Synthesis of Enantiopure 4-Amino-6-fluoro-3-(hydroxymethyl)chromanes *via* Intramolecular Nitrone Cycloadditions

J. Chem. Research (S), 1997, 36–37
J. Chem. Research (M), 1997, 0301–0313

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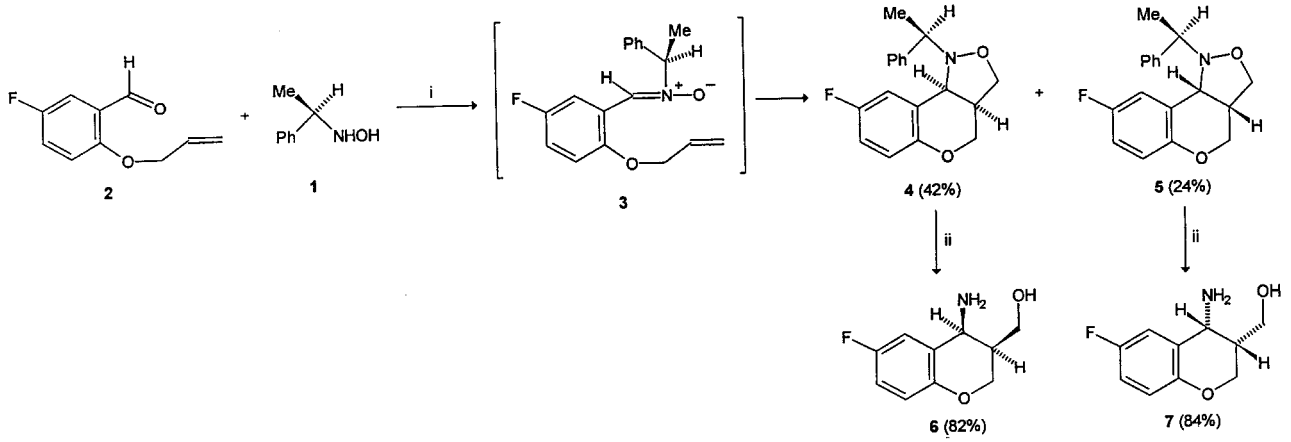
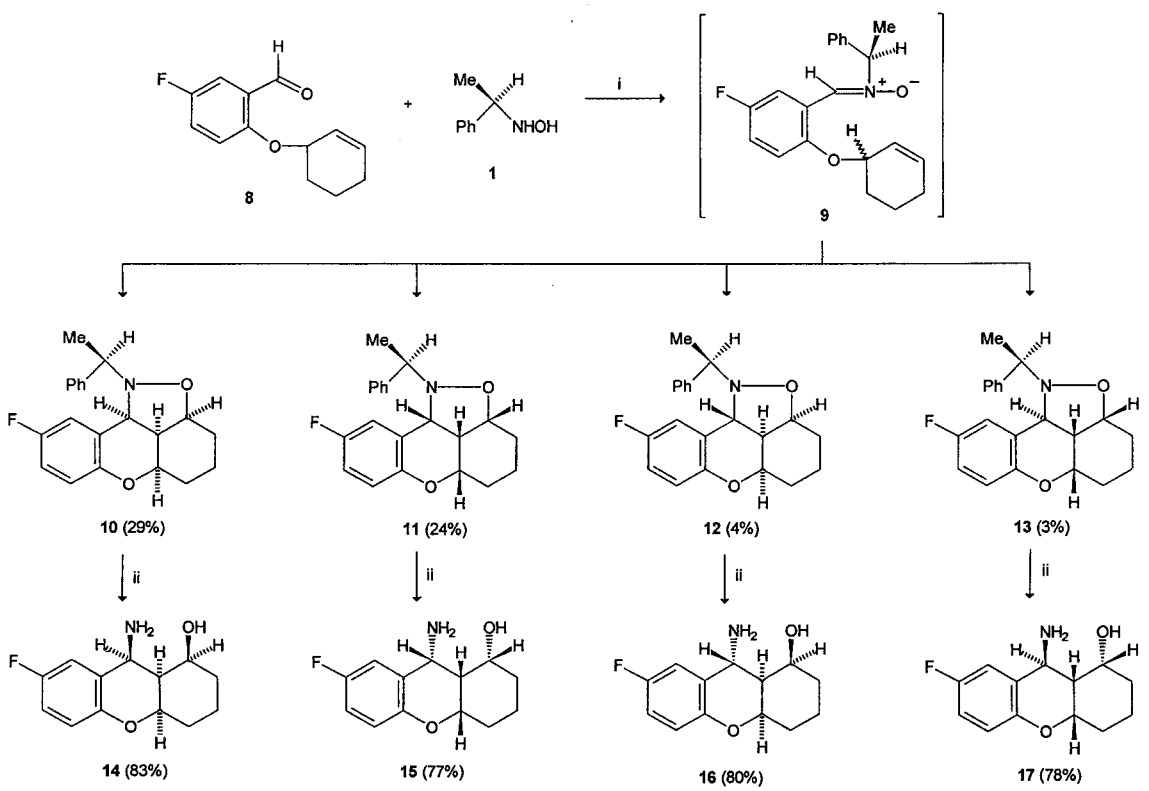
Enantiopure 4-amino-6-fluoro-3-(hydroxymethyl)chromanes are synthesised starting from 5-fluorosalicylaldehyde and using (*R*)-(+)-(1-phenylethyl)hydroxylamine as chiral auxiliary.

4-Aminochromane derivatives are becoming increasingly utilised in the medicinal chemistry field of potassium channel openers,[1–5] and the fundamental role of the absolute configuration in their physiological activity is well documented.[6–9] In a continuation of our research aimed at the synthesis of fluorinated heterocyclic compounds *via* intramolecular nitrone cycloadditions,[10] we describe here a version of this strategy leading to enantiopure 4-amino-6-fluoro-3-(hydroxymethyl)chromanes.

Nitrones derived from allyl-type ethers of 5-fluorosalicylaldehyde and (*R*)-(+)-(1-phenylethyl)hydroxylamine (**1**) were envisioned as appropriate intermediates. Accordingly,



Scheme 1 *Reagents and conditions:* i, $CaCl_2$, toluene, reflux; ii, H_2, Pd/C, acetic acid, r.t.



Scheme 2 *Reagents and conditions:* i, $CaCl_2$, toluene, reflux; ii, H_2, Pd/C, acetic acid, r.t.

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we synthesised compounds **2** and **8** and treated them with hydroxylamine **1**, Schemes 1 and 2.

Hydrogenolytic treatment of the cycloadducts resulted in both the removal of the benzyl-like *N*-pendant and the cleavage of the isoxazolidine ring, so disclosing the masked functionalities and resulting in the optically active amino alcohols **6**, **7**, **14–17**, as three pairs of enantiomers. Their enantiomeric purity was proven to be $\geq 98\%$ by NMR analysis in the presence of (*R*)-*O*-acetylmandelic acid.

We thank the C.N.R. (Rome) and the MURST for financial support.

Techniques used: IR, ^{1}H NMR, mass spectrometry, microanalysis, polarimetry

References: 14

Schemes: 2

Received, 27th September 1996; Accepted, 22nd October 1996
Paper E/6/06616J

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