The First Enantiomerically Pure Synthesis of (*S*)- and (*R*)-Naftopidil Utilizing Hydrolytic Kinetic Resolution of (±)-(α-Naphthyl) Glycidyl Ether

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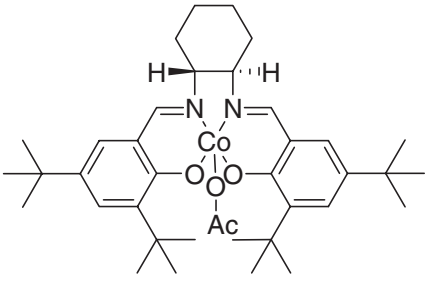
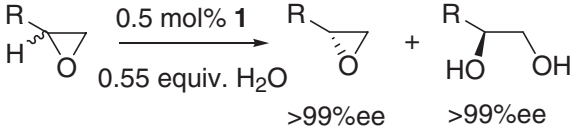
Hydrolytic Kinetic Resolution (HKR) of (±)-(α-Naphthyl) glycidyl ether with (*R*,*R*)-salen Co(III) OAc complex provided enatiomerically pure (*S*)-naphthyl glycidyl ether and (*R*)-1-naphthyl glycerol; opening of the corresponding pure terminal epoxide with 1-(2-methoxyphenyl)piperizine gave the enantiomerically pure (*S*)- and (*R*)-Naftopidil.

The importance of chirality in the context of biological function has been fully appreciated and the *R* and *S* forms of most drugs are metabolized by different biochemical paths and at different rates. For example, (*R*)-thalidomide is an effective sedative where as the (*S*)-enantiomer is highly teratogenic and causes fetal abnormalities.[1]

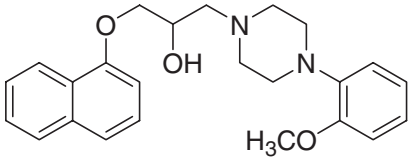


(*R*,*R*)- Salen Co (III) OAc Complex (**1**)



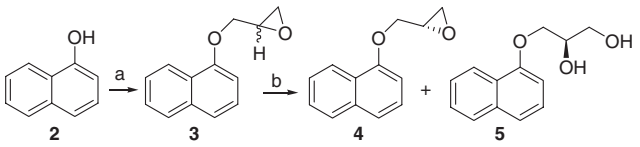
Scheme 1.

Terminal epoxides are versatile starting materials for the preparation of bioactive molecules;[2] it is pertinent to mention the different methods to obtain enantiomerically pure epoxides, which include classical optical resolution via diastereomers, chromatographic separation, enzymatic resolution, chemical kinetic resolution, and asymmetric synthesis. However, the recently reported technique of Hydrolytic Kinetic Resolution (HKR) of terminal epoxide by Jacobsen[3] has been unexplored for preparation of chiral building blocks. This process uses water as the only reagent without solvent and low loading of a recyclable chiral (*R*,*R*)-salen cobalt(III) OAc catalyst (**1**) affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric enrichment (Scheme 1). This method is also extremely simple to work with compared to other approaches for chiral glycidyl ethers. Chiral glycidyl derivatives are perhaps one of the most versatile C3-chiral synthons with neumorous applications for β-blockers, MAO inhibitors, alkyl glycerophospholipids and other pharmaceuticals as well as in organic synthesis.[4]



Naftopidil

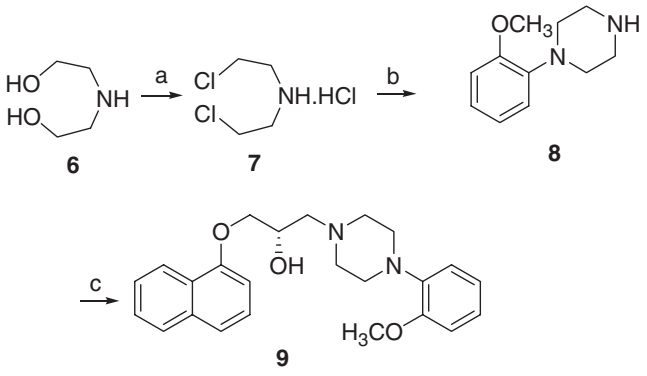
Naftopidil (BM-15275)[5] is a vasodilator from the piperizine derivative series. Pharmacologically, naftopidil is a novel α_1-adrenoceptor antagonist (α_1-blocker), renal urologic drug, used for the treatment of arterial hypertension. Asahi Chemicals has launched naftopidil (Flivas[R]) in Japan, where it is indicated for the treatment of dysuria of men with benign prostatic hypertrophy as racemic mixture. In the investigations of the safety of naftopidil in racemic form, it was found that urine and electrolyte excretion was slightly reduced at doses active on blood pressure, with some other sedative properties,[6] and also found that the drug affects on phenylephrine-induced increases in prostatic and blood pressure in anesthetized dogs.[7] All these information necessitate preparation of optically pure (*S*)- and (*R*)-naftopidil and investigation of their pharmacokinetics as individual molecular entities.



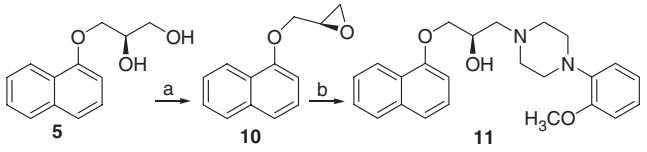
Scheme 2. a) Epichlorohydrin, K_2CO_3, acetone, reflux, 12 h, 90%; b) 0.5 mol % **1**, water (0.55%), rt, 24 h.

The truly fascinating Hydrolytic Kinetic Resolution of racemic glycidyl ethers[8] promoted us to undertake the synthesis of optically pure (*S*)- and (*R*)-naftopidil. α-Naphthol (**2**) was treated with racemic epichlorohydrine to afford racemic (α-naphthyl) glycidyl ether (**3**). Compound **3**, catalyst salen complex (**1**) and 0.55 equiv. of water stirred for 24 h at room temperature (Scheme 2). Chromatographic purification of the reaction mixture gave (*S*)-1-(α-naphthyl) glycidyl ether (**4**) in 45% yield {$[\alpha]_D = +30.1^\circ$ ($c = 1.5$, MeOH); lit.[9] $[\alpha]_D = +31.4^\circ$ ($c = 1.5$, MeOH)} and (*R*)-1-(α-naphthyl) glycerol (**5**) in 45% yield {$[\alpha]_D = -5.2^\circ$ ($c = 0.7$, EtOH); lit.[10] $[\alpha]_D = -4.9^\circ$ ($c = 0.7$, EtOH)} as a light yellow solid (mp 108 °C, lit.[10] 108–109 °C).

Piperizine derivative, 1-(2-methoxyphenyl)piperizine (**8**) was obtained from the coupling of *O*-anisidine and bis(2-chloroethyl) amine hydrochloride (**7**), which was prepared from diethanolamine (**6**) (Scheme 3). (*S*)-epoxide (**4**) was treated with pi-



Scheme 3. a) $SOCl_2$, benzene, reflux, 5 h, 74%; b) *O*-Anisidine, aq. $NaHCO_3$, 100 °C, 24 h, 85%; c) **5**, ^{i}PrOH, reflux, 30 h, 93%.



Scheme 4. a) DEAD, TPP, benzene, reflux, 24 h, 87%; b) **8**, ^{i}PrOH, reflux, 30 h, 90%.

perizine derivative (**8**) in ^{i}PrOH under reflux condition to afford the (*S*)-naftopidil (**9**) in 93% yield {$[\alpha]_D = +3.8^\circ$ ($c = 1.5$, MeOH)} as a light yellow solid (mp 127 °C).[11]

Subsequently, diol (**5**) was subjected to Mitsunobu invertion with DEAD and Ph_3P in bezene under reflux to afford the (*R*)-1-(naphthyl) glycidyl ether (**10**) {$[\alpha]_D = -33.2^\circ$ ($c = 1.5$, MeOH); lit.[9] $[\alpha]_D = -33.9^\circ$ ($c = 1.55$, MeOH)}. (*R*)-epoxide on treatment with piperizine derivative (**8**) in ^{i}PrOH under reflux gave the (*R*)-naftopidil (**11**) in 90% yield {$[\alpha]_D = -3.94^\circ$ ($c = 1.5$, MeOH)} as a light yellow solid (mp 127–128 °C) (Scheme 4).

The pharmacokinetic findings suggest that in ten patients (9M/1F) with severe hepatic impairment or evidence for marked changes in hepatic blood flow the dose of naftopidil may require adjustment to the lower end of the therapeutic range and/or may be limited to once daily.[12] In conclusion, it is pertinent to mention that first optically pure (*S*)- and (*R*)-naftopidil was synthesized utilizing Jacobsen's HKR method for the resolution of racemic (α-naphthyl) glycidyl ether. This will promote the investigation of their pharmacokinetics as individual molecular entities and will be reported soon.

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11 (*S*)-Naftopidil (**9**), mp: 127 °C. $[\alpha]_D = +3.8^\circ$ ($c = 1.5$, MeOH). IR: 3450, 3020, 2980, 2920, 1230 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22–8.18 (dd, $J = 2.3$, 7.1 Hz, 1H); 7.8–7.74 (dd, $J = 2.3$, 7.1 Hz, 1H); 7.5–6.74 (m, 9H); 4.22–4.03 (m, 5H); 3.9 (s, 3H); 3.58–3.17 (m, 9H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 154.51; 154.33; 138.19; 134.36; 127.33; 126.26; 125.74; 125.49; 125.29; 125.05; 124.06; 121.85; 121.1; 120.36; 111.79; 104.8; 70.12; 68.38; 61.73; 57.99; 55.31; 51.26; 44.58; 42.51. EIMS: 329 (M^+).
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