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# PREPARATION OF THE ENANTIOMERS OF THE ANALGESIC E-3710.

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***Abstract.***Both enantiomers of E-3710, a novel analgesic, were prepared by a practical resolution method and their absolute stereochemistries assigned by asymmetric synthesis from ethyl (*R*)-mandelate. Their pharmacological properties were compared with those of the racemic compound, and no significant difference was observed.

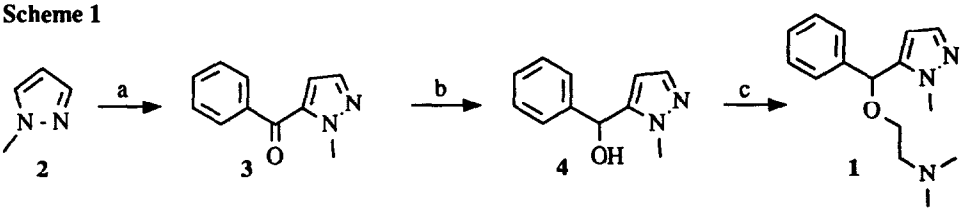
As a result of our research on CNS active agents, compound E-3710[1,2](1) has emerged as a potent analgesic which is at present under phase I clinical trials[3]. The presence of a chiral centre in this molecule prompted us to obtain each enantiomer separately in order to compare them with racemic E-3710.

Our first efforts were directed towards the formation of diastereomeric salts with some chiral acids[4], but we were not successful and none of the salts formed proved to be a crystallisable solid.

Simultaneously, a study tending to the separation of the enantiomers by preparative HPLC over triacetylcellulose as the chiral stationary phase was undertaken, but the resulting enantiomeric enrichment[5] was disappointingly low (only 18% on the dextrorotatary enantiomer)[6].

We then turned our attention to the possibility of resolving an intermediate of the synthesis of racemic **1** depicted in Scheme 1. At first sight it seemed reasonable to try asymmetric reduction of ketone **3**. A battery of conditions were tested (diisopinocampheylborane[7], chirally modified lithium aluminium hydride[8] or lithium borohydride[9], and bakers yeast[10]) but no optical rotation were detected and the reduction was not further studied.

**Scheme 1**




**Reagents and conditions:** a) i) BuLi, THF-$Et_2O$, 0°C, 12h; ii) PhCN (60%). b) $NaBH_4$, MeOH, rt (95%).
c) (2-chloroethyl)dimethylamine hydrochloride, n-$Bu_4NBr$, tol-aqNaOH(40%), reflux, 24h (75%).

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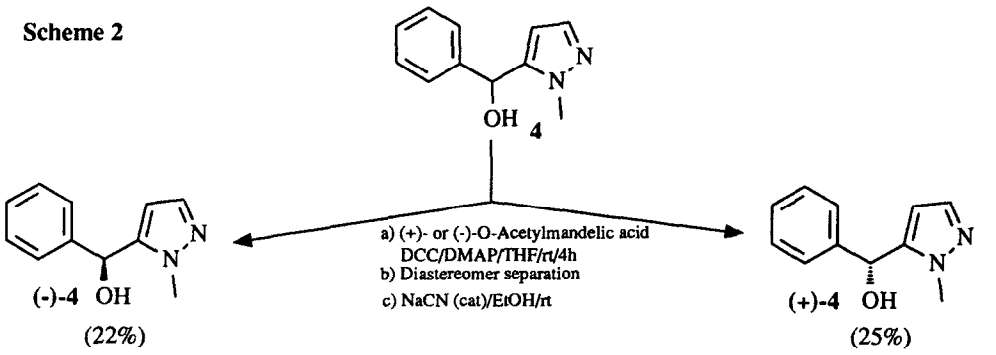
Resolution of alcohol **4** as its diastereomeric O-acetylmandelate esters[11] was finally successful, as presented in Scheme 2. Thus, esterification of alcohol **4** with (*R*)- or(*S*)-O-acetylmandelic acid by the DCC method afforded a mixture of diastereomeric esters, which were separated either by column chromatography over silica gel or by fractional crystallization[12]. Each of them was then saponified in EtOH in the presence of catalytic amounts of NaCN[13] to yield the enantiomerically pure alcohols (+)-**4**($[\alpha]_D$ +16.8) and (-)-**4**($[\alpha]_D$ -18.8) in 25% and 22% total yield respectively. These alcohols showed themselves to be enantiomerically pure by their $^1$H NMR spectra in presence of β-cyclodextrine, and by the $^1$H and $^{13}$C NMR spectra of their respective Mosher derivatives[14].

**Scheme 2**




Finally, these alcohols were transformed by the alkylation procedure previously described[1,15] on to the corresponding (+)-**1** (citrate, $[\alpha]_D$ +8.32) and (-)-**1** (citrate, $[\alpha]_D$ -8.24) shown to be enantiomerically pure by HPLC[16] and $^1$H NMR in the presence of a chiral europium derivative[5].

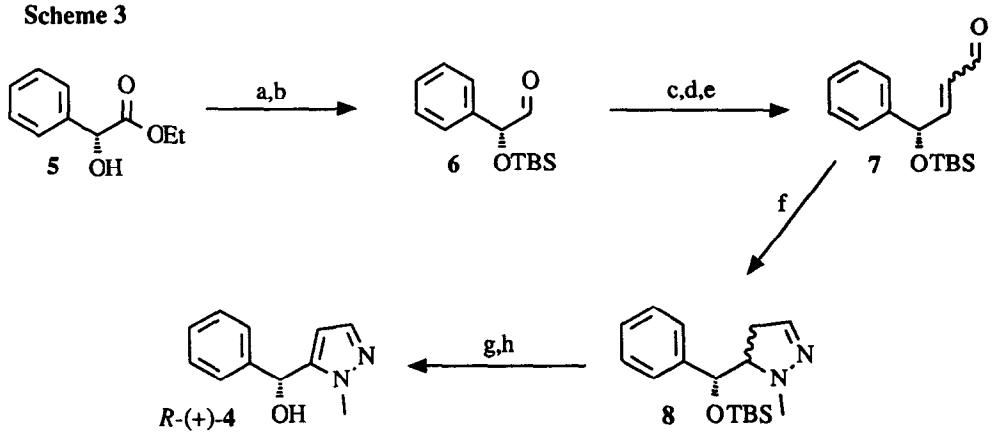
With both enantiomers in hand, it was felt necessary to determine their absolute configurations. To accomplish this task, we undertook the enantiomerically pure compound (EPC) synthesis of one of them. Ethyl (*R*)-mandelate **5** was chosen as the starting material. At first we tried a direct cyclization of this compound, as its THP-derivative[17], with N'-methyl acetaldehyde hydrazone and butyllithium, following the method described by Beam[18], but the desired **4** was not formed.

An alternative procedure was then devised and is shown in Scheme 3. Compound **5** was protected as its *tert*-butyldimethylsilyl ether and reduced with DIBAH to aldehyde **6**[19]. Direct elongation to aldehyde **7** with formylmethylenetriphenylphosphorane proved unsuccessful. This problem was circumvented by treatment of **6** with ethoxycarbonylmethylenetriphenylphosphorane, followed by reduction of the unsaturated ester thus formed to the alcohol and subsequent oxidation to compound **7**, which was obtained as a mixture of E,Z isomers. Cyclization by reaction with methylhydrazine afforded a mixture of pyrazolines **8** together with their regioisomers in 60% overall yield[20]. Oxidation and deprotection allowed us to isolate the alcohol (+)-**4**. Its optical rotation ($[\alpha]_D$ +17.6) was practically identical to that obtained for the resolved (+)-**4** ($[\alpha]_D$ +16.8) and the $^1$H NMR spectrum of its Mosher derivative showed it to be a single isomer. At this point we could then

assess the *R* absolute configuration to alcohol (+)-**4** and thus to the end product (+)-**1**. Conversely, (-)-**4** and (-)-**1** possess the *S* absolute configuration.

With regard to biological activity, the aforementioned compounds were tested for their analgesic activity by the phenylquinone-induced writhing test in mice[21], using diclofenac ($ED_{50}$ 87 mg/Kg, po) as the reference compound[2]. The (*R*)-(+)-**1** enantiomer [$ED_{50}$ 13 (iv), 21 (sc) and 37 (po) mg/Kg] was slightly more active than the racemic compound (±)-**1** [$ED_{50}$ 16 (iv), 70 (sc) and 56 (po) mg/Kg] and than the (*S*)-(-)-**1** enantiomer [$ED_{50}$ 28 (iv), 127 (sc) and 67 (po) mg/Kg]. These differences were however not significant. In addition, the CNS effects were studied by the Irwin test in the mouse[22]. In this context, no difference in behaviour was seen between groups of mice treated with the racemic compound or with its enantiomers at a dose of 160 mg/Kg, (ip, po and sc), and 80 mg/kg (iv).

**Scheme 3**




**Reagents and conditions:** a) TBSCl, imidazole, DMF, 0°C. b) DIBAH, tol-cyclohex (1:1), -78°C, 90 min (96%) 2 steps). c) $Ph_3PCHCO_2Et$, MeOH, rt, 90 min. d) DIBAH (2 eq), tol-cyclohex (1:1), -78°C. e) i) $(COCl)_2$, DMSO, $CH_2Cl_2$, -60°C; ii) $Et_3N$ (70% 3 steps). f) $MeNHNH_2$, $CH_2Cl_2$, rt, 12h (60%). g) $MnO_2$, benzene, reflux, 30 min. h) n-$Bu_4NF$, THF, rt, 60 min (20% 2 steps).

In conclusion, we have developed a practical method for the preparation of the enantiomers of the analgesic E-3710 and assessed their absolute configuration by EPC synthesis. The biological data showed that they very closely resemble the racemic compound, and there therefore seemed to be no advantage in working with only one enantiomer instead of the racemic compound.

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## References and Notes

1.- Colombo, A.; Parés, J.; Frigola, J. *European Patent* EP 289,380 (02.11.1988).

2.- Farré, A.J.; Colombo, A.; Colombo, M.; Fort, M.; Gutiérrez, B. *Rev. Farm. Clin. Exp.*, **1989**, *6*, 233.

**3.**- As the citrate salt (E-4018).

**4.**- A variety of acids were tested: camphorsulphonic, mandelic, tartaric and various aminoacids. None of them proved capable of forming crystalline salts under a variety of conditions.

**5.**- Deduced from the integration of bencylic proton signals (δ6.55 for the *levo* and δ6.44 for the *dextro* enantiomer) observed in the $^1$H NMR spectrum recorded in the presence of europiumtris[D-3-heptafluorobutyrylcamphorate] as a chiral shift reagent.

**6.**- More successful were the results of analytical HPLC in which we could obtain an acceptable degree of separation with an Enantiopac$^{Tm}$ stationary phase.

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**10.**- Kometani T, Kitatsuji E, Matsuno R. *Chem. Lett.* **1989**, 1465.

**11.**- Other esters were tried, but the one which best suited our purposes was O-acetylmandelic acid, obtained by acetylation of mandelic acid with acetyl chloride in $CH_2Cl_2$-$Et_3N$ at 0°C.

**12.**- Chromatographic separation with chloroform/methanol or fractional crystallization from ethyl acetate/n-hexane afforded (*R*)-(-)-O-acetylmandelate ester of (+)-**4** (mp 90-92°C) and (*R*)-(-)-O-acetylmandelate ester of (-)-**4** (mp 58-60°C).

**13.**- Mori K, Tominaga M, Takigawa T. *Synthesis* **1973**, 790.

**14.**- Dale JA, Dull DL, Mosher AS. *J. Org. Chem.* **1969**, *34*, 2543.

**15.**- No racemization was observed, but there was a small amount of oxidation to ketone **3**. This transformation was also observed when we tried to alkylate **4** with NaH and chloroethyldimethylamine in THF in order to obtain **1** under less severe conditions. In this case ketone **3** was the main product, together with small quantities of the desired compound.

**16.**- In the conditions described in ref. 6.

**17.**- Obtained by the usual method (DHP-TsOH).

**18.**- Beam CF, Sandifer RM, Foote RS, Hauser CR. *Synth. Commun.* **1975**, *6*, 5.

**19.**- Kobayashi Y, Takemoto Y, Ito Y, Terashima S. *Tetrahedron Lett.* **1990**, *31*, 3031.

**20.**- The separation of regioisomers was achieved by column chromatography over silica gel with n-hexane/ethyl acetate, affording **8** in 51% yield.

**21.**- Siegmund E, Cadmus R, Lu G. *Proc. Soc. Exp. Biol. Med.*, **1957**, *95*, 729.

**22.**- Irwin S. *Science*, **1962**, *136*, 123.