Blaise Reaction of Ethyl 3-Bromodifluoromethyl-3-benzyloxyacrylate with Nitriles: A Convenient Synthesis of α-Difluorovinyl-Substituted β-Enaminoesters and β-Ketoesters

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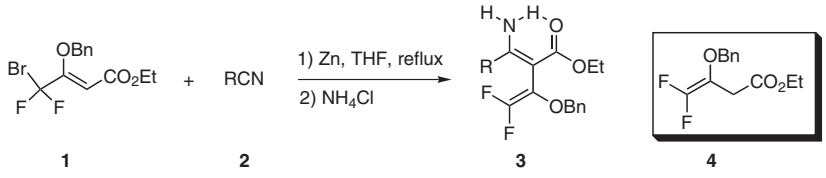
Abstract: The Blaise reaction between the zinc dienolate of ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate and a variety of nitriles gave a series of α-difluorovinyl substituted β-enaminoesters in good yield, which readily underwent hydrolysis to the corresponding β-ketoesters. Direct coupling of this zinc dienolate with acyl chloride also furnished the same α-difluorovinyl substituted β-ketoester, though in low yield, while the tetrakis(dimethylamino)ethylene (TDAE) mediated reaction provided γ-CF_2 carbon and oxygen acylated products.

Key words: zinc dienolate, nitrile, Blaise reaction, β-enaminoesters, β-ketoester

The addition of zinc ester enolates to nitriles, named the Blaise reaction after its discoverer,[2] is a very useful methodology for the synthesis of β-enaminoesters[3] and β-ketoesters. Several modifications have dramatically improved the reaction[3–5] and overcome the inherent drawbacks of low yield, narrow substrate scope, requirement of excess α-bromoester, and competing self-condensation. This straightforward transformation can easily introduce functionalities into the resultant product, and has been successfully used to synthesize β-aminoesters and heterocycles from multifunctionalized β-enaminoesters or β-ketoesters.[6] The Blaise reaction of zinc ester dienolates which, to the best of our knowledge, has never been investigated, extends the scope of this reaction through its dualistic reactivity affording either the α- or γ-carbon-coupling-mode product with nitriles.

It has been found that the difluorovinyl moiety forms the crucial structural element of a number of mechanism-based fluoroolefin-derived enzyme inhibitors, which have been receiving increasing attention in medicinal and agrochemical science.[7] In previous studies, the application of ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate (**1**) as a fluorine-containing building-block for conveniently introducing CF_2 into newly formed hydroxyl esters or amino esters was exploited.[8] During this research it was noted that the nucleophilic addition reaction of **1**, in the presence of zinc and acetonitrile, unexpectedly gave the Blaise reaction product, though in low yield. The zinc reagent of **1**, a zinc dienolate species in solution, has two possible modes of addition to acetonitrile, either with its α-carbon or γ-CF_2 carbon. In fact, **1** condensed with acetonitrile solely through its α-carbon to give the corresponding β-enaminoester **3a**, in which, fascinatingly, a 2,2-difluoro-1-benzyloxy-1-vinyl group was attached at the α-position. This compound was quite stable, could be purified by silica gel column chromatography and was fully characterized.

This reaction was further investigated. When an equimolar mixture of **1** and acetonitrile was refluxed for three hours in THF in the presence of zinc, the condensation product **3a** was isolated in moderate yield, with the only side-product being the zinc-reduced compound **4** (Scheme 1). After thorough examination, we found that slow addition of **1** into a refluxing mixture of zinc and excess acetonitrile in THF minimized the reduction of **1** and gave the highest yield of the corresponding enaminoester **3** (Scheme 1). Results obtained with a range of nitriles under these optimum conditions are assembled in Table 1. It is worth noting that, due to hydrogen bonding between the amino group and the ethoxy carbonyl group, the two protons on the amino group are greatly differentiated and appear with ^{1}H NMR shifts of 5.12 and 9.00 ppm.



1 2 3 4

Scheme 1 Condensation of **1** with nitriles **2** and the reduced side product (boxed)

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Table 1 Blaise Reaction of Ethyl 3-Bromodifluoromethyl-3-benzyloxyacrylate (**1**) with Nitriles **2**

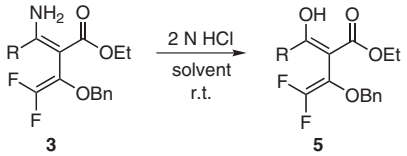
Entry	Nitrile (**2**)	Reflux time (h)	Product (%)[a]
1	**2a** R = CH_3	2	**3a** (72)
2	**2b** R = CH_3CH_2	3	**3b** (69)
3	**2c** R = $PhCH_2$	3	**3c** (62)
4	**2d** R = Ph	3	**3d** (85)
5	**2e** R = 3-MeC_6H_4	4	**3e** (81)
6	**2f** R = 2,4-$Cl_2C_6H_3$	4.5	**3f** (89)
7	**2g** R = *trans*-CH_3CH=CH	4	**3g** (31)
8	**2h** R = $(CH_3)_2CH$	4	–[b]

[a] Isolated yield.
[b] No β-enaminoester product detected.

This reaction worked generally well with both aryl and alkyl nitriles, though the yield employing the former was higher than that with the latter. This difference in yield is probably due, to some extent, to the ability of the relatively acidic α-protons of the alkyl nitriles to quench the zinc dienolate reactive species. The α-branched alkyl nitrile **2h** failed to condense with **1**, presumably due to its unfavorable steric hindrance (Table 1, Entry 8), with only the reduced product being detected. The aforementioned results are consistent with those reported by Cason et al.[9] The reaction of **1** with the α,β-unsaturated nitrile **2g** was complicated by a competing Michael addition of the zinc reagent to this nitrile, and resulted in a relatively low yield of the corresponding enaminoester **3g**.

The enaminoester **3** readily underwent hydrolysis to the corresponding α-difluorovinyl substituted β-ketoester **5** under acidic conditions at room temperature. The enaminoesters **3a–c**, with R as alkyl group, gave β-ketoesters **5a–c** in good yield, while the aryl- substituted enaminoesters **3d–e** gave inferior yield of β-ketoesters **5d–e** (Table 2) with defluorination products **6** (Scheme 2) isolated in 20–30% yield. It is proposed that, for compounds **3d–e**, stabilization by the aryl group of the enamino moiety might result in a much slower rate of hydrolysis and, for these compounds, hydrolysis of the benzyl vinyl ether subunit leading to the tricarbonyl intermediate **I** may become significant. This proposed intermediate is not stable under acidic conditions and undergoes further hydrolysis to give the new β-ketoester **6** through the loss of difluoroacetic acid (Scheme 2).[10] Indeed, in the reaction of enaminoester **3f**, only the defluorination product **6f** could be obtained in 46% yield (Table 2, Entry 7). The reaction of **3g** proved to be very complex and no meaningful product could be isolated (Table 2, Entry 8).

Table 2 Hydrolysis of β-Enaminoesters **3**

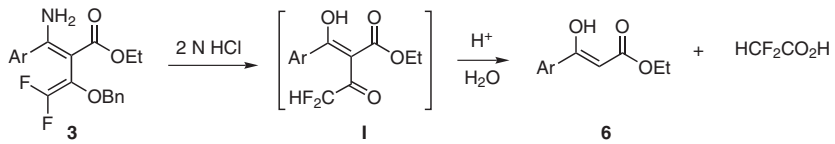


3 **5**

Entry	β-Enaminoester **3**	Solvent	Time	Product (%)[a]
1	**3a** R = CH_3	AcOEt	17 h	**5a** (72)
2	**3b** R = CH_3CH_2	EtOH	3 d	**5b** (82)
3	**3c** R = $PhCH_2$	EtOH	3 d	**5c** (85)
4	**3d** R = Ph	AcOEt	1 d	**5d** (28)
5	**3d** R = Ph	EtOH	60 h	**5d** (53)[b]
6	**3e** R = 3-MeC_6H_4	EtOH	3 d	**5e** (52)[b]
7	**3f** R = 2,4-diClC_6H_3	EtOH	3 d	–
8	**3g** R = *trans*-CH_3CH=CH	EtOH	3 d	–

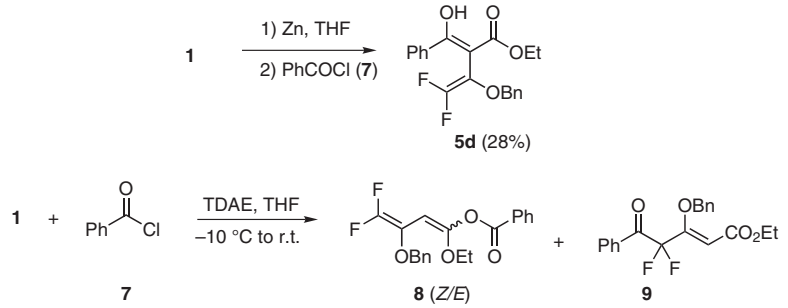
[a] Isolated yield.
[b] The defluorination product **6** was also isolated.

Since the above two-stage procedure afforded the corresponding aryl-substituted β-ketoesters **5d–e** in only moderate yield, we tried to develop an alternative method for the synthesis of this kind of β-ketoester. The cross-coupling of this zinc regent with acid chlorides is known to be a versatile method of preparing ketones.[11] Unfortunately, treatment of the zinc dienolate of **1** with benzoyl chloride **7** furnished the difluorovinyl-substituted β-ketoester **5d** only in low yield (28%) (Scheme 3). Addition of copper or palladium catalyst to this reaction failed to improve the yield. The reduced product **4** was predominantly formed instead of the coupling product, and this is ascribed to the high tendency of the zinc dienolate towards protonation. The tetrakis(dimethylamino)ethylene (TDAE) mediated condensation of fluorocarbon iodides with acyl chloride was reported to lead readily to the corresponding ketone.[12] Because the fluorine-containing nucleophilic species, formed in situ under the promotion of TDAE, was trapped immediately by the electrophile, the reduction product of the fluorocarbon iodides was minimized. It was interesting to find that when TDAE was used in the direct cou-



3 **I** **6**

Scheme 2 Proposed formation of the defluorination product **6**.



Scheme 3 Direct coupling of **1** with benzoyl chloride

pling of **1** with benzoyl chloride **7**, the reaction afforded a stereoisomeric mixture of oxygen-acylated product **8** (*Z*/*E*) and γ-CF_2-carbon-acylated product **9** with a ratio of 1:1:2 in a combined yield of around 60% (Scheme 3), instead of the α-carbon-acylation product **5**.

In summary, we have demonstrated that the zinc dienolate of ethyl 3-bromodifluoromethyl-3-benzyloxyacrylate **1** condensed with a variety of nitriles **2**. The Reformatsky reaction-like mode of addition provided a series of new α-difluorovinyl-substituted β-enaminoesters **3** in good yield, which readily hydrolyzed to the corresponding β-ketoesters **5**. This is the first investigation of the condensation of a metal dienolate with nitriles. Our attempts at direct coupling of this zinc dienolate with benzoyl chloride furnished the β-ketoester **5** in low yield, while TDAE-mediated reaction of **1** with the same electrophile provided both the oxygen-acylated product **8** and CF_2-carbon-acylated product **9**.

NMR spectra were recorded on a Varian-360L, a Varian VXR400S or a Bruker AM-300 spectrometer with TMS as internal standards, $CFCl_3$ as external standards and $CDCl_3$ as solvent, unless otherwise stated. For ^{19}F NMR spectra, up-field shifts are quoted as negative. Mass spectra were recorded on a HP 5989a spectrometer; accurate mass measurements were performed on a Finnigan MAT instrument. IR spectra were obtained with a Perkin–Elmer 983G spectrophotometer on KBr disks and elemental analyses were performed in-house. TLC was performed on silica gel plates and column chromatography over silica gel (purchased from Qingdao Ocean Chemicals). The preparation of **1** was performed as described previously.[13] All other reagents were obtained from commercial sources and used as such. Solvents were purified by conventional methods prior to use (THF–Na wire, DMF–CaH_2).

Blaise Reaction of Acrylate 1 with Nitriles 2; General Procedure

To a refluxing mixture of activated zinc powder (100 mg, 1.5 mmol) and nitrile **2** (5 mmol) in THF (4 mL) under N_2 was added acrylate **1** (335 mg, 1 mmol) dropwise over 30 minutes. The mixture was refluxed for 2 h then quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography (*n*-hexane–EtOAc, either 5:1 or 3:1) to give the α-difluorovinyl substituted β-enamino esters **3** as slightly yellow oils.

Ethyl 3-Amino-2-(1-benzyloxy-2,2-difluoro-1-vinyl)-2-butenoate (3a)

IR (KBr): 3426, 3314, 3032, 2981, 2933, 1756, 1664, 1614, 1522, 1454, 1370, 1260, 1138, 1106, 1031, 927, 793, 740, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.0 Hz, 3 H), 1.89 (s, 3 H), 4.12 (q, *J* = 7.0 Hz, 2 H), 4.69 (s, 2 H), 5.02 (br s, 1 H), 7.24–7.35 (m, 5 H), 8.87 (br s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –102.5 (d, *J* = 64.6 Hz, 1 F), –111.4 (d, *J* = 64.6 Hz, 1 F).

MS (EI, 70 eV): *m*/*z* (%) = 252 (1) [M^+ – OEt], 207 (4), 206 (40), 178 (33), 156 (7), 130 (23), 128 (11), 110 (5), 92 (9), 91 (100), 65 (15), 42 (21).

Anal. Calcd for $C_{15}H_{17}F_2NO_3$: C, 60.60; H, 5.76; N, 4.71. Found: C, 60.59; H, 5.83; N, 4.54.

Ethyl 3-Amino-2-(1-benzyloxy-2,2-difluoro-1-vinyl)-2-pentenoate (3b)

IR (KBr): 3430, 3312, 3031, 2981, 2939, 1756, 1663, 1611, 1519, 1455, 1370, 1260, 1138, 1106, 1066, 1033, 959, 900, 799, 739, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.7 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 2.27 (br s, 2 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.70 (s, 2 H), 5.14 (br s, 1 H), 7.24–7.36 (m, 5 H), 8.99 (br s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.5 (d, *J* = 62.6 Hz, 1 F), –110.1 (d, *J* = 62.6 Hz, 1 F).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 169.3 (dd, $^4J_{C-F}$ = 3.0, 1.8 Hz), 168.2 (dd, $^4J_{C-F}$ = 3.8, 1.1 Hz), 154.1 (dd, $^1J_{C-F}$ = 290.4, 274.5 Hz), 137.7, 112.9 (dd, $^2J_{C-F}$ = 41.5, 19.6 Hz), 83.9 (t, $^3J_{C-F}$ = 3.7 Hz), 70.6 (t, $^4J_{C-F}$ = 2.4 Hz), 59.2, 26.8, 14.3, 11.8.

MS (EI, 70 eV): *m*/*z* (%) = 312 (7) [M + H^+], 295 (2), 266 (24), 246 (2), 220 (62), 204 (10), 192 (29), 170 (8), 144 (31), 124 (4), 96 (3), 92 (9), 91 (100), 65 (11), 56 (16), 41 (3).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{19}F_2NO_3$: 311.133; found: 311.131.

Ethyl 4-Phenyl-3-amino-2-(1-benzyloxy-2,2-difluoro-1-vinyl)-2-butenoate (3c)

IR (KBr): 3467, 3306, 3031, 2980, 1755, 1662, 1606, 1514, 1497, 1454, 1367, 1256, 1135, 1099, 1031, 929, 791, 739, 699, 457 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 3.64 (d, *J* = 13.2 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.75 (s, 2 H), 4.87 (br s, 1 H), 7.13–7.38 (m, 10 H), 9.03 (br s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.0 (d, *J* = 61.5 Hz, 1 F), –109.6 (d, *J* = 61.5 Hz, 1 F).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 169.3 (dd, $^4J_{C-F}$ = 3.1, 1.7 Hz), 164.8 (t, $^4J_{C-F}$ = 1.5 Hz), 138.0, 135.4, 113.3 (dd, $^2J_{C-F}$ = 40.6, 18.8 Hz), 85.4 (t, $^3J_{C-F}$ = 3.4 Hz), 71.0, 59.5, 39.2, 14.5.

MS (EI, 70 eV): *m/z* (%) = 374 (1) [M + H$^+$], 328 (3), 282 (59), 254 (50), 232 (3), 218 (2), 206 (11), 186 (36), 158 (5), 130 (8), 118 (9), 115 (6), 92 (9), 91 (100), 77 (4), 65 (14), 41 (4).

HRMS (EI): *m/z* [M$^+$ – OEt] calcd for $C_{19}H_{16}F_2NO_2$: 328.115; found: 328.113.

Ethyl 4,4-Difluoro-3-benzyloxy-2-(aminophenylmethene)-3-butenoate (3d)

IR (KBr): 3463, 3418, 3306, 3032, 2980, 1754, 1663, 1598, 1575, 1523, 1488, 1444, 1366, 1263, 1141, 1024, 965, 774, 739, 699, 541 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.71 (s, 2 H), 5.12 (br s, 1 H), 7.24–7.44 (m, 10 H), 9.00 (br s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –100.9 (d, *J* = 65.4 Hz, 1 F), –109.4 (d, *J* = 65.4 Hz, 1 F).

MS (EI, 70 eV): *m/z* (%) = 314 (1) [M$^+$ – OEt], 269 (6), 268 (40), 240 (28), 222 (5), 218 (7), 192 (14), 190 (8), 145 (2), 129 (6), 117 (3), 104 (41), 92 (11), 91 (100), 77 (9), 65 (16), 43 (21).

Anal. Calcd for $C_{20}H_{19}F_2NO_3$: C, 66.84; H, 5.33; N, 3.90. Found: C, 66.77; H, 5.43; N, 4.20.

Ethyl 4,4-Difluoro-3-benzyloxy-2-[amino(3-methylphenyl)methene]-3-butenoate (3e)

IR (KBr): 3462, 3419, 3305, 2981, 2931, 1755, 1663, 1599, 1583, 1519, 1482, 1455, 1367, 1266, 1215, 1133, 1102, 1028, 1001, 965, 913, 792, 736, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3 H), 2.33 (s, 3 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.70 (s, 2 H), 5.08 (br s, 1 H), 7.20–7.34 (m, 9 H), 8.99 (br s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.5 (d, *J* = 64.6 Hz, 1 F), –110.1 (d, *J* = 64.6 Hz, 1 F).

MS (EI, 70 eV): *m/z* (%) = 328 (1) [M$^+$ – OEt], 282 (50), 254 (34), 236 (11), 232 (14), 214 (1), 206 (15), 204 (7), 186 (5), 159 (2), 143 (7), 130 (4), 118 (40), 103 (2), 92 (8), 91 (100), 77 (4), 65 (15), 51 (2), 41 (1).

Anal. Calcd for $C_{21}H_{21}F_2NO_3$: C, 67.55; H, 5.67; N, 3.75. Found: C, 67.46; H, 5.79; N, 3.57.

Ethyl 4,4-Difluoro-3-benzyloxy-2-[amino(2,4-dichlorophenyl)methene]-3-butenoate (3f)

IR (KBr): 3459, 3412, 3304, 2981, 2934, 1755, 1666, 1602, 1556, 1527, 1474, 1370, 1267, 1246, 1144, 1102, 1053, 1026, 966, 824, 796, 738, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 4.68 (s, 2 H), 5.19 (br s, 1 H), 7.16–7.43 (m, 3 H), 8.96 (br s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –100.6 (br s, 1 F), –108.4 (br s, 1 F).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 169.1 (dd, $^4J_{C-F}$ = 2.9, 1.5 Hz), 160.6 (dd, $^4J_{C-F}$ = 4.2, 1.9 Hz), 154.2 (dd, $^1J_{C-F}$ = 291.1, 277.2 Hz), 112.8 (dd, $^2J_{C-F}$ = 41.0, 20.2 Hz), 87.9 (t, $^3J_{C-F}$ = 3.8 Hz), 65.5, 59.8, 14.2.

MS (EI, 70 eV): *m/z* (%) = 382 (1) [M$^+$ – OEt], 338 (25), 336 (38), 310 (23), 308 (35), 288 (4), 286 (6), 262 (7), 260 (13), 197 (3), 185 (1), 174 (12), 172 (18), 92 (7), 91 (100), 65 (8).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{20}H_{17}{}^{35}Cl_2F_2NO_3$: 427.055; found: 427.055.

Anal. Calcd for $C_{20}H_{17}Cl_2F_2NO_3$: C, 56.09; H, 4.00; N, 3.27. Found: C, 56.57; H, 4.09; N, 2.99.

Ethyl 3-Amino-2-(1-benzyloxy-2,2-difluoro-1-vinyl)-2,4-hexadienoate (3g)

IR (KBr): 3446, 3313, 2980, 1755, 1665, 1650, 1597, 1505, 1455, 1367, 1252, 1136, 1032, 962, 915, 739, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2Hz, 3 H), 1.81 (d, *J* = 5.7 Hz, 3 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 4.70 (s, 2 H), 6.17–6.21 (m, 2 H), 7.26–7.33 (m, 5 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.3 (d, *J* = 62.9 Hz, 1 F), –110.6 (d, *J* = 62.9 Hz, 1 F).

MS (EI, 70 eV): *m/z* (%) = 323 (1) [M$^+$], 294 (1), 278 (1), 248 (1), 232 (21), 204 (14), 186 (2), 182 (11), 173 (2), 156 (10), 136 (7), 118 (2), 92 (8), 91 (100), 68 (12), 65 (7).

Anal. Calcd for $C_{17}H_{19}F_2NO_3$: C, 63.15; H, 5.92; N, 4.33. Found: C, 63.43; H, 6.05; N, 4.28.

Hydrolysis of Enaminoesters 3; General Procedure

To a solution of enaminoester **3** (1 mmol) in either EtOH or EtOAc (25 mL) was added HCl (2 N, 8 mL). The mixture was stirred at r.t. for the time specified in Table 2 until TLC analysis showed complete conversion of the enaminoester, then H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography (*n*-hexane–EtOAc, 40:1) to give the α-difluorovinyl substituted β-ketoesters **5** as colorless oils.

Ethyl 3-Hydroxy-2-(1-benzyloxy-2,2-difluoro-1-vinyl)-2-butenoate (5a)

IR (KBr): 2984, 2937, 1755, 1644, 1608, 1455, 1404, 1381, 1338, 1271, 1235, 1133, 1063, 1014, 941, 878, 740, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H), 1.97 (s, 3 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 4.72 (s, 2 H), 7.27–7.37 (m, 5 H), 13.40 (s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –100.0 (d, *J* = 62.0 Hz, 1 F), –109.0 (d, *J* = 62.0 Hz, 1 F).

MS (EI, 70 eV): *m/z* (%) = 207 (15) [M$^+$ – Bn], 190 (1), 179 (5), 157 (2), 129 (1), 111 (1), 92 (11), 91 (100), 65 (11), 43 (22).

Anal. Calcd for $C_{15}H_{16}F_2O_4$: C, 60.40; H, 5.41. Found: C, 60.36; H, 5.50.

Ethyl 3-Hydroxy-2-(1-benzyloxy-2,2-difluoro-1-vinyl)-2-pentenoate (5b)

IR (KBr): 3034, 2983, 2942, 2881, 1756, 1644, 1603, 1466, 1455, 1403, 1374, 1345, 1274, 1230, 1133, 1093, 1039, 739, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.2 Hz, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H), 2.24 (q, *J* = 7.2 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.62 (s, 2 H), 7.21–7.28 (m, 5 H), 13.41 (s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –100.2 (d, *J* = 60.1 Hz, 1 F), –109.1 (d, *J* = 60.1 Hz, 1 F).

MS (EI, 70 eV): *m/z* (%) = 221 (15) [M$^+$ – Bn], 193 (6), 175 (2), 146 (1), 92 (7), 91 (100), 77 (1), 69 (1), 65 (7), 57 (13).

Anal. Calcd for $C_{16}H_{18}F_2O_4$: C, 61.53; H, 5.81. Found: C, 61.92; H, 5.78.

Ethyl 4-Phenyl-3-hydroxy-2-(1-benzyloxy-2,2-difluoro-1-vinyl)-2-butenoate (5c)

IR (KBr): 3032, 2983, 2933, 1755, 1642, 1596, 1570, 1496, 1454, 1401, 1377, 1343, 1273, 1231, 1131, 1041, 944, 862, 739, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 3.65 (d, *J* = 6.9 Hz, 2 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 4.67 (s, 2 H), 7.23–7.35 (m, 10 H), 13.49 (s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –99.1 (d, *J* = 56.4 Hz, 1 F), –107.7 (d, *J* = 56.4 Hz, 1 F).

MS (EI, 70 eV): *m*/*z* (%) = 283 (5) [M^+ – Bn], 255 (2), 237 (10), 220 (1), 205 (2), 181 (1), 131 (1), 118 (2), 92 (8), 91 (100), 77 (1), 65 (12), 51 (2).

Anal. Calcd for $C_{21}H_{20}F_2O_4$: C, 67.37; H, 5.38. Found: C, 67.40; H, 5.22.

Ethyl 4,4-Difluoro-3-benzyloxy-2-(hydroxyphenylmethene)-3-butenoate (5d)

IR (KBr): 2983, 1751, 1695, 1642, 1609, 1595, 1570, 1493, 1447, 1399, 1375, 1342, 1271, 1246, 1141, 1021, 849, 774, 739, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 6.9 Hz, 3 H), 4.28 (q, *J* = 6.9 Hz, 2 H), 4.77 (s, 2 H), 7.24–7.73 (m, 10 H), 13.84 (s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ (enolized form, 86%) = –98.5 (d, *J* = 62.0 Hz, 1 F), –107.9 (d, *J* = 62.0 Hz, 1 F). δ (non-enolized form, 14%) = –96.9 (d, *J* = 64.9 Hz, 1 F), –108.7 (d, *J* = 64.9 Hz, 1 F).

MS (EI, 70 eV): *m*/*z* (%) = 269 (8) [M^+ – Bn], 241 (3), 223 (7), 197 (2), 163 (1), 146 (1), 127 (1), 105 (36), 92 (8), 91 (100), 77 (19), 65 (10), 51 (7).

Anal. Calcd for $C_{20}H_{18}F_2O_4$: C, 66.66; H, 5.03. Found: C, 66.68; H, 5.14.

Ethyl 4,4-Difluoro-3-benzyloxy-2-[hydroxy(3-methylphenyl)methene]-3-butenoate (5e)

IR (KBr): 3033, 2983, 2929, 1751, 1693, 1642, 1614, 1576, 1497, 1455, 1398, 1374, 1340, 1276, 1251, 1208, 1134, 1028, 925, 867, 802, 787, 737, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.0 Hz, 3 H), 2.84 (s, 3 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 4.70 (s, 2 H), 7.16–7.29 (m, 9 H), 13.76 (s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ (enolized form, 85%) = –98.4 (d, *J* = 61.8 Hz, 1 F), –107.9 (d, *J* = 61.8 Hz, 1 F); δ (non-enolized form, 15%) = –96.7 (d, *J* = 64.0 Hz, 1 F), –108.6 (d, *J* = 64.0 Hz, 1 F).

MS (EI, 70 eV): *m*/*z* (%) = 374 (1) [M^+], 329 (1), 283 (20), 263 (3), 255 (6), 237 (6), 211 (1), 189 (1), 181 (1), 163 (1), 141 (4), 119 (33), 92 (11), 91 (100), 77 (1), 65 (12), 51 (1).

Anal. Calcd for $C_{21}H_{20}F_2O_4$: C, 67.37; H, 5.38. Found: C, 67.73; H, 5.39.

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