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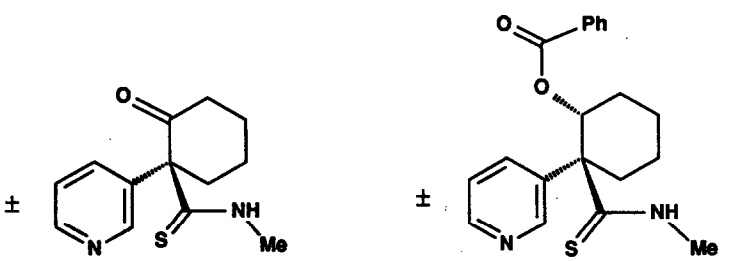
The Synthesis of RP 66471. A Potent Potassium Channel Opener.

T.W. Hart,* D. Guillochon, G. Perrier, B.W. Sharp, M.P. Toft, B. Vacher and R.J.A. Walsh.

Rhône-Poulenc Rorer Central Research, Dagenham Research Centre
Dagenham, Essex, RM10 7XS, U.K.

Abstract: The potent, homochiral, potassium channel opener, RP 66471, has been synthesised and shown to possess the (1R, 2S) configuration.

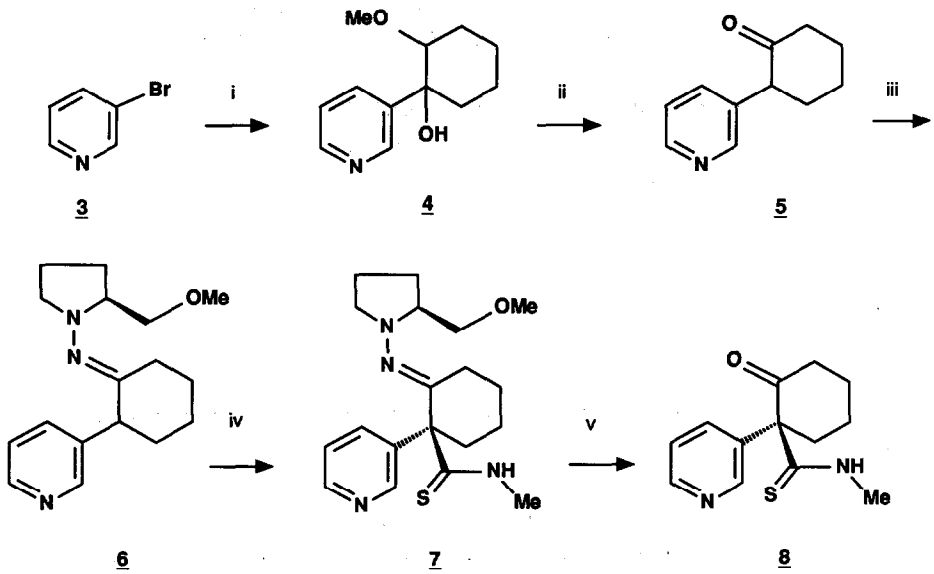
Potassium channel openers have attracted considerable attention because of their therapeutic potential in a number of disease states such as hypertension, irritable bladder syndrome and asthma.[1] Recently we reported[2] the synthesis of the key intermediate **1** (Scheme 1) and its conversion to the racemic, potent potassium channel opener, **2**, which possesses sub-nanomolar biological activity.



Scheme 1

We describe herein a simple, direct synthesis of both the enantiomers of **2**, so as to allow the separate evaluation of their biological properties, and, as a consequence, the further refinement of computer modelling studies. In addition, because our earlier route[2] for the preparation of the versatile intermediate, **5**, (Scheme 2) was not readily amenable to large scale work, we report herein a more convenient procedure for its synthesis.

Lithiation of commercially available 3-bromopyridine, 3, using n-butyl lithium in diethyl ether, followed by treatment with 2-methoxycyclohexanone afforded the tertiary alcohol, 4 (oil, b.p. 195°C at 0.6 mmHg, 81%)[3] as a 4:1 mixture of cis and trans isomers. Dehydration of this mixture on the 200g scale using concentrated sulphuric acid, followed by hydrolysis of the resultant enol ether, afforded 2-(3-pyridyl)cyclohexanone, 5, (m.p. 78-80°C, 87%) in high overall yield.



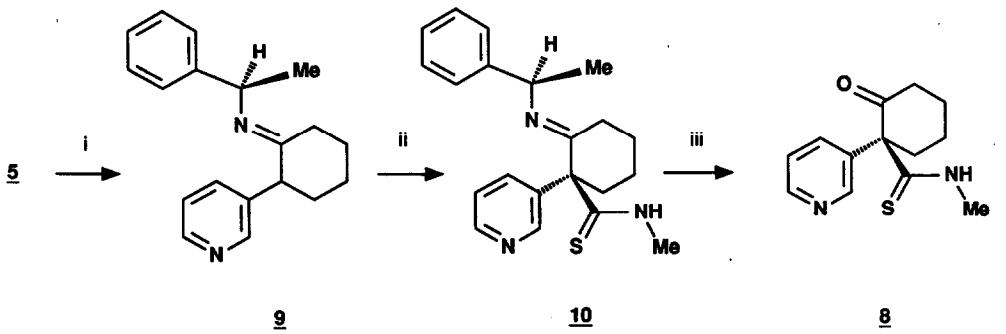
i. n-BuLi, Et_2O, -78°C. then 2-methoxycyclohexanone. ii. Conc. H_2SO_4, then H_2O.
iii. SAMP, toluene, PTSA, reflux. iv. n-BuLi, THF, then MeNCS. v. 1.0 M HCl, 20°C.

Scheme 2.

Condensation of 5 with (S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) using the methodology of Enders[4] gave the hydrazone, 6, in almost quantitative yield. Lithiation of 6 at -78°C, followed by treatment with methyl isothiocyanate produced a crude mixture containing, for the most part, the diastereoisomer, 7, (oil, 70% yield) in 80% diastereomeric excess as measured by HPLC. Various attempts to improve the yield and diastereomeric excess of this particular reaction employing different bases, solvents and reaction conditions met with no success. However, acid hydrolysis of the crude reaction mixture furnished the (S)-ketone thioamide, 8,[5] which, because it was much more soluble in common organic solvents than the racemate, 1, could be easily purified to homochirality after one recrystallisation from methanol (m.p. 196-198°C, $[\alpha]_D^{25}$ = -84 (c= 0.6 , $CHCl_3$) 45% overall yield from 5).

Although this procedure worked reasonably well, owing to the intractable difficulties encountered in recycling the chiral auxiliary agent, it was not considered to be practical for large scale work. Therefore, we decided to investigate the use of other, less expensive, commercially available chiral auxiliary agents.

Thus, condensation of **5** with (R)-(+)-α-methylbenzylamine[6,7] afforded the Schiff base, **9**, in essentially quantitative yield (Scheme 3). Lithiation of **9** followed by treatment with methyl isothiocyanate furnished the thioamide, **10**, (m.p. 131-133°C, $[\alpha]_D^{25}$ = +10.6 (c= 0.5, CH_2Cl_2)), which could be isolated, but was normally hydrolysed *in situ* to afford the (S)-ketone thioamide, **8**, (m.p. 196-198°C, $[\alpha]_D^{25}$ = -83 (c= 0.5, $CHCl_3$)) in 44% yield, and the racemic material, **1**, (m.p. 188-190°C, 9%). It is important to note that, using this procedure, the conversion of **5** to the thioamide, **8**, could be regularly accomplished on the hundred gram scale.



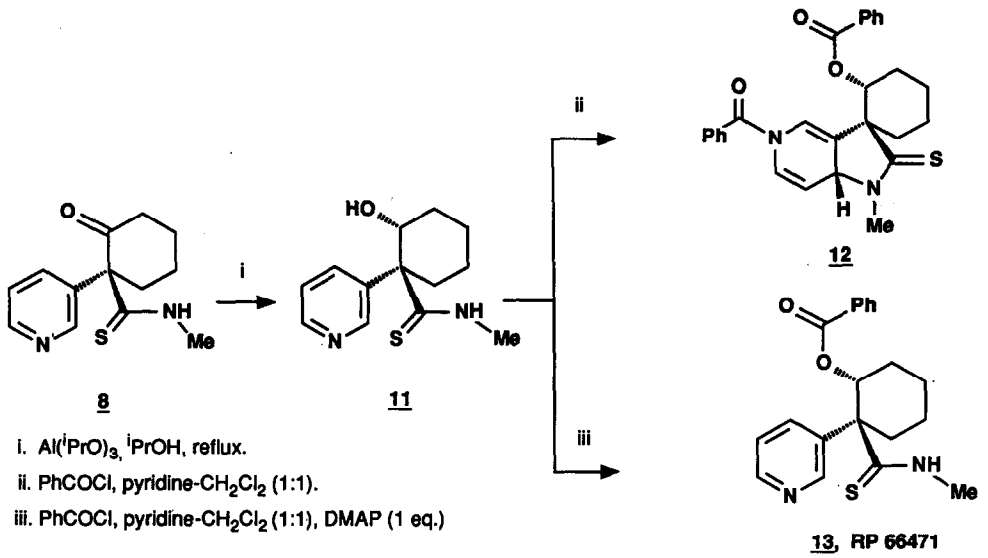
9 **10** **8**

i. (R)-PhCHMeNH$_2$, Toluene, PTSA, reflux. ii. n-BuLi, THF, -78°C, then MeNCS. iii. H_3O^+.

Scheme 3

The diastereomeric excess for the imine thiamidation reaction was estimated to be 80% ± 3%, as measured by HPLC of the crude reaction mixtures containing **10** over a number of experiments. Moreover, these values are also compatible with the enantiomeric excess calculated after isolation of the final ketone thioamide products **8** and **1**, which were regularly obtained in an overall chemical yield of 45% ± 10%.

Our interpretation of these unexpected results, which are particularly interesting because they occur with a non-chelating ligand, and yet are remarkably similar to those obtained with the SAMP chelation-induced reaction (*vide supra*), will be published in more detail elsewhere. However, we consider that, at low temperatures, the powerful π-π interactions between the juxtaposed pyridyl and phenyl rings in the Schiff base, **9**, serve to constrain the molecule and, in so doing, play the most vital role in determining the stereoselectivity of the subsequent imine thioamidation reaction.



Scheme 4.

The conversion of the thioamide, **8**, to the alcohol, **11**, (m.p. 156°C, 90%, $[\alpha]_D^{25}$= -146 (c= 1.0, $CHCl_3$)) was conveniently achieved on the large scale using aluminium isopropoxide. However, the apparently straightforward esterification of **11** with benzoyl chloride yielded substantial amounts (> 30%) of the unusual dihydropyridine, **12** (m.p. 185-188°C, ($[\alpha]_D^{25}$= +56 (c= 0.5, CH_2Cl_2)). This unexpected problem was overcome by prior incorporation of a stoichiometric amount of DMAP in the reaction, to afford the desired (1R, 2S)-benzoate ester, **13**,[5] **RP 66471** (m.p. 174°C, >85%, $[\alpha]_D^{25}$= -138 (c= 0.5, $CHCl_3$)), which was found to be an extremely potent potassium channel opener with approximately twice the activity of **2**.

This methodology was repeated using (S)-(-)-α-methylbenzylamine[6] to prepare the (1S,2R) enantiomer of **13**, which was found to be over 1000 fold less active than **13** as a potassium channel opener, and, hence, confirms that the active enantiomer of **2** possesses the (1R, 2S) configuration.

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1. Weston A.H. in 'The Pharmacology of Antihypertensive Therapeutics', Ganter D. and Murlow P.J. Eds., Springer, Heidelburg, 1989, p. 643.
2. Hart T.W., Guillochon D., Perrier G., Sharp B.W. and Vacher B., *Tet. Letters*, 1992, 33, 5117.
3. All new compounds gave satisfactory elemental and spectroscopic analyses.
4. Enders D. and Eichenauer H., *Angew. Chem. Int. Ed.*, 1976, 15, 549.
5. The assignment of stereochemistry is deduced from previous work[2] and the X-ray data obtained on **13**.
6. Commercially available from Aldrich in 98% purity.
7. Pfau M., Revial G., Guingant A. and d'Angelo J., *J. Am. Chem. Soc.*, 1985, 107, 273 and refs. therein.

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