Trifluoromethylated Furans *via* Iodocyclisation of γ-Unsaturated Ethyl Trifluoroacetoacetates

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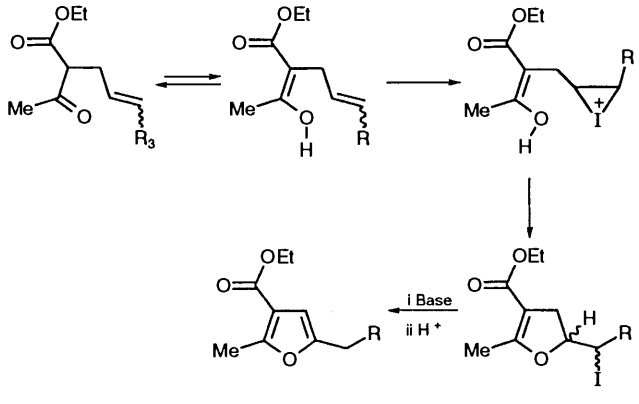
Under iodoetherification conditions, γ-unsaturated ethyl trifluoroacetoacetates **1a–c** exhibit a specific reactivity. Conditions were found for the synthesis of cyclic iodo hemiketals **2a–c** and for their subsequent conversion into either α-trifluoromethylated furans or trifluoromethylated dioxabicyclo[2.2.1]-heptanes.

Trifluoromethylated compounds are receiving an increased amount of attention because of their wide range of applications from pharmaceuticals to high-performance materials.[1] In particular, fluorine-containing heterocycles are an important target for many organic chemists. The introduction of fluorine atoms at a late stage in synthesis often produces technical and economical problems.[2] Trifluoromethylfurans are a good example of the difficulty of fluorination[3] or trifluoromethylation[4] in regards to yield and selectivity. An alternative approach for the synthesis of trifluoromethylfurans is to start from an easily available building block, where the required fluorine atoms are held in place throughout all stages of the synthesis.[5,6]

We report the preparation of substituted α-trifluoromethylfurans through the iodocyclization of γ,δ unsaturated ethyl trifluoroacetoacetate. The iodocyclization of γ,δ unsaturated alcohols is a classical route to tetrahydrofurans.[7] This methodology has been applied to γ,δ unsaturated β-keto esters because of their high acidity.[8] We have investigated this reaction with alkylated ethyl trifluoroacetoacetates which are easily accessible from ethyl trifluoroacetoacetate by alkylation.[9]

Iodoetherification is usually performed in an aprotic solvent such as MeCN or dichloromethane in the presence of sodium carbonate or hydrogen carbonate and iodine.[7,8] The proposed mechanism involves attack on the iodonium ion by the oxygen atom of the enolate, leading to a dihydrofuran (Scheme 1).



Scheme 1

Substituted furans are formed by two further steps, dehydrohalogenation and aromatisation by isomerisation of the double bond. To the best of our knowledge, this methodology has never been applied to fluorinated β-keto esters in order to prepare α-trifluoromethylfurans.

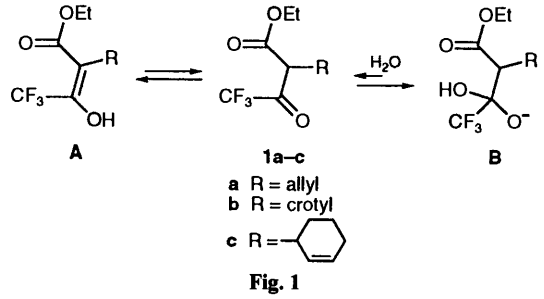


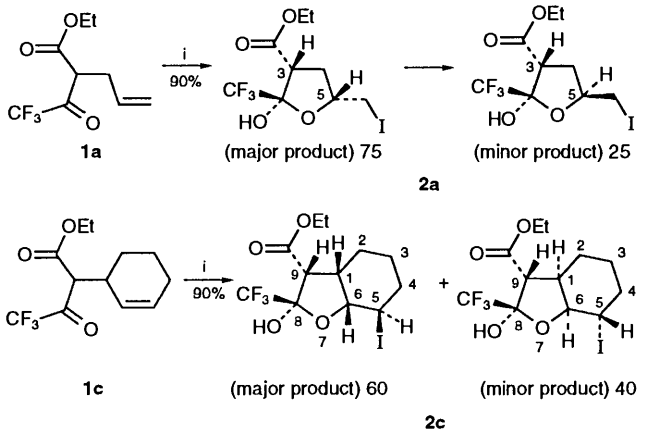
Fig. 1

Results and Discussion

Under the classical conditions in anhydrous media as described by Antonioletti *et al.*[8] the iodoetherification reaction failed with β-keto esters **1a–c**, prepared from the commercially available ethyl trifluoroacetoacetate by alkylation with allylic halides.[9] The failure of these reactions can be attributed to the weakening of the nucleophilic character of the enolate oxygen by the trifluoromethyl substituent. We have already shown that enolates of ethyl trifluoroacetoacetates can be generated even with weak bases and are particularly stable.[9] Considering the ease of the addition of water to a fluoro ketonic carbonyl group and the stability of the resulting hydrate,[10] a higher nucleophilicity of the corresponding alcoholate can be expected (Fig. 1) since the donating effect of the hydroxy group will increase the nucleophilic character of the alcoholate and thus oppose the deactivating effect of the trifluoromethyl group (Fig. 1).

The iodoetherification reaction was therefore performed on the γ,δ unsaturated β-keto esters **1a–c**, with hydrated sodium carbonate (5 H_2O) (1 equiv.) and iodine (2 equiv.) in dichloromethane at room temperature. The iodo hemiketals **2a–c** were obtained in excellent yields (90%) as a mixture of two stereoisomers (75:25 for **2a** and 60:40 for **2c**) (Scheme 2). From the *trans* and *cis* (85:15) crotyl derivatives **1b**, a mixture of four stereoisomers **2b** (67:16:12:4) were obtained.

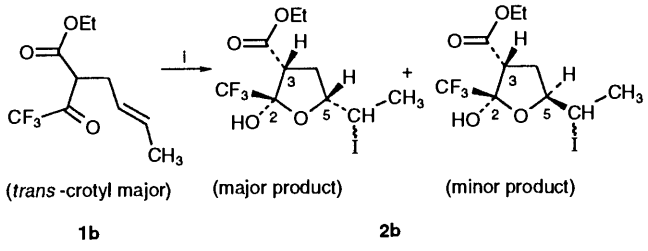
Heteronuclear NOE difference experiments with ^{19}F irradiation indicate, that in both pairs of isomers of **2a** and **2c**, a *cis* relationship between 3-H for **2a** and 9-H for **2c** and CF_3 and therefore between hydroxy and ethoxycarbonyl groups exists [in **2a** and **2c**, about 15% enhancement of the 3-H (**2a**)/9-H (**2c**) proton integration under a mild CF_3 irradiation was observed]. This can only be explained if the relative configuration of the C-2, C-3 stereocentres in the hydrated form of **1a** and **1c** is fixed. This can arise if a chelation of the hydroxy and ethoxycarbonyl groups by water takes place. In this set configuration, the iodonium ion can be formed on either of the two faces of the double bond. The expected *anti*-attack on the thus formed



Scheme 2 *Reagents and conditions:* i, I_2 (2 equiv.), $Na_2CO_3 \cdot 5H_2O$ (1 equiv.), CH_2Cl_2, 20 °C

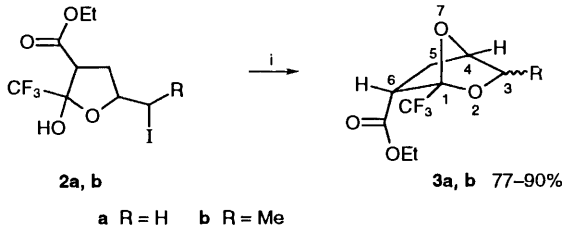
iodonium ions by the alkoxide effectively gives a mixture of two diastereoisomers as reflected by the ratio of products obtained, 75:25 from **1a** and 60:40 from **1c**. In the NOE difference experiments only the major product of **2a** and **2c** exhibits an enhancement of the 5-H (**2a**)/6-H (**2c**) proton integration (5%) demonstrating the *cis* relationship between 5-H (**2a**)/6-H (**2c**) and CF_3. The *trans* relationship between the CF_3 group and the iodine-substituted chain in major products **2a** and **2c** reflects the easier approach of the iodine molecule on the opposite face to that of the CF_3 group in the starting materials **1a** and **c**. The *anti*-attack from the alkoxide hydrate combined with the chelation control provides a good stereoselectivity since, when at least three stereocentres are created, only two stereoisomers are selectively formed.

For **1b**, products have not been separated and relative configurations have not been determined. However, it is likely that the same stereocontrol occurs and the postulated structure of the major isomer of **2b** is represented in Scheme 3.



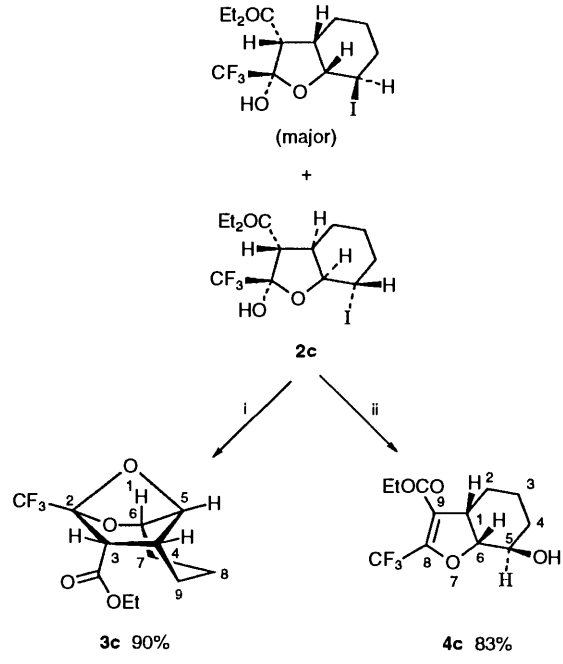
Scheme 3 *Reagents and conditions:* i, I_2 (2 equiv.), $Na_2CO_3 \cdot 5H_2O$ (1 equiv.), 20 °C

In order to prepare the desired furans, the iodo hemiketals **2** were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3 equiv. for **2a** and **b**, 1 equiv. for **2c**) in refluxing benzene (Schemes 4 and 5). The two isomers of **2a** and **2c** gave one bicyclic ketal **3a** and **3c** respectively in very good yield, instead of the expected dehydrohalogenated products. This result



Scheme 4 *Reagents and conditions:* i, DBU (3 equiv.), benzene, reflux, 1 h

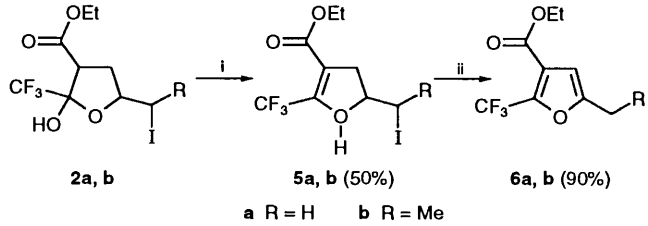
indicates that the hemiketalic hydrogen is more acidic than the 5-H (**2a**)/6-H (**2c**) hydrogen. Similarly, the four iodo hemiketals **2b** gave the cyclic ketals **3b** as a mixture (80:20) of the two isomers (methyl *endo* and methyl *exo*). The minor isomers of **2a–c**, which cannot undergo the intramolecular substitution of the iodine, were not recovered. This strongly suggests that the hemiketal ring closure **1** → **2** is a reversible process finally providing the isomer where 5-H (**2a–b**)/6-H (**2c**) and CF_3 are *cis*. More strikingly, the iodo ketal **2c**, when treated with 2 equiv. of DBU, provided the dihydrofuran **4c** from the dehydration of **3c** through a β-elimination of 3-H (Scheme 5).



Scheme 5 *Reagents and conditions:* i, DBU (1 equiv.), benzene, reflux, 1 h; ii, DBU (2 equiv.), benzene, reflux, 2 h

Such ring opening has not been observed for **3a** and **3b** and seems to be due to steric strain in the tricyclic compound **3c**.

In order to avoid this intramolecular substitution of the iodine atom by the hydroxy group in the hemiketals **2a–c**, they were dehydrated by treatment with P_2O_5. The hemiketals **2a, b** gave the desired iododihydrofurans **5a** and **5b** in moderate yields, but **2c** gave only uncharacterisable tars. Conversion of **5a** and **5b** into the desired α-trifluoromethylfurans **6a** and **6b** in excellent yield was achieved directly by treatment with DBU in refluxing benzene (Scheme 6). The isomerisation step was not necessary, unlike the non-fluorinated series.[8]



Scheme 6 *Reagents and conditions:* i, P_2O_5 (10 equiv.), pentane, room temp., 72 h; ii, DBU (2 equiv.), benzene, reflux, 1 h

The trifluoromethyl group reduces the reactivity of enolates to such an extent that the iodoetherification reaction failed under classical conditions. However, taking advantage of the increased nucleophilicity of the hydrate of the ketonic group, we were able to prepare the desired hemiketals in high yields.

Conditions were found to convert them into α-trifluoromethylfurans.

Experimental

General.—All the reactions were performed in an oven-dried apparatus under an atmosphere of argon. ^{19}F NMR, ^{1}H NMR and ^{13}C NMR spectra were recorded on 200 or 300 MHz multinuclear spectrometers. All chemical shifts are reported in parts per million downfield (positive) from the standard; *J* values are given in Hz. ^{19}F NMR spectra are referenced with external $CFCl_3$, ^{1}H NMR and ^{13}C NMR spectra with tetramethylsilane. To determine fine coupling constants an acquisition of 16K data points, a Lorentz–Gauss transformation of the FID, and a zero filling to 64 K were performed in order to obtain a minimum resolution of 0.2 Hz/pt (^{1}H and ^{19}F) or 0.5 Hz/pt (^{13}C). COSY, COSYLR and XHCORR Brucker programs were used for 2D NMR experiments. High resolution MS and GC–MS analyses were obtained at 70 eV (capillary column CPSIL-5, 25 m). GC–MS spectra were obtained at 70 eV in the electron-impact mode. GC analyses were performed using 5% SE 30 or CP-SIL-5 capillary columns (10 or 25 m). Chromatography was performed with Merck-Kieselgel 60 (230–400 mesh ASTM).

Iodocyclization of β-*Keto Ester* **1a**.—A solution of β-keto ester **1a** (3.6 g, 16 mmol) in CH_2Cl_2 (200 cm^3) was treated with $Na_2CO_3{\cdot}5H_2O$ (4.5 g, 16 mmol, 1 mol equiv.) and iodine (8.1 g, 32 mmol, 2 mol equiv.), at room temperature for 12 h, under argon with stirring. The mixture was then hydrolysed and extracted with Et_2O (200 cm^3). The organic layer was washed with aq. sodium thiosulfate (0.1 mol dm^{-3}; 3 × 30 cm^3) and with brine (3 × 20 cm^3), dried over anhydrous $MgSO_4$ and then evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 70–230 mesh) with pentane–diethyl ether (Et_2O) (85:15), as eluent and gave the product **2a** (5.2 g, 95%) (Found: C, 29.3; H, 3.2. $C_9H_{12}F_3IO_4$ requires C, 29.34; H, 3.26%). Further chromatography on SiO_2 (pentane–Et_2O, 90:10) yielded successively the two diastereoisomers of ethyl 2-hydroxy-5-iodomethyl-2-trifluoromethylfuran-3-carboxylate **2a**.

Compound **2a** *major isomer.* (3.8 g, 73%), m.p. 89–90 °C; δ_F − 84.5; δ_H 1.3 (3 H, t, ^{3}J 7, OCH_2CH_3), 2.16 (1 H, td, $^{3}J_{4A,3}$ 12.3, $^{2}J_{4A,4B}$ 12.3, $^{3}J_{4A,5}$ 9.4, 4-H_A), 2.7 (1 H, ddd, $^{3}J_{4B,3}$ 8, $^{2}J_{4B,4A}$ 12.3, $^{3}J_{4B,5}$ 5.9, 4-H_B), 3.22 (1 H, dd, $^{3}J_{A,5}$ 8.9, $^{2}J_{A,B}$ 9.8, CH_AH_BI), 3.3 (1 H, dd, $^{3}J_{3,4A}$ 12.3, $^{3}J_{3,4B}$ 8, 3-H), 3.43 (1 H, dd, $^{3}J_{B,5}$ 4.5, $^{2}J_{B,A}$ 9.8, CH_AH_BI), 4.25 (2 H, m, OCH_2CH_3), 4.37 (1 H, dddd, $^{3}J_{5,4A}$ 9.1, $^{3}J_{5,4B}$ 5.8, $^{3}J_{5,A}$ 4.6, $^{3}J_{5,B}$ 9, 5-H) and 5.5 (1 H, s, OH); δ_C 6.9 (CH_2I), 13.6 (OCH_2CH_3), 35.5 (C-4), 46.5 (C-3), 62.3 (OCH_2CH_3), 80 (C-5), 101.5 (q, $^{2}J_{C,F}$ 34.4, C-2), 121.8 (q, $^{1}J_{C,F}$ 285.2, CF_3) and 171.5 (CO_2Et); *m/z* 351 (30%, $M^+ + 1 - H_2O$), 223 (100), 151 (29) and 43 (29).

Compound **2a** *minor isomer.* (1.1 g, 21%), m.p. 77–78 °C; δ_F −84.2; δ_H 1.3 (3 H, t, ^{3}J 7, OCH_2CH_3), 2.3 (1 H, ddd, $^{3}J_{4A,3}$ 9.3, $^{2}J_{4A,4B}$ 12.8, $^{3}J_{4A,5}$ 4.9, 4-H_A), 2.5 (1 H, ddd, $^{3}J_{4B,3}$ 9.3, $^{2}J_{4B,4A}$ 12.8, $^{3}J_{4B,5}$ 7.8, 4-H_B), 3.14 (1 H, dd, $^{3}J_{A,5}$ 7.3, $^{2}J_{A,B}$ 9.9, CH_AH_BI), 3.26 (1 H, dd, $^{3}J_{B,5}$ 4.3, $^{2}J_{B,A}$ 9.9, 1 H, CH_AH_BI), 3.4 (1 H, t, $^{3}J_{3,4A}$ 9.3, 3-H), 4.25 (m, OCH_2CH_3), 4.5 (1 H, dddd, $^{3}J_{5,4A}$ 4.9, $^{3}J_{5,4B}$ 7.8, $^{3}J_{5,A}$ 7.3, $^{3}J_{5,B}$ 4.3, 5-H) and 5.5 (1 H, s, OH); δ_C 6.9 (CH_2I), 13.6 (OCH_2CH_3), 34.3 (C-4), 45.3 (C-3), 62.0 (OCH_2), 78.6 (C-5), 101.5 (q, $^{2}J_{C,F}$ 34.4, C-2), 121.8 (q, $^{1}J_{C,F}$ 285.2, CF_3) and 171.9 (CO_2Et); *m/z* 323 (2%, M^+ − EtOH), 223 (19), 69 (10) and 40 (100).

Iodocyclization of β-*Keto Ester* **1b**.—A solution of β-keto ester **1b** (1.2 g, 5 mmol) in CH_2Cl_2 (120 cm^3) was treated with $Na_2CO_3{\cdot}5H_2O$ (2.8 g, 10 mmol, 2 mol equiv.) and iodine (5 g, 20 mmol, 2 mol equiv.) at room temperature for 12 h, under argon with stirring. After the extractive work-up, the crude product was purified by column chromatography (SiO_2) with pentane–Et_2O (90:10) as eluent and gave the product **2b** (2 g, 92%) as a mixture of four diastereoisomers (62.5:17:13:7.5) (Found: C, 32.1; H, 3.5. $C_{10}H_{14}F_3IO_4$ requires C, 31.41; H, 3.66); δ_F −87.0 (7.5%), −86.4 (62.5%), −85.0 (17%) and −83.7 (13%); δ_H 1.25 (3 H, t, ^{3}J 7, OCH_2CH_3), 2.0 (3 H, d, ^{3}J 6.4, CH_3CHI), 2.1–3.9 (2 H, m, cyclic-CH_2), 3.4 (1 H, m, 3-H), 4.2 (1 H, m, CH_3CHI), 4.3 (2 H, m, OCH_2CH_3), 4.8 (1 H, m, 5-H) and 5.6 (1 H, br s, OH).

Preparation of Ethyl 2-(*Cyclohex-2-enyl*)*trifluoroacetoacetate* **1c**.—A solution of 1-bromocyclohex-2-ene [11] (18 g, 0.11 mol. 1.1 mol equiv.) in acetone was added dropwise to a suspension of the sodium enolate [9] of ethyl trifluoroacetoacetate (21 g, 0.1 mol) in acetone (80 cm^3) containing KI (0.25 g, 1.5 mmol). The reaction mixture was refluxed and stirred for 72 h. Acetone was evaporated under reduced pressure and the solid residue was hydrolysed with 10% aqueous HCl (15 cm^3). After extraction with Et_2O, the combined organic layers were washed with brine, dried ($MgSO_4$) and then concentrated. Chromatography on silica gel (pentane–Et_2O, 90:10) gave β-keto ester **1c** (23 g, 90%); δ_F −78.6; δ_H 1 (3 H, t, ^{3}J 7.1, OCH_2CH_3), 1.6 (6 H, m, 3 × CH_2), 4.0 (2 H, q, ^{3}J 7.1, OCH_2CH_3), 5.3 and 5.6 (2 H, m, $HC{=}CH$); δ_C 13.7, 20.6, 24.7, 26.2, 35.0, 57.8, 62.0, 115.1 (q, $^{1}J_{C,F}$ 292, CF_3), 126.2, 130.2, 165.6 and 185.6 (q, $^{2}J_{C,F}$ 36, CF_3CO); *m/z* 264 (M^+, 2%), 167 (12), 139 (10) 81 (100) and 79 (13).

Iodocyclization of β-*Keto Ester* **1c**.—A solution of β-keto ester **1c** (2 g, 7.5 mmol) in CH_2Cl_2 (300 cm^3) was treated with $Na_2CO_3{\cdot}5H_2O$ (4.4 g, 15 mmol, 2 mol equiv.), iodine (4 g, 15 mmol, 2 mol equiv.) and water (1 cm^3), at room temperature for 48 h, under argon with stirring (addition of water accelerates the reaction). After the extractive work-up, the crude product was filtered through a SiO_2 column, with pentane–Et_2O (85:15) as eluent and gave ethyl 5-iodo-8-hydroxy-8-trifluoromethyl-7-oxabicyclo[4.3.0]nonane-9-carboxylate **2c** (2.7 g, 88%) as a mixture of two diastereoisomers (3:2) (Found: C, 35.3; H, 3.8. $C_{12}H_{16}F_3IO_4$ requires C, 35.29; H, 3.92%). Further chromatography on SiO_2 (pentane–Et_2O 90:10 and then 50:50) gave successively the two diastereoisomers of **2c**.

Compound **2c** *major isomer.* (1.6 g, 52%), m.p. 94–96 °C; δ_F −86.1; δ_H 1.4 (3 H, t, ^{3}J 7, OCH_2CH_3), 1.6 (2 H, m, 2-H), 1.8 (4 H, m, 3-H and 4-H), 2.9 (1 H, m, $^{3}J_{1,9}$ 6.3, $^{3}J_{1,2}$ 3.3, $^{3}J_{1,6}$ 2.6, 1-H), 3.2 (1 H, d, $^{3}J_{9,1}$ 6.3, 9-H), 4.24 (1 H, qd, ^{3}J 7, $^{2}J_{A,B}$ 9.8, $OCH_AH_BCH_3$), 4.27 (1 H, qd, ^{3}J 7, $^{2}J_{A,B}$ 9.8, $OCH_AH_BCH_3$), 4.42 (1 H, dd, $^{3}J_{6,5}$ 2.3, $^{3}J_{6,1}$ 3.3, 6-H), 4.65 (1 H, m, $^{3}J_{5,6}$ 2.3, $^{3}J_{5,4ax}$ 2.5, $^{3}J_{5,4eq}$ 2.5, 5-H) and 7.1 (1 H, s, OH); δ_C 13.6 (OCH_2CH_3), 20.0, 22.6, 28.6 (C-2, C-3, C-4), 28.0 (C-5), 36.5 (C-1), 47.3 (C-9), 62.2 (OCH_2CH_3), 82.3 (C-6), 100.4 (q, $^{2}J_{C,F}$ 33.8, C-8), 123 (q, $^{1}J_{C,F}$ 287, CF_3) and 171.9 (CO_2Et); *m/z* 390 ($M^+ - H_2O$, 4%), 263 (47) and 157 (14).

Compound **2c** *minor isomer.* (1 g, 33%), m.p. 92–93 °C; δ_F −84.6; δ_H 1.2 (3 H, t, ^{3}J 7, OCH_2CH_3), 1.4 (6 H, m, 3 × CH_2), 2.8 (1 H, ddt, $^{3}J_{1,9}$ 11.6, $^{3}J_{1,6}$ 6.9, $^{3}J_{1,2ax}$ 5, $^{3}J_{1,2eq}$ 5, 1-H), 3.1 (1 H, d, $^{3}J_{9,1}$ 11.6, 9-H), 3.9 (1 H, ddd, $^{3}J_{5,6}$ 8.6, $^{3}J_{5,4ax}$ 11.56, $^{3}J_{5,4eq}$ 4.1, 5-H), 4.23 (1 H, dq, $^{2}J_{B,A}$ 10.8, $^{3}J_{B,Me}$ 7.2, $OCH_ACH_BCH_3$), 4.38 (1 H, dq, $^{2}J_{A,B}$ 10.8, $^{3}J_{A,Me}$ 7.2, $OCH_AH_BCH_3$), 4.5 (1 H, m, $^{3}J_{6,1}$ 6.9, $^{3}J_{6,1}$ 8.7, 6-H) and 5.4 (1 H, br s, OH); δ_C 14.0 (OCH_2CH_3), 22.5, 23.9, 35.6 (C-2, C-3, C-4), 28.7 (C-5), 41.3 (C-1), 47.6 (C-9), 62.4 (OCH_2CH_3), 85.2 (C-6), 100 (q, $^{2}J_{C,F}$ 34.3, C-8); 121 (q, ^{1}J 284.6, CF_3) and 170.9 (CO_2Et); *m/z* 408 (M^+, 4%), 390 ($M^+ - H_2O$, 2), 281 (19), 185 (28) and 79 (100).

Treatment of Compound **2a** *with DBU.*—A solution of **2a** (1.4 g, 3.8 mmol) in benzene (25 cm^3) was refluxed with DBU

(1.8 g, 12 mmol, 3 mol equiv.) for 1 h. The reaction mixture was filtered on SiO_2 (Et_2O as eluent). The resulting ethereal solution was washed with 1% aqueous HCl, and with brine and then dried ($MgSO_4$). Evaporation of the solvent after filtration on SiO_2 gave ethyl 1-trifluoromethyl-2,7-dioxabicyclo[2.2.1]-heptane-6-carboxylate **3a** (800 mg, 90%); δ_F −77.5; δ_H 1.3 (3 H, t, ^3J 7, OCH_2CH_3), 2.18 (1 H, dddd, $^2J_{5A,5B}$ 12.2, $^3J_{5A,6}$ 11.1, $^3J_{5A,4}$ 4.8, $^3J_{5A,3A}$ 2.9, 5-H_A), 2.32 (1 H, dd, $^2J_{5B,5A}$ 12.2, $^3J_{5B,6}$ 3.6, 5-H_B), 3.27 (1 H, dd, $^3J_{6,5A}$ 11.1, $^3J_{6,5B}$ 3.6, 6-H), 3.8 (1 H, ddd, $^2J_{3A,3B}$ 6.5, $^3J_{3A,4}$ 3.5, $^3J_{3A,5A}$ 2.9, 3-H_A), 4.0 (1 H, d, $^2J_{3A,3B}$ 6.5, 3-H_B), 4.11 (1 H, dq, $^2J_{A,B}$ 10.75, $^3J_{A,Me}$ 7.2, $OCH_AH_BCH_3$), 4.22 (1 H, dq, $^2J_{B,A}$ 10.75, $^3J_{B,Me}$ 7.2, $OCH_AH_BCH_3$) and 5.0 (1 H, dd, $^3J_{4,3A}$ 3.5, $^3J_{4,5A}$ 4.8, 4-H); δ_C 13.3 (OCH_2CH_3), 32.1 (C-5), 49.0 (C-6), 60.9 (OCH_2CH_3), 71.3 (C-3), 78.0 (C-4), 103.7 (q, $^2J_{C,F}$ 36, C-1), 120.7 (q, $^1J_{C,F}$ 280, CF_3) and 168.5 (CO_2Et).

Treatment of Compound **2b** *with DBU*.—A solution of **2b** (1 g, 2.6 mmol) in benzene (20 cm^3) was refluxed with DBU (1.26 g, 7.8 mmol, 3 mol equiv.) for 1 h. Work-up and chromatography on SiO_2 (pentane–Et_2O, 1:1) gave **3b** (500 mg, 77%); δ_F −77.5 (major) and −77.2 (minor); δ_H 1.22 (3 H, t, ^3J 7, OCH_2CH_3), 1.3 (3 H, d, ^3J 6.4, CH_3), 2.4 (2 H, m, 5-H), 3.2 (1 H, dd, $^3J_{6,5A}$ 4, $^3J_{6,5B}$ 11, 6-H), 3.9 (1 H, m, 3-H), 4.2 (2 H, q, ^3J 7, OCH_2CH_3) and 4.4 (1 H, m, $^3J_{4,3}$ 4.6, 4-H) (minor 4.62, $^3J_{4,3}$ 5.1); δ_C 13.5 (minor 13.4) (OCH_2CH_3), 19.1 (minor 19.0) (CH_3CH), 32.0, (C-5) 48.5 (C-6), 61.0 (OCH_2CH_3), 79 (C-3), 81.6 (minor 80.3) (C-4), 104.0 (minor 104.5) (q, $^2J_{C,F}$ 36, C-1), 120 (minor 119) (q, $^1J_{C,F}$ 280, CF_3), 168.8 (minor 169.2) (CO_2Et).

Treatment of Compound **2c** *with DBU* (1 *Equiv.*).—A solution of **2c** (600 mg, 1.46 mmol) in benzene (10 cm^3) was refluxed with DBU (230 mg, 1.46 mmol, 1 mol equiv.) for 1.5 h. Work-up and chromatography on SiO_2 (pentane–Et_2O, 1:1) gave the tricyclic compound **3c** (370 mg, 90%); δ_F −77.7 (d, $^5J_{6-H,F}$ 1); δ_H 1.4–1.65 (4 H, m, 6-H_{ax}, 7-H_{ax}, 8-H_{ax}, 8-H_{eq}), 1.8 (1 H, br d, ^3J 11.5, 1 H, 7-H_{eq}), 3.04 (2 H, m, 3-H, 4-H), 4.15 (2 H, m, $^2J_{A,B}$ 10.7, $^3J_{A,Me}$ 7.1, $^3J_{B,Me}$ 7.1, $OCH_AH_BCH_3$), 4.25 (1 H, m, 6-H) and 4.59 (1 H, dd, $^3J_{5,4}$ 4.8, $^3J_{5,6}$ 2.3, 5-H); δ_C 13.2 (OCH_2CH_3), 13.6, 23.2, 25.1 (C-7, C-8, C-9), 37.9 (C-4), 53.3 (C-3), 61.3 (OCH_2CH_3), 76.8, 76.3 (C-5, C-6), 105.3 (q, $^2J_{C,F}$ 35.2, C-2), 120.7 (q, $^1J_{C,F}$ 280, CF_3) and 169.3 (CO_2Et); *m/z* 280 (M^+, 42%), 190 (58), 162 (100) and 121 (99).

Treatment of Compound **2c** *with DBU* (2 *Equiv.*).—A solution of **2c** (720 mg, 1.76 mmol) in benzene (15 cm^3) was refluxed with DBU (560 mg, 3.5 mmol, 2 mol equiv.) for 3 h. Work-up and chromatography on SiO_2 (pentane–Et_2O, 10:1) gave ethyl 5-hydroxy-8-trifluoromethyl-7-oxabicyclo[4.3.0]non-8-ene-9-carboxylate **4c** (420 mg, 83%); δ_F −66.6; δ_H 1.13 (3 H, t, ^3J 7.1, OCH_2CH_3), 1.2–2.2 (6 H, m), 2.98 (1 H, m, 1 H, $^3J_{1,6}$ 2, $^3J_{1,2}$ 3, 1-H), 3.82 (1 H, dd, $^3J_{6,5}$ 3, $^3J_{6,1}$ 2, 6-H), 4.18 (2 H, m, $^2J_{A,B}$ 10.2, $^3J_{A,Me}$ = $^3J_{B,Me}$ 7.1, $OCH_AH_BCH_3$) and 4.5 (1 H, qd, $^3J_{5,6}$ 2, $^3J_{5,4}$ 4, 5-H); δ_C 13.7 (OCH_2CH_3), 15.2, 29.2, 31.9 (C-2, C-3, C-4), 36.8 (C-1), 61.4 (OCH_2CH_3), 65.7 (C-5), 76.7 (C-6), 107.4 (q, $^3J_{C,F}$ 2, C-9), 119.3 (q, $^1J_{C,F}$ 275, CF_3), 147.2 (q, $^2J_{C,F}$ 36.9, C-8) and 166.2 (CO_2Et); *m/z* 281 (M^+, 9%), 191 (28), 166 (58), 138 (100), 121 (71) and 93 (91).

Dehydration of Hemiketal **1a**.—A suspension of P_2O_5 (2 g, 14 mmol, 10 mol equiv.) in a solution of **1a** (500 mg, 1.4 mmol) in pentane–CH_2Cl_2, 10:2 (12 cm^3) was stirred at room temperature for 72 h. The organic layer was separated and then concentrated. Chromatography on SiO_2 with pentane–Et_2O (4:1) as eluent gave ethyl 5-iodomethyl-2-trifluoromethyl-4,5-dihydrofuran-3-carboxylate **5a** (245 mg, 52%); δ_F −64.7; δ_H 1.3 (3 H, t, ^3J 7, OCH_2CH_3), 2.9 (1 H, m, 4-H_A), 3.2 (1 H, m, 4-H_B), 3.3 (2 H, m, CH_2I), 4.2 (2 H, q, ^3J 7, OCH_2CH_3) and 4.8 (1 H, m, 5-H); δ_C 6.8 (CH_2I), 14.0 (OCH_2CH_3), 37.5 (C-4), 61.0 (OCH_2CH_3), 81.6 (C-5), 109.0 (q, $^3J_{C,F}$ 2.6, C-3), 115.0 (q, $^1J_{C,F}$ 273, CF_3), 150.8 (q, $^2J_{C,F}$ 39.8, C-2) and 162 (CO_2Et).

Dehydration of Hemiketal **1b**.—A suspension of P_2O_5 (6 g, 40 mmol, 10 mol equiv.) in a solution of **1b** (1.4 g, 3.6 mmol) in pentane–CH_2Cl_2, 10:2 (12 cm^3) was stirred at room temperature for 72 h. The organic layer was separated and then concentrated. Chromatography on SiO_2 with pentane–Et_2O (4:1) as eluent gave dihydrofuran **5b** (600 mg, 50%); δ_F −64.8; δ_H 1.25 (3 H, t, ^3J 7, OCH_2CH_3), 1.85 (3 H, d, ^3J 7, CH_3CHI), 2.9 (1 H, m, 4-H_A), 3.2 (1 H, m, 4-H_B), 4.2 (2 H, q, ^3J 7, OCH_2CH_3), 4.25 (1 H, t, ^3J 7, CHI) and 4.5 (1 H, m, 5-H); δ_C 13.9 (OCH_2CH_3), 23.5 (CHI), 28.2 (CH_3CHI), 37.4 (C-4), 61.0 (OCH_2CH_3), 86.5 (C-5), 109.0 (q, $^3J_{C,F}$ 2.6, C-3), 118.0 (1, $^1J_{C,F}$ 273, CF_3), 150.3 (q, $^2J_{C,F}$ 39.7, C-2) and 162 (CO_2Et).

Ethyl 5-Methyl-2-trifluoromethylfuran-3-carboxylate **6a**.—A solution of **5a** (200 mg, 0.57 mmol) and DBU (175 mg, 1.14 mmol) in benzene (10 cm^3) was refluxed for 1 h. The reaction mixture was filtered through SiO_2 (pentane–Et_2O, 1:1 as eluent). After concentration under reduced pressure furan **6a**[5] was obtained (120 mg, 93%) (HRMS Found: M^+, 222.1639. $C_9H_9F_3O_3$ requires *M*, 222.1635); δ_F −61.4; δ_H 1.2 (3 H, t, ^3J 7, OCH_2CH_3), 2.3 (3 H, s, CH_3), 4.3 (2 H, q, ^3J 7, OCH_2CH_3) and 6.5 (1 H, s, C=CH); δ_C 10.9 (CH_3), 13.2 (OCH_2CH_3), 61.2 (OCH_2CH_3), 108.7 (C-4), 118.6 (q, ^1J 268, CF_3), 120.4 (q, $^3J_{C,F}$ 2.4, C-3), 141.0 (q, $^2J_{C,F}$ 42.5, C-2), 153.9 (C-5) and 161.0 (CO_2Et).

Ethyl 5-Ethyl-2-trifluoromethylfuran-3-carboxylate **6b**.—A solution of **5b** (500 mg, 1.35 mmol) and DBU (410 mg, 2.7 mmol) in benzene (15 cm^3) was refluxed for 2 h. The reaction mixture was filtered through SiO_2 (pentane–Et_2O, 1:1 as eluent). After concentration under reduced pressure **6b** was obtained (200 mg, 90%) (Found: M^+, 236.1898. $C_{10}H_{11}F_3O_3$ requires *M*, 236.1903); δ_F −61.2; δ_H 1.2 (3 H, t, ^3J 7.6, CH_2CH_3), 1.3 (3 H, t, ^3J 7.2, OCH_2CH_3), 2.6 (2 H, q, ^3J 7.6, CH_2CH_3), 4.3 (2 H, q, ^3J 7.2, OCH_2CH_3) and 6.4 (1 H, s, C=CH); δ_C 11.5 (CH_2CH_3), 13.9 (OCH_2CH_3), 21 (CH_2CH_3), 61.3 (OCH_2CH_3), 107.2 (C-4), 118.7 (q, ^1J 269, CF_3), 120.0 (q, $^3J_{C,F}$ 2.5, C-3), 128 (C-5), 141.6 (q, $^2J_{C,F}$ 42.4, C-2) and 159.3 (CO_2Et).

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