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A new enzymatic approach to (*R*)-Tamsulosin hydrochloride

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Abstract—An enantioselective baker's yeast mediated approach to the pharmacologically active (*R*)-enantiomer of Tamsulosin hydrochloride is reported.

1. Introduction

Nine of the top 10 drugs contain a chiral active ingredient, and for six of them this ingredient is a single enantiomer small molecule.[1] The demand of enantiopure chiral intermediates as well as finished products for pharmaceutical applications is growing rapidly. A typical target value for the enantiomeric purity is 99.5%.[2] High values of enantio- and diastereoselectivity can be reached by biocatalytic processes.[3] Furthermore, rapid screening and optimisation of enzymatic activity, along with available, easy-to-use enzymes are now making biocatalysis a handy tool for chiral synthesis.

Tamsulosin hydrochloride (*R*)-**1**·HCl is the international non-proprietary name of (−)-(*R*)-5-[2-[[2-(*o*-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride (Scheme 1), and is employed in the symptomatic treatment of benign prostatic hyperplasia. It was first developed by Yamanouchi Pharmaceuticals[4] and is currently marketed as a single enantiomer. The preparation of (*R*)-**1**,[4,5] is based on the reaction of (*R*)-**2** with an *o*-ethoxyphenoxy derivative, that is, compounds **3**,[4b,c,5b] or **4**.[5a] Intermediate (*R*)-**2** could be prepared by functionalisation of amine (*R*)-**5**[4b,c,5a] or by the reaction of ketone **6** with amine (*R*)-**7**,[5b] followed by imine reduction and concomitant debenzylation. Amine (*R*)-**2** was also prepared by the classical resolution of the corresponding racemic mixture by employing tartaric acid as the resolving agent.[6] Classical resolution of racemic Tamsulosin was attempted using (+)-camphor-10-sulfonic acid.[7]

Recently, an enzymatic approach was patented:[8] derivative (*R*)-**8** was obtained by lipase-mediated esterification of racemic **5** with ethyl chloroacetate. Reaction of (*R*)-**8** first with chlorosulfonic acid, then with NH_4OH, gave intermediate (*R*)-**9**. This latter was treated with the potassium salt of 2-ethoxyphenol, followed by $NaBH_4$–$BF_3{\cdot}Et_2O$ reduction, to afford (*R*)-**1**.

Most of the known synthetic sequences to (*R*)-**1** make use of amine **5**, which is actually *p*-methoxyamphetamine. This latter compound is included in the Green List[9] of psychotropic substances under international control, compiled by the International Narcotics Control Board (INCB). We have devised a synthetic approach to pharmacologically active (*R*)-**1**, which does not involve the manipulation of amine **5**, and which is based on an enantioselective biocatalysed reaction. We report herein on this new synthetic route.

2. Results and discussion

According to our previous experience,[10] incubation of anisaldehyde with very actively fermenting baker's yeast, in the presence of glucose, yielded after 72 h a 7:3 mixture of anisic alcohol, and of diol **10** (Scheme 2). Extraction of the reaction mixture with hexane allowed the removal of most of the anisic alcohol. Subsequent extraction with ethyl acetate gave a residue from which diol (1*R*,2*S*)-**10** could be recovered by crystallisation from hexane. The relative stereochemistry of diol **10** was assigned on the basis of ^1H NMR spectroscopy,[11] and the absolute configuration is known.[11c] Hydrogenolysis of (1*R*,2*S*)-**10** gave alcohol (*S*)-**11** (ee >99% by chiral GC of the corresponding acetate). We could obtain this alcohol also by baker's yeast reduction[12] of ketone **12**: after 72 h incubation time we could

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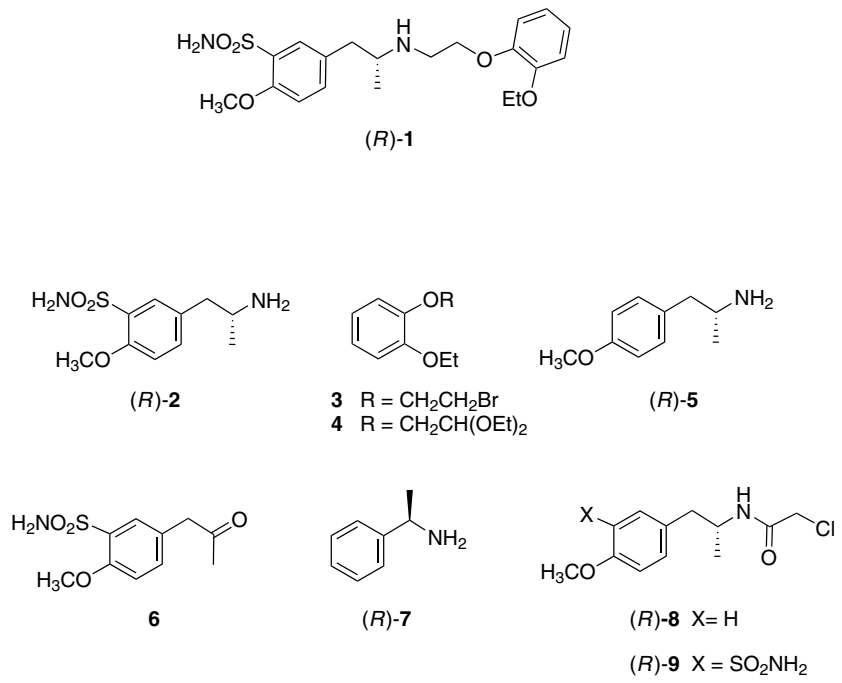
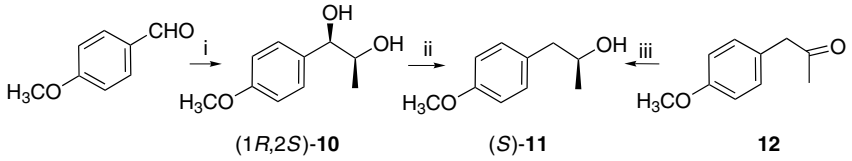


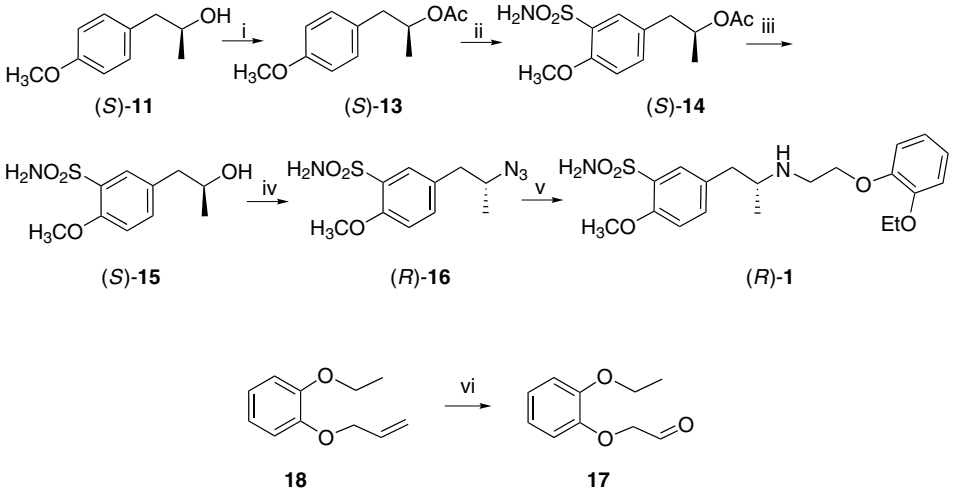
Scheme 1.



Scheme 2. Reagents and conditions: (i) baker's yeast, glucose, water, rt, 72 h; (ii) H_2, Pd/C, $HClO_4$, EtOH; (iii) baker's yeast, glucose, water, rt, 72 h.

recover alcohol (*S*)-**11** in 27% yield showing ee = 98% (chiral GC of the corresponding acetate).

Alcohol (*S*)-**11** was converted into acetyl derivative (*S*)-**13** (Scheme 3), and treated first with chlorosulfonic acid, then with ammonium hydroxide in THF. Acetate (*S*)-**14** was recovered, and hydrolysed to afford alcohol (*S*)-**15**. Treatment with mesyl chloride in pyridine, and reaction with sodium azide in DMF gave azide (*R*)-**16**. Hydrogenation of the azide group, imine formation by the reaction with alde-



Scheme 3. Reagents and conditions: (i) Ac_2O, pyridine; (ii) $ClSO_3H$; then NH_4OH in THF; (iii) KOH, MeOH; (iv) CH_3SO_2Cl, pyridine; then NaN_3 in DMF; (v) H_2, Pd/C, EtOH and aldehyde **17**; (vi) O_3, MeOH–CH_2Cl_2; then $NaBH_4$.

hyde **17** and imine reduction were conducted one pot in the same reaction vessel.

Aldehyde **17** was obtained by ozonolysis of derivative **18**, prepared by reaction of the sodium salt of *o*-ethoxyphenol with allyl bromide. After the final workup the hydrochloride of enantiopure (*R*)-**1** was recovered.

3. Conclusions

A simple approach to Tamsulosin hydrochloride **1** is reported. No hallucinogen substances were involved and high enantiomeric purity was obtained by means of a baker's yeast-mediated reaction. The optically active key intermediate (*S*)-**11** (ee >99%) could be synthesised by hydrogenolysis of diol **10**, prepared in turn by an enantioselective bio-catalysed reaction. Alcohol (*S*)-**11** was also accessible in 98% ee by baker's yeast reduction of ketone **12**. Crystalline diol **10** could be isolated and purified very easily without the use of column chromatography. The method shows great advantages for a practical application: it combines highly stereoselective baker's yeast-mediated reactions with unexceptional organic synthesis procedures, to afford the pharmacologically active enantiomer of Tamsulosin.

4. Experimental

4.1. General

GC–MS analyses were performed on a HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 μm). The following temperature program was employed: 60° (1 min)/6°/min/150° (1 min)/12°/min/280° (5 min). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer (400 MHz ^{1}H, 100.6 MHz ^{13}C), in $CDCl_3$ solution at rt unless otherwise stated, using TMS as an internal standard; *J* values are given in Hertz. All the chromatographic separations were carried out on silica gel columns. Chiral GC: DANI-HT-86.10 gas chromatograph; enantiomer excesses determined on a Chirasil-DEX-CB column with the following temp. program; 50 °C (3 min)–3.5 °C/min–180 °C (5 min); t_R in min (*S*)-**13**-t_R = 22.89 min, (*R*)-**13**-t_R = 23.32 min. Optical rotations were measured on a Dr. Kernchen Propol digital automatic polarimeter. The ESI spectrum was acquired on a Bruker Esquire 3000 plus instrument. Ketone **12** was prepared by Dakin West reaction starting from 4-methoxyphenyl acetic acid according to Ref. 13.

4.2. (1*R*,2*S*)-1-(4-Methoxyphenyl)propane-1,2-diol (1*R*,2*S*)-10

Anisaldehyde (50.0 g, 0.368 mol) was added in ethanolic solution (50 mL) to a suspension of fermenting baker's yeast (500 g) in tap water (1.5 L), in the presence of glucose (200 g). The reaction was stirred at room temperature for 72 h, to give a final 7:3 mixture of anisic alcohol and diol **10**. After the addition of acetone (500 mL), a first extraction with hexane allowed the recovery of most anisic alcohol (26.3 g, 52%). Ethyl acetate extraction, performed after filtration on a Celite pad, gave a residue from which compound (1*R*,2*S*)-**10** was obtained as a white solid (16.1 g, 21%) by crystallisation from hexane: mp 98 °C; $[\alpha]_D^{24} = -26.7$ (*c* 1.0, $CHCl_3$) [lit.[11c] for (1*R*,2*S*)-**10** ee = 98% $[\alpha]_D = -26.2$ (*c* 1.30, $CHCl_3$); Ref. 10 $[\alpha]_D = -22.4$ (*c* 1.0, EtOH)]; ^{1}H NMR[11] (400 MHz, $CDCl_3$): δ 7.28 (d, 2H, $J = 8.6$ Hz, aromatic hydrogens), 6.90 (d, 2H, 8.6 Hz, aromatic hydrogens), 4.59 (d, 1H, $J = 4.6$ Hz, Ar*CH*OH), 3.98 (m, 1H, CH_3*CH*OH), 3.81 (s, 3H, OCH_3), 1.10 (3H, d, $J = 6.2$ Hz, *CH*$_3$CH); ^{13}C NMR[11a,1b] (100.6 MHz, $CDCl_3$): δ 159.1, 132.5, 127.8, 113.6, 77.1, 71.2, 55.7, 17.2.

4.3. (*S*)-1-(4-Methoxyphenyl)propan-2-ol (*S*)-11

Compound (1*R*,2*S*)-**10** (15.9 g, 0.087 mol) was treated with H_2 at atmospheric pressure and room temperature, in ethanol (100 mL) in the presence of $HClO_4$ (1 mL), using Pd/C 5% (0.800 g) as a catalyst. After the usual workup, the crude product was purified by column chromatography on a silica gel column (hexane/AcOEt 9:1) to afford (*S*)-**11** (12.5 g, 86%): ee >99% (chiral GC of the corresponding acetate); $[\alpha]_D^{24} = +32.6$ (*c* 1.1, $CHCl_3$) [Ref. 12a ee = 95%, $[\alpha]_D = +27$ (*c* 4.4; $CHCl_3$); Ref. 12b ee = 94%, $[\alpha]_D = +30.9$ (*c* 1, $CHCl_3$)]; ^{1}H NMR[12] (400 MHz, $CDCl_3$): δ 7.12 (d, 2H, $J = 8.7$ Hz, aromatic hydrogens), 6.85 (d, 2H, 8.6 Hz, aromatic hydrogens), 3.97 (m, 1H, *CH*OH), 3.79 (s, 3H, OCH_3), 2.73 (dd, 1H, $J = 13.5$, 4.8 Hz, Ar*CH*), 2.62 (dd, 1H $J = 13.5$, 7.9 Hz, Ar*CH*), 1.22 (3H, d, $J = 6.2$ Hz, *CH*$_3$CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 157.8, 130.4, 130.0, 113.6, 68.6, 54.9, 44.5, 22.3; GC–MS: $t_R = 15.62$ min, *m*/*z* (%) 166 (M^+, 18), 121 (100), 107 (10). Compound (*S*)-**11** (1.36 g, 27%) was also obtained by baker's yeast[12a] (50 g) incubation (72 h, rt) of ketone **12** (5.00 g, 0.030 mol) in the presence of glucose in tap water. After the usual workup alcohol (*S*)-**11** was recovered with ee = 98% (chiral GC of the corresponding acetate).

4.4. (*S*)-1-(4-Methoxyphenyl)propan-2-yl acetate (*S*)-13

Alcohol (*S*)-**11** (12.3 g, 0.074 mol) was treated with acetic anhydride (20 mL) in pyridine solution (30 mL). After the usual workup, acetate (*S*)-**13** was recovered by column chromatography, eluting with hexane–ethyl acetate 9:1 (13.8 g, 90%): ee >99% (chiral GC); $[\alpha]_D^{24} = +7.5$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (m, 2H, aromatic hydrogens), 6.82 (m, 2H, aromatic hydrogens), 5.06 (m, 1H, *CH*OAc), 3.78 (s, 3H, OCH_3), 2.85 (dd, 1H, $J = 13.8$, 6.5 Hz, Ar*CH*), 2.69 (dd, 1H, $J = 13.8$, 6.5 Hz, Ar*CH*), 1.99 (s, 3H, OAc), 1.20 (3H, d, $J = 6.2$ Hz, *CH*$_3$CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.3, 158.2, 130.2, 129.6, 113.6, 71.5, 55.0, 41.2, 21.1, 19.2; GC–MS: $t_R = 18.53$ min, *m*/*z* (%) 208, (M^+, 2), 148 (100), 121 (81).

4.5. (*S*)-1-(3-(Chlorosulfonyl)-4-methoxyphenyl)propan-2-yl acetate

Compound (*S*)-**13** (13.5 g, 0.065 mol) was added to chlorosulfonic acid (80 g) at −10 °C. The reaction mixture was stirred at 0 °C for 1 h, then poured into ice water, and extracted with ethyl acetate. The organic phase was washed

with a saturated aqueous sodium hydrogen carbonate solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was employed without any further purification (16.9 g, 85%) (chemical purity by GC–MS 94%): $[\alpha]_D^{24} = +2.7$ (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, 1H, $J = 2.1$ Hz, H–C(2) aromatic), δ 7.51 (dd, 1H, $J = 8.3$, 2.1 Hz, H–C(6) aromatic), 7.05 (d, 1H, $J = 8.3$ Hz, H–C(5) aromatic), 5.07 (m, 1H, *CH*OAc), 4.04 (s, 3H, OCH_3), 2.88 (dd, 1H, $J = 13.9$, 7.2 Hz, Ar*CH*), 2.80 (dd, 1H, $J = 13.9$, 5.5 Hz, Ar*CH*), 1.98 (s, 3H, CH_3COO), 1.21 (3H, d, $J = 6.2$ Hz, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): 170.2, 155.9, 137.9, 131.5, 130.3, 130.0, 113.2, 70.6, 56.5, 40.8, 21.0, 19.4. GC–MS: $t_R = 25.44$ min, *m*/*z* (%) 271 (M^+-35, 7), 246 (100), 219 (15), 148 (23), 90 (38).

4.6. (*S*)-1-(4-Methoxy-3-sulfamoylphenyl)propan-2-yl acetate (*S*)-14

Chlorosulfonyl compound (16.5 g, 0.054 mol) was dissolved in THF (50 mL), and a concentrated aqueous ammonia solution (200 mL) was added. The mixture was stirred at room temperature for 1 h, then diluted with water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), and the residue was crystallised from methanol to give compound (*S*)-**14** (12.2 g, 79%): mp 94 °C; $[\alpha]_D^{24} = +7.6$ (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, 1H, $J = 2.1$ Hz, H–C(2) aromatic), 7.36 (dd, 1H, $J = 8.6$, 2.1 Hz, H–C(6) aromatic), 6.98 (d, 1H, $J = 8.6$ Hz, H–C(5) aromatic), 5.20 (br s, 2H, NH_2), 5.04 (m, 1H, *CH*OAc), 3.99 (s, 3H, OCH_3), 2.86 (dd, 1H, $J = 14.2$, 7.3 Hz, Ar*CH*), 2.75 (dd, 1H, $J = 14.2$, 5.5 Hz, Ar*CH*), 1.98 (s, 3H, CH_3COO), 1.21 (3H, d, $J = 6.2$ Hz, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.5, 154.6, 134.9, 130.1, 129.8, 128.9, 112.2, 71.0, 56.4, 40.9, 21.0, 19.3. GC–MS: $t_R = 26.96$ min, *m*/*z* (%) 227 (M^+-60, 100), 200 (17), 120 (20), 90 (25). Anal. Calcd for $C_{12}H_{17}NO_5S$: C, 50.16; H, 5.96; N, 4.87; S, 11.16. Found: C, 50.21; H, 5.89; N, 4.81; S, 11.09.

4.7. (*S*)-5-(2-Hydroxypropyl)-2-methoxybenzenesulfonamide (*S*)-15

Compound (*S*)-**14** (12.0 g, 0.042 mol) was treated with KOH (3.51 g, 0.062 mol) in methanol (50 mL). After the usual workup, compound (*S*)-**15** was obtained as a white solid (9.36 g, 91%); mp 168–170 °C; $[\alpha]_D = +24.1$ (*c* 1, MeOH); ^1H NMR (400 MHz, DMSO-d_6): δ 7.57 (d, 1H, $J = 2.0$ Hz, H–C(2) aromatic), 7.37 (dd, 1H, $J = 8.2$, 2.1 Hz, H–C(6) aromatic), 7.09 (d, 1H, $J = 8.2$ Hz, H–C(5) aromatic), 6.95 (br s, 2H, NH_2), 4.52 (d, 1H, $J = 4.5$ Hz, OH), 3.87 (s, 3H, OCH_3), 3.78 (m, 1H, *CH*OH), 2.63 (dd, 1H, $J = 13.7$, 6.5, Ar*CH*), 2.58 (dd, 1H, $J = 13.7$, 6.1 Hz, Ar*CH*), 1.04 (3H, d, $J = 6.2$ Hz, CH_3CH); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 154.2, 134.4, 131.1, 130.7, 128.1, 112.3, 67.1, 56.0, 43.9, 22.9; GC–MS: $t_R = 26.45$ min, *m*/*z* (%) 245 (M^+, 5), 200 (22), 120 (100), 90 (85). Anal. Calcd for $C_{10}H_{15}NO_4S$: C, 48.97; H, 6.16; N, 5.71; S, 13.07. Found: C, 49.05; H, 6.23; N, 5.80; S, 13.15.

4.8. (*S*)-1-(4-Methoxy-3-sulfamoylphenyl)propan-2-yl methanesulfonate

Compound (*S*)-**15** (9.20 g, 0.037 mol) was dissolved in pyridine (30 mL) and methanesulfonyl chloride (5.48 g, 0.0481 mol) was added at 0 °C. After 2 h at room temperature the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound (10.5 g, 88%) which was employed without any further purification (chemical purity by GC–MS 92%): $[\alpha]_D^{24} = +10.7$ (*c* 0.77, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 1H, $J = 2.4$ Hz, H–C(2) aromatic), 7.42 (dd, 1H, $J = 8.3$, 2.4 Hz, H–C(6) aromatic), 7.01 (d, 1H, $J = 8.3$ Hz, H–C(5) aromatic), 5.14 (br s, 2H, NH_2), 4.92 (m, 1H, *CH*OSO_2), 4.00 (s, 3H, OCH_3), 2.99 (dd, 1H, $J = 14.2$, 7.2 Hz, Ar*CH*), 2.92 (dd, 1H, $J = 14.2$, 5.2 Hz, Ar*CH*), 2.81 (s, 1H, OSO_2CH_3), 1.43 (3H, d, $J = 6.6$ Hz, CH_3CH); GC–MS: $t_R = 28.12$ min, *m*/*z* (%) 228 (M^+-95, 100), 200 (50), 148 (37).

4.9. (*R*)-5-(2-Azidopropyl)-2-methoxybenzenesulfonamide (*R*)-16

A solution of sodium azide (4.10 g, 0.063 mol) and of the mesyl derivative (10.2 g, 0.032 mol) in DMF (20 mL) was heated at 40 °C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. After column chromatography (hexane/ethyl acetate 7:3), compound (*R*)-**16** was recovered (5.44g, 63%): $[\alpha]_D^{24} = -26.4$ (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1H, $J = 2.4$ Hz, H–C(2) aromatic), 7.37 (dd, 1H, $J = 8.3$, 2.4 Hz, H–C(6) aromatic), 7.00 (d, 1H, $J = 8.3$ Hz, H–C(5) aromatic), 5.35 (br s, 2H, NH_2), 3.98 (s, 3H, OCH_3), 3.66 (m, 1H, *CH*N_3), 2.72 (m, 2H, ArCH_2), 1.25 (3H, d, $J = 6.6$ Hz, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 154.7, 134.9, 130.1, 129.8, 128.6, 112.2, 58.6, 56.3, 41.1, 18.8; GC–MS: $t_R = 27.13$ min, *m*/*z* (%) 270 (M^+, 1), 242 (93), 200 (71), 120 (90), 90 (100). Anal. Calcd for $C_{10}H_{14}N_4O_3S$: C, 44.43; H, 5.22; N, 20.73; S, 11.86. Found: C, 44.36; H, 5.15; N, 20.66; S, 11.94.

4.10. (*R*)-5-(2-(2-(2-Ethoxyphenoxy)ethylamino)propyl)-2-methoxybenzenesulfonamide hydrochloride (*R*)-1

A solution of azide (5.20 g, 0.019 mol) in ethanol (80 mL) was treated with H_2 in the presence of Pd/C (0.500 mg) as a catalyst. After 1 h at room temperature, the hydrogen flux was stopped and aldehyde **17** (5.07 g, 0.0285 mol) was added. The reaction mixture was stirred at room temperature for 1 h, then hydrogen was supplied again for 2 h. After the usual workup, the residue was treated with HCl ethanolic. The solid recovered by filtration was crystallised from methanol to give (*R*)-**1** HCl (2.30 g, 27%): mp 227–229 °C, $[\alpha]_D^{24} = -4.1$ (*c* 0.45, MeOH) [lit.[4b,c] $[\alpha]_D = -4.0$ (*c* 0.35, MeOH)]; ^1H NMR (400 MHz, DMSO-d_6): δ 7.64 (d, 1H, $J = 2.2$ Hz, aromatic), 7.45 (dd, 1H, $J = 8.4$, 2.2 Hz, aromatic), 7.18 (d, 1H, $J = 8.4$ Hz, aromatic), 7.07 (dd, $J = 8.0$, 1.6 Hz, aromatic), 7.04 (br s, 2H, SO_2NH_2), 7.03 (dd, $J = 8.0$, 1.6 Hz, aromatic), 6.97 (dt, $J = 7.8$, 1.7 Hz, aromatic), 6.90 (dt, $J = 7.8$, 1.7 Hz, aro-

matic), 4.31 (t, $J = 5.3$ Hz, OCH_2CH_2), 4.03 (q, $J = 7.0$ Hz, OCH_2CH_3), 3.89 (s, 3H, OCH_3), 3.54 (m, 1H, *CH*N), 3.41 (m, 2H, NCH_2), 3.30 (dd, 1H, $J = 13.2$, 3.5 Hz, ArCH), 2.70 (dd, 1H, $J = 13.2$, 10.8 Hz, ArCH), 1.27 (3H, d, $J = 6.9$ Hz, CH_3CH), 1.16 (d, 3H, $J = 6.5$ Hz, CH_3); ESI MS: m/z 409 (M^+(**1**)+1).

4.11. 1-(Allyloxy)-2-ethoxybenzene 18

To a suspension of NaH (60% dispersion in mineral oil, 13.2 g, 0.33 mol) in DMF (70 mL), a solution of *o*-ethoxyphenol (30.0 g, 0.22 mol) in DMF (20 mL) was added. After 30 min, allyl bromide (39.6 g, 0.33 mol) was added. After the usual workup, compound **18** could be recovered by column chromatography eluting with hexane–ethyl acetate 9:1 (27.1 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92–6.85 (m, 4H, aromatic), 6.08 (m, 1H, *CH*═), 5.40 (dmultiplet, $J = 17.3$ Hz, ═*CH*H), 5.26 (dmultiplet, $J = 10.8$ Hz, ═*CH*H), 4.59 (m, 2H, OCH_2CH═), 4.08 (q, 2H, $J = 6.9$ Hz, CH_2CH_3), 1.43 (t, 3H, $J = 6.9$ Hz, CH_2CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 149.0, 148.6, 133.6, 121.2, 120.8, 116.7, 114.7, 114.0, 69.8, 64.3, 14.6; GC–MS: $t_R = 14.26$ min, m/z (%) 178 (M^+, 42), 137 (28), 109 (100), 81 (30). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.21; H, 7.86.

4.12. 2-(2-Ethoxyphenoxy)acetaldehyde 17

Compound **17** (26.8 g, 0.150 mol) was treated with O_3 in a 2:1 CH_2Cl_2 solution (150 mL) at −78 °C. The reaction mixture was treated with $NaBH_4$. After the usual workup, aldehyde **17** was recovered, and was employed without any further purification (16.7 g, 62%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (t, 1H, $J = 1.4$ Hz, CHO), 7.03–6.83 (m, 4H, aromatic), 4.57 (m, 2H, OCH_2CHO), 4.12 (q, 2H, $J = 6.9$ Hz, CH_2CH_3), 1.45 (t, 3H, $J = 6.9$ Hz, CH_2CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 200.4, 149.6, 147.7, 123.0, 120.8, 116.1, 113.9, 93.3, 64.2, 14.6; GC–MS: $t_R = 14.26$ min, m/z (%) 180 (M^+, 100), 152 (20), 121 (50), 109 (90). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.58; H, 6.65.

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