Synthesis of pentafluorobenzyloxy mono- to tetra-fluoroacetophenones

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Abstract

Pentafluorobenzyloxyacetophenones are formed by reacting 2',3',4',5',6'-pentafluoroacetophenone and 2',3',4',5'-tetrafluoroacetophenone with pentafluorobenzyl alcohol (PFBA) in refluxing toluene under phase-transfer conditions. This provided seven new such acetophenones. Pentafluorobenzyloxy-substituted mono- and difluoroacetophenones were synthesized by reacting *p*-hydroxyacetophenone with pentafluorobenzyl bromide.

Introduction

Studies are being undertaken in our laboratories on electrophoric derivatives of acetophenone as molecular labels to replace radioisotopes in some analytical procedures. An electrophore is a compound that readily combines with an electron in the gas phase, and hence can be measured by gas chromatography using electron capture detection (GC–ECD) or a related technique. Previously, we have described in detail the use of electrophores as labels [1], including the synthesis of *p*-(pentafluorobenzyloxy)acetophenone, and have detected electrophore-labeled DNA and albumin as a combined sample by GC–ECD methods [2]. Establishing a diversity of electrophoric derivatives of acetophenone is of interest since a key advantage of electrophores as labels is the potential for measuring many of them as a mixture by GC–ECD methods. In particular, polyfluoro derivatives of acetophenone are attractive because fluorine atoms promote volatility and electron capture. Here we report some reactions which help to build up the diversity of volatile pentafluorobenzyloxy-substituted mono- to tetra-fluoroacetophenones.

Results and discussion

Recently, we have found that the pentafluorobenzyl group is lost when 2,6-difluorophenyl pentafluorobenzyl ether is subjected to Friedel–Crafts acetylation conditions [3]. Hence, such reaction conditions are not attractive for the formation of pentafluorobenzyloxy-acetophenones from the corresponding pentafluorobenzyl aromatic ethers. Both *o*- and *p*-fluorophenyl acetate are known to undergo the Fries rearrangement smoothly in the presence of Lewis acid catalysts [4]. However, no examples have been reported of the Fries rearrangement of difluoroaryl esters. As shown below, we have prepared 3'-fluoro- and 3',5'-difluoro-4'-hydroxyacetophenone (**3** and **4**) under Fries rearrangement conditions. The former compound forms more readily, providing a 65% yield of **3** after 3 h and a 52% yield of **4** after 5 h at 140–150 °C. By reacting pentafluorobenzyl bromide (PFB-Br) with **3** and **4** in the presence of potassium carbonate in refluxing acetone, we obtained 3'-fluoro- and 3',5'-difluoro-4'-pentafluorobenzyloxy-acetophenones (**5** and **6**) in high yield (91% and 88%, respectively).

It is well known that polyfluoroaromatics undergo nucleophilic substitution reactions [5], and 2',3',4',5',6'-pentafluoroacetophenone (**7**) has been ring-substituted previously with sodium azide (4'-substitution) [6], sodium sulfide (4'-substitution) [7] and aliphatic or aromatic amines (2'- and 4'-substitutions) [8, 9]. The acetyl group of **7** has been removed by alkoxide [10, 11] and such conditions have also caused **7** to undergo self-condensation instead of nucleophilic displacement of the fluorine [12]. A low yield of such displacement with ethanol has been observed in the presence of excess potassium cyanide [13].

Reaction of **7** with 2',3',4',5',6'-pentafluorobenzyl alcohol (PFBA) in DMF in the presence of potassium carbonate for 3 h at 120 °C was least successful for our purposes, giving little product diversity: 66% of **8**

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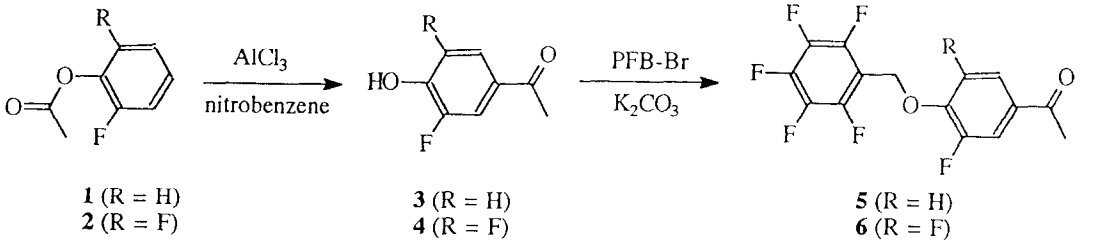
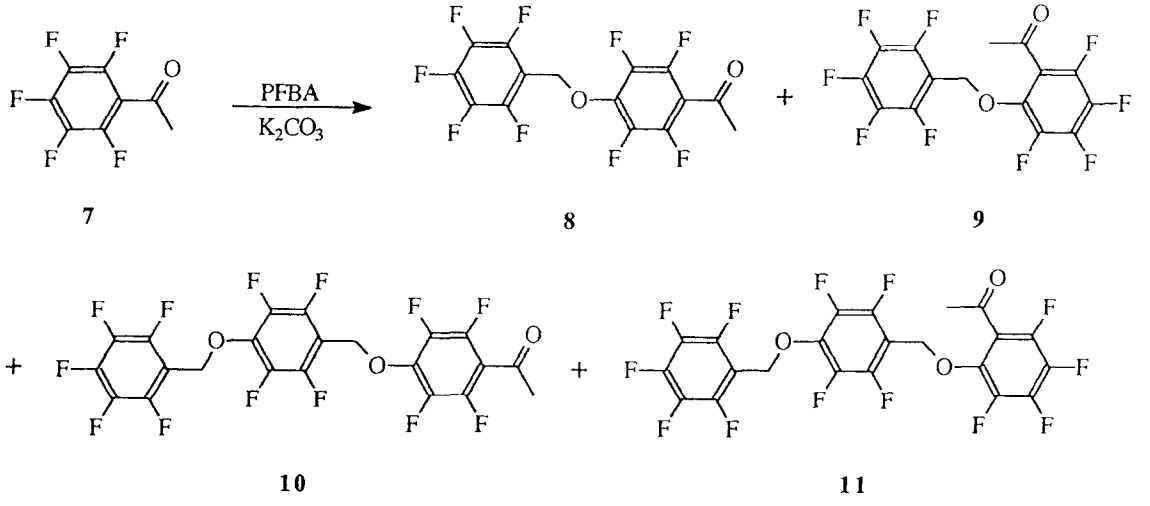


1 (R = H)
2 (R = F)

3 (R = H)
4 (R = F)

5 (R = H)
6 (R = F)

Scheme 1.



7 8 9

10 11

Scheme 2.

and 2% of **9**. These results are similar to those observed by Kobrina *et al.* [8], who used nitromethane as the solvent to obtain mainly *para* substitution of **7** with amines. By changing to refluxing toluene, and adding 0.1 g of 18-crown-6 as a phase-transfer catalyst, we obtained much more product diversity: **8** (46%), **9** (16%), **10** (5%) and **11** (2%). All of these products are acetophenone derivatives as desired. It is possible that **10** and **11** are derived from **8** and **9**, rather then via a *para*-ether dimer of PFBA, since we did not find any such dimer in the product mixture.

Nucleophilic substitution of tetrafluoroacetophenone has not been reported. Reaction of 2',3',4',5'-tetrafluoroacetophenone (**12**) with PFBA as above (refluxing toluene, 18-crown-6) was also successful in producing some diversity, as shown here.

The major product was *para*-substituted **13** (71% yield). Whilst no *ortho*-substituted product was observed, the *meta*-substituted product **14** formed in a small amount (2%). Perhaps formation of some **14** is not too surprising, given that hydrogen on a polyfluorophenyl ring tends to direct substitution to the *ortho* and *para* positions [5]. Compound **15** (5%) was also obtained, apparently, via **13**.

Thus, we have added nine new compounds to the category of volatile pentafluorobenzyloxy acetophenones to help the development of electrophoric labels for analytical purposes.

Experimental

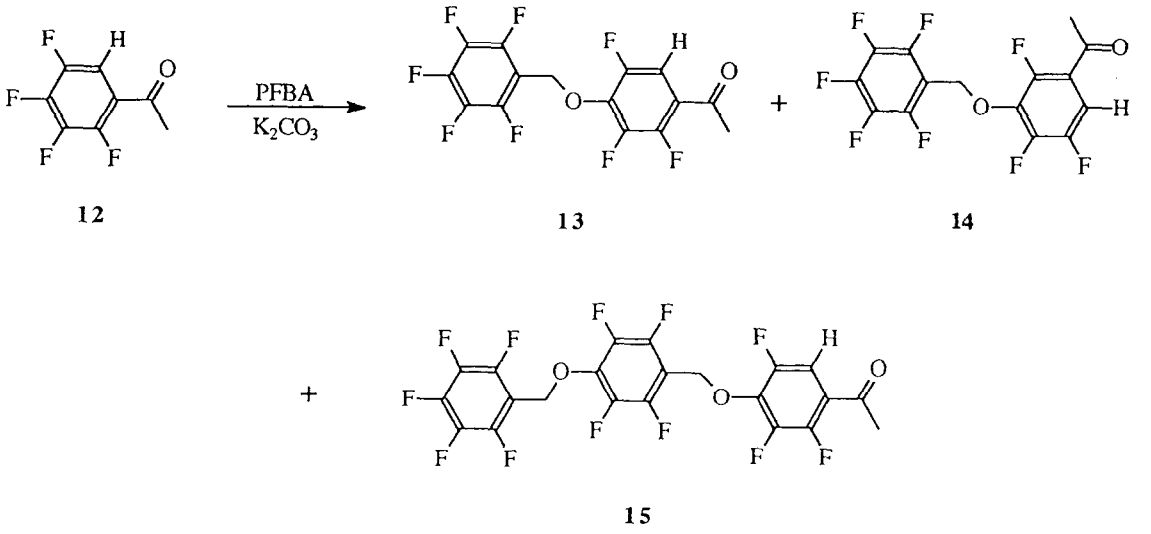
General

^1H and ^{13}C NMR spectra in ppm (δ) were obtained on a Varian XL-300FT instrument; $CDCl_3$ was used as the solvent and tetramethylsilane (TMS) was used as the internal standard. Infrared (IR) spectra were taken on a Perkin-Elmer model 588B spectrophotometer. Preparative gas chromatographic separations were run on a Varian 3300 instrument and helium was used as the carrier gas; column A: 20% SE-30/Chromosorb W (NAW, 60–80 mesh), 6 ft. × 1/4 in. aluminum column; column B: 10% SE-30/Chromosorb W (NAW, 60–80 mesh), 3 ft. × 1/4 in. aluminum column.

3'-Fluoro-4'-pentafluorobenzyloxyacetophenone (5)

Synthesis of 2'-fluorophenyl acetate (1)

To a mixture of 2-fluorophenol (5 g, 45 mmol), 50 ml of ether and potassium carbonate (16 g), 5 ml of acetic anhydride was added. After stirring under reflux for 3 h, the reaction mixture was stirred at room temperature overnight. The solid was removed by fil-



12 13 14

15

Scheme 3.

tration and washed three times with ether. The filtrate was evaporated to remove the solvent and distilled to obtain **1** (4.43 g, 64%). ^{1}H NMR δ: 2.32 (s, 3H, CH_3); 6.90–7.27 (m, 4H, H-Ar) ppm. ^{13}C NMR δ: 20.3 (CH_3CO); 116.6 ($^4J_{C-F}$=19 Hz, C5′); 123.7 (C4′/C6′); 124.4 ($^3J_{C-F}$=4 Hz, C6′/C4′): 127.0 ($^2J_{C-F}$=7 Hz, C3′); 138.1 ($^2J_{C-F}$=13 Hz, C1′); 154.1 (J_{C-F}=249 Hz, C2′); 168.3 (C=O) ppm.

Synthesis of 3′-fluoro-4′-hydroxyacetophenone (3)

A mixture consisting of **1** (1.54 g, 10 mmol) and aluminum chloride (1.70 g, 12.5 mmol) in 10 ml of nitrobenzene was stirred at 140–150 °C for 3 h. After cooling to room temperature, 15 ml of ice/water was added followed by 30 ml of 3 N HCl. The water layer was extracted with ether (3×30 ml) and the combined organic layers were washed three times with concentrated potassium carbonate solution and then the combined water layer was acidified with 2 N HCl. After extraction three times with ether, the organic layer was dried over anhydrous $MgSO_4$. Removal of ether by evaporation afforded 1.0 g of **3** (65%). This was used directly for the next step.

Synthesis of 5

A mixture consisting of **3** (1 g, 6.5 mmol) and PFB-Br (6.5 mmol), 30 ml of acetone and 5 g of potassium carbonate was stirred under reflux for 5 h. After addition of 5 g of Celite 521, the reaction mixture was filtered and the residue washed with acetone (3×30 ml). The filtrate was then evaporated on a Rotavapor. After recrystallization (hexane/ether), 1.98 g of product (91%) was obtained, m.p. 99–100 °C. ^{1}H NMR δ: 2.51 (s, 3H, CH_3CO); 5.24 (s, 2H, CH_2O); 7.11 (t, 1H, J_{5-6}=8.8 Hz, $^4J_{H-F}$=8.2 Hz, H-C5′); 7.62 (d, 1H, $^3J_{H-F}$=11.2 Hz, H-C2′); 7.70 (d, 1H, J_{6-5}=8.8 Hz, H-C6′) ppm. ^{13}C NMR δ: 25.9 (CH_3–CO); 58.5 (CH_2O); 109.1 (C1″, $^2J_{C-F}$=17 Hz); 114.4 (C5′); 116.0 (C2′, $^2J_{C-F}$=19 Hz); 125.4 (C6′, $^4J_{C-F}$=3 Hz); 131.7 (C1′, $^3J_{C-F}$=5 Hz); 137.4 (C2″ and C6″, J_{C-F}=254 Hz); 141.9 (C4″, J_{C-F}=256 Hz); 145.7 (C3″ and C5″, J_{C-F}=251 Hz); 149.8 (C4′, $^2J_{C-F}$=11 Hz); 152.2 (C3′, J_{C-F}=249 Hz); 195.5 (C=O) ppm. MS (EI) *m/z*: 334 ($M^{+\bullet}$) MS (ECNI) *m/z*: 153 ([M-PFBz]$^-$, 100%).

3′,5′-Difluoro-4′-pentafluorobenzyloxyacetophenone (6)

Synthesis of 2′,6′-difluorophenyl acetate (2)

To a stirred mixture consisting of 2,6-difluorophenol (3.6 g, 27.7 mmol), 30 ml of toluene and 30 ml of pyridine was added 3 ml of acetyl chloride at room temperature. After stirring for 5 h, 30 ml of water was added. The organic layer was separated and evaporated. The residue was diluted with 40 ml of ether and then washed with 30 ml of 5% HCl followed by 30 ml of 5% sodium carbonate. After drying over anhydrous $MgSO_4$, distillation afforded 4.3 g of product (90%). ^{1}H NMR δ: 2.33 (s, 3H, CH_3CO); 6.94 (t, 2H, J_{H-F}=J_{H-H}=7.9 Hz, H-C3 and H-C5); 7.12 (m, 1H, H-C4) ppm. ^{13}C NMR δ: 19.5 (CH_3CO); 111.9 (C3 and C5, $^2J_{C-F}$=22 Hz, $^4J_{C-F}$=6 Hz); 126.3 (C4, $^3J_{C-F}$=9 Hz); 155.2 (C2 and C6, J_{C-F}=250 Hz, $^3J_{C-F}$=4 Hz); 167.2 (C=O) ppm. IR (film) ν_{max} (cm^{-1}): 3010 (w); 1730 (vs) (C=O); 1565 (m); 1440 (s); 1335 (m); 1255 (s); 1210 (m); 1120 (vs) (C–O); 1010 (m); 965 (s); 860 (s); 740 (s); 710 (m); 670 (w).

Synthesis of 3′,5′-difluoro-4′-hydroxyacetophenone (4)

A mixture consisting of **2** (4.2 g, 24.4 mmol) and aluminum chloride (6.0 g, 4.5 mmol) in 100 ml of nitrobenzene was stirred at 140–150 °C for 5 h. Work-up was the same as for the synthesis of **3**. Product **4** (2.2 g) was obtained (52%). ^{1}H NMR δ: 2.32 (s, 1H,

OH); 2.57 (s, 3H, CH_3); 7.53 (d, 2H, J=8.1 Hz, HC2′ and HC6′) ppm. ^{13}C NMR δ: 25.4 (CH_3); 111.8 ($^2J_{C-F}$=22 Hz, $^4J_{C-F}$=8 Hz, C2′ and C6′); 117.8 ($^3J_{C-F}$=9 Hz, C1′); 139.1 ($^2J_{C-F}$=16 Hz, C4′); 151.6 (J_{C-F}=245 Hz, $^3J_{C-F}$=7 Hz, C3′ and C5′); 196.0 (C=O) ppm.

Synthesis of 6

A mixture consisting of **4** (2.2 g, 12.8 mmol), PFB-Br (12.8 mmol), 30 ml of acetone and 5 g of potassium carbonate was stirred under reflux for 5 h. Work-up was as usual, giving 4 g of product (88%), m.p. 62–63 °C. ^1H NMR δ: 2.58 (s, 3H, CH_3CO); 5.38 (s, 2H, CH_2O); 7.52 (d, 2H, $^3J_{H-F}$=8.7 Hz, H-C2′ and H-C6′) ppm. ^{13}C NMR δ: 25.8 (CH_3CO); 62.3 (CH_2O); 109.5 (C1″, $^2J_{C-F}$=17 Hz); 112.3 (C2′ and C6′, $^2J_{C-F}$=24 Hz, $^4J_{C-F}$=8 Hz); 132.8 (C1′, $^3J_{C-F}$=7 Hz); 137.4 (C2″ and C6″, J_{C-F}=252 Hz); 138.2 (C4′, $^2J_{C-F}$=15 Hz); 142.0 (C4″, J_{C-F}=256 Hz); 145.8 (C3″ and C5″, J_{C-F}=253 Hz); 155.5 (C3′ and C5′, J_{C-F}=251 Hz, $^3J_{C-F}$=5 Hz); 194.4 (C=O) ppm. MS (EI) *m/z*: 352 ($M^{+\cdot}$). MS (ECNI) *m/z*: 171 ($[M-PFBz]^-$, 100%).

4′-Pentafluorobenzyloxy-2′,3′,5′-trifluoroacetophenone (13)

A mixture consisting of **12** (0.96 g, 5 mmol), PFBA (1.0 g, 5 mmol), potassium carbonate (7 g), toluene (30 ml) and 18-crown-6 (0.1 g) was stirred under reflux for 8 h. After cooling to room temperature and adding 2 g Celite 521, the reaction mixture was filtered and the residue washed three times with ether. After evaporation of the filtrate on a Rotavapor, the crude products were separated by preparative gas chromatography using column A, giving 1.31 g of product (71%), m.p. 76–77 °C. ^1H NMR δ: 2.65 (d, 3H, $^5J_{H-F}$=5.2 Hz, CH_3-CO); 5.42 (s, 2H, CH_2O); 7.46 (ddd, 1H, $^2J_{H-F}$=11.3 Hz, $^3J_{H-F}$=6.1 Hz, $^4J_{H-F}$=2.4 Hz, H-C6′) ppm. ^{13}C NMR δ: 31.1 (CH_3CO, $^4J_{C-F}$=8 Hz); 62.6 (CH_2O); 109.1 (C1″, $^2J_{C-F}$=19 Hz); 111.1 (C6′, $^2J_{C-F}$=21 Hz, $^3J_{C-F}$=3 Hz); 121.0 (C1′); 137.5 (C2″ and C6″, J_{C-F}=250 Hz); 142.2 (C4″, J_{C-F}=249 Hz); 144.6 (C3′, J_{C-F}=253 Hz, $^2J_{C-F}$=17 Hz, $^3J_{C-F}$=5 Hz); 145.8 (C3″ and C5″, J_{C-F}=251 Hz); 148.2 (C2′, J_{C-F}=254 Hz, $^2J_{C-F}$=13 Hz, $^4J_{C-F}$=3 Hz); 151.0 (C5′, J_{C-F}=248 Hz, $^3J_{C-F}$=$^4J_{C-F}$ 3 Hz); 168.4 (C4′); 192.4 (C=O) ppm. MS (EI) *m/z*: 370 $[M]^{+\cdot}$. MS (ECNI) *m/z*: 189 ($[M-PFBz]^-$, 100%).

4′-Pentafluorobenzyloxy-2′,3′,5′,6′-tetrafluoroacetophenone (8)

A mixture consisting of **7** (1.05 g, 5 mmol), PFBA (1.0 g, 5 mmol), potassium carbonate (7 g), toluene (30 ml) and 18-crown-6 (0.1 g) was stirred under reflux for 8 h. Work-up was the same as for the synthesis of **13**, giving 0.89 g of product (46%), m.p. 76–77 °C. ^1H NMR δ: 2.62 (t, 3H, $^5J_{H-F}$=2.0 Hz, CH_3CO); 5.41 (s, 2H, CH_2O) ppm. ^{13}C NMR δ: 32.3 (CH_3CO); 63.0 (CH_2O); 108.9 (C1″, $^2J_{C-F}$=17 Hz); 114.4 (C1′, $^2J_{C-F}$=16 Hz); 137.5 (C2″ and C6″, J_{C-F}=258 Hz); 138.6 (C4′); 141.2 (C3′ and C5′, J_{C-F}=249 Hz); 142.4 (C4″, J_{C-F}=257 Hz); 144.8 (C2′ and C6′, J_{C-F}=263 Hz); 145.8 (C3″ and C5″, J_{C-F}=252 Hz); 195.5 (C=O) ppm. MS (EI) *m/z*: 388 ($M^{+\cdot}$). MS (ECNI) *m/z*: 207 ($[M-PFBz]^-$, 100%). In addition to **8**, 0.31 g (16%) of 2′-pentafluorobenzyloxy-3′,4′,5′,6′-tetrafluoroacetophenone (**9**), 142 mg (5%) of 4′-(4″-pentafluorobenzyloxy-2″,3″,5″,6″-tetrafluorobenzyl)oxy-2′,3′,5′,6′-tetrafluoroacetophenone (**10**) and 57 mg (2%) of 2′-(4″-pentafluorobenzyloxy-2″,3″,5″,6″-tetrafluorobenzyl)oxy-3′,4′,5′,6′-tetrafluoroacetophenone (**11**) were also obtained by preparative gas chromatography separation.

Compound **9**: ^1H NMR δ: 2.51 (d, 3H, $^5J_{H-F}$=1.6 Hz, CH_3CO); 5.25 (s, 2H, with fine splitting, CH_2O) ppm. ^{13}C NMR δ: 32.3 (CH_3CO); 63.7 (CH_2O); 108.9 (C1″, $^2J_{C-F}$=18 Hz); 120.9 (C1′); 137.5 (C2″ and C6″, J_{C-F}=253 Hz); 137.7 (C4′ and C5′, J_{C-F}=253 Hz); 138.2 (C2′); 142.1 (C4″, J_{C-F}=252 Hz); 142.2 (C3′/C6′, J_{C-F}=252 Hz); 143.8 (C6′/C3′, J_{C-F}=254 Hz); 145.8 (C3″ and C5″, J_{C-F}=259 Hz); 194.0 (C=O) ppm.

Compound **10**: ^1H NMR δ: 2.62 (t, 3H, $^5J_{H-F}$=1.9 Hz, CH_3CO); 5.38 (s, 2H, CH_2O); 5.39 (s, 2H, CH_2O) ppm. ^{13}C NMR δ: 32.5 (CH_3CO); 63.0 (CH_2O); 63.3 (CH_2O); 108.6 (C1″ and C1#, $^2J_{C-F}$=18 Hz); 127.5 (C1′); 137.6 (C2# and C6#, J_{C-F}=246 Hz); 137.7 (C4′/C4″); 138.0 (C4″/C4′); 141.2 (C3′, C5′, C2″ and C6″, J_{C-F}=256 Hz); 142.2 (C4#, J_{C-F}=244 Hz); 144.8 (C2′ and C6′, J_{C-F}=250 Hz); 145.9 (C3″, C5″, C3# and C5#, J_{C-F}=251 Hz); 191.7 (C=O) ppm.

Compound **11**: ^1H NMR δ: 2.51 (d, 3H, $^5J_{H-F}$=1.5 Hz, CH_3CO); 5.21 (s, 2H, CH_2O); 5.36 (s, 2H, CH_2O) ppm. ^{13}C NMR δ: 32.3 (CH_3CO); 62.9 (CH_2O); 63.5 (CH_2O); 109.1 (C1″ and C1#, $^2J_{C-F}$=18 Hz); 120.9 (C1′); 137.5 (C4′, C5, C2# and C6#, J_{C-F}=250 Hz); 137.6 (C4″); 138.8 (C2′); 141.5 (C4#, J_{C-F}=252 Hz); 142.4 (C2″ and C6″, J_{C-F}=252 Hz); 144.0 (C3′/C6′, J_{C-F}=250 Hz); 145.8 (C3″, C5″, C3# and C5#, J_{C-F}=251 Hz); 146.1 (C6′/C3′, J_{C-F}=249 Hz); 191.7 (C=O) ppm.

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