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Design, Synthesis and Evaluation of a Chiral Propranolol Selector.

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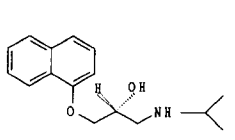
Abstract: Synthesis of enantiomerically pure (*S*)-(-)-propranolol, the most active of the widely used beta-blockers adrenergics, was achieved using a new chiral stationary phase (CSP) for the separation of a derivative. This simple methodology shows a significant improvement in the separation of the enantiomers of a propranolol derivative over previous methods.

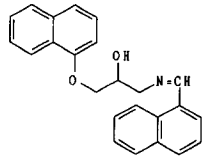
Introduction

It is now recognized that the stereochemistry of drug molecules governs their biological activity[1]. Betablockers with the aryloxy-1-(alkylamino)-2-propranolol stucture such as propranolol **1**, are a group of drugs whose activity resides almost exclusively in the (*S*)-enantiomer[2], so therefore, the asymmetric synthesis of these beta-blockers has received attention. Several methods have been reported involving non-enzymatic asymmetric synthesis, enzymatic resolution and chiral building blocks[3]. Recently, a synthetic chiral selector has been described for Naproxen, an (*S*)-2-aryl-propionic acid, and an important group of nonsteroidal antiinflammatory drugs, which show stereoselective activity and disposition[4].

In this work we describe a synthesis of (*S*)-(-)-propranolol **1**, based in the resolution of the racemate of the imino-alcohol **2** by using a chiral selector phase. Recently, b-cyclodextrins have been used for monitoring biological fluids for homochiral b-blockers[5]. Two chiral stationary phases (CSPs), capable of separating the enantiomers of **2**, have been designed and synthesized. The CSPs used as potential selectors have a capability for shape binding by hydrogen bonding and donor-acceptor (DA) *pi-pi* interactions (Pirkle-type). These interactions are the most important in chromatographic separations of racemic compounds[6]. This novel CSP **3** has two hydrogen bond acceptor sites and one conjugated *pi*-electron acceptor system, with at least three interaction points, for the guest **2**, one of which is stereochemically dependent. This interaction is recognised as being very important for a receptor to exhibit enantioselectivity as a chiral selector[7]. In our CSP, this stereochemical interaction is the stereogenic carbon of (*R*)- or (*S*)- aspartic acid. Therefore two different enantiomeric CSPs could be obtained: one with the (R)- and another with the (*S*)-aminoacid.



1

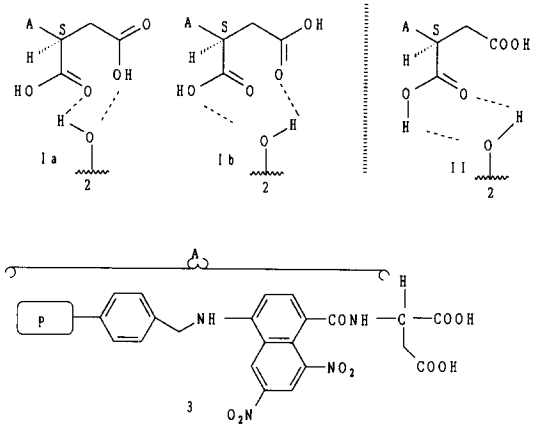


2

Results and Discussion

Conformational analysis: To explore whether our hypothesis was feasible a MD study was carried out using HYPERCHEM 3 program. The high temperature molecular dynamics method was chosen in a search for the putative minimum energy conformation of the compounds because of its efficiency in crossing energy barriers in the multidimensional conformational space. One of the risks inherent to this methodology is that the structures can get trapped in high-energy local minima. To avoid this problem, additional molecular dynamics was deemed necessary. Finally the minimum energy conformers were minimized using MM calculations and Fletcher-Reeves algorithm (RMS gradient 0.01 Kcal/Å.mol). Both selector **3** and the iminoalcohol **2** gave conformers with similar energy for the (R)- and (S)- enantiomers. Nevertheless the complex selector + iminoalcohol show different minimum energy conformers depending on (1) the configuration of the stereogenic centers of both molecules (2) the interaction of the hydroxyl group of the stereogenic center of the imino-alcohol and the COOH groups of the selector. Two extreme interactions have been considered as show in the case of the interaction of CSP-(S)-Asp and **2**: **Interaction I**-both carboxylic acids interact with the OH group from imino-alcohol **2**. **Interaction II**-only one carboxylic group interacts with the -OH from the imino-alcohol **2**. In Table I we show the energy of the minimum energy conformer of the complex selector + imino-alcohol obtained according to the computational methodology.

Scheme 1.- Postulated interactions between CSP and **2**.



From the results we deduce that interaction II gives higher energy conformers than interaction I. These values are independent of the configuration of the sterogenic centers in both in **3** and **2**. Therefore, this interaction cannot be useful for discriminating between the stereomers of the iminoalcohol **2** using **3** as a chiral selector. In contrast, the interaction I discriminates between iminoalcohols **2**, especially in the case of the interaction between the S enantiomers((S)-**2** and (S)-**2**) which gives the lowest energy conformers of the complex **3** + **2** (Schemes 2 and 3). This situation is dramatic in the case of the interaction Ia that favours the formation of a Pirkle interaction between the aromatic rings of the naphthalenes (Scheme 2). This situation cannot be reached in the interaction Ib[8] (Scheme 3). Therefore the theoretical results described above give us the support to explore, the resolution of the iminoalcohol **2** with the chiral selector phase (S)- **3** (CSP-(S)Asp).

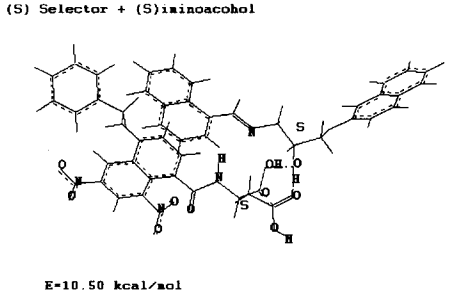
Table I. Minimum energy conformers of the complex selector **3** + iminoalcohol **2**.

Conformer	Stereochemistry selector **3**	inminoalcohol**2**	Interaction	E(Kcal/mol)
C-1	S	S	Ia	10.5
C-2	S	S	Ib	20.7
C-3	S	S	II	37.63
C-4	S	R	II	33.15
C-5	R	S	II	34.7
C-6	R	R	II	36.5
C-7	R	R	Ia	26.7
C-8	R	R	Ib	27.7

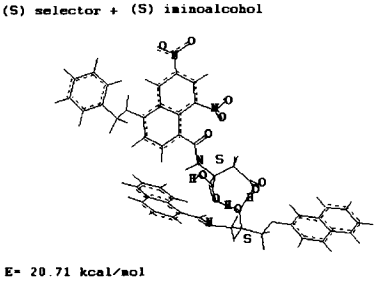
Several solvents were tested and low poarity solvents such as n-hexane or cyclohexane were the best solvents to achieve the most interesting difference between both enantiomers in the elution process. Eluent (95/5 v/v hexane/iPrOH) at a flux of 1ml/min was used and the high concentration of (R)-iminoalcohol **2** is achivied at 30 min. After that, an increase in the proportion of the another enantiomer is observed. A final washing with dichloromethane allowed us to recover the another enantiomer (S)-**2**.

The synthesis of the iminoalcohol **2** (Scheme 4) was carried out by conventional methodologies described in the literature[9]. The reaction of the chlohydrin **4**, with gaseous ammonia in ammonium acetate, gives the aminoalcohol **5** which reacts with naphthalene-2-carbaldehyde giving the (RS)-iminoalcohol **2**.

Scheme 2.-Minimum energy conformer of the complex CSP-(S)-Asp + (S)-**2**. Interaction **Ia**



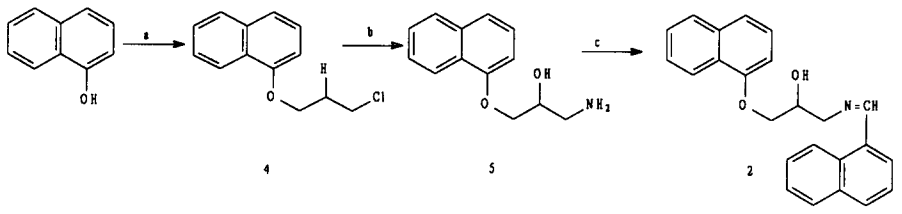
Scheme 3.- Minimum energy conformer of the complex CSP-(R)-Asp+(S)-**2**.Interaction **Ib**.



This reaction of **5** protects the amino group avoiding the competition between the -NH_2 and the -OH (on the stereogenic center) for the H-bonding sites of CSP. Also the introduction of *pi*-donating naphthalene rings in **2** favors the Pirkle-type interaction between **2** favours the *pi*-electron-acceptor dinitro-naphthalene ring of **3**. On the other hand, the presence of two naphthalene rings in the "guest" molecule confers fluorescence and UV-visible properties. This is very important

to "view" the chromatographic separation of the enantiomers in the chromatographic column.

Scheme 4- Synthesis of (R,S)iminoalcohol.



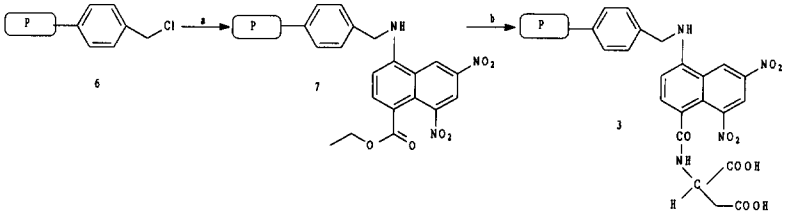
a) epichlorhydrine/pyridin, r.t., 254h., HCl, 0-5°C, 90%.b) NH_3/ammonium acetate, H_2O, r.t., 16h., 77%.

c) naftaleno-2-carbaldehyde, Cl_4C/molecular sieves, 10°C, 4h., 60%.

The synthesis of the CSP (Scheme 5) uses a chloromethylated polystyrene matrix **6**[10]. The polymeric matrix is transformed into dinitronaphthyl-derivative **7**, by reaction with ethyl 4-amino-6,8-dinitro-1-naphthalene carboxylate, obtained from 4-amino-1-naphthtalenecarbonitrile. The reaction of the acylchloride of **7**, with (R)- or (S)- aspartic acid give the chiral stationary phase **3**.

The resolution of the racemic **2**, was carried out by means of the host/guest interaction between the stationary phase **3** and the racemic iminoalcohol **2** according to the relative energy of the conformers of the complexes **3**(CSP-(S)-Asap) + **2**, (S)-**2** remains in the column (more stable complex) and (R)-**2** (less stable complex) is eluted first (95/5 v/v hexane/2-propanol).

Scheme 5- Synthesis of CSP.

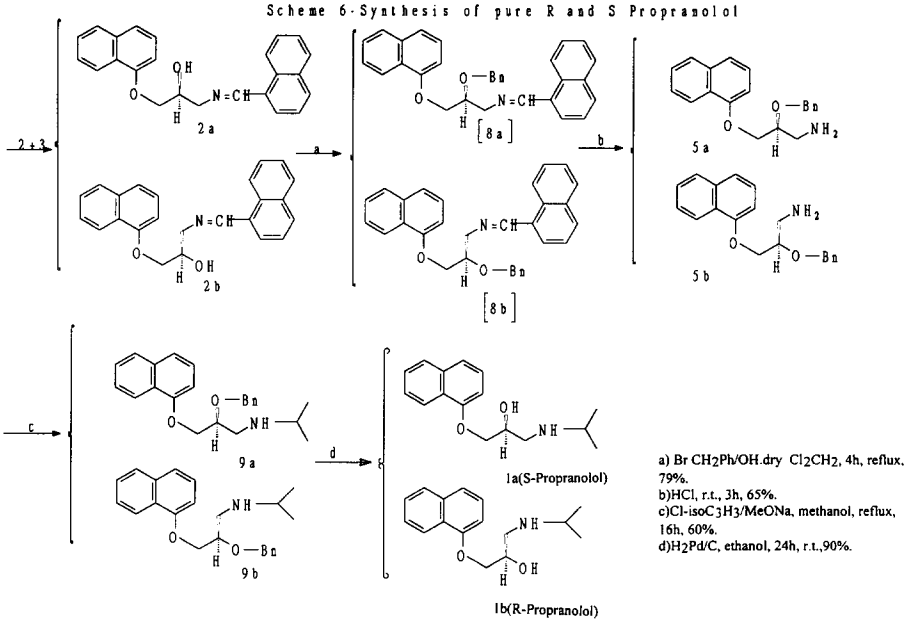


a)Ethy4-amino-6,8-dinitro-1-naphthalenecarboxylate/NaOH, reflux, 16h., 85%. b) HCl/$SOCl_2$,2-propanol, r.t., (R)- or (S)- aspartic acid, reflux, 6h., 70%.

The CSP was packed in one MPLC column (10-200 mm). The enantiomers of **2** were separated using hexane/2-propanol (95/5 v/v) as the eluent. The absolute configuration of (R)- and (S)- enantiomers was determined by ^{1}H-NMR of the corresponding acetates[11]. The synthesis of pure homochiral propranolol **1** can easily accomplished (Scheme 6). The benzylation of the hydroxyl group of **2a** and **2b** carries to **8a** and **8b** that are hydrolyzed "in situ" to **5a** and **5b**. treatment of these compounds with isopropyl chloride in sodium methoxide yields **9a** and **9b** that are hydrogenolyzed with Pd/C, to **1a** and **1b**. The (S)-propranolol obtained **1a**, has the same analytical data e.g. melting point and specific rotation, as those published for the pure enantiomer in the literature[12]. The application of these CSPs for the resolution of other racemic mixtures is now in progress.

Conclusion: This new methodology for the separation of the enantiomers of adrenergic beta-blocker precursors is a relevant simplification compared to the described methodologies and another use of the molecular recognition to solve problems in stereoselective organic chemistry.

Scheme 6-Synthesis of pure R and S Propranolol



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11. ^{1}H- NMR spectra of 0.2 M **2a** and **2b** in the presence of 0.2 M,3-(heptafluoropropyl)hydroxymethylene)-d-camphorate europium (III) (chiral lanthanide shift reagent), baseline separation of the acetate signals was obtained.
12. (S)-(-)-propranolol, **1**; M.p.:70-72° (lit.72-73°C); $[\alpha]^{20}_D$= 9.98 (c=0.97,EtOH) (lit.$[\alpha]^{20}_D$= 10.21(c=1.02,EtOH).

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