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New derivatives of trifluoroacetyl acetaldehyde and trifluoroaldol

Ivan S. Kondratov[a], Igor I. Gerus[a,*], Aleksey D. Kacharov[a], Marina G. Gorbunova[a], Valery P. Kukhar[a], Roland Fröhlich[b]

[a]*Institute of Bioorganic Chemistry and Petrochemistry of National Ukrainian Academy of Science, Murmanska 1, Kiev 02094, Ukraine*
[b]*Organisch-Chemisches Institut der Universität Münster, Corrensstraße 40, D-48149 Münster, Germany*

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Dedicated to Prof. Richard D. Chambers on the occasion of his 70th birthday.

Abstract

The reaction of β-ethoxyvinyl trifluoromethyl ketone **1** with *O*-nucleophiles such as alcohols and diols leads to various derivatives of trifluoroacetyl acetaldehyde, such as β-alkoxyvinyl trifluoromethyl ketones **3** and cyclic keto acetals **4**. Several derivatives synthesized contain chiral auxiliaries. Reduction of the compounds **1**, **3**, **4** under various reaction conditions leads to the trifluoroaldol derivatives **6**, **7**, **9**, **10** containing a protected aldehyde group. The compounds obtained are useful building blocks in fluoroorganic synthesis.

Keywords: Fluorinated β-alkoxyvinyl ketones; Fluorinated β-keto acetals; *O*-nucleophiles; Chiral auxiliary; Reduction

1. Introduction

The exchange of a methyl group by a trifluoromethyl group is a possible strategy for the design of new biologically active compounds [1,2]. Along with a number of methods based on trifluoromethylation reagents suitable for direct introducing of the trifluoromethyl group into certain position of the molecules, methods, based on the use of available CF_3-containning reactive compounds as building blocks, are actual too [3,4].

Typical examples of such building blocks are fluorinated 1,3-dicarbonyl compounds [5,6]. Fluorine containing β-diketones and β-ketoesters are used widely in synthetic practice and one can expect that fluorinated β-ketoaldehydes can be beneficial in fluoroorganic synthesis. However, fluorinated β-ketoaldehydes are mostly unknown. Trifluoroacetyl acetaldehyde building blocks attract the most attention due to their availability and, the diversity of trifluoromethyl compounds, which can be synthesized using them [7].

Among various known derivatives of trifluoroacetyl acetaldehyde the most popular are available β-alkoxyvinyl trifluoromethyl ketones (Fig. 1) [7,8], which are prepared easily by trifluoroacetylation of corresponding alkylvinyl ethers [9,10]. This route to the β-alkoxyvinyl trifluoromethyl ketones becomes more complicated when it is necessary to use non-commercial alkyl vinyl ethers, for example with chiral alkoxy group such as α-phenylethoxy. In this case it was demonstrated only once for the asymmetric synthesis of trifluoromethyl containing deoxysugars (Scheme 1) [11].

Substitution of an ethoxy group in β-ethoxyvinyl trifluoromethyl ketone **1** with any alkoxy group looks very attractive and useful for the synthesis of various β-alkoxyvinyl trifluoromethyl ketones. Earlier substitution of the methoxy group in β-methoxy-β-methylvinyl trifluoromethyl ketone with some alkoxygroups in β-methoxy-β-methylvinyl trifluoromethyl ketone (a derivative of trifluoracetyl acetone) by heating in CCl_4 with dry SiO_2 was described [12]. However, the reactivity of β-methoxy-β-methylvinyl trifluoromethyl ketone is lower than that of the enone **1** [13]. For example, we have observed previously, that the latter reacts with methanol at room temperature in contrast to its nonfluorinated analogue and β-methoxy-β-methylvinyl trifluoromethyl ketone [14].

This article describes reactions of β-ethoxyvinyl trifluoromethyl ketone **1** with *O*-nucleophiles as a convenient

* Corresponding author. Tel.: +380 445 732 598; fax: +380 445 732 552.
E-mail address: igerus@hotmail.com (I.I. Gerus).

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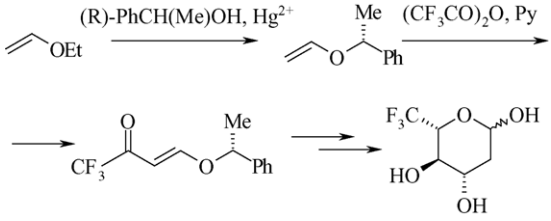
Trifluoroacetyl acetaldehyde β-Alkoxyvinyl trifluoromethyl ketones

Fig. 1. Trifluoroacetyl acetaldehyde, β-alkoxyvinyl trifluoromethyl ketones.



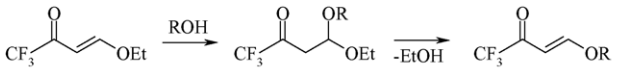
Scheme 1. Asymmetric synthesis of trifluoromethyl containing deoxysugars.

method for the synthesis of trifluoroacetyl acetaldehyde derivatives.

2. Results and discussion

Enone **1** reacts easily with various alcohols and new corresponding β-alkoxyvinyl trifluoromethyl ketones **3** are obtained in good to high yields (Scheme 2). The reaction is similar to *trans*-esterification because enone **1** is a vinylog of ethyl trifluoroacetate. The first step is Michael addition of alcohols to the C=C double bond of enone **1** with the formation of the corresponding mixed keto acetals **2**, which eliminate ethanol easily with the formation of products **3**. The formation of intermediate keto acetals **2** can be observed by ^{1}H and ^{19}F NMR spectra of the reaction mixtures, but after vacuum distillation only products **3** were obtained.

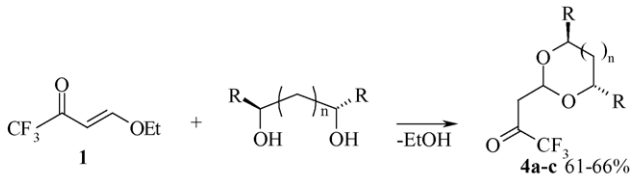
The reaction conditions depend on the nature of the alcohol ROH. Thus, at room temperature, enone **1** reacts with ethanol slowly (about 10 days in a 10% solution). More hindered alcohols such as *i*-propanol and *t*-butanol react too slowly and the reaction was carried out with heating. We also used various catalysts to accelerate the reaction. Basic catalysts (K_2CO_3, KOH) work well for the fast addition of an alkoxy group to C=C double bond of the enone **1** but in addition they provoke further side condensation of the intermediate acetals **2** as a result of interaction between the carbonyl and methylene groups. However, only basic



1 **2a-i** **1, 3b-i** 41-90%

R=Et (**a**), *i*-Pr (**b**), *t*-Bu (**c**), *i*-Amyl (**d**), $C_2H_5CH(CH_3)CH_2$ (**e**), CH_2Ph (**f**), *rac*-CH(Me)Ph (**g**), *(-)*-Menthyl (**h**), *(-)*-Bornyl (**i**)

Scheme 2. Reaction of enone **1** with alcohols.



1 **4a-c** 61-66%

R = H, n=0 (**a**), R = COOEt, n=0 (**b**), R = H, n=1 (**c**)

Scheme 3. Reaction of enone **1** with diols.

catalysts allowed us to isolate acetal **2a** in moderate yield. Some of the mixed keto acetals **2** (R = Me, Et, allyl, propargyl) were obtained earlier as hydrates by the reaction of enone **1** with an alcohol in water solution in presence of sodium azide [15]. Acidic catalysts (*p*-toluenesulfonic acid and its pyridinium salt) also accelerate addition of the alkoxy group to enone **1** but under these conditions the intermediate acetals **2** are unstable and enones **3** were obtained as the main products. Thus, for the preparation of the majority of alkoxyenones **3** the typical reaction conditions are *p*-toluenesulfonic acid as a catalyst with the azeotropic removal of ethanol in solvents such as benzene or toluene. Only in the case of the reaction between enone **1** with α-phenylethanol an acidic catalyst cannot be used because of the formation of styrene.

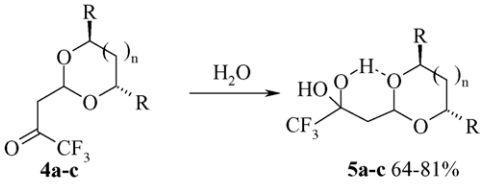
The reaction with alcohols is of particular interest as a simple, one step method for obtaining enones **3** with chiral auxiliaries. We have synthesized enones **3** with the menthyl (**h**), bornyl (**i**) and α-phenylethyl (**g**) chiral alkoxy groups. The synthesis of the last compound, **3g**, seems to be more convenient than that described [11], because the chiral alcohol was involved at the last step. All of the enones **3** obtained are colourless liquids with specific smell as starting enone **1**. The structures of the compounds were proved by NMR spectra, and we have found that C=C double bond has the *E*-configuration ($^{3}J_{HH} \sim 12$ Hz).

Enone **1** reacts with various diols with heating both neat and in toluene solution, with catalytic quantity of *p*-toluenesulfonic acid and simultaneous removal of ethanol. Corresponding cyclic keto acetals **4** were obtained in high yields (Scheme 3).

Similarly to the reaction of enone **1** with alcohols, the interaction with diols also involves Michael addition of one hydroxy group of the diol to the C=C double bond of enone **1** in the first step. The following intramolecular nucleophilic substitution of the ethoxy group by the second hydroxy group of the diol gives cyclic keto acetals **4** as the result of their higher stability in comparison with acyclic acetals **2**. Compounds **4** are trifluoroacetyl acetaldehyde derivatives with protected aldehyde groups and may be new building blocks for fluoroorganic synthesis. The chiral keto acetal **4b** was synthesized when diethyl L-tartrate was used as a diol.

Keto acetals **4a–c** react easily with water and corresponding hydrates **5a–c** were obtained as crystalline and quite stable compounds in high yields (Scheme 4).

We can explain the stability of the hydrates **5** by an influence of the electron withdrawing trifluoromethyl



R = H, n=0 (**a**), R = COOEt, n=0 (**b**), R = H, n=1 (**c**).

Scheme 4. Formation of hydrates **5**.

group and formation of the intramolecular hydrogen bond between the hydroxy group and the oxygen atom of the acetal cycle. The explanation of the stabilisation of ketone hydrates by a heteroatom at the β-position to carbonyl group was previously described for β-*N*,*N*-dialkylamino trifluoromethyl ketones [16]. The X-ray analysis data of the compound **5c** confirmed our assumption that intramolecular hydrogen bond is formed (Fig. 2). The main geometric parameters of the H-bonds: intramolecular O(81)···O(2) 2.696 Å, O(81)H(O81)O(2) 142°; intermolecular O(82**)···O(6) 2.753 Å, O(82**)H(O82**)O(6) 169°.

We have found that hydrates **5a–c** partially dissociate in solutions to give ketones **4a–c** and water. The equilibrium was observed by ^{1}H and ^{19}F NMR spectra: in $CDCl_3$ solution hydrates **5** are present as a mixture of the compounds **4** and **5** in about 1:4 ratio and the signal of water protons at ~1.7 ppm is present. The easiest way to control the equilibrium between **4** and **5** is the observation by ^{19}F NMR spectra because signals of CF_3-group of the ketones **4** are observed at −80.2 ppm whereas the signals of hydrates **5** are strongly shifted ~8 ppm to higher field (up to −88 ppm). This methodology allowed us to determine the ratio formed of hydrate **5b** to ketone **4b** when dissolving **5b** in various solvents. The degree of dissociation depends on the polarity of the solvents; the percentage of hydrate **5b** decreases with the decrease of the solvent polarity (Table 1). This tendency was detected also by IR spectroscopy. IR spectra of hydrates **5** in KBr plates contained a broadened band due to

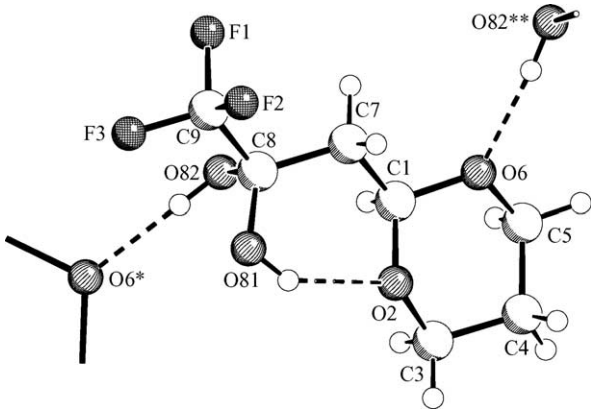
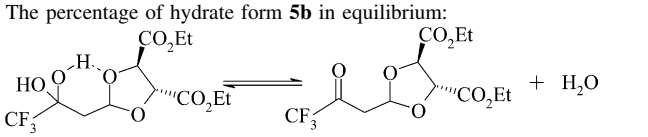


Fig. 2. An ORTEP view of keto acetal hydrate **5c**.

Table 1
The percentage of hydrate form **5b** in equilibrium:



5b **4b**

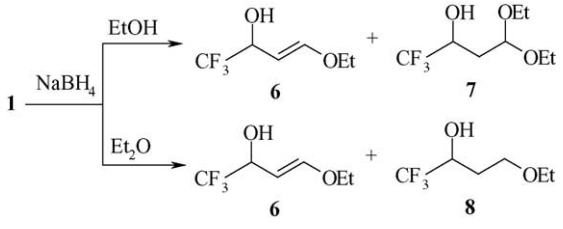
Solvent	Percentage of hydrate **5b** (%)
H_2O	100
CH_3CN	88
$CHCl_3$	80
$PhCH_3$	71.5
CCl_4	58.5

hydroxyl-groups involved in hydrogen bond formation (at ν_{OH} 3430 cm^{-1}) and no band due to $COCF_3$-group, whereas in $CHCl_3$ solution additional bands of free water (at ν_{OH} 3670 cm^{-1}) and the carbonyl group of the $COCF_3$-fragment (at $\nu_{C=O}$ 1770 cm^{-1}) were observed.

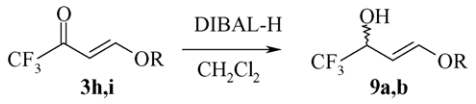
To demonstrate the possibilities of the synthetic use of compounds **3** and **4** we have studied reduction of their free carbonyl group and the diastereoselectivity of the reaction was evaluated for the chiral compounds **3h–i** and **4b**.

We have found that reduction of enone **1** with sodium borohydride leads to the formation of a mixture of products (Scheme 5). The structures of the products determined by NMR spectroscopy depend on the nature of a solvent. When the reduction was carried out in ethanol solution, the mixture of alcohol **6** (the carbonyl group reduction product) and hydroxy acetal **7** (product of ethanol addition to the C=C double bond followed by the reduction of the intermediate keto acetal) was formed. Use of aprotic solvents such as ether, dioxane or dichloromethane for this reaction gives the mixture of the products **6** and **8** (product of total reduction).

Alcohols **9a**,**b** were obtained as sole products when reducing agent DIBAL-H was used for the reduction of chiral enones **3h**,**i**; unfortunately, yields and diastereoselectivity were low (Scheme 6). The ratio between the diastereomers was observed by ^{19}F NMR spectra due to the difference in the chemical shifts of the signals of CF_3-groups of the diastereomeric alcohols. In the ^{1}H NMR spectra of the diastereomers **9a** signals of the protons of the C=CH–O fragment also have different chemical shifts but other signals overlapped. Low diastereoselectivity can be explained by the long distance between the chiral alkoxy fragment and the reacting carbonyl group. Compounds **9** and

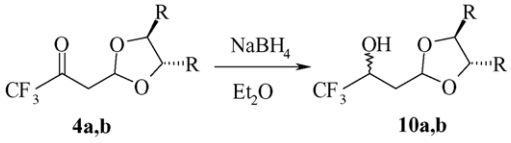


Scheme 5. The reduction of enone **1** with $NaBH_4$.



R = *(-)*-Menthyl (**9a**) 10% yield, d.e.~0%, *(-)*-Bornyl (**9b**) 13.5% yield, d.e.~34%

Scheme 6. The reduction of enones **3h**,**i** with DIBAL-H.



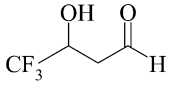
R = H (**a**), 90% yield, COOEt (**b**), 69.6% yield, d.e.~15%

Scheme 7. The reduction of keto acetals **4a**,**b** with $NaBH_4$.

6 have an *E*-configuration of C=C double bond ($^3J_{HH}$ = 12–13 Hz).

In contrast to the formation of mixtures of products and low yields for the reduction of enones **1** and **3**, reduction of keto acetals **4a**,**b** by sodium borohydride in ether gives corresponding hydroxy acetals **10a**,**b** in high yields (Scheme 7). For the chiral keto acetal **4b** poor diastereoselectivity of the reduction was observed by ^{19}F NMR spectroscopy in a similar manner as for the compounds **9**.

Compounds **9** and **10** are derivatives of trifluoroaldol with a protected aldehyde group and potential building blocks for the synthesis of trifluoromethyl containing compounds. Easy determination of the diastereomeric ratio of alcohols **9** or **10** by ^{19}F NMR spectroscopy makes these compounds attractive for the investigation of diastereoselective reduction by the chiral reducing reagents or in the presence of chiral catalysts



Trifluoroaldol

3. Conclusions

The reaction of β-ethoxyvinyl trifluoromethyl ketone **1** with various *O*-nucleophiles makes it possible to synthesize new derivatives of trifluoroacetyl acetaldehyde. Several derivatives contain chiral auxiliaries and can be used in asymmetric synthesis. Reduction of the trifluoroacetyl acetaldehyde derivatives leads to the synthetic equivalents of trifluoroaldol. The compounds synthesized are potentially useful building blocks for fluoroorganic synthesis.

4. Experimental

4.1. General

^1H and ^{19}F NMR spectra were recorded on a Varian VXR instrument (300 and 282.2 MHz) in $CDCl_3$ solutions using TMS and CCl_3F as internal standards, respectively. IR spectra were recorded on ''Specord M-80''. A data set for X-ray analysis was collected with a Nonius KappaCCD diffractometer, equipped with a rotating anode generator Nonius FR591. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN [17], structure solution SHELXS-97 [18], structure refinement SHELXL-97 (G.M. Sheldrick, Universität Göttingen, 1997), graphics SCHAKAL (E. Keller, 1997). The conversion of reactions was monitored by GLC-chromatography on a ''Chrom-5'' instrument (FID, thermostat temperature: 100–250 °C, gas-carrier-nitrogen (20–30 ml min^{-1}), steel column 3 mm × 2400 mm, stationary phase SE-30 (5%)) or by TLC-plates (silica gel 60 F_{254}, Merck). Column chromatography was carried out on silica gel 60 (Merck no. 109385, particle size 0.040-0.063). Starting materials were commercially available (Aldrich, Fluka, Merck). All solvents and liquid reagents were distilled before using. Starting enone **1** was prepared according to the literature procedure [9].

4.2. 4,4-Diethoxy-1,1,1-trifluoro-2-butanone (*2a*)

The mixture of enone **1** (5.8 g, 35 mmol), ethanol (4.7 g, 102 mmol) and catalytic amount of KOH (0.2 g) was stirred for 24 h at 20 °C. The product was distilled in vacuum and corresponding compound **2a** (6.1 g, 81%) was obtained. b.p. 50–51 °C (12 Torr). ^1H NMR δ_H 1.13 t (6H, $2CH_3$, J_{HH} = 6.8 Hz), 3.0 d (2H, $CO–CH_2$, J_{HH} = 5.0 Hz), 3.55 m (4H, $2OCH_2$), 4.95 t (1H, CHO_2, J_{HH} = 5.0 Hz). ^{19}F NMR: δ_F −80.00 s (CF_3). Anal. Calcd. for $C_8H_{13}F_3O_3$: C, 44.86; H, 6.06. Found: C, 44.75; H, 6.30%. Spectroscopic data are corresponded to literature data [15].

4.3. (E)-1,1,1-Trifluoro-4-isopropoxy-3-buten-2-one (*3b*)

Enone **1** (4.2 g, 25 mmol) was refluxed in excess of isopropyl alcohol (6 g, 100 mmol). The conversion was monitored by GLC. After about 5 h the equilibrium between **1** and **3** was reached and the product was distilled in vacuum and corresponding compound **3b** (2.2 g, 48% as mixture with 18% of starting enone **1**) was obtained. b.p. 53–54 °C (12 Torr). ^1H NMR: δ_H 1.37 d (6H, $2CH_3$, J_{HH} = 6.2 Hz), 4.41 sept (1H, CH, J_{HH} = 6.2 Hz), 6.00 d (1H, C=CH–C, J_{HH} = 11.9 Hz), 7.89 d (1H, C=CH–O, J_{HH} = 11.9 Hz); ^{19}F NMR: δ_F −78.60 s (CF_3). Anal. Calcd. for $C_7H_9F_3O_2$: C, 46.16; H, 4.98. Found: C, 45.67; H, 4.88%.

4.4. (E)-Trifluoro-4-(tert-butoxy)-3-buten-2-one (3c)

3c was obtained in conditions as described above for enone **3b** (Section 4.3) from 4.2 g (25 mmol) of enone **1** in 7.4 g (100 mmol) of *tert*-butyl alcohol. Yield: 2.0 g (41% as mixture with 15% of starting enone **1**). b.p. 58–62 °C (12 Torr). ^{1}H NMR: δ_H 1.43 s (9H, $3CH_3$), 5.96 d (1H, C–CH=C, J_{HH} = 11.5 Hz), 8.06 d (1H, C=CH–O, J_{HH} = 11.5 Hz). ^{19}F NMR: δ_F −78.62 s (CF_3). Anal. Calcd. for $C_8H_{11}F_3O_2$: C, 48.98; H, 5.65. Found: C, 48.38; H, 5.49%.

4.5. (E)-1,1,1-Trifluoro-4-(isopentyloxy)-3-buten-2-one (3d)

The mixture of enone **1** (3 g, 18 mmol), 4 g (45 mmol) of 3-methyl-1-butanol, 10 ml of benzene and catalytic amount of *p*-toluenesulfonic acid (10 mg) was refluxed with simultaneous distillation of ethanol/benzene azeotrope. The conversion was monitored by GLC and, if it was necessary, additional portion of benzene was added until enone **1** disappeared by GLC. After about 2 h benzene was removed and the residue was distilled in vacuum and 2.55 g (68.0%) of corresponding compound **3d** was obtained. b.p. 98–100 °C (20 Torr). ^{1}H NMR: δ_H 0.95 d (6H, $2CH_3$, J_{HH} = 6.5 Hz), 1.65 dt (2H, C–CH_2–C, J_{HH} = 6.7, 6.8 Hz), 1.74 t sept (1H, CH, J_{HH} = 6.5, 6.8 Hz), 4.06 t (2H, CH_2O, J_{HH} = 6.7 Hz), 5.86 d (1H, C–CH=C, J_{HH} = 12.2 Hz), 7.90 d (1H, C=CH–O, J_{HH} = 12.2 Hz). ^{19}F NMR: δ_F −78.25 s (CF_3). Anal. Calcd. for $C_9H_{13}F_3O_2$: C, 51.43; H, 6.23. Found: C, 51.95; H, 6.34%.

4.6. (E)-1,1,1-Trifluoro-4-(2-methylbutoxy)-3-buten-2-one (3e)

3e was obtained in conditions as described above for enone **3d** (Section 4.5) from 3 g (18 mmol) of enone 1, 4 g (45 mmol) of 2-methylbutanol and 10 mg of *p*-toluenesulfonic acid. Yield: 2.41 g (64.3%). b.p. 97–98 °C (18 Torr). ^{1}H NMR: δ_H 0.94 m (6H, $2CH_3$), 1.48 m (2H, C–CH_2–C), 1.84 m (1H, C–CH–C), 3.82 dd (1H, H_a of CH_2O, J_{HH} = 6.6, 9.8 Hz), 3.90 dd (1H, H_b of CH_2O, J_{HH} = 5.8, 9.8 Hz), 5.86 d (1H, C–CH=C, J_{HH} = 12.2 Hz), 7.91 d (1H, C=CH–O, J_{HH} = 12.2 Hz). ^{19}F NMR: δ_F −78.27 s (CF_3). Anal. Calcd. for $C_9H_{13}F_3O_2$: C, 51.43; H, 6.23. Found: C, 51.81; H, 6.27%.

4.7. (E)-4-(Benzyloxy)-1,1,1-trifluoro-3-buten-2-one (3f)

3f was obtained in conditions as described above for enone **3d** (Section 4.5) from 1.2 g (7 mmol) of enone **1** and 0.64 g (6 mmol) of benzyl alcohol in 10 ml of toluene. Yield: 1.07 g (78.6%). b.p. 125–127 °C (11 Torr). ^{1}H NMR: δ_H 5.08 s (2H, CH_2), 6.00 d (1H, C–CH=C, J_{HH} = 12.3 Hz), 7.42 m (5H, C_6H_5), 8.01 d (1H, O–CH=C, J_{HH} = 12.3 Hz). ^{19}F NMR: δ_F −78.23 s (CF_3). Anal. Calcd. for $C_{11}H_9F_3O_2$: C, 57.40; H, 3.94. Found: C, 57.73; H, 3.81.

4.8. (E)-1,1,1-Trifluoro-4-(1-phenylethoxy)-3-buten-2-one (3g)

3g was obtained in conditions as described above for enone **3d** (Section 4.5) from 1.2 g (7 mmol) of enone **1** and 0.73 g (6 mmol) of 1-phenylethanol in 10 ml of toluene. Yield: 0.92 g (60.7%). b.p. 74–76 °C (0.1 Torr). ^{1}H NMR: δ_H 1.68 d (3H, CH_3, J_{HH} = 6.4 Hz), 5.21 q (1H, CHO, J_{HH} = 6.4 Hz), 5.95 d (1H, C=CH–C, J_{HH} = 12.1 Hz), 7.38 m (5H, C_6H_5), 7.88 d (1H, C=CH–O, J_{HH} = 12.1 Hz). ^{19}F NMR: δ_F −77.7 s (CF_3).). Anal. Calcd. for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 59.34; H, 4.43%. Spectroscopic data corresponded to literature data [11].

4.9. (E)-1,1,1-Trifluoro-4-[((1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl)oxy]-3-buten-2-one (3h)

3h was obtained in conditions as described above for enone **3d** (Section 4.5) from 4.2 g (25 mmol) of enone **1**, 3.9 g (25 mmol) of (−)-menthol and 10 mg of *p*-toluenesulfonic acid in 15 ml of toluene. Yield: 6.21 g (90.1%). b.p. 138–140 °C (11 Torr). $[\alpha]_D^{24} = -73.75$ (c = 4, $CHCl_3$). ^{1}H NMR: δ_H 0.76–1.22 m (12H, protons of menthol skeleton), 1.40–1.53 m (2H, protons of menthol skeleton), 1.72 m (2H, protons of menthol skeleton), 2.00 m (2H, protons of menthol skeleton), 3.91 dt (1H, CHO of menthol skeleton, J_{HH} = 10.6, 4.6 Hz), 5.92 d (1H, C–CH=C, J_{HH} = 12.0 Hz), 7.91 d (1H, C=CH–O, J_{HH} = 12.0 Hz). ^{19}F NMR: δ_F −78.18 s (CF_3). IR ($CHCl_3$, cm^{-1}): ν 3030, 2960, 2925, 2875, 1700, 1600, 1260, 1190, 1145, 1050, 970. Anal. Calcd. for $C_{14}H_{21}F_3O_2$: C, 60.42; H, 7.61. Found: C, 60.89; H, 7.70%.

4.10. (E)-1,1,1-Trifluoro-4-[(endo-(1S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]-3-buten-2-one (3i)

3i was obtained in conditions as described above for enone **3d** (Section 4.5) from 4.2 g (25 mmol) of enone **1**, 3.85 g (25 mmol) of (−)-borneol and 10 mg of *p*-toluenesulfonic acid in 15 ml of toluene. Yield: 5.5 g (79.7%). b.p. 139–140 °C (11 Torr). $[\alpha]_D^{24} = -46,67$ (c = 3, $CHCl_3$). ^{1}H NMR: δ_H 0.9 m (9H, $3CH_3$), 1.09–1.42 m (3H, protons of borneol skeleton), 1.69–2.00 m (3H, protons of borneol skeleton), 2.38 m (1H, proton of borneol skeleton), 4.31 ddd (1H, CHO of borneol sceleton, J_{HH} = 10.0, 2.9, 1.9 Hz), 5.84 d (1H, C–CH=C, J_{HH} = 12.2 Hz), 7.90 d (1H, C=CH–O, J_{HH} = 12.2 Hz). ^{19}F NMR: δ_F −78.37 s (CF_3). IR ($CHCl_3$, cm^{-1}): ν 3025, 2955, 2870, 1705, 1600, 1580, 1250, 1195, 1150, 1070, 1035, 1015. Anal. Calcd. for $C_{14}H_{19}F_3O_2$: C, 60.86; H, 6.93. Found: C, 61.04; H, 7.01%.

4.11. 3-(1,3-Dioxolan-2-yl)-1,1,1-trifluoroacetone (**4a**)

4a was obtained in conditions as described above for enone **3d** (Section 4.5) from 4 g (24 mmol) of enone **1** and 1.55 g (25 mmol) of ethylene glycol in 10 ml of benzene. Yield 2.7 g (61.6%). b.p. 50–52 °C (13 Torr). ^{1}H NMR: δ_H 3.09 d (2H, CH_2–C=O, J_{HH} = 4.8 Hz), 3.85–4.10 m (4H, CH_2CH_2), 5.37 t (1H, CHO_2, J_{HH} = 4.8 Hz). ^{19}F NMR: δ_F −79.99 s (CF_3). Anal. Calcd. for $C_6H_7F_3O_3$: C, 39.14; H, 3.83. Found: C, 39.47; H, 3.87%.

4.12. Diethyl (4R, 5R)-2-(3,3,3-trifluoro-2-oxopropyl)-1,3-dioxolane-4,5-dicarboxylate (**4b**)

The mixture of enone **1** (4.8 g, 28.5 mmol), diethyl L-tartrate (6 g, 28.5 mmol) and catalytic amount of *p*-toluenesulfonic acid (10 mg) was heated at 100–150 °C and ethanol was distilled. The conversion was controlled by GLC. After about 2 h the residue was distilled in vacuum and 5.5 g (61%) of compound **4b** was obtained. b.p. 125–127 °C (0.1 Torr). ^{1}H NMR: δ_H 1.29–1.38 m (6H, $2CH_3$), 3.26 dd (1H, H_a of CF_3COCH_2–C, J_{HH} = 18.0, 4.0 Hz), 3.36 dd (1H, H_b of CF_3COCH_2–C, J_{HH} = 18.0, 5.0 Hz), 4.23–4.38 m (4H, $2CH_2O$), 4.77 d (1H, proton of CHCH-fragment, J_{HH} = 2.8 Hz), 4.83 d (1H, proton of CHCH-fragment, J_{HH} = 2.8 Hz), 5.82 m (1H, CHO_2). ^{19}F NMR: δ_F −80.22 s (CF_3). Anal. Calc. for $C_{12}H_{15}F_3O_7$: C, 43.91; H, 4.61. Found: C, 43.45; H, 4.63%.

4.13. 3-(1,3-Dioxan-2-yl)-1,1,1-trifluoroacetone (**4c**)

4c was obtained in conditions as described above for enone **3d** (Section 4.5) from 4 g (24 mmol) of enone **1** and 1.88 g (25 mmol) of 1,3-propanediol in 10 ml of benzene. Yield: 3.1 g (65.8%). b.p. 50–52 °C (13 Torr). ^{1}H NMR: δ_H 1.37 m (1H, H_a of fragment C–CH_2–C), 2.11 m (1H, H_b of fragment C–CH_2–C), 3.02 d (2H, CF_3COCH_2–C, J_{HH} = 5.2 Hz), 3.81 ddd (2H, H_a of CH_2O-fragments of acetal cycle, J_{HH} = 12.2, 11.0, 2.4 Hz), 4.11 ddd (2H, H_b of CH_2O-fragments of acetal cycle, J_{HH} = 12.2, 5.2, 1.2 Hz), 5.07 t (1H, CHO_2, J_{HH} = 5.2 Hz). ^{19}F NMR: δ_F −80.26 s (CF_3). Anal. Calcd. for $C_7H_9F_3O_3$: C, 42.43; H, 4.58. Found: C, 42.68; H, 4.66%.

4.14. 3-(1,3-Dioxolan-2-yl)-1,1,1-trifluoromethyl-2,2-propanediol (**5a**)

The mixture of 0.5 g (2.7 mmol) of acetal **4a** and water (5 ml) was heated for 15 min at 80–90 °C and was left for 2 h at room temperature. Crystals obtained were filtered and crystallised from a mixture of hexane/CCl_4 giving 0.35 g (64.8%) of compound **5a** as colourless crystals. m.p. 45–47 °C (with decomposition). NMR data described are only for gem-diol **5a** (see Section 2): ^{1}H NMR: δ_H 2.19 d (2H, C–CH_2–C, J_{HH} = 5.0 Hz), 3.87–4.15 m (4H, $2CH_2O$), 4.64 s (2H, 2OH), 5.26–5.46 t (1H, CHO_2, J_{HH} = 5.0 Hz); ^{19}F NMR: δ_F −87.49 s (CF_3). IR ($CHCl_3$, cm^{-1}): ν 3585, 3455, 3030, 2995, 2900, 1770, 1275, 1185, 1130, 1105, 945. Anal. Calcd. for $C_6H_9F_3O_4$: C, 35.65; H, 4.49. Found: C, 35.33; H, 4.57%.

4.15. Diethyl (4R, 5R)-2-(3,3,3-trifluoro-2,2-dihydroxypropyl)-1,3-dioxolane-4,5-dicarboxylate (**5b**)

5b was obtained in conditions as described above for hydrate **5a** (Section 4.14) from 0.5 g (1.6 mmol) of acetal **4b**. Yield: 0.41 g (77.4%). m.p. 53–55 °C (with decomposition). $[\alpha]_D^{24} = -5.56$ (c = 2.7, H_2O). NMR data described are only for gem-diol **5b** (see Section 2): ^{1}H NMR: δ_H 1.29–1.38 m (6H, $2CH_3$), 2.19 dd (1H, H_a of CF_3COCH_2–C, J = 14.3, 7.3 Hz), 2.46 dd (1H, H_b of CF_3COCH_2–C, J_{HH} = 14.3, 3.4 Hz), 4.00 s (1H, OH), 4.23–4.38 m (4H, $2CH_2O$), 4.84 d (1H, proton of CHCH-fragment, J_{HH} = 2.8 Hz), 4.90 d (1H, proton of CHCH-fragment, J_{HH} = 2.8 Hz), 5.12 s (1H, OH), 5.82 m (1H, CHO_2); ^{19}F NMR: δ_F −87.85 s (CF_3). IR ($CHCl_3$, cm^{-1}): ν 3692, 3577, 3495, 3018, 2986, 2941, 1748, 1373, 1274, 1191, 1146, 1095, 1024, 946, 859; (KBr, cm^{-1}): ν 3515, 3460, 3005, 2990, 1762, 1747, 1478, 1384, 1304, 1247, 1188, 1176, 1132, 1108, 1003, 948, 852. Anal. Calcd. for $C_{12}H_{17}F_3O_8$: C, 41.63; H, 4.95. Found: C, 41.42; H, 5.06%.

4.16. 3-(1,3-Dioxan-2-yl)-1,1,1-trifluoromethyl-2,2-propanediol (**5c**)

5c was obtained in conditions as described above for hydrate **5a** (Section 4.14) from 0.5 g (2.53 mmol) of acetal **4c**. Yield: 0.44 g (80.8% yield). m.p. 45–47 °C (with decomposition). Described NMR data are only for gem-diol **5c** (see Section 2): ^{1}H NMR: δ_H 1.44 m (1H, H_a of fragment C–CH_2–C), 2.14 m (1H, H_b of fragment C–CH_2–C), 2.14 d (2H, CF_3COCH_2–C, J_{HH} = 5.2 Hz), 3.86 ddd (2H, H_a of CH_2O-fragments of acetal cycle, J_{HH} = 12.1, 10.9, 2.3 Hz), 4.18 ddd (2H, H_b of CH_2O-fragments of acetal cycle, J_{HH} = 10.8, 5.2, 1.2 Hz), 4.78 s (2H, 2OH), 5.12 t (1H, CHO_2, J_{HH} = 5.2 Hz), ^{19}F NMR: δ_F −87.77 s (CF_3). IR ($CHCl_3$, cm^{-1}): ν 3674, 3580, 3018, 2984, 2962, 2929, 2869, 1768, 1603, 1432, 1380, 1287, 1238, 1184, 1164, 1140, 1113, 1076, 1021, 928; (KBr, cm^{-1}): ν 3432, 2979, 2952, 2886, 2178, 1468, 1441, 1284, 1240, 1166, 1108, 1072, 1009, 969, 824. Anal. Calc. for $C_7H_{11}F_3O_4$: C, 38.90; H, 5.13. Found: C, 38.59; H, 5.21%.

X-ray crystal structure analysis for **5c**: formula $C_7H_{11}F_3O_4$, M = 216.16, colourless crystal 0.20 mm × 0.20 mm × 0.15 mm, a = 10.470(1), b = 9.187(1), c = 19.080(1) Å, V = 1835.3(3) Å^3, ρ_{calc} = 1.565 g cm^{-3}, μ = 1.62 cm^{-1}, no absorption correction ($0.968 \leq T \leq 0.976$), Z = 8, orthorhombic, space group *Pbca* (No. 61), λ = 0.71073 Å, T = 198 K, ω and φ scans, 4057 reflections collected ($\pm h$, $\pm k$, $\pm l$), [sin θ/λ] = 0.66 Å^{-1}, 2183 independent (R_{int} = 0.018) and 1702 observed reflections [$I \geq 2\sigma(I)$], 129 refined parameters, R = 0.036, wR^2 =

0.106, maximum residual electron density 0.24 electrons $Å^{-3}$ (−0.23), hydrogen atoms calculated and refined.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-252154. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, CambridgeCB21EZ, UK [fax: +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk].

4.17. Reduction of enone **1** with sodium borohydride

4.17.1. Reduction in ethanol

The solution of enone **1** (0.45 g, 2.7 mmol) in 5 ml of ethanol was added to a stirred suspension of $NaBH_4$ (0.051 g, 1.35 mmol) in 5 ml of ethanol at 0 °C. The reaction was stirred for 2 h at room temperature. Then 10 ml of water were added and mixture was stirred for 15 min. The solution was extracted with diethyl ether (3 × 10 ml), combined ether portion were dried under $MgSO_4$. Ether was removed in vacuum and 0.35 g of mixture of compounds **6** and **7** as colourless liquid (in 1:1 ratio) was obtained.

*4.17.1.1. (E)-4-Ethoxy-1,1,1-trifluoro-3-buten-2-ol (**6**).* ^{1}H NMR: δ_H 1.31 t (3H, CH_3, J_{HH} = 7.0 Hz), 2.36 s (1H, OH), 3.82 q (2H, CH_2O, J_{HH} = 7.0 Hz), 4.33 dq (1H, CF_3CHO, J_{HH} = 8.6 Hz, J_{HF} = 6.5 Hz), 4.82 dd (1H, C–CH=C, J_{HH} = 8.6, 12.7 Hz), 6.67 d (1H, C=CH–O, 12.7 Hz). ^{19}F NMR: δ_F −80.34 d (CF_3, J_{HF} = 6.5 Hz).

*4.17.1.2. 4,4-Diethoxy-1,1,1-trifluoro-2-butanol (**7**).* ^{1}H NMR: δ_H 1.16 t (6H, CH_3, J_{HH} = 5 Hz), 1.91 m (2H, O=C–CH_2), 3.55 m (4H, $2CH_2O$), 4.1 m (2H, $CHCF_3$ and OH), 4.71 t (1H, CHO_2, J_{HH} = 5 Hz). ^{19}F NMR: δ_F −80.39 d (CF_3, J_{HF} = 6.1 Hz).

4.17.2. Reduction in diethyl ether

The solution of enone **1** (0.45 g, 2.7 mmol) in 5 ml of diethyl ether was added to a stirred suspension of $NaBH_4$ (0.051 g, 1.35 mmol) in 5 ml of diethyl ether at 0 °C. The reaction mixture was stirred for 12 h at room temperature. Then 10 ml of water were added and mixture was stirred for 15 min. Ether layer was separated, and water layer was extracted with diethyl ether (3 × 5 ml). Combined ether portions were dried under $MgSO_4$, ether was removed in vacuum and 0.38 g of mixture of compounds **6** and **8** (in 2:1 ratio) as colourless liquid was obtained. Similar results were obtained in dichloromethane and dioxane.

*4.17.2.1. 4-Ethoxy-1,1,1-trifluoro-2-butanol (**8**).* ^{1}H NMR: δ_H 1.21 t (3H, CH_3, J_{HH} = 7.0 Hz), 1.91–2.23 m (2H, C–CH_2–C), 3.54 q (2H, CH_2O of ethoxy group, J_{HH} = 7.0 Hz), 3.60–4.03 m (3H, OH, CH_2O of CH_2CH_2O-fragment), 4.24 m (1H, CF_3CHO). ^{19}F NMR: δ_F −80.34 d (CF_3, J_{HF} = 6.5 Hz).

4.18. (E)-1,1,1-Trifluoro-4-[((1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl)oxy]-3-buten-2-ol (**9a**)

Two milliliters of 1 M DIBAL-H solution in toluene was added dropwise to a stirred solution of 0.556 g (2 mmol) enone **3h** in 5 ml of CH_2Cl_2 at −78 °C via the syringe. Then the mixture was warmed to room temperature and stirred for 2 h. To the stirred mixture 1 ml of methanol was added and after 5 min 1 ml of water was added also. After aluminium hydroxide precipitation, 1 g of $MgSO_4$ was added and the mixture was stirred for 30 min. The precipitate was filtered, washed with CH_2Cl_2 (2 × 10 ml) and the solvent was removed in vacuum. Product **9a** was isolated and purified by column chromatography (eluent: CH_2Cl_2; R_f = 0.6). Yield: 0.055 g (10%, de ∼ 0%). ^{1}H NMR: δ_H 0.72–1.10 m (12H, protons of menthol skeleton, OH), 1.29–1.48 m (2H, protons of menthol skeleton), 1.58–1.73 m (2H, protons of menthol skeleton), 1.98–2.12 m (3H, protons of menthol skeleton, OH), 3.52–3.63 m (1H, CHO of menthol skeleton), 4.32 m (1H, CF_3CHO), 4.92 dd (1H, C–CH=C, J_{HH} = 12.4, 8.5 Hz), 6.56 d (0.5H, C=CH–O, J_{HH} = 12.4 Hz), 6.57 d (0.5H, C=CH–O, J_{HH} = 12.4 Hz). Last two signals belong to different diastereomers. ^{19}F NMR: δ_F −80.30 d (0.5CF_3, J_{HF} = 6.6 Hz), −80.31 d (0.5CF_3, J_{HF} = 6.6 Hz). Anal. Calcd. for $C_{14}H_{23}F_3O_2$: C, 59.98; H, 8.27. Found: C, 60.25; H, 8.39%.

4.19. (E)-1,1,1-Trifluoro-4-[(endo-(1S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]-3-buten-2-ol (**9b**)

9b was obtained in conditions as described above for alcohol **9a** (Section 4.17) from 0.553 g (2.0 mmol) of enone **3i** and was purified by column chromatography (eluent: CH_2Cl_2. R_f = 0.54). Yield: 0.075 g (13.5%, de ∼ 34%). ^{1}H NMR: δ_H 0.79–0.94 m (9H, $3CH_3$), 1.07 m (1H, proton of borneol skeleton), 1.63–1.81 m (2H, protons of borneol skeleton), 1.89–2.07 (2H, proton of borneol skeleton, OH), 2.19–2.31 (2H, protons of borneol skeleton), 4.01–4.09 m (1H, CHO of borneol skeleton), 4.32 m (1H, $CH(CF_3)O$), 4.76 dd (1H, C–CH=C, J_{HH} = 12.6, 9.0 Hz), 6.62 d (1H, C–C=CHO, J_{HH} = 12.6 Hz). ^{19}F NMR: δ_F −80.22 d (0.33CF_3, J_{HF} = 6.6 Hz, minor diastereomer), −80.32 d (0.67CF_3, J_{HF} = 6.6 Hz, major diastereomer). Anal. Calcd. for $C_{14}H_{21}F_3O_2$: C, 60.42; H, 7.61. Found: C, 60.53; H, 7.73%.

4.20. 3-(1,3-Dioxolan-2-yl)-1,1,1-trifluoropropan-2-ol (**10a**)

10a was obtained in conditions as described above for the reduction of enone **1** in diethyl ether (Section 4.16) from 0.5 g (2.7 mmol) of acetal **4a**. Yield: 0.45 g (89%). ^{1}H NMR: δ_H 1.96–2.17 m (2H, C–CH_2–C), 3.12 s (1H, OH), 3.87–4.11 m (4H, OCH_2CH_2O), 4.30 m (1H, CF_3CHO), 5.14 t (1H, CHO_2, J_{HH} = 4.2 Hz). ^{19}F NMR: δ_F −80.52 d (CF_3, J_{HF} = 8.5 Hz). IR ($CHCl_3$, cm^{-1}): ν 3605, 3496, 2976, 2896, 1401, 1272, 1212, 1176, 1136, 1067, 1034, 944, 856, 824. Anal. Calcd. for $C_6H_9F_3O_3$: C, 38.72; H, 4.87. Found: C, 38.78; H, 4.99%.

*4.21. Diethyl (4R, 5R)-2-(3,3,3-trifluoro-2-hydroxypropyl)-1,3-dioxolane-4,5-dicarboxylate (**10b**)*

10b was obtained in conditions as described above for the reduction of enone **1** in diethyl ether (Section 4.16) from 0.84 g (2.7 mmol) of acetal **4b**. Product was purified by column chromatography (eluent: ethyl acetate/hexane 1/1; $R_f = 0.75$). Yield: 0.59 g (69.6% yield, de ∼ 15%). ^{1}H NMR: δ_H 1.27–1.39 m (6H, $2CH_3$), 2.08–2.28 m (2H, C–CH_2–C), 3.47 s (1H, OH), 4.19–4.46 m (5H, $2CH_2O$, CF_3CHO), 4.72–4.83 m (2H, CH–CH), 5.57 m (1H, CHO_2). ^{19}F NMR: δ_F −80.12 d (0.43CF_3, $J_{HF} = 7$ Hz, minor diastereomer), −80.65 d (0.57CF_3, $J_{HF} = 7$ Hz, major diastereomer). IR ($CHCl_3$, cm^{-1}): ν 3470, 3030, 2990, 2950, 2910, 1750, 1270, 1225, 1210, 1175, 1140, 1110, 1075, 1015. Anal. Calcd. for $C_{12}H_{17}F_3O_7$: C, 43.64; H, 5.19. Found: C, 43.87; H, 5.23%.

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