

67. Synthesis of Selectively Trifluoromethylated Pyridine Derivatives as Potential Antihypertensives

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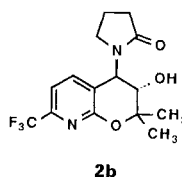
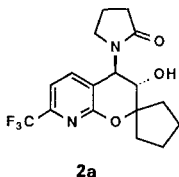
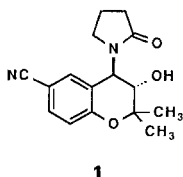
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A general synthesis of selectively 6-(trifluoromethyl)-substituted 2(1*H*)-pyridinones is described. Further transformation of one of these compounds leads to the new CF₃-containing potassium-channel openers **2a** and **2b**.

The benzopyran derivative *BRL 34915* (**1**) is a novel and potent vasodilator [1] which may prove clinically useful in the management of essential hypertension. Its mechanism of action is new. It has been shown that *BRL 34915* hyperpolarizes vascular smooth muscle cell membranes and opens potassium channels [2].

The structure-activity relationship around **1** shows that electron-withdrawing substituents in the benzene ring increase its biological activity [1]. Therefore, electron-deficient pyrano[2,3-*b*]pyridine derivatives such as **2a** and **2b** seemed to be very promising new target molecules with the potential of being active as potassium-channel openers.

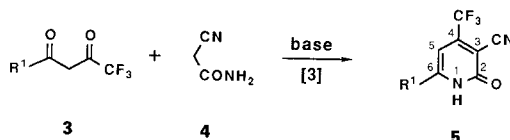


This paper describes a general synthesis of 6-CF₃-substituted 2(1*H*)-pyridinones and further transformations of one of these new compounds, namely 3-acetyl-6-(trifluoromethyl)-2(1*H*)-pyridinone (**10d**) into the new pyrano[2,3-*b*]pyridine derivatives **2a** and **2b**.

Synthesis of 6-(Trifluoromethyl)-Substituted 2(1*H*)-Pyridinones. – In 1965, Portnoy described a novel synthesis of CF₃-substituted 2(1*H*)-pyridinones by reacting cyanoacetamide (**4**) with various CF₃-substituted 1,3-dicarbonyl compounds **3** [3] (*Scheme 1*). It was speculated first [3] and proven later [4] that this particular base-induced condensation leads exclusively to the 4-CF₃-substituted regioisomers **5**¹⁾.

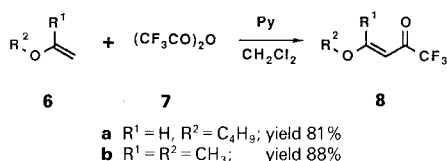
¹⁾ The m.p. of **5** (R¹ = CH₃) is 232–234° [3] ([4]: 238°), and the ¹H-NMR spectrum ((D₆)DMSO) shows resonances for H–C(5) at 6.65 and for CH₃–C(6) at 2.41 ppm. The ¹³C-NMR spectrum ((D₆)DMSO) shows resonances at 160.58 (C(2)), 156.90 (C(6)), 146.17 (C(4)), 121.26 (CF₃), 113.45 (CN), 101.59 (C(5)), 96.41 (C(3)), and 19.65 ppm (CH₃) [4].

Scheme 1



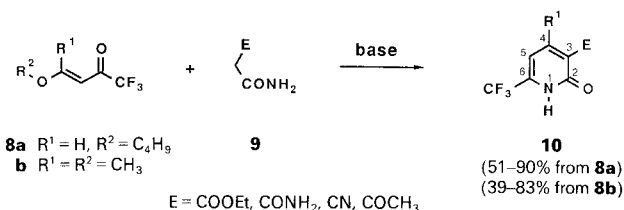
A very efficient trifluoroacetylation reaction of simple vinyl ethers has been published recently by *Hojo et al.* [5] (**6** + **7** → **8**, see *Scheme 2*). This synthesis of particularly useful synthetic equivalents **8** of CF_3 -substituted 1,3-dicarbonyl compounds **3** can be applied to a variety of aryl- and alkyl-substituted vinyl ethers of which two examples are shown in *Scheme 2*.

Scheme 2



In contrast to the regioselectivity reported by *Portnoy* [3], the 6- CF_3 -substitution pattern of **10** was observed exclusively, when various additionally activated acetamides of type **9** were allowed to react under similar conditions with compounds of type **8** (*Scheme 3*). Thus, a 1,4-substitution reaction with C-nucleophiles generated from **9** seems to dominate in the case of type-**8** compounds, whereas in the case of type-**3** compounds, the same C-nucleophiles preferentially attack the more electrophilic carbonyl group adjacent to the CF_3 group. As a matter of fact, this change of regioselectivity can easily be analyzed

Scheme 3

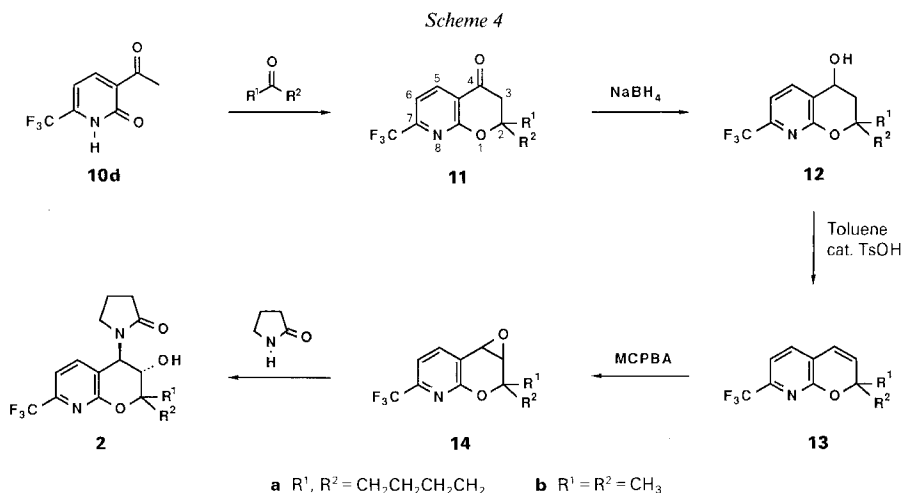
Table 1. 2-(1H)-Pyridinones **10** from **8** and **9** (see *Scheme 3*)

Product	M.p.	Starting materials	Yield ^{a)}
10a $R^1 = H$, $E = COOEt$	38–39°	8a + 9 ($E = COOEt$)	79 %
10b $R^1 = H$, $E = CONH_2$	220–222°	8a + 9 ($E = CONH_2$)	90 %
10c $R^1 = H$, $E = CN$	210–211°	8a + 9 ($E = CN$)	51 %
10d $R^1 = H$, $E = COCH_3$	89–90°	8a + 9 ($E = COCH_3$)	61 %
10e $R^1 = CH_3$, $E = COOEt$	oil	8b + 9 ($E = COOEt$)	70 %
10f $R^1 = CH_3$, $E = CONH_2$	> 300°	8b + 9 ($E = CONH_2$)	83 %
10g $R^1 = CH_3$, $E = CN$	211–212°	8b + 9 ($E = CN$)	74 %
10h $R^1 = CH_3$, $E = COCH_3$	152–154°	8b + 9 ($E = COCH_3$)	39 %

^{a)} Reaction conditions: NaOEt/EtOH at reflux overnight. Non-optimized yields.

by comparing the physical data of the pyridinone **5** ($R^1 = \text{CH}_3$; see *Footnote 1*) with those of **10g** (Table 2; see *Exper. Part*). All the condensation products **10** which can be prepared by combining the substitution patterns of **8** and **9** as shown in *Scheme 3* are listed in Table 1.

Synthesis of Pyrano[2,3-*b*]pyridine Derivatives **2a and **2b**.** – The synthesis of **2a** and **2b** follows mainly the reaction procedures reported by *Evans* and coworkers [1]. The condensation of 3-acetyl-6-(trifluoromethyl)-2(1*H*)-pyridinone (**10d**) with either cyclopentanone or acetone gave, in analogy to [6], the desired pyrano[2,3-*b*]pyridin-4-ones **11a** and **11b**, respectively. The NaBH_4 reduction of **11** yielded the alcohols **12a** and **12b** which were dehydrated in the presence of a catalytic amount of TsOH in toluene to the olefins **13a** and **13b**, respectively. Epoxidation of **13** with *m*-chloroperbenzoic acid (MCPBA) in CCl_4 at r.t. led to **14**. The nucleophilic ring-opening of **14** with pyrrolidinone in the presence of $\text{K}(t\text{-BuO})$ in DMF yielded the racemic *trans*-3,4-dihydropyrano[2,3-*b*]pyridine derivatives **2a** and **2b** (*Scheme 4*).



As expected, both target molecules **2a** and **2b** were active in the ^{86}Rb -efflux assay [2] and thus acted as potassium-channel openers. The spirocyclopentane derivative **2a** was less potent than **2b**, and **2b** was slightly less potent than *BRL 34915* (**1**).

The authors would like to thank Miss *B. Haefeli*, Miss *J. Schaub*, and Mr. *P. Bechtel* for their skillful assistance in the laboratory. We are grateful to our colleagues in the Physical and Analytical Departments for performing the spectral and elemental analyses.

Experimental Part

General. Unless otherwise noted, materials and solvents were obtained from commercial suppliers and used without further purification. Chemical yields refer to non-optimized reaction conditions. Flash chromatography (FC; [7]): Merck silica gel 60 (230–400 mesh ASTM). M.p.: Tottoli capillary melting-point apparatus (uncorrected). IR ($\bar{\nu}$ [cm⁻¹]): Perkin-Elmer IR 298. ¹H-NMR and ¹³C-NMR (δ [ppm] relative to internal TMS in CDCl₃ unless otherwise noted; J [Hz] = apparent coupling constant): Varian T 60, Varian HA 100, Varian XL 300, Bruker WM 250, Bruker WH 360, or Bruker WM 400 spectrometer (for ¹H-NMR), and Varian XL 100 or Varian XL 300 (for ¹³C-NMR). MS: Varian CH-7 MAT and CEC 21/100, at 70 eV.

1. (E)-4-Butoxy-1,1,1-trifluoro-3-buten-2-one (**8a**). Acylation of butyl vinyl ether (**6a**) by using the trifluoroacetic anhydride/pyridine system according to [5] afforded **8a** as a pale yellow oil in 81% yield. B.p. 78–79°/18 Torr. IR (neat): 2960m, 2930 (sh), 2870w, 1710m, 1615s, 1595s, 1200s, 1150s, 1070s. ¹H-NMR (60 MHz, CDCl₃): 7.90 (d, J = 12, OCH=CH); 5.90 (d, J = 12, OCH=CH); 4.10 (t, J = 6, CH₂O); 2.10–1.15 (m, 6 H); 0.95 (t, J = 6, CH₃).

2. 1,1,1-Trifluoro-4-methoxy-3-penten-2-one (**8b**). Following the above procedure, **8b** was isolated starting from 2-methoxypropene (**6b**) as a colourless oil in 88% yield. B.p. 144–146°/760 Torr. IR (neat): 2980w, 2950w, 2850w, 1710s, 1585s (br.), 1330s, 1205s, 1145s, 1100s. ¹H-NMR (60 MHz, CDCl₃): 5.70 (s, C=CH); 3.80 (s, CH₃O); 2.40 (s, 3 H–C(5)).

3. General Procedure for the Synthesis of 6-(Trifluoromethyl)-Substituted 2(1H)-Pyridinones **10**. One equiv. each of **8**, **9**, and NaOEt (see Table 1) were heated at reflux temp. in EtOH overnight. After quenching with 15% HCl soln., the 2(1H)-pyridinone **10** was isolated by liquid-liquid extraction using CHCl₃ or AcOEt and recrystallized or purified by column chromatography. The physical data of **10a–h** are summarized in Tables 1 and 2.

4. 3',4'-Dihydro-7'-(trifluoromethyl)-spiro[cyclopentane-1,2'-2'H-pyrano[2,3-b]pyridin]-4-one (**11a**). To a soln. of 26.0 g (0.127 mol) of 3-acetyl-6-(trifluoromethyl)-2(1H)-pyridinone (**10d**), 15 ml (0.169 mol) of cyclopentanone, and 3 ml (0.036 mol) of pyrrolidine in 200 ml of dry toluene, 30 g of molecular sieve (3 Å) were added. The mixture was stirred for 20 h at 50°. After filtration and dilution with AcOEt, the product was washed with H₂O. The org. layers were dried (Na₂SO₄) and evaporated. Purification by FC (CH₂Cl₂/petroleum ether 2:1) and crystallization from EtOH/H₂O gave 22.0 g (64%) of **11a**. M.p. 75–77°. IR (CH₂Cl₂): 1705s, 1600s, 1585s. ¹H-NMR (250 MHz, CDCl₃): 8.37 (d, J = 8, H–C(5')); 7.40 (d, J = 8, H–C(6')); 2.93 (s, 2 H–C(3')); 1.6–2.3 (m, 4 CH₂). Anal. calc. for C₁₃H₁₂F₃NO₂ (271.24): C 57.57, H 4.46, F 21.01, N 5.17; found: C 57.86, H 4.52, F 20.98, N 5.07.

5. 3,4-Dihydro-2,2-dimethyl-7-(trifluoromethyl)-2H-pyrano[2,3-b]pyridin-4-one (**11b**). To a soln. of 30.8 g (0.150 mol) of **10d** in 300 ml of acetone, 3 ml (0.036 mol) of pyrrolidine and 10 g of molecular sieve (3 Å) were added. The mixture was stirred at r.t. for 2 days, evaporated at r.t., and then purified by FC (toluene/AcOEt 95:5). Thus, 14.7 g (40%) of **11b** were isolated as an orange oil. IR (CH₂Cl₂): 1710s, 1600s, 1585s. ¹H-NMR (360 MHz, CDCl₃): 8.38 (d, J = 8, H–C(5)); 7.42 (d, J = 8, H–C(6)); 2.83 (s, 2 H–C(3)); 1.58 (s, 2 CH₃).

6. 3',4'-Dihydro-7'-(trifluoromethyl)-spiro[cyclopentane-1,2'-2'H-pyrano[2,3-b]pyridin]-4'-ol (**12a**). To a soln. of 27.1 g (0.10 mol) of **11a** in 200 ml of abs. EtOH, 1.9 g (0.050 mol) of NaBH₄ were added within 15 min. After stirring for 1 h at r.t., 5 ml of H₂O were added, and the mixture was evaporated. The residue was dissolved in AcOEt and washed with 0.5N HCl and brine. The combined org. layers were dried (Na₂SO₄) and evaporated. FC (toluene/AcOEt 4:1) and crystallization from toluene/petroleum ether gave 22.9 g (84%) of **12a** as white crystals. M.p. 135–137°. IR (CH₂Cl₂): 3600m, 1600s, 1590s. ¹H-NMR (250 MHz, CDCl₃): 8.00 (d, J = 8, H–C(5')); 7.28 (d, J = 8, H–C(6')); 4.94 (dd, J = 10, 5, H–C(4')); 1.50–2.34 (m, 4 CH₂). Anal. calc. for C₁₃H₁₄F₃NO₂ (273.25): C 57.14, H 5.17, F 20.86, N 5.13; found: C 57.06, H 5.13, F 20.86, N 5.03.

7. 3,4-Dihydro-2,2-dimethyl-7-(trifluoromethyl)-2H-pyrano[2,3-b]pyridin-4-ol (**12b**). NaBH₄ reduction of **11b** in analogy to the procedure described above afforded, after FC (toluene/AcOEt 95:5) and crystallization from Et₂O/petroleum ether, 70% of **12b**. M.p. 103–104°. IR (CH₂Cl₂): 3600m, 1600s, 1590s. ¹H-NMR (300 MHz, CDCl₃): 8.03 (d, J = 8, H–C(5)); 7.27 (d, J = 8, H–C(6)); 4.97 (dd, J = 10, 5, H–C(4)); 2.28 (dd, J = 14, 5, 1 H–C(3)); 2.10 (br. s, OH); 1.74 (d, J = 14, 10, 1 H–C(3)); 1.55 (s, CH₃); 1.41 (s, CH₃).

8. 7'-(Trifluoromethyl)-spiro[cyclopentane-1,2'-2'H-pyrano[2,3-b]pyridine] (**13a**). A soln. of 20.5 g (0.075 mol) of **12a** and 1.43 g (0.0075 mol) of TsOH in 300 ml of toluene was refluxed for 20 h and the H₂O removed by using a separator. After cooling, the mixture was diluted with AcOEt and washed with sat. NaHCO₃ soln. and H₂O. The combined org. layers were dried (Na₂SO₄) and evaporated. FC (toluene/AcOEt 99:1) of the residue and crystallization from CH₂Cl₂/petroleum ether gave 10.9 g (57%) of **13a**. M.p. 95–97°. IR (CH₂Cl₂): 1580w, 1460w, 1415s, 1390s, 1345s. ¹H-NMR (250 MHz, CDCl₃): 7.34 (d, J = 6, H–C(5')); 7.16 (d, J = 6, H–C(6')); 6.35 (d, J = 9, H–C(4')); 5.80 (d, J = 9, H–C(3')); 1.50–2.34 (m, 4 CH₂).

Table 2. Physical Data of the 2(*I*H)-Pyridinones **10a–h**

	¹ H-NMR (CDCl ₃ , 250 MHz) ^{a)}	¹³ C-NMR ((D ₆)DMSO) ^{b)}								
		R ¹ -C(4)	H-C(5)	C(2)	C(3)	C(4)	C(5)	C(6)	CN	CF ₃
10a	R ¹ = H, E = COOEt	8.40 (<i>J</i> = 8)	7.32 (<i>J</i> = 8)							
10b	R ¹ = H, E = CONH ₂	8.45 (<i>J</i> = 8)	7.38 (<i>J</i> = 8)							
10c	R ¹ = H, E = CN	8.46 (<i>J</i> = 8)	7.48 (<i>J</i> = 8)	164.4	99.6	146.8	111.8 (<i>J</i> = 2)	147.4 (<i>J</i> = 34)	114.9	120.6 (<i>J</i> = 274)
10d	R ¹ = H, E = COCH ₃	8.33 (<i>J</i> = 8)	7.33 (<i>J</i> = 8)	165.2	118.0	142.9	112.5 (<i>J</i> = 3)	151.0 (<i>J</i> = 34)	–	120.5 (<i>J</i> = 274)
10e	R ¹ = CH ₃ , E = COOEt	2.55	6.95							
10f	R ¹ = CH ₃ , E = CONH ₂	2.30	7.25							
10g	R ¹ = CH ₃ , E = CN	2.54	7.44	164.6	99.9	158.4	113.1 (<i>J</i> = 2)	145.8 (<i>J</i> = 34)	114.2	120.8 (<i>J</i> = 274)
10h	R ¹ = CH ₃ , E = COCH ₃	2.36	6.72	160.4	126.8	148.8	114.4 (<i>J</i> = 3)	143.1 (<i>J</i> = 32)	–	121.0 (<i>J</i> = 274)

^{a)} In (D₆)DMSO for **10b**, **10c**, **10f**, and **10g**; δ [ppm], *J* (H,H) [Hz] in parentheses.
^{b)} δ [ppm], *J* (F,C) [Hz] in parentheses.

a) In (D₆)DMSO for **10b**, **10c**, **10f**, and **10g**; δ[ppm], *J*(H, H) [Hz] in parentheses.b) δ[ppm], *J*(F, C) [Hz] in parentheses.

9. 2,2-Dimethyl-7-(trifluoromethyl)-2H-pyrano[2,3-b]pyridine (**13b**). H₂O elimination from **12b** as described above yielded, after recrystallization from EtOH/H₂O, 78% of **13b**. M.p. 64–65°. IR (CH₂Cl₂): 1645w, 1580w, 1460w, 1415s, 1390s, 1380s, 1345s. ¹H-NMR (300 MHz, CDCl₃): 7.39 (d, *J* = 7, H–C(5)); 7.19 (d, *J* = 7, H–C(6)); 6.33 (d, *J* = 9, H–C(4)); 5.80 (d, *J* = 9, H–C(3)); 1.56 (s, 2 CH₃).

10. 3',4'-Epoxy-3',4'-dihydro-7'-(trifluoromethyl)-spiro[cyclopentane-1,2'-2'H-pyrano[2,3-b]pyridine] (**14a**). A soln. of 25.5 g (0.10 mol) of **13a** in 200 ml of CCl₄ was treated with 21.8 g (0.11 mol) of *m*-chloroperbenzoic acid (Fluka, 85%), and stirred at r.t. overnight. The mixture was then diluted with CH₂Cl₂, washed with sat. NaHCO₃ soln. and H₂O. The combined org. layers were dried (Na₂SO₄) and evaporated. Crystallization from Et₂O/petroleum ether gave 24.4 g (90%) of **14a**. M.p. 110–112°. IR (CH₂Cl₂): 1690w, 1596w, 1470w, 1445w, 1410s, 1365s, 1340s. ¹H-NMR (250 MHz, CDCl₃): 7.84 (d, *J* = 7, H–C(5')); 7.30 (d, *J* = 7, H–C(6')); 3.99 (d, *J* = 4, H–C(4')); 3.61 (d, *J* = 4, H–C(3')); 1.50–2.36 (m, 4 CH₂). Anal. calc. for C₁₃H₁₂F₃NO₂ (271.24): C 57.57, H 4.46, F 21.01, N 5.17; found: C 57.29, H 4.51, F 21.02, N 5.34.

11. 3,4-Epoxy-3,4-dihydro-2,2-dimethyl-7-(trifluoromethyl)-2H-pyrano[2,3-b]pyridine (**14b**). The epoxidation of **13b** as described above yielded, after FC (toluene/AcOEt 10:1) and crystallization from CH₂Cl₂/Et₂O/petroleum ether, 94% of **14b**. M.p. 123–125°. IR (CH₂Cl₂): 1588w, 1577w, 1445w, 1423s, 1386s, 1350w, 1337s, 1316s. ¹H-NMR (300 MHz, CDCl₃): 7.88 (d, *J* = 7, H–C(5)); 7.30 (d, *J* = 7, H–C(6)); 4.00 (d, *J* = 5, H–C(4)); 3.60 (d, *J* = 5, H–C(3)); 1.66 (s, CH₃); 1.40 (s, CH₃). Anal. calc. for C₁₁H₁₀F₃NO₂ (245.20): C 53.88, H 4.11, N 5.71; found: C 54.02, H 4.16, N 5.76.

12. rac-trans-3',4'-Dihydro-4'-(2'-oxopyrrolidin-1'-yl)-7'-(trifluoromethyl)-spiro[cyclopentane-1,2'-2'H-pyrano[2,3-b]pyridin]-3'-ol (**2a**). To a soln. of 1.70 g (0.020 mol) of 2-pyrrolidinone in 20 ml of DMF, 2.15 g (0.020 mol) of K(*t*-BuO) were added. The suspension was stirred for 1 h at r.t. Then, the mixture was cooled to –20°, treated with 2.71 g (0.010 mol) of **14a**, and stirred first for 2 h at –20° and then overnight at 0°. The mixture was diluted with AcOEt and washed 3 times with H₂O. The org. layers were dried (Na₂SO₄) and evaporated. Crystallization of the residue from AcOEt/MeOH gave 1.75 g (49%) of **2a**. M.p. 244–246°. ¹H-NMR (300 MHz, (D₆)DMSO): 7.62 (d, *J* = 7, H–C(5')); 7.43 (d, *J* = 7, H–C(6')); 5.83 (d, *J* = 5, H–C(4')); 5.00 (d, *J* = 10, OH); 4.00 (dd, *J* = 10, 5, H–C(3')); 3.34 (br. *m*, 1 H); 2.96 (br. *m*, 1 H); 2.47–1.48 (m, 12 aliph. H). Anal. calc. for C₁₇H₁₉F₃N₂O₃ (356.34): C 57.30, H 5.38, F 16.00, N 7.86; found: C 57.34, H 5.28, F 15.92, N 7.97.

13. rac-trans-3,4-Dihydro-2,2-dimethyl-4-(2'-oxopyrrolidin-1'-yl)-7-(trifluoromethyl)-2H-pyrano[2,3-b]pyridin-3-ol (**2b**). The ring-opening of **14b** with 2-pyrrolidinone in analogy to the procedure described above yielded, after FC (toluene/AcOEt 1:1) and crystallization from CH₂Cl₂/Et₂O/petroleum ether, 40% of **2b**. M.p. 218–220°. ¹H-NMR (300 MHz, (D₆)DMSO): 7.63 (d, *J* = 7, H–C(5)); 7.42 (d, *J* = 7, H–C(6)); 5.78 (d, *J* = 5, H–C(4)); 5.03 (d, *J* = 10, OH); 3.81 (dd, *J* = 10, 5, H–C(3)); 3.35 (br. *m*, 1 H); 2.97 (br. *m*, 1 H); 2.47–2.33 (m, 2 H); 2.05–1.88 (m, 2 H); 1.48 (s, CH₃); 1.25 (s, CH₃). Anal. calc. for C₁₅H₁₇F₃N₂O₃ (330.31): C 54.55, H 5.19, F 17.26, N 8.48; found: C 54.33, H 5.11, F 17.26, N 8.71.

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