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A new Approach to the Synthesis of Efaroxan

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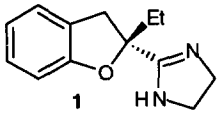
Abstract: efaroxan was synthetised by cyclisation of the tertiary alcohol **2** which was prepared by the ring opening of the gem-disubstituted epoxide **3** with *ortho*-metallated fluorobenzene.

Key words: efaroxan, dihydrobenzofurane, epoxide, cyclisation

2-[2-(2-Ethyl-2,3-dihydrobenzofuranyl)]-2-imidazoline **1**, also named efaroxan, has several interesting therapeutic properties. Originally investigated as an antidepressant and antidiabetic, it showed antagonist properties at the α_2-adrenoreceptors with high potency and selectivity.[1] Dexefaroxan **1**, possessing the R configuration, is the active enantiomer. At present time, this compound is undergoing preclinical evaluation in models related to central neurodegenerative disorders.



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In the course of pharmacological studies, we needed to develop a short and convergent synthesis of the enantiomerically pure **1** and its analogs. The most obvious chemical problem posed in the synthesis of **1** is the construction of the quaternary carbon bearing the imidazoline ring and the ethyl group.

Although many routes have been reported for the synthesis of dihydrobenzofuran derivatives [1,2], none could be easily extended to the preparation of optically pure compounds. In the previous paper, a methodology

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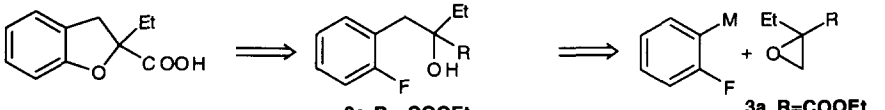
involving an intramolecular ring closure of a tertiary alcohol with an *ortho* fluoroaromatic compound is described.[3] Herein, we disclose a concise synthesis of efaroxan also featuring as the key step the intramolecular cyclisation of intermediate **2** (Scheme 1). However, we decided to develop a new route to the tertiary alcohol **2a** or **2b.** Indeed, we anticipated that they could be readily obtained by the ring opening of the gem-disubstituted epoxides **3a** or **3b** using an ortho-metallated fluorobenzene. The main reason for using an epoxide as key intermediate is the possibility to easily extend this strategy to the preparation of



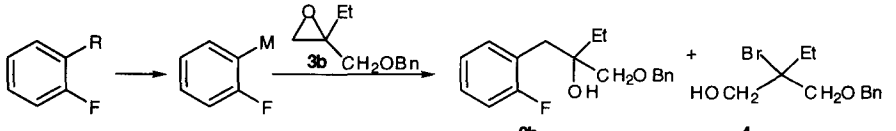
2a R= COOEt
2b R=CH_2OBn

3a R=COOEt
3b R=CH_2OBn

enantiomerically pure efaroxan and its derivatives.

Scheme 1

We preferred the epoxide **3b** as the starting material material for two reasons. The epoxide **3b** could be readily obtained enantiomerically pure using a procedure described in the literature[11] and the presence of the ester group on the epoxide **3a** could lead to further complications in the presence of the Grignard reagent. In order to validate the feasibility of our strategy, racemic epoxide **3b** was readily prepared from commercially available 2-ethylacroleine.[4] With compound **3b** in hand, an extensive investigation was undertaken to evaluate the ring opening of epoxide **3** with *ortho*-metallated fluorobenzene (Scheme 2, Table 1).



R=Br or H

M= MgBr or Li

2b

4

Scheme 2

The *ortho*-metallated fluorobenzene was prepared either from *ortho*-bromofluorobenzene by metal/halogen exchange [5] or magnesium insertion, [6] or from fluorobenzene by hydrogen/metal exchange [7]. The epoxide **3b** was allowed to react with *ortho*-metallated fluorobenzene under several conditions. [8] In all cases, the opening of the epoxide regiospecifically occured at the least hindered site and the best yield (72%, entry 4) was obtained by the addition of the *ortho*-fluorophenyl magnesium bromide in tetrahydrofuran in the presence of 10%mol of cuprous bromide and 10%mol of potassium carbonate (entry 4). In the absence of

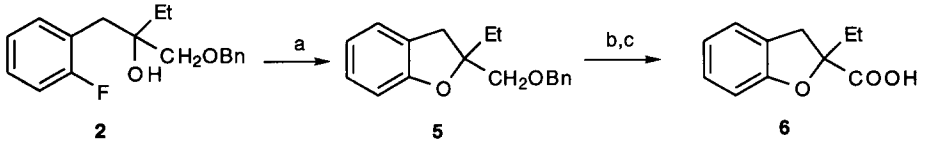
cuprous bromide, the only product isolated from the reaction was compound **4** resulting from the ring opening of epoxide **3b** with $MgBr_2$ generated *in situ* during the formation of the Grignard reagent (entry 2). The opening of the epoxide **3b** with *ortho*-lithiated fluorobenzene was less efficient and needed the presence of $BF_3.Et_2O$ (entries 1, 5 and 6).

Table 1: Synthesis of alcohol **2b** by the ring opening of the epoxide **3b**

entry	starting material	conditions	yield **2b** (%)[a]
1	o-bromofluorobenzene	nBuLi/THF/$BF_3.Et_2O$	39
2	o-bromofluorobenzene	Mg/THF	0[b]
3	o-bromofluorobenzene	Mg/THF/10%CuBr	67
4	o-bromofluorobenzene	Mg/THF/10%CuBr/K_2CO_3	72[c]
5	fluorobenzene	nBuLi/THF/ $BF_3.Et_2O$	39
6	fluorobenzene	nBuLi/THF	0

a: yields of purified compounds; b: the only product was compound **4** (81%); c: concomitant formation of **4** (20%).

The cyclisation of the alcohol **2b** with sodium hydride proceeded smoothly in DMF to afford the benzyl protected cyclised product **5** in 73% yield.[3] Conversion of compound **5** into the corresponding carboxylic acid **6** was accomplished by the removal of the benzyl group with H_2/Pd/C followed by the oxidation of the resulting alcohol with Jones reagent (Scheme 3). The carboxylic acid **6** is a direct precursor of efaroxan.[1,3,9]



2 **5** **6**

a: 2eq. NaH, DMF, 100°C, 73%; b: H_2,Pd-C, EtOH/rt, 94%; c: CrO_3/H_2SO_4/acetone, rt, 100%

Scheme 3

The intramolecular cyclisation of a carbinol on fluoroaromatics proved to be valuable for the synthesis of efaroxan. To obtain the key intermediate, the strategy based on the Darzens reaction is easy to scale up but will not give easy access to chiral dihydrobenzofuran derivatives.[10] The main advantage of this new synthetic strategy for the preparation of the efaroxan backbone, compared to other ways, is that it can easily

be extended to the asymmetric synthesis of (+) or (-) efaroxan by using the corresponding optically pure epoxide. Indeed, the enantiomerically pure (+) or (-)-epoxides **3b** are readily available using Sharpless epoxidation of the corresponding allylic alcohol.[11]

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