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New Practical Synthesis of Tamsulosin

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ABSTRACT The medicine called Tamsulosin was produced 25 years ago and since then almost 10 new synthesis route has been known. Each process shows the researchers' workstyle, every year, which mainly differs in the way of separating the enantiomers. The applied reaction steps also reflect the development over the past 25 years and the new synthesis is influenced by the antecedents. The key-intermediate used in our new method is a racemic secondary amine derivative, which is unknown in the literature before and for resolving it, we worked out a quite advantegeous process. By using an optically active secondary amine, side reactions can be avoided. *Chirality 20:790–795, 2008.*

KEY WORDS: resolution; diastereomers; enantiomers; optically active amine

INTRODUCTION

Tamsulosin ***1*** (*R*-(−)-5-[2-[[2-(2-ethoxy)phenoxy)ethyl]-amino]propyl-2-methoxybenzene-sulfonamide] hydrochloride) (Scheme 1) is a well-known medicine for curing benignus prostata hyperplasia (BHP).[1]

The first synthesis (Scheme 2) of the optically active substance was achieved by the researchers of the Yamanouchi Pharma.[2]

Ten years later, *R*-(+)-α-methyl-benzylamine was used to form the chiral center by its reductive condensation with the key substance sulfamoyl acetone derivative ***2*** (Scheme 3).[3,4] The resulting two diastereomers were separated by fractional crystallization and they got the optically active amine ***3*** by hydrogenolysis of the desired diastereomer. In this reaction, the *R*-(+)-α-methyl-benzylamine used for the introduction of amino group and resolution was practically lost.

To get the final product, the amine ***3*** was reacted with a large excess of 2-(2-ethoxy-phenoxy)ethyl bromid.

Our aim was to develop a new way to obtain the (*R*-(−)-5-[2-[[2-(2-ethoxy)phenoxy)ethyl]amino]propyl-2-methoxybenzene-sulfonamide] hydrochloride) which is suitable for industrial reproduction and production (Scheme 4).

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 1000 spectrophotometer in KBr pellet with 4 cm^{-1} resolution. NMR spectra were recorded on a Varian ^{UNITYI}*NOVA* NMR spectrometer operating at 500 MHz (^{1}H) and 125 MHz (^{13}C) with a ^{1}H{^{13}C, ^{15}N} PFG 5 mm probe. Chemical shifts are given relative to TMS (δ_{TMS} = 0.00 ppm). Complete assigments were made by standard one- and two-dimensional NMR methods (1D: DPFGSENOE, 2D: PFG-HSQC, PFG-HMBC, and PFG-MQFCOSY). For quantitation of the enantiomeric purity by NMR, selective decoupling of the H-(8) proton was utilized with continuous low power pulse applied during acquisition. Control experiments were carried out to exclude the potential spill-over effects during decoupling. Sufficiently long relaxation delay (30 sec) was used to avoid distortion of the integral values over accumulation. All new compounds were analyzed correctly within 0.4% of theory for C, H, N, and S.

(±)-5-[2-(N-Benzylamino)propyl]-2-methoxy-benzenesulphonamide hydrochloride (±)4

In a 500-ml flask, 18 g (0.074 mol) of (4-methoxy-3-sulfamoylphenyl)acetone, 200 ml of methanol, and 7.92 (0.074 mol) of benzylamine were added. The mixture was refluxed for 2 h, cooled to 35–40°C and the mixture of 2.74 g (0.074 mol) of sodium borohydride in 30 ml methanol and 1 ml of 40% sodium hydroxide was added dropwise. The reaction mixture was stirred for 2 h at this temperature. After the reaction was over 100 ml of water was added and the methanol solvent was evaporated under reduced pressure. The residual aqueous solution was extracted one time with 40 ml and twice with 25 ml of methyl isobutylketone. The combined organic phases were dried over sodium sulfate. The filtrate was acidified with ethanolic hydrochloric acid to pH 1 (approximately 10 ml). The precipitated crystal suspension is stirred at 8–10°C for 30 min, filtered and washed with methyl isobutylketone and dried at 80°C to give 15.12 g (yield: 55.2%) of the title compound.

(Found: C, 54.99; H, 6.11; N, 7.41; S, 8.49. Calc for $C_{17}H_{23}ClN_2O_3S$ (370.90): C, 55.05; H, 6.25; N, 7.55; S, 8.65%).

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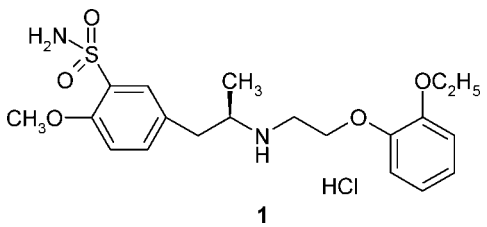

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Scheme 1. Tamsulosin *1* (*R*-(−)-5-[2-[[2-(2-ethoxy.phenoxy)-ethyl]-amino]-propyl-2-methoxy-benzene-sulfonamide] hydrochloride).

IR (KBr, cm^{-1}): 3211–2400, 3330, 3161, 1606, 1590, 1328, 1281, 1161, 755, 705, 700; ^1H NMR (DMSO-d_6, 500 MHz, TMS): 1.21 (d, J = 6.5 Hz, 3H, H_3-9); 2.76 (dd, J = 12.9, 10.4 Hz, 1H, H_x-7); 3.30–3.45 (m, 2H, (H_y-7, H-8); 3.90 (s, 3H, OCH_3); 4.17–4.30 (m, 2H, H_2-11); 7.07 (s, 2H, SO_2NH_2); 7.19 (d, J = 8.5 Hz, 1H, H-6); 7.40–7.48 (m, 4H, H_2-14, H-15, H-5); 7.61 (d, J = 2.3 Hz, 1H, H-3); 7.66–7.71 (m, 2H, H_2-13); 9.68 (br s, 2H, N(10)H*HCl); ^{13}C NMR (DMSO-*d*6, 125 MHz, TMS): 14.8 (C-9), 37.1 (C-7), 47.2 (C-11), 54.5 (C-8), 56.1 (OCH_3), 112.9 (C-6), 128.0 (C-3), 128.3 (C-4), 128.5 (C-14), 128.7 (C-15), 130.0 (C-13), 131.2 (C-2), 132.3 (C-14), 134.4 (C-5), 154.8 (C-1).

*(R)-5-[2-(*N*-Benzylamino)propyl]-2-methoxy-benzenesulphonamide (−)4*

In a 500-ml flask, 18.5 g (0.05 mol) of (±)-5-[2-(*N*-benzyl-amino)propyl]-2-methoxy-benzenesulphonamide hydrochloride **(±)4** and 210 ml of methanol are added. The obtained suspension is warmed with stirring to 70°C. In another flask 9 g (0.024 mol) of dibenzoyl(d)tartaric acid monohydrate and 1.26 g (0.012 mol) of sodium carbonate are dissolved in 90 ml of water at 70°C and the mixture is poured to the methanol solution. The obtained suspension is dissolved quickly then allowed to cool to room temperature. The crystallization is started at 25°C and stirred for 48 h at 5–10°C. The diastereomer salt is filtered and recrystallized from the mixture of 120 ml methanol and water (2:1). The hot solution is cooled to 5–10°C and stirred for an hour at this temperature. The precipitated crystals are filtered and washed with 10 ml of water, to give 16.8 g of the wet product.

The specific rotation of the dry product is $[\alpha]_D^{20} = -70°$ (c = 2-methanol).

The above wet product is suspended in 80 ml of water and then 80 ml of ethyl acetate and 7 ml of concentrated ammonium hydroxide are added. The mixture was stirred for dissolution. The phases are separated and the aqueous phase is extracted with 20 ml of ethyl acetate. The combined organic phases are dried over sodium sulfate, filtered and the solution is evaporated under reduced pressure. The residue is crystallized from isopropanol, filtered, dried to give 5.4 g (65% yield calculated on *R* enantiomer) of the title compound.

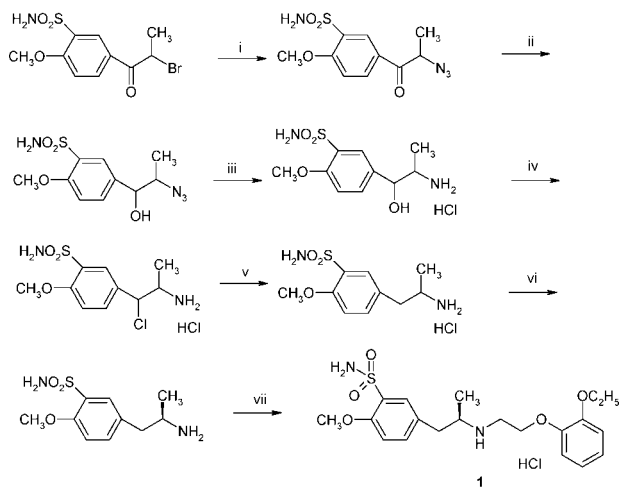
The melting point is 116–119°C, $[\alpha]_D^{20} = -21.4°$ (c = 2-methanol).

(Found: C, 61.19; H, 6.49; N, 8.24; S, 9.42 Calc for $C_{17}H_{22}N_2O_3S$ (334.44): C, 61.05; H, 6.62; N, 8.38; S, 9.59%).

IR (KBr, cm^{-1}): 3100–2500, 3330, 3195, 1604, 1326, 1257, 1159, 795, 745, 705; ^1H NMR (DMSO-d_6, 500 MHz, TMS): 0.93 (d, J = 6.1 Hz, 3H, H_3-9); 1.86 (br s, 1H, N(10)H); 2.45–2.52 (m, 1H, H_x-7); 2.72–2.81 (m, 3H, H_y-7, H-8); 3.72 (d, J = 13.9 Hz, 1H, H_x-11); 3.77 (d, J = 13.9 Hz, 2H, H_2-11); 3.87 (s, 3H, OCH_3); 6.98 (br s, 2H, SO_2NH_2); 7.09 (d, J = 8.5 Hz, 1H, H-6); 7.18–7.22 (m, 1H, H-15); 7.26–7.32 (m, 4H, H_2-13, H_2-14); 7.34 (dd, J = 8.5, 2.4 Hz, 1H, H-5); 7.56 (d, J = 2.4 Hz, 1H, H-3); ^{13}C NMR (DMSO-d_6, 125 MHz, TMS): 19.5 (C-9), 41.5 (C-7), 50.3 (C-11), 53.4 (C-8), 56.0 (OCH_3), 112.3 (C-6), 126.3 (C-15), 127.8 (C-13), 128.0 (C-14, C-3), 130.8 (C-4), 131.2 (C-2), 134.3 (C-5), 141.2 (C-12), 154.2 (C-1).

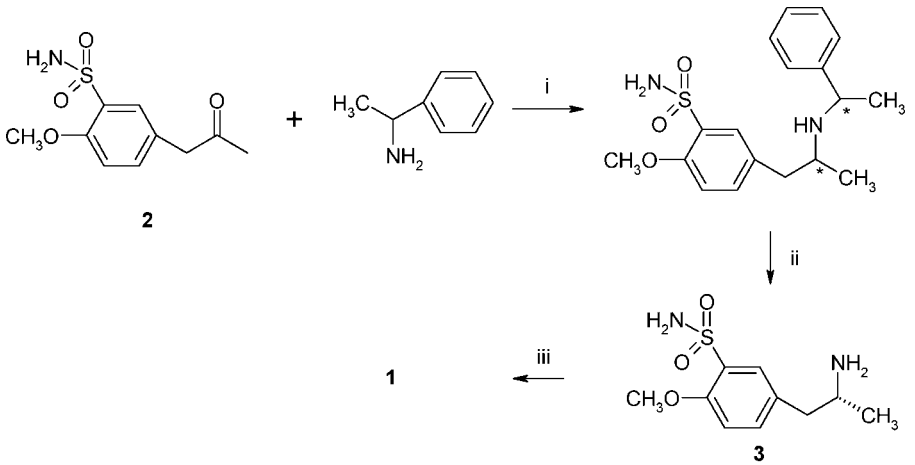
R-*5-[[2-[*N*-(2-Ethoxy-phenoxy)ethyl]-*N*-benzyl] amino]propyl-2-methoxy-benzenesulphonamide* 6

About 5.5 g (0.016 mol) of (*R*)-5-[2-(*N*-benzyl-amino)-propyl]-2-methoxy-benzenesulphonamide **(−)4,** 6.24 g (0.024 mol) of 5-ethoxy-1-(2-mesyloxyethyl)oxybenzene and 0.97 g (0.024 mol) of magnesium oxide are dissolved in 50 ml of xylene in a 250-ml flask. The mixture is refluxed for 37 h with intensive stirring. The reaction mixture is cooled to 20°C, the magnesium salts are filtered and washed twice with 5 ml of xylene. The combined xylene solution is washed twice with 10 ml of 1% aqueous acetic acid and then 80 ml of methanol is added. The mixture is cooled below 10°C and 80 ml of aqueous hydrochloric acid solution (74.5 ml of water and 5.5 ml of 10% hydrochloric acid) is added to adjust the pH 2–3. The phases are separated and the aqueous phase is washed with 10 ml of xylene. The aqueous phase is stirred with activated carbon at 20–25°C for half an hour, then filtered and washed with the mixture of 10 ml of methanol–water in the ratio of 1:1. Methanol is evaporated under reduced pressure and 75 ml of ethyl acetate is added to the aqueous residue. The solution is alkalified with 10% sodium hydroxide solution to pH 10 below 15°C. The phases are separated and the aqueous phase is extracted with 75 ml of ethyl acetate. The combined organic phases are washed with 40 ml of saturated sodium chloride solution and then with 40 ml of water. The solution is dried over sodium sulfate below



i:NaN_3; ii: reduction; iii: reduction; iv: $SOCl_2$; v: reduction; vi: optical resolution; vii: alkylation

Scheme 2. The first synthesis of Tamsulozin.



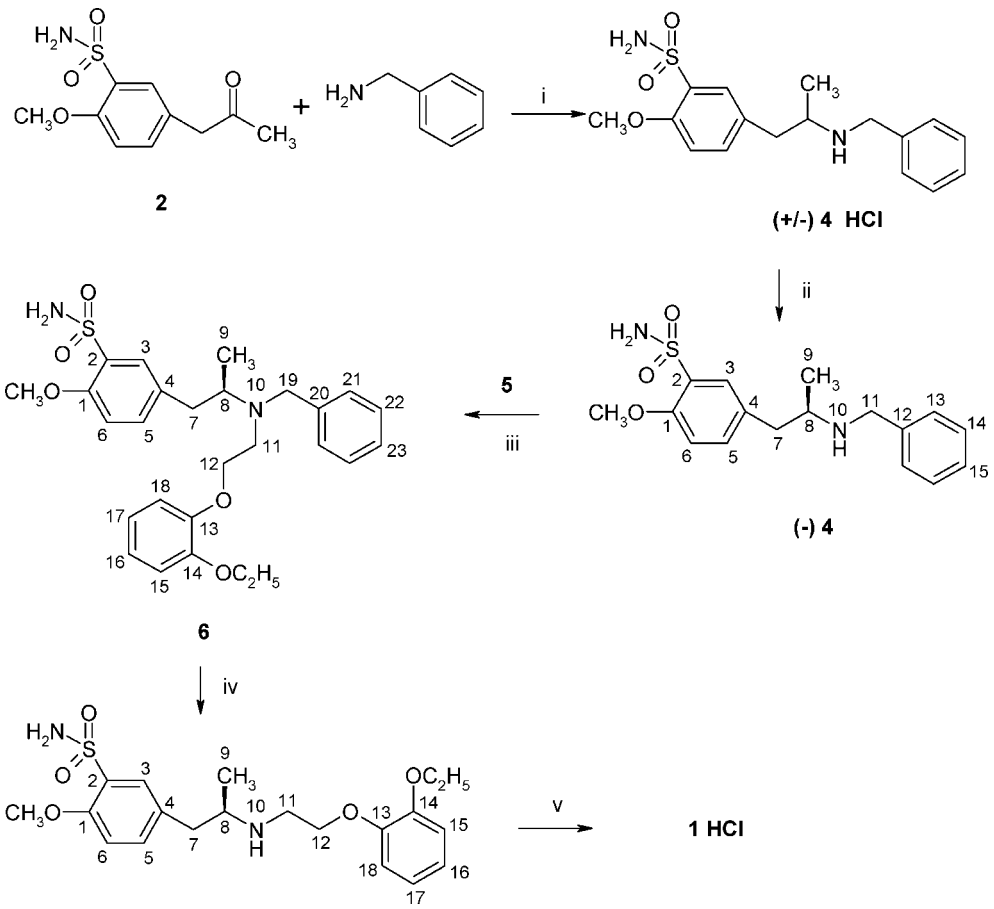
Scheme 3. An another procedure for synthesis of Tamsulozin using as key substance sulfamoyl aceton derivative 2.

15°C and filtered. The solution is evaporated under reduced pressure. The residue is crystallized from hexane, filtered off, and dried.

Yield: 5.1 g (63.9%).

The melting point is 65–68°C, $[\alpha]_D^{20} = -16.7^\circ$ (c = 1-methanol).

(Found: C, 64.89; H, 6.74; N, 5.46; S, 6.29 Calc for $C_{27}H_{34}N_2O_5S$ (498.61): C, 65.04; H, 6.87, N, 5.62; S, 6.43%).



Scheme 4. The rational synthesis, which is usable as an industrial process.

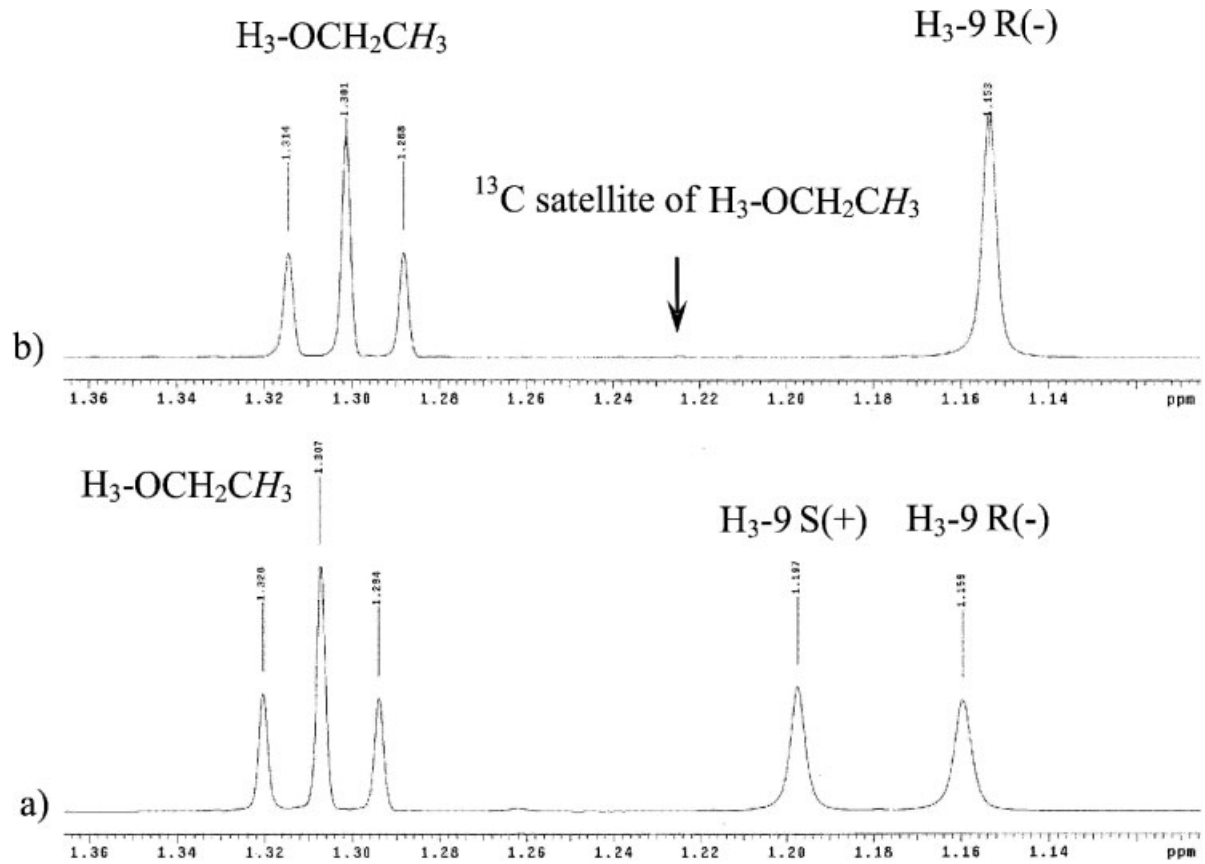


Fig. 1. Upfield region of the ^{1}H NMR spectrum of (**a**) racemic tamsulosin base, (**b**) pure *R*(−) tamsulosin base in the presence of Mosher acid as a chiral additive (^{1}H 500 MHz, CD_2Cl_2, 21°C). Chemical shift difference is observed on H_3-9 methyl signals due to the *R*(−) and *S*(+) enantiomers. The H_3-(9) signals show up as singlet due to selective spin decoupling of the H-(8) proton during acquisition.

IR (KBr, cm^{-1}): 3200–2400, 3365, 1606, 1474, 1347, 1279, 1256, 1165, 827, 753, 701; ^{1}H NMR (Pyridine-d_5, 500 MHz, TMS): 1.03 (d, J = 6.0 Hz, 3H, H_3-9); 1.27 (t, J = 7.2 Hz, 3H OCH_2CH_3); 2.52 (dd, J = 12.9, 9.1 Hz, 1H, H_x-7); 3.10–3.38 (br m, 4H, H_y-7, H_2-11, H-8); 3.73 (s, 3H, OCH_3); 3.97 (q, J = 7.2 Hz, 2H, (OCH_2CH_3); 3.92–4.15 (br m, 2H, H_2-19); 4.27 (br, 2H, H_2-12); 6.95 (d, J = 8.1 Hz, 1H, H-6); 6.95–7.04 (m, 4H, H-15, H-16, H-17, H-18); 7.28 (t, J = 7.5 Hz 1H, H-23); 7.35 (dd, J = 8.1, 2.1 Hz, 1H, H-5); 7.39 (t, J = 7.5 Hz, 2H, H_2-22); 7.60–7.70 (br m, 2H, H_2-21); 8.15 (d, J = 2.1 Hz, 1H, H-3); 8.40 (br s, 2H, H_2-SO_2NH_2); 13.03 (br s, 1H, HCl); ^{13}C NMR (Pyridine-d5, 125 MHz, TMS): 14.3 (C-9), 15.1 (OCH_2CH_3), 38.1 (C-7), 49.2 (C-11), 55.6 (C-19), 56.1 (OCH_3), 58.5 (C-8), 64.5 (OCH_2CH_3), 68.1 (C-12), 112.9 (C-6), 114.1*, 114.5* (C-15, C-18), 121.4*, 121.8* (C-17, C-16), 127.8 (C-23), 128.8 (C-22), 129.4 (C-3), 129.8 (C-21), 132.2 (C-4), 132.4 (C-2), 134.6 (C-5), 138.8 br (C-20), 149.2 (C-13), 149.6 (C-14), 155.3 (C-1). *, interchangeable assignments.

(R)-(−)-Tamsulosine HCl 1

To the 7.8 g (0,0156 mol) of *R*-***6***, 230-ml of methanol is added and hyrogenated in the presence of 1.4 g of palladium carbon. The catalyst is filtered, washed thrice with 10 ml of methanol and the filtrate is evaporated under reduced pressure. The residue is crystallized from 80 ml of ethyl acetate with 0.25 g of activated carbon. The solution is cooled to 0–5°C and stirred for 1 h. The precipitated crystals are filtered, washed with 5 ml of ethyl acetate and then recrystallized again from 70 ml of ethyl acetate. The solution is cooled to 0–5°C and stirred for 1 hour. The crystals are filtered, washed with 5 ml of ethyl acetate and dried. The above residue is dissolved in 46 ml of methanol at 60°C and 0.92 ml of concentrated hydrochloric acid is added dropwise. (pH 2–3). The crystallization starts already at 60°C, it is cooled to 0°C in 1 h and stirred for further 1 h.

The precipitated product is filtered and washed twice with 20 ml of 0°C methanol and dried to give 4.54 g (65.2%).

Melting point is: 234°C, $[\alpha]_D^{20} = -4.4°$ (c = 1-methanol).

IR (KBr, cm^{-1}): 3400–2300, 1610, 1590, 1506, 1338, 1160, 1250, 819, 749, 577; ^{1}H NMR (DMSO-d_6, 500 MHz, TMS): 1.20 (d, J = 6.5 Hz, 3H, H_3-9); 1.26 (t, J = 7.0 Hz, 3H, OCH_2CH_3); 2.76 (dd, J = 11.5, 12.5 Hz, 1H, H_x-7); 3.36-3.50 (m, 3H, H_y-7 and H_2-11); 3.50-3.64 (br m, 1H, H-8); 3.91 (s, 3H, OCH_3); 4.02 (q, J = 7.0 Hz, 2H, OCH_2CH_3); 4.39 (t, J = 5.5 Hz, 2H, H_2-12); 6.90 (td, J = 8.0, 2.0 Hz, 1H, H-17); 6.96 (td, J = 8.0, 1.5 Hz, 1H, H-16); 7.00 (dd, J = 8.0, 2.0 Hz, 1H, H-15); 7.06-7.14 (m, 3H, SO_2NH_2 and H-18]; 7.19 (d, J = 8.5 Hz, 1H, H-6); 7.47 (dd, J = 8.5, 2.0 Hz,

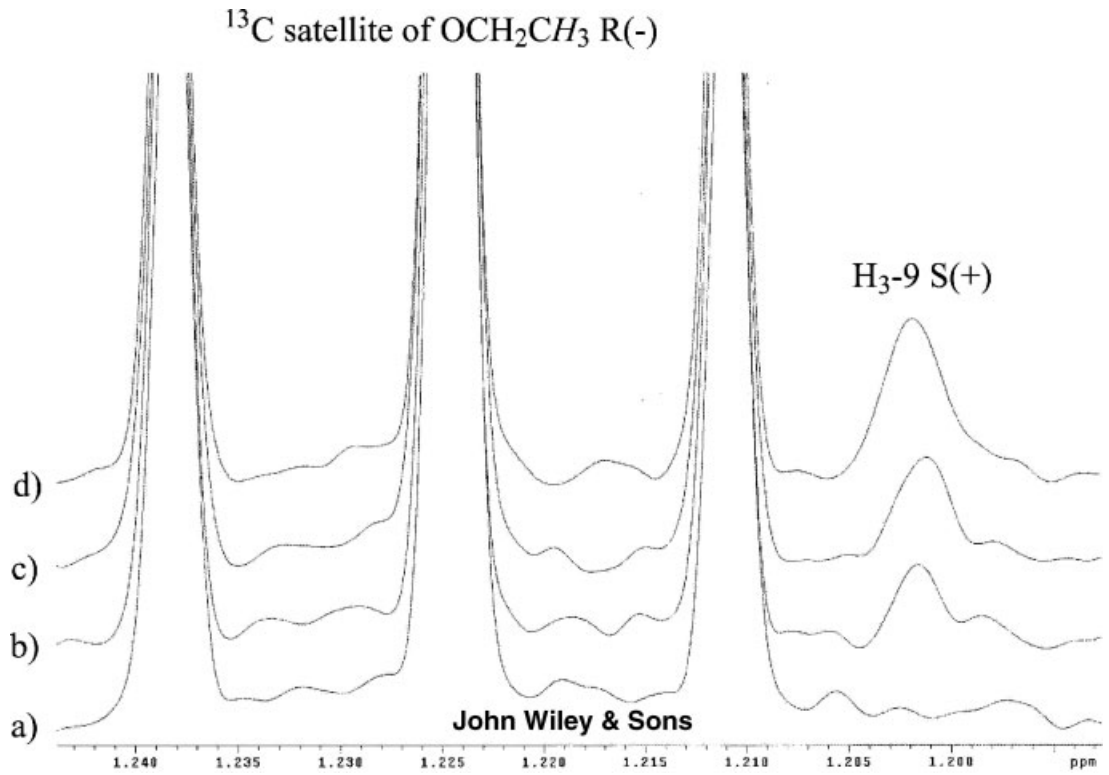


Fig. 2. (**a**) Upfield region of the ^{1}H NMR spectrum of pure *R*(−) tamsulosin base in the presence of Mosher acid as a chiral additive (^{1}H 500 MHz, CD_2Cl_2, 21°C) by applying selective decoupling of the H-8 proton during acquisition. *R*(−) tamsulosin base spiked with (**b**) 0.01%, (**c**) 0.03%, (**d**) 0.05% *S*(+) tamsulosin base in the presence of Mosher acid.

1H, H-5); 7.67 (d, J = 2.0 Hz, 1H, H-3); 9.71 (br s, 2H, N(10)*H***H*Cl); ^{13}C NMR (DMSO-d_6, 125 MHz, TMS): 14.6 (OCH_2CH_3), 14.8 (C-9), 37.2 (C-7), 43.0 (C-11), 54.7 (C-8), 56.1 (OCH_3), 63.7 (OCH_2CH_3), 65.1 (C-12), 112.9 (C-6), 113.6 (C-15), 115.4 (C-18), 120.7 (C-17), 122.3 (C-16), 128.1 (C-3), 128.3 (C-4), 131.2 (C-2), 134.4 (C-5), 147.3 (C-13), 148.7 (C-14), 154.9 (C-1).

RESULTS AND DISCUSSION

We also started from the sulfamoyl acetone derivative ***2***. To introduce an amino group we used the cheap benzylamin in reductive condensation. The racemic secundary amine (±)**4** obtained is an unknown compound. **(±)4** having one asymmetric center was resolved with *R,R*-(−)-*O,O*′-dibenzoyl-tartaric acid. The optically pure enantiomer **(−)4** was N-alkylated with 2-ethoxy-1-(2-mesyloxyethyl)oxybenzene **5** boiling xylene in the presence of magnesium oxide. The use of stronger bases as an acid absorbent led to the alkylation of the sulfamid group as well. The magnesium oxide is such a weak base that we did not get the alkylated product on the sulfamid group (Scheme 4).

The optically pure tertiary amine **(−)6,** a new substance, was debenzylated by catalitic hydrogenation at atmospheric pressure to give tamsulosin base which was transformed into the hydrochlorid salt. The chemical purity of the product analyzed by HPLC was over 99.85%. The *S*(+) enantiomer could not be detected at the 0.01% level by NMR analysis (see later); thus, the developed synthetic route results in the *R*(+) tamsulosin with excellent enantiomeric purity.

A chiral NMR method was used to determine the enantiomeric purity of *R*(−) tamsulosin base. Determination of the enantiomeric purity is based on the chemical shift difference between the *R*(−) and *S*(+) enantiomers observed on the H_3-(9) signal in the ^{1}H spectrum in the presence of Mosher acid[5] [(*S*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid] applied as chiral additive. Twenty five milligrams of tamsulosin base was dissolved in 0.7 ml of CD_2Cl_2 and equimolar Mosher acid was added to the solution. By applying selective decoupling of the H-(8) proton during acquisition the H_3-(9) proton gives two singlet signals due to the *R*(−) and *S*(+) enantiomers, respectively (see Fig. 1). The enantiomeric purity of the *R*(−) enantiomer can be determined by comparing the integrated intensity of the H_3-(9) *S*(+) signal with the intensity of the ^{13}C satellite signal of $H_3—OCH_2CH_3$ (see Fig. 2). Spectral deconvolution was used for measuring the *S*(+) enantiomer content spiked in the optically pure *R*(−) tamsulosin base, resulting in excellent agreement with the theoretical impurity content [*S*(+) measured: 0.012%, 0.029%, 0.046%; *S*(+) theoretical: 0,014%, 0.032%, 0.048%]. Even 0.01% *S*(+) enantiomer can be

detected with the developed method. The *S*(+) enantiomer could not be detected in the final *R*(−) tamsulosin base by NMR.

CONCLUSION

The most important step, the key-move to produce a chiral pharmaceutical-agent is the synthesis of a racemic compound suitable for selective substitution and which is separable into its enantiomers as well. In the new industrial synthesis of Tamsulozin **1,** the intermedier **4** fulfills both of these requirements.

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