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1-Bromo-2-trifluoroacetylcyclobutenes as novel building blocks for the construction of trifluoromethyl substituted heterocycles. Part 1: Synthesis of 5-(trifluoromethyl)-2(5*H*)-furanones condensed with substituted cyclobutenes

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ABSTRACT

The regioselective reduction of substituted 1-bromo-2-trifluoroacetylcyclobutenes by lithium aluminium hydride affords corresponding brominated alcohols, which, under the treatment of two equivalents of butyllithium, give new lithiated cyclobutenes. Their carboxylation followed by lactonization induced by trifluoroacetic anhydride appeared to be an effective approach towards 5-trifluoromethylated furanones condensed with substituted cyclobutene rings.

1. Introduction

Because of the unique physical and biological properties imparted by the CF_3 group [1], at present, there is an increasing interest in the synthesis of specifically trifluoromethylated organic molecules, which have been found diverse applications in the areas of materials science [2], agrochemistry and biological chemistry [3]. Although various new approaches for the direct trifluoromethylation were recently proposed [4], they do not always assure the introduction of CF_3 group in required position of the organic molecule. An attractive alternative preparation for a variety of fluorinated heterocycles could be achieved via versatile intermediates carrying CF_3 function [5]. Hence, the search for new trifluoromethylated building blocks, especially appropriate for diverse types of cyclizations is an important challenge of organofluorine chemistry.

Recently we have described the synthesis of halogenated trifluoroacetylacetylenes [6,7] using available bis(trimethylstannyl)acetylene [8] as a parent compound. It was also discovered that these highly activated acetylenes possess unique ability to form [2 + 2]-cycloadducts **1a–d** (Fig. 1) with simple alkenes under mild conditions in the absence of catalysts and irradiation [6,7]. Due to very simple procedure of separation from the isomeric ene adducts, these unsaturated strained ketones can be obtained in a large scale with the exception of **1c** which is less available.

The presented series of publications is devoted to the study of synthetic potential of cyclobutenes (**1a–d**) as versatile building blocks for various types of heterocycles. An important feature of the target products is that all they retain cyclobutene bicyclic moiety.

Since butenolides are known to have diverse biological activities and to be starting compounds in the synthesis of natural products [9], initially we have investigated the potential of ketones **1a–d** for the synthesis of 5-trifluoromethylated furanones. To the best of our knowledge the only simplest 5-(trifluoromethyl)-2(5*H*)-furanon was described till now [9], its properties in Michael reactions were also investigated [10]. Herein we describe a general route towards 5-(trifluoromethyl)-2(5*H*)-furanones, fused with cyclobutene rings with bicyclic conjunctions. Apparently such structures are of interest for biochemical research and as useful intermediates for further diverse transformations.

2. Results and discussion

The traditional construction of heterocycles via β-halogeno-α,β-unsaturated aldehydes and ketones includes their reactions with different binucleophiles (hydrazines, ureas, enamines, etc.). However, in this work we report the synthesis of trifluoromethylated butenolides using novel organolithiums, generated in two steps from ketones **1a–d**. First, it was stated that the reduction of

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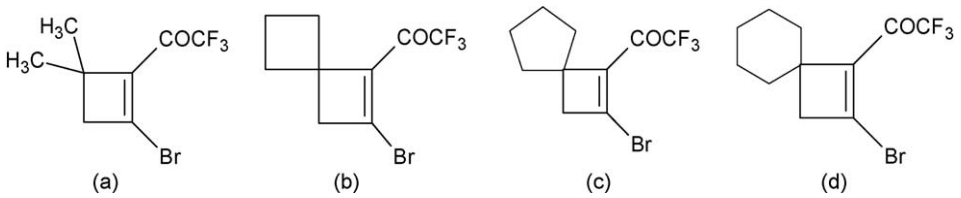
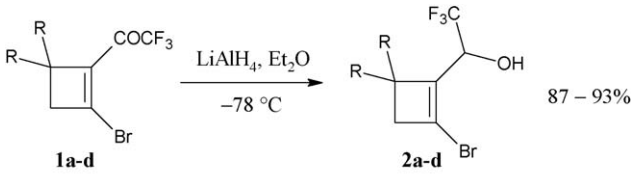


Fig. 1. The starting [2 + 2]-cycloaddition adducts.



a (R,R = Me), **b** (R,R = $(CH_2)_3$),

c (R,R = $(CH_2)_4$), **d** (R,R = $(CH_2)_5$)

Scheme 1. Reduction of ketones **1a–d** by $LiAlH_4$.

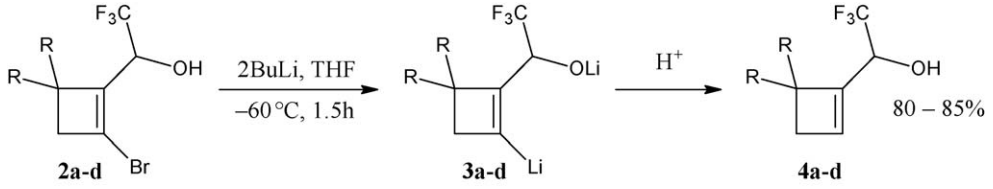
1a–d by $LiAlH_4$ proceeding in Et_2O at low temperature affords the corresponding unsaturated alcohols (**2a–d**) in excellent yields (Scheme 1). The reduction of C=C– and C–Br bonds did not occur. An employment of THF as a solvent gave much worse results.

At the next stage we attempted to generate new organolithium compounds treating compounds **2a–d** by butyllithium. The addition of the first equivalent of butyllithium led to exothermic formation of the corresponding alkoholates, which are very soluble in THF even at −70 °C. The interaction with the second equivalent of butyllithium for 1.5–2 h at −60 °C caused the Br–Li exchange and formation of dilithiated derivatives (**3a–d**) as white crystalline precipitates. Initially in order to estimate the yields of organolithiums we added to the reaction mixtures an excess of diluted hydrochloric acid and the resulting debrominated alcohols (**4a–d**) were isolated in high yields (Scheme 2).

Next, we tried to carry out the carboxylation of organolithiums **3a–d** and then to induce cyclization of corresponding acids (**5a–d**) to the target unsaturated lactones (**6a–d**). The best yields of high-melting acids **5a–d** were obtained by passing a strong stream of CO_2 over the surface of stirred suspensions of **3a–d** in THF followed by acidification (Scheme 3). It is well known that γ-hydroxyacids often spontaneously form γ-butyrolactones upon heating. To our surprise compounds **5a–d** proved to be extremely resistant to thermal lactonization, for example refluxing in toluene in the presence of TsOH with Dean–Stark apparatus afforded only the starting materials and products of their partial decomposition. The use of such systems as dicyclohexylcarbodiimide–pyridine, TsCl–pyridine and P_2O_5 was also unsuccessful. Eventually it was found that lactonization is effectively promoted by excess of trifluoroacetic anhydride (Scheme 3).

Unlike starting acids **5a–d**, compounds **6a–d** thus prepared, are oils or low melting solids, some of them (**6a**, **b**) can be even distilled in vacuum.

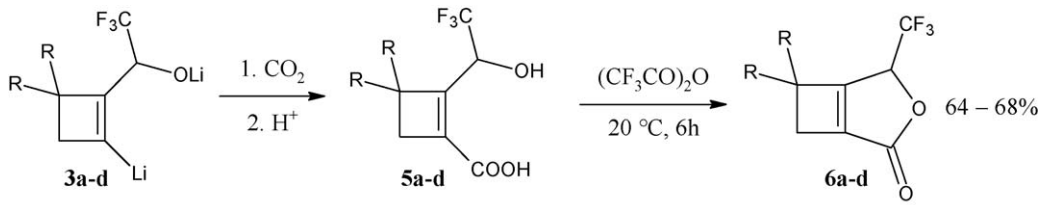
Studying the other types of [2 + 2]-cycloadducts **1** [7] and [2 + 4]-cycloadducts [11] we have found that they also form corresponding butenolides in the same reaction sequence (Scheme



a (R,R = Me), **b** (R,R = $(CH_2)_3$),

c (R,R = $(CH_2)_4$), **d** (R,R = $(CH_2)_5$)

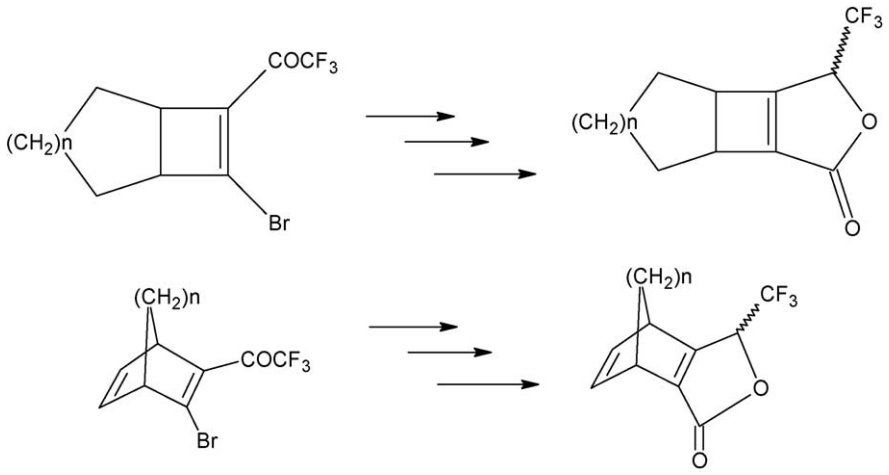
Scheme 2. The generation and determination of the yields of dilithiums **3a–d**.



a (R,R = Me), **b** (R,R = $(CH_2)_3$),

c (R,R = $(CH_2)_4$), **d** (R,R = $(CH_2)_5$)

Scheme 3. The synthesis of lactones **6a–d**.



Scheme 4.

4), but the resulting diastereomeric mixtures required difficult chromatographic separations resulting in significant losses of material.

In future we hope to overcome this difficulty by diastereoselective reduction of the carbonyl function in the starting ketones **1**.

3. Conclusion

In summary we have developed a new method for the construction of novel 5-(trifluoromethyl)-2(5*H*)-furanones, containing strained cyclobutene ring with the variable spiro-conjunctions. This approach includes the reduction of carbonyl function of the available [2 + 2]-cycloadducts **1** to afford the brominated carbinols **2**, the generation of new organolithiums **3**, which, in turn, have been transformed to the corresponding γ-hydroxyacids **5** followed by lactonization. It also should be expected that organolithiums **3a–d** can serve as useful reagents for a variety of transformations.

4. Experimental

Cycloadducts **1a–d** have been prepared according to described procedures [6,7]. Manipulations with organolithiums were carried out in argon atmosphere. Trifluoroacetic anhydride was distilled over P_2O_5 prior to use. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on "Bruker AMX 400" spectrometer at 400 and 100 MHz respectively, chemical shifts are reported in ppm relative to 0 for TMS. IR spectra were recorded on "Bruker IFS 25" spectrometer and are reported in terms of frequency of absorption (cm^{-1}).

4.1. General procedure for reduction of ketones 1a–d by $LiAlH_4$. Synthesis of alcohols 2a–d

To a stirred, at −70 °C, suspension of $LiAlH_4$ (0.19 g, 5 mmol) in dry Et_2O (30 mL), the solution of corresponding ketone **1** (10 mmol) in Et_2O (10 mL) was added dropwise. The resulting mixture was stirred for 45 min at −70 °C and then methanol (1.5 mL) was added to it at the same temperature. The temperature was then allowed to rise to −30 °C after which diluted hydrochloric acid (10 mL of 7% aqueous HCl) was added dropwise. The organic and water phases were carefully decanted from bulky residue, which was additionally washed with ether (2× 10 mL) and water solution was extracted with ether (2× 10 mL). The combined organic solutions were dried over Na_2SO_4 and subsequently concentrated in vacuum. Distillation of the remaining liquid gave the alcohols **2** in high yields.

4.1.1. 1-(2-Bromo-4,4-dimethylcyclobut-1-en-1-yl)-2,2,2-trifluoroethanol (2a)

Colorless oil, yield 2.38 g (92%), bp 75 °C (7 Torr). IR (film) ν: 3474, 3010, 2996, 1645, 1309, 1290, 1187 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, s, CH_3), 1.34 (3H, s, CH_3), 2.59–2.62 (2H, m, CH_2), 2.86 (1H, br s, H–O), 4.61 (1H, q, *J* = 7.2 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8 (CH_3), 20.7 (CH_3), 45.4 (CH_2), 49.5 (C–CH_2), 67.0 (q, *J* = 33 Hz, C–CF_3), 119.9 (C=), 122.0 (q, *J* = 290 Hz, CF_3), 144.5 (C=); Anal. Calcd. for $C_8H_{10}BrF_3O$: C, 37.09; H, 3.89; Br, 30.84; F 22.00. Found: C, 37.12; H, 3.95; Br, 30.70; F, 21.88.

4.1.2. 1-(2-Bromospiro[3.3]hept-1-en-1-yl)-2,2,2-trifluoroethanol (2b)

Colorless oil, yield 2.44 g (90%), bp 82–83 °C (7 Torr). IR (film) ν: 3464, 3012, 2996, 1647, 1310, 1271, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.16–2.29 (4H, m, 4C–H in cyclobutene), 2.54 (2H, dd, *J* = 12.4, 8.0 Hz, 2C–H in cyclobutene), 2.80–2.83 (2H, m, CH_2–C=C), 2.89 (1H, br s, H–O), 4.68 (1H, q, *J* = 7.2 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 28.1, 29.8 (–(CH_2)$_3$–); 47.3 (CH_2–C=C), 51.9 (C–C=C), 68.8 (q, *J* = 33 Hz, C–CF_3), 120.8 (C=), 122.7 (q, *J* = 290 Hz, CF_3), 145.3 (C=); Anal. Calcd. for $C_9H_{10}BrF_3O$: C, 39.88; H, 3.72; Br, 29.48; F, 21.03. Found: C, 40.06; H, 3.80; Br, 29.33; F, 20.96.

4.1.3. 1-(2-Bromospiro[3.4]oct-1-en-1-yl)-2,2,2-trifluoroethanol (2c)

Colorless oil, yield 2.51 g (88%), bp 73–74 °C (1 Torr). IR (film) ν: 3480, 3012, 2995, 1643, 1310, 1268, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.70–2.02 (8H, m, –(CH_2)$_4$–), 2.57–2.60 (2H, m, CH_2–C=C), 2.81 (1H, br s, H–O), 4.66 (1H, q, *J* = 7.2 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 25.0, 31.8, 33.0 (–(CH_2)$_4$–), 48.7 (CH_2–C=C), 50.4 (C–C=C), 68.1 (q, *J* = 33 Hz, C–CF_3), 121.0 (C=), 124.0 (q, *J* = 289 Hz, CF_3), 146.3 (C=); Anal. Calcd. for $C_{10}H_{12}BrF_3O$: C, 42.13; H, 4.24; Br, 28.03; F, 19.99. Found: C, 41.95; H, 4.20; Br, 27.96; F, 19.87.

4.1.4. 1-(2-Bromospiro[3.5]non-1-en-1-yl)-2,2,2-trifluoroethanol (2d)

Colorless oil, yield 2.60 g (87%), bp 82–83 °C (1 Torr). IR (film) ν: 3480, 3010, 2960, 1644, 1308, 1276, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14–1.40 (m), 1.52–1.80 (m) (10H, –(CH_2)$_5$–), 2.55–2.58 (2H, m, CH_2–C=C), 2.79 (1H, br s, H–O), 4.60 (1H, q, *J* = 7.1 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 24.2, 25.0, 33.8, 34.6 (–(CH_2)$_5$–), 48.1 (CH_2–C=C), 51.5 (C–C=C), 67.3(q, *J* = 33 Hz, C–CF_3), 118.8 (C=), 123.4 (q, *J* = 289 Hz, CF_3), 147.6 (C=); Anal. Calcd. for $C_{11}H_{14}BrF_3O$: C, 44.17; H, 4.72; F, 19.05. Found: C, 41.06; H, 4.56; F, 19.03.

*4.2. General procedure for preparation of organolithiums **3a–d**. Synthesis of debrominated alkohols **4a–d***

To the stirred, at −70 °C, solution of the corresponding alcohol **2a–d** (7 mmol) in THF (10 mL) the solution of BuLi in hexane (9.4 mL of 1.6N solution, 15 mmol) was added dropwise. The resulting solution was stirred at −60 °C for 1.5 h after which the formation of white crystalline precipitates of organolithiums **3a–d** was observed. The reaction mixture was allowed to warm spontaneously to −40 °C and aqueous solution of 3N HCl (5 mL) was then added. The organic layer was separated and water phase was extracted with ether (2× 10 mL). The combined organic solutions were dried over Na_2SO_4 and subsequently concentrated in vacuum. Distillation of the remaining liquid gave alcohols **4a–d** in high yields.

*4.2.1. 1-(4,4-Dimethylcyclobut-1-en-1-yl)-2,2,2-trifluoroethanol (**4a**)*

Colorless oil, yield 1.08 g (85%), bp 42–43 °C (8 Torr). IR (film) ν: 3450, 2995, 1641, 1370, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, s, CH_3), 1.26 (3H, s, CH_3), 2.19–2.22 (2H, m, CH_2), 2.58 (1H, br s, H–O), 4.69 (1H, q, J = 7.4 Hz, H–C–CF_3), 6.15 (1H, t, J = 1.2 Hz, CH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5 (CH_3), 20.2 (CH_3), 41.7 (CH_2), 44.5 (C–CH_2), 64.5 (q, J = 33.4 Hz, C–CF_3), 122.3 (q, J = 290 Hz, CF_3), 127.3 (C=), 138.5 (C=); Anal. Calcd. for $C_8H_{11}F_3O$: C, 53.33; H, 6.15; F, 31.63. Found: C, 53.20; H, 6.18; F, 31.51.

*4.2.2. 2,2,2-Trifluoro-1-spiro[3.3]hept-1-en-1-ylethanol (**4b**)*

Colorless oil, yield 1.09 g (81%), bp 51–52 °C (8 Torr). IR (film) ν: 3442, 3005, 2992, 1640, 1370, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.14–2.25 (4H, m, 4C–H in cyclobutene), 2.49 (2H, dd, J = 12.0, 7.8 Hz, 2C–H in cyclobutene), 2.70–2.73 (2H, m, CH_2–C=C), 2.91 (1H, br s, H–O), 4.77 (1H, q, J = 7.2 Hz, H–C–CF_3), 6.18 (1H, t, J = 1.2 Hz, CH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 26.1, 26.7 (–(CH_2)$_3$–), 48.7 (CH_2–C=C), 52.2 (C–C=C), 65.3 (q, J = 33 Hz, C–CF_3), 121.9 (q, J = 290.1 Hz, CF_3), 130.3 (C=), 141.3 (C=); Anal. Calcd. for $C_9H_{11}F_3O$: C, 56.25; H, 5.77; F, 29.66. Found: C, 56.17; H, 5.66; F, 29.58.

*4.2.3. 2,2,2-Trifluoro-1-spiro[3.4]oct-1-en-1-ylethanol (**4c**)*

Colorless oil, yield 1.18 g (82%), bp 60–61 °C (8 Torr). IR (film) ν: 3458, 3000, 2990, 1643, 1371, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.68–1.99 (8H, m, –(CH_2)$_4$–), 2.52–2.55 (2H, m, CH_2–C=C), 2.84 (1H, br s, H–O), 4.61 (1H, q, J = 7.3 Hz, H–C–CF_3), 6.14 (1H, t, J = 1.1 Hz, CH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 22.8, 29.8, 31.4 (–(CH_2)$_4$–), 46.7 (CH_2–C=C), 50.0 (C–C=C), 69.3 (q, J = 32.7 Hz, C–CF_3), 123.3 (q, J = 288 Hz, CF_3), 127.4 (C=), 140.7 (C=); Anal. Calcd. for $C_{10}H_{13}F_3O$: C, 58.25; H, 6.35; F, 27.64. Found: C, 58.40; H, 6.39; F, 27.56.

*4.2.4. 2,2,2-Trifluoro-1-spiro[3.5]non-1-en-1-ylethanol (**4d**)*

Colorless oil, yield 1.28 g (83%), bp 52–53 °C (1 Torr). IR (film) ν: 3440, 3007, 2988, 1645, 1370, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.11–1.36 (m), 1.50–1.80 (m) (10H, –(CH_2)$_5$–), 2.47–2.50 (2H, m, CH_2–C=C), 2.85 (1H, br s, H–O), 4.65 (1H, q, J = 7.3 Hz, H–C–CF_3), 6.09 (1H, t, J = 1.2 Hz, CH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 24.8, 25.1, 34.6, 34.8 (–(CH_2)$_5$–), 48.8 (CH_2–C=C), 50.9 (C–C=C), 68.4 (q, J = 32.4 Hz, C–CF_3), 123.9 (q, J = 288.5 Hz, CF_3), 129.7 (C=), 142.0 (C=); Anal. Calcd. for $C_{11}H_{15}F_3O$: C, 59.99; H, 6.87; F, 25.88. Found: C, 60.17; H, 6.91; F, 25.85.

*4.3. General procedure for carboxylation of organolithiums **3a–d**. Synthesis of α,β-unsaturated γ-hydroxyacids (**5a–d**)*

To the stirred, at −70 °C, suspension of the corresponding organolithium **3a–d** prepared as described in Section 4.2, a strong stream of CO_2 was introduced for 5 min over the surface of the reaction mixture. The resulting thick suspension was allowed to warm to 0 °C after which an aqueous solution of 2N HCl (10 mL) was added. The organic phase was separated and water solution was extracted with ether (5× 10 mL). The combined organic solutions were dried over Na_2SO_4 and subsequently concentrated in vacuum. The residual solid was washed with cold hexane and dried in vacuum to afford corresponding acid **5a–d**.

*4.3.1. 3,3-Dimethyl-2-(2,2,2-trifluoro-1-hydroxyethyl)cyclobut-1-ene-1-carboxylic acid (**5a**)*

White crystals, yield 1.14 g (73%), mp 171–172 °C. IR (mineral oil) ν: 3630, 3407, 3012, 2969, 1662, 1640, 1374, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.62–2.65 (2H, m, CH_2), 2.96 (1H, br s, H–O), 4.70 (1H, q, J = 7.1 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5 (CH_3), 26.8 (CH_3), 40.2 (CH_2), 47.7 (C–CH_2), 68.3 (q, J = 33.2 Hz, C–CF_3), 124.4 (q, J = 284.0 Hz, CF_3), 138.7 (C=), 163.2 (C=), 166.9 (C=O); Anal. Calcd. for $C_9H_{11}F_3O_3$: C, 48.22; H, 4.95; F, 25.43. Found: C, 48.34; H, 5.02; F, 25.38.

*4.3.2. 1-(2,2,2-Trifluoro-1-hydroxyethyl)spiro[3.3]hept-1-ene-2-carboxylic acid (**5b**)*

White crystals, yield 1.24 g (75%), mp 189–190 °C. IR (mineral oil) ν: 3619, 3410, 3000, 2980, 1664, 1641, 1374, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.19–2.33 (4H, m, 4C–H in cyclobutene), 2.50 (2H, dd, J = 12.2, 8.2 Hz, 2 C–H in cyclobutene), 2.87–2.90 (2H, m, CH_2–C=C), 3.05 (1H, br s, H–O), 4.94 (1H, q, J = 7.4 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 29.9, 31.2 (–(CH_2)$_3$–), 42.3 (CH_2–C=C), 51.6 (C–C=C), 68.8 (q, J = 34.1 Hz, C–CF_3), 124.8 (q, J = 288.0 Hz, CF_3), 140.0 (C=), 163.6 (C=), 168.5 (C=O); Anal. Calcd. for $C_{10}H_{11}F_3O_3$: C, 50.85; H, 4.69; F, 24.13. Found: C, 50.65; H, 4.66; F, 4.07.

*4.3.3. 1-(2,2,2-Trifluoro-1-hydroxyethyl)spiro[3.4]oct-1-ene-2-carboxylic acid (**5c**)*

White crystals, yield 1.26 g (72%), mp 203–204 °C. IR (mineral oil) ν: 3600, 3413, 3005, 2980, 1665, 1638, 1370, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.74–2.19 (8H, m, –(CH_2)$_4$–), 2.49–2.52 (2H, m, CH_2–C=C), 2.72 (1H, br s, H–O), 4.54 (1H, q, J = 7.2 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9, 26.5, 33.1, 35.0 (–(CH_2)$_4$–), 40.2 (CH_2–C=C), 50.0 (C–C=C), 66.3 (q, J = 33.4 Hz, C–CF_3), 122.6 (q, J = 289 Hz, CF_3), 135.9 (C=), 160.2 (C=), 166.2 (C=O); Anal. Calcd. for $C_{11}H_{13}F_3O_3$: C, 52.80; H, 5.24; F, 22.78. Found: C, 52.98; H, 5.28; F, 22.62.

*4.3.4. 1-(2,2,2-Trifluoro-1-hydroxyethyl)spiro[3.5]non-1-ene-2-carboxylic acid (**5d**)*

White crystals, yield 1.39 g (75%), mp 220–221 °C. IR (mineral oil) ν: 3636, 3413, 3010, 2973, 1660, 1636, 1374, 1228 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19–1.45 (m), 1.56–1.80 (m) (10H, –(CH_2)$_5$–), 2.54–2.57 (2H, m, CH_2–C=C), 2.76 (1H, br s, H–O), 4.66 (1H, q, J = 7.2 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 24.7, 25.1, 33.5, 34.2 (–(CH_2)$_5$–), 39.0 (CH_2–C=C), 48.3 (C–C=C), 67.0 (q, J = 33.5 Hz, C–CF_3), 124.4 (q, J = 284 Hz, CF_3), 136.9 (C=), 163.9 (C=), 166.4 (C=O); Anal. Calcd. for $C_{12}H_{15}F_3O_3$: C, 54.54; H, 5.72; F, 21.57. Found: C, 54.64; H, 5.58; F, 21.49.

*4.4. General procedure for preparation of lactones (**6a–d**)*

A suspension of acid **5a–d** (10 mmol) in trifluoroacetic anhydride (10 mL) was stirred at 20 °C until the dissolution of the solid was complete and the solution formed was stirred additionally for 6 h. An excess of trifluoroacetic anhydride was carefully distilled off, the residue was diluted with ether (50 mL) and rapidly washed with cold saturated solution of $NaHCO_3$ (20 mL) and consequently dried

over Na_2SO_4. The solution was concentrated under reduced pressure and the residue was distilled in vacuum or subjected to chromatographic purification (see below) to afford lactones **6a–d**.

*4.4.1. 6,6-Dimethyl-4-(trifluoromethyl)-3-oxabicyclo[3.2.0]hept-1(5)-en-2-one (**6a**)*

Colorless oil, yield 1.43 g (65%), bp 93–94 °C (0.6 Torr). IR (film) ν: 3008, 2995, 1797, 1374, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.71–2.74 (2H, m, CH_2), 5.32 (1H, q, J = 6.0 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9 (CH_3), 27.0 (CH_3), 44.7 (CH_2), 52.2 (C–CH_2), 79.6 (q, J = 35.9 Hz, C–CF_3), 124.8 (q, J = 290.0 Hz, CF_3), 136.4 (C=), 153.5 (C=), 173.9 (C=O); Anal. Calcd. for $C_9H_9F_3O_2$: C, 52.43; H, 4.40; F, 27.65. Found: C, 52.63; H, 4.47; F, 27.54.

*4.4.2. 4-(Trifluoromethyl)-3-oxaspiro[bicyclo[3.2.0]heptane-6,1′-cyclobutane]-1(5)-en-2-one (**6b**)*

Colorless oil, yield 1.46 g (67%), bp 101–102 °C (0.6 Torr). IR (film) ν: 3014, 2995, 1802, 1370, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.26–2.39 (4H, m, 4C–H in cyclobutene), 2.56 (2H, dd, J = 11.7, 7.9 Hz, 2C–H in cyclobutene), 2.93–2.96 (2H, m, CH_2–C=C), 5.34 (1H, q, J = 5.9 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 32.3, 33.5 (–$(CH_2)_3$–), 46.7 (CH_2C=C), 54.9 (C–C=C), 78.4 (q, J = 35.6 Hz, C–CF_3), 124.3 (q, J = 290.0 Hz, CF_3), 138.0 (C=), 155.6 (C=), 173.6 (C=O); Anal. Calcd. for $C_{10}H_9F_3O_2$: C, 55.05; H, 4.16; F, 26.12. Found: C, 55.19; H, 4.10; F, 26.10.

*4.4.3. 4-(Trifluoromethyl)-3-oxaspiro[bicyclo[3.2.0]heptane-6,1′-cyclopentane]-1(5)-en-2-one (**6c**)*

Colorless oil, yield 1.48 g (64%). The substance was purified by column chromatography (silica gel, hexane/AcOEt = 5: 1). IR (film) ν: 3014, 2998, 1800, 1376, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.70–2.06 (8H, m, –$(CH_2)_4$–), 2.68–2.71 (2H, m, CH_2–C=C), 5.30 (1H, q, J = 6.0 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.8, 35.8, 35.3 (–$(CH_2)_4$–), 42.5 (CH_2–C=C), 50.4 (C–C=C), 78.0 (q, J = 35.9 Hz, C–CF_3), 123.2 (q, J = 290.0 Hz, CF_3), 134.4 (C=), 152.4 (C=), 172.5 (C=O); Anal. Calcd. for $C_{11}H_{11}F_3O_2$: C, 56.90; H, 4.77; F, 24.55. Found: C, 57.08; H, 4.69; F, 24.38.

*4.4.4. 4-(Trifluoromethyl)-3-oxaspiro[bicyclo[3.2.0]heptane-6,1′-cyclohexane]-1(5)-en-2-one (**6d**)*

White crystals, yield 1.67 g (68%), mp 39–40 °C. The substance was purified by column chromatography (silica gel, hexane/AcOEt = 5:1). IR (mineral oil) ν: 3019, 2998, 1797, 1376, 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22–1.44 (m), 1.59–1.93 (m) (10H, –$(CH_2)_5$–), 2.70–2.73 (2H, m, CH_2–C=C), 5.32 (1H, q, J = 6.0 Hz, H–C–CF_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 25.8, 26.0, 34.4, 35.2 (–$(CH_2)_5$–), 42.2 (CH_2–C=C), 50.7(C–C=C), 78.3 (q, J = 35.7 Hz, C–CF_3), 122.6 (q, J = 290.0 Hz, CF_3), 133.5 (C=), 152.2 (C=), 171.9 (C=O); Anal. Calcd. for $C_{12}H_{13}F_3O_2$: C, 58.53; H, 5.32; F, 23.15. Found: C, 58.71; H, 5.40; F, 23.06.

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