67. Synthesis of Selectively Trifluoromethylated Pyridine Derivatives as Potential Antihypertensives

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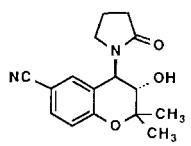
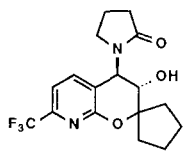
A general synthesis of selectively 6-(trifluoromethyl)-substituted 2(1*H*)-pyridinones is described. Further transformation of one of these compounds leads to the new CF_3-containing potassium-channel openers **2a** and **2b**.

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].

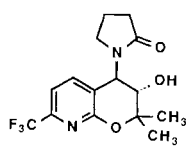
The structure-activity relationship around **1** shows that electron-withdrawing substituents in the benzene ring increase its biological activity [1]. Therefore, electron-deficient pyrano[2,3-*b*]pyridine derivatives such as **2a** and **2b** seemed to be very promising new target molecules with the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



1



2a



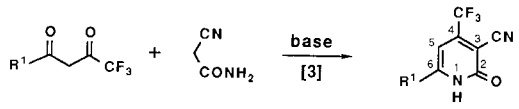
2b

This paper describes a general synthesis of 6-CF_3-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 CF_3-substituted 2(1*H*)-pyridinones by reacting cyanoacetamide (**4**) with various CF_3-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-CF_3-substituted regioisomers **5**[1]).

[1]) The m.p. of **5** ($R^1 = CH_3$) is 232–234° [3] ([4]: 238°), and the ^{1}H-NMR spectrum ((D$_6$)DMSO) shows resonances for H–C(5) at 6.65 and for CH_3–C(6) at 2.41 ppm. The ^{13}C-NMR spectrum ((D$_6$)DMSO) shows resonances at 160.58 (C(2)), 156.90 (C(6)), 146.17 (C(4)), 121.26 (CF_3), 113.45 (CN), 101.59 (C(5)), 96.41 (C(3)), and 19.65 ppm (CH_3) [4].

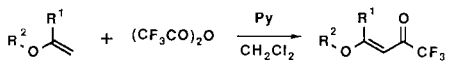
Scheme 1



3 **4** **5**

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

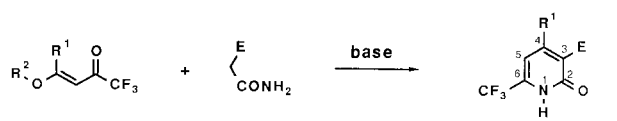


6 **7** **8**

a $R^1 = H$, $R^2 = C_4H_9$; yield 81%
b $R^1 = R^2 = CH_3$; yield 88%

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



8a $R^1 = H$, $R^2 = C_4H_9$
b $R^1 = R^2 = CH_3$

9

10
(51–90% from **8a**)
(39–83% from **8b**)

E = COOEt, $CONH_2$, CN, $COCH_3$

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

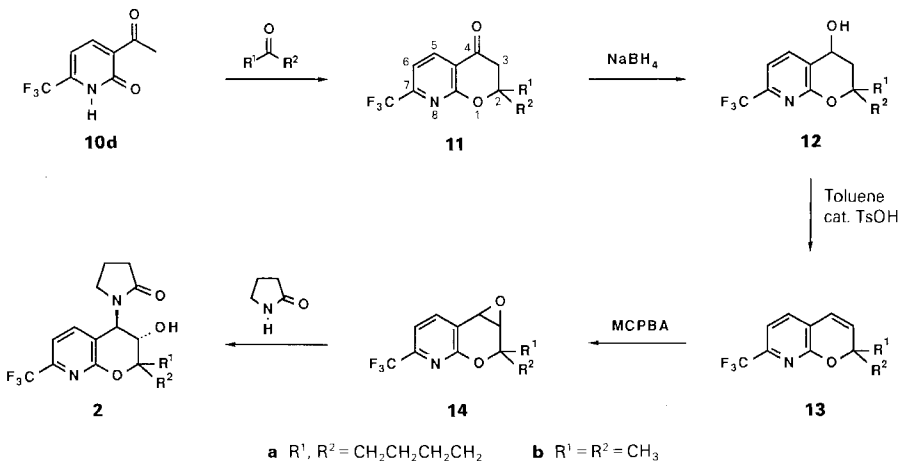
Product	M.p.	Starting materials	Yield[a])
10a $R^1 = H$, E = COOEt	38–39°	**8a** + **9** (E = COOEt)	79%
10b $R^1 = H$, E = $CONH_2$	220–222°	**8a** + **9** (E = $CONH_2$)	90%
10c $R^1 = H$, E = CN	210–211°	**8a** + **9** (E = CN)	51%
10d $R^1 = H$, E = $COCH_3$	89–90°	**8a** + **9** (E = $COCH_3$)	61%
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** ($R^1 = CH_3$; 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 K(*t*-BuO) in DMF yielded the racemic *trans*-3,4-dihydropyrano[2,3-*b*]pyridine derivatives **2a** and **2b** (*Scheme 4*).

Scheme 4



a $R^1, R^2 = CH_2CH_2CH_2CH_2$ **b** $R^1 = R^2 = CH_3$

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 ($\tilde{\nu}$ [cm^{-1}]): *Perkin-Elmer IR 298*. ^{1}H-NMR and ^{13}C-NMR (δ [ppm] relative to internal TMS in $CDCl_3$ unless otherwise noted; J[Hz] = apparent coupling constant): *Varian T60, Varian HA 100, Varian XL 300, Bruker WM 250, Bruker WH 360,* or *Bruker WM 400* spectrometer (for ^{1}H-NMR), and *Varian XL 100 or Varian XL 300* (for ^{13}C-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): 2960*m*, 2930 (sh), 2870*w*, 1710*m*, 1615*s*, 1595*s*, 1200*s*, 1150*s*, 1070*s*. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.90 (*d*, J = 12, OC*H*=CH); 5.90 (*d*, J = 12, OCH=C*H*); 4.10 (*t*, J = 6, CH_2O); 2.10–1.15 (*m*, 6 H); 0.95 (*t*, J = 6, CH_3).

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): 2980*w*, 2950*w*, 2850*w*, 1710*s*, 1585*s* (br.), 1330*s*, 1205*s*, 1145*s*, 1100*s*. ^{1}H-NMR (60 MHz, $CDCl_3$): 5.70 (*s*, C=C*H*); 3.80 (*s*, CH_3O); 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(1*H*)-pyridinone **10** was isolated by liquid-liquid extraction using $CHCl_3$ 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(1*H*)-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 H_2O. The org. layers were dried (Na_2SO_4) and evaporated. Purification by FC (CH_2Cl_2/petroleum ether 2:1) and crystallization from EtOH/H_2O gave 22.0 g (64%) of **11a**. M.p. 75–77°. IR (CH_2Cl_2): 1705*s*, 1600*s*, 1585*s*. ^{1}H-NMR (250 MHz, $CDCl_3$): 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 CH_2). Anal. calc. for $C_{13}H_{12}F_3NO_2$ (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 (CH_2Cl_2): 1710*s*, 1600*s*, 1585*s*. ^{1}H-NMR (360 MHz, $CDCl_3$): 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 CH_3).

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 $NaBH_4$ were added within 15 min. After stirring for 1 h at r.t., 5 ml of H_2O 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 (Na_2SO_4) 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 (CH_2Cl_2): 3600*m*, 1600*s*, 1590*s*. ^{1}H-NMR (250 MHz, $CDCl_3$): 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 CH_2). Anal. calc. for $C_{13}H_{14}F_3NO_2$ (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**). $NaBH_4$ reduction of **11b** in analogy to the procedure described above afforded, after FC (toluene/AcOEt 95:5) and crystallization from Et_2O/petroleum ether, 70% of **12b**. M.p. 103–104°. IR (CH_2Cl_2): 3600*m*, 1600*s*, 1590*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (*dd*, J = 14, 10, 1 H–C(3)); 1.55 (*s*, CH_3); 1.41 (*s*, CH_3).

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 H_2O removed by using a separator. After cooling, the mixture was diluted with AcOEt and washed with sat. $NaHCO_3$ soln. and H_2O. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (toluene/AcOEt 99:1) of the residue and crystallization from CH_2Cl_2/petroleum ether gave 10.9 g (57%) of **13a**. M.p. 95–97°. IR (CH_2Cl_2): 1580*w*, 1460*w*, 1415*s*, 1390*s*, 1345*s*. ^{1}H-NMR (250 MHz, $CDCl_3$): 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 CH_2).

Table 2. *Physical Data of the 2(1H)-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 (J = 8)	7.32 (J = 8)							
10b	R^1 = H, E = $CONH_2$	8.45 (J = 8)	7.38 (J = 8)							
10c	R^1 = H, E = CN	8.46 (J = 8)	7.48 (J = 8)	164.4	99.6	146.8	111.8 (J = 2)	147.4 (J = 34)	114.9	120.6 (J = 274)
10d	R^1 = H, E = $COCH_3$	8.33 (J = 8)	7.33 (J = 8)	165.2	118.0	142.9	112.5 (J = 3)	151.0 (J = 34)	–	120.5 (J = 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 (J = 2)	145.8 (J = 34)	114.2	120.8 (J = 274)
10h	R^1 = CH_3, E = $COCH_3$	2.36	6.72	160.4	126.8	148.8	114.4 (J = 3)	143.1 (J = 32)	–	121.0 (J = 274)

[a]) In (D_6)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)-2*H*-pyrano[2,3-*b*]pyridine* (**13b**). H_2O elimination from **12b** as described above yielded, after recrystallization from EtOH/H_2O, 78% of **13b**. M.p. 64–65°. IR (CH_2Cl_2): 1645*w*, 1580*w*, 1460*w*, 1415*s*, 1390*s*, 1380*s*, 1345*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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 CH_3).

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 CCl_4 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 CH_2Cl_2, washed with sat. $NaHCO_3$ soln. and H_2O. The combined org. layers were dried (Na_2SO_4) and evaporated. Crystallization from Et_2O/petroleum ether gave 24.4 g (90%) of **14a**. M.p. 110–112°. IR (CH_2Cl_2): 1690*w*, 1596*w*, 1470*w*, 1445*w*, 1410*s*, 1365*s*, 1340*s*. ^{1}H-NMR (250 MHz, $CDCl_3$): 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 CH_2). Anal. calc. for $C_{13}H_{12}F_3NO_2$ (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)-2*H*-pyrano[2,3-*b*]pyridine* (**14b**). The epoxidation of **13b** as described above yielded, after FC (toluene/AcOEt 10:1) and crystallization from CH_2Cl_2/Et_2O/petroleum ether, 94% of **14b**. M.p. 123–125°. IR (CH_2Cl_2): 1588*w*, 1577*w*, 1445*w*, 1423*s*, 1386*s*, 1350*w*, 1337*s*, 1316*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, CH_3); 1.40 (*s*, CH_3). Anal. calc. for $C_{11}H_{10}F_3NO_2$ (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 H_2O. The org. layers were dried (Na_2SO_4) and evaporated. Crystallization of the residue from AcOEt/MeOH gave 1.75 g (49%) of **2a**. M.p. 244–246°. ^{1}H-NMR (300 MHz, (D_6)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 $C_{17}H_{19}F_3N_2O_3$ (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)-2*H*-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 CH_2Cl_2/Et_2O/petroleum ether, 40% of **2b**. M.p. 218–220°. ^{1}H-NMR (300 MHz, (D_6)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*, CH_3); 1.25 (*s*, CH_3). Anal. calc. for $C_{15}H_{17}F_3N_2O_3$ (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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