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THE ASYMMETRIC SYNTHESIS OF BOTH ENANTIOMERS OF ELIPRODIL

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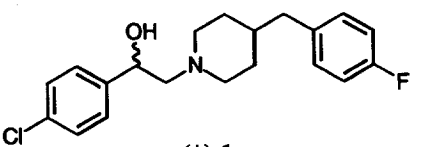
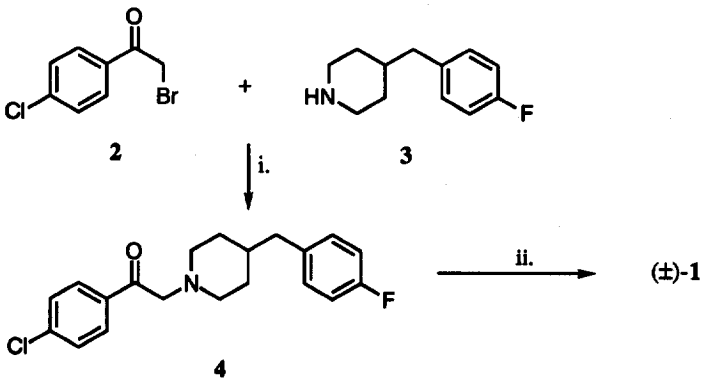
Abstract: The asymmetric synthesis of both enantiomers of the racemic NMDA antagonist eliprodil was accomplished in a novel application of Sharpless' asymmetric dihydroxylation (AD) methodology. A difference in neuroprotective activity was noted for the enantiomers in an *in vivo* model of rat focal cerebral ischemia.

The excitatory amino acid neurotransmitter glutamate has been implicated in the mechanism of neuronal degeneration found in many clinical conditions such as stroke,[1] Huntingdon's disease,[2] Alzheimer's disease[3] and neurotrauma.[4] There is now considerable evidence to suggest that the N-Methyl-D-Aspartate (NMDA) subtype of glutamate receptors is involved in the degenerative processes.[5]
Eliprodil (SL 82.0715) **1**, a novel racemic piperidine alcohol antagonist acting at the polyamine modulatory site of the NMDA receptor complex, is currently under evaluation due to its promising neuroprotective activity.[6]



(±)-**1**

The only reported synthesis of eliprodil involves the alkylation of 2-bromo-4'-chloroacetophenone **2** with 4-(4'-fluorobenzyl)-piperidine **3** and subsequent reduction of the ketone **4** with potassium borohydride (**Scheme 1**).[7] In a recent publication a similar strategy was used to synthesise a series of oxindole analogues of **1**.[8] The single enantiomers of **1** have been obtained by fractional crystallisation of their diastereomeric phenyl-1-ethyl carbamates and subsequent treatment with lithium aluminium hydride.[9] In a later publication,[10] no significant difference was noted in an *in vitro* receptor affinity study for the two enantiomers of **1**.

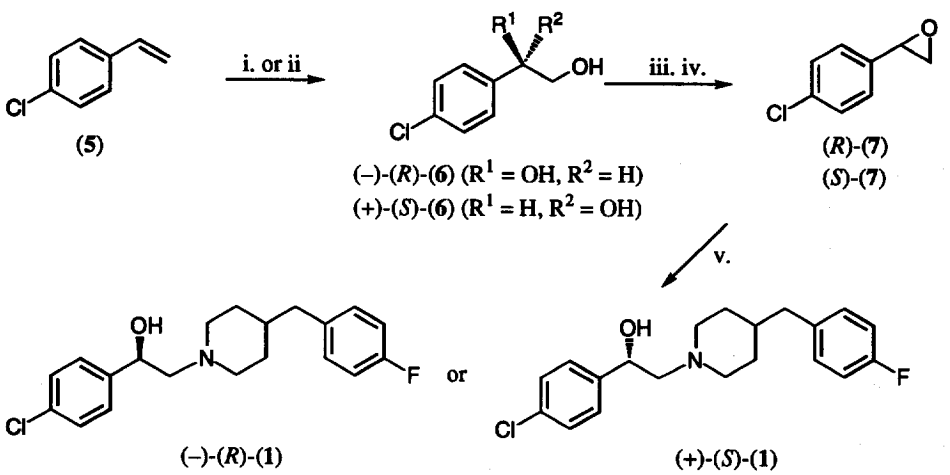


i. K_2CO_3, EtOH, Δ. ii. KBH_4, MeOH, r.t. 8 hrs

Scheme 1

The ability of piperidines analogous to **3** to open styrene oxides is well known.[11] We wished to exploit this approach, coupled with Sharpless' asymmetric dihydroxylation (AD) procedure[12] and epoxide generation from 1,2–diols[13] to effect asymmetric syntheses of the single enantiomers of eliprodil **1**. The results we obtained are the subject of this Letter.

The asymmetric synthesis of the enantiomers of **1** is outlined in **Scheme 2**.



i. AD-mix-β, $^tBuOH/H_2O$, 0°C, 6h, >95% of (–)-(*R*)-(**6**), >95% ee; ii. AD-mix-α, $^tBuOH/H_2O$, 0°C, 6h, >95% of (+)-(*S*)-(**6**), >95% ee; iii. TMS-Cl, $MeC(OMe)_3$, anhydrous CH_2Cl_2, 0°C, 1h; iv. K_2CO_3, MeOH, r.t., 2h; v. **3**, ^iPrOH, reflux, 4 h, 63% from **6**.

Scheme 2

Treatment of 4-chlorostyrene **5** with AD-mix-β gave the diol (-)-(*R*)-**6** in near quantitative yield. The absolute configuration of the product is based both on Sharpless' model for the selectivity of the AD

reaction[12,14] and on comparison of the optical rotation of the product[15] with the literature value of a sample prepared by biooxidation with *Pseudomonas putida* by Hudlicky and co-workers.[16] Similarly, AD-mix-α gave the corresponding (+)-(*S*)-**6** in excellent yield. Treatment of the enantiomers of **6** with trimethylsilyl chloride and trimethylorthoacetate in dichloromethane, then with potassium carbonate in methanol gave the corresponding epoxides **7** which were sufficiently pure to be used in the following step without chromatographic purification.[17] The epoxides (*R*)- and (*S*)-**7** were opened by heating in isopropanol with 4-(4-fluorobenzyl)-piperidine **3**[18] to give the corresponding isomers of **1** in reasonable yield. The optical purity of both enantiomers was checked by forming their MTPA ester derivatives[19] from samples of the crude reaction products and examining the reaction mixture by 500MHz ^{1}H NMR. No evidence for the presence of the undesired MTPA ester diastereoisomers was found in either case.

We wished to study the relationship between the stereochemistry of the molecules and their *in vivo* neuroprotective activity in the rat model of focal cerebral ischemia induced by permanent occlusion of the middle cerebral artery (MCA).[20] Pre-ischemia (5 min) administration of (*R,S*)-eliprodil **1** or of its (–)-(*R*)-enantiomer at 1mg/kg i.v. produced a significant reduction of the infarction volume of 59% and 55% respectively (see **Table**). At the same dose however, (+)-(*S*)-**1** demonstrated a much lower neuroprotective activity, reducing the infarction volume by 29% with respect to the vehicle.

Table

Compound	Infarction volume ($mm^3 \pm$ S.E.M¤.)
(±)-**1**	33.3 ± 9.2 (n = 7)*
(–)-**1**	37.7 ± 4.0 (n = 9)*
(+)-**1**	58.9 ± 10.9 (n = 9)
Vehicle	83.1 ± 11.8 (n = 11)

*$p<0.05$ *vs. vehicle (Dunnett T test)* ¤ S.E.M = Standard Error Mean

These results suggest that the (–)-(*R*)- rather than the (+)-(*S*)- enantiomer contributes significantly to the *in vivo* biological activity of the racemic form of eliprodil **1**. The reasons for the discrepancies between the *in vitro*[10] and *in vivo* data are not clear. Differences in penetration through the blood - brain barrier or metabolic fate of the enantiomers are possibile explanations. Alternatively, there exists the possibility of differing affinities of the enantiomers for other receptors, such as the α1 adrenergic receptor[21] or neuronal voltage-operated calcium channels.[6] Further studies will be necessary to better understand this phenomenon. A more detailed account of the biological results obtained will be given elsewhere.

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