleo-

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<sup>\*</sup> Corresponding author.



Scheme 1.

philic ylide ( $[\text{Et}_2\text{N}]_3\text{P}^+\text{CF}_2^-$ ), which afforded **3** in 53% yield (Scheme 2).

We also attempted to synthesize the isomeric 3- $\beta$ , $\beta$ -difluorovinyl compound **5** from 3-methyl salicylic acid via ylide-carbene chemistry [8]. The carboxyl and phenolic groups were protected as in **4**, and the methyl group was brominated with NBS to form **6**. Conversion of **6** to the phosphonium salt and then to the ylide **7** proceeded normally. Several attempts to convert **7** to **5**, using chlorodifluoromethane in triglyme [8], were unsuccessful (Scheme 3).

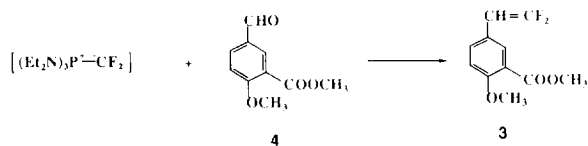
We then prepared compound **8**, the 2-acetoxy analog of the phosphonium salt of **6**, and attempted another ylide-carbene reaction with  $\text{CHClF}_2$ . Instead of the desired difluorovinyl compound, a fluorine-free product, characterized as the benzofuran carboxylic ester **9**, was isolated in 20% yield

(Scheme 4). The formation of **9** is readily explained by the intramolecular reaction of the ylide with the carbonyl of the ortho acetoxy group, another example of the favorable 5-exo-trig ring closure [9]. This type of reaction to form heterocyclic compounds has been described previously [10].

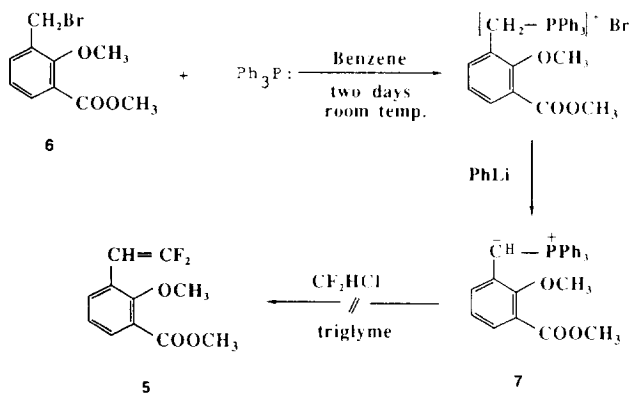
### 2.3. 5-Polyfluoroisopropenyl salicylic acid derivatives

The preparation of compound **10** (Scheme 5) was readily accomplished by palladium-catalyzed cross-coupling of **2** (X=I) with the pentafluoroisopropenyl zinc reagent **11**, which was prepared by the procedure of Burton et al. [11].

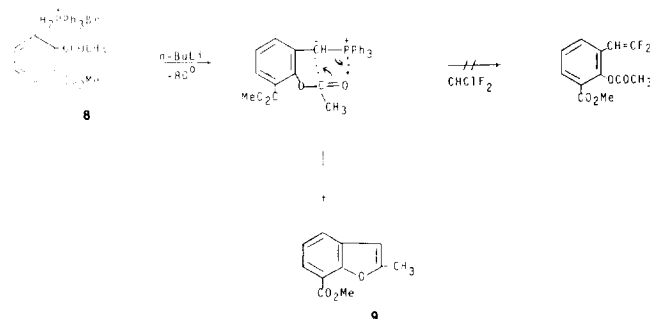
The coupling of **2** and the trifluoroisopropenyl zinc reagent **12** gave a mixture of two compounds, the diester **13** (25%)



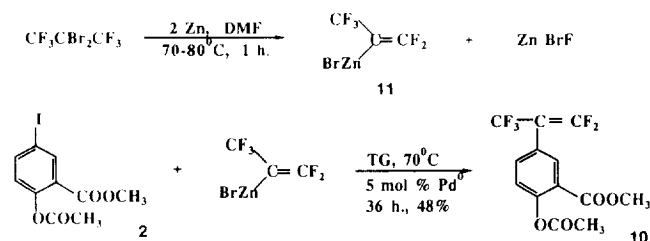
Scheme 2.



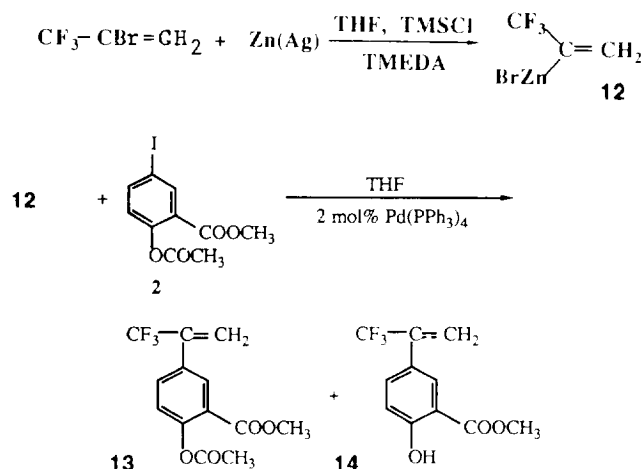
Scheme 3.



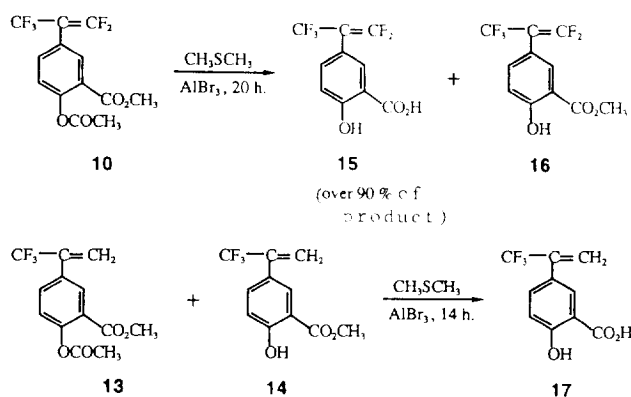
Scheme 4.



Scheme 5.



Scheme 6



Scheme 7.

and the partially hydrolyzed monoester **14** (27%) (Scheme 6).

In contrast to the facile preparation of alkenylzinc reagent **11**, reagent **12** could not be obtained from  $\text{CF}_3\text{CBr=CH}_2$  (BTFP) and activated (acid-washed) zinc powder in ether, THF or dimethoxyethane solvent. However, a zinc–silver couple was prepared and treated with trimethylchlorosilane (TMSCl) to make the couple spongy. TMEDA was added to a mixture of BTFP and  $\text{Zn(Ag)}$  in THF to form an activated complex of **12** [12], which was thermally stable at 70 °C. The complex was then used for coupling with **2**.

#### 2.4. Hydrolysis of 5-polyfluoroisopropenyl salicylic acid derivatives

In considering the hydrolytic cleavage of the fluorovinyl salicylic acid diesters, we sought to avoid reactions involving alkaline media because of the susceptibility of the fluorovinyl groups to nucleophilic attack. The observation (Scheme 6) of the partial and preferential hydrolysis of the acetoxy group in **13** to form the phenolic ester **14** is probably attributable to the generation of HCl by reaction of TMSCl with small amounts of moisture.

We have conducted exploratory studies on the hydrolysis of several of these esters using  $\text{AlBr}_3\text{-Me}_2\text{S}$  [13]. Both the

acetoxy and carbomethoxy groups in **10**, **13** and **14** are readily hydrolyzed to give good yields of the corresponding salicylic acids (Scheme 7).

### 3. Experimental details

All infrared spectra were run on a Nicolet 5MX FT-IR spectrophotometer.  $^1\text{H}$  NMR spectra were taken on either a 60 MHz Varian T-60 spectrometer, a 300 MHz NT-300 spectrometer or a 300 MHz VRX-300 spectrometer.  $^{13}\text{C}$  NMR spectra were taken on a 300 MHz VRX-300 spectrometer. All chemical shifts are reported in parts per million downfield of the internal standard, TMS.

Elemental analyses were performed at Midwest Microlab, Indianapolis, IN. All melting and boiling points are uncorrected.

#### 3.1. Methyl-5-bromo- (or iodo)salicylate

To a one-necked flask fitted with a magnetic stirring bar and fixed with a reflux condenser, topped by a  $\text{CaCl}_2$  drying tube, was added 20 g (0.092 mol) of 5-bromosalicylic acid or 24.3 g (0.092 mol) of 5-iodosalicylic acid dissolved in 37.3 ml (0.9 mol) of methanol and 5 ml of concentrated  $\text{H}_2\text{SO}_4$ . The mixture was heated at 70–80 °C for 8 h, then allowed to cool to room temperature. The reaction mixture was poured slowly into 500 ml of ice water with stirring, and the white crystals which precipitated were collected by filtration and washed with sufficient 5% aqueous sodium bicarbonate until the acid was neutralized. After washing with water several times, the crystals were collected and dried in an oven at about 50 °C. Recrystallization of the product from  $\text{CH}_3\text{OH-H}_2\text{O}$  (90:10) gave white crystals: m.p. 57–60 °C (literature: 61 °C [14a]) in 58% yield. (Methyl 5-iodosalicylate: m.p. 73–75 °C (literature: 78 °C [14b]), in 74% yield.) Unreacted 5-bromo(iodo)salicylic acid was recovered by acidification of the  $\text{NaHCO}_3$  solution. For the iodo compound:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  10.695 (s, 1H, OH), 8.107–8.114 (d, 2.1 Hz, 1H, 6-position aromatic proton), 7.654–7.691 (t, 11.1 Hz, 1H, 3-position aromatic proton), 6.738–6.767 (d, 8.7 Hz, 1H, 4-position aromatic proton), 3.936 (s, 3H,  $\text{OCH}_3$ ). FT-IR ( $\text{CDCl}_3$ ): 3100 (m, O–H stretch), 1675 (s, C=O stretch)  $\text{cm}^{-1}$ .  $m/z$  Calc. for  $\text{C}_{10}\text{H}_9\text{IO}_4$ , 320; found, 320, 289 ( $-\text{OCH}_3$ ).

#### 3.2. Methyl-5-bromo- (or iodo)acetylsalicylate (**2**)

In a one-necked flask charged with methyl 5-bromosalicylate, 10 g (0.043 mol) (methyl-5-iodosalicylate, 11.95 g, 0.043 mol) was added 9.3 ml (0.098 mol) of acetic anhydride and three drops of concentrated  $\text{H}_2\text{SO}_4$ . The flask was tightly stoppered and stirred magnetically at room temperature for three days. The solution was washed with 130 ml of 3%  $\text{NaHCO}_3$ , 40 ml of  $\text{CHCl}_3$  were added to dissolve the organic material, and another 40 ml of chloroform were added to

extract the water layer again. The organic phases were combined, washed with water several times, then dried over anhydrous magnesium sulfate. After the chloroform had been distilled off, a colorless oil distilled at (125 °C, 0.7 Torr) (m.p. 33–35 °C [14a]) to give 9.7 g (83%) of product. (Methyl 5-iodoacetylsalicylate, m.p. 41–44 °C, 97% yield.) For the iodo compound:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.286–8.293 (d, 2.1 Hz, 1H, 6-position aromatic proton), 7.799–7.838 (m, 8.9 Hz, 1H, 3-position aromatic proton), 6.816–6.844 (d, 8.4 Hz, 1H, 4-position aromatic proton), 3.842 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 2.310 (s, 3H,  $\text{OCOCH}_3$ , FT-IR ( $\text{CDCl}_3$ ): 1740 (s, acetyl  $\text{C}=\text{O}$  stretch), 1700 (s, methyl ester  $\text{C}=\text{O}$  stretch)  $\text{cm}^{-1}$ .

### 3.3. Trifluoroiodovinyl zinc reagent

A three-necked flask fitted with a water condenser and a magnetic stirring bar was charged with 8.43 g (0.129 mol) of Zn powder and 50 ml of THF and the system flushed with nitrogen. Then, 10.6 g (0.051 mol) of iodotrifluoroethylene was added dropwise. An ice bath was used to carefully maintain the reaction near room temperature because of the vigorous exothermic reaction. After all of the  $\text{CF}_2=\text{CFI}$  had been added and the temperature remained constant, the ice bath was removed and the mixture was stirred for an additional 4 h. After filtering under nitrogen, the zinc reagent solution was transferred to another dry three-necked flask, to be used immediately in the next step.

### 3.4. Methyl-5-( $\alpha,\beta,\beta$ )-Trifluorovinylacetylsalicylate (1) (nc)

To the zinc reagent solution under nitrogen flush was added methyl-5-bromoacetylsalicylate, 9 g (0.033 mol), followed by 0.6 g (0.00052 mol) of  $\text{Pd}(\text{PPh}_3)_4$ , and a small amount of 2,6-di-*tert*-butyl-4-methylphenol (to minimize polymerization of the product). After the reaction had been maintained at 50–55 °C for about 40 h, the reaction mixture was allowed to cool to room temperature, the product was extracted with 30 ml of diethyl ether and washed three times with water, and the organic layer dried overnight over  $\text{MgSO}_4$ . The ether was removed with a rotary evaporator. The concentrated yellow solution was kept in the refrigerator to give methyl 5-trifluorovinylacetylsalicylate as yellow crystals. White crystals, m.p. 48–50 °C, were obtained by recrystallization from petroleum ether. The crude yield was about 4 g (44%). IR ( $\text{CCl}_4$ ): 1725 and 1770  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$  stretch).  $^1\text{H NMR}$  ( $\text{CCl}_4$ ):  $\delta$  2.21 (s, 3H,  $\text{OCOCH}_3$ ), 3.80 (s, 3H,  $\text{COOCH}_3$ ), 6.95–8.00 (3H, aromatic protons). *Anal.* Found: C, 52.47; H, 3.28.  $\text{C}_{12}\text{H}_9\text{O}_4\text{F}_3$ . Calc.: C, 52.57; H, 3.30.

### 3.5. Methyl-5-formylsalicylate

5-Formylsalicylic acid, 7 g (0.042 mol), was added to 23 ml (0.56 mol) of methanol in a one-necked flask fitted with a magnetic stirring bar and reflux condenser topped with a  $\text{CaCl}_2$  drying tube.  $\text{H}_2\text{SO}_4$  (1.9 ml) was added to the solution

and the reaction mixture was heated under reflux for 20 h. At first, the 5-formylsalicylic acid did not dissolve in methanol, but after 20 h, the reaction mixture was all in solution. Diethylether (20 ml) was added to the solution. When the solution had cooled to room temperature, it was poured into cold water, the organic phase was washed with 5%  $\text{NaHCO}_3$  solution, then washed with water and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The ether was removed by rotary evaporation to yield 6 g (80%) of crude crystals, m.p. 78 °C (literature: 82–83 °C [14a]). IR ( $\text{CCl}_4$ ) 1680  $\text{cm}^{-1}$  and 1705  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$  stretch), 3100  $\text{cm}^{-1}$  (OH stretch);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  4.05, (s, 3H,  $\text{COOCH}_3$ ), 6.97–8.30 (3 H, aromatic protons), 9.77 (s, 1H,  $\text{CHO}$ ), 11.12 (s, 1H,  $\text{COOH}$ ).

### 3.6. Methyl-5-formylmethylsalicylate (4)

In a three-necked round bottom flask, fitted with a magnetic stirring bar and a reflux condenser topped with a  $\text{CaCl}_2$  drying tube, was placed 8 g (0.044 mol) of methyl 5-formylsalicylate in 68 ml of acetone, 6.2 g (0.045 mol) of anhydrous potassium carbonate, and then 9.4 g (0.066 mol) of iodomethane was added. The solution was heated at reflux (about 54 °C) for 6 h and then filtered. Acetone was removed on a rotary evaporator and the residue was dissolved in 30 ml of chloroform. The solution was washed with a cooled 5% solution of  $\text{K}_2\text{CO}_3$ , followed by water, then dried over  $\text{Na}_2\text{SO}_4$ . Crude crystals formed on removal of chloroform. Recrystallization from 95% ethanol gave 4.3 g (50%), m.p. 81–83 °C (literature: 81–82 °C [14a]). IR ( $\text{CHCl}_3$ ): 1680 and 1720  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$  stretch).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  3.85 (s, 3H,  $\text{OCH}_3$ ), 3.94 (s, 3H,  $\text{COOCH}_3$ ), 6.88–8.22 (3H, aromatic protons), 9.84 (s, 1H,  $\text{CHO}$ ).

### 3.7. Methyl-5-( $\beta,\beta$ )-difluorovinylmethylsalicylate (3) (nc)

Tris(diethylamino)phosphine, 7 g (0.028 mol) in 14 ml of dry triglyme was added under nitrogen to 2.94 g (0.014 mol) of dibromodifluoromethane in 21 ml of triglyme at 0 °C. A copious precipitate formed and the solution immediately changed to a brown color. After the reaction was maintained at 0 °C over a 20 min interval, 2.4 g (0.0124 mol) of methyl 5-formylmethylsalicylate was added, and the reaction was kept at room temperature for 6 h, after which the amount of precipitate decreased. The solution was filtered and the filtrate poured into 50 ml of water. Some crystals separated from the water and were collected. After extraction with diethyl ether and removal of the ether, the remaining oil was stored in the refrigerator to yield crude crystals, 1.5 g (53%). On recrystallization from petroleum ether, 1.2 g (42%) of white crystals, m.p. 47–48 °C, were isolated. IR ( $\text{CCl}_4$ ): 1723  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$  stretch).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  3.93 (s, 3H,  $\text{COOCH}_3$ ), 5.00–5.49 (q, 1H, vinyl proton), 6.86–7.75 (3H, aromatic protons). *Anal.* Found: C, 57.69; H, 4.41.  $\text{C}_{11}\text{H}_{10}\text{O}_3\text{F}_2$ . Calc.: C, 57.89; H, 4.42.

### 3.8. Methyl-3-methylsalicylate

The same procedure was employed as described for methyl 5-bromosalicylate. After reaction was complete, the solution was poured into 500 ml of ice water to form two layers. The organic layer was dissolved in 20 ml of chloroform, then another 20 ml of chloroform was used to wash the aqueous phase. The organic layers were combined, washed with 5% NaHCO<sub>3</sub> solution, then with water, and dried over anhydrous MgSO<sub>4</sub>. The product was obtained by distillation: b.p. 60–62 °C, 0.12 Torr, (literature: b.p. 110 °C, 110 Torr, m.p. 28–30 °C [14b]); yield, 73%. IR (neat): 1660 (C=O stretch), 3170 cm<sup>-1</sup> (OH stretch). <sup>1</sup>H NMR (DCCl<sub>3</sub>): δ 2.22 (s, 3H, CH<sub>3</sub>), 3.85 (s, 3H, COOCH<sub>3</sub>), 6.51–7.66 (3H, aromatic protons), 11.04 (s, 1H, COOH).

### 3.9. Methyl-3-methylacetylsalicylate (nc)

The same procedure was used as with 5-bromoacetylsalicylate. The product (76%) was obtained by distillation (96 °C, 0.05 Torr). IR (CCl<sub>4</sub>): 1710 and 1752 cm<sup>-1</sup> (C=O stretch). <sup>1</sup>H NMR: δ 2.04 (s, 3H, CH<sub>3</sub>), 2.14 (s, 3H, OCOCH<sub>3</sub>), 3.63 (s, 3H, COOCH<sub>3</sub>), 6.79–7.70 (3H, aromatic protons). *m/z* Calc. for C<sub>11</sub>H<sub>12</sub>O<sub>4</sub>, 208; found, 208, 177 (–OCH<sub>3</sub>).

### 3.10. Methyl-3-bromomethylacetylsalicylate (nc)

Methyl 3-methylacetylsalicylate, 10 g (0.048 mol) and benzoyl peroxide, 0.0097 g (0.04 mmol) were dissolved in 34 ml of carbon tetrachloride and heated to reflux under a flow of nitrogen. A mixture of 9.39 g (0.0528 mol) of *N*-bromosuccinimide and 0.07 g (0.29 mmol) of benzoyl peroxide was added in portions over 20 min. The reaction mixture was heated for an additional 5 h under UV light. After reaction was complete, the solution was filtered immediately before it cooled to room temperature. The crude product was obtained by keeping the solution in the refrigerator. A pure sample was prepared by recrystallization from CCl<sub>4</sub> (m.p. 94–97 °C); yield, 6 g (43%). IR (CCl<sub>4</sub>): 1720 and 1760 cm<sup>-1</sup> (C=O stretch). <sup>1</sup>H NMR (DCCl<sub>3</sub>): δ 2.28 (s, 3H, OCOCH<sub>3</sub>), 3.82 (s, 3H, COOCH<sub>3</sub>), 4.41 (s, 2H, CH<sub>2</sub>Br), 6.82–8.05 (3H, aromatic protons). *m/z* Calc. for C<sub>11</sub>H<sub>11</sub>BrO<sub>4</sub>, 287; found, 287, 244 (–COCH<sub>3</sub>), 207 (–Br).

### 3.11. Methyl-2-methyl-7-benzofurancarboxylate (9) (nc)

Triphenylphosphine, 3.4 g (0.013 mol), was dissolved in 12 ml of dry benzene and 3 g (0.01 mol) of methyl-3-bromomethylacetylsalicylate was added. The flask was tightly stoppered and maintained at room temperature for about two days. The white powdery phosphonium salt (**8**) was collected by filtration. The phosphonium salt was kept over P<sub>2</sub>O<sub>5</sub> for 8 h at 0.01 Torr at room temperature until immediately before use. *n*-BuLi, 5.7 ml (0.0091 mol) (1.6 M solution in hexane) was added dropwise to 5 g (0.0091 mol) of phosphonium

salt in 20 ml of THF solution under N<sub>2</sub> flush at 0 °C. After 2 h of further reaction at room temperature, the precipitate was removed by filtration. The THF was then removed by rotary evaporation to give a crude oily product, which was purified by column chromatography on silica gel (elution with benzene): b.p. 196 °C. *Anal.* Found: C, 69.37; H, 5.29. C<sub>11</sub>H<sub>10</sub>O<sub>3</sub>. Calc.: C, 69.46; H, 5.30. IR (CCl<sub>4</sub>): 1700 cm<sup>-1</sup> (C=O stretch). <sup>1</sup>H NMR: δ 2.42 (s, 3H, CH<sub>3</sub>), 3.90 (s, 3H, COOCH<sub>3</sub>), 6.26 (q, 1H, vinyl proton), 6.92–7.83 (3H, aromatic protons).

### 3.12. 2,2-Dibromo-1,1,1,3,3,3-hexafluoropropane [15]

This isomerization reaction was carried out at 150 °C in a Parr Hastelloy-C pressure reactor equipped with a 2000 lbf in<sup>-2</sup> Inconel rupture disc. The reaction was complete in three days when a pressure reactor head with a mechanical stirring apparatus was utilized. The reaction required nine days to achieve 100% conversion in a sealed pressure reactor without stirring. We used an unstirred vessel, as the corrosive nature of the reaction mixture (AlCl<sub>3</sub>, Br<sub>2</sub>) and the high temperature destroyed the seals and bearings of the stirrer. 1,2-Dibromo-1,1,2,3,3,3-hexafluoropropane (600 g, 1.94 mol) and aluminum chloride (71.9 g, 0.54 mol) were placed in a sealed 2-l Hastelloy-C pressure reactor equipped with a blow-out seal<sup>1</sup> (2000 lbf in<sup>-2</sup>) and heated to 150 °C for nine days. After cooling to room temperature, the dark reaction mixture was washed with water (3 × 400 ml) and 5% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (3 × 300 ml), and the chunky, dark organic residue was steam-distilled. The organic layer of this distillate was separated, melted on a hot plate, and the upper aqueous layer removed by pipet. The 232 g (39%) of colorless solid/liquid CF<sub>3</sub>CBr<sub>2</sub>CF<sub>3</sub> which remained after cooling was used for preparation of the zinc reagent. FT-IR (neat): 1240 (m), 1220 (m) cm<sup>-1</sup>.

### 3.13. Pentafluoroisopropenylzinc reagent (II)

A four-necked 250 ml round-bottom flask was equipped with a pressure-dropping funnel controlled by positive nitrogen pressure, an immersion thermometer, a Teflon-coated magnetic stirring bar, a gas inlet tube attached to a nitrogen source, and dry ice/isopropyl alcohol condenser attached to a CaCl<sub>2</sub> drying tube. The apparatus was purged with nitrogen and charged with freshly activated zinc powder (15 g, 229 mmol) and 60 ml of DMF. A solution of CF<sub>3</sub>CBr<sub>2</sub>CH<sub>3</sub> (29 g, 90 mmol) in 40 ml of DMF was transferred to the dropping funnel and added dropwise to the well-stirred reaction mixture over a period of 40 min to 1 h at a rate that maintained the internal temperature at 70–80 °C. The induction period was approximately 1 min if pure reagents were employed, and reaction was apparent when the solution became warm and turned light green, then black. Excess zinc was removed

<sup>1</sup> The blow-out seal should be examined after each reaction, as the corrosive reaction mixture will pit and eventually compromise the seal.

by filtration through a medium-frit Schlenk funnel under positive nitrogen pressure, and the filtrate was stored for further use.

### 3.14. Methyl-5- $\beta$ , $\beta$ -difluoro- $\alpha$ -(trifluoromethyl)vinylacetyl-salicylate (**10**) (nc)

A three-necked 500 ml round-bottom flask was equipped with a Teflon-coated magnetic stirring bar, a gas inlet tube attached to a nitrogen source, and a simple distillation apparatus. The system was purged with nitrogen, when charged with 100 ml of triglyme and the above-mentioned filtrate which contained the zinc reagent **11** in DMF. The DMF solvent was quickly removed at 30–31 °C, 0.1 Torr using an oil bath. The simple distillation apparatus was replaced by a condenser topped with a CaCl<sub>2</sub> drying tube. The flask was then charged with methyl-5-iodoacetylsalicylate (10.24 g, 32 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (1.85 g, 5 mol.%). The dark reaction mixture was stirred and heated in an oil bath to about 70 °C for 36 h. The progress of the reaction was monitored by TLC using a 100:1 mixture of petroleum ether (60–90 °C) and ethyl acetate as the eluent. After cooling, the reaction mixture was poured into *n*-hexane (600 ml). The residue was filtered and the yellow filtrate concentrated under vacuum, and the residue thus obtained was purified by flash column chromatography on silica gel (50 g, 70–250 mesh), using a 2:1 mixture of petroleum ether (60–90 °C) and methylene chloride as the eluent. The fractions were collected and the solvents evaporated to give 5.0 g (48%) of **10** as a light yellow solid, m.p. 34–36 °C, which became an orange oil at room temperature after standing for a week. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.009 (s, 1H, 6-position aromatic proton), 7.511 (m, 1H, 3-position aromatic proton), 7.164–7.187 (d, 6.9 Hz, 1H, 4-position aromatic proton), 3.874 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 2.352 (s, 3H, OCOCH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  169.601 (s), 164.400 (s), 160.900 (d, 14 Hz), 156.928 (t, 68 Hz), 152.948 (d, 50 Hz), 151.936 (s), 135.478 (m, 117 Hz), 133.955 (s), 125.050 (s), 124.496 (q, 69 Hz), 120.925 (d, 23 Hz), 52.284 (s), 21.406 (s). IR (neat): 1775 (s, acetyl C=O stretch), 1740 (s, methyl ester C=O stretch) cm<sup>-1</sup>. Anal. Found: C, 48.72; H, 2.91. C<sub>13</sub>H<sub>9</sub>O<sub>4</sub>F<sub>5</sub>. Calc.: C, 48.15; H, 2.78.

### 3.15. Trifluoroisopropenylzinc reagent (**12**)

A zinc–silver couple was prepared by stirring under reflux a solution of silver acetate (20 mg) in glacial acetic acid (20 ml). Zinc powder (20 g) was added all at once and the mixture stirred for 30 min and then quickly cooled. The zinc–silver couple so formed, was isolated by simple decantation, washed several times with anhydrous diethyl ether (6 × 20 ml) (it is necessary to remove all traces of acetic acid), dried under vacuum and stored at room temperature. Similar results were obtained with material freshly prepared or after storage for several months.

A three-necked 100 ml round-bottom flask was equipped with a pressure-dropping funnel controlled by positive nitro-

gen pressure, a Teflon-coated magnetic stirring bar, a gas inlet tube attached to a nitrogen source, and a condenser topped with a CaCl<sub>2</sub> drying tube. The flask was purged with nitrogen, then charged with the zinc–silver couple (2.5 g, 38 mmol) and 20 ml of THF. Trimethylchlorosilane (0.5 ml) was added while stirring the mixture. The Zn(Ag) couple turned spongy. After 10 min, tetramethylenediamine (6 ml, 25 mmol) was added and then 2-bromo-3,3,3-trifluoropropene (4.4 g, 25 mmol) was added dropwise at room temperature. After addition, the mixture was heated at 60 °C in an oil bath for 9 h. After cooling to room temperature, the resulting yellow solution of **12** with excess Zn(Ag) couple was filtered under positive nitrogen pressure and stored.

### 3.16. Methyl-5- $\alpha$ -(trifluoromethyl)vinylacetylsalicylate (**13**) (nc) and methyl-5- $\alpha$ -(trifluoromethyl)-vinylsalicylate (**14**) (nc)

A three-necked 100 ml round-bottom flask was equipped with a Teflon-coated magnetic stirring bar, a gas inlet tube attached to a nitrogen source, and a condenser topped with a CaCl<sub>2</sub> drying tube. The flask was purged with nitrogen, then charged with the above-mentioned solution **12** in THF, methyl-5-iodoacetylsalicylate (3.2 g, 10 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.23 g, 2 mol.%). The mixture was heated at reflux (67 °C) for 36 h. After cooling to room temperature, the deep red mixture was poured into 100 ml of *n*-hexane and the resulting solid was filtered. The fractions were isolated by column chromatography on silica gel (Aldrich, chromatographic grade) (30 g, 70–250 mesh). Compound **14**, 0.66 g (27%), was eluted first with 100:1 mixture of petroleum ether (60–90 °C) and ethyl acetate; 0.72 g (25%) of **13** was then eluted with 2:1 mixture of petroleum ether (60–90 °C) and methylene chloride.

**13**: light yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.229–8.237 (d, 2.4 Hz, 1H, 6-position aromatic proton), 7.742–7.749 (m, 2.1 Hz, 1H, 3-position aromatic proton), 7.244–7.273 (d, 8.7 Hz, 1H, 4-position aromatic proton), 6.142–6.146 (d, 1.2 Hz, 1H, vinyl proton), 5.945–5.950 (d, 1.5 Hz, 1H, vinyl proton), 4.007 (s, 3H, -OCH<sub>3</sub>), 2.482 (s, 3H, -COCH<sub>3</sub>). FT-IR (neat): 1760 cm<sup>-1</sup> (s, acetyl C=O stretch), 1720 cm<sup>-1</sup> (s, methyl ester C=O stretch). Anal. Found: C, 53.72; H, 3.88. C<sub>13</sub>H<sub>11</sub>O<sub>4</sub>F<sub>3</sub>. Calc.: C, 54.17; H, 3.82.

**14**: light yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  10.870–10.872 (d, 2.4 Hz, 1H), 7.926–7.934 (d, 2.4 Hz, 1H, 6-position aromatic proton), 7.518–7.555 (t, 11 Hz, 1H, 3-position aromatic proton), 6.973–7.004 (t, 9.3 Hz, 1H, 4-position aromatic proton), 5.904–5.912 (d, 2.4 Hz, 1H, vinyl proton), 5.713–5.718 (d, 1.5 Hz, 1H, vinyl proton), 3.962 (s, 3H, -OCH<sub>3</sub>). FT-IR (neat) 3180 cm<sup>-1</sup> (m, O–H stretch), 1660 cm<sup>-1</sup> (s, methyl ester C=O stretch). Anal. Found: C, 53.46; H, 3.76. C<sub>13</sub>H<sub>9</sub>O<sub>3</sub>F<sub>3</sub>. Calc.: C, 53.66; H, 3.66.

### 3.17. Hydrolysis of methyl-5- $\beta$ , $\beta$ -difluoro- $\alpha$ -(trifluoromethyl)vinylacetylsalicylate (**10**)

A three-necked 25 ml round-bottom flask was fitted with a magnetic stirring bar, a gas inlet tube attached to a nitrogen

source, and a condenser attached to a CaCl<sub>2</sub> drying tube. The flask was purged with nitrogen, then charged with AlBr<sub>3</sub> (1.33 g, 5 mmol) and 10 ml of CH<sub>3</sub>SCH<sub>3</sub>. Compound **10** (0.628 g, 2 mmol) was added and the mixture was stirred at room temperature for 12 h. The mixture was extracted with CH<sub>3</sub>SCH<sub>3</sub> (2 × 10 ml). The combined organic phases were washed with water (2 × 10 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The fractions were isolated by column chromatography on silica gel (Aldrich, chromatographic grade) (30 g, 60–200 mesh). Compound **15** was first eluted with a 2:1 mixture of petroleum ether and methylene chloride to give 0.48 g (90%) of **15**. Compound **16** was then eluted with a 5:1 mixture of methylene chloride and methanol.

**15**: yellow solid, m.p. 226–229 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.599 (s, 1H, -OH), 7.950 (s, 1H, 6-position aromatic proton), 7.525 (m, 1H, 3-position aromatic proton), 7.150 (m, 1H, 4-position aromatic proton). IR (KBr): 3420 cm<sup>-1</sup> (broad, COO-H and O-H stretch), 1725 cm<sup>-1</sup> (s, C=O stretch).

**16**: yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 11.005 (s, 1H, -OH), 7.960 (s, 1H, 6-position aromatic proton), 7.450 (m, 1H, 3-position aromatic proton), 7.100 (m, 1H, 4-position aromatic proton), 4.050 (s, 3H, -OCH<sub>3</sub>). IR (KBr): 3150 cm<sup>-1</sup> (s, O-H stretch), 1745 cm<sup>-1</sup> (s, C=O stretch).

### 3.18. Hydrolysis of 2:1 mixture of **13** and **14**

Using the procedure described above, a yellow oil was obtained, which was not fully characterized. The <sup>1</sup>H NMR

spectrum was devoid of absorption at δ 2.5 and δ 4.0, associated with the ester methyl groups.

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