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Fluorinated butanolides and butenolides Part 9. Synthesis of 2-(trifluoromethyl)butan-4-olides by Wittig reaction using methyl 3,3,3-trifluoropyruvate☆,☆☆

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Abstract

2-(Trifluoromethyl)butan-4-olides **13** and **14** were prepared by a three-step synthesis starting from a Wittig reagent and methyl 3,3,3-trifluoropyruvate (**1**) as a building block. The Wittig reaction of (2-oxoalkyl)triphenylphosphonium bromides with pyruvate **1** gave intermediate 4-oxobutenoates **8** and **9**, which were stepwise selectively reduced with zinc borohydride firstly at the double bond and subsequently at the oxo group to afford unstable 4-hydroxy-2-trifluoromethylalkanoates **11** and **12**, which cyclised spontaneously to the end butenolides **13** and **14**.

Keywords: Methyl 3,3,3-trifluoropyruvate; Wittig reaction; 4-Oxo-2-(trifluoromethyl)alk-2-enoates; Zinc borohydride; Selective borohydride reduction; 2-(Trifluoromethyl)butan-4-olides; 2,3-Dibromo-2-trifluoromethyl-butanoate; Photo-α,β-didehalogenation

1. Introduction

Contemporary interest in the chemistry of trifluoromethylated butanolides and butenolides together with synthetic approaches and areas of potential applications have been summarised in our preceding paper [1]. Among them, the synthesis of 4-methyl-2-trifluoromethylbutan-4-olide as a dopant for ferroelectric liquid crystals [2] and 4-phenyl-2-trifluoromethylbutan-4-olide for ring-opening polymerisation studies [3] have been reported. In the meantime, a novel synthetic approach using palladium-catalysed cyclocarbonylation has been published [4].

Applications of the Wittig reaction and its modifications have been so far applied in the synthesis of fluorinated but-2-en-4-olides [5–7], but not in a synthesis of fluorinated butanolides. In this paper, we present the application of the Wittig reaction with methyl 3,3,3-trifluoropyruvate in the synthesis of 4-substituted 2-(trifluoromethyl)butan-4-olides.

2. Results and discussion

2.1. Wittig reaction

The key synthetic step has been the reaction of a suitable Wittig reagent with methyl 3,3,3-trifluoropyruvate (**1**, Scheme 1). We have found only one reference on this reaction in the literature [8], viz. the reaction of (ethoxycarbonylmethylene)triphenylphosphorane that afforded predominantly (60% relative intensity) the more strained maleate structure. To get knowledge on the stereoselectivity of the Wittig reactions with **1**, we carried out the reaction with two phosphonium salts (**2** and **3**) prepared from alkyl bromides with different chain length (Scheme 1, Table 1). The Wittig reagents were prepared according to the literature [9–12]. As shown in Table 1, the stereoselectivity was low for both alkyls (products **6** and **7**) favouring the more strained (*E*)-isomers **6a** and **7a**. The isomer excess for **7a** with propyl at the double bond product was lower relatively to (*E*)-but-2-enoate **6a** with a less bulky methyl at the double bond.

In contrast, much more positive results from the point of view of the synthesis of the target compounds **13** and **14** were obtained in the Wittig reaction of oxophosphonium salts **4** and **5**, which were prepared from chloroacetone or α-bromoacetophenone (phenacyl bromide) (Scheme 1, Table 1) according to the literature [13,14]: the (*E*)-isomers

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☆☆ Part 8, [1].

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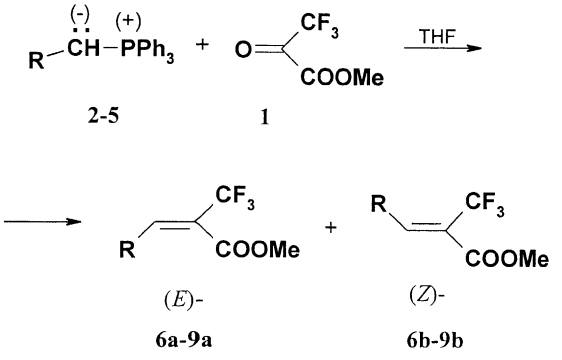


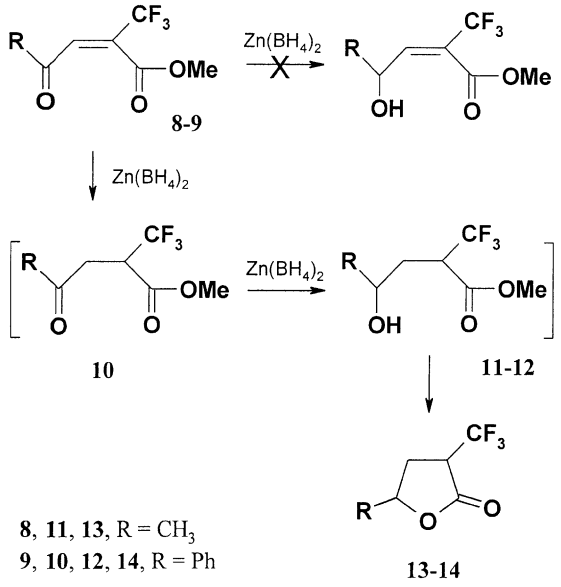
Scheme 1. Reaction of methyl 3,3,3-trifluoropyruvate (**1**) with Wittig reagents **2**–**5**.

8a and **9a** with a convenient *cis*-configuration of the ester and γ-keto groups prevailed in the resulting **8** and **9**.

Elucidation of the (*E*)- and (*Z*)-configurations was done on the basis of NMR spectra according to the data reported for trifluoromethylated α,β-unsaturated esters [1,15,16]. In ^{1}H NMR, the coupling of =CH and CF_3 groups in (*E*)-isomers **6a**–**9a** was observed as a quadruplet. This coupling was not observed for any (*Z*)-isomer **6b**–**9b**. In ^{19}F NMR, the coupling between =CH and CF_3 groups has a coupling constant of ca. 1.5 Hz, which was observed in the spectra of (*E*)-isomers **8a** and **9a**. In addition, (*E*)-isomers **6a**–**9a** display characteristic chemical shifts of ca. −65 ppm, while the signals of (*Z*)-isomers **6b**–**9b** appear at ca. −60 ppm.

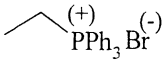
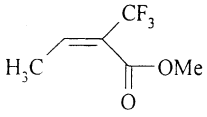
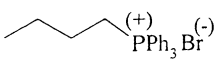
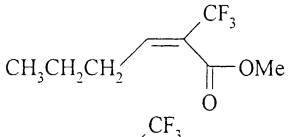
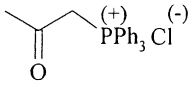
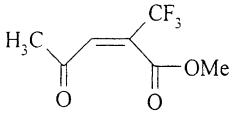
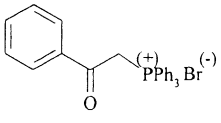
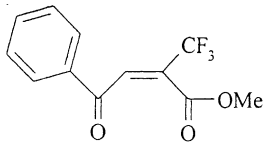
2.2. Selective hydride reduction

For the selective reduction of the oxo group in 2-hydroxy-4-oxo-2-trifluoromethylalkanoates, we successfully applied sodium borohydride in the preceding paper [1]. However, when this method was applied to oxoalkenoates **8** and **9** a complex mixture of compounds was obtained. Therefore, we employed the milder zinc borohydride [17] in diethyl ether. The reduction of oxoalkenoates **8** and **9** proceeded in two distinct steps: in the first step the double bond was reduced in **9** when the reaction was carried out at 0 °C (Scheme 2, Table 2). The reduction could easily be followed by ^{19}F NMR as the signals of the trifluoromethyl groups in 2-trifluoromethylbutenoate **9** and 2-trifluoromethylbutanoate **10** display rather different chemical shifts: the signals of the CF_3 groups in alkanoates appear in the range from −70 to −80 ppm [1], while signals in 2-trifluoromethylalk-2-enoates are shifted downfield to ca. −60 ppm.



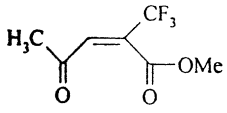
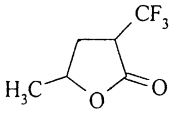
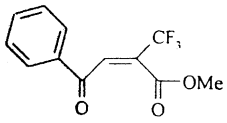
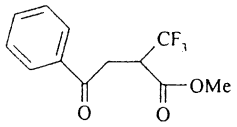
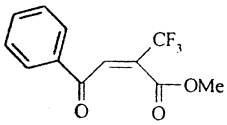
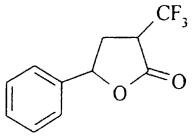
Scheme 2. Selective hydride reduction of 4-oxo-2-alkenoates **8**–**9**; spontaneous cyclisation to butanolides **13**–**14**.

Table 1
Results of reactions of Wittig reagents with methyl 3,3,3-trifluoropyruvate: yields and configuration of isomers

Phosphonium reagent		(*E*)-products		(*E*):(*Z*) (%)	Yield (%)
2		**6a**[a]		55:45	68.8
3		**7a**		43:57	69.7
4		**8a**		92:8	71.9
5		**9a**		84:16	78.4

[a] The **6a**–**9a** products with (*E*)-configuration; **6b**–**9b** isomeric products with (*Z*)-configuration.

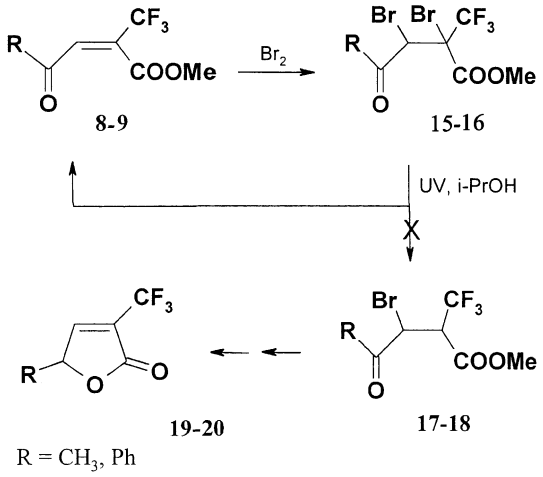
Table 2
Results of zinc borohydride reductions of α,β-unsaturated γ-ketoesters

Starting compound		Conditions	Product		Diastereoisomers (% relative intensity)	Yield (%)
8		Et_2O rt	**13**		60:40	90
9		Et_2O 0 °C	**10**			51
9		Et_2O rt	**14**		53:47	85

The reduction of **8** at room temperature afforded directly lactone **13**, as the intermediate γ-hydroxyalkanoate **11** cyclised spontaneously in the reaction mixture (Scheme 2). On the other hand, the reduction of **9** gave γ-hydroxyalkanoate **12**, which was stable in the reaction mixture (checked by ^{19}F NMR), but completely cyclised during purification on a silica gel column to 4-phenyl-4-trifluoromethylbutan-4-olide (**14**, Scheme 2). The lactones **13** and **14**, which are mixtures of diastereoisomers (Table 2), were not separated in this work to the individual configurational stereoisomers because the methodologies for the separation have recently been reported [2,3].

2.3. Attempts to prepare substituted 3-bromo-2-trifluoromethylbutan-4-olides

3-Bromo-4-oxo-2-trifluoromethylalkanoates **17** and **18** could be potential intermediates in the synthesis of butenolides **19** and **20** (Scheme 3). In a retrosynthetic view, bromoalkanoates **17** and **18** are accessible by a selective photoreduction of dibromoalkanoates **15** and **16** [18–20], which are in turn easily prepared by the reaction of alkenoates **8** and **9** with bromine according to [21,22] (Scheme 3). Photoreductions of dibromoalkanoates **15** and **16** were performed in a photoreactor with 2-propanol as hydrogen donor and acetone as a photosensitiser and the reaction was followed by TLC to check the complete conversion of the starting dibromoalkanes. However, instead of the expected bromoalkanoates **17** and **18**, a photo-α,β-didehalogenation occurred to afford surprisingly the starting alkenoates **8** and **9**.



Scheme 3. Attempt to prepare β-bromobutanolide.

3. Experimental

3.1. General experimental procedures

Temperature data were not corrected. Distillations of high boiling compounds were carried out on a Vacuubrand RC5 high vacuum oil pump. Column chromatography (d = 2.5 cm): CC1, column 20 cm; CC2, column 30 cm; CC3, column 50 cm. GC analyses were performed on a Micromat HRGC 412 (GCa, Nordion Analytical; FID, 25 m glass capillary column, SE-30) and Chrom 5 (GCb, Laboratorní prístroje, Prague; FID, 380 × 0.3 cm packed column, SE-301 on Chromaton N-AW-DMCS (Lachema, Brno), nitrogen) instruments. NMR spectra were recorded on a Bruker 400 AM (FT, ^{19}F at 376.6 MHz, ^{31}P at 202.46 MHz), Varian Gemini 300 HC (FT, ^{1}H at 300.07 MHz, ^{13}C at 75.46 MHz) instruments: TMS, $CFCl_3$ and H_3PO_4 as the internal standards, chemical shifts in ppm (s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet), coupling constants J in Hz, solvent $CDCl_3$. MS spectra were scanned on a Hewlett-Packard MSD 5971A instrument (1989, EI 70 eV).

Chemicals used were as follows: methyl 3,3,3-trifluoropyruvate (**1**) was prepared from hexafluoropropene-1,2-oxide

according to our procedure [23,24]; silica gel (60–100 μm, Merck), ethyl bromide (distilled, bp 37–40 °C), butyl bromide (distilled, bp100–104 °C), α-bromoacetophenone (Aldrich), (2-oxopropyl)triphenylphosphonium chloride (**4**) (Aldrich), triphenylphoshine (Aldrich), butyllithium in hexane (Aldrich), zinc borohydride (prepared from sodium borohydride and zinc chloride, [15]), diethyl ether (distilled over Na), hexane (distilled over $CaCl_2$, bp 69 °C), methylene chloride (distilled, bp 42 °C), tetrahydrofuran (dried by sodium benzophenone ketyl and distilled prior to use), acetone (Lachema, Brno), toluene (distilled, bp 111 °C), 2-propanol UV pure (Lachema, Brno), 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113, Spolek pro chemickou a hutní výrobu, Ústí nad Labem).

3.2. Phosphonium salts (compounds 2, 3 and 5)

3.2.1. General procedure

The reactions were carried out in a round bottomed flask equipped with a reflux condenser with drying tube ($CaCl_2$). The reaction mixture was refluxed on an oil bath while stirring (magnetic spinbar). The complete conversion of triphenylphosphine was checked by ^{31}P NMR, solvent and/or reactant were removed on a rotary evaporator and the residue was crystallised in a hexane:-diethyl ether (10:1) mixture to give pure phosphonium salts **2**, **3**, **5**.

3.2.2. Ethyl(triphenyl)phosphonium bromide (2)

A mixture of ethyl bromide (74.9 g, 687 mmol) and triphenylphosphine (15 g, 57.2 mmol) was refluxed for 48 h. Yield of **2**: 20.8 g (98%), mp 204–206 °C (literature [9]: mp 203–205 °C, literature [10]: mp 205–206 °C).

^1H NMR (300.07 MHz, $CDCl_3$): δ 1.37 (dt, 3H, CH_3, $^3J_{HH} = 7.2$ Hz, $^3J_{HP} = 20.3$ Hz); 3.83 (dq, 2H, CH_2, $^3J_{HH} = 7.2$ Hz, $^2J_{HP} = 12.6$ Hz); 7.62–7.89 (m, 15H, PPh_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 6.29 (d, CH_3, $^2J_{CP} = 5.1$ Hz); 16.55 (d, CH_2, $^1J_{CP} = 51$ Hz); 117.34 (d, Ph, $^1J_{CP} = 85.9$ Hz); 130.02 (d, Ph, $^2J_{CP} = 12.6$ Hz); 133.04 (d, Ph, $^3J_{CP} = 10.3$ Hz); 134.6 (s, Ph) ppm. ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 26.83 (s, PPh_3) ppm.

3.2.3. Butyl(triphenyl)phosphonium bromide (3)

A mixture of butyl bromide (10 g, 73 mmol), triphenylphosphine (19.2 g, 73 mmol) and toluene (100 ml) was refluxed for 48 h. Yield of **3**: 27.9 g (95.6%), mp 240–242 °C (literature [11]: mp 244–245 °C, literature [12]: mp 239–241 °C). ^1H NMR (300.07 MHz, $CDCl_3$): δ 0.91 (t, 3H, CH_3, $^3J_{HH} = 6.6$ Hz); 1.64 (m, 4H, $(CH_2)_2$); 3.88 (m, 2H, CH_2); 7.65–7.92 (m, 15H, PPh_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 13.4 (CH_3); 22.31 (d, CH_2, $^1J_{CP} = 49.8$ Hz); 23.37 (d, CH_2, $^2J_{CP} = 16$ Hz); 24.24 (d, CH_2, $^3J_{CP} = 4$ Hz); 117.89 (d, Ph, $^1J_{CP} = 85.9$ Hz); 130.22 (d, Ph, $^2J_{CP} = 12.6$ Hz); 133.27 (d, Ph, $^3J_{CP} = 10.9$ Hz); 134.75 (d, Ph, $^4J_{CP} = 2.9$ Hz) ppm. ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 24.98 (s, PPh_3) ppm.

3.2.4. (2-Oxo-2-phenylethyl)triphenylphosphonium bromide (5)

A mixture of α-bromacetophenone (10 g, 50.2 mmol), triphenylphosphine (13.2 g, 50.2 mmol) and toluene (100 ml) was refluxed for 48 h. Yield of **5**: 21.6 g (93.2%), mp 279–281 °C (literature [13]: mp 279–280 °C, literature [14]: mp 280–281 °C). ^1H NMR (300.07 MHz, $CDCl_3$): δ 6.41 (d, 2H, CH_2, $^2J_{HP} = 12.1$ Hz); 7.49 (t, 2H, Ph); 7.64 (m, 7H, Ph); 7.74 (m, 3H, Ph); 7.95 (m, 6H, Ph); 8.38 (d, 2H, Ph) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 38.76 (d, CH_2, $^1J_{CP} = 61.3$ Hz); 128.91 (Ph); 129.91 (Ph); 134.73 (Ph); 135.15 (d, Ph, $^3J_{CP} = 5.7$ Hz); 118.87 (d, Ph, $^1J_{CP} = 89.3$ Hz); 130.06 (d, Ph, $^2J_{CP} = 13.1$ Hz); 134 (d, Ph, $^3J_{CP} = 10.9$ Hz); 134.64 (d, Ph, $^4J_{CP} = 2.3$ Hz) ppm. ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 22.57 (s, PPh_3) ppm.

3.3. The Wittig reaction

3.3.1. General procedure

The reactions were carried out in a round bottomed flask (250 ml, magnetic spinbar) under a dry atmosphere. The dry flask was charged with phosphonium salt (**2**–**5**), THF (100 ml) was then added dropwise and the mixture was stirred for 30 min, then cooled to ca. −70 °C (dry ice–ethanol) and a solution of butyllithium was added dropwise. The mixture was allowed to warm to rt over 2 h and stirred for additional 1 h. The dark-red mixture was again cooled to ca. −70 °C and pyruvate **1** was added dropwise. The complete conversion of **1** was checked by ^{19}F NMR. The mixture was then warmed to rt, filtered through a short column (CC2, silica gel 30 g, CH_2Cl_2) to remove triphenylphosphine oxide and salts. Pure compounds **6**–**9** were obtained by distillation in vacuum on a short-pass micro-apparatus.

3.3.2. Methyl 2-(trifluoromethyl)but-2-enoate (6)

Phosphonium salt **2** (2.42 g, 6.51 mmol), THF (50 ml), butyllithium (2.7 ml, 6.51 mmol) and pyruvate **1** (1.02 g, 6.51 mmol) were reacted according to Section 3.3.1. The yield of **6**: 0.57 g (69%), bp 40–49 °C/2 mmHg, as a mixture of isomers *E* and *Z* (55:45).

The **6a**, (*E*)-isomer: ^1H NMR (300.07 MHz, $CDCl_3$): δ 1.95 (d, 3H, CH_3, $^3J_{HH} = 6.6$ Hz); 3.91 (s, 3H, $COOCH_3$); 7.46 (m, ^1H, CH) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −64.66 (s, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 14.18 (CH_3); 53.31 ($COOCH_3$); 121.28 (q, CF_3, $^1J_{CF} = 287.9$ Hz); 128.64 (s, CH); 164.88 ($COOCH_3$) ppm (the signal of C–CF_3 was not observed in the spectrum).

The **6b**, (*Z*)-isomer: ^1H NMR (300.07 MHz, $CDCl_3$): δ 2.17 (d, 3H, CH_3, $^3J_{HH} = 2.2$ Hz); 3.94 (s, 3H, $COOCH_3$); 7.64 (m, 1H, CH) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −59.31 (s, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): owing to low intensity, NMR signals were not observed. Anal. calcd. for $C_6H_7F_3O_2$: C, 42.9; H, 4.2. Found: C, 43.0; H, 4.0%.

*3.3.3. Methyl 2-(trifluoromethyl)hex-2-enoate (**7**)*

Phosphonium salt **3** (3.62 g, 9.05 mmol), THF (50 ml), butyllithium (3.7 ml, 9.05 mmol) and pyruvate **1** (1.41 g, 9.05 mmol) were reacted according to Section 3.3.1. The yield of **7**: 1.24 g (69.7%), bp 45–58 °C/2 mmHg, a mixture of isomers *E* and *Z* (43:57).

The **7a**, (*E*)-isomer: ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 0.97 (t, 3H, CH_3, $^3J_{HH} = 7.6$ Hz); 1.55 (m, 2H, CH_2); 2.58 (m, 2H, CH_2); 3.83 (s, 3H, $COOCH_3$); 6.84 (tq, 1H, CH, $^3J_{HH} = 7.7$ Hz, $^4J_{HF} = 1.1$ Hz) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −65.11 (s, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 13.57 (CH_3); 21.71 (CH_2); 30.51 (CH_2); 51.94 ($COOCH_3$); 122.50 (q, CF_3, $^1J_{CF} = 274.2$ Hz); 123.45 (q, C–CF_3, $^2J_{CF} = 34.3$ Hz); 150.93 (q, CH, $^3J_{CF} = 5.2$ Hz); 163.41 ($COOCH_3$) ppm.

The **7b**, (*Z*)-isomer: ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 0.97 (t, 3H, CH_3, $^3J_{HH} = 7.6$ Hz); 1.55 (m, 2H, CH_2); 2.46 (m, 2H, CH_2); 3.81 (s, 3H, $COOCH_3$); 7.22 (t, 1H, CH, $^3J_{HH} = 7.7$ Hz) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −59.81 (s, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 13.54 (CH_3); 21.85 (CH_2); 30.97 (CH_2); 52.34 ($COOCH_3$); 122.07 (q, CF_3, $^1J_{CF} = 272.6$ Hz); 123.48 (q, C–CF_3); 153.83 (q, CH, $^3J_{CF} = 2.3$ Hz); 162.8 ($COOCH_3$) ppm. Anal. calcd. for $C_8H_{11}F_3O_2$: C, 49.0; H, 5.7. Found: C, 48.9; H, 5.9%.

*3.3.4. Methyl 4-oxo-2-(trifluoromethyl)pent-2-enoate (**8**)*

Phosphonium salt **4** (5.13 g, 14.5 mmol), THF (50 ml), butyllithium (6 ml, 14.5 mmol) and pyruvate **1** (2.26 g, 14.5 mmol) were reacted according to the Section 3.3.1. The yield of **8**: 2.04 g (71.9%), bp 67–75 °C/2 mmHg, mixture of isomers *E* and *Z* (92:8).

The **8a**, (*E*)-isomer: ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 2.39 (s, CH_3); 3.85 (s, 3H, $COOCH_3$); 6.96 (q, 1H, CH, $^4J_{HF} = 1.1$ Hz) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −65.68 (d, CF_3, $^4J_{HF} = 1.3$ Hz) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 29.21 (CH_3); 52.67 ($COOCH_3$); 120.81 (q, CF_3, $^1J_{CF} = 273.7$ Hz); 127.22 (q, C–CF_3, $^2J_{CF} = 32.7$ Hz); 141.37 (q, CH, $^3J_{CF} = 4.6$ Hz); 161.34 ($COOCH_3$); 197.65 (C=O) ppm.

The **8b**, (*Z*)-isomer: ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 2.39 (s, CH_3); 3.88 (s, 3H, $COOCH_3$); 7.39 (s, 1H, CH) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −60.83 (s, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 146.05 (q, CH, $^3J_{CF} = 2.9$ Hz) ppm; owing to low intensity, the other NMR signals were not assigned. Anal. calcd. for $C_7H_7F_3O_3$: C, 42.9; H, 3.6. Found: C, 42.6; H, 3.7%.

*3.3.5. Methyl 4-oxo-4-phenyl-2-(trifluoromethyl)but-2-enoate (**9**)*

Phosphonium salt **5** (3.84 g, 8.33 mmol), THF (50 ml), butyllithium (3.5 ml, 8.33 mmol) and pyruvate **1** (1.3 g, 8.33 mmol) were reacted according to Section 3.3.1. The yield of **9**: 2.15 g (78.4%), bp 85–99 °C/2 mmHg, as a mixture of isomers *E* and *Z* (84:16).

The **9a**, (*E*)-isomer: ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 3.69 (s, 3H, $COOCH_3$); 7.46 (q, 1H, CH, $^4J_{HF} = 1.7$ Hz); 7.49–7.91 (m, 5H, Ph) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −65.59 (d, CF_3, $^4J_{HF} = 1.2$ Hz) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 52.82 ($COOCH_3$); 75.20 (q, C–CF_3, $^2J_{CF} = 29.8$ Hz); 120.97 (q, CF_3, $^1J_{CF} = 274.3$ Hz); 128.56, 129.01, 134.38, 134.96 (Ph); 141.23 (q, CH, $^3J_{CF} = 5.2$ Hz); 161.14 ($COOCH_3$); 190.56 (C=O) ppm.

The **9b**, (*Z*)-isomer: ^{1}H NMR (300.07 MHz, $CDCl_3$): δ 3.94 (s, 3H, $COOCH_3$); 7.81 (s, 1H, CH); 7.49–7.91 (m, 5H, Ph) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −60.92 (s, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 53.19 ($COOCH_3$); 123.19 (q, CF_3, $^1J_{CF} = 286.9$ Hz); 128.12, 128.79, 134.73, 135.02 (Ph); 145.05 (q, CH, $^3J_{CF} = 2.9$ Hz); 161.59 ($COOCH_3$); 191.02 (C=O) ppm (the signal of C–CF_3 was not observed in the spectrum). Anal. calcd. for $C_{12}H_9F_3O_3$: C, 55.8; H, 3.5. Found: C, 55.5; H, 3.7%.

*3.4. Selective one-step reduction of **9** with $Zn(BH_4)_2$; methyl 4-oxo-4-phenyl-2-(trifluoromethyl)butanoate (**10**)*

A round bottomed flask (50 ml, 2 magnetic spinbars) was charged at 0 °C with butenoate **9** (0.1 g, 0.39 mmol), $Zn(BH_4)_2$ (0.11 g, 1.16 mmol) and diethyl ether (10 ml), the mixture was stirred at 0 °C and after 30 min methanol (1 ml) was added. The reaction was followed by TLC (CH_2Cl_2) until the conversion of **9** was complete. The mixture was then chromatographed on a short column (CC1, silica gel 10 g, diethyl ether). The solvent was removed in vacuum, raw **10** was purified by CC2 (silica gel 30 g, CH_2Cl_2), and crystallised from hexane. The yield of **10**: 0.05 g (51%), mp 75–80 °C.

^{1}H NMR (300.07 MHz, $CDCl_3$): δ 3.29 (dt, 1H, CH_2, $^2J_{HH} = 17.3$ Hz, $^3J_{HH} = 2.4$ Hz); 3.75 (dt, 1H, CH_2, $^2J_{HH} = 17.3$ Hz, $^3J_{HH} = 10.9$ Hz); 3.75 (s, 3H, $COOCH_3$); 3.83 (dtq, 1H, CH, $^3J_{HH} = 2.4$ Hz, $^3J_{HH} = 10.8$ Hz, $^3J_{HH} = 8.2$ Hz); 7.41–7.92 (m, 5H, Ph) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ −68.17 (d, CF_3, $^3J_{HF} = 7.9$ Hz) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 35.16 (CH_2); 45.51 (q, CH, $^3J_{CF} = 28.1$ Hz); 53.11 ($COOCH_3$); 124.73 (q, CF_3, $^1J_{CF} = 280$ Hz); 128.13, 128.78, 133.86, 135.64 (Ph); 167.31 ($COOCH_3$); 192.62 (C=O) ppm. Anal. calcd. for $C_{12}H_{11}F_3O_3$: C, 55.4; H, 4.3. Found: C, 55.3; H, 4.6%.

*3.5. Selective two-step reduction of **8** and **10** with $Zn(BH_4)_2$; butanolides **13** and **14***

3.5.1. General procedure

A round bottomed flask (100 ml, 2 magnetic spinbars) was charged with butenoates **8** and **10**, $Zn(BH_4)_2$ and diethyl ether (50 ml). The reactions were carried out at rt and followed by ^{19}F NMR.

*3.5.2. 2-(Trifluoromethyl)pentan-4-olide (**13**)*

A mixture of pentenoate **8** (0.47 g, 2.42 mmol), $Zn(BH_4)_2$ (0.5 g, 5.28 mmol) and diethyl ether was reacted for 8 h. The reaction mixture, which did not contain any pentanoate **11** (checked by ^{19}F NMR), was then chromatographed on

a short column (CC1, silica gel 10 g, diethyl ether), the solvent was removed in vacuum and the raw butanolide **13** was purified by CC3 (silica gel 50 g, CH_2Cl_2). The yield of liquid **13**: 0.33 g (80%) diastereoisomer ratio 60:40.

^{1}H NMR (300.07 MHz, $CDCl_3$): diastereoisomer A: δ 1.48 (d, 3H, CH_3, $^3J_{HH} = 6$ Hz); 2.02 (dt, 1H, CH_2, $^2J_{HH} = 14.3$ Hz, $^3J_{HH} = 6$ Hz); 2.67 (m, 1H, CH_2); 3.50 (m, 1H, CH); 4.63 (qdt, 1H, CH, $^3J_{HH} = 6.2$ Hz, $^3J_{HH} = 10$ Hz, $^3J_{HH} = 6$ Hz); diastereoisomer B: δ 1.43 (d, 3H, CH_3, $^3J_{HF} = 6.6$ Hz); 2.18 (m, 1H, CH_2); 2.62 (m, 1H, CH_2); 3.44 (m, 1H, CH); 4.81 (qdt, 1H, CH, $^3J_{HH} = 6.6$ Hz, $^3J_{HH} = 6.3$ Hz, $^3J_{HH} = 7.3$ Hz) ppm.

^{19}F NMR (376.6 MHz, $CDCl_3$): diastereoisomer A: δ −69.23 (d, CF_3, $^3J_{HF} = 8.6$ Hz); diastereoisomer B: δ −69.02 (d, CF_3, $^3J_{HF} = 9.3$ Hz) ppm.

^{13}C NMR (75.46 MHz, $CDCl_3$): diastereoisomer A: δ 20.7 (CH_3); 31.32 (CH_2); 46.02 (q, CH–CF_3, $^2J_{CF} = 30.7$ Hz), 75.13 (CH); 123.8 (q, CF_3, $^1J_{CF} = 277.1$ Hz); 169.11 (C=O); diastereoisomer B: δ 20.71 (CH_3); 30.34 (CH_2); 45.94 (q, CH–CF_3, $^2J_{CF} = 30$ Hz), 75.29 (CH); 124.03 (q, CF_3, $^1J_{CF} = 279.03$ Hz; 169.20 (C=O) ppm. MS ($M_r = 168$), *m/z* (% relative intensity): EI: 169/1 ($M^+ + 1$), 168/1.5 (M^+), 167/3 ($M^+ - 1$), 153/30, 147/7, 133/38, 124/91, 105/71, 104/17, 96/63, 95/41, 77/88, 69/26, 55/100, 43/48.

3.5.3. 4-Phenyl-2-(trifluoromethyl)butan-4-olide (**14**)

A flask (100 ml) was charged with butenoate **9** (0.76 g, 2.96 mmol), $Zn(BH_4)_2$ (0.52 g, 5.48 mmol) and diethyl ether (50 ml) and the mixture reacted for 9 h. In the mixture, hydroxybutanoate **12** (diastereoisomer ratio 55:45) was observed (^{19}F NMR and GC–MS) that cyclised spontaneously to butanolide **14**.The mixture was treated as in Section 3.5.2 and pure **14** was obtained by crystallisation from hexane. The yield of **14**: 0.58 g (85.3%), mp 78–83 °C, diastereoisomer ratio 53:47 (literature [3]: mp 76–88 °C).

^{1}H NMR (300.07 MHz, $CDCl_3$): diastereoisomer A: δ 2.38 (dt, 1H, CH_2, $^2J_{HH} = 23.1$ Hz, $^3J_{HH} = 12.6$ Hz); 2.92 (m, 1H, CH_2); 3.65 (m, 1H, CH); 5.46 (dt, 1H, CH, $^3J_{HH} = 6$ Hz, $^3J_{HH} = 10.4$ Hz); 7.28–7.56 (m, 5H, Ph); diastereoisomer B: δ 2.55 (m, 1H, CH_2); 2.92 (dt, 1H, CH_2, $^2J_{HH} = 14.3$ Hz, $^3J_{HH} = 7.7$ Hz) 3.47 (m, 1H, CH), 5.67 (t, 1H, CH, $^3J_{HH} = 7.1$ Hz); 7.29–7.47 (m, 5H, Ph) ppm.

^{19}F NMR (376.6 MHz, $CDCl_3$): diastereoisomer A: δ −68.72 (d, CF_3, $^3J_{HF} = 9.2$ Hz); diastereoisomer B: δ −69.05 (d, CF_3, $^3J_{HF} = 8.4$ Hz) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): diastereoisomer A: δ 31.98 (CH_2); 45.06 (q, CH–CF_3, $^2J_{CF} = 30.9$ Hz); 79.24 (CH); 123.71 (q, CF_3, $^1J_{CF} = 277.7$ Hz); 125.47, 128.72, 128.79, 137.99 (Ph); 169 (C=O); diastereoisomer B: δ 31.09 (CH_2), 44.32 (q, CH–CF_3, $^2J_{CF} = 29.8$ Hz); 79.08 (CH); 124.05 (q, CF_3, $^1J_{CF} = 278.3$ Hz); 124.94, 128.52, 128.93, 137.27 (Ph); 169.20 (C=O) ppm. Anal. calcd. for $C_{11}H_9F_3O_2$: C, 57.4; H, 3.9. Found: C, 57.3; H, 4.3%.

3.5.4. Methyl 4-hydroxy-4-phenyl-2-(trifluoromethyl)butanoate (**12**)

^{19}F NMR (376.6 MHz, $CDCl_3$): diastereoisomer A: δ −68.75 (d, CF_3, $^3J_{HF} = 9.2$ Hz); diastereoisomer B: δ −70.32 (d, CF_3, $^3J_{HF} = 10.2$ Hz) ppm. MS ($M_r = 262$), *m/z* (% relative intensity): EI: 231/10 ($M^+ - 31$), 230/92, 229/21, 147/9, 124/16, 117/55, 115/26, 107/100, 105/77, 96/56, 95/23, 77/52, 69/12, 51/39.

3.6. Bromo derivatives

3.6.1. Addition of bromine to 4-oxoalkenoates **8** and **9**; compounds **15** and **16**

3.6.1.1. General procedure. A round bottomed flask (25 ml, magnetic spinbar) was charged with alkenoate **8** or **9** and CFC-113 (5 ml). The flask was immersed in a dry-ice cooled bath and a solution of bromine in CFC-113 was added dropwise while stirring. The progress of the reaction was followed by ^{19}F NMR. When the conversion of alkenoate was complete, solvent and volatile components were removed on a rotary evaporator.

*3.6.1.2. Methyl 2,3-dibromo-4-oxo-2-(trifluoromethyl)-pentanoate (**15**)*. A mixture of pentenoate **8** (0.107 g, 0.55 mmol), bromine (0.1 g, 0.6 mmol) in CFC-113 was reacted for 2 h. The yield of liquid **15**: 0.18 g (94.8%), diastereoisomer ratio 71:29.

^{1}H NMR (300.07 MHz, $CDCl_3$): diastereoisomer A: δ 2.49 (s, 3H, CH_3), 3.92 (s, 3H, $COOCH_3$); 5.07 (s, 1H, CH); diastereoisomer B: δ 2.46 (s, 3H, CH_3), 3.93 (s, 3H, $COOCH_3$); 5.21 (s, 1H, CH) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): diastereoisomer A: δ −66.87 (s, CF_3); diastereoisomer B: δ −68.75 (s, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): diastereoisomer A: δ 27.75 (CH_3), 49.92 ($COOCH_3$); 54.97 (CH); 121.85 (q, CF_3, $^1J_{CF} = 284.8$ Hz); 162.07 ($COOCH_3$); 196.17 (C=O); diastereoisomer B: δ 27.61 (CH_3), 51.37 ($COOCH_3$); 55.02 (CH); 122.12 (q, CF_3, $^1J_{CF} = 284.2$ Hz); 163.49 ($COOCH_3$); 189.75 (C=O) ppm. MS ($M_r = 356$), *m/z* (% relative intensity): EI: 327/6 ($M^+ - 29$), 325/14, 323/7, 277/19, 275/20, 261/5, 259/8, 245/4, 243/4, 235/11, 233/14, 215/35, 213/33, 203/59, 201/54.

*3.6.1.3. Methyl 2,3-dibromo-4-phenyl-4-oxo-2-(trifluoromethyl)butanoate (**16**)*. A mixture of pentenoate **9** (0.124 g, 0.48 mmol), bromine (0.09 g, 0.53 mmol) in CFC-113 was reacted for 2 h. The yield of liquid **16**: 0.205 g (98%), diastereoisomer ratio 78:22.

^{1}H NMR (300.07 MHz, $CDCl_3$): diastereoisomer A: δ 3.80 (s, 3H, $COOCH_3$); 5.93 (s, 1H, CH); 7.47–7.99 (m, 5H, Ph); diastereoisomer B: δ 3.96 (s, 3H, $COOCH_3$); 5.92 (s, 1H, CH); 7.47–7.99 (m, 5H, Ph) ppm.

^{19}F NMR (376.6 MHz, $CDCl_3$): diastereoisomer A: δ −68.85 (s, CF_3); diastereoisomer B: δ −66.66 (s, CF_3) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$): diastereoisomer A: δ 45.29

($COOCH_3$); 54.87 (CH); 62.6 (q, C–CF_3, $^2J_{CF} = 28.8$ Hz); 122.34 (q, CF_3, $^1J_{CF} = 284.4$ Hz); 128.72, 128.84, 133.14, 134.19 (Ph); 163.56 ($COOCH_3$); 189.42 (C=O); diastereoisomer B: δ 42.13 ($COOCH_3$); 54.72 (CH); 61.38 (q, C–CF_3, $^2J_{CF} = 29$ Hz); 122.2 (q, CF_3, $^1J_{CF} = 284.2$ Hz); 128.72, 128.94, 133.13, 134.43 (Ph); 162.02 ($COOCH_3$); 188.38 (C=O) ppm. MS ($M_r = 418$), *m/z* (% relative intensity): EI: 309/38 ($M^+ - 109$), 307/40, 261/13, 259/27, 258/89, 239/13, 229/27, 228/14, 227/39, 209/21, 199/38, 183/29, 181/51, 179/42, 169/13, 153/15, 151/41.

3.6.2. Photodehalogenations of dibromo derivatives **15** and **16**; alkenoates **8** and **9**

3.6.2.1. General procedure. Apparatus: the reactions were carried out in a round-shaped two-necked (with septa) quartz cell of volume ca. 20 ml (diameter 5 cm, thickness 1 cm, plane-parallel sites) irradiated externally by a medium pressure UV lamp (Tesla, RVK 250W), placed in a reflecting-metal cylindrical housing, with a round window (diameter 5 cm).

Reaction: the reaction mixture, which consisted of dibromoalkanoate (**15** or **16**), propan-2-ol and acetone was deaerated for 1 h at ca. −70 °C (dry ice–ethanol) with a stream of argon (inlet–outlet by needles through septa) then allowed to warm to rt and irradiated for ca. 3 h. The progress of the dehalogenation was followed by TLC (CH_2Cl_2) until the conversion of the starting compound was complete. Volatile components were then removed on a rotary evaporator.

*3.6.2.2. Methyl 4-oxo-2-(trifluoromethyl)pent-2-enoate (**8**).* A mixture of dibrompentanoate **15** (0.18 g, 0.52 mmol), propan-2-ol (11.9 g, 197 mmol) and acetone (1.05 g, 18.1 mmol) afforded **8** in a yield of 0.08 g (81.7%) as a mixture of *E* and *Z* isomers (52:48).

*3.6.2.3. Methyl 4-phenyl-4-oxo-2-(trifluoromethyl)but-2-enoate (**9**).* A mixture of dibromobutanoate **16** (0.2 g, 0.47 mmol), 2-propanol (10.9 g, 183 mmol) and acetone (0.99 g, 17.7 mmol) afforded **9** in the yield of 0.1 g (85.2%) as a mixture of isomers *E* and *Z* (66:34).

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