Reaction of α,β-unsaturated trifluoromethyl ketones with cyclic enamines

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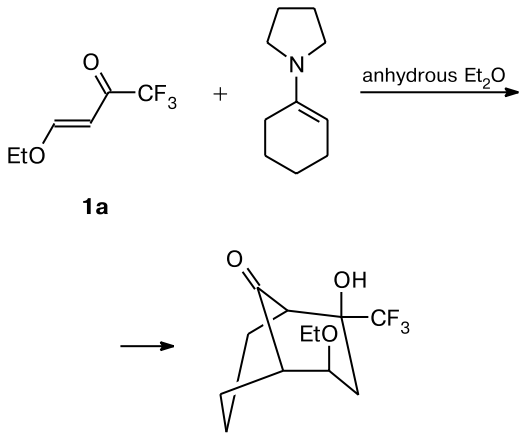
The reactions of α,β-unsaturated trifluoromethyl ketones containing aromatic and heteroaromatic substituents with 1-morpholinocyclopentene, 1-morpholinocyclohexene, and 1-methyl-4-morpholino-1,2,5,6-tetrahydropyridine were studied. The reactions proceeded stereospecifically to give the corresponding bicyclo[3.2.1]octane, bicyclo[3.3.1]nonane, and azabicyclo[3.3.1]nonane derivatives.

Key words: unsaturated trifluoromethyl ketones, enamines, stereochemistry, cycloaddition.

In recent years, considerable attention has been given to the development of new procedures for the synthesis of fluorine-containing compounds, which are often used in both medicine and agricultural chemistry.[1,2] α,β-Unsaturated trifluoromethyl ketones serve as convenient building blocks for the introduction of the trifluoromethyl group into different classes of acyclic, carbocyclic, and heterocyclic compounds. However, their properties have not been adequately investigated.[3,4]

The reaction of the only unsaturated trifluoromethyl ketone, *viz.*, 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1a**), with 1-pyrrolidinocyclohexene in anhydrous Et_2O was described in the literature.[5] The reaction gave rise to 4-ethoxy-2-hydroxy-2-trifluoromethylbicyclo[3.3.1]nonan-9-one as a single diastereomer (Scheme 1).

Scheme 1



In all cases, the reactions of trifluoromethyl ketones **1a** and **1b** with enamines **2a—c** in aqueous EtOH (Scheme 2) afforded a product (in a nearly quantitative yield), which was identified as 1,1,1-trifluoro-4-(morpholin-4-yl)but-3-en-2-one (**4**), instead of the expected bicyclic hydroxy ketone **3a**. Apparently, this reaction pathway is associated with the influence of the polar solvent, and the reaction proceeds at the nitrogen atom of the amino fragment of enamine rather than at the α-carbon atom.

It is known that α,β-unsaturated trifluoromethyl ketones containing a substituent, which is capable of being eliminated, at position 4 can differ radically in the reactivity and the reaction pathway from α,β-unsaturated trifluoromethyl ketones devoid of such substituents.[4] In this connection, we studied the reactions of ketones containing aryl and hetaryl substituents[6—8] with various cyclic enamines.

We chose 1,1,1-trifluoro-4-phenylbut-3-en-2-one (**1c**) and 1-morpholinocyclohexene (**2b**) as model substrates. The reactions were carried out in 96% EtOH at ≈20 °C followed by treatment of the reaction mixture with an aqueous NH_4Cl solution to hydrolyze iminium intermediates. Bicyclic ketone **3c** was isolated from the reaction mixture. Therefore, the reaction is not finished at the step of formation of the Michael adduct and results in cyclization of the iminium intermediate to give a bicyclic derivative (Scheme 3).

Bicyclic hydroxy ketone **3c** was isolated as a single diastereomer. To confirm the structure and reveal the orientations of the substituents, we carried out X-ray diffraction analysis and established that the phenyl substituent and the hydroxy group are in the axial positions, whereas the trifluoromethyl group is in the equatorial position (Fig. 1). It was found that there is no intramolecular hydrogen bond between the proton of the hydroxy group and the oxygen atom of the carbonyl group, whereas the proton of the hydroxy group and the oxygen atom of

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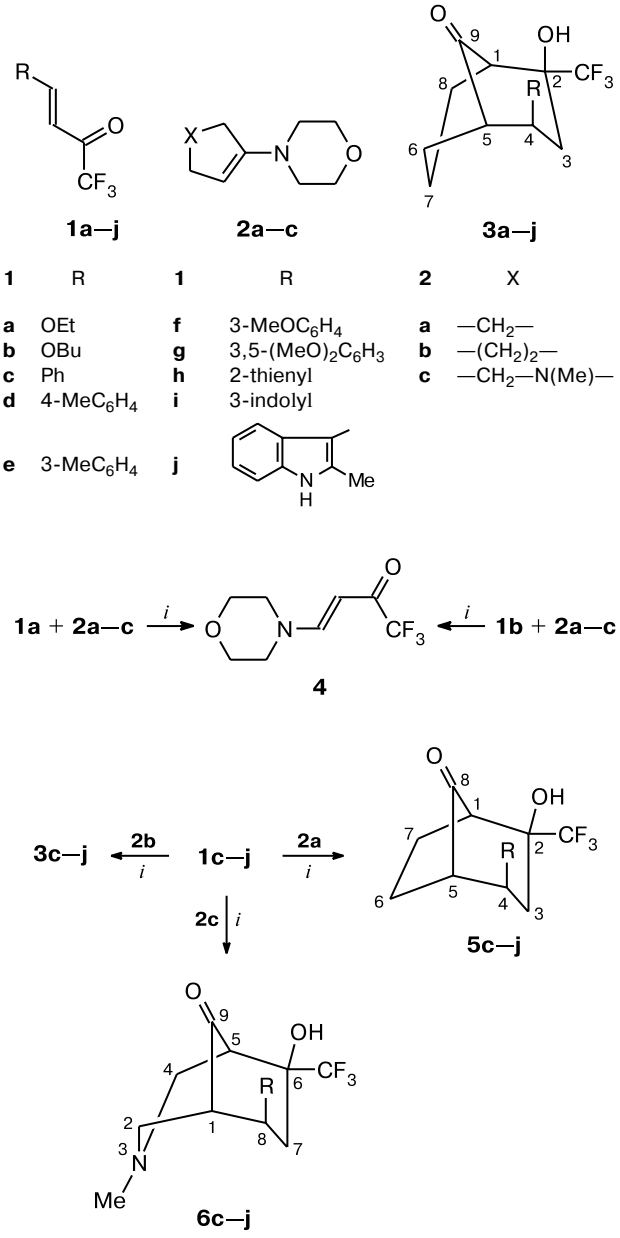
Scheme 2

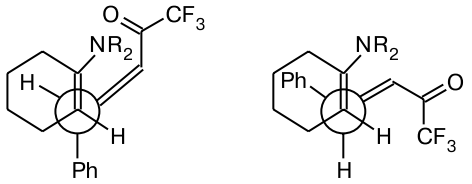


i. EtOH, H_2O, 20 °C.

the carbonyl group of the adjacent molecule are involved in an intermolecular hydrogen bond.

In addition, the 2D $^1H—^1H$ COSY NMR spectrum of compound **3c** completely confirms the assignment of the protons in the ^1H NMR spectrum and is consistent with the three-dimensional structure established by X-ray diffraction analysis.

To explain the fact that the phenyl substituent in compound **3c** is in the axial position rather than in the energetically more favorable equatorial position, two transition states (**A** and **B**) were discussed in the study.[5] Of these two forms, the transition state **B** gives a product with the above-mentioned stereochemistry. As can be seen from the projection of **B**, this transition state is characterized by minimum steric hindrances caused by interactions between the trifluoroacetyl group and the amino moiety of enamine, due to which the reaction proceeding through this intermediate affords a product with the axial orientation of the phenyl substituent.



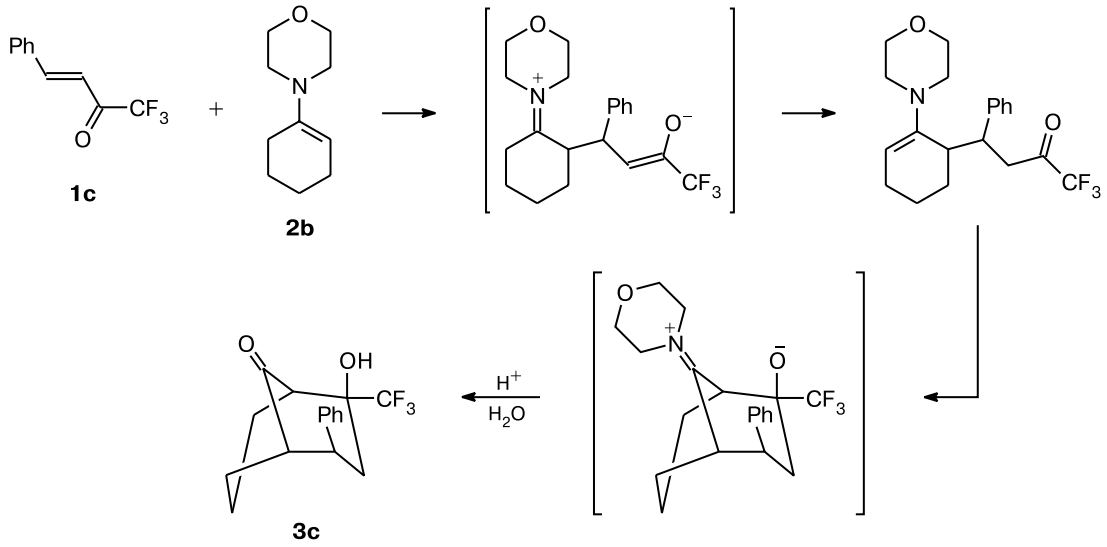
Therefore, the first step of this reaction, *viz.*, the Michael addition, is kinetically controlled. The second step, which is responsible for the orientation of the hydroxy group, also proceeds under kinetically controlled conditions, because the bulky CF_3 group is in the equatorial position. We demonstrated that hydrolysis of the reaction mixture with 6 *M* hydrochloric acid afforded a mixture of diastereomers of compound **3c**. Therefore, the formation of the diastereomer with the axial orientation of the phenyl group is attributed to the kinetic control over the reaction.

We also carried out the reactions of 1-morpholinocyclohexene (**2b**) with ketones **1d—j**. At ≈20 °C, these reactions proceeded rather slowly and necessitated refluxing (except for the reactions with ketones **1i** and **1j** containing the 3-indolyl and 2-methylindol-3-yl substituents, respectively; these reactions did not proceed due, apparently, to the high electron-donating ability of these substituents and the bulkiness of the substituent at the β position). In all cases, the reactions proceeded stereospecifically to give the only diastereomer in a virtually quantitative yield. The configuration of the latter is, apparently, analogous to that of compound **3c**. The electron-donating properties of the substituent in the starting trifluoromethyl ketone have only a slight effect on the yield of the reaction product but influence substantially the reaction time.

To compare the reactivities of enamines, we carried out the reactions with 1-morpholinocyclopentene (**2a**) and 1-methyl-4-morpholino-1,2,5,6-tetrahydropyridine (**2c**), which proceeded analogously to that with **2b** to give the corresponding bicyclic products **5** and **6** (see Scheme 2, Table 1).

As expected, due to a higher steric strain of the ring, 1-morpholinocyclopentene (**2a**) exhibits much higher reactivity compared to that of morpholinocyclohexene (**2b**) and is involved in the reaction at ≈20 °C. 1-Methyl-4-morpholino-1,2,5,6-tetrahydropyridine (**2c**) is also more

Scheme 3



reactive than **2b**. The reactions of both these enamines proceeded stereospecifically to give the corresponding bicyclic ketones **5** and **6** in high yields. For these enamines, the dependence of the reaction rate on the electron-donating properties of the substituent in the starting ketone is analogous to that observed for 1-morpholinocyclohexene (**2b**).

To summarize, we demonstrated that the reactions of unsaturated trifluoromethyl ketones with enamines proceed stereospecifically to form the corresponding derivatives of bicyclic hydroxy ketones. The structures of these compounds and the orientations of the functional groups were established by X-ray diffraction analysis.

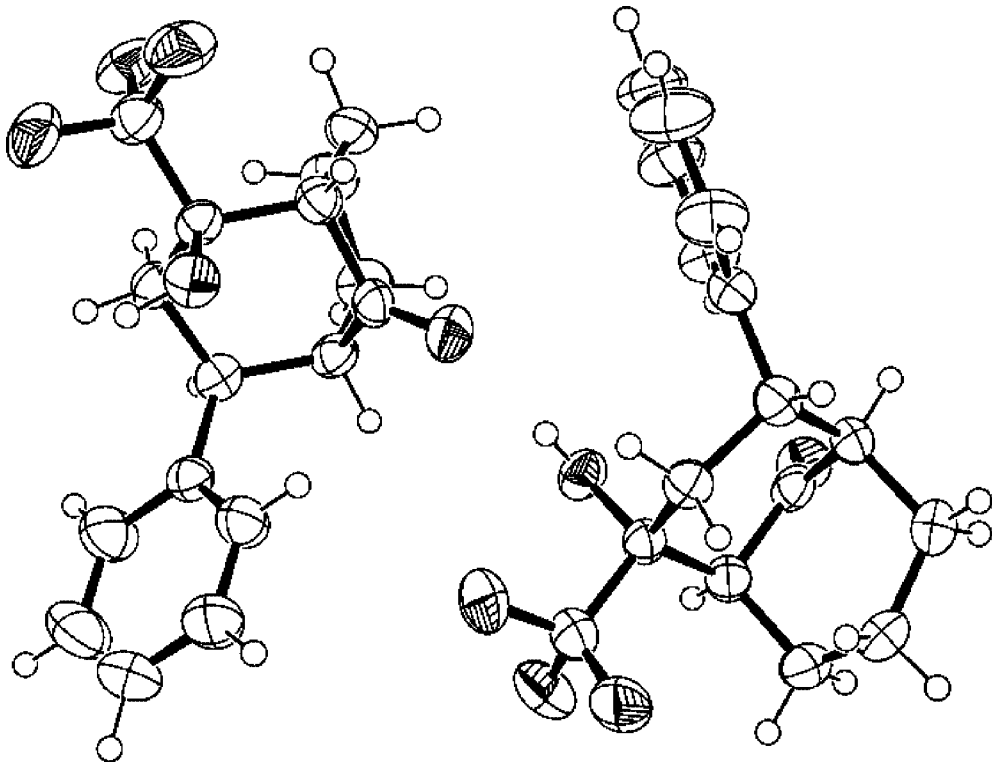


Fig. 1. Structure of compound **3c** based on X-ray diffraction analysis.

Table 1. Reactions of trifluoromethyl ketones **1c—j*** with enamines **2a—c**

Starting ketone, *R*	**3**		**5**		**6**	
	τ/h refluxing	Yield (%)	τ/h	Yield (%)	τ/h	Yield (%)
1c, Ph	6—7	95	6	99	8	70
1d, 4-MeC_6H_4	14	83	14	82	12	61
1e, 3-MeC_6H_4	12	98	12	94	**	**
1f, 3-$MeOC_6H_4$	16	92	16	88	16	79
1g, 2,5-$(MeO)_2C_6H_4$	16	99	48	87	50	50
1h, 2-thienyl	48	87	16	99	14	66
1i, 3-indolyl	***	***	48	52	50	51

* The reaction with **1j** did not proceed.
** The reaction was not carried out.
*** The reaction did not proceed.

Experimental

The ^1H, ^{13}C, and COSY NMR spectra of compound **3c** were recorded on a Bruker Avance-600 spectrometer (at 600 and 150 MHz for ^1H and ^{13}C, respectively) in $CDCl_3$, CD_3CN, or $(CD_3)_2SO$ with Me_4Si as the internal standard. The ^1H and ^{13}C NMR spectra for all other compounds were measured on a Varian VXR-400 spectrometer (at 400 and 100 MHz, respectively) in $CDCl_3$, CD_3CN, or $(CD_3)_2SO$ with Me_4Si as the internal standard. The IR spectra were recorded on a UR-20 spectrometer in Nujol mulls. The TLC analysis was performed on Silufol UV-254 plates; visualization was carried out with an acidified solution of $KMnO_4$ and iodine vapor. 1,1,1-Trifluoro-4-dimethylaminobut-3-en-2-one was synthesized according to a procedure described earlier.[6]

Synthesis of α,β-unsaturated trifluoromethyl ketones (general procedure).[6] A solution of BuLi (0.1 mol) in anhydrous THF (200 mL) cooled to −70 °C was placed in a three-neck flask, which was flame-dried in an argon flow and equipped with an internal thermometer and a dropping funnel, and a solution of the corresponding aryl bromide (0.1 mol) in anhydrous THF (20 mL) was added dropwise. The resulting suspension of aryllithium was stirred at this temperature for 30 min. Then a solution of 1,1,1-trifluoro-4-dimethylaminobut-3-en-2-one (0.1 mol) in anhydrous THF (20 mL) was added dropwise to the reaction mixture, the temperature of no higher than −60 °C being maintained. Then the temperature of the reaction mixture was raised to +10 °C during ≈1 h and 4 *M* HCl (60 mL) was added. The mixture was stirred at ≈20 °C for 30 min, the upper organic layer was separated, and the lower aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The combined extracts were dried with Na_2SO_4, the solution was concentrated, and the reaction product, which was obtained as a dark oil, was chromatographed on a column with silica gel (hexane—AcOEt, 15 : 1—3 : 1, as the eluent).

1,1,1-Trifluoro-4-(4-methylphenyl)but-3-en-2-one (1d).* The yield was 42%, m.p. 35 °C. Found (%): C, 63.02; H, 5.11. $C_{12}H_{11}F_3O$. Calculated (%): C, 63.16; H, 4.86. IR, ν/cm^{-1}: 1730 (C=O); 1620 (C=C). ^1H NMR ($CDCl_3$), δ: 2.40 (s, 3 H, Me); 6.96 (d, 1 H, C<u>H</u>=CHCO, *J* = 15.9 Hz); 7.26 (d, 2 H, 4-$MeC_6\underline{H}_4$, H(2′), H(6′), *J* = 7.7 Hz); 7.54 (d, 2 H, 4-$MeC_6\underline{H}_4$, (H(3′), H(5′), *J* = 7.7 Hz); 7.94 (d, 1 H, CH=C<u>H</u>CO, *J* = 15.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 21.33 (Me); 115.3 (<u>C</u>H=CHCO); 116.5 (q, <u>C</u>F_3, *J* = 291.5 Hz); 129.2, 129.8, 130.6, 143.3 (4-MeC_6H_4); 150.0 (CH=<u>C</u>HCO); 179.8 (q, <u>C</u>=O, *J* = 35.1 Hz).

1,1,1-Trifluoro-4-(3-methylphenyl)but-3-en-2-one (1e). The yield was 65%, pale-yellow oil. Found (%): C, 63.44; H, 5.01. $C_{12}H_{11}F_3O$. Calculated (%): C, 63.16; H, 4.86. IR, ν/cm^{-1}: 1735 (C=O); 1630 (C=C). ^1H NMR ($CDCl_3$), δ: 2.40 (s, Me); 7.00 (d, 1 H, C<u>H</u>=CHCO, *J* = 15.9 Hz); 7.28—7.37 (m, 2 H, 3-$MeC_6\underline{H}_4$, H(2′), H(4′)); 7.42—7.46 (m, 2 H, 3-$MeC_6\underline{H}_4$, H(5′), H(6′)); 7.94 (d, 1 H, CH=C<u>H</u>CO, *J* = 15.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 20.9 (Me); 116.1 (<u>C</u>H=CHCO); 116.4 (q, <u>C</u>F_3, *J* = 291.5 Hz); 126.4, 128.5, 128.9, 129.6, 133.1, 138.9 (3-$Me\underline{C}_6H_4$); 150.0 (CH=<u>C</u>HCO); 179.7 (q, <u>C</u>=O, *J* = 35.1 Hz).

1,1,1-Trifluoro-4-(3-methoxyphenyl)but-3-en-2-one (1f). The yield was 67%, pale-yellow oil. Found (%): C, 59.18; H, 4.67. $C_{12}H_{11}F_3O_2$. Calculated (%): C, 59.02; H, 4.54. IR, ν/cm^{-1}: 1730 (C=O); 1630 (C=C). ^1H NMR ($CDCl_3$, δ: 3.86 (s, OMe); 6.99 (dd, 1 H, C<u>H</u>=CHCO, *J* = 15.9 Hz, *J* = 0.8 Hz); 7.04 (ddd, 1 H, 3-$MeOC_6\underline{H}_4$, H(2′), *J* = 8.0 Hz; *J* = 2.5 Hz; *J* = 0.8 Hz); 7.13 (t, 1 H, 3-$MeOC_6\underline{H}_4$, H(4′), *J* = 2.5 Hz); 7.23 (dt, 1 H, 3-$MeOC_6\underline{H}_4$, H(6′), *J* = 8.0 Hz; *J* = 0.8 Hz); 7.36 (t, 1 H, 3-$MeOC_6\underline{H}_4$, H(5′), *J* = 8.0 Hz); 7.93 (d, 1 H, CH=C<u>H</u>CO, *J* = 15.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.1 (OMe); 116.4 (q, <u>C</u>F_3, *J* = 291.5 Hz); 116.6 (<u>C</u>H=CHCO); 113.8, 118.1, 121.8, 130.1, 134.5, 160.0 (3-$MeO\underline{C}_6H_4$); 150.0 (CH=<u>C</u>HCO); 179.8 (q, <u>C</u>=O, *J* = 36.6 Hz).

1,1,1-Trifluoro-4-(2,5-dimethoxyphenyl)but-3-en-2-one (1g). The yield was 69%, m.p. 42—43 °C. Found (%): C, 57.13; H, 4.77. $C_{12}H_{11}F_3O_2$. Calculated (%): C, 56.94; H, 4.78. IR, ν/cm^{-1}: 1710 (C=O); 1615 (C=C). ^1H NMR ($CDCl_3$), δ: 3.81 and 3.88 (both s, 3 H each, OMe); 6.88 (d, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(3′), *J* = 9.0 Hz); 7.02 (dd, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(4′), *J* = 9.0 Hz; *J* = 3.0 Hz); 7.09 (d, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(6′), *J* = 3.0 Hz); 7.10 (d, 1 H, C<u>H</u>=CHCO, *J* = 16.2 Hz); 8.25 (d, 1 H, CH=C<u>H</u>CO, *J* = 16.2 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.7 (OMe); 55.9 (OMe); 112.5 (<u>C</u>H=CHCO); 116.5 (q, <u>C</u>F_3, *J* = 290.5 Hz); 113.8, 116.9, 119.7, 122.6, 153.5, 154.1 (2,5-$(MeO)_2\underline{C}_6H_3$); 145.4 (CH=<u>C</u>HCO); 180.2 (q, <u>C</u>=O, *J* = 34.9 Hz).

* Hereinafter, the atoms of the aryl substituents are primed.

The remaining unsaturated ketones were prepared according to known procedures.[6—8]

Reactions of trifluoromethyl ketones 1 with 1-morpholinocyclohexene (2b) (general procedure). Freshly distilled 1-morpholinocyclohexene (**2b**) [9] (1.1 mmol) was added to a solution of the corresponding α,β-unsaturated trifluoromethyl ketone **1** (1 mmol) in 95% EtOH (5 mL). The reaction mixture was refluxed until the reaction was completed (TLC control, hexane—AcOEt, 3 : 1). Then a solution of NH_4Cl (300 mg) in water (5 mL) was added and the reaction mixture was kept at ≈20 °C for 3 h, diluted with water to ≈20 mL, and extracted with CH_2Cl_2 (4×10 mL). The combined extracts were filtered through a silica gel layer. The solvent was evaporated and the residue was recrystallized from a 3 : 1 hexane—AcOEt mixture.

Single crystals of compound **3c** were prepared by recrystallization from 96% EtOH. X-ray diffraction study was carried out on an Enraf-Nonius CAD-4 diffractometer (β filter, Mo-Kα radiation, λ = 0.71073 Å) at 293 K using the θ/2θ scanning technique. The principal details of X-ray diffraction study and crystallographic data for compound **3c** are given in Table 2. The structure was solved by direct methods. The positions of the nonhydrogen atoms were refined by the full-matrix least-squares method with anisotropic thermal parameters. The hydrogen atoms were refined isotropically. Calculations were carried out using the SHELXTL PLUS program package.

In the crystal structure, the molecules are linked in chains by intermolecular O—H...O=C hydrogen bonds (d_{O-H} = 0.896 Å, $d_{H...O}$ = 1.95 Å, the O—H—O angle is 167.5°). The molecule whose carbonyl group is involved in the hydrogen bond is related to the molecule whose hydroxy group is involved in this bond by the transformation $(2 - x, y - 1/2, 3/2 - z)$.

(2*R,4*S**)-2-Hydroxy-4-phenyl-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (3c).** The yield was 95%, m.p. 184 °C. Found (%): C, 64.42; H, 5.74. $C_{16}H_{17}F_3O_2$. Calculated (%): C, 64.57; H, 5.77. IR, ν/cm^{-1}: 1710 (C=O); 3320 (O—H). ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 1.60—1.68 (m, 1 H, H_{ax}(7)); 1.96—2.05 (m, 1 H, H_{ax}(8)); 2.07—2.22 (m, 3 H, H(5), H_{ax}(6), H_{eq}(6)); 2.15 (d, 1 H, H_{ax}(3), *J* = 15.6 Hz); 2.24—2.29 (dm, 1 H, H_{eq}(7)); 2.35 (br.d, 1 H, H_{eq}(8), *J* = 14.6 Hz); 2.66 (dd, 1 H, H(1), *J* = 6.4 Hz, *J* = 1.9 Hz); 2.99 (br.s, 1 H, OH); 3.03 (dd, 1 H, H_{eq}(3), *J* = 15.6 Hz, *J* = 9.3 Hz); 3.60 (d, 1 H, H(4), *J* = 9.3 Hz); 7.16 (t, 1 H, $C_6\underline{H}_5$, H(4′), *J* = 7.3 Hz); 7.29 (t, 2 H, $C_6\underline{H}_5$, H(2′), H(6′), *J* = 7.3 Hz); 7.29 (t, 2 H, $C_6\underline{H}_5$, H(3′), H(5′), *J* = 7.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$), δ: 18.9 (C(7)); 30.6 (C(6)); 35.3 (C(4)); 37.6 (C(8)); 45.8 (C(3)); 50.1 (C(1)); 52.5 (C(5)); 81.6 (q, C(2), *J* = 27.5 Hz); 125.0 (q, $\underline{C}F_3$, *J* = 279.6 Hz); 127.1, 128.2, 129.3, 147.2 ($\underline{C}_6H_5$); 215.7 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(4-methylphenyl)-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (3d).** The yield was 83%, m.p. 168 °C. Found (%): C, 65.37; H, 5.99. $C_{17}H_{19}F_3O_2$. Calculated (%): C, 65.37; H, 6.13. IR, ν/cm^{-1}: 1710 (C=O); 3320 (O—H). ^{1}H NMR ($CDCl_3$), δ: 1.60—1.68 (m, 1 H, H_{ax}(7)); 1.96—2.07 (m, 1 H, H_{ax}(8)); 2.07—2.31 (m, 4 H, H(5), H_{ax}(6), H_{eq}(6), H_{eq}(7)); 2.13 (d, 1 H, H_{ax}(3), *J* = 13.8 Hz); 2.28 (s, Me); 2.31—2.38 (m, 1 H, H_{eq}(8)); 2.70—2.74 (m, 1 H, H(1)); 2.98 (br.s, OH); 3.02 (dd, 1 H, H_{eq}(3), *J* =15.4 Hz, *J* = 9.1 Hz); 3.57 (d, 1 H, H(4), *J* = 9.1 Hz); 7.06 (d, 2 H, 4-Me$C_6\underline{H}_4$, H(3′), H(5′), *J* = 8.2 Hz); 7.17 (d, 2 H, 4-Me$C_6\underline{H}_4$, H(2′), H(6′), *J* = 8.2 Hz). ^{13}C NMR (DMSO-d_6), δ: 18.4 (C(7)); 20.5 (Me); 30.3 (C(6)); 33.4 (C(4)); 37.0 (C(8)); 44.8 (C(3)); 50.7 (C(1)); 51.9 (C(5)); 79.3 (q, C(2), *J* = 26.3 Hz); 126.2 ($\underline{C}F_3$, *J* = 288.4 Hz); 127.5, 128.4, 134.4, 144.4 (4-Me$\underline{C}_6H_4$); 214.7 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(3-methylphenyl)-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (3e).** The yield was 98%, m.p. 163 °C. Found (%): C, 65.69; H, 6.41. $C_{17}H_{19}F_3O_2$. Calculated (%): C, 65.37; H, 6.13. IR, ν/cm^{-1}: 1710 (C=O); 3370 (O—H). ^{1}H NMR (DMSO-d_6), δ 1.48—1.58 (m, 1 H, H_{ax}(7)); 1.78—2.28 (m, 1 H, H_{ax}(8)); 2.07—2.31 (m, 3 H, H_{ax}(6), H_{eq}(6), H_{eq}(7)); 2.16 (d, 1 H, H_{ax}(3), *J* = 14.3 Hz); 2.21—2.29 (m, 1 H, H_{eq}(8)); 2.23 (s, 3 H, Me); 2.58 (br.s, 1 H, H(5)); 2.62 (br.s, 1 H, H(1)); 2.83 (dd, 1 H, H_{eq}(3), *J* = 15.4 Hz, *J* = 9.6 Hz); 3.59 (d, 1 H, H(4), *J* = 9.6 Hz); 6.02 (br.s, 1 H, OH); 6.93 (d, 1 H, 3-Me$C_6\underline{H}_4$, H(2′), *J* = 7.2 Hz); 7.02—7.14 (m, 3 H, 3-Me$C_6\underline{H}_4$, H(4′), H(5′), H(6′)). ^{13}C NMR (DMSO-d_6), δ: 18.4 (C(7)); 21.1 (Me); 30.5 (C(6)); 33.3 (C(4)); 37.1 (C(8)); 45.1 (C(3)); 50.6 (C(1)); 51.9 (C(5)); 78.9 (q, C(2), *J* = 26.4 Hz); 124.7, 126.2, 127.7, 128.4, 136.6, 147.3 (3-Me$\underline{C}_6H_4$); 125.5 (q, $\underline{C}F_3$, *J* = 288.4 Hz); 214.7 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(3-methoxyphenyl)-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (3f).** The yield was 92%, m.p. 125 °C. Found (%): C, 62.17; H, 5.81. $C_{17}H_{19}F_3O_3$. Calculated (%): C, 62.19; H, 5.83. IR, ν/cm^{-1}: 1715 (C=O); 3325 (O—H). ^{1}H NMR (DMSO-d_6), δ: 1.48—1.59 (m, 1 H, H_{ax}(7)); 1.71—1.92 (m, 1 H, H_{ax}(8)); 1.93—2.10 (m, 3 H, H(5), H_{ax}(6), H_{eq}(6)); 1.98 (d, 1 H, H_{ax}(3), *J* = 15.0 Hz); 2.17 (d, 1 H, H_{eq}(7), *J* = 14.4 Hz); 2.24 (br.d, 1 H, H_{eq}(8), *J* = 12.0 Hz); 2.60 (d, 1 H, H(1), *J* = 12.0 Hz); 2.83 (dd, 1 H, H_{eq}(3), *J* = 15.0 Hz, *J* = 9.6 Hz); 3.59 (d, 1 H, H(4), *J* = 9.6 Hz); 3.69 (s, 3 H, O$C\underline{H}_3$); 6.04 (br.s, 1 H, OH); 6.70 (d, 1 H, 3-MeOC_6H_4, H(2′), *J* = 7.5 Hz); 6.82 (d, 1 H, 3-Me$OC_6\underline{H}_4$, H(6′), *J* = 7.2 Hz); 6.90 (d, 1 H, 3-Me$OC_6\underline{H}_4$, H(4′), *J* = 7.9 Hz); 7.13 (t, 1 H, 3-Me$OC_6\underline{H}_4$, H(5′), *J* = 7.9 Hz). ^{13}C NMR (DMSO-d_6), δ: 18.4 (C(7)); 30.3 (C(6)); 33.2 (C(4)); 37.0 (C(8)); 45.1 (C(3)); 50.7 (C(1)); 52.0 (C(5)); 54.8 (OMe); 78.9 (q, C(2), *J* = 26.3 Hz); 110.8, 113.8,

Table 2. Principal details of X-ray diffraction study and crystallographic data for compound **3c**

Parameter	Characteristic
Molecular formula	$C_{16}H_{17}F_3O_2$
Molecular weight	298.30
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	9.954(2)
b/Å	11.259(2)
c/Å	12.742(3)
α/deg	90
β/deg	98.60(3)
γ/deg	90
V/Å^3	1412.0(5)
Z	4
d/g cm^{-3}	1.403
μ/mm^{-1}	0.117
Scan range	$2.07° \le \theta \le 24.97°$
Number of independent reflections	2466
Number of reflections with $I \ge 2\sigma(I)$	1749
Number of parameters in refinement	259
R_1 ($I = 2\sigma(I)$)	0.0285
wR_2 (based on all reflections)	0.0886

120.0, 128.8, 148.9, 158.9 (3-MeO$\underline{C}_6H_4$); 125.5 (q, $\underline{C}F_3$, J = 288.4 Hz); 214.6 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(2,5-dimethoxyphenyl)-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (3g).** The yield was 99%, m.p. 190 °C. Found (%): C, 60.37; H, 5.99. $C_{18}H_{21}F_3O_4$. Calculated (%): C, 60.33; H, 5.91. IR, ν/cm^{-1}: 1705 (C=O); 3370 (O—H). ^{1}H NMR (DMSO-d_6), δ: 1.47—1.58 (m, 1 H, H_{ax}(7)); 1.78—1.90 (m, 1 H, H_{ax}(8)); 1.90—2.12 (m, 2 H, H_{ax}(6), H_{eq}(6)); 1.94 (d, 1 H, H_{ax}(3), J = 15.0 Hz); 2.16 (d, 1 H, H_{eq}(7), J = 15.0 Hz); 2.23 (br.d, 1 H, H_{eq}(8), J = 12.0 Hz); 2.57 (br.s, 2 H, H(1), H(5)); 2.72 (dd, 1 H, H_{eq}(3), J = 15.0 Hz, J = 9.6 Hz); 3.63 (s, 3 H, C(5′)OCH_3); 3.74 (s, 3 H, C(2′)OCH_3); 3.82 (d, 1 H, H(4), J = 9.6 Hz); 5.97 (br.s, 1 H, OH); 6.68 (dd, 1 H, 2,5-(MeO)$_2$C$_6\underline{H}_3$, H(4′), J = 8.6 Hz, J = 2.8 Hz); 6.82 (d, 1 H, 2,5-(MeO)$_2$C$_6\underline{H}_3$, H(3′), J = 8.6 Hz); 6.85 (d, 1 H, 2,5-(MeO)$_2$C$_6\underline{H}_3$, H(6′), J = 2.8 Hz). ^{13}C NMR (DMSO-d_6), δ: 18.4 (C(7)); 30.3 (C(6)); 31.5 (C(4)); 37.1 (C(8)); 38.2 (C(3)); 50.2 (C(1)); 52.0 (C(5)); 55.1 (OMe); 55.7 (OMe); 79.4 (q, C(2), J = 26.4 Hz); 110.4, 110.7; 115.3, 136.0, 149.8, 152.6 (2,5-(MeO)$_2\underline{C}_6H_3$); 125.4 (q, $\underline{C}F_3$, J = 288.3 Hz); 215.2 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(2-thienyl)-2-trifluoromethylbicyclo[3.3.1]nonan-9-one (3h).** The yield was 87%, m.p. 128 °C. Found (%): C, 55.31; H, 4.84. $C_{14}H_{15}F_3O_2S$. Calculated (%): C, 55.25, H, 4.97. IR, ν/cm^{-1}: 1710 (C=O); 3325 (O—H). ^{1}H NMR (DMSO-d_6), δ: 1.48—1.57 (m, 1 H, H_{ax}(7)); 1.78—2.21 (m, 4 H, H_{ax}(6), H_{eq}(6), H_{eq}(7), H_{ax}(8)); 2.11 (d, 1 H, H_{ax}(3), J = 15.4 Hz); 2.26 (br.d, 1 H, H_{eq}(8), J = 15.8 Hz); 2.59 (br.s, 1 H, H(5)); 2.69 (br.s, 1 H, H(1)); 2.86 (dd, 1 H, H_{eq}(3), J = 15.4 Hz, J = 8.9 Hz); 3.90 (d, 1 H, H(4), J = 8.9 Hz); 6.06 (br.s, 1 H, OH); 6.85 (t, 1 H, 2-$C_4\underline{H}_3$S, H(4′), J = 3.2 Hz); 6.88 (d, 1 H, 2-$C_4\underline{H}_3$S, H(5′), J = 3.2 Hz); 7.26 (d, 1 H, 2-$C_4\underline{H}_3$S, H(3′), J = 4.8 Hz). ^{13}C NMR (DMSO-d_6), δ: 18.4 (C(7)); 30.2 (C(6)); 33.5 (C(4)); 36.1 (C(8)); 40.7 (C(3)); 51.7 (C(1)); 52.1 (C(5)); 78.8 (q, C(2), J = 26.4 Hz); 123.4, 124.4, 126.4, 149.8 (2-$\underline{C}_4H_3$S); 125.4 (q, $\underline{C}F_3$, J = 288.4 Hz); 213.2 (C=O).

Reactions of trifluoromethyl ketones 1 with 1-morpholinocyclopentene (2a) and 1-methyl-4-morpholino-1,2,5,6-tetrahydropyridine (2c) (general procedure). Freshly distilled enamine **2a** or **2c** (1.1 mmol) was added to a solution of the corresponding α,β-unsaturated trifluoromethyl ketone **1** (1 mmol) in 96% EtOH (5 mL) and the reaction mixture was kept at ≈20 °C until the reaction was completed (TLC control, a hexane—AcOEt mixture, 3 : 1). Then a solution of NH_4Cl (300 mg) in water (5 mL) was added and the reaction mixture was kept at ≈20 °C for 3 h, diluted with water to ≈20 mL, and extracted with CH_2Cl_2 (4×10 mL). The combined extracts were filtered through a silica gel layer. The solution was concentrated and the residue was recrystallized from a 3 : 1 hexane—AcOEt mixture. Enaminoketone **4** was prepared from ketones **1a** and **1b**. Its characteristics are identical to those published in the literature.[10]

(2*R,4*S**)-2-Hydroxy-4-phenyl-2-trifluoromethylbicyclo[3.2.1]octan-8-one (5c).** The yield was 99%, m.p. 175 °C. Found (%): C, 63.47; H, 5.03. $C_{15}H_{15}F_3O_2$. Calculated (%): C, 63.38; H, 5.32. IR, ν/cm^{-1}: 1735 (C=O); 3320 (O—H). ^{1}H NMR ($CDCl_3$), δ: 1.81—2.03 (m, 2 H, H_{ax}(6), H_{ax}(7)); 2.07—2.30 (m, 3 H, H_{eq}(6), H_{eq}(7), OH); 2.19 (d, 1 H, H_{ax}(3), J = 15.0 Hz); 2.41—2.65 (d, 1 H, H(5), J = 6.7 Hz); 2.69 (dd, 1 H, H_{eq}(3), J = 15.0 Hz, J = 8.2 Hz); 2.78, 2.92 (dm, 1 H, H(1), J = 4.4 Hz); 3.48 (dd, 1 H, H(4), J = 8.2 Hz, J = 1.5 Hz); 7.18 (t, 1 H, C$_6\underline{H}_5$, H(4′), J = 7.3 Hz); 7.28 (t, 2 H, C$_6\underline{H}_5$, H(2′), H(6′), J = 7.3 Hz); 7.44 (t, 2 H, C$_6\underline{H}_5$, H(3′), H(5′), J = 7.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 18.6 (C(6)); 23.4 (C(7)); 30.1 (C(4)); 46.1 (C(3)); 47.8 (C(5)); 48.6 (C(1)); 81.1 (q, C(2), J = 29.0 Hz); 124.6 (q, $\underline{C}F_3$, J = 285.4 Hz); 126.4, 127.4, 128.9, 143.2 ($\underline{C}_6H_5$); 212.7 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(4-methylphenyl)-2-trifluoromethylbicyclo[3.2.1]octan-8-one (5d).** The yield was 82%, m.p. 180 °C. Found (%): C, 64.61; H, 5.71. $C_{16}H_{17}F_3O_2$. Calculated (%): C, 64.42; H, 5.74. IR, ν/cm^{-1}: 1720 (C=O); 3320 (O—H). ^{1}H NMR ($CDCl_3$), δ: 1.84—1.98 (m, 2 H, H_{ax}(6), H_{ax}(7)); 2.04 (br.s, 1 H, OH); 2.07—2.30 (m, 2 H, H_{eq}(6), H_{eq}(7)); 2.17 (d, 1 H, H_{ax}(3), J = 15.2 Hz); 2.29 (s, 3 H, Me); 2.42—2.58 (dm, 1 H, H(5), J = 6.7 Hz); 2.67 (dd, 1 H, H_{eq}(3), J = 15.2 Hz, J = 8.0 Hz); 2.78—2.93 (dm, 1 H, H(1), J = 7.9 Hz); 3.46 (dd, 1 H, H(4), J = 8.0 Hz, J = 1.2 Hz); 7.09 (d, 2 H, 4-MeC$_6\underline{H}_4$, H(2′), H(6′), J = 8.0 Hz); 7.33 (d, 2 H, 4-MeC$_6\underline{H}_4$, H(3′), H(5′), J = 8.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 18.6 (C(6)); 20.9 (Me); 23.4 (C(7)); 30.2 (C(4)); 46.1 (C(3)); 47.5 (C(5)); 48.7 (C(1)); 81.2 (q, C(2), J = 29.0 Hz); 124.6 (q, $\underline{C}F_3$, J = 286.9 Hz); 127.3, 129.1, 136.0 140.0 (4-Me$\underline{C}_6H_4$); 212.6 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(3-methylphenyl)-2-trifluoromethylbicyclo[3.2.1]octan-8-one (5e).** The yield was 94%, m.p. 121—122 °C. Found (%): C, 64.41; H, 5.77. $C_{16}H_{17}F_3O_2$. Calculated (%): C, 64.42; H, 5.74. IR, ν/cm^{-1}: 1740 (C=O); 3380 (O—H). ^{1}H NMR ($CDCl_3$), δ: 1.83—2.02 (m, 2 H, H_{ax}(6), H_{ax}(7)); 2.07 (br.s, 1 H, OH); 2.13—2.25 (m, 2 H H_{eq}(6), H_{eq}(7)); 2.19 (d, 1 H, H_{ax}(3), J = 15.0 Hz); 2.32 (s, Me); 2.43—2.60 (dm, 1 H, H(5), J = 6.7 Hz); 2.68 (dd, 1 H, H_{eq}(3), J = 15.0 Hz, J = 8.5 Hz); 2.77—2.86 (dm, 1 H, H(1), J = 4.7 Hz); 3.70 (dd, 1 H, H(4), J = 8.5 Hz, J = 2.0 Hz); 7.00 (t, 1 H, 3-MeC$_6\underline{H}_4$, H(2′), J = 7.3 Hz); 7.18 (t, 1 H, 3-MeC$_6\underline{H}_4$, H(4′), J = 7.3 Hz); 7.23—7.29 (m, 2 H, 3-MeC$_6H_4$, H(5′), H(6′)). ^{13}C NMR ($CDCl_3$), δ: 18.6 (C(8)); 21.5 (Me); 23.4 (C(7)); 30.3 (C(4)); 46.0 (C(3)); 47.7 (C(5)); 48.6 (C(1)); 81.2 (q, C(2), J = 29.0 Hz); 124.4, 127.2, 128.3, 128.4, 138.0, 143.1 (3-Me$\underline{C}_6H_4$); 124.5 (q, $\underline{C}F_3$, J = 285.4 Hz); 212.5 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(3-methoxyphenyl)-2-trifluoromethylbicyclo[3.2.1]octan-8-one (5f).** The yield was 88%, m.p. 98 °C. Found (%): C, 61.49; H, 5.19. $C_{16}H_{17}F_3O_3$. Calculated (%): C, 61.14; H, 5.45. IR, ν/cm^{-1}: 1735 (C=O); 3370 (O—H). ^{1}H NMR ($CDCl_3$), δ: 1.83—2.02 (m, 2 H, H_{ax}(6), H_{ax}(7)); 2.11—2.23 (m, 2 H H_{eq}(6), H_{eq}(7)); 2.19 (d, 1 H, H_{ax}(3), J = 15.0 Hz); 2.28 (br.s, 1 H, OH); 2.43—2.58 (dm, 1 H, H(5), J = 7.0 Hz); 2.67 (dd, 1 H, H_{eq}(3), J = 15.0 Hz, J = 8.5 Hz); 2.77—2.93 (dm, 1 H, H(1), J = 4.7 Hz); 3.45 (dd, 1 H, H(4), J = 8.2 Hz, J = 2.0 Hz); 3.77 (s, 3 H, OMe); 6.73 (dd, 1 H, 3-MeOC$_6\underline{H}_4$, H(2′), J = 8.2 Hz, J = 2.0 Hz); 6.76—6.84 (m, 1 H, 3-MeOC$_6\underline{H}_4$, H(4′), J = 2.0 Hz); 6.97—7.07 (m, 1 H, 3-MeOC$_6\underline{H}_4$, H(6′)); 7.19 (t, 1 H, 3-MeOC$_6\underline{H}_4$, H(5′), J = 7.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 18.6 (C(6)); 23.4 (C(7)); 30.1 (C(4)); 46.2 (C(3)); 47.9 (C(5)); 48.6 (C(1)); 55.1 (OMe); 81.2 (q, C(2), J = 29.0 Hz); 111.9, 113.4, 119.8, 129.3, 144.8, 159.5 (3-MeO$\underline{C}_6H_4$); 125.2 (q, $\underline{C}F_3$, J = 285.4 Hz); 212.7 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(2,5-dimethoxyphenyl)-2-trifluoromethylbicyclo[3.2.1]octan-8-one (5g).** The yield was 87%, m.p. 145 °C. Found (%): C, 59.75; H, 5.60. $C_{17}H_{19}F_3O_4$. Calculated (%): C, 59.30; H, 5.56. IR, ν/cm^{-1}: 1740 (C=O); 3390 (O—H). ^{1}H NMR ($CDCl_3$), δ: 1.85—2.02 (m, 2 H, H_{ax}(6), H_{ax}(7)); 2.05—2.26 (m, 3 H, H_{eq}(6), H_{eq}(7), OH); 2.13 (d, 1 H, H_{ax}(3), J = 15.8 Hz); 2.47—2.60 (dm, 1 H, H(5), J = 7.0 Hz);

2.58 (dd, 1 H, $H_{eq}(3)$, J = 15.8 Hz, J = 8.8 Hz); 2.63—2.70 (dm, 1 H, H(1), J = 5.0 Hz); 3.70 (dd, 1 H, H(4), J = 8.8 Hz, J =2.0 Hz); 3.74 (s, 3 H, OMe); 3.78 (s, 3 H, OMe); 6.73 (d, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(3′), J = 2.6 Hz); 6.75—6.79 (m, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(6′)); 7.36 (d, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(4′), J = 2.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 18.6 (C(6)); 23.7 (C(7)); 28.3 (C(4)); 42.4 (C(3)); 46.2 (C(5)); 48.4 (C(1)); 55.6 (OMe); 55.7 (OMe); 81.2 (q, C(2), J = 27.5 Hz); 110.7, 112.7, 115.0, 132.7, 150.2, 153.9 (2,5-$(MeO)_2\underline{C}_6H_3$); 124.4 (q, $\underline{C}F_3$, J = 285.4 Hz); 213.7 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(2-thienyl)-2-trifluoromethylbicyclo[3.2.1]octan-8-one (5h).** The yield was 99%, m.p. 105 °C. Found (%): C, 53.94; H, 4.41. $C_{13}H_{13}F_3O_2S$. Calculated (%): C, 53.78; H, 4.51. IR, ν/cm^{-1}: 1730 (C=O); 3310 (O—H). ^1H NMR ($CDCl_3$), δ: 1.80—2.03 (m, 2 H, $H_{ax}(6)$, $H_{ax}(7)$); 2.13—2.24 (m, 2 H $H_{eq}(6)$, $H_{eq}(7)$); 2.27 (d, 1 H, $H_{ax}(3)$, J = 15.2 Hz); 2.34 (br.s, 1 H, OH); 2.46—2.61 (dm, 1 H, H(1), J = 6.7 Hz); 2.64 (dd, 1 H, $H_{eq}(3)$, J = 15.2 Hz, J = 7.6 Hz); 2.79—2.92 (dm, 1 H, H(5), J = 6.7 Hz); 3.68 (dd, 1 H, H(4), J = 7.6 Hz, J = 2.6 Hz); 6.89 (dd, 1 H, 2-$C_4\underline{H}_3S$, H(4′), J = 5.0 Hz, J = 3.5 Hz); 7.10 (dt, 1 H, 2-$C_4\underline{H}_3S$, H(3′), J = 3.5 Hz, J = 1.2 Hz); 7.15 (dd, 1 H, 2-$C_4\underline{H}_3S$, H(5′), J = 5.0 Hz, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$), δ: 18.6 (C(6)); 22.7 (C(7)); 30.4 (C(4)); 43.8 (C(3)); 47.3 (C(5)); 49.0 (C(1)); 81.2 (q, C(2), J = 29.0 Hz); 124.5 (q, $\underline{C}F_3$, J = 285.4 Hz); 123.9, 125.1, 127.0, 145.8 (2-$\underline{C}_4H_3S$); 211.5 (C=O).

(2*R,4*S**)-2-Hydroxy-4-(3-indolyl)-2-trifluoromethylbicyclo[3.2.1]octan-8-one (5i).** The yield was 52%, m.p. 168 °C. Found (%): C, 63.07; H, 4.88. $C_{17}H_{16}F_3NO_2$. Calculated (%): C, 63.15; H, 4.99. IR, ν/cm^{-1}: 1730 (C=O); 3260 (N—H); 3410 (O—H). ^1H NMR ($CDCl_3$), δ: 1.89—2.05 (m, 2 H, $H_{ax}(6)$, $H_{ax}(7)$); 2.12—2.25 (m, 2 H, $H_{eq}(6)$, $H_{eq}(7)$); 2.27 (br.s, 1 H, OH); 2.29 (d, 1 H, $H_{ax}(3)$, J = 15.0 Hz); 2.48—2.64 (d, 1 H, H(1), J = 6.5 Hz); 2.68 (dd, 1 H, $H_{eq}(3)$, J = 15.0 Hz, J = 7.6 Hz); 2.76—2.89 (dm, 1 H, H(5), J = 6.2 Hz); 3.74 (d, 1 H, H(4), J = 7.6 Hz); 7.12 (t, 1 H, 3-$C_8\underline{H}_6N$, H(5′), J = 7.6 Hz); 7.19 (t, 1 H, 3-$C_8\underline{H}_6N$, H(6′), J = 7.6 Hz); 7.34 (d, 1 H, 3-$C_8\underline{H}_6N$, H(7′), J = 7.9 Hz); 7.38 (br.s, 1 H, 3-$C_8\underline{H}_6N$, H(2′)); 7.49 (d, 1 H, 3-C_8H_6N, H(4′), J = 7.6 Hz); 8.10 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 18.8 (C(6)); 23.2 (C(7)); 28.6 (C(4)); 40.1 (C(3)); 47.2 (C(5)); 49.0 (C(1)); 81.6 (q, C(2), J = 29.0 Hz); 111.5, 118.1, 119.6, 122.3, 122.8, 123.5, 126.2, 135.9 (3-$\underline{C}_8H_6N$); 124.5 (q, $\underline{C}F_3$, J = 285.4 Hz); 213.7 (C=O).

6-Hydroxy-3-methyl-8-phenyl-6-trifluoromethyl-3-azabicyclo[3.3.1]nonan-9-one (6c). The yield was 70%, m.p. 148 °C. Found (%): C, 61.15; H, 5.87. $C_{16}H_{18}F_3NO_2$. Calculated (%): C, 61.33; H 5.79. IR, ν/cm^{-1}: (C=O) 1715; 3370 (O—H). ^1H NMR ($CDCl_3$), δ: 2.06 (d, 1 H, $H_{ax}(7)$ J = 14.1 Hz); 2.24 (br.s, 1 H, OH); 2.29 (s, 3 H, MeN); 2.46 (dd, 1 H, $H_{ax}(4)$, J = 12.1 Hz, J = 1.8 Hz); 2.65 (dd, 1 H, $H_{ax}(2)$, J = 11.0 Hz, J = 2.6 Hz); 2.58—2.70 (dm, 1 H, H(1), J = 2.6 Hz); 2.87—2.98 (dm, 1 H, H(5), J = 1.8 Hz); 3.25 (dt, 1 H, $H_{eq}(2)$, J = 11.0 Hz, J = 2.6 Hz); 3.30 (d, 1 H, $H_{eq}(4)$, J = 12.1 Hz); 3.73 (d, 1 H, H(8), J = 8.8 Hz); 3.83 (dd, 1 H, $H_{eq}(7)$, J = 14.1 Hz, J = 8.8 Hz); 7.16 (t, 1 H, $C_6\underline{H}_5$, H(4′), J = 7.0 Hz); 7.22—7.39 (m, 4 H, $C_6\underline{H}_5$, H(2′), H(3′), H(5′), H(6′)). ^{13}C NMR ($CDCl_3$), δ: 35.9 (C(8)); 44.4 (C(7)); 45.9 (NMe); 50.9 (C(1)); 52.7 (C(5)); 58.1 (C(2)); 65.0 (C(4)); 80.0 (q, C(6), J = 29.0 Hz); 124.8 (q, $\underline{C}F_3$, J = 285.4 Hz); 126.3, 127.5, 128.6, 145.8 ($\underline{C}_6H_5$); 212.7 (C=O).

6-Hydroxy-3-methyl-8-(4-methylphenyl)-6-trifluoromethyl-3-azabicyclo[3.3.1]nonan-9-one (6d). The yield was 61%, m.p. 209 °C. Found (%): C, 62.51; H, 6.31. $C_{17}H_{20}F_3NO_2$. Calculated (%): C, 62.38; H, 6.16. IR, ν/cm^{-1}: 1730 (C=O); 3410 (O—H). ^1H NMR ($CDCl_3$), δ: 1.73 (br.s, 1 H, OH); 2.04 (d, 1 H, $H_{ax}(7)$, J = 14.3 Hz); 2.28 (br.s, 6 H, 4-$C\underline{H}_3C_6H_4$, MeN); 2.45 (dd, 1 H, $H_{ax}(4)$, J = 12.0 Hz, J = 1.5 Hz); 2.64 (dd, 1 H, $H_{ax}(2)$, J = 11.0 Hz, J = 2.6 Hz); 2.61—2.75 (dm, 1 H, H(1), J = 2.6 Hz); 2.91 (br.s, 1 H, H(5)); 3.24 (dt, 1 H, $H_{eq}(2)$, J = 11.0 Hz, J = 2.6 Hz); 3.29 (d, 1 H, $H_{eq}(4)$, J = 12.0 Hz); 3.70 (d, 1 H, H(8), J = 8.5 Hz); 3.81 (dd, 1 H, $H_{eq}(7)$, J = 14.3 Hz, J = 8.5 Hz); 7.07 (d, 2 H, 4-$CH_3C_6\underline{H}_4$, H(2′), H(6′), J = 8.0 Hz); 7.17 (d, 2 H, 4-$CH_3C_6H_4$, H(3′), H(5′), J = 8.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 20.8 (4-$\underline{C}H_3C_6H_4$); 35.9 (C(8)); 44.3 (C(7)); 45.5 (NMe); 51.0 (C(1)); 52.7 (C(5)); 58.1 (C(2)); 65.0 (C(4)); 80.3 (q, C(6), J = 29.0 Hz); 127.3, 129.2, 135.9, 142.8 (4-$CH_3\underline{C}_6H_4$); 124.6 (q, $\underline{C}F_3$, J = 286.9 Hz); 212.8 (C=O).

6-Hydroxy-8-(3-methoxyphenyl)-3-methyl-6-trifluoromethyl-3-azabicyclo[3.3.1]nonan-9-one (6e). The yield was 79%, m.p. 119 °C. Found (%): C, 59.31; H, 5.81. $C_{17}H_{20}F_3NO_3$. Calculated (%): C, 59.47; H, 5.87. IR, ν/cm^{-1}: 1720 (C=O); 3400 (O—H). ^1H NMR ($CDCl_3$), δ: 1.85 (br.s, 1 H, OH); 2.06 (d, 1 H, $H_{ax}(7)$, J = 14.4 Hz); 2.28 (s, 3 H, MeN); 2.45 (dd, 1 H, $H_{ax}(4)$, J = 12.3 Hz, J = 1.8 Hz); 2.64 (dd, 1 H, $H_{ax}(2)$, J = 11.0 Hz, J = 2.6 Hz); 2.58—2.73 (dm, 1 H, H(1), J = 2.6 Hz); 2.77—2.95 (dm, 1 H, H(5), J = 1.8 Hz); 3.23 (dt, 1 H, $H_{eq}(2)$, J = 11.0 Hz, J = 2.6 Hz); 3.29 (d, 1 H, $H_{eq}(4)$, J = 12.3 Hz); 3.70 (d, 1 H, H(8), J = 8.8 Hz); 3.76 (s, 3 H, MeO); 3.81 (dd, 1 H, $H_{eq}(7)$, J = 14.4 Hz, J = 8.8 Hz); 6.71 (dd, 1 H, 3-$MeOC_6\underline{H}_4$, H(2′), J = 7.3 Hz, J = 2.3 Hz); 6.87 (d, 2 H, 3-$MeOC_6\underline{H}_4$, H(4′), H(5′), J = 7.3 Hz); 7.17 (t, 1 H, 3-$MeOC_6\underline{H}_4$, H(6′), J = 7.6 Hz). ^{13}C NMR ($CDCl_3$), δ: 35.8 (C(8)); 44.4 (C(7)); 45.9 (NMe); 51.0 (C(1)); 52.7 (C(5)); 55.1 (OMe); 58.1 (C(2)); 65.3 (C(4)); 80.2 (q, C(6), J = 29.0 Hz); 112.5, 113.9, 120.4, 130.3, 148.3, 160.5 (3-$MeO\underline{C}_6H_4$); 126.2 (q, $\underline{C}F_3$, J = 285.4 Hz); 212.6 (C=O).

8-(2,5-Dimethoxyphenyl)-6-hydroxy-3-methyl-6-trifluoromethyl-3-azabicyclo[3.3.1]nonan-9-one (6f). The yield was 50%, m.p. 158 °C. Found (%): C, 57.74; H, 5.81. $C_{18}H_{22}F_3NO_4$. Calculated (%): C, 57.90; H, 5.94. IR, ν/cm^{-1}: 1720 (C=O); 3340 (O—H). ^1H NMR ($CDCl_3$), δ: 1.89 (br.s, 1 H, OH); 1.98 (d, 1 H, $H_{ax}(7)$, J = 15.0 Hz); 2.29 (s, 3 H, MeN); 2.45 (dd, 1 H, $H_{ax}(4)$, J = 12.0 Hz, J = 1.8 Hz); 2.62 (dd, 1 H, $H_{ax}(2)$, J = 11.1 Hz, J = 2.6 Hz); 2.67 (br.s, 1 H, H(1)); 2.68—2.82 (dm, 1 H, H(5), J = 1.8 Hz); 3.25 (dt, 1 H, $H_{eq}(2)$, J = 11.1 Hz, J = 2.6 Hz); 3.29 (d, 1 H, $H_{eq}(4)$, J = 12.0 Hz); 3.65 (dd, 1 H, $H_{eq}(7)$, J = 15.0 Hz, J = 9.1 Hz); 3.71 (s, 3 H, MeO); 3.80 (s, 3 H, MeO); 4.00 (d, 1 H, H(8), J = 9.1 Hz); 6.70 (dd, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(2′), J = 8.8 Hz, J = 2.9 Hz); 6.75 (d, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(4′), J = 8.8 Hz); 6.97 (d, 1 H, 2,5-$(MeO)_2C_6\underline{H}_3$, H(6′), J = 2.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 33.6 (C(8)); 39.8 (C(7)); 44.4 (NMe); 51.3 (C(1)); 52.8 (C(5)); 55.6 ($(OMe)_2$); 58.1 (C(2)); 65.2 (C(4)); 80.3 (q, C(6), J = 29.0 Hz); 110.9, 112.4, 114.1, 134.9, 149.9, 153.4 (2,5-$(MeO)_2\underline{C}_6H_3$); 124.8 (q, CF_3, J = 285.4 Hz); 213.4 (C=O).

6-Hydroxy-3-methyl-8-(2-thienyl)-6-trifluoromethyl-3-azabicyclo[3.3.1]nonan-9-one (6g). The yield was 66%, m.p. 141 °C. Found (%): C, 52.79; H, 5.02. $C_{14}H_{16}F_3O_2S$. Calculated (%): C, 52.65; H, 5.05. IR, ν/cm^{-1}: 1720 (C=O); 3350 (O—H). ^1H NMR ($CDCl_3$), δ: 1.99 (br.s, 1 H, OH); 2.23 (d, 1 H, $H_{ax}(7)$, J = 14.4 Hz); 2.27 (s, 3 H, MeN); 2.43 (dd, 1 H, $H_{ax}(4)$, J = 11.4 Hz, J = 1.5 Hz); 2.62 (dd, 1 H, $H_{ax}(2)$, J = 11.1 Hz, J = 2.6 Hz); 2.66 (br.s, 1 H, H(1)); 2.97 (br.s, 1 H, H(5)); 3.25 (dt,

1 H, $H_{eq}(2)$, J = 11.1 Hz, J = 2.6 Hz); 3.30 (d, 1 H, $H_{eq}(4)$, J = 11.4 Hz); 3.83 (dd, 1 H, $H_{eq}(7)$, J = 14.4 Hz, J = 8.2 Hz); 3.94 (d, 1 H, H(8), J = 8.2 Hz); 6.87 (dd, 1 H, 2-$C_4\underline{H}_3S$, H(4′), J = 5.0 Hz, J = 3.5 Hz); 6.94 (dt, 1 H, 2-$C_4\underline{H}_3S$, H(3′), J = 3.5 Hz, J = 1.0 Hz); 7.12 (dd, 1 H, 2-$C_4\underline{H}_3S$, H(5′), J = 5.0 Hz, J = 1.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 35.9 (C(8)); 41.7 (C(7)); 44.3 (NMe); 51.8 (C(1)); 53.1 (C(5)); 57.9 (C(2)); 64.0 (C(4)); 80.2 (q, C(6), J = 29.0 Hz); 123.7, 124.6, 127.2, 148.5 (2-$C_4\underline{H}_3S$); 125.5 (q, CF_3, J = 286.9 Hz); 211.0 (C=O).

6-Hydroxy-8-(3-indolyl)-3-methyl-6-trifluoromethyl-3-azabicyclo[3.3.1]nonan-9-one (6h). The yield was 51%, m.p. 148 °C. Found (%): C, 61.16; H, 5.34. $C_{18}H_{19}F_3NO_2$. Calculated (%): C, 61.36; H, 5.44. IR, ν/cm^{-1}: 1725 (C=O); 3410 (O—H). ^{1}H NMR ($CDCl_3$), δ: 2.03 (br.s, 1 H, OH); 2.27 (d, 1 H, $H_{ax}(7)$, J = 14.4 Hz); 2.31 (s, 3 H, MeN); 2.45 (dd, 1 H, H(4), J = 12.1 Hz, J = 2.3 Hz); 2.67 (dd, 1 H, $H_{ax}(2)$, J = 11.4 Hz, J = 2.9 Hz); 2.71 (br.s, 1 H, H(1)); 2.92 (br.s, 1 H, H(5)); 3.31 (dd, 1 H, $H_{eq}(2)$, J = 12.0 Hz, J = 2.9 Hz); 3.33 (d, 1 H, $H_{eq}(4)$, J = 12.1 Hz); 3.81 (dd, 1 H, $H_{eq}(7)$, J = 14.4 Hz, J = 7.9 Hz); 4.00 (d, 1 H, H(8), J = 7.9 Hz); 7.13 (m, 2 H, 3-$C_8\underline{H}_6N$, H(2′), H(5′), J = 7.6 Hz); 7.20 (t, 1 H, 3-$C_8\underline{H}_6N$, H(4′), J = 8.2 Hz); 7.34 (d, 1 H, 3-$C_8\underline{H}_6N$, H(6′), J = 7.9 Hz); 7.54 (d, 1 H, 3-$C_8\underline{H}_6N$, H(7′), J = 7.6 Hz); 8.23 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 33.4 (C(8)); 37.8 (C(7)); 44.4 (NMe); 51.8 (C(1)); 53.4 (C(5)); 58.0 (C(2)); 64.5 (C(4)); 80.6 (q, C(6), J = 29.0 Hz); 111.5, 118.2, 119.6, 119.8, 122.1, 122.3, 125.8, 136.0 (3-$\underline{C}_8H_6N$); 124.3 (q, $\underline{C}F_3$, J = 285.4 Hz); 213.3 (C=O).

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