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SYNTHESIS OF BRL 55834 - A NOVEL, POTENT AIRWAYS-SELECTIVE POTASSIUM CHANNEL ACTIVATOR

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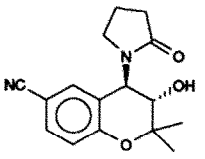
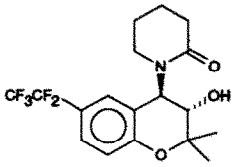
Abstract: An efficient synthesis of the potassium channel activator, BRL 55834 (**2**), is described and its absolute stereochemistry established as 3S,4R by X-ray crystallographic analysis of the corresponding (S)-α-methylbenzyl carbamate **12**. BRL 55834 is the first compound of this pharmacological class to demonstrate selectivity for the smooth muscle of the airways compared with that of the vasculature.

The potassium channel activators, cromakalim **1a**, and its active (3S,4R) enantiomer BRL 38227 **1b** are potent relaxants of vascular and airways smooth muscle which have shown potential in the therapy of both hypertension and asthma.[1] It is generally recognised, however, that tissue selectivity would be an advantage in the use of potassium channel activators in diseases such as asthma, and we have recently described the first compound to display such selectivity.[2,3] In this paper the synthesis and structural characterisation of this compound, BRL 55834 (**2**, *trans*-(3S,4R)-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-6-pentafluoroethyl-2*H*-1-benzopyran-3-ol) is described.



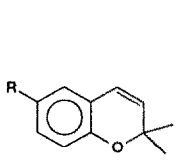
1a Cromakalim (racemic)
1b BRL 38227 (3S,4R)



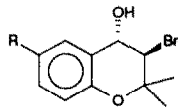
2 BRL 55834 (3S,4R)

A crucial stage in the synthesis of racemic **2** involves the introduction of the pentafluoroethyl moiety, which may be added in either a single step from suitable precursors or built up in a two-stage process. For both routes the initial reaction involved the formation of 6-bromo-2,2- dimethylbenzopyran **3**, which was readily prepared from 5-bromo-2-hydroxyacetophenone in 59% overall yield as previously described.[4] In the initial experiments, the Grignard reagent derived from the benzopyran **3** was treated with trifluoroacetic anhydride to furnish the ketone **4** (THF, 0°C, 16 h, 69%), which on reaction with diethylaminosulphur

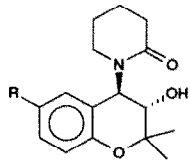
trifluoride[5] was converted smoothly into the pentafluoroethyl benzopyran **5** (CH_2Cl_2, 20°C, 16 h, 84%, bp 62°C at 0.3 mm). A more direct synthesis of compound **5** was achieved by displacement of the bromine atom of the benzopyran **3** with sodium pentafluoropropionate following the procedure of Freskos[6] (CuI, DMF/toluene, 130-145°C, 18 h, 61%). There was little further improvement in yield when the 6-iodo compound **6** was used instead of the 6-bromo derivative **3**, although the reaction time was reduced to under 4 h.[7] Bromohydrin formation was subsequently accomplished in quantitative yield following the established procedure for analogous compounds (NBS, DMSO/H_2O),[4,8] and the resulting compound **7** (mp 86°C) was readily converted, via the intermediate epoxide, into the required racemic benzopyranol **9** on treatment with the anion derived from piperidinone (KOBu^t, DMSO, 20°C, 6 h, 90%, mp 165.5-166.5°C).



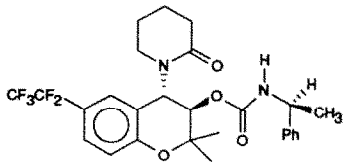
3 R=Br
4 R=CF_3CO
5 R=CF_3CF_2
6 R=I



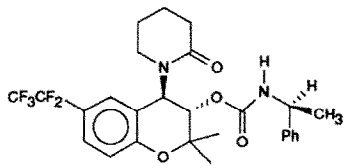
7 R=CF_3CF_2
8 R=CF_3CO



9 R=CF_3CF_2
10 R=CF_3



11

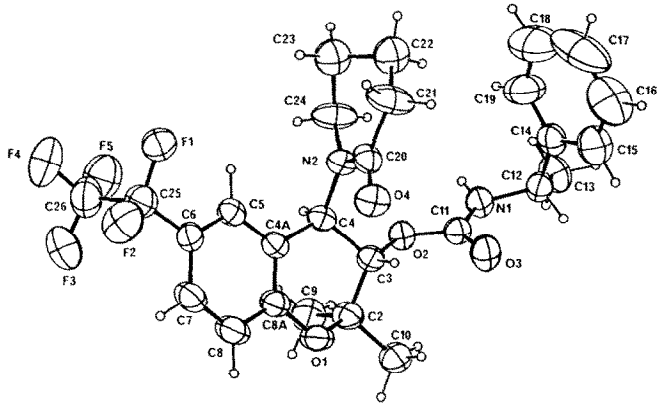


12

The resolution of the benzopyranol **9** was accomplished by reaction with (S)-α-methylbenzylisocyanate[4,8] and chromatographic separation of the diastereoisomeric carbamates **11** and **12** on silica (ether:chloroform [1:4]). In this manner the less polar 3R,4S diastereoisomer **11** (mp 156-157°C, $[\alpha]_D^{25}$ -54.4° {c = 0.82, $CHCl_3$}) was eluted first followed by the 3S,4R diastereoisomer **12** (mp 190-191°C, $[\alpha]_D^{25}$ -20.0° {c = 0.48, EtOH}). Trichlorosilane cleavage[9] of each diastereoisomer provided BRL 55834 (**2**) (mp 143°C, $[\alpha]_D^{25}$ -71.8° {c = 1.1, EtOH}) and its optical antipode (mp 142-143°C, $[\alpha]_D^{25}$ +70.8° {c = 1.14, EtOH}) in >99% optical purity.[10]

The absolute configuration of BRL 55834 was established as 3S,4R by X-ray crystallographic analysis of the carbamate **12** (Figure 1),[11] and is the same as that previously shown for BRL 38227.[12] An unusual feature of this structure was the position of the carbonyl group of the C-4 amide moiety. Thus, whilst still in a plane orthogonal to the benzopyran nucleus, in contrast to the structures of the previously reported (S)-α-methylbenzyl carbamate derivative of WAY 120,491[13] and the parent compounds of other structurally similar potassium channel activators,[14,15] the carbonyl group was aligned away from rather than towards

the C-4 proton. The reason for this difference is not known, but it is clearly not simply dependent on the presence of the carbamate moiety and may reflect conformational differences between the piperidinone ring of **12** and pyrrolidinone or planar six-membered ring systems of other compounds.[14,15]



Atom	X	Y	Z	Atom	X	Y	Z
F1	0.2947 (4)	0.8975 (2)	0.1204 (3)	C9	0.4432 (7)	0.5159 (4)	0.3473 (5)
F2	0.1801 (4)	0.8275 (3)	0.0288 (3)	C10	0.2636 (8)	0.4706 (4)	0.4342 (4)
F3	0.4009 (5)	0.8816 (4)	-0.0304 (3)	C11	0.3382 (5)	0.6269 (4)	0.5752 (4)
F4	0.4915 (4)	0.8106 (3)	0 0658 (3)	C12	0.3806 (6)	0.6523 (4)	0.7252 (4)
F5	0.3842 (5)	0.7462 (4)	-0 0258 (3)	C13	0.4863 (7)	0.6333 (5)	0.7826 (4)
01	0.2340 (5)	0.5472 (3)	0 3077 (3)	C14	0 3309 (6)	0.7406 (4)	0.7385 (4)
02	0 3935 (3)	0.6247 (3)	0 4978 (2)	C15	0.2093 (7)	0.7519 (5)	0.7701 (5)
03	0.2286 (4)	0.6158 (3)	0 5866 (3)	C16	0.1629 (9)	0.8318 (6)	0.7859 (6)
04	0.1457 (3)	0.7753 (3)	0 3961 (3)	C17	0.235 (1)	0.9013 (6)	0.7685 (6)
N1	0.4197 (4)	0.6397 (3)	0 6376 (3)	C18	0.361 (1)	0.8927 (6)	0.7339 (8)
N2	0.3532 (4)	0.7819 (3)	0 4059 (3)	C19	0.4003 (8)	0 8115 (5)	0.7222 (6)
C2	0.3200 (6)	0 5402 (4)	0 3794 (4)	C20	0 2374 (6)	0.8136 (4)	0.4183 (4)
C3	0 3168 (5)	0.6261 (4)	0 4247 (4)	C21	0 2268 (8)	0.8997 (4)	0.4620 (6)
C4A	0.3102 (5)	0.6898 (4)	0.2795 (3)	C22A	0 347 (1)	0.934 (1)	0.502 (1)
C4	0.3669 (5)	0.6960 (3)	0 3680 (4)	C22B	0 357 (1)	0.9518 (9)	0.4636 (9)
C5	0.3201 (5)	0.7561 (4)	0 2224 (4)	C23A	0 450 (1)	0.923 (1)	0.434 (1)
C6	0.2689 (6)	0.7495 (4)	0.1427 (4)	C23B	0.450 (1)	0.896 (1)	0.495 (1)
C7	0.2032 (7)	0.6752 (4)	0 1188 (4)	C24	0 4662 (6)	0.8243 (4)	0.4301 (5)
C8A	0.2499 (6)	0.6152 (4)	0 2553 (4)	C25	0.2830 (7)	0.8213 (4)	0.0792 (4)
C8	0.1950 (7)	0.6086 (4)	0 1745 (4)	C26	0 3937 (8)	0.8141 (6)	0.0202 (5)

Figure 1. X-Ray structure, positional parameters and estimated standard deviations of compound **12**

BRL 55834 is a potent and efficaceous relaxant of spontaneous and induced tone in guinea-pig isolated trachealis with an IC_{50} value of 19 nM,[2] some 20-fold lower than that of BRL 38227. BRL 55834 is unusual in that unlike other reported potassium channel activators it shows a marked relative selectivity for smooth muscle of the airways,[2] for example in relation to the trifluoromethyl compound **10**.[4] Moreover, *in vivo* experiments in the guinea-pig and rat have shown that BRL 55834 protects animals from the respiratory effects of histamine and methacholine respectively when administered either orally[3] or by

inhalation[16] at doses which have no effect on resting blood pressure. The 3R,4S enantiomer showed substantially less potency *in vitro* and has not been evaluated further. The enhanced selectivity profile of BRL 55834 warrants further evaluation for its potential as a novel anti-asthmatic agent.

Acknowledgements

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10. Assayed by HPLC on Chiralcel OC 4.6 mm diameter column and isocratic elution with hexane:ethanol (99:1) at a flow rate of 1.0 ml min^{-1}.
11. Crystal data for **12**: $C_{27}H_{29}F_5N_2O_4$, FW = 540.54, plates from CH_3CN/CH_3OH, a = 11.002(9) Å b = 15.709(7) Å, c = 15.764(7) Å, orthorhombic, $P2_12_12_1$, Z = 4, D_c = 1.318 $g.cm^{-3}$, CuK_α radiation ($\lambda k\alpha$ = 1.5418 Å), 2733 unique observations, $2^\circ \leq 2\theta \leq 135^\circ$, 2586 observed ($I \geq 3\sigma(I)$). Data were corrected for Lorentz and polarization effects and for the effects of absorption. The structure was solved by direct methods and refined by full matrix least squares techniques (on F). Refinement of 341 variables (including disorder for the piperidone ring atoms C 22 and C 23) converged (max Δ/σ =0.02) at values of the standard crystallographic residuals R = 0.067, R_w = 0.068 with S = 2.148.
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