Polyhalogenated heterocyclic compounds. Part 41. Cycloaddition reactions involving hexafluorobut-2-yne and 1,1,1,2,4,4,4-heptafluorobut-2-ene

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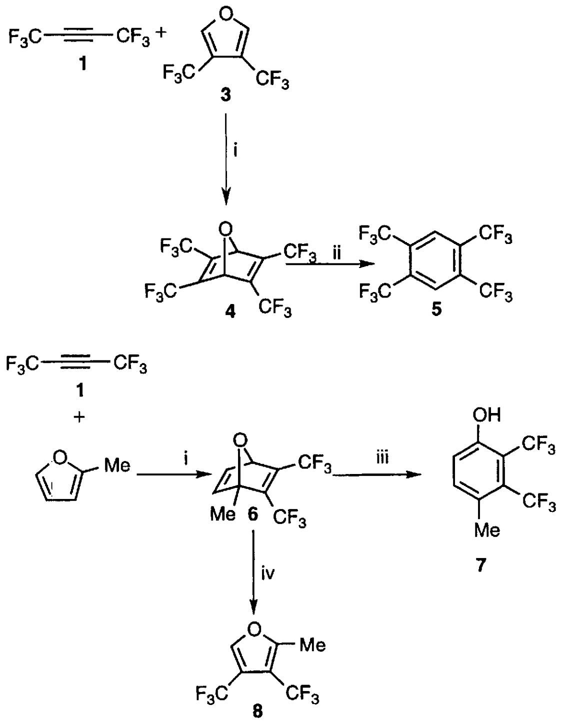
Cycloadducts, formed by addition of hexafluorobut-2-yne, may be transformed into bis(trifluoromethyl)-benzene, -phenol and -furan derivatives. Tetrakis(trifluoromethyl)benzene may also be produced. Heptafluorobut-2-ene 2 is also a very efficient dienophile for reactions with cyclopentadiene and furan. Reaction of 2 with furan derivatives at elevated temperatures gives a very effective 'one pot' synthesis of 3,4-bis(trifluoromethyl)furan derivatives.

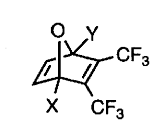
Other workers[1-6] have demonstrated that hexafluorobut-2-yne **1** is an excellent synthon for introducing two trifluoromethyl groups into furan or benzenoid systems, through initial cycloaddition reactions, followed by various ring-opening procedures on the products (see later for examples from our own work). Hexafluorobut-2-yne **1** *could* be accessible, but currently it is either very expensive to purchase or unattractive to make in the laboratory because the most efficient procedure involves anhydrous hydrogen fluoride.[7] In contrast, 1,1,1,2,4,4,4-heptafluorobut-2-ene **2** is relatively easy to make in the laboratory, from hexachlorobuta-1,3-diene and potassium fluoride,[8] and we have recently shown that hexafluorobut-2-yne **1** can be obtained from **2**.[9] In this paper, we describe further use of hexafluorobut-2-yne **1** for introduction of trifluoromethyl groups into aromatic systems, but we also demonstrate for the first time the direct use of **2** in cycloadditions, without the need to form the butyne **1** as an intermediate. Some of these reactions have been remarkably successful, and one-step procedures have been developed for bis(trifluoromethyl)furan derivatives.

Results and discussion

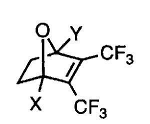
Hexafluorobut-2-yne **1** reacts readily with furan and its derivatives to give cycloaddition products,[1] and Scheme 1 shows further examples of this process. Moreover, we have shown that these cycloaddition products may be further transformed to bis(trifluoromethyl)furan derivatives, first by selective reduction of the unsubstituted double bond, followed by pyrolytic elimination of ethene. We have also shown that the cycloadducts may be transformed into bis(trifluoromethyl)-benzene derivatives by reaction with a low-valent titanium reagent (titanium tetrachloride–lithium aluminium hydride–triethylamine), and also into phenol derivatives by the action of boron trifluoride–diethyl ether complex.



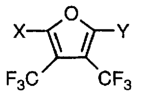
Scheme 1 *Reagents and conditions:* i, 100–200 °C; ii, $TiCl_4$–$LiAlH_4$–Et_3N; iii, BF_3–Et_2O; iv, H_2–Pt/C; 400 °C



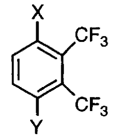
9 X=H, Y=CH_2OH
10 X=CH_2OH, Y=CH_2OH
11 X=H, Y=Br



12 X=H, Y=CH_2OH
13 X=CH_2OH, Y=CH_2OH



14 X=H, Y=CH_2OH
15 X=CH_2OH, Y=CH_2OH

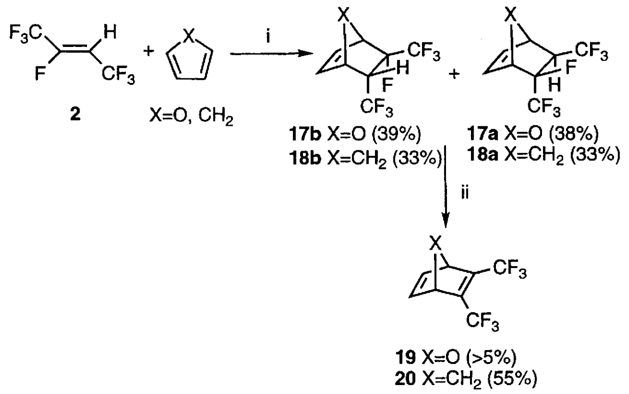


16 X=H, Y=CH_2OH

Further examples of compounds that we have produced by this methodology include **9–16**, and therefore hexafluorobut-2-yne **1** is a potentially useful 'building block' for the synthesis of a variety of molecules containing two trifluoromethyl groups.

We now find, however, that more easily accessible[8] heptafluorobut-2-ene **2** participates easily in cycloaddition reactions to both furan and cyclopentadiene, and the reaction temperatures required are comparable to those used for hexafluorobutyne **1**. Examples are shown in Scheme 2. Characterisation of the geometric isomers of **17a** and **17b**, and **18a** and **18b** was possible on the basis of their ^1H NMR spectra, where coupling of the bridgehead hydrogen to the adjacent $C\mathit{H}CF_3$ site depends on the dihedral angle (Karplus rule[10]). For the isomer with the hydrogen in the *exo* position, *J* values are of the order of 4 Hz, while for the corresponding *endo* hydrogen, the values were approximately zero.

Adducts **17a** and **17b**, and **18a** and **18b** reacted with potassium *tert*-butoxide, and diene **20** resulted from **18a** and



Scheme 2 *Reagents and conditions*: i, 120 °C, 8 h; ii, Bu^{t}OK, Bu^{t}OH, reflux

Table 1 Reaction of **2** with furan, effect of temperature

		Product (%)		
Conditions	T/°C	**17a, 17b**	**19**	**3**
a	120	78	—	—
b	150	5	19	—
c	150	8	4	—
d	200	—	—	25
e	300	—	—	70

[a] Carius tube, agitated by horizontal rotation, for 4 d. [b] Quartz tube (*ca.* 5 cm^3 volume), no agitation. [c] As *a*, but with water as solvent. [d] Rocked sealed metal tube, 1 week. [e] Rocked sealed metal tube, 8 h.

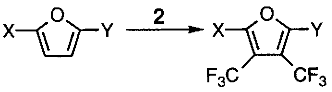


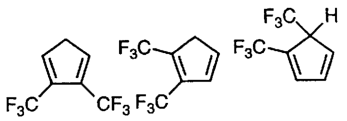
Table 2 Synthesis of 3,4-bis(trifluoromethyl)furan derivatives

Starting furan			Product furan			
X	Y	T/°C	X	Y	Compound	Yield (%)
H	H	300	H	H	**3**	70
Me	Me	200	Me	Me	**21**	61
H	CN	250	H	CN	**22**	71
			H	H	**3**	21
H	CO_2H	300	H	H	**3**	39
H	CO_2Me	250	H	CO_2Me	**23**	85
H	CO_2Et	250	H	CO_2Et	**24**	89
H	CHO	225	H	CHO	**25**	51

18b. However, an intractable tar resulted from **17a** and **17b**, and characterisation could not be made. It seems reasonable to conclude, therefore, that opening of the oxygen bridge occurs in **19**, followed by a polymerisation process.

We noted in the product mixture from the reaction of **2** with furan a small amount of the product of dehydrofluorination **19**, and therefore, we explored the effect of reaction temperature on the product range (Table 1). Indeed, the percentage of diene **19** increased at first with increasing temperature, but we also noted that at 200 °C, bis(trifluoromethyl)furan **3** was also present. This encouraged further investigation of temperature and, quite remarkably, at 300 °C, **3** was not only the sole product, but also present in 70% yield. Therefore, this constitutes a useful 'one-pot' synthesis of **3**.

Table 2 demonstrates that this process may also be applied to some furan derivatives, and 2-ethyl furanoate is particularly effective. In contrast, decarboxylation occurred starting with 2-furoic acid, but the corresponding product **26** was obtained indirectly by the basic hydrolysis of the ester derivatives **23** and **24**.

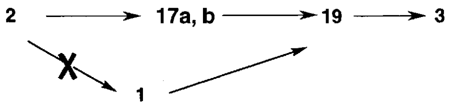


27a **27b** **27c**

Table 3 Attempted syntheses of bis(trifluoromethyl)cyclopentadienes

	Products (%)		
T/°C	**18a, 18b**	**20**	**27a–c**
400	40		
450	6	18	6
500	7	17	5

The reaction pathway in these 'one-pot' reactions clearly involves the cycloadducts formed from heptafluorobutene **2**, rather than possible preliminary thermal elimination of hydrogen fluoride from **2** giving **1**, followed by cycloaddition to furan (Scheme 3). This follows from the observation that no significant formation of **1** results from the heating of **2** under equivalent conditions.



Scheme 3

We investigated corresponding approaches to 'one-pot' procedures for the synthesis of bis(trifluoromethyl)cyclopentadiene **27** and derivatives, but up to 200 °C, little elimination of hydrogen fluoride occurred from **18a** and **18b**, and at higher temperatures, only low yields of diene **20** were obtained. The difficulty does not rest solely with the stage involving the elimination of hydrogen fluoride because the pyrolysis of diene **20** at 30 °C gave none of cyclopentadiene **27**, although small amounts of **27a–27c** were obtained at even higher temperatures (Table 3). We can attribute the difference between formation of furan **3** and **27** as being due to the driving force for formation of an aromatic molecule in the case of **3**.

Experimental

^1H NMR spectra were recorded on a Bruker AC250 spectrometer operating at 250.13 MHz, a Varian Gemini VXR200 spectrometer operating at 199.98 MHz or a Varian VXR400S spectrometer operating at 399.96 MHz. ^{19}F NMR spectra were recorded on the Bruker AC250 spectrometer operating at 235.34 MHz or on the Varian VXR400S spectrometer operating at 376.29 MHz. ^{13}C spectra were recorded on the Varian VXR400S spectrometer operating at 100.58 MHz, or the Varian Gemini VXR200 spectrometer operating at 50.29 MHz. All spectra were recorded with Me_4Si and fluorotrichloromethane as internal references. J Values are given in Hz. GLC–MS mass spectra were recorded on a Fisons Trio 1000 spectrometer linked to a Hewlett Packard 5890 series II gas chromatograph fitted with a 20 m cross-linked methyl silicone capillary column. All GLC–MS mass spectra were generated by electron impact. FAB mass spectra were recorded using a VG7070E spectrometer, and glycerol as a solvent. FTIR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. Solid samples were run as KBr discs, liquid samples were run as thin films between KBr plates, and volatile samples were run in a gas cell fitted with KBr plates. Ether refers to diethyl ether and petrol refers to light petroleum (bp 40–60 °C).

Synthesis of 2,3,5,6-tetrakis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hepta-2,5-diene 4

A mixture of 3,4-bis(trifluoromethyl)furan **3** (3.0 g, 0.017 mol) and hexafluorobut-2-yne **1** (3.35 g, 0.02 mol) was heated at 100 °C in a rocking furnace for 6 h. The resulting crude white solid was sublimed (50 °C oil bath temperature) to produce 2,3,5,6-*tetrakis*(*trifluoromethyl*)-7-*oxabicyclo*[2.2.1]*hepta*-2,5-*diene*[1] **4** (5.12 g, 85%) (Found: C, 32.5; F, 62.5. Calc. for $C_{10}H_2F_{12}O$: C, 32.7; H, 0.005; F, 62.3%); ν_{max}/cm^{-1} 3050, 1700, 1350, 1275, 1200–1100 and 1050; δ_H(250 MHz; $CDCl_3$) 5.65 (s, C*H*); δ_F(235 MHz; $CDCl_3$) −63.4 (s, C*F*$_3$); *m*/*z* 366 (M^+, 19%), 204 (100) and 69 (95).

Synthesis of 1,2,4,5-tetrakis(trifluoromethyl)benzene 5

Tetrahydrofuran (100 cm^3) was added to titanium tetrachloride (10 cm^3, 0.60 mol) at 0 °C, with stirring, under an atmosphere of dry nitrogen. To this suspension lithium aluminium hydride (0.27 g) and triethylamine (1.6 g, 0.19 mol) were added separately. After heating at reflux for 15 min, the reaction was allowed to cool to room temperature before 2,3,5,6-tetrakis-(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene **4** (2.0 g, 0.006 mol) was added. Once the addition was completed the reaction was stirred at room temperature for 48 h, then poured into water (40 cm^3) and extracted with dichloromethane. The dichloromethane solution was dried ($MgSO_4$) and evaporated. Sublimation of the crude solid (60 °C oil bath temperature) gave 1,2,4,5-tetrakis(trifluoromethyl)benzene[11] **5** (1.3 g, 60%) (Found: C, 35.5; F, 64.8. Calc. for $C_{10}H_2F_{12}$: C, 34.3; H, 0.005; F, 65.1%); ν_{max}/cm^{-1} 3010, 1350–1250, 1200–1075, 900 and 750; δ_H(250 MHz; $CDCl_3$) 8.5 (s, C*H*); δ_F(235 MHz; $CDCl_3$) −59.5 (s, C*F*$_3$); *m*/*z* 350 (M^+, 37%), 201 (100) and 69 (35).

Synthesis of 1-methyl-2,3-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hepta-2,5-diene 6

A mixture of 2-methylfuran (8.4 g, 0.1 mol), **1** (16 g, 0.1 mol) and tetrahydrofuran (14 g) was heated at 130 °C in a rocking furnace for 24 h. Excess **1** was removed under vacuum (100 mmHg) to leave a liquid (38.1 g). This liquid was distilled to give 1-*methyl*-2,3-*bis*(*trifluoromethyl*)-7-*oxabicyclo*[2.2.1]-*hepta*-2,5-*diene* **6** (21.1 g, 86%), bp 118 °C at 760 mmHg (Found: C, 44.5; H, 2.45; F, 47.1. Calc. for $C_9H_7F_6O$: C, 44.2; H, 2.45; F, 46.7%); ν_{max}/cm^{-1} 3000, 1700, 1400, 1375–1100, 950, 850 and 700–600; δ_H(250 MHz; $CDCl_3$) 2.00 (3 H, s, C*H*$_3$), 5.66 (1 H, s, 4-C*H*), 7.20 (1 H, s, 5-C*H*) and 7.30 (1 H, s, 6-C*H*); δ_F(235 MHz; $CDCl_3$) −62.23 (3 F, s, 2-CC*F*$_3$) and −63.37 (3 F, s, 3-CC*F*$_3$); *m*/*z* 244 (M^+, 19%) and 218 (100).

Synthesis of 1-methyl-2,3-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hept-2-ene

1-Methyl-2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene (21.0 g, 0.086 mol) was dissolved in tetrahydrofuran (100 cm^3) and hydrogenated in the presence of a platinum catalyst on activated carbon (0.1 g) in a Parr apparatus. The hydrogen uptake ceased sharply after the consumption of one equivalent of hydrogen. The reaction mixture was filtered through a bed of Celite and distilled to yield 1-*methyl*-2,3-*bis*(*trifluoromethyl*)-7-*oxabicyclo*[2.2.1]*hept*-2-*ene* (19.8 g, 93%), bp 104 °C at 50 mmHg (Found: C, 43.9; H, 3.2; F, 47.1. $C_9H_8F_6O$ requires C, 43.9; H, 3.25; F, 46.7%); ν_{max}/cm^{-1} 3000–2950, 1700, 1400, 1375–1100, 900 and 775; δ_H(250 MHz; $CDCl_3$) 1.70 (3 H, s, C*H*$_3$), 1.90 (2 H, s, C*H*$_2$), 2.10 (2 H, s, 6-C*H*$_2$) and 5.70 (1 H, s, 4-C*H*); δ_F(235 MHz; $CDCl_3$) −59.83 (3 F, s, 2-CC*F*$_3$) and −60.71 (3 F, s, 3-CC*F*$_3$); *m*/*z* 218 (M^+ − 28, 100%) and 149 (40).

Synthesis of 2-methyl-3,4-bis(trifluoromethyl)furan 8

1-Methyl-2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hept-2-ene (20.0 g, 0.05 mol) was passed dropwise through a glass tube packed with glass wool at 400 °C in a slow current of nitrogen. Volatile material was collected in a trap maintained at −78 °C and was distilled to give 2-*methyl*-3,4-*bis*(*trifluoromethyl*)*furan* **8** (10.5 g, 96%), bp 88 °C at 760 mmHg (Found: C, 38.8; H, 2.0; F, 52.7. $C_7H_4F_6O$ requires C, 38.6; H, 1.8; F, 52.3%); ν_{max}/cm^{-1} 3100, 1600, 1450, 1250–1100, 950 and 800–700; δ_H(250 MHz; $CDCl_3$) 2.41 (3 H, s, C*H*$_3$) and 7.60 (1 H, s, C*H*); δ_F(235 MHz; $CDCl_3$) −57.57 (3 F, s, 4-CC*F*$_3$) and −60.00 (3 F, s, 3-CC*F*$_3$); *m*/*z* 218 (M^+, 100%).

Synthesis of 4-methyl-2,3-bis(trifluoromethyl)phenol 7

A mixture of 1-methyl-2,3-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hept-2,5-diene **6** (1.0 g, 0.04 mol) and boron trifluoride–diethyl ether complex (0.05 mol) was stirred at room temperature for 3 h, then neutralised with aqueous potassium carbonate and extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated under reduced pressure to leave an orange solid (0.71 g). Sublimation (100 °C oil bath temperature) gave 4-*methyl*-2,3-*bis*(*trifluoromethyl*)*phenol* **7** (0.58 g, 64%) (Found: C, 44.4; H, 2.1; F, 46.7. $C_9H_4F_6O$ requires C, 44.25; H, 2.4; F, 46.7%); ν_{max}/cm^{-1} 3600–3100, 2975–2800, 1800, 1650 and 1500–1100; δ_H(250 MHz; $CDCl_3$) 2.48 (3 H, s, C*H*$_3$), 7.33 (2 H, br, C*H* and C*H*) and 9.80 (1 H, br, O*H*); δ_F(235 MHz; $CDCl_3$) −53.70 (3 F, s, 2-CC*F*$_3$) and −55.00 (3 F, s, 3-CC*F*$_3$); *m*/*z* 244 (M^+, 100%) and 196 (63).

Synthesis of 1-(hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxa-bicyclo[2.2.1]hepta-2,5-diene 9

A mixture of 2-(hydroxymethyl)furan (10.0 g, 0.1 mol), hexafluorobut-2-yne **1** (16.0 g, 0.1 mol) and tetrahydrofuran (14 g) was heated at 130 °C in a rocking furnace for 24 h. Excess **1** was removed under vacuum (100 mmHg) to leave a liquid (40.0 g), which was distilled to give 1-(*hydroxymethyl*)-2,3-*bis*(*trifluoromethyl*)-7-*oxabicyclo*[2.2.1]*hepta*-2,5-*diene* **9** (23.9 g, 92%), bp 142 °C at 760 mmHg (Found: C, 41.2; H, 2.1; F, 44.4. $C_9H_6F_6O_2$ requires C, 41.5; H, 2.3; F, 43.9%); ν_{max}/cm^{-1} 3600–3100, 1625, 1375–1100, 900 and 700; δ_H(250 MHz; $CDCl_3$) 3.00 (1 H, br, O*H*), 4.23 (2 H, s, C*H*$_2$), 5.61 (1 H, s, 4-C*H*), 7.08 (1 H, s, 5-C*H*) and 7.21 (1 H, s, 6-C*H*); δ_F(235 MHz; $CDCl_3$) −62.54 (br, C*F*$_3$); *m*/*z* 260 (M^+, 2%) and 182 (100).

Synthesis of 1-(hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxa-bicyclo[2.2.1]hept-2-ene 12

1-(Hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hepta-2,5-diene **9** (18.2 g, 0.07 mol) was dissolved in tetrahydrofuran (100 cm^3) and hydrogenated in the presence of a platinum catalyst on activated carbon (0.1 g) in a Parr apparatus. The hydrogen uptake ceased sharply after the consumption of one equivalent of hydrogen. The reaction mixture was filtered through a bed of Celite and distilled to give 1-(*hydroxymethyl*)-2,3-*bis*(*trifluoromethyl*)-7-*oxabicyclo*[2.2.1]-*hept*-2-*ene* **12** (17.5 g, 90%), bp 105 °C at 50 mmHg (Found: C, 41.0; H, 2.9; F, 43.4. $C_9H_8F_6O_2$ requires C, 41.2, H, 3.0; F, 43.5%); ν_{max}/cm^{-1} 3600–3100, 3000–2800, 1700, 1400–1100, 900–850 and 700; δ_H(250 MHz; CD_3COCD_3) 1.88 (2 H, m, 5-C*H*$_2$), 2.13 (2 H, m, 6-C*H*$_2$), 2.54 (1 H, m, O*H*), 4.18 (2 H, m, C*H*$_2$OH) and 5.17 (1 H, m, 4-C*H*); δ_F(235 MHz; CD_3COCD_3) −59.97 (3 F, s, 2-CC*F*$_3$) and −60.13 (3 F, s, 3-CC*F*$_3$); *m*/*z* 234 (M^+ − 28, 100%) and 185 (86).

Synthesis of 2-(hydroxmethyl)-3,4-bis(trifluoromethyl)furan 14

1-(Hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hept-2-ene **12** (16.0 g, 0.06 mol) was passed dropwise through a glass tube packed with glass wool at 400 °C in a slow current of nitrogen. Volatile material was collected in a trap maintained at −78 °C, and distillation gave 2-(*hydroxymethyl*)-3,4-*bis*(*trifluoromethyl*)*furan* **14** (13.8 g, 97%), bp 108 °C at 760 mmHg (Found: C, 35.7; H, 1.8; F, 49.2. $C_7H_4F_6O_2$ requires C, 35.9; H, 1.7; F, 48.7%); ν_{max}/cm^{-1} 3600–3000, 2800, 1575, 1400, 1325–1275, 1200, 1100, 900 and 700; δ_H(250 MHz; $CDCl_3$) 3.26 (1 H, br, O*H*), 4.26 (2 H, s, C*H*$_2$) and 7.40 (1 H, s, C*H*); δ_F(235 MHz; $CDCl_3$) −55.78 (3 F, s, 3-CC*F*$_3$) and −58.29 (3 F, s, 4-CC*F*$_3$); *m*/*z* 234 (M^+, 99%) and 135 (100).

Synthesis of 2,3-bis(trifluoromethyl)benzyl alcohol 16

Tetrahydrofuran (100 cm^3) was added to titanium tetrachloride (10 cm^3, 0.60 mol) at 0 °C, with stirring, under an atmosphere of dry nitrogen. To this suspension lithium aluminium hydride (0.27 g) and triethylamine (1.6 g, 0.016 mol) were added *separately*. After heating at reflux for 15 min, the reaction was allowed to cool to room temperature before 1-(hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene **9** (2.0 g, 7.7 mmol) was added. Once the addition was completed the reaction was stirred at room temperature for 48 h, then poured into water (40 cm^3) and extracted with dichloromethane. The dichloromethane solution was dried ($MgSO_4$) and evaporated, and the desired product was isolated by preparative scale GLC (10% SE30, 100 °C), giving 2,3-*bis(trifluoromethyl)benzyl alcohol* **16** (1.2 g, 65%) (Found C, 4.5; H, 2.4. $C_9H_6F_6O$ requires C, 44.2; H, 2.45; F, 46.72%); ν_{max}/cm^{-1} 3600–3100, 2900, 1300, 1200–1100, 800 and 750; δ_H(250 MHz; CD_3COCD_3) 3.69 (1 H, br, O*H*), 5.71 (2 H, s, C*H*$_2$) and 8.71–9.06 (3 H, m, C*H*); δ_F(235 MHz; CD_3COCD_3) −54.83 (3 F, s, 2-CC*F*$_3$) and −57.78 (3 F, s, 3-CC*F*$_3$); *m/z* 244 (M^+, 27%), 175 (100) and 127 (86).

Synthesis of 1,4-bis(hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene 10

A mixture of 2,5-bis(hydroxymethyl)furan (12.8 g, 0.1 mol) **1** (16.0 g, 0.1 mol) and tetrahydrofuran (20 g) was heated at 100 °C in a rocking furnace for 24 h. Excess **1** was removed under vacuum (100 mmHg) to leave a colourless liquid (48.4 g). Solvent was removed under reduced pressure to leave an off-white solid, which was recrystallised from MeOH to give 1,4-*bis(hydroxymethyl)*-2,3-*bis(trifluoromethyl)*-7-*oxabicyclo*[2.2.1]*hepta*-2,5-*diene* **10** (25.1 g, 87%), mp 130 °C (Found: C, 41.3; H, 2.75; F, 39.2. $C_{10}H_8F_6O_3$ requires C, 41.3; H, 2.75; F, 39.3%); ν_{max}/cm^{-1} 3600–3100, 2900, 1625, 1350–1050, 875 and 700; δ_H(250 MHz; CD_3COCD_3) 4.11 (4 H, s, C*H*$_2$), 4.42 (2 H, br, O*H*), 7.21 (2 H, s, C*H*); δ_F(235 MHz; CD_3COCD_3) −60.97 (s, C*F*$_3$); *m/z* 271 (M^+ − 19, 4%), 213 (100) and 145 (62).

Synthesis of 1,4-bis(hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hept-2-ene 13

1,4-Bis(hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hepta-2,5-diene **10** (20.2 g, 0.07 mol) was dissolved in tetrahydrofuran (100 cm^3) and hydrogenated in the presence of a platinum catalyst on activated carbon (0.1 g) in a Parr apparatus. The hydrogen uptake ceased sharply after the consumption of one equivalent of hydrogen. The reaction mixture was filtered through a bed of Celite and evaporation of the solvent gave an off-white solid, which was recrystallised from MeOH to give 1,4-*bis(hydroxymethyl)*-2,3-*bis(trifluoromethyl)*-7-*oxabicyclo*[2.2.1]*hept*-2-*ene* **13** (17.3 g, 85%), mp 152 °C (Found: C, 41.1; H, 3.4; F, 39.5. $C_{10}H_{10}F_6O_3$ requires C, 41.0; H, 3.4; F, 39.0%); ν_{max}/cm^{-1} 3500–3200, 2950–2800, 1450, 1400–1050, 900 and 700; δ_H(250 MHz; CD_3COCD_3) 1.52–2.04 (4 H, m, 5 and 6-C*H*$_2$), 3.99 (4 H, s, C*H*$_2$OH) and 4.20 (2 H, br, O*H*); δ_F(235 MHz; CD_3COCD_3) −59.85 (s, C*F*$_3$); *m/z* 263 (M^+ − 19, 54%), 212 (100) and 149 (33).

Synthesis of 2,5-bis(hydroxymethyl)-3,4-bis(trifluoromethyl)-furan 15

1,4-Bis(hydroxymethyl)-2,3-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hept-2-ene **13** (8.0 g, 0.027 mol) was passed dropwise through a glass tube packed with glass wool at 400 °C in a slow current of nitrogen. Volatile material was collected in a trap maintained at −78 °C, and recrystallisation from MeOH gave 2,5-*bis(hydroxymethyl)*-3,4-*bis(trifluoromethyl)furan* **15** (6.9 g, 96%), mp 64 °C (Found: C, 36.3; H, 2.3; F, 43.2. $C_8H_6F_6O_3$ requires C, 36.4; H, 2.3; F, 43.1%); ν_{max}/cm^{-1} 3600–3050, 2950, 1600, 1425, 1350, 1225–1176, 1100, 750 and 700; δ_H(250 MHz; CD_3COCD_3) 4.66 (4 H, s, C*H*$_2$) and 5.00 (2 H, br, O*H*); δ_F(235 MHz; CD_3COCD_3) −56.46 (s, C*F*$_3$); *m/z* 264 (M^+, 48%) and 247 (100).

Synthesis of 1-bromo-2,3-bis(trifluoromethyl)-7-oxabicyclo-[2.2.1]hepta-2,5-diene 11

A mixture of 2-bromofuran (6.4 g, 0.045 mol), hexafluorobut-2-yne **1** (8.0 g, 0.05 mol) and tetrahydrofuran (14 g) was heated at 140 °C in a rocking furnace for 24 h. Excess **1** was removed under vacuum (100 mmHg) to leave a dark brown liquid (28.4 g) and the desired product was isolated by preparative scale GLC (10% SE30, 110 °C), giving 1-*bromo*-2,3-*bis(trifluoromethyl)*-7-*oxabicyclo*[2.2.1]*hepta*-2,5-*diene* **11** (1.5 g, 11%) (Found: C, 33.0; H, 1.4; F, 39.4. $C_8H_3BrF_6O$ requires C, 32.9; H, 1.0; F, 39.1%); ν_{max}/cm^{-1} 3010, 1700, 1350, 1100, 100–850 and 700; δ_H(250 MHz; $CDCl_3$) 5.53 (1 H, s, 4-C*H*) and 7.10–7.16 (2 H, m, 5 and 6-C*H*); δ_F(235 MHz; $CDCl_3$) −61.90 (3 F, s, 2-CC*F*$_3$) and −62.99 (3 F, s, 3-CC*F*$_3$); *m/z* 281 (M^+ − 26, 100%) and 201 (60).

Synthesis of isomers of 5-fluoro-5,6-bis(trifluoromethyl)-7-oxa-bicyclo[2.2.1]hept-2-ene 17a,b

A mixture of furan (4.5 g, 0.066 mol) and 1,1,1,2,4,4,4-heptafluorobut-2-ene **2** (12.0 g, 0.066 mol) was heated in a rocking furnace for 24 h. Excess **2** was removed under vacuum (100 mmHg), and the residual liquid was shown to contain two pairs of *diastereoisomers* which were isolated by preparative scale GLC (10% SE30, 50 °C).

5-*exo*-Fluoro-5,6-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]-hept-2-ene 17a. (6.8 g, 38%) (Found: C, 38.8; H, 2.11; F, 52.9. $C_8H_5F_7O$ requires C, 38.5; H, 2.0; F, 53.2%); ν_{max}/cm^{-1} 3000, 1400, 1300–1125, 900, 700 and 675; δ_H(250 MHz; $CDCl_3$) 3.17 (1 H, dq, *J* 12.2 and 9.0, C*H*CF$_3$), 5.42 (2 H, m, C*H*O), 6.42 (1 H, m, C*H*CHO) and 6.74 (1 H, m, C*H*CHO); δ_F(235 MHz; $CDCl_3$) −64.96 (3 F, s, CFC*F*$_3$), −75.99 (3 F, s, CHC*F*$_3$) and −182.91 (1 F, s, C*F*); *m/z* 249 (M^+ + 1, 5%), 214 (51), 181 (23), 145 (50), 69 (24) and 68 (100).

5-*endo*-Fluoro-5,6-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]-hept-2-ene 17b. (6.8 g, 39%) (Found: C, 38.7; H, 2.22. $C_8H_5F_7O$ requires C, 38.5; H, 2.0%); ν_{max}/cm^{-1} 3000, 1400, 1300–1125, 900, 700 and 675; δ_H(250 MHz; $CDCl_3$) 3.62 (1 H, dqd, *J* 12.6, 8.9 and 4.3, C*H*CF$_3$), 5.40 (2 H, m, C*H*O), 6.68 (1 H, m, C*H*CHO) and 6.91 (1 H, m, C*H*CHO); δ_F(235 MHz; $CDCl_3$) −68.81 (3 F, s, CFC*F*$_3$), −79.23 (3 F, s, CHC*F*$_3$) and −183.75 (1 F, s, C*F*); *m/z* 214 (M^+ − 34, 42%), 145 (100) and 69 (18).

Synthesis of isomers of 5-fluoro-5,6-bis(trifluoromethyl)-bicyclo[2.2.1]hept-2-ene 18a,b

A mixture of cyclopentadiene (4.35 g, 0.066 mol) and 1,1,1,2,4,4,4-heptafluorobut-2-ene **2** (12.0 g, 0.066 mol) was heated in a rocking furnace for 24 h. Excess **2** was removed under vacuum (100 mmHg), and the residual liquid (16.1 g) was shown to contain two pairs of *diastereoisomers* which were isolated by preparative scale GLC (10% SE30, 50 °C).

5-*exo*-Fluoro-5,6-bis(trifluoromethyl)bicyclo[2.2.1]hept-2-ene 18a. (5.4 g, 33%) (Found: C, 44.0; H, 2.8; F, 53.6. $C_9H_7F_7$ requires C, 43.6; H, 2.8; F, 53.6%); ν_{max}/cm^{-1} 2950, 1375, 1250, 1200–1100, 725 and 600–400; δ_H(250 MHz; $CDCl_3$) 1.37 (2 H, AB, *J* 7.9, C*H*$_2$), 2.55 (1 H, m, C*H*CF$_3$), 3.23 (2 H, m, C*H*CH$_2$), 5.96 (1 H, m, C*H*CH) and 6.20 (1 H, m, CHC*H*); δ_F(235 MHz; $CDCl_3$) −65.16 (3 F, s, CFC*F*$_3$), −77.18 (3 F, s, CHC*F*$_3$ and −176.86 (1 F, s, C*F*); *m/z* 248 (M^+, 2%), 109 (10) and 66 (100).

5-*endo*-Fluoro-5,6-bis(trifluoromethyl)bicyclo[2.2.1]hept-2-ene 18b. (5.4 g, 33%) (Found: C, 44.0; H, 2.8; F, 53.6. $C_9H_7F_7$ requires C, 43.6; H, 2.8; F, 53.6%); ν_{max}/cm^{-1} 2950, 1375, 1250, 1200–1100, 725 and 600–400; δ_H(250 MHz; $CDCl_3$) 2.00 (2 H, AB, *J* 7.9, C*H*$_2$), 2.77 (1 H, m, C*H*CF$_3$), 3.40 (2 H, m, C*H*CH$_2$), 6.22 (1 H, m, C*H*CH) and 6.43 (1 H, m, CHC*H*); δ_F(235 MHz; $CDCl_3$) −65.16 (3 F, s, CFC*F*$_3$) −78.73 (3 F, s, CHC*F*$_3$) and −180.26 (1 F, s, C*F*); *m/z* 248 (M^+, 2%), 109 (9) and 66 (100).

Synthesis of 2,3-bis(trifluoromethyl)bicyclo[2.2.1]hepta-2,5-diene 20

A mixture of **18a** and **18b** (3.7 g, 0.015 mol) was added dropwise to a stirred solution of potassium *tert*-butoxide (3.35 g, 0.035 mol) in *tert*-butyl alcohol (25 cm^3). After heating at reflux for 1 h, the reaction mixture was poured into water (15 cm^3), extracted with ether, dried (MgSO$_4$) and evaporated to give a pale yellow liquid (3.8 g). The desired compound was isolated by preparative scale GLC (10% SE30, 100 °C), giving 2,3-*bis*(*trifluoromethyl*)*bicyclo*[2.2.1]*hepta*-2,5-*diene* **20** (1.9 g, 55%) (Found: C, 47.7; H, 2.6; F, 50.5. Calc. for $C_9H_6F_6$: C, 47.4; H, 2.6; F, 50.0%); ν_{max}/cm^{-1} 3000, 2925, 1400–1100, 800–700 and 550–475; δ_H(250 MHz; CDCl$_3$) 2.29 (2 H, m, C*H*$_2$), 3.93 (2 H, s, C*H*CH$_2$) and 6.96 (2 H, s, C*H*CH); δ_C(100 MHz; CDCl$_3$) 53.07 (s, *C*H$_2$), 74.12 (s, *C*HCH$_2$), 122.8 (q, *J* 269.4, *C*F$_3$), 143.0 (s, *C*HCH) and 149.5 (q, *J* 17.9, *C*CF$_3$); δ_F(235 MHz; CDCl$_3$) −62.04 (s, C*F*$_3$); *m*/*z* 228 (M$^+$, 19%) and 159 (100)

Synthesis of 3,4-bis(trifluoromethyl)furan 3

Fluoroalkene **2** (12.0 g, 65.9 mmol) was transferred, under reduced pressure, into a sealed metal tube which had previously been charged with furan (2.8 g, 41.2 mmol) under a counter current of dry nitrogen. The tube was evacuated, sealed and rocked in a furnace maintained at 300 °C for 3 d. It was then cooled to liquid air temperature, opened and unreacted **2** was removed by distillation at room temperature and atmospheric pressure. The residual solution was filtered and distilled to give 3,4-bis(trifluoromethyl)furan **3**, (5.9 g, 70%) bp 87–89 °C (lit.,[1] 88–89 °C) (Found: C, 35.2; H, 1.1. Calc. for $C_6H_2OF_6$: C, 35.3; H, 1.0%); ν_{max}/cm^{-1} 3100, 1550, 1350–1150, 900, 750, 600 and 400; δ_H(250 MHz; CDCl$_3$) 7.85 (s, C*H*); δ_C(100 MHz; CDCl$_3$) 115.8 (q, *J* 41.0, *C*CF$_3$), 120.0 (q, *J* 267.8, *C*F$_3$) and 140.4 (s, *C*H); δ_F(235 MHz; CDCl$_3$) −59.87 (s, C*F*$_3$); *m*/*z* 204 (M$^+$, 88%),185 (100) and 69 (35).

Synthesis of 2,5-dimethyl-3,4-bis(trifluoromethyl)furan 21

Fluoroalkene **2** (6.8 g, 37.4 mmol) was transferred, under reduced pressure, into a sealed metal tube which had previously been charged with 2,5-dimethylfuran (2.0 g, 20.8 mmol) under a counter current of dry nitrogen. The tube was evacuated, sealed and heated in a furnace maintained at 200 °C for 2 d. It was then cooled to liquid air temperature, opened and unreacted **2** was removed by distillation at room temperature and atmospheric pressure. The residual solution was filtered and distilled to give 2,5-dimethyl-3,4-bis(trifluoromethyl)furan **21** (2.96 g, 61%), bp 52–56 °C at 12 mmHg (lit.,[6] 77–78 °C at 88 mmHg); ν_{max}/cm^{-1} 2975–2850, 2350, 1700–1400, 1150 and 1000; δ_H(250 MHz; CDCl$_3$) 2.47 (s, C*H*$_3$); δ_C(100 MHz; CDCl$_3$) 12.8 (s, *C*H$_3$), 109.8 (q, *J* 19.6, *C*CF$_3$), 123.2 (q, *J* 264.9, *C*F$_3$) and 152.4 (s, *C*CH$_3$); δ_F(235 MHz; CDCl$_3$) −55.72 (s, C*F*$_3$); *m*/*z* 232 (M$^+$, 50%), 163 (73), 69 (12) and 43 (100) by comparison with literature data.[6]

Synthesis of 3,4-bis(trifluoromethyl)-2-furonitrile 22

Fluoroalkene **2** (1.2 g, 6.6 mmol) was transferred, under reduced pressure, into a quartz tube which had previously been charged with 2-furonitrile (0.4 g, 4.3 mmol) under a counter current of dry nitrogen. The tube was evacuated, sealed and heated in a furnace maintained at 250 °C for 24 h. It was then cooled to liquid air temperature, opened and unreacted **2** was removed by distillation at room temperature and atmospheric pressure. The residual solution was filtered and was shown by GLC–MS to consist of two components in a 7:2 ratio. Distillation of this mixture at 0 °C and 0.1 mbar gave 3,4-bis(trifluoromethyl)furan **3** (0.2 g, 21%), as above.

This left a pale brown liquid identified as 3,4-*bis*(*trifluoromethyl*)-2-*furonitrile* **22** (0.7 g, 71%). An analytical sample was isolated by preparative GLC (SE30, 50 °C) (Found: C, 36.9; H, 0.5; N, 6.3. C_7HF_6NO requires C, 36.7; H, 0.4; N, 6.1%); ν_{max}/cm^{-1} 2950, 2250, 1750–1500, 1375–1100, 800 and 550–425; δ_H(250 MHz; CDCl$_3$) 7.62 (s, C*H*); δ_C(100 MHz; CDCl$_3$) 115.17 (s, *C*CN), 117.44 (q, *J* 39.7, *C*CF$_3$), 118.24 (q, *J* 40.3, *C*CF$_3$), 120.49 (q, *J* 269.7, *C*F$_3$), 121.33 (q, *J* 269.6, *C*F$_3$), 121.54 (s, *C*N) and 146.24 (s, *C*H); δ_F(235 MHz; CDCl$_3$) −59.37 (s, C*F*$_3$) and −64.32 (s, C*F*$_3$); *m*/*z* 229 (M$^+$, 95%), 210 (100) and 69 (86).

Attempted synthesis of 3,4-bis(trifluoromethyl)-2-furoic acid 26

Fluoroalkene **2** (11.1 g, 61.0 mmol) was transferred, under reduced pressure, into a sealed metal tube which had previously been charged with 2-furoic acid (4.5 g, 40.1 mmol) under a counter current of dry nitrogen. The tube was evacuated, sealed and rocked in a furnace maintained at 300 °C for 24 h. It was then cooled to liquid air temperature, opened and unreacted **2** was removed by distillation at room temperature and atmospheric pressure. The residual solution was filtered and distilled to give 3,4-bis(trifluoromethyl)furan **3** (3.2 g, 39%) as above.

Synthesis of methyl 3,4-bis(trifluoromethyl)-2-furoate 23

Fluoroalkene **2** (1.6 g, 8.8 mmol) was transferred, under reduced pressure, into a quartz tube which had previously been charged with methyl 2-furoate (0.8 g, 6.3 mmol) under a counter current of dry nitrogen. The tube was evacuated, sealed and heated in a furnace maintained at 250 °C for 24 h. It was then cooled to liquid air temperature, opened and unreacted **2** was removed by distillation at room temperature and atmospheric pressure. The residual solution was filtered and identified as methyl 3,4-bis(trifluoromethyl)-2-furoate **23** (1.2 g, 85%); ν_{max}/cm^{-1} 3200, 2950, 1800–1700, 1500, 1350–1100, 800 and 550–450; δ_H(250 MHz; CDCl$_3$) 3.82 (3 H, s, C*H*$_3$) and 7.91 (1 H, s, C*H*); δ_C(100 MHz; CDCl$_3$) 52.95 (s, *C*H$_3$), 117.89 (q, *J* 41.1, *C*CF$_3$), 119.01 (q, *J* 39.8, *C*CF$_3$), 120.55 (q, *J* 270.1, *C*F$_3$), 121.09 (q, *J* 269.8, *C*F$_3$), 145.43 (s, *C*O$_2$Me), 146.06 (s, *C*H) and 156.56 (s, *C*O$_2$); δ_F(235 MHz; CDCl$_3$) −55.75 (s, C*F*$_3$) and −58.40 (s, C*F*$_3$); *m*/*z* 262 (M$^+$, 25%), 231 (100) and 126 (52) by comparison with literature data.[3]

Synthesis of ethyl 3,4-bis(trifluoromethyl)-2-furoate 24

Fluoroalkene **2** (1.6 g, 8.8 mmol) was transferred, under reduced pressure, into a quartz tube which had previously been charged with ethyl 2-furoate (0.8 g, 5.7 mmol) under a counter current of dry nitrogen. The tube was evacuated, sealed and heated in a furnace maintained at 250 °C for 24 h. It was then cooled to liquid air temperature, opened and unreacted **2** was removed by distillation at room temperature and atmospheric pressure. Ether (20 cm^3) was added to the residual pale yellow oil, which was then filtered. Rotary evaporation produced a pale yellow oil which was partially crystalline, identified as ethyl 3,4-bis(trifluoromethyl-2-furoate **24** (1.4 g, 89%); ν_{max}/cm^{-1} 3000, 1750, 1500, 1350–1300, 1250–1050, 1000 and 500; δ_H(250 MHz; CDCl$_3$) 1.00 (3 H, t, *J* 7.0, C*H*$_3$), 3.97 (2 H, q, *J* 7.0, C*H*$_2$) and 8.18 (1 H, s, C*H*); δ_C(100 MHz; CDCl$_3$) 17.38 (s, *C*H$_3$), 66.11 (s, *C*H$_2$), 118.19 (q, *J* 41.2, *C*CF$_3$), 119.21 (q, *J* 42.0, *C*CF$_3$), 120.23 (q, *J* 269.5, *C*F$_3$), 121.01 (q, *J* 270.2, *C*F$_3$), 145.89 (s, *C*H), 146.06 (s, *C*CO$_2$Et) and 157.90 (s, *C*O$_2$); δ_F(235 MHz; CDCl$_3$) −59.37 (s, C*F*$_3$) and −64.32 (s, C*F*$_3$); *m*/*z* 276 (M$^+$, 4%), 248 (46) and 231 (100) by comparison with literature data.[3]

Synthesis of 3,4-bis(trifluoromethyl)furan-2-carbaldehyde 25

Fluoroalkene **2** (1.5 g, 8.2 mmol) was transferred, under reduced pressure, into a quartz tube which had previously been charged with furan-2-carbaldehyde (0.5 g, 5.2 mmol) under a counter current of dry nitrogen. The tube was evacuated, sealed and heated in a furnace maintained at 225 °C for 24 h. It was then cooled to liquid air temperature, opened and unreacted **2** was removed by distillation at room temperature and atmospheric pressure. The residue was filtered and was shown by GLC–MS and NMR to contain a mixture of unreacted starting aldehyde (43%) and 3,4-bis(trifluoromethyl)furan-2-

carbaldehyde **25** (51%); δ_H(250 MHz; $CDCl_3$) 8.07 (1 H, s, C*H*) and 9.88 (1 H, s, C*H*O); δ_C(100 MHz; $CDCl_3$) 118.47 (q, *J* 40.1, *C*CF_3), 119.62 (q, *J* 40.0, *C*CF_3), 120.42 (q, *J* 269.5, *C*F_3), 121.68 (q, *J* 270.1, *C*F_3), 148.75 (s, *C*H), 151.66 (s, *C*CHO) and 178.45 (s, *C*HO); δ_F(235 MHz; $CDCl_3$) −55.82 (s, C*F*$_3$) and −58.29 (s, C*F*$_3$); *m/z* 232 (M^+, 100%) and 213 (30) by comparison with literature data.[3]

Preparation of 3,4-bis(trifluoromethyl)-2-furoic acid 26

Methyl 3,4-bis(trifluoromethyl)-2-furoate **23** (0.8 g, 3.05 mmol) was added to a round-bottomed flask which had previously been charged with potassium *tert*-butoxide (2.7 g, 24.1 mmol), water (0.2 g, 11.1 mmol) and acetonitrile (10 cm^3). The reaction was stirred vigorously for 16 h, and then water (20 cm^3) was added and the solution was acidified to pH 1 using H_2SO_4. Ether (30 cm^3) was added, and the ethereal layer was separated and evaporated to produce a yellow oil. This oil was dissolved in petrol–chloroform (4:1), filtered and slowly evaporated to give pale yellow needles identified as 3,4-bis(trifluoromethyl)-2-furoic acid **26** (0.6 g, 79%) mp 123–124 °C, (lit.,[3,5] 124–127 °C) (Found: C, 33.9; H, 0.90. Calc. for $C_7H_2F_6O_3$: C, 33.87; H, 0.81%); ν_{max}/cm^{-1} 3600–2800, 2350, 2200, 1750–1675, 1550, 1300, 1200–1100 and 1000; δ_H(250 MHz; $CDCl_3$) 7.75 (s, C*H*); δ_C(100 MHz; $CDCl_3$) 118.27 (q, *J* 40.1, *C*CF_3), 119.41 (q, *J* 40.2, *C*CF_3), 120.29 (q, *J* 270.2, *C*F_3), 121.21 (q, *J* 269.6, *C*F_3), 146.80 (s *C*CO_2H), 147.29 (s, *C*H) and 173.27 (s, *C*O_2H); δ_F(235 MHz; $CDCl_3$) −58.27 (s, C*F*$_3$) and −60.14 (s, C*F*$_3$); *m/z* 248 (M^+, 28%), 231 (42), 112 (75) and 95 (100).

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