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Versatile Intramolecular Reactions Starting from a Conformationally Restricted Epoxyalcohol

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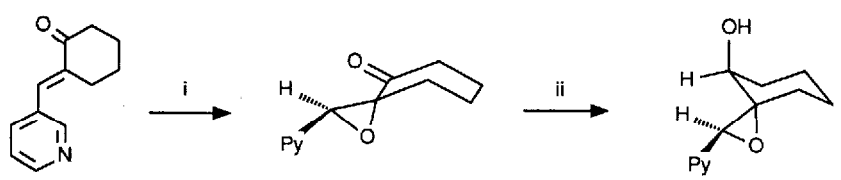
Abstract: *The novel epoxyalcohol, 3, has been converted, using a variety of stereoselective intramolecular cyclisation reactions, to several highly substituted cyclohexane derivatives. In addition carbon disulphide has been shown to be a powerful intramolecular sulphur transfer agent.*

Potassium channel openers have therapeutic potential in a number of disease states such as hypertension and asthma.[1] As part of our continuing programme to discover novel bronchodilators,[2] we needed ready access to the previously unknown cyclohexane derivatives of type 7, possessing highly defined stereochemistry (schemes 2 and 3). However, although many synthetically useful and biologically active 2-amino-1,3-diols are known,[3] we were surprised to find no information in the literature regarding the alicyclic derivatives which we required. We report herein a short, stereospecific synthesis of the alicyclic 2-amino-1,3-diols, 7, from the previously unknown, conformationally restricted epoxyalcohol, 3.



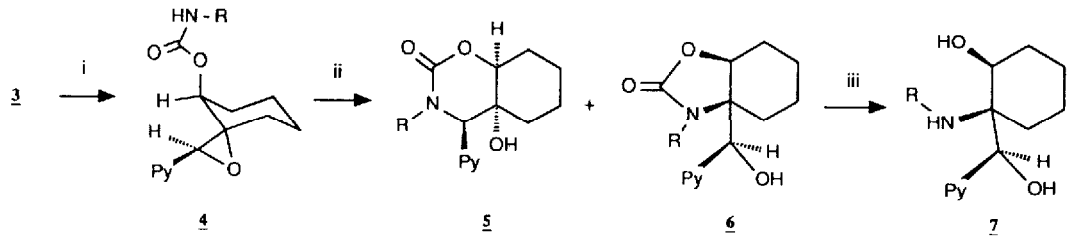
1 2 3

i. H_2O_2, NaOH, CH_3OH, 0-5°C ii. KBH_4, CH_2Cl_2-EtOH, -15°C

Scheme 1

Epoxidation of the known (E)-enone,[4] 1, afforded the novel epoxyketone, 2, (m.p. 115-116°C; 70%),[5] which was then reduced diastereospecifically to the trans epoxy-alcohol 3 (m.p. 99-101°C; 95%) using potassium borohydride (scheme 1).

Our first attempt at the conversion of the epoxyalcohol, **3**, to the aminodiols, **7a** and **7b** (scheme 2), using an intramolecular carbamate cyclisation reaction[3] met with limited success. Thus, while cyclisation of the the epoxycarbamates **4a** and **4b**, formed from the reaction of **3** with methyl or benzyl isocyanate respectively, did lead to the desired cis oxazolidinones **6a** (m.p. 124-125°C; 66%) and **6b** (m.p. 157-158°C; 40%), approximately 20% of the analogous six-membered ring heterocycles **5a** and **5b** were also obtained. Furthermore, although base hydrolysis afforded both the secondary aminodiols **7a** (m.p. 156-158°C; 39%) and **7b**, only the former could be obtained in a synthetically useful, albeit moderate, overall yield.



3 **4** **5** **6** **7**

a R = Me

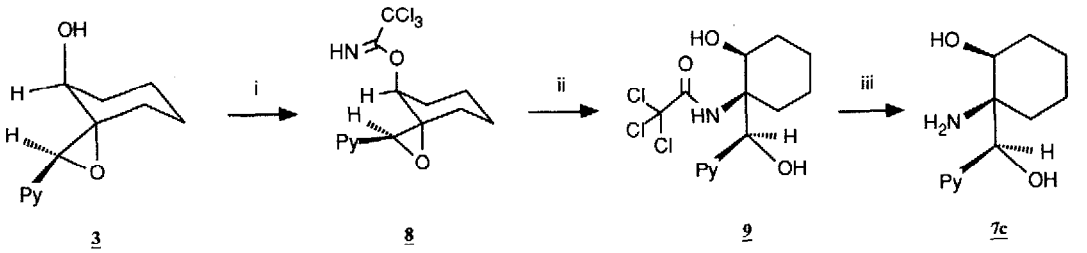
b R = CH_2Ph

i. RNCO, NEt_3, CH_2Cl_2, 25°C ii. NaH, THF, 25°C iii. LiOH, EtOH, H_2O, 80°C

Scheme 2

In an attempt to improve upon both the yield and the regioselectivity of the cyclisation step, we decided to modify both the electrophilicity of the oxirane and the nucleophilicity of the participating nitrogen atom. Hence, after condensation of **3** with trichloroacetonitrile under basic conditions[6] to furnish the imidate, **8**, (m.p. 65-66°C; 63%) (scheme 3), a boron trifluoride etherate promoted cyclisation afforded directly the trichloroacetamidodiol, **9**, as the sole product (m.p.166-167°C; 90%). The required primary aminodiol **7c** was subsequently isolated, after base hydrolysis of the trichloroacetamido group, as its dihydrochloride salt in 44% yield.

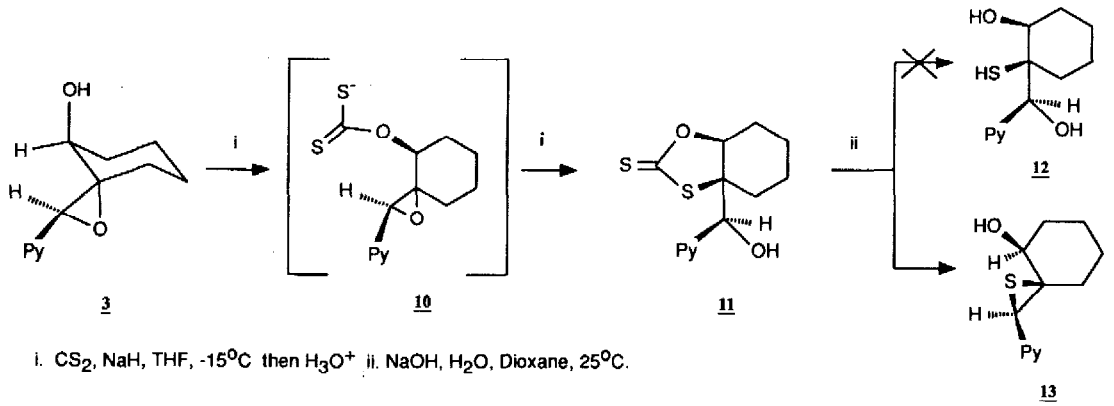
It is important to note that this particular imidate cyclisation proceeds in good overall yield, and allows the complete control of the relative stereochemistry of the three contiguous centres of asymmetry present in **9**, without the formation of the analogous six-membered ring products. Moreover, because many routes to enantiomerically pure epoxyalcohols have now been described,[7] an asymmetric synthesis of 2-amino-1,3-diols of the type **7** should now also be synthetically feasible.



i. Cl_3CCN, NaH, THF, 0^oC ii. $BF_3.OEt_2$, $C_2H_4Cl_2$, 0^oC iii. LiOH, $EtOH-H_2O$, reflux.

Scheme 3.

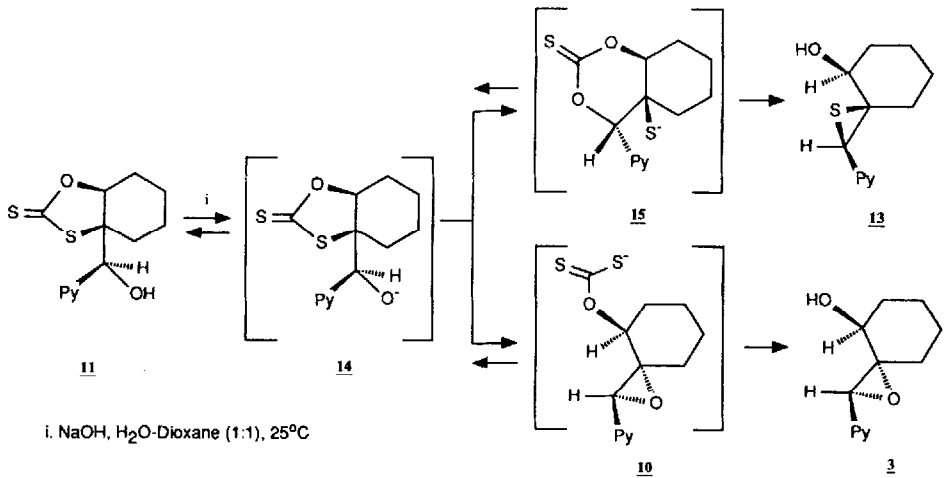
With the aim of exploiting the susceptibility of the epoxyalcohol, **3**, to undergo a regioselective intramolecular cyclisation reaction, we attempted to prepare the analogous 2-thiol-1,3-diol, **12**, using carbon disulphide as an intramolecular sulphur transfer agent (scheme 4). Thus reaction of the sodium salt of **3** with carbon disulphide gave the novel, cis fused heterocycle **11** (m.p. 145-147°C; 68%). However, base hydrolysis of **11** under standard conditions afforded two compounds, which were identified as the epoxyalcohol **3** (30%) and the episulphide **13** (m.p. 55-57°C; 55%).



i. CS_2, NaH, THF, -15^oC then H_3O^+ ii. NaOH, H_2O, Dioxane, 25^oC.

Scheme 4

A reasonable explanation for this surprising and interesting result is that, under the relatively non-polar aprotic conditions such as those that occur during the synthesis of **11**, **14** is the most stable charged entity. However, in aqueous basic medium, it would seem likely that an equilibrium is established between **11**, **14**, **10** and **15**, and the subsequent loss of thiocarbonate ion or xanthate ion becomes an irreversible driving force. Thus **15** undergoes another intramolecular displacement to afford, after hydrolysis, the episulphide **13** , while **10** is converted to the epoxyalcohol, **3**.



Scheme 5

Finally, the sequence depicted in scheme 4 highlights the power of carbon disulphide as a useful intramolecular sulphur transfer agent, especially since neither **12** nor **13** could be formed from **3** using standard methods involving thiourea or potassium thiocyanate.[8]

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