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Synthesis of novel trifluoromethylated β-acetal-diols and their application to the synthesis of 3-ethoxy-5-hydroxy-5-trifluoromethyl-pyrrolidin-2-one

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Abstract

The synthesis of a series of novel trifluoromethylated β-acetal-*gem*-diols, 4-alkoxy-4-ethoxy-1,1,1-trifluoro-butane-2,2-diols (**4a** = methoxy, **4b** = ethoxy, **4c** = allyloxy, **4d** = ynyloxy) and 1-(2-alkoxytetrahydro-furan-3-yl)-2,2,2-trifluoro-ethane-1,1-diols (**6a** = methoxy, **6b** = ethoxy, **6c** = allyloxy, **6d** = ynyloxy) from the reaction of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) and 1-(4,5-dihydro-furan-3-yl)-2,2,2-trifluoro-ethanone (**2**) with sodium azide in hydro-alcoholic medium, is presented. From these reactions, a small amount (ca. of 20%) of the parent trifluoromethylated β-acetal-ketones, 4-alkoxy-4-ethoxy-1,1,1-trifluoro-butan-2-ones (**3a–d**) and 2,2,2-trifluoro-1-(2-alkoxy-tetrahydro-furan-3-yl)-ethanones (**5a–d**) were also obtained. The synthetic potential of the trifluoromethylated β-acetal-diols was demonstrated by its application to the synthesis of 3-ethoxy-5-hydroxy-5-trifluoromethyl-pyrrolidin-2-one (**7**).

Keywords: Diols; Acetals; Pyrrolidinones; Ketones

1. Introduction

Organic hydrates (*gem*-diols) are relatively rare compounds because their synthesis and stability depend on the existence of strong electron withdrawing groups on the α-carbonyl position, such as trifluoromethyl or trichloromethyl groups [1–6]. 4-Ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) and 1-(4,5-dihydro-furan-3-yl)-2,2,2-trifluoro-ethanone (**2**), which have been used extensively by our research group in the synthesis of heterocycles of five [7–13], six [14–18] and seven [19,20] membered rings, show favorable structural features for their use as trifluoromethylated β-acetal-diols precursors. Compounds **1** and **2** have a trifluoromethyl group α to a carbonyl that also is conjugated to an alkoxyvinyl group, allowing a Michael addition of an alcohol molecule to the β position of **1** or **2**, followed by a hydration of the carbonyl group.

The addition of hydrazoic acid to conjugated systems such as acrolein, methyl acrylate, acrylic acid, acrylonitrile, mesityl oxide, β-nitrostyrene, and α-vinylpyridine to give the corresponding dihydro β-azido derivatives, was reported by Broyer [21] in 1951. More recently, Lakshmipathi and Rao [22] reported a base catalysed addition of hydrogen azide to enoates to form β-azido esters or lactones. Applying Broyer's condition to the vinyl ketone **1**, a complex mixture of unidentified compounds was obtained. However, when a solution of sodium azide in water was added to a solution of **1** in alcohol, the unexpected formation of trifluoromethylated β-acetal-diols was observed. In this case, the sodium azide acted as a base rather than a nucleophile.

Trifluoromethylated β-acetal-diols have not yet been reported. This situation prompts us to report the synthesis of a series of trifluoromethylated β-acetal-diols from the reactions of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) and 1-(4,5-dihydro-furan-3-yl)-2,2,2-trifluoro-ethanone (**2**) in alcohols and treated of sodium azide in water (Scheme 1). In addition, we are reporting an application of the 4-diethoxy-1,1,1-trifluoro-butane-2,2-diol to the synthesis of 5-hydroxy-5-trifluoromethyl-3-ethoxy pyrrolidin-2-one

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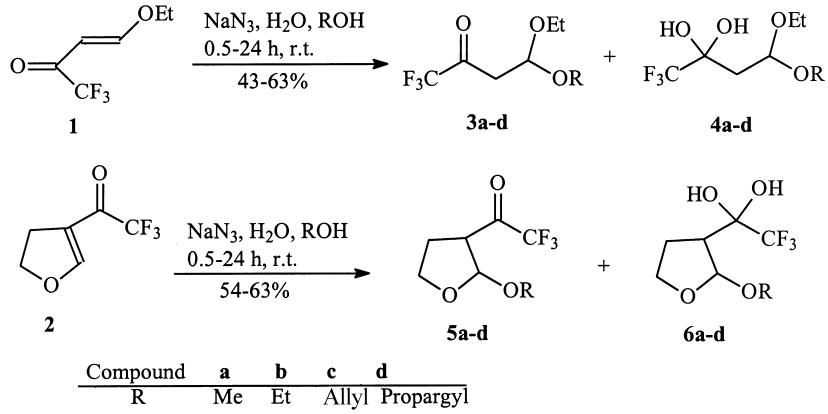


Scheme 1.

as an indication of a possible synthetic usefulness of the trifluoromethylated β-acetal-diols.

2. Results and discussion

The synthesis of 4-alkoxy-4-ethoxy-1,1,1-trifluoro-butane-2,2-diols (**4a–d**) and 1-(2-alkoxytetrahydro-furan-3-yl)-2,2,2-trifluoro-ethane-1,1-diols (**6a–d**) is carried out by the reaction of the respective trifluoromethyl vinyl ketones **1** and **2,** in the presence of sodium azide in alcohol/water, at room temperature (Scheme 1). The ketones **1** and **2** were dissolved in alcohols which were used as the reaction solvents and a solution of sodium azide in water was added to the mixture at room temperature. The reaction has been tested with a series of alcohols, such as methanol, ethanol, allyl- and propargyl-alcohols (Scheme 1).

The reaction time depended greatly on the structure of the ketones **1** and **2** and the alcohols, ranging from 30 min to 24 h (see Table 1).

The products are isolated by extraction of the reaction mixture with dichloromethane and the organic phase dried with anhydrous magnesium sulfate. A light yellow oil was obtained which was analyzed by NMR without further purification. In all reactions, a small amount of the parent β-acetal-ketones (ca. of 20% at room temperature) was obtained together with the β-acetal-diol. A variable temperature study done by ^{1}H-NMR on the mixture of compounds **3a/4a** showed that the ratio of β-acetal-diol/β-acetal-ketone remains unchanged (ca. 4:1, respectively) from −50 to 40°C (see Table 1). However, the mixture of **3a/4a** reaches a ratio of 1:1 at 55°C. On cooling the NMR sample to room temperature, the mixture of products slowly re-establish the starting population ratio. The mixture of products **3a/4a** and **3b/4b**, solidified in the refrigerator and were recrystallized from hexane to obtain the β-acetal-diols **4a** and **4b** in a pure form. Tentative of purification of the acetals by acidic silica gel column chromatography resulted in decomposition, probably, due to the acid sensitive nature of the products [23]. ^{1}H- and ^{13}C-NMR data of compounds **3a–d**, **4a–d**, **5a–d**, and **6a–d**, are presented in Tables 2–5, respectively.

The β-acetal-ketones **3a–d** and **5a–d** resulted from a Michael addition of an alcohol molecule to the β-carbon of the ketones **1** and **2** and the β-acetal-diols **4a–d** and **6a–b** resulted from a further addition of a water molecule to the carbonyl of compounds **3a–d** and **5a–d**.

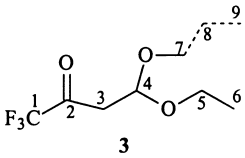
A possible synthetic usefulness of the β-acetal-diol **4b** was investigated. We found that the 4-diethoxy-1,1,1-trifluoro-butane-2,2-diol (**4b**) reacted with an aqueous solution of sodium cyanide furnishing the 3-ethoxy-5-hydroxy-5-

Table 1
Reaction conditions used in the synthesis and IR data of compounds **3a–d**, **4a–d**, **5a–d**, **6a–d**[a]

Compound	Reaction time (h:min)	Yields (%)[b]	Reaction product	Ratio (%)[c]	IR (sol. CCl_4) ν (cm^{-1})
1	030	63	**4a** + **3a**	80:20	3365, 1755
1	030	52	**4b** + **3b**	82:18	3365, 1760
1	2400	47	**4c** + **3c**	83:17	3365, 1750
1	145	43	**4d** + **3d**	81:19	3375, 1755
2	110	55	**6a** + **5a**	84:16	3355, 1755
2	120	63	**6b** + **5b**	88:12	3350, 1750
2	2400	54	**6c** + **5c**	75:25	3380, 1755
2	230	60	**6d** + **5d**	82:18	3370, 1755

[a] The reactions were carried out at room temperature in a substrate/azide ratio of 1:1.
[b] The yield of the mixture of compounds **3** and **4** were calculated considering only the molecular weight of the β-acetal-diol.
[c] Product ratio was determined by ^{1}H-NMR integrals at 27°C. The product ratio of **4a/3a** remains unchanged from −50 to 40°C.

Table 2
^{1}H- and ^{13}C-NMR spectral data of compounds **3a–d**



3

Compound	^{1}H-NMR, δ_{ppm} (multiplicity, no. of protons, J_{Hz}, assignment) ^{13}C-NMR, δ_{ppm}, J_{CF} (Hz)[a]
3a	3.04 (d, 2H, $J_{34} = 5.6$, H-3), 5.00 (d, b, H-4), 3.78, 3.66 (qua, $J_{56} = 7.0$, H-5), 1.28 (t, $J_{65} = 7.0$, H-6), 3.44 (s, 3H, H-7) 115.3 (q, $^{1}J_{CF} = 291.5$, CF_3), 187.9 (q, $^{2}J_{CF} = 36.3$, C2), 41.3 (C3), 99.3 (C4), 62.9 (C5), 14.8 (C6), 53.3 (C7)
3b	3.06 (d, 2H, $J_{34} = 5.0$, H-3), 5.04 (m, 1H, b, H-4), 3.75, 3.68 (qua, 4H, $J_{56} = 7.0$, H-5, H-7), 1.25 (t, 6H, $J_{65} = 7.0$, H-6, H-8) 115.2 (q, $^{1}J_{CF} = 291.4$, CF_3), 188.2 (q, $^{2}J_{CF} = 36.3$, C2), 41.7 (C3), 98.3 (C4), 65.5 (C5, C7), 18.0 (C6, C8)
3c	3.09 (d, 2H, $J_{34} = 5.4$, H-3), 5.08–5.31 (m, 1H, b, H-4), 3.57–3.76 (m, 2H, b, H-5), 1.24 (t, 3H, $J_{65} = 7.0$, H-6), 4.11 (m, 2H, b, H-7), 5.88–6.07 (m, 1H, b, H-8), 5.08–5.32 (m, 1H, b, H-9, H-9′) c (CF_3), c (C2), 41.6 (C3), 97.8 (C4), 62.8 (C5), 14.7 (C6), 65.4 (C7), 137.1 (C8), 117.8 (C9)
3d	3.12 (d, 2H, $J_{34} = 5.6$, H-3), 5.00 (m, 1H, b, H-4), 3.50–4.20 (m, 2H, b, H-5), 1.15–1.50 (m, 3H, b, H-6), 4.30 (d, 2H, $J_{79} = 2.4$, H-7), 2.52 (t, 1H, $J_{97} = 2.4$, H-9) 122.5(q, $^{1}J_{CF} = 286.0$, CF_3), c (C2), 41.5 (C3), 97.4 (C4), 65.4 (C5), 14.7 (C6), 53.8 (C7), 87.1 (C8), 75.2 (C9)

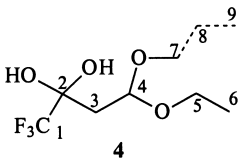
[a] The NMR spectral data were obtained from the mixture of compounds **3** and **4**; [b] Multiplicity and coupling constants are difficult to obtain because the signals of compound **3** are totally or partially superimposed with the signal of the corresponding nuclei of compound **4**; [c] Signal was not observed due to the low signal/noise ratio of the minor isomer.

trifluoromethyl-pyrrolidin-2-one (**7**) as the only product of the reaction in 70% yield (Scheme 2). A mixture of 3-ethoxy- and 3-methoxy-5-hydroxy-5-trifluoromethyl-pyrrolidin-2-one was obtained from the reaction of sodium cyanide with β-acetal-diols bearing different alkoxy groups, such as the compound **4a**.

The pyrrolidinone **7** has two asymmetric carbons and two diastereoisomers were formed. The reaction shows little stereoselectivity giving a pair of stereoisomers in a ratio of 60:40% as determined from the ^{1}H-NMR integrals. The mixture of diastereoisomers was shown by two sets of signals in both ^{1}H- and ^{13}C-NMR spectra. The reaction, however, is highly regioselective furnishing only the pyrrolidinone **7** with the exclusion of the 4-ethoxy-5-imino-2-trifluoromethyltetrahydro-furan-2-ol.

In conclusion, we have shown that 4-alkoxy-4-ethoxy-1,1,1-trifluoro-butane-2,2-diols (**4a–b**), and 1-(2-alkoxytetrahydro-furan-3-yl)-2,2,2-trifluoro-ethane-1,1-diols (**6a–d**), in equilibrium with the parent β-acetal-ketones (**3a–d**, and **5a–d**) are readily available from the reaction of 4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (**1**) and 1-(4,5-dihydro-furan-3-yl)-2,2,2-trifluoro-ethanone (**2**) with sodium

Table 3
^{1}H- and ^{13}C-NMR spectral data of compounds **4a–d**

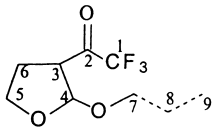


4

Compound	^{1}H-NMR, δ_{ppm} (multiplicity, no. of protons, J_{Hz}, assignment) ^{13}C-NMR, δ_{ppm}, J_{CF} (Hz)[a]
4a	2.11 (d, 2H, $J_{34} = 4.0$, H-3), 5.00 (t, 1H, b, H-4), 3.78; 3.66 (m, 2H, b, H-5), 1.28 (t, 3H, $J_{65} = 7.0$, H-6), 3.44 (s, 3H, H-7), 5.24 (s, OH) 122.6 (q, $^{1}J_{CF} = 285.7$, CF_3), 92.9 (q, $^{2}J_{CF} = 32.8$, C1), 34.8 (C3), 100.7 (C4), 63.0 (C5), 15.1 (C6), 53.7 (C7)
4b	2.12 (d, 2H, $J_{34} = 5.6$, H-3), 5.04 (d, 1H, b, H-4), 3.75, 3.68 (m, 4H, b, H-5, H-7), 1.25 (t, 6H, $J_{65} = 7.0$, H-6, H-8), 5.17 (s, OH) 122.7 (q, $^{1}J_{CF} = 285.8$, CF_3), 92.9 (q, $^{2}J_{CF} = 32.7$, C2), 35.4 (C3), 99.8 (C4), 62.8 (C5, C5′), 14.9 (C6, C6′)
4c	2.09 (d, 2H, $J_{34} = 5.8$, H-3), 5.08–5.31 (m, 1H, b, 4-H), 3.57–3.76 (m, 2H, b, H-5), 1.24 (t, 3H, $J_{65} = 7.0$, H-6), 4.11 (m, 2H, b, H-7), 5.88–6.07 (m, 1H, b, H-8), 5.08–5.32 (m, 1H, b, H-9, H-9′), 5.09 (s, OH) 122.7 (q, $^{1}J_{CF} = 285.8$, CF_3), 92.8 (q, $^{2}J_{CF} = 32.7$, C2), 35.4 (C3), 99.3 (C4), 63.8 (C5), 15.0 (C6), 67.7 (C7), 133.4 (C8), 115.2 (C9)
4d	2.17 (d, 2H, $J_{34} = 5.4$, H-3), 5.00 (m, 1H, b, H-4), 3.50-4.20 (m, 2H, b, H-5), 1.15–1.50 (m, 3H, b, H-6), 4.27 (d, 2H, $J_{78} = 2.4$, H-7), 2.48 (t, 1H, $J_{97} = 2.4$, H-9), 5.60 (s, OH)
.	122.6 (q, $^{1}J_{CF} = 286.0$, CF_3), 92.7 (q, $^{2}J_{CF} = 32.8$, C2), 35.6 (C3), 98.9 (C4), 63.2 (C5), 14.9 (C6), 50.5 (C7), 88.1 (C8), 73.7 (C9)

[a] The NMR spectral data were obtained from the mixture of compounds **3** and **4**; [b] Multiplicity and coupling constants are difficult to obtain because the

Table 4
^{1}H- and ^{13}C-NMR spectral data of compounds **5a–d**

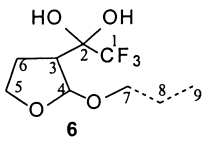


5

Compound	^{1}H-NMR, δ_{ppm} (multiplicity, no. of protons, J_{Hz}, assignment)[a] ^{13}C-NMR, δ_{ppm}, J_{CF} (Hz)[b]
5a	3.54–3.60 (m, 1H, c, H-3), 5.34 (d, 1H, J_{43} = 5.6, H-4), 4.00 (t, 2H, J_{56} = 7.0, H-5), 1.90–2.10 (m, 2H, c, H-6), 3.32 (s, 3H, H-7) 115.5 (q, $^{1}J_{CF}$ = 290.4, CF_3), 190.2 (q, $^{2}J_{CF}$ = 34.9, C2), 52.8 (C3), 102.8 (C4), 66.8 (C5), 23.3 (C6), 55.0 (C7) **5a′**: 115.4 (q, $^{1}J_{CF}$ = 289.9, CF_3), 186.7 (q, $^{2}J_{CF}$ = 35.5, C2), 51.9 (C3), 102.7 (C4), 66.3 (C5), 23.0 (C6), 54.9 (C7)
5b	3.52–3.60 (m, 1H, c, H-3), 5.48 (d, 1H, J_{43} = 5.6, H-4), 3.99 (t, 2H, J_{56} = 8.2, H-5), 2.00–2.15 (m, 2H, c, H-6), 3.69 (m, 2H, c, H-7), 1.22 (m, 3H, c, H-8) 115.4 (q, $^{1}J_{CF}$ = 291.6, CF_3), 190.6 (q, $^{2}J_{CF}$ = 35.5, C2), 50.1 (C3), 101.4 (C4), 66.1 (C5), 26.6 (C6), 62.0 (C7), 14.7 (C8) **5b′**: 116.4 (q, $^{1}J_{CF}$ = 289.7, CF_3), d (C2), 51.8 (C3), 102.0 (C4), 65.5 (C5), 27.0 (C6), 62.5 (C7), 15.6 (C8)
5c	3.52–3.64 (m, 1H, c, H-3), 5.10–5.40 (m, 1H, c, H-4), 3.90–4.10 (m, 2H, c, H-5), 1.90–2.40 (m, 2H, c, H-6), 3.90–4.10 (m, 2H, c, H-7), 5.80–6.10 (m, 1H, c, H-8), 5.10–5.40 (m, 1H, c, H-9, H-9′) 115.6 (q,$^{1}J_{CF}$ = 291.6, CF_3), 190.6 (q, $^{2}J_{CF}$ = 35.7, C2), 51.0 (C3), 100.8 (C4), 67.1 (C5), 21.5 (C6), 63.8 (C7), 137.1 (C8), 115.2 (C9) **5c′**: 115.4 (q, $^{1}J_{CF}$ = 292.4, CF_3), 186.8 (q, $^{2}J_{CF}$ = 35.2, C2), 52.9 (C3), 100.8 (C4), 66.4 (C5), 23.4 (C6), 64.5 (C7), 134.8 (C8), 114.3 (C9)
5d	3.56–3.60 (m, 1H, c, H-3), 5.40–5.70 (m, 1H, c, H-4), 3.80–4.10 (m, 2H, c, H-5), 1.90–2.30 (m, 2H, c, H-6), 4.10–4.40 (m, 2H, c, H-7), 2.40–2.50 (m, 1H, c, H-9) 123.2 (q, $^{1}J_{CF}$ = 288.3, CF_3), 189.5 (q, $^{2}J_{CF}$ = 35.3, C2), 52.6 (C3), 99.6 (C4), 66.6 (C5), 22.9 (C6), 54.4 (C7), 78.1 (C8), 74.8 (C9) **5d′**: 122.8 (q, $^{1}J_{CF}$ = 287.7 (CF_3), 186.6 (q, $^{2}J_{CF}$ = 35.7, C2), 51.7 (C3), 99.5 (C4), 66.1 (C5), 23.2 (C6), 54.0 (C7), 78.2 (C8), 74.4 (C9)

[a] The NMR spectral data were obtained from the mixture of compounds **5** and **6**.
[b] Signals of the two stereoisomers obtained; [c] Multiplicity and coupling constants are difficult to obtain because the signals of compound **5** are totally or partially superimposed with the signal of the corresponding nuclei of compound **6**; [d] Signal was not observed due to the low signal/noise ratio of the minor isomer.

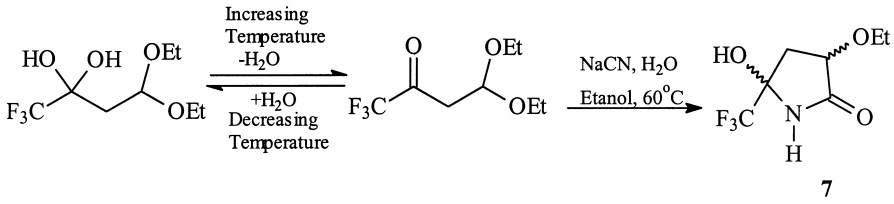
Table 5
^{1}H- and ^{13}C-NMR spectral data of compounds **6a–d**



6

Compound	^{1}H-NMR, δ_{ppm} (multiplicity, no. of protons, J_{Hz}, assignment)[a] ^{13}C-NMR, δ_{ppm}, J_{CF} (Hz)[b]
6a	2.50–2.67 (m, 1H, c, H-3), 5.14 (d, 1H, J_{43} = 4.4, H-4), 4.08 (t, 2H, J_{56} = 7.0, H-5), 2.10–2.23 (m, 2H, c, H-6), 3.43 (s, 3H, H-7), 5.56 (s, OH) 122.8 (q, $^{1}J_{CF}$ = 285.2, CF_3), 94.2 (q, $^{2}J_{CF}$ = 32.2, C2), 45.5 (C3), 104.2 (C4), 67.0 (C5), 27.0 (C6), 54.3 (C7) **6a′**: 122.9 (q, $^{1}J_{CF}$ = 288.5, CF_3), 96.0 (q, $^{2}J_{CF}$ = 30.4, C2), 46.7 (C3), 105.1 (C4), 67.3 (C5), 26.8 (C6), 54.3 (C7)
6b	2.50–2.70 (m, 2H, c, H-3), 5.26 (d, 1H, J_{43} = 4.2, H-4), 4.23 (t, 2H, J_{56} = 6.20, H-6), 2.00–2.15 (m, 2H, c, H-6), 3.69 (m, 2H, c, H-7), 1.22 (t, 3H, J_{87} = 7.0, c, H-8), 5.20 (s, OH) 122.9 (q, $^{1}J_{CF}$ = 287.0, CF_3), 93.6 (q, $^{2}J_{CF}$ = 32.1, C2), 45.5 (C3), 102.7 (C4), 66.8 (C5), 32.6 (C6), 63.0 (C7), 14.6 (C8) **6b′**: 123.3 (q, $^{1}J_{CF}$ = 287.8, CF_3), 93.2 (q, $^{2}J_{CF}$ = 31.3, C2), 46.6 (C3), 103.7 (C4), 66.6 (C5), 30.8 (C6), 63.3 (C7), 14.3 (C8)
6c	2.50-2.60 (m, 1H, H-3), 5.10–5.40 (m, 1H, H-4), 3.90–4.10 (m, 2H, H-5), 1.90–2.40 (m, 2H, H-6), 3.90–4.10 (m, 2H, H-7), 5.80–6.10 (m, 1H, H-8), 5.10–5.40 (m, 1H, H-9, H-9′), 5.05 (s, OH) 116.5 (q, $^{1}J_{CF}$ = 289.8, CF_3), 93.8 (q, J_{CF} = 32.2, C2), 45.5 (C3), 102.4 (C4), 67.9 (C5), 26.8 (C6), 62.1 (C7), 133.3 (C8), 117.9 (C9) **6c′**: 117.1 (q, $^{1}J_{CF}$ = 285.9, CF_3), d (C2), 46.5 (C3), 103.4 (C4), 68.4 (C5), 27.1 (C6), 61.7 (C7), 133.7 (C8), 117.2 (C9)
6d	2.50–2.70 (m, 1H, c, H-3), 5.40–5.70 (m, 1H, c, H-4), 3.80–4.10 (m, 2H, c, H-5), 1.90–2.30 (m, 2H, c, H-6), 4.10–4.40 (m, 2H, c, H-7), 2.40–2.50 (m, 1H, c, H-9), 5.10 (s, OH) 115.3 (q, $^{1}J_{CF}$ = 292.2, CF_3), 93.5 (q, $^{2}J_{CF}$ = 32.2, C2), 45.8 (C3), 101.7 (C4), 67.2 (C5), 26.9 (C6), 50.3 (C7), 81.0 (C8), 73.6 (C9) **6d′**: 117.0 (q, $^{1}J_{CF}$ = 280.7, CF_3), 96.3 (q, $^{2}J_{CF}$ = 31.2, C2), 46.4 (C3), 102.8 (C4), 67.0 (C5), 26.6 (C6), 50.1 (C7), 78.1 (C8), 74.0 (C9)

[a] The NMR spectral data were obtained from the mixture of compounds **5** and **6**.
[b] Signals of the two obtained stereoisomers; [c] Multiplicity and coupling constants are difficult to obtain because the signals of compound **6** are totally or partially superimposed with the signal of the corresponding nuclei of compound **5**; [d] Signal was not observed due to the low signal/noise ratio of the minor



Scheme 2.

azide in alcohol–water media. In addition, the β-acetal-diols and/or the β-acetal-ketones may be important building blocks for the synthesis of heterocyclic compounds.

3. Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. The β-alkoxyvinyl trifluoro methyl ketones (**1**, **2**) were prepared according to reference [7]. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) or on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) in $CDCl_3$, using TMS as the internal reference. IR spectra were recorded on a Bruker IFS 28 FT-IR spectrometer. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. Elemental analysis was performed on a Vario EL Elementar Analysensysteme.

3.1. Synthesis of β-acetal-diols: general procedure

To a solution of **1** or **2** (5 mmol) in methanol (3 ml), a solution of sodium azide (5 mmol, 0.39 g) in water (3 ml) was added under magnetic stirring. The reactions were carried out at room temperature with reaction times ranging from 30 min to 24 h (see Table 1). The reaction mixture was extracted with dichloromethane (3 × 20 ml) and the combined organic layers were dried with magnesium sulfate. Evaporation of the solvent afforded a pale yellow oil which was a mixture of β-acetal-diols and β-acetal-ketones (∼80:20%), respectively. The products ratio were determined by ^{1}H-NMR integration, at 27°C. The mixture of **4a/3a** and **4b/3b** solidified in the refrigerator and were recrystallized from hexane to obtain pure **4a** and **4b**. Tentative of purification by column chromatography resulted in decomposition of the products. Nonetheless, the crude mixture of products were comprised by a considerably pure mixture of β-acetal-diols and β-acetal-ketones and they were fully characterized by ^{1}H- and ^{13}C-NMR and IR without further purification. Selected physical and spectral data of compound **4a**: molecular formula and (weight) $C_7H_{13}F_3O_4$ (218.17), elemental analysis: calculated: C 38.53%; H 5.96%; found: C, 38.53%; H, 5.75%; mp: 52–54°C; IR (KBr), ν (cm^{-1}): 3365, 3300, 1105.

Compound **4b**: molecular formula and (weight) $C_8H_{15}F_3O_4$ (232.19); elemental analysis: calculated: C, 41.38%; H, 6.51%; found: C, 41.20%; H, 6.55%; mp: 53–55°C; IR (KBr), ν (cm^{-1}): 3365, 3300, 1140.

3.2. Synthesis of 5-hydroxy-5-trifluoromethyl-3-ethoxy pyrrolidin-2-one (7)

To a warm solution (∼60°C) of (**4b**) (0.58 g, 2.5 mmol) in ethanol (3 ml) a solution of sodium cyanide (0.16 g, 3.25 mmol) in water (3 ml) was added and the reaction was heated for 4 h at 60°C under magnetic stirring. The reaction was extracted with ethyl ether, dried under anhydrous magnesium sulfate and the solvent evaporated. A clear liquid (0.40 g, 70% yield) was obtained and identified as 3-ethoxy-5-hydroxy-5-trifluoromethyl-pyrrolidin-2-one (**7**). The product **7** showed two sets of signals in both ^{1}H- and ^{13}C-NMR spectra, indicating the presence of two diastereoisomers in a ratio of 60:40%. Major isomer; ($CDCl_3$), δ: 9.40 (ws, 1H, N–H), 8.40 (s, 1H, OH), 4.14 (t, 1H, $^{3}J_{H3-H4H4'} = 7.8$ Hz, H-3), 2.93 (d/d, 1H, $^{2}J_{H4-H4'} = 14.4$ Hz, $^{3}J_{H4-H3} = 8.4$ Hz, H-4), 2.15 (d/d, 1H, $^{2}J_{H4'-H4} = 14.4$ Hz, $^{3}J_{H4'-H3} = 7.2$ Hz, H-4′), 3.80–3.60 (m, 2H, –OCH_2^-), 1.23 (t, 3H, $^{3}J_{H-H} = 7.0$ Hz, –CH_3). ^{13}C-NMR ($CDCl_3$), δ: 175.39 (C-2), 123.38 (q, $^{1}J_{CF} = 284$ Hz, CF_3), 84.31 (q, $^{2}J_{CF} = 34$ Hz, C-5), 75.20 (C-3), 67.04 (–OCH_2^-), 37.80 (C-4), 14.87 (–CH_3). GC/MS (%), EI (70 eV): 169 (100), 100 (50), 73 (18), 56 (38). IR (neat), cm^{-1}: 3250, 1717. Analysis: calc. for $C_7H_{10}F_3NO_3$ (213.16): C, 39.44; H, 4.73; N, 6.57. Found: C, 38.85; H, 4.70; N, 6.39.

Minor isomer: ^{1}H-NMR ($CDCl_3$), δ: 9.40 (ws, 1H, N–H), 8.32 (s, 1H, OH), 4.40 (t, 1H, $^{3}J_{H3-H4H4'} = 7.8$ Hz, H-3), 2.58 (d/d, 1H, $^{2}J_{H4-H4'} = 13.6$ Hz, $^{3}J_{H4-H3} = 8.0$ Hz, H-4), 2.29 (d/d, 1H, $^{2}J_{H4'-H4} = 13.6$ Hz, $^{3}J_{H4'-H3} = 7.6$ Hz, H-4′), 3.80–3.60 (m, 2H, –OCH_2^-), 1.23 (t, 3H, $^{3}J_{H-H} = 7.0$ Hz, –CH_3). ^{13}C-NMR ($CDCl_3$), δ: 176.89 (C-2), 122.93 (q, $^{1}J_{CF} = 284$ Hz, CF_3), 84.22 (q, $^{2}J_{CF} = 34$ Hz, C-5), 74.44 (C-3), 66.48 (–OCH_2^-), 36.46 (C-4), 14.96 (–CH_3).

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