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Stereoselective synthesis of the (R)- and (S)-1-(2-amino-3-nitrophenoxy)-3-(tert-butylamino)-2-propanol from the enantiomeric glycidyl tosylates

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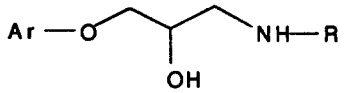
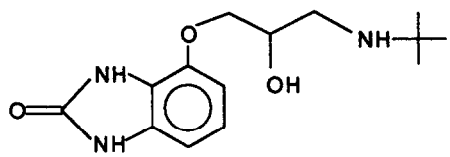
Abstract : The preparation of both enantiomers of 1-(2-amino-3-nitrophenoxy)-3-(tert-butylamino)-2-propanol from the enantiomeric glycidyl tosylates is described.

Many analogues of the 3-aryloxy-1-(alkylamino)-2-propanol type (Scheme I) have been prepared and some presented highly active β-adrenergic blocking properties[1,2]. The absolute configuration of these molecules is extremely important in the determination of pharmacological properties. The β-adrenergic blocking activity often resides in the (S)-(-)-isomers[3,4].



aryloxypropanolamine type



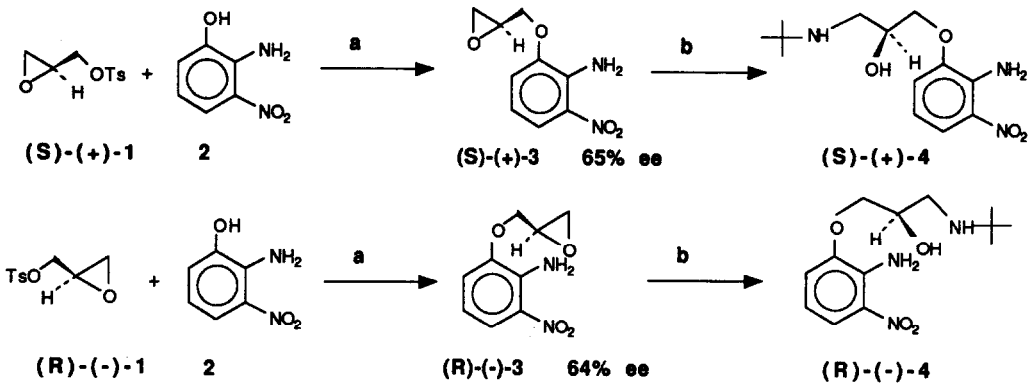
CGP 12177

SCHEME I

4-(3-tert-butylamino-2-hydroxypropoxy)-benzimidazol-2-one (CGP 12177) was shown to binds to β-adrenergic receptors[5]. Racemic CGP 12177 has been already labelled[6] with Carbon-11 (β^+ emittor, half life = 20.4 mn) for Positron Emission Tomography studies[7], but optically active molecules are desired. In order to label the enantiomers with Carbon-11 Phosgene, 1-(2,3-diaminophenoxy)-3-(tert-butylamino)-2-propanol is the starting material.

In this paper, we utilized the enantiomeric glycidyl tosylates 1[8] previously used by Sharpless[9], in the synthesis of both enantiomers of 1-(2-amino-3-

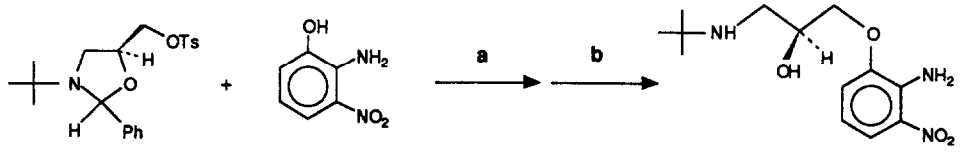
nitrophenoxy)-3-(tert-butylamino)-2-propanol **4**[10], which are the precursors of the (R)-and (S)-isomers of CGP 12177.



a) K_2CO_3 / acetone / reflux / 18 h b) tert-butylamine / EtOH / 6h

SCHEME II

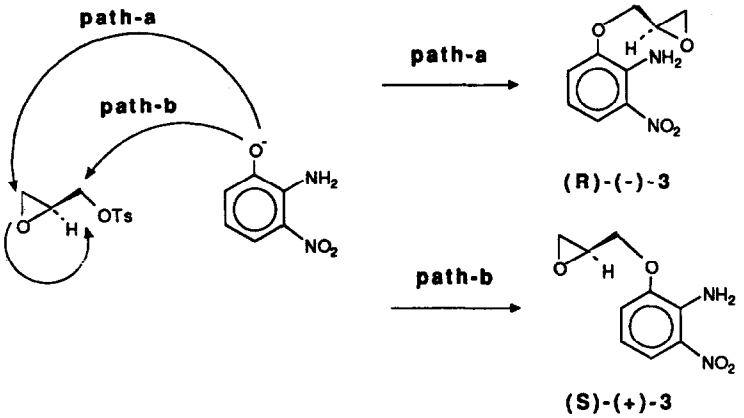
When an acetone solution containing **2** (1 equivalent), K_2CO_3 (1 equivalent) and S-(+)-**1** (2 equivalents) was heated under reflux for 18 h, the epoxyde S-(+)-**3**[11] was obtained in 80% yield with 65% ee[12]. Reaction of crude (S)-(+)-**3** with tert-butylamine (10 equivalents) in ethanol at room temperature for 6 hours gave the corresponding aryloxypropanolamine (S)-(+)-**4**[13] in 82% yield after crystallisation from diethyl ether. This compound is easily recrystallized to an enantiomeric purity of 92%[14]. This approach could be used to prepare both isomers of **4** from the enantiomeric glycidyl tosylates **1**.



a) NaH / DMF b) aq. HCl

SCHEME III

The absolute configuration of **3** was established by the reaction with tert-butylamine to give **4**, which was then compared with chirally pure (S)-(+)-**4**[15] synthesized from (S)-**5**[16] (Scheme III). Therefore the (S) configuration was assigned to C_2 of **3** and **4** derived from (S)-(+)-**1**.



SCHEME IV

The relatively low optical purity resulted from the competition of the nucleophilic attack of glycidyl tosylate by the 2-amino-3-nitrophenoxide ion (Scheme IV). Under the acetone-K_2CO_3 conditions, path b was favorised at 80%.

The rotation signs of the enantiomers formed (S)-(+)-**4** and (R)-(-)-**4** are the opposite of those normally associated with aryloxypropanolamine. After reduction of (S)-(+)-**4** to (S)-(+)-1-(2,3-diaminophenoxy)-3-(tert-butylamino)-2-propanol, (S)-(-)-CGP 12177 was obtained by reaction of phosgene on this diamino precursor. Research in this area is in progress in our laboratories.

References and Notes

1. M.E. Connolly, F. Kersting, C.T. Dollery, Prog. Cardiovasc. Dis., 1976,*19*, 203.
2. A.F. Crowther, R. Howe, B.J. MacLaughin, K.B. Mallion, B.S. Rao, L.H. Smith, R.W. Turner, J. Med. Chem., 1972, *15*, 260.
3. B.K. Wasson, W.K. Gibson, R.S. Stuart, H.W.R. Williams, C.H. Yates, J. Med. Chem., 1972,*15*, 651.
4. M.E. Jung, T.J. Shaw, J. Am. Chem. Soc., 1980, *102*, 6304.
5. M. Staehelin, P. Simon, K. Jaeggi, N. Wigger, J. Biol. Chem., 1983, *258*, 3496.
6. C. Boullais, C. Crouzel, A. Syrota, J. Label. Compounds Radiopharm., 1986, *5*, 565.
7. A. Syrota, Int. J. Microcirc.: Clin. Exp., 1989, *8*, 411.
8. (R)-(-)- and (S)-(+)-1 were from Aldrich.
9. J.M. Klunder, S.Y. Ko, K.B. Sharpless, J. Org. Chem., 1986, *51*, 3710.

10. **4** is more stable that 1-(2,3-diaminophenoxy)-3-(tert-butylamino)-2-propanol which is obtain by reduction of **4** and directly use for synthesis of CGP 12177.
11. ^{1}H NMR ($CDCl_3$) δ 2.7 (m,1H), 3.0 (t, 1H, J=3 Hz), 3.4 (m, 1H), 4.0 (m, 1H), 4.4 (dd, 1H, J=9 Hz, 2 Hz), 6.2-6.5 (m, 2H), 6.6 (ABt, 1H, J=8 Hz), 6.9 (d, 1H, J=8 Hz), 7.8 (d, 1H, J=8 Hz).
12. The ee was determined by an examination of the ^{1}H NMR spectra of **3** in the presence of a chiral shift reagent, Eu(hfbc)$_3$.
13. mp 62-64 °C; ^{1}H NMR ($CDCl_3$) δ 1.1 (s, 9H), 2.3-2.5 (m, 2H), 2.6 (m, 1H), 2.9 (m, 1H), 4.0 (m, 3H), 6.5-6.6 (m, 3H), 6.9 (d, 1H, J=8 Hz), 7.7 (d, 1H, J=8 Hz); $[\alpha]_D^{20}$= +14.0 (c=1, CH_3OH).
14. $[\alpha]_D^{20}$= +20.5 (c= 1, CH_3OH) compared with chirally pure (S)-(+)-**4** ($[\alpha]_D^{20}$= +22.5 (c= 1.2, CH_3OH)) synthesized from (S)-**5**.
15. mp 61-63 °C, $[\alpha]_D^{20}$= +22.5 (c= 1.2, CH_3OH).
16. J.J. Baldwin, R. Hirschmann, P.K. Lumma, W.C.Jr. Lumma, G.S. Ponticello, C.S. Sweet, A. Scriabine, J. Med. Chem., 1977, *20*, 1024.