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Stereoselective Synthesis of Substituted Bicyclo-[3.3.1]-nonan-9-ones by Additions of Enamines of Cyclohexanones to 4-Ethoxy-1,1,1-trifluorobut-3-ene-2-one

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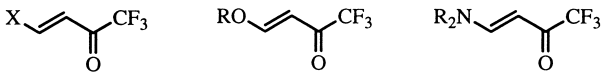
Abstract—Addition of the pyrrolidine enamine of cyclohexanone to 4-ethoxy-1,1,1-trifluorobut-3-ene-2-one affords a single diastereoisomer of 4-ethoxy-2-hydroxy-2-trifluoromethylbicyclo[3.3.1]nonan-9-one. Similarly the pyrrolidine enamine of 4-methylcyclohexanone also in a highly diastereoselective manner affords a single bicyclic ketone. In the latter case a single crystal X-ray diffraction analysis permits unambiguous determination of all stereochemical detail. Other examples of addition to 4-ethoxy-1,1,1-trifluorobut-3-ene-2-one are discussed. The mechanistic explanation of the unusually high selectivity is discussed.

Introduction

The present importance of organofluorine compounds, whether they be aromatic, aliphatic or alicyclic,[1] has stimulated the development of new synthetic routes. The problems of direct introduction of fluorine witnessed by the comment[2] 'difficulties in the synthesis of C–F bonds persist—even for experts' have encouraged the synthesis of building blocks incorporating the desired fluorinated subgroups. There has been extensive recent interest in the use of 4-substituted-1,1,1-trifluorobut-3-ene-2-ones (**1**) as building blocks. In other papers[3,4] we describe their use in a general synthesis of aliphatic unsaturated ketones and in the synthesis of fluorinated aromatics. In this paper we describe their use in the synthesis of fluorinated alicyclic ketones.

There have been earlier studies with substituted 1,1,1-trifluorobut-3-ene-2-ones (**1**) having chlorine, oxygen, sulfur or nitrogen substituted at the 4-position. The chlorinated derivatives have been prepared and used to permit the synthesis[5] of a wide series of enaminoketones via nucleophilic displacements. The access to the 4-alkoxy series has been well developed based on Friedel and Crafts acylation[6] of the appropriate vinyl ether. A similar route from vinyl sulfides has been used[7] to prepare sulfur substituted derivatives.

With subsequent oxidation to afford intermediate sulfones a new route[8] to heteroaryl substituted trifluoromethyl ketones has been established. A number of routes to the enaminoketones have been described. A rather specific route, lacking generality, is the reaction of trifluoroacetic anhydride with tertiary amines. Discovered in Russia[9] and developed by Schreiber[10] the reaction is limited in utility to triethylamine, but has been used[11] in the synthesis of fluorinated heterocycles. A more general route developed by Hojo et al.[12] is based on nucleophilic substitutions of other β-substituted unsaturated ketones. A third route[13] is based on the reaction of lithium derivatives of enamines with electrophiles such as ethyl trifluoroacetate, or on the direct acylation[14] of enamines. The progress in preparation of β-substituted unsaturated trifluoromethylketones is further illustrated by the preparation[15] of β-tellurium substituted ketones. With a ready access to this broad range of β-substituted unsaturated trifluoromethylketones it is surprising that their use as building blocks has been relatively less investigated. Here we describe their first use in the synthesis of fluorinated alicyclics. We were interested to explore the chemistry of the more readily available 4-alkoxy-1,1,1-trifluorobut-3-ene-2-ones (**2**) and 4-dialkylamino-1,1,1-trifluorobut-3-ene-2-ones (**3**) as building blocks with other nucleophilic reagents such as enamines. We discuss here the products of reaction with enamines of cyclic ketones and in particular we describe the highly stereo- and regio-selective addition of pyrrolidine enamines of cyclohexanones to 4-ethoxy-1,1,1-trifluorobut-3-ene-2-one (**4**). The resulting high selectivity permits an efficient route to be established to fluorinated bicyclo[3.3.1]nonanones. With enamines of acyclic ketones fluorinated monocyclic products can be obtained.



(**1**) (**2**) (**3**)

Keywords: addition; enamines; organofluorine; phenols; X-ray diffraction.
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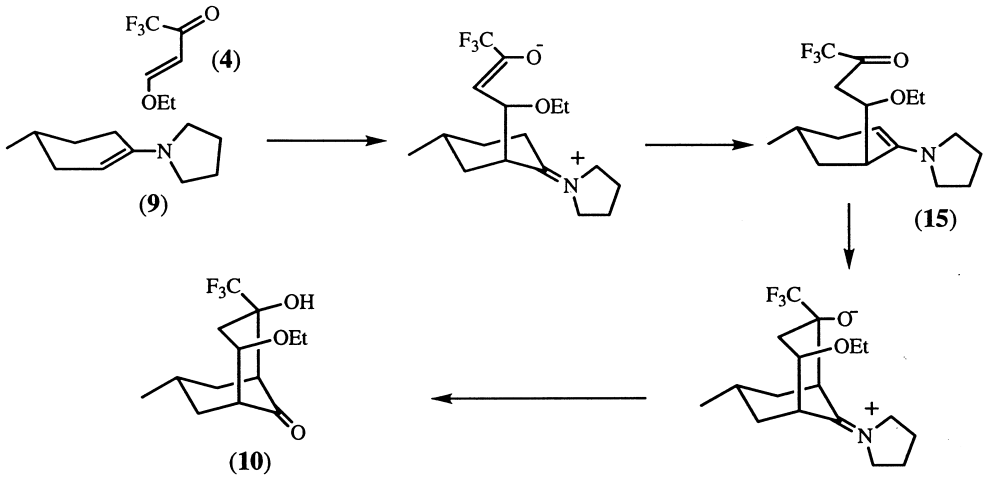
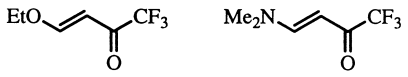


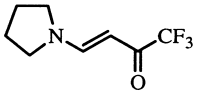
Scheme 1.

Results and Discussion

The study of reaction of 4-substituted-1,1,1-trifluoro-3-buten-2-ones (**1**) with enamines was initiated with the 4-dimethylaminobutenone (**5**). Attempted reaction of the pyrrolidino enamine of cyclohexanone (**6**) with the ketone (**5**) failed to afford products via carbon–carbon bond formation. Instead some exchange of the enamines was observed affording mixtures containing the pyrrolidino enamino ketone (**7**). To circumvent this exchange reaction the pyrrolidino enamino ketone (**7**) was reacted with the pyrrolidino enamine of cyclohexanone (**6**). However, no addition products were observed either by reaction in ether at room temperature or under reflux in toluene.



(**4**) (**5**)



(**7**)

However, the 4-alkoxy-1,1,1-trifluorobut-3-ene-2-ones (**2**) are more reactive than their enamine analogues. Reaction of 4-ethyloxy-1,1,1-trifluorobut-3-ene-2-one (**4**), used crude from ethyl vinyl ether, with the pyrrolidino-enamine of cyclohexanone gave the bicyclic ketone (**8**), after hydrolysis, as a single diastereoisomer in 88% overall yield. The generality of the reaction was established by addition of other enamines to the alkoxyketone (**4**). The high stereoselectivity was maintained in the reaction of the enamine (**9**) of 4-methylcyclohexanone, which gave the bicyclic ketone (**10**) in 90% yield. Additions to other enamines of cyclic and acyclic ketones were illustrated by synthesis of the bicyclic ketone (**11**) from the enamine of cycloheptanone (**12**) in 44% yield and of the cyclohexenone (**13**) from the enamine of 3-pentanone (**14**) in 39% yield. Most of the structural features of the products can be understood by analysis of the likely course of the reactions. In the most complex case, addition to the enamine of 4-methylcyclohexanone can be rationalised mechanistically, but the outcome was also confirmed by a single crystal X-ray analysis of the structure of the hydroxyketone product (**10**). The first step, a Michael addition, is followed by a proton transfer to afford an intermediate enamino ketone (**15**) (see Scheme 1). The initial carbon–carbon bond forming step takes place from a pseudo-chair conformation with the methyl group occupying an equatorial position and with the addition occurring from the less hindered *trans* face. A similar stereochemical outcome is observed[16,17] in other reactions of enamines of 4-methylcyclohexanone. Reaction with acrolein[16] affords a bicyclononanone having the methyl group in the same *exo*, equatorial position. Similarly only *exo*-7-methylbicyclononane-2,9-dione is isolated[17] following reaction with acrylolyl chloride. The stereochemical outcome of the addition defining the stereochemistry of the ethyloxy group follows from Newman projections (A) and (B) (Fig. 1). In the former case leading to the observed product, steric interactions are minimised. It is probable that those steps leading to this intermediate (**15**) are mainly kinetically controlled. In contrast the step which determines the stereochemistry of the hydroxyl group, could be kinetically or thermodynamically controlled. The possibility of strong hydrogen bonding between the axial

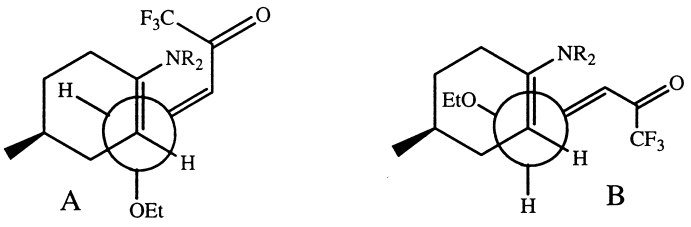


Figure 1. Newman projections of diastereoisomeric transition states A and B.

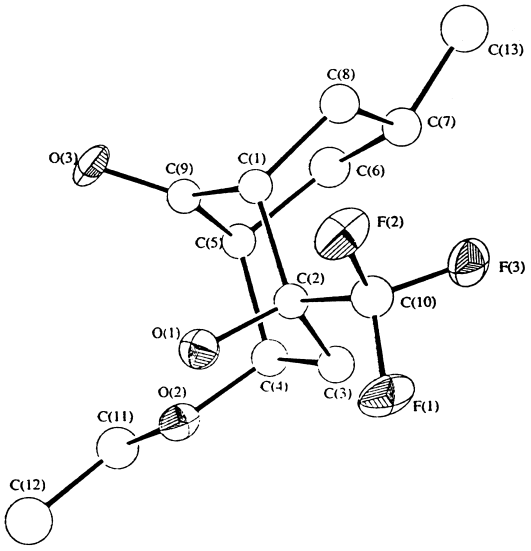
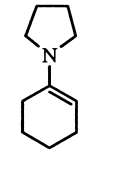
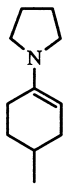


Figure 2. Structure of 4-(ethyloxy)-2-hydroxy-7-methyl-2-(trifluoromethyl)bicyclo[3.3.1]nonan-9-one (**10**).

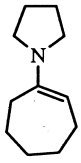
hydroxy and ethyloxy groups could define the observed stereochemistry of the product (**10**). The structure of the product (**10**) from 4-methylcyclohexanone was established by an X-ray study (see Fig. 2). This X-ray analysis both supported the mechanistic commentary and showed interesting structural features. Deformations of the more substituted ring, associated with the reflex effect[18] can be observed. The pinching imposed by the bicyclic skeleton leads to a splaying apart of the ethyloxy and hydroxy groups. Based on the established structure of the hydroxyketone (**10**) derived from 4-methylcyclohexanone, a similar stereochemistry could be assigned to the products (**8**) and (**11**) derived from cyclohexanone and cycloheptanone, respectively. The three bicyclic hydroxyketones (**8**), (**10**) and (**11**) have common NMR spectral features, notably the position of the equatorial proton adjacent to the ethyloxy group, which is observed at 4.03 ppm in the ketone (**8**), at 4.04 ppm in the methyl analogue (**10**) and at 3.97 ppm in the bicyclododecanone (**11**). The monocyclic hydroxyketone (**13**) is obtained as a mixture of diastereoisomers. The two isomers can be efficiently dehydrated to give the fluorinated phenol (**16**) in 73% yield. In the light of the present interest in fluoroaromatics as pharmaceutical intermediates, this novel entry to fluorinated phenols is noteworthy.



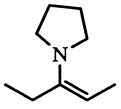
(**6**)



(**9**)



(**12**)



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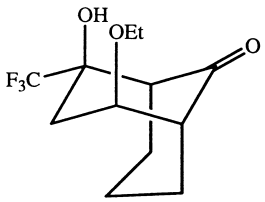
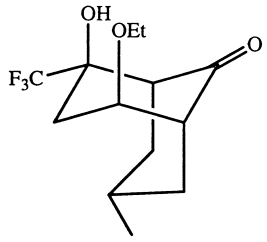


(**8**)



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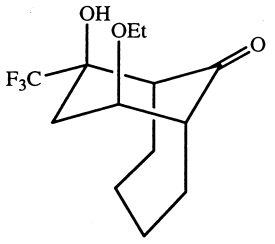

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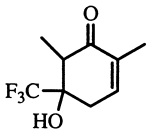
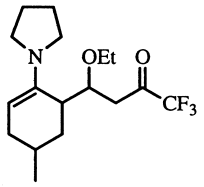
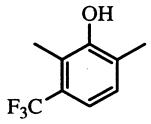


(**13**)



(**15**)



(**16**)

In summary these additions illustrate the utility of 4-alkoxy-1,1,1-trifluorobut-3-ene-2-ones (**2**) as synthons. Whereas with more reactive nucleophiles use[3] of 4-dialkylamino-1,1,1-trifluorobut-3-ene-2-ones (**3**) offers some advantage, in reactions with enamines the greater reactivity of the alkoxy substituted ketones is required to permit efficient reaction.

Experimental

General techniques

Petroleum ether refers to the fraction boiling within the range 40–60°C. Dimethylformamide was distilled from molecular sieves, dichloromethane and triethylamine from calcium hydride, diethyl ether and toluene from sodium, and anhydrous ethanol by distilling over magnesium. Melting points were determined using an electrothermal Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer as Nujol mulls, dichloromethane solutions or using sodium chloride disks. Mass spectra were recorded on a VG Analytical 70-250-SE spectrometer for FAB and EI spectra and on a

Micromass Platform quadrupole mass analyser for APCI and ES spectra. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WH-300 spectrometer and chemical shifts, expressed in ppm, are relative to the internal reference, tetramethylsilane. Coupling constants are quoted in Hz. ^{19}F NMR spectra were recorded using hexafluorobenzene as an internal standard. Analytical thin layer chromatography (TLC) was performed on precoated Macherey-Nagel ALUGRAM SIL G/UV$_{254}$ aluminium backed plates and compounds were visualised by UV light, iodine or sulfuric acid. Flash column chromatography was performed using silica gel 60 (Macherey-Nagel, 230–400 mesh). Elemental analyses were undertaken at University College, London.

4-(Ethyloxy)-2-hydroxy-2-(trifluoromethyl)bicyclo[3.3.1]-nonan-9-one (8). To a stirred solution of 4-dimethylaminopyridine (1 mg, 8×10^{-3} mmol) and trifluoroacetic anhydride (0.27 g, 1.3 mmol) in anhydrous dichloromethane (1.5 ml) was added dropwise at −10°C ethyl vinyl ether (0.08 g, 1.1 mmol). After stirring for 19 h at 0°C the mixture was allowed to warm to room temperature and the solvent removed in vacuo. To the stirred resulting oil was added dropwise at room temperature a solution of freshly distilled 1-(1-cyclohexenyl)tetrahydro-1*H*-pyrrole (**6**) (0.36 g, 2.4 mmol) in anhydrous ether (2 ml). After stirring for 77 h at room temperature, water (5 ml) and diethyl ether (5 ml) were added. The two phases were separated and the aqueous phase extracted with diethyl ether (5×5 ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo. The resultant orange oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 1:1) to give the title compound (**8**) as a solid (0.26 g, 88%) and (*E*)-1,1,1-trifluoro-4-tetrahydro-1*H*-1-pyrrolyl-3-buten-2-one (**7**) (0.02 g, 9%) as colourless crystals. Recrystallisation of the title compound (**8**) from diethyl ether afforded colourless crystals, mp 75–76°C; Found: C, 54.3; H. 6.1. $C_{12}H_{17}F_3O_3$ requires C, 54.1; H, 6.4%; δ_H 4.21 (1H, s, O*H*), 4.03 (1H, br t, J=4.0 Hz, H_{eq}-4), 3.63 (1H, dq, J=9.0 Hz, 7.0, OCH_2CH$_3$), 3.42 (1H, dq, J=9.0, 7.0 Hz, OCH_2CH$_3$), 2.82 (2H, br s H_{eq}-1, H_{eq}-5), 2.63 (1H, dd, J=15.4, 4.0 Hz, H_{eq}-3), 2.29 (2H, m, H_{ax}-3, H_{eq}-6 or H_{eq}-8), 2.00 (4H, m, H_{eq}-7, H_{ax}-6, H_{ax}-8 and H_{eq}-6 or H_{eq}-8), 1.58 (1H, m, H_{ax}-7), 1.15 (3H, t, J=7.0 Hz, OCH$_2$CH_3); δ_C 213.09 (C-9), 124.68 (q, J_{C-F}=284 Hz, *C*F$_3$), 81.40 (C-4), 79.36 (q, J_{C-F}=29 Hz, C-2), 65.19 (O*C*H$_2$CH$_3$), 54.39 (C-1), 50.08 (C-5), 33.17 (C-3), 30.82 and 30.29 (C-6 and C-8), 18.29 (C-7) and 15.37 (OCH$_2$*C*H$_3$); δ_F −81.57 (C*F*$_3$); ν_{max} (cm^{-1}) 3345 (OH), 2975, 2862, 1718 (CO), 1462, 1281, 1155, 1138, 1023, 972, 873; Found M$^+$ 266.1115, $C_{12}H_{17}F_3O_3$ requires M$^+$ 266.1130 *m/z* 266 (M$^+$,17%), 248 (27), 220 (20), 204 (45), 169 (97), 151 (17), 141 (100) and 98 (33).

4-(Ethyloxy)-2-hydroxy-7-methyl-2-(trifluoromethyl)bicyclo[3.3.1]nonan-9-one (10). To a stirred solution of 4-dimethylaminopyridine (1 mg, 8×10^{-3} mmol) and trifluoroacetic anhydride (0.27 g, 1.3 mmol) in anhydrous dichloromethane (1.5 ml) was added dropwise at −10°C ethyl vinyl ether (0.08 g, 1.1 mmol). After stirring for 19 h at 0°C the mixture was allowed to warm to room temperature and the solvent removed in vacuo. To the stirred resulting oil was added dropwise at room temperature a solution of freshly distilled 1-(4-methyl-1-cyclohexenyl)tetrahydro-1*H*-pyrrole (**9**) (0.40 g, 2.4 mmol) in anhydrous ether (2 ml). After stirring for 72 h at room temperature, water (5 ml) and diethyl ether (5 ml) were added, the reaction mixture was worked up as described above and the resultant red oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 7:3) to give the title compound (**10**) as a solid (0.28 g, 90%) and (*E*)-1,1,1-trifluoro-4-tetrahydro-1*H*-1-pyrrolyl-3-buten-2-one (**7**) (0.02 g, 9%) as colourless crystals. Recrystallisation of the title compound (**10**) from *n*-pentane afforded colourless crystals, mp 66–67°C; Found: C, 55.7; H. 6.6. $C_{13}H_{19}F_3O_3$ requires C, 55.7; H, 6.8%; δ_H 4.14 (1H, s, O*H*), 4.04 (1H, br t, J=4.0 Hz, H_{eq}-4), 3.62 (1H, dq, J=9.0, 7.0 Hz, OCH_2CH$_3$), 3.42 (1H, dq, J=9.0, 7.0 Hz, OCH_2CH$_3$), 2.78 (2H, m, H_{eq}-1, H_{eq}-5), 2.68 (1H, dd, J=15.4, 4.0 Hz, H_{eq}-3), 2.25 (3H, m, H_{ax}-3, H_{ax}-7, H_{eq}-6 or H_{eq}-8), 2.08 (1H, m, H_{eq}-6 or H_{eq}-8), 1.72 (1H, ddd, J=14.3, 12.1, 5.5 Hz, H_{ax}-6 or H_{ax}-8), 1.56 (1H, m, H_{ax}-6 or H_{ax}-8), 1.14 (3H, t, J=7.0 Hz, OCH$_2$CH_3) and 0.88 (3H, t, J=7.0 Hz, CH_3); δ_C 213.40 (C-9), 124.67 (q, J_{C-F}=284 Hz, *C*F$_3$), 81.31 (C-4), 79.34 (q, J_{C-F}=29 Hz, C-2), 65.18 (O*C*H$_2$CH$_3$), 54.18 (C-1), 49.98 (C-5), 39.28 and 38.62 (C-6 and C-8), 33.43 (C-3), 24.75 (C-7), 22.27 (*C*H$_3$) and 15.37 (OCH$_2$*C*H$_3$); δ_F −81.57 (C*F*$_3$); ν_{max} (cm^{-1}) 3458 (OH), 2961, 2875, 1728 (CO), 1460, 1276, 1160, 1118, 1021; found M$^+$ 280.1278, $C_{13}H_{19}F_3O_3$ requires M$^+$ 280.1286 *m/z* 280 (M$^+$, 20%), 262 (16), 234 (15), 218 (34), 169 (100), 151 (7), 141 (74) and 112 (36).

9-(Ethyloxy)-7-hydroxy-7-(trifluoromethyl)bicyclo[4.3.1]-decan-10-one (11). To a stirred solution of 4-dimethylaminopyridine (1 mg, 8×10^{-3} mmol) and trifluoroacetic anhydride (0.27 g, 1.3 mmol) in anhydrous dichloromethane (1.5 ml) was added dropwise at −10°C ethyl vinyl ether (0.08 g, 1.1 mmol). After stirring for 19 h at 0°C the mixture was allowed to warm to room temperature and the solvent removed in vacuo. To the stirred resulting oil was added dropwise at room temperature a solution of freshly distilled 1-(1-cycloheptenyl)tetrahydro-1*H*-pyrrole (**12**) (0.40 g, 2.4 mmol) in anhydrous ether (2 ml). After stirring for 76 h at room temperature, 5% aqueous acetic acid (20 ml) was added and the mixture was heated under reflux for 90 min. The mixture was cooled to room temperature, worked up as described above and the resultant brown oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 3:2) to give the title compound (**11**) as a solid (0.14 g, 44%) and (*E*)-1,1,1-trifluoro-4-tetrahydro-1*H*-1-pyrrolyl-3-buten-2-one (**7**) (0.03 g, 14%) as a colourless solid. Recrystallisation of the title compound (**11**) from *n*-pentane afforded colourless needles, mp 82–83°C; Found: C, 55.7; H. 6.6. $C_{13}H_{19}F_3O_3$ requires C, 55.7; H, 6.8%; δ_H 3.97 (1H, dt, J=10.2, 6.0 Hz, H_{ax}-9), 3.53 (1H, dq, J=9.0, 7.0 Hz, OCH_2CH$_3$), 3.49 (1H, s, O*H*), 3.41 (1H, dq, J=9.0, 7.0 Hz, OCH_2CH$_3$), 3.19 (1H, dt, J=9.8, 4.9 Hz, H_{eq}-1), 2.76 (1H, br t, J=5.1 Hz, H_{eq}-6), 2.18 (1H, d, J=5.2 Hz, H_{eq}-8), 2.17 (1H, d, J=10.7 Hz, H_{ax}-8), 1.65 (8H, m, H-2, H-3, H-4, H-5), 1.18 (3H, t, J=7.0 Hz, OCH$_2$CH_3; δ_C 211.63 (C-10), 125.21 (q, J_{C-F}=286 Hz, *C*F$_3$, 75.54 (q, J_{C-F}=29 Hz, C-7), 73.16 (C-9), 64.13 (O*C*H$_2$CH$_3$), 55.99 (C-6), 51.83 (C-1), 30.12 (C-8), 25.78, 25.04 and 21.54 (C-2, C-3, C-4 and C-5), and 15.49 (OCH$_2$*C*H$_3$); δ_F −81.98 (C*F*$_3$); ν_{max} (cm^{-1}) 3422 (OH), 2936, 2873, 1703 (CO), 1456, 1280, 1164, 1109, 1076;

Found M^+ 280.1283, $C_{13}H_{19}F_3O_3$ requires M^+ 280.1286 *m/z* 280 (M^+, 29%), 262 (26), 234 (16), 218 (25), 169 (100), 141 (78) and 112 (32).

5-Hydroxy-2,6-dimethyl-5-(trifluoromethyl)-2-cyclohexen-1-one (13). To a stirred solution of 4-dimethylaminopyridine (1 mg, 8×10^{-3} mmol) and trifluoroacetic anhydride (0.27 g, 1.3 mmol) in anhydrous dichloromethane (1.5 ml) was added dropwise at −10°C ethyl vinyl ether (0.08 g, 1.1 mmol). After stirring for 19 h at 0°C the mixture was allowed to warm to room temperature and the solvent removed in vacuo. To the stirred resulting oil was added dropwise at room temperature a solution of freshly distilled 1-(*Z*-1-ethyl-1-propenyl)tetrahydro-1*H*-pyrrole (**14**) (0.33 g, 2.4 mmol) in anhydrous ether (2 ml). After stirring for 74 h at room temperature, 5% aqueous acetic acid (20 ml) was added and the mixture was heated under reflux for 90 min. The mixture was allowed to cool to room temperature, worked up as described above and the resultant brown oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 7:3) to give the title compound (**13**) as a yellow oil (0.09 g, 39%) and (*E*)-1,1,1-trifluoro-4-tetrahydro-1*H*-1-pyrrolyl-3-buten-2-one (**7**) (0.03 g, 14%) as a colourless solid. The title compound (**13**) was isolated as a mixture (3:2) of diastereoisomers, δ_H 6.52 (1H, br s, H-3), 3.50 (0.6H, br s, O*H*), 3.18 (0.4H, br s O*H*) 2.69 (3H, m, H-4, H-6), 1.79 (3H, s, C-2-CH_3), 1.25 (1.2H, dd, *J*=7.0, 1.1 Hz, C-6-CH_3), 1.17 (1.8H, dd, *J*=7.4, 1.5 Hz, C-6-CH_3); δ_C 200.15 (C-1), 198.17 (C-1), 137.57 (C-3), 137.38 (C-3), 134.92 (C-2), 133.87 (C-2), 125.43 (q, J_{C-F}=287 Hz, CF_3), 125.16 (q, J_{C-F}=286 Hz, CF_3), 76.65 (q, J_{C-F}=28 Hz, C-5), 76.58 (q, J_{C-F}=28 Hz, C-5), 48.25 (C-6), 46.16 (C-6), 32.34 (C-4), 29.34 (C-4), 15.93 (C-2-*C*H_3), 15.87 (C-2-*C*H_3), 13.33 (C-6-*C*H_3) and 8.77 (C-6-*C*H_3); δ_F −82.40 (CF_3); ν_{max} (cm^{-1}) 3426 (OH), 2983, 2928, 1673 (CO), 1303, 1172, 1130; Found M^+ 208.0720, $C_9H_{11}F_3O_2$ requires M^+ 208.0711 *m/z* 208 (M^+, 39%), 191 (6), 163 (19), 139 (13), 82 (100). The minor fraction was recrystallised from petroleum ether to afford (*E*)-1,1,1-trifluoro-4-tetrahydro-1*H*-pyrrolyl-3-buten-2-one (**7**), mp 68–69°C; Found: C, 49.6; H, 5.0; N, 7.2. $C_8H_{10}F_3NO$ requires C, 49.7; H, 5.2; N, 7.3%; δ_H 8.07 (1H, d, *J*=12.1 Hz, H-4), 5.23 (1H, d, *J*=12.1 Hz, H-3), 3.62 (2H, t, *J*=6.6 Hz, NCH_2), 3.31 (2H, t, *J*=6.6 Hz, NCH_2), 2.08 (2H, dquin, *J*=1.5, 6.6 Hz, CH_2), 1.99 (2H, dquin, *J*=1.5, 6.6 Hz, CH_2); δ_C 176.86 (q, J_{C-F}=33 Hz, C-2), 152.67 (C-4), 118.02 (q, J_{C-F}=291 Hz, C-1), 88.39 (C-3), 53.24 (NCH_2), 47.70 (NCH_2), 25.20 (CH_2), 25.06 (CH_2); δ_F −84.67 (CF_3); ν_{max} (cm^{-1}) 2984, 2884, 1654, 1572, 1256, 1173, 1090, 894 and 769; Found M^+ 193.0714, $C_8H_{10}F_3NO$ requires M^+ 193.0714 *m/z* 193 (M^+, 29%), 124 (100), and 96 (5).

2,6-Dimethyl-1-hydroxy-3-(trifluoromethyl)benzene (16). To a stirred solution of 5-hydroxy-2,6-dimethyl-5-(trifluoromethyl)-2-cyclohexen-1-one (**13**) (0.06 g, 0.3 mmol) in anhydrous ether (2 ml) was added dropwise at room temperature under nitrogen anhydrous triethylamine (0.12 g, 1.2 mmol) followed by methanesulfonyl chloride (0.07 g, 0.6 mmol). After stirring for 24 h at room temperature, 2 M hydrochloric acid (5 ml) and dichloromethane (5 ml) were added. The two phases were separated and the aqueous phase extracted with dichloromethane (2×5 ml). The combined organic phases were washed with 2 M sodium hydroxide solution (5 ml) and the aqueous phase extracted with dichloromethane (2×5 ml). The combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo. The resultant brown oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 88:12) to give the title compound (**16**) as a colourless oil (0.04 g, 73%); δ_H 7.14 (1H, d, *J*=8.1 Hz, H-5), 7.05 (1H, d, *J*=8.1 Hz, H-4), 4.25 (1H, br s, O*H*), 2.35 (3H, d, *J*=1.1 Hz, C-6-CH_3), 2.30 (3H, s, C-2-CH_3); δ_C 152.99 (C-1), 127.87 (C-5), 127.13 (C-2), 124.65 (q, J_{C-F}=273 Hz, CF_3), 121.92 (C-6), 117.82 (q, J_{C-F}=6 Hz, C-4), 16.36 (C-6-*C*H_3) and 11.76 (C-2-*C*H_3); δ_F −94.92 (CF_3); ν_{max} (cm^{-1}) 3780 (OH), 2985, 2935, 1320, 1241, 1173, 1119, 1013; *m/z* 190 (M^+, 75%), 121 (34), 86 (100).

X-Ray structural analysis of 4-(ethyloxy)-2-hydroxy-7-methyl-2-(trifluoromethyl)bicyclo[3.3.1]nonan-9-one (10). A rather weakly diffracting crystal (0.35×0.22×0.18 mm) was obtained by recrystallisation from *n*-pentane. Crystal data: $C_{13}H_{19}F_3O_3$, *M*=280.29, triclinic space group *P*-1 (#2), *a*=12.435(7), *b*=12.561(6), *c*=10.068(4) Å, α=90.60(4), β=98.19(4), γ=117.74(3)°, *V*=1372(1) $Å^3$, *Z*=4. D_{calc}=1.356 g cm^{-3}, μ=1.20 cm^{-1}, *F*(000)=592. Data collection used a Rigaku AFC7S four-circle diffractometer [λ(Mo-K_α)=0.71073 Å] operating at 150 K. 2923 unique data were collected (R_{int}=0.034) of which 1913 with $I>2.5\sigma(I)$ were used in all calculations. The structure was solved using SHELXS-86[19] and refined using TEXSAN,[20] which revealed two essentially indistinguishable independent molecules in the asymmetric unit. The O and F atoms were refined anisotropically and H atoms were included in fixed calculated positions. *R*=0.051, R_w=0.59, Goof=2.47, $w^{-1}=\sigma^2(F)$.

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References

1. Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993; Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131.
2. Banks, R. E.; Tatlow, J. C. Synthesis of Organofluorine Compounds. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994; pp 25–55.
3. Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7261.
4. Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7267.
5. Bartnik, R.; Bensadat, A.; Cal, D.; Faure, R.; Khatimi, N.; Laurent, A.; Laurent, E.; Rizzon, C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 725.
6. Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499.
7. Hojo, M.; Masuda, R.; Kamitori, Y. *Tetrahedron Lett.* **1976**, 1009.
8. Nenajdenko, V. G.; Krasovsky, A. L.; Lebedev, M. V.; Balenkova, E. S. *Synlett* **1997**, 1349.

9. Platoshkin, A. M.; Cheburkov, Y. A.; Knunyants, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1969**, 112.
10. Schreiber, S. L. *Tetrahedron Lett.* **1980**, *21*, 1027; Schreiber, S. L. U.S. Patent, 4,322,537, 1982.
11. Soufyane, M.; Mirand, C.; Levy, J. *Tetrahedron Lett.* **1993**, *34*, 7737.
12. Hojo, M.; Masuda, R.; Okada, E. *Tetrahedron Lett.* **1989**, *30*, 6173.
13. Keller, H.; Schlosser, M. *Tetrahedron* **1996**, *52*, 4637.
14. Simchen, G.; Schmidt, A. *Synthesis* **1997**, 117.
15. Mo, X.-S.; Huang, Y.-Z. *Synlett* **1995**, 180.
16. Appleton, R. A.; Baggaley, K. H.; Egan, C.; Davies, J. M.; Graham, S. H.; Lewis, D. O. *J. Chem. Soc. B* **1968**, 2032; Sokolova, I. M.; Matveeva, I. A.; Petrov, A. A. *Neftekhimya* **1973**, *13*, 361.
17. Butkus, E.; Stoncius, A. *Synlett* **1999**, 234.
18. Sandris, C.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1958**, 1524; Biellmann, J.-F.; Hanna, R.; Ourisson, G.; Sandris, C.; Waegell, B. *Bull. Soc. Chim. Fr.* **1960**, 1429.
19. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
20. TEXSAN: Crystal Structure Package, Molecular Structure Corporation, The Woodlands, Texas, 1995.