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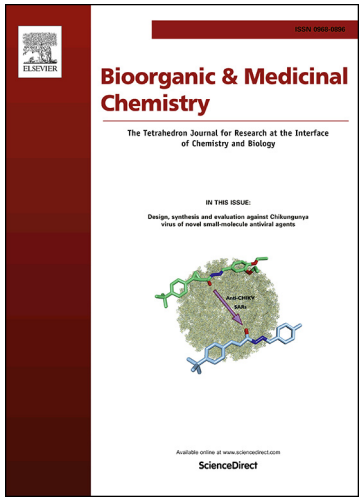

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Synthesis of enantiopure antiobesity drug lorcaserin

Ivana Gazic Smilovic[a], Jerome Cluzeau[a], Frank Richter[b], Sven Nerdinger[b,*], Erwin Schreiner[b], Gerhard Laus[c], Herwig Schottenberger[c]

[a]Lek Pharmaceuticals DD, Kolodvorska 27, 1234 Mengeš, Slovenia

[b]Sandoz GmbH, Biochemiestrasse 10, 6250 Kundl, Austria

[c]Leopold-Franzens University, Innrain 80–82, 6020 Innsbruck, Austria

Abstract

Acylation of enantiomerically pure (*R*)-2-(3-chlorophenyl)propan-1-amine using chloroacetyl chloride, followed by borane reduction and aluminum chloride catalyzed cyclization yielded enantiopure lorcaserin.

Keywords: enantiopure, lorcaserin, obesity, 5-HT agonist

*Corresponding author

E-mail address: sven.nerdinger@sandoz.com

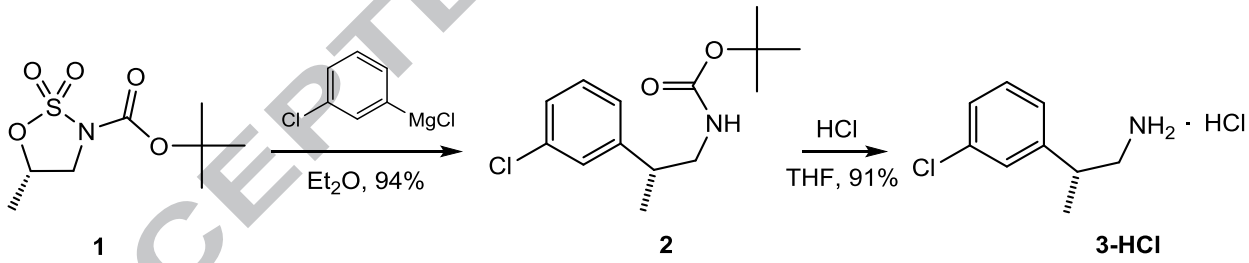
Introduction

Obesity is defined as excessive fat accumulation and poses a substantial public health challenge. Recent estimates indicate that roughly 600 million adults worldwide are obese.[1] Whereas lifestyle modification is considered first-line therapy for obese patients, concomitant pharmacotherapy may be beneficial to maintain the weight loss achieved. Clinical trials of new promising antiobesity drugs have been reviewed previously.[2] The 5-HT_{2C} receptor selective agonist lorcaserin[3] has the best safety and tolerability profile of currently available medications.[4] There are numerous methods of preparation disclosed in the patent literature,[5–13] frequently necessitating separation of enantiomers. Recent syntheses involve oxidative ring expansion,[14] ultrafine-tuned reaction conditions for a key intermediate,[15] and a convenient procedure suitable for scale-up, however, requiring the use of a protection group and chiral resolution.[16]

Here we describe a new synthesis of enantiopure (*R*)-lorcaserin.

Results and discussion

Our synthetic approach was centered on (*R*)-2-(3-chlorophenyl)propan-1-amine (**3**) as readily available chiral starting material. A selective ring opening[17] (Scheme 1) of a cyclic sulfamidate **1**, prepared from commercial (*S*)-(−)-1-amino-2-propanol, and subsequent removal of a Boc group from **2** provided the enantiomerically pure amine **3**.

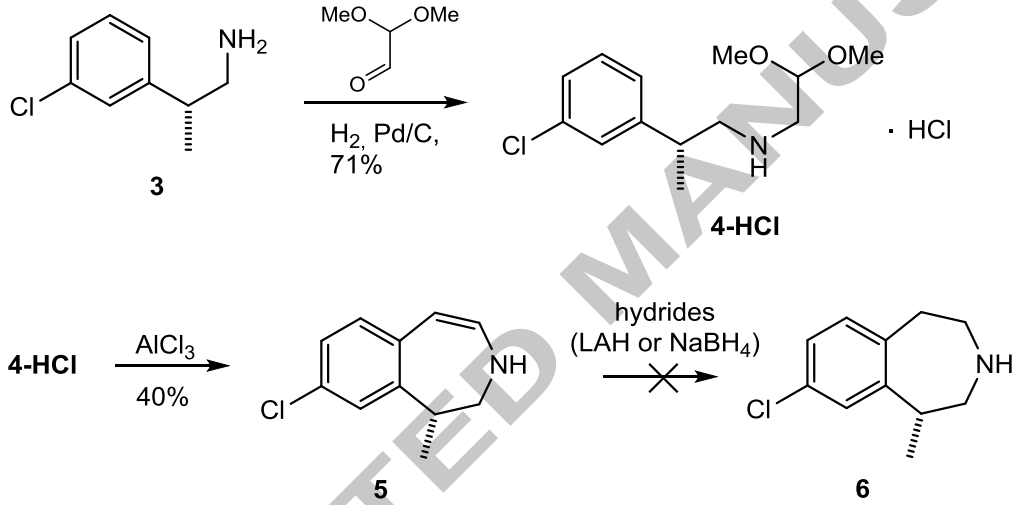


Scheme 1. Preparation of chiral amine **3** hydrochloride.

Very recently, the crystal structure of the opposite enantiomer of the chiral cyclic sulfamidate **1** has been determined.[18] The initial configuration is retained throughout the whole synthetic sequence.

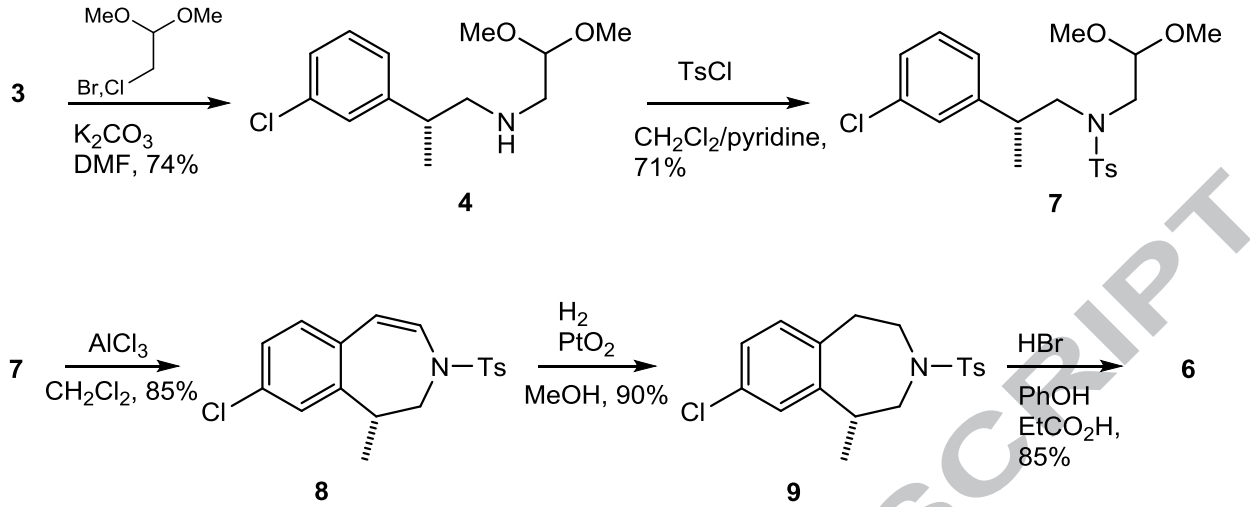
The basic concept consisted of adding C_2 building blocks to the primary amino group of **3**, suitable for ring closure to obtain the seven-membered ring without disturbing the chiral centre. The building blocks we used were chloroacetaldehyde dimethyl acetal, dimethoxy acetaldehyde,

and chloroacetyl chloride in order to obtain the intermediates **4** and **10**. A different attempt to prepare intermediate **4** by condensation of the amine **3** with chloroacetaldehyde and subsequent reduction was not successful. It was also tried to synthesize the amide **10** using bromoacetyl chloride instead of chloroacetyl chloride; however, numerous byproducts were observed in contrast to the prior synthesis. In all cases, the intended cyclization was effected by heating the linear precursors **4**, **7**, **11** or their hydrochlorides in the presence of aluminum chloride under solvent-free conditions. However, in our hands, attempted cyclization of **10** did not produce satisfactory results with less than 20% conversion. Catalytic hydrogenation was employed for the reduction of the carbon–carbon double bonds in compounds **8** but reduction failed in case of compound **5**, whereas a borane reduction was adequate for the carbonyl group in compound **10**.



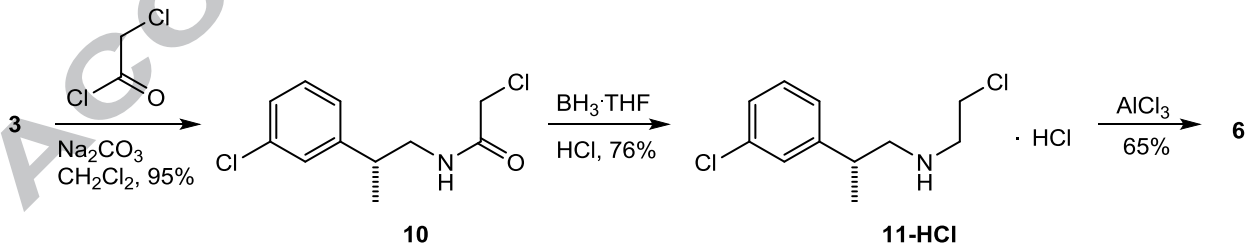
Scheme 2. Synthesis of lorcaserin via unprotected acetal **4**.

The reaction pathway[19] via acetal **4** and dihydroazepine **5** (Scheme 2) was straightforward but furnished a good number of byproducts. It was concluded that a protective group for the secondary amine during the cyclization step was needed. Thus, the acetal **4** was tosylated to give compound **7**, which on treatment with aluminum chloride was transformed to the protected dihydroazepine **8**, followed by catalytic hydrogenation to the protected tetrahydroazepine **9** (Scheme 3).



Scheme 3. Synthesis of lorcaserin via tosyl-protected acetal **7**.

Removal of the tosyl group by acidic hydrolysis finally gave lorcaserin **6**. Chromatography was employed for the purification of intermediates **4**, **7** and **9**. However, for industrial exploitation the use of chromatographic separation has to be avoided. Another important issue was reducing the number of steps. It was found that protection obviously was not necessary when the synthetic pathway was chosen carefully. Removal of the unsaturation or its equivalent prior to the Friedel-Crafts reaction permitted omission of the protection/deprotection procedure. The lack of a double bond indicated higher stability towards the Lewis acid. The use of the protective group was therefore dropped. This third pathway not only was the shortest, but was also standing out due to the excellent yield. The amide **10** was obtained in almost quantitative yield and reduced to the amine **11** in high yield. Cyclization afforded the desired product **6** (Scheme 4).



Scheme 4. Three-step synthesis of enantiopure lorcaserin **6** via amide **10**.

The preparation of the hydrochloride **6-HCl** was straightforward.[20] Identity and purity were confirmed by HPLC–MS as described previously.[19]

Experimental section

*(S)-3-(tert-Butyloxycarbonyl)-5-methyl-1,2,3-oxathiazolidine 2,2-dioxide (**1**)*

Prepared according to the published procedure for the opposite enantiomer.[18]

*tert-Butyl (R)-(2-(3-chlorophenyl)propyl)carbamate (**2**)*

In analogy with the published procedure using 3-chloroiodobenzene.[17] Yield: 94%, colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, 3H), 1.39 (s, 9H), 2.90 (m, 1H), 3.15 (m, 1H), 3.32 (m, 1H), 4.45 (br, 1H), 7.03–7.08 (m, 1H), 7.15–7.24 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 28.6 (3C), 40.1, 47.4, 79.5, 125.7, 126.9, 127.6, 130.1, 134.6, 146.6, 156.1 (C=O).

*(R)-2-(3-Chlorophenyl)propan-1-amine hydrochloride (**3-HCl**)*

Hydrochloric acid (32 mL, 6M) was added to a solution of the Boc derivative **2** (9.8 mmol) in THF (20 mL). The emulsion was stirred at 45 °C for 3 h to give a clear solution. The solvent was evaporated, the residue dissolved in H_2O (65 mL) made alkaline with NaOH (1M). The mixture was extracted with EtOAc (1 × 60 mL, 2 × 30 mL). The combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield 1.60 g of the crude base. Hydrogen chloride in Et_2O (12 mL, 1M) was added dropwise to a solution of the base in Et_2O (20 mL). The precipitated hydrochloride was filtered, washed with Et_2O (3 × 5 mL) and dried in vacuum: 1.63 g (81%). M.p. 192 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (d, J = 6.9 Hz, 3H), 2.98 (m, 2H), 3.12 (m, 1H), 7.26-7.40 (m, 4H), 8.16 (br, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.2, 37.2, 44.5, 126.1, 126.9, 127.2, 130.5, 133.2, 145.4. IR (neat) ν 2967 (m), 2865 (s), 2819 (m), 1598 (m), 1507 (m), 1467 (m), 1435 (m), 1394 (m), 879 (m), 798 (m), 786 (s), 697 (s) cm^{-1}.

*(R)-2-(3-Chlorophenyl)propan-1-amine (**3**)*

A solution of 1M NaOH (5 mL) was added to a solution of the hydrochloride **3-HCl** (1.0 g, 4.9 mmol) in H_2O (30 mL) and the mixture was extracted with EtOAc (1 × 50 mL, 2 × 25 mL). The combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield 0.75 g (91 %) of a colourless liquid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.16 (d, 3H), 1.9

(br s, 2H), 2.66 (m, 3H), 7.16-7.34 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.7, 42.6, 49.0, 125.8, 125.9, 127.1, 130.0, 132.9, 148.5. IR (neat) ν 2959, 2926, 1595, 1570, 1476, 1429, 1081, 780, 696 cm^{-1}.

*(R)-2-(3-Chlorophenyl)-N-(2,2-dimethoxyethyl)propan-1-amine (**4**)*

To a solution of 2-(3-chlorophenyl)propan-1-amine (**3**) (19.6 mmol, 3.3 g) in DMF (50 mL) were added K_2CO_3 (29.4 mmol, 4.1 g) and 2-chloro-1,1-dimethoxyethane (29.4 mmol, 3.3 mL) under nitrogen atmosphere. The reaction mixture was stirred overnight at 120 °C. After cooling it down to room temperature, H_2O (30 mL) was added and extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with brine (60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc : *n*-heptane; EtOAc gradient elution 12–100 %) to yield a colourless oil (1.5 g, 28 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (m, 3H), 7.10 (d, 1H), 4.41 (t, 1H), 3.33 (s, 6H), 2.91(m, 1H), 2.74 (m, 4H), 1.24 (d, 3H).

*(R)-2-(3-Chlorophenyl)-N-(2,2-dimethoxyethyl)propan-1-amine hydrochloride (**4-HCl**)*

2-(3-Chlorophenyl)propan-1-amine (**3**) (1 g, 4.8 mmol) in MeOH (2 mL) was treated with dimethoxyacetaldehyde (60% in H_2O, 1.46 mL, 2 equiv.) and the solution was stirred at room temperature for 48 hours. 10% Pd/C (100 mg, 10 wt%) was added and the reaction vessel was flushed several times with nitrogen and hydrogen alternatively. Hydrogen pressure was set at 1 atm and the reaction was stirred for 4 h. The mixture was filtered through Celite and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with brine and HCl (20 / 10 mL 1M). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in toluene (40 mL) and the solution was extracted three times with H_2O (3 × 30 mL). The combined water phase was saturated with NaCl and was extracted twice with CH_2Cl_2 (2 × 30 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give the pure product in 62% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.22 (m, 3H), 7.18 (d, *J* = 7.2 Hz, 1H), 4.89 (t, *J* = 5.0 Hz, 1H), 3.49 (m, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.31 (m, 1H), 3.19 (m, 1H), 3.08 (m, 1H), 3.00 (m, 1H), 1.44 (d, *J* = 6.9 Hz, 3H).

*(R)-8-Chloro-1-methyl-2,3-dihydro-1H-benzo[d]azepine (**5**)*

Acetal hydrochloride **4-HCl** (50 mg, 0.25 mmol) was mixed with anhydrous $AlCl_3$ (69 mg, 3 equiv.). Fine mixture was heated to 90 °C to obtain molten phase and stirred overnight. Solution was diluted with CH_2Cl_2 (20 mL) and washed brine (20 mL). The phases were separated and water phase was re-extracted with CH_2Cl_2 (10 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The obtained crude mixture was analyzed and the final product was / detected with GC-MS analysis (m/z 193) and characterized by ^{1}H NMR (estimated yield by ^{1}H-NMR was 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (m, 2H), 6.98 (m, *J* = 9.1 Hz, 1H), 6.22 (d, *J* = 9.7 Hz, 1H), 5.06 (1H, *J* = 9.7 Hz, 1H), 3.32 (m, 1H), 3.24 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H).

*(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**6**) from **9***

A mixture of 8-chloro-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**9**) (0.17 mmol, 59 mg), phenol (0.55 mmol, 53 mg), 48 % HBr (0.45 mL) and propionic acid (0.09 mL) was stirred under reflux for 6 h. After cooling to room temperature, the reaction mixture was quenched with H_2O (2 mL) and washed with Et_2O (2 × 5 mL). The aqueous phase was basified with 8M NaOH (pH ≥ 9) and the product was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated to dryness. The desired product was obtained in 80% yield and agreed with known literature[3] data.

*(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**6**) from **11-HCl***

Liquid precursor **11-HCl** (0.5 mmol) was placed into a test tube equipped with a magnetic stir bar. Anhydrous $AlCl_3$ (1.75 equiv according to starting material) was added and efficiently mixed to obtain a paste. The mixture was slowly heated (10 °C/min) to 150 °C and stirred overnight. A saturated solution of NaCl was added and the mixture was cooled. The pH was adjusted to 9.5-10 using 1M NaOH and then extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained crude mixture was analyzed using ^{1}H NMR spectroscopy (estimated yield by ^{1}H-NMR was 62%). The NMR data were in agreement with known literature or patent data.[19]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (m, H), 7.11 (m, H), 7.00-6.94 (m, H), 3.20-2.78 (m, 5H), 2.75 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H).

*(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride (**6-HCl**)*

To a solution of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (0.73 g, 3.7 mmol) in CH_2Cl_2 (2 ml) was added 1M HCl/Et_2O (6 ml). The mixture was stirred and the product was collected by filtration, washed with Et_2O (3 ml) and dried, as described previously.[20] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (d, *J* = 7.3 Hz, 3H), 2.62 (m, 1H), 2.79 (m, 2H), 2.87 (m, 3H), 3.05 (m, 1H), 3.65 (br s, 2H), 7.10 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 17.5, 37.9, 40.9, 47.5, 53.9, 125.4, 126.3, 130.5, 131.3, 140.4, 148.0. IR (neat) ν 2979, 2939, 2879, 2684, 2643, 2598, 2499, 2429, 2399, 1580, 1484, 1390, 1104, 932, 876, 814, 645, 528, 466 cm^{-1}.

*(R)-N-(2-(3-Chlorophenyl)propyl)-N-(2,2-dimethoxyethyl)-4-methyl benzenesulfonamide (**7**)*

A solution of 2-(3-chlorophenyl)-N-(2,2-dimethoxyethyl)propan-1-amine (**4**) (2.95 mmol, 0.76 g) in CH_2Cl_2/pyridine (8/1, 4.2 mL) was cooled to 0 °C and a solution of TsCl (5.31 mmol, 1.0 g) in CH_2Cl_2 (1.8 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. The reaction mixture was washed with 2M HCl (2 × 4.3 mL) and saturated aqueous solution of $NaHCO_3$ (4.3 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (eluent: EtOAc/*n*-heptane, EtOAc gradient 7-60 %) to yield a colourless oil (0.85 g, 71 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, 2H), 7.28 (d, 2H), 7.19 (m, 2H), 7.08 (m, 2H), 4.43 (t, 1H), 3.45 (m, 1H), 3.36 (d, 6H), 3.13 (m, 4H), 2.42 (s, 3H), 1.25 (d, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 143.4, 136.6, 134.2, 129.8, 129.7, 127.6, 127.2, 126.7, 125.5, 104.6, 56.5, 55.3, 55.1, 50.8, 38.2, 21.5, 18.6.

*(R)-8-Chloro-1-methyl-3-tosyl-2,3-dihydro-1H-benzo[d]azepine (**8**)*

To a suspension of $AlCl_3$ (8.3 mmol, 1.1 g) in CH_2Cl_2 (15 mL) was added a solution of N-(2-(3-chlorophenyl)propyl)-N-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (**7**) (2.1 mmol, 0.85 g) in CH_2Cl_2 (10 mL) under nitrogen atmosphere. The reaction mixture was stirred for 10 min at room temperature and then was cooled to 0 °C. After quenching with NaOH (11 mL 1M) and

H_2O (11 mL), the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed by evaporation to give a yellow solid (0.6 g, 85 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 2H), 7.32 (d, 2H), 7.10 (m, 1H), 7.05 (m, 2H), 6.89 (dd, 1H), 5.55 (d, 1H), 4.06 (m, 1H), 3.14 (m, 2H), 2.42 (s, 3H), 1.17 (d, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 144.2, 135.8, 132.2, 131.8, 131.5, 130.0, 129.4, 128.1, 127.0, 126.6, 126.1, 107.4, 50.3, 40.1, 21.6, 18.0.

*(R)-8-Chloro-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**9**)*

To a solution of 8-chloro-1-methyl-3-tosyl-2,3-dihydro-1H-benzo[d]azepine (**8**) (0.54 mmol; 0.19 g) in MeOH (3 mL) was added PtO_2 (20 mg) and several drops of HCl. The reaction mixture was stirred at 25 °C under 5 bar of H_2 for 48 h. After filtration through Celite pad, the solvent was removed by evaporation under reduced pressure. The residue was dissolved in EtOAc (6 mL), washed with H_2O (6 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash chromatography (eluent: *n*-heptane/EtOAc, EtOAc gradient 7-60 %), to give **7** in 30 % yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 2H), 7.27 (d, 2H), 7.07 (m, 2H), 7.05 (m, 2H), 6.97 (d, 1H), 3.28-2.92 (m, 2H), 2.40 (s, 3H), 1.40 (d, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0, 143.3, 137.8, 135.2, 132.4, 131.3, 129.7, 127.5, 127.1, 126.3, 53.5, 48.1, 40.0, 35.9, 21.5, 17.5.

*(R)-2-Chloro-N-(2-(3-chlorophenyl)propyl)acetamide (**10**)*

Into a cold solution of 2-(3-chlorophenyl)propan-1-amine (**3**) (250 mg, 1.5 mmol) in CH_2Cl_2 (4 mL) Na_2CO_3 (1.6 mmol) was added and the mixture was stirred for 15 min at 5-10 °C. Then chloroacetyl chloride (1.6 mmol) was slowly dropped into the reaction system and stirred for a few hours at 25 °C. The reaction mixture was diluted with H_2O, phases were separated, the organic phase was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford an oily product (350 mg, 95 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.18 (m, 3H), 7.10 (m, 1H), 4.00 (s, 2H), 3.65 (m, 1H), 3.34 (m, 1H), 2.97 (m, 1H), 1.32 (d, J = 8.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 145.8, 134.8, 130.2, 127.5, 127.3, 125.6, 46.4, 42.8, 39.6, 19.0. IR (neat) ν 3291 (br), 1656, 1537, 1381 cm^{-1}.

*(R)-N-(2-chloroethyl)-2-(3-chlorophenyl)propan-1-amine hydrochloride (**11-HCl**)*

A round bottom flask was charged with 2-chloro-N-(2-(3-chlorophenyl)propyl)acetamide (**10**) (2 mmol) and BH_3-THF complex (1M solution in THF; 2.5 equiv.) was slowly added. The reaction mixture was vigorously stirred for 15 h at 25 °C. Afterwards the mixture was cooled to 5 °C, quenched with MeOH and the solvent was evaporated under reduced pressure. The organic residue was then diluted in Et_2O and a solution of HCl was added dropwise. The reaction mixture was stirred at room temperature for 1 h and then slowly cooled to precipitate white solid material which was filtered off and dried in vacuum (353 mg, 76 % yield); mp. 160 °C).

^{1}H NMR (500 MHz, $CDCl_3$/acetone-d_6) δ 7.24-7.16 (m, 4H), 3.91 (m, 2H), 3.44 (m, 1H), 3.21 (m, 4H), 1.38 (d, J = 8.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$/acetone-d_6) δ 144, 134.9, 130.6, 127.9, 127.4, 125.7, 54.3, 49.3, 38.4, 36.7, 19.9. IR (neat) ν 2931, 2743, 1594, 1444, 1029 cm^{-1}.

Conclusion

In summary, three processes for the preparation of enantiopure lorcaserin have been described. The final process involved three synthetic transformations and proceeded in 47 % overall yield from the chiral amine **3** in a straightforward manner to enantiopure lorcaserin.

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