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Practical chemical and enzymatic technologies for (*S*)-1,4-benzodioxan-2-carboxypiperizine intermediate in the synthesis of (*S*)-doxazosin mesylate

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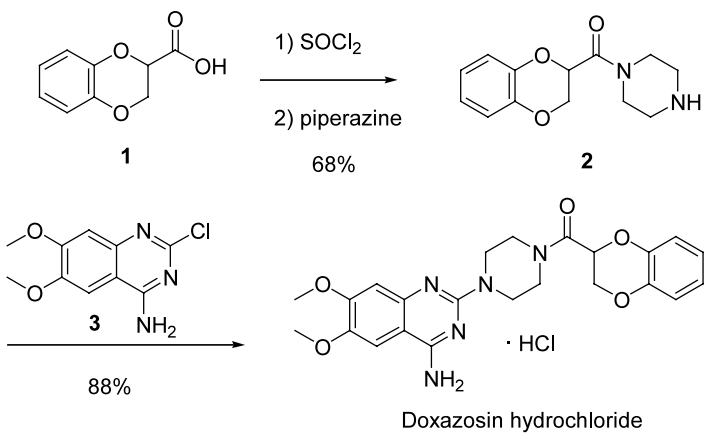
Abstract—(*S*)-1,4-Benzodioxan-2-carboxypiperazine (*S*)-**2**, the key chiral intermediate for the synthesis of (*S*)-doxazosin, was prepared utilizing two approaches: (i) enzymatic resolution of ethyl 1,4-benzodioxan-2-carboxylate with an esterase (*Serratia*) followed by amide formation; (ii) direct resolution of 1,4-benzodioxan-2-carboxypiperazine **2** with D-tartaric acid. An efficient process for the conversion of (*S*)-**2** to (*S*)-doxazosin mesylate was developed (80% yield, 99.9% e.e.).

1. Introduction

(±)-Doxazosin mesylate, marketed as CARDURA® in the US, is a newer member of the important quinazoline family of drugs and is indicated for the treatment of hypertension. More recently, it has proven effective in the treatment of benign prostatic hyperplasia (BPH).[1] The mode of action of doxazosin is believed to be a selective inhibition of the α_1-subtype of the alpha adrenergic receptor. Pre-clinical studies have suggested that the (*S*)-enantiomer of doxazosin would offer both reduced side effects (e.g. asthenia, dizziness), and improved efficacy over the racemate for the treatment of BPH. As a result, (*S*)-doxazosin is being investigated in clinical studies. Due to the importance and structural similarity of these quinazolines (doxazosin, prazosin, terazosin, and alfuzosin), a general synthetic strategy for this class of compounds has been well established.[2] The last step in the synthesis usually involves the coupling of chloro-quinazoline substrate **3** with an amine



Scheme 1.

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derivative. Scheme 1 outlines the synthesis of (±)-doxazosin hydrochloride[3] starting from the benzodioxane-2-carboxylic acid **1** and quinazoline **3**. The synthesis of (*S*)-**1** was also reported by resolution with dehydroabietylamine in very low yield (ca 1%).[4] In order to carry out in vitro and in vivo efficacy and pharmacokinetic studies of (*S*)-doxazosin, we required an efficient and practical method for the synthesis (*S*)-2 and its conversion to (*S*)-doxazosin mesylate.

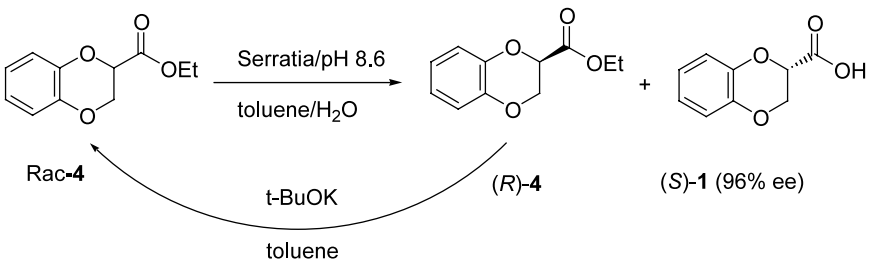
Herein, we describe two new methods for the preparation of enantiomerically pure (*S*)-1,4-benzodioxan-2-carboxypiperizine (*S*)-**2**. The first method involved hydrolytic kinetic resolution of ethyl 1,4-benzodioxan-2-carboxylate **4** by an esterase enzyme, followed by amide formation. The second employed the direct chemical resolution of (±)-**2** with D-tartaric acid. In addition, we report an efficient process for the conversion of the key intermediate (*S*)-**2** to (*S*)-doxazosin mesylate in high chemical yield, chemical purity and enantiomeric purity.

2. Results and discussion

2.1. Enzymatic approach to (*S*)-1

Our first approach to (*S*)-**1** involved the use of an esterase enzyme. After screening a variety of commonly used enzymes, a microbial esterase derived from *Serratia marcescens*[5] was found to stereoselectively catalyze the hydrolysis of ethyl (*S*)-1,4-benzodioxan-2-carboxylate **4** with high activity (*E* value of 273) on 50 g scale.[6] (±)-**4** was easily prepared in 93% yield by reaction of catechol and ethyl dibromopropionate.

The stereoselective hydrolysis of **4** was carried out in a two-phase system of toluene and an aqueous solution of sodium bicarbonate (Scheme 2). The pH of the reaction mixture was maintained with an auto titrator between pH 8.6 and 9.0 by the addition of aqueous sodium hydroxide. The final conversion (45–46%) was conveniently determined by the quantity of sodium hydroxide consumed. (*R*)-**4** remained in the toluene phase and was removed by phase separation. The recovered (*R*)-**4** was racemized with a catalytic amount of potassium *tert*-butoxide in toluene. The crude (*S*)-**1** (41–43%, 95.6–98.4% e.e.) was isolated from the aqueous phase by extraction with ethyl acetate after pH adjustment of the aqueous phase to pH 0.3–1.0. Enantiomerically pure (*S*)-**1** (21–25% yield, 99.8% e.e.) was obtained by crystallization of the crude product in toluene on a 1–2 kg scale. The lower isolated yield of the product (*S*)-**1** compared to the conversion (45–46%) was mainly due to the necessary enrichment by crystallization during the isolation. Fig. 1 shows a phase diagram of the acid **1** obtained by differential scanning calorimetry (DSC). The conglomerate has an



Scheme 2.

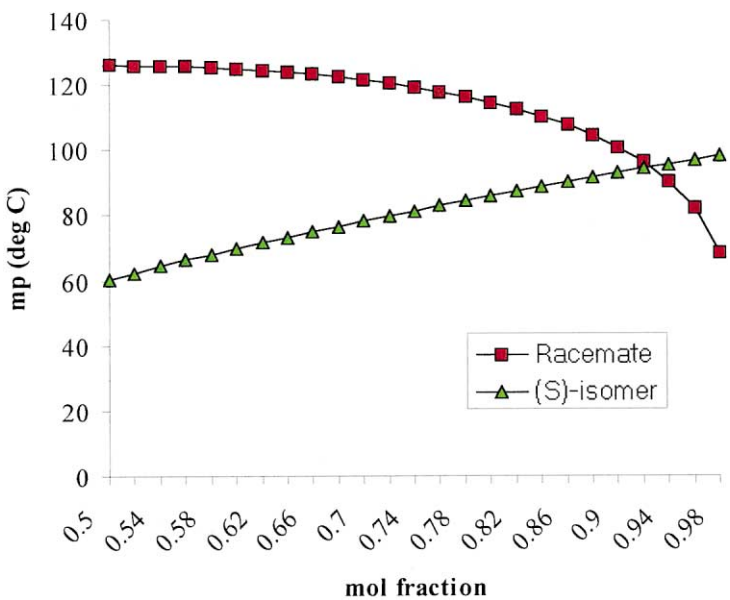


Figure 1.

unfavorable eutectic point, therefore, enrichment of (*S*)-**1** is not efficient and recovery by crystallization was low.[7]

2.2. Synthesis of *(S)*-2 from (*S*)-1

While a number of coupling reagents were explored for the formation of (*S*)-**2** from (*S*)-**1**, it was found that racemization occurred during the reaction.[8] Therefore, the amination reaction was conducted utilizing the available method[3] with modification to minimize the formation of diamide **5** as outlined in Scheme 3.

(*S*)-**1** was converted to the corresponding acid chloride by treatment with thionyl chloride. One equivalent of acid chloride was then slowly added to excess piperazine monohydrochloride (3 equiv.) in water and methanol over 4 h by sub-surface addition. Formation of the highly insoluble by-product **5** was minimized to about 10% and **5** could be readily removed by filtration from the reaction mixture. The product (*S*)-**2** was isolated after extraction with dichloromethane and recrystallization from toluene in 75–80% yield (99.94% e.e., 99.90% chemical purity).

The enzymatic route was successfully used to prepare multi-kilogram quantities of (*S*)-**2**. However, the overall isolated yield of enantiomerically pure (*S*)-**2** (99.94% e.e.) from (±)-**4** is low, primarily due to the unfavorable eutectic point of the conglomerate in the upgrade of the e.e. of (*S*)-**1** to >99.50%. In addition, amination of (*S*)-**1** by (*S*)-**2** produced 10% of undesired **5**. To circumvent these problems, our attention turned to developing a direct resolution method for the preparation of (*S*)-**2**.

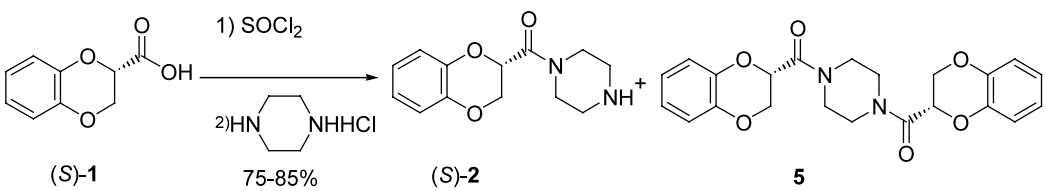
2.3. Resolution approach to (*S*)-2

Recently, a number of practical methods for the preparation of (±)-**2** have been developed.[9] In particular, Chou[9a] described the high yielding and direct coupling of piperazine with **4** (94%), making (±)-**2** a readily available and attractive candidate for resolution. After screening a number of chiral acids (tartaric acid, ditoluoyl tartaric acid, dibenzoyl tartaric acid, and mandelic acid), tartaric acid was found to be an excellent resolving agent for **2** (Scheme 4).

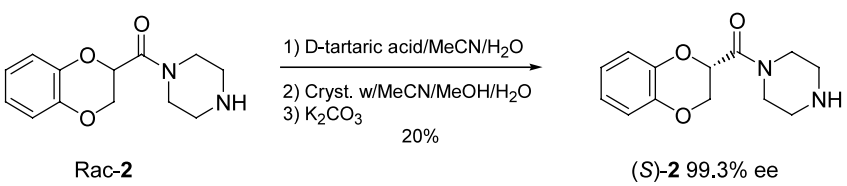
(±)-**2** was treated with 1 equiv. of D-tartaric acid in acetonitrile/water (1:1) to give the diastereomerically enriched salt in 39% yield (75–80% d.e.). Crystallization of this salt in a mixture of solvents (acetonitrile, methanol and water) gave the salt in 50% yield (99% d.e.). After salt breakage, (*S*)-**2** was isolated in 20% overall yield after crystallization from toluene (e.e. = 99.3%). In addition, (*R*)-**2** was readily recovered from the reaction mother liquors, racemized with potassium *tert*-butoxide,[10] and recycled. This direct, simple and practical resolution procedure has been demonstrated on 50 gram scale. Currently, this new resolution technology is under development for the multi-kilogram production of (*S*)-**2**.

2.4. Synthesis of (*S*)-doxazosin mesylate

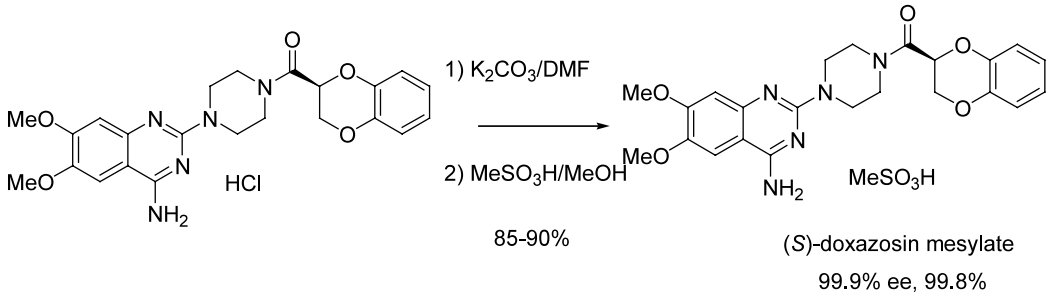
Coupling of **3** with (*S*)-**2** proceeded smoothly to give (*S*)-doxazosin hydrochloride in a 95% yield (99.9% e.e.).[3] both the hydrochloride salt, and the free amine were insoluble in common solvents (e.g. water, DMSO, EtOAc, toluene), which made it impractical to use a neutralization and extraction protocol to obtain the free base. It was found that when the HCl salt was suspended in DMF/water and treated with concentrated sodium hydroxide (1.1 equiv.), followed by dilution with water, the free base precipitated from the aqueous phase and was isolated in 95% yield and high chemical purity. To our surprise, the doxazosin free base was partially racemized (90% e.e.) due to the high pH. To avoid racemization, weaker bases were evaluated. When potassium carbonate (1.2 equiv.) was used under similar conditions, the free amine precipitated without racemization, and was easily collected by filtration. The free amine was in turn treated with methanesulfonic acid in methanol to give the mesylate salt in 85–90% overall yield, as outlined in Scheme 5.



Scheme 3.



Scheme 4.



Scheme 5.

3. Conclusion

In conclusion, complementary enzymatic and chemical resolution methods for the preparation of the key intermediate (*S*)-**2** were developed. The direct resolution of readily available (±)-**2** with tartaric acid provided the most practical and economical solution. In addition, an efficient, practical and non-epimerizable protocol for the conversion of (*S*)-**2** to (*S*)-doxazosin mesylate (> 99.9% e.e., 99.8% chemical purity) was developed. Work is continuing on the direct resolution of (±)-**2** for further process optimization.

4. Experimental

4.1. General

Solvents and reagents were commercial grade. All lab-scale reactions were carried out in oven-dried glassware under an argon atmosphere. All kilo-scale reactions were performed using a 60 L Buchi under an argon atmosphere. ^1H and ^{13}C NMR were performed on a 300 MHz Varian instrument. HPLC analysis was performed on a Waters system, using a Waters μ-Bondapak C18 300×3.9 mm column, ChiralPak OD, 10 μm, 4.6 mm×25 cm, ChiralPak AD, 10 μm, 4.6 mm×25 cm, or ChiralPak OD-R, 10 μm, 4.6 mm×25 cm.

4.2. Ethyl 1,4-benzodioxan-2-carboxylate 4

A 60 L Buchi reactor was charged with catechol (2.5 kg), potassium carbonate (anhydrous powder, 6.8 kg) and acetone (23 kg). The reactor was heated to reflux, and to it was added ethyl 2,3-dibromopropionate (5.8 kg) over a 1.5 h period. After the addition, the reaction mixture was heated under reflux for 4 h and the reaction volume was reduced by distillation to 10 L. To the residue was added toluene (17 L) to give a suspension, which was distilled to remove residual acetone. The toluene suspension was washed with water (10 L), NaOH (0.1N, 6 L), water (6 L), and then concentrated to give a solution of **4** in toluene (16 kg). The chemical purity of **4** solution was 95% by HPLC analysis (Waters μ-Bondapak C18 300×3.9 mm, 50% acetonitrile/50% buffer (0.05 M $NaHClO_4 \cdot H_2O$, pH 2.0), 1.0 mL/min). A total of 4.3 kg (92%) of **4** was produced. This solution was used in the next step without purification.

4.3. (*S*)-1,4-Benzodioxan-2-carboxylic acid (*S*)-1

To a 60 L Buchi reactor equipped with mechanical stirrer, and pH meter auto-titrator was charged with aqueous $NaHCO_3$ (0.1N, 12 L, pH 8.6), and **4** (4.0 kg) in toluene. The mixture was stirred for 5 min at 25°C. *Serratia* enzyme (180 mL) was added. The pH of the reaction mixture was maintained between 8.5 and 9.0 by addition of 2N NaOH. After 6.5 h (25% conversion), stirring was stopped and the aqueous phase was separated and stored. Additional $NaHCO_3$ (0.1N, 6 L) was added to the organic phase, followed by additional *Serratia* (60 mL). The pH of the reaction mixture was maintained between 8.5 and 9.0 for an additional 13 h. Based on consumption of the 2N NaOH solution, the overall conversion was 45%. The aqueous phase was separated and combined. The combined aqueous phases were acidified with concentrated HCl to pH 1, then saturated with NaCl (2.5 kg), and extracted with EtOAc (30 L). The extract was washed with water (2 L) and concentrated to give crude (*S*)-**1** as a solid (1.5 kg) with e.e. of 96.5% determined by HPLC analysis (Chiralpak OD, 10 μm, 4.6 mm×25 cm, 90% hexane/10% IPA/0.1% TFA, 1.0 mL/min (*S*)-**1**: 7.9 min (*R*)-**1**: 9.3 min). Crystallization of the crude product from toluene gave (*S*)-**1** (808 g, 24% yield, >99.94% e.e.); ^1H NMR ($CDCl_3$): δ 4.30–4.50 (m, 2H), 4.90 (m, 1H), 6.80–6.95 (m, 3H), 7.00 (m, 1H), 8.20 (br s, 1H).

4.4. (*S*)-1,4-Benzodioxan-2-carbonyl chloride[3]

To a 1 L round bottom flask was charged (*S*)-**1** (400 g, 2.2 mol) and $SOCl_2$ (33 mL). DMF (0.80 mL) was added to the flask, and the reaction was heated to 84°C for 1.5 h. The reaction was allowed to cool to 30°C. The excess thionyl chloride was carefully distilled at a temperature not exceeding 50°C. The solution was again cooled to 25°C. With agitation, EtOAc (0.8 kg) was added, and the mixture was used in the next reaction.

4.5. (*S*)-*N*-(1,4-Benzodioxan-2-carbonyl)piperazine (*S*)-2[3]

To a 60 L Buchi reactor equipped with mechanical stirrer and a pH meter auto-titrator was charged piperazine (2.6 kg, 30.1 mol) and water (6.0 kg). The reactor was charged with methanol (6.3 kg). With agitation, the slurry was cooled to 0°C. To the reactor was slowly added concentrated hydrochloric acid (3.9 kg) while

maintaining the reaction at a temperature below 30°C. At 30–35°C, an EtOAc solution of the acid chloride (10.0 mol, from 1.79 kg (*S*)-**1**) was slowly added to the reactor over a 4 h period. The reaction mixture was stirred for an additional 30 min, and was then vacuum distilled to a final volume of 15 L while maintaining the reactor temperature at <50°C. After cooling the reactor to 25°C, water (23 kg) was charged. The solids **5** were filtered through a Büchner funnel, and washed with water (1.7 kg). The filtrate was charged with aqueous NH_4OH (5.0 kg) maintaining the temperature at 22± 5°C, and dichloromethane (14.3 kg) was added. After mixing for 10 min, the phases were separated. The aqueous phase was extracted further with dichloromethane (2×7.6 kg). The combined dichloromethane phases were washed with water (7.77 kg). The phases were separated and the dichloromethane solution was concentrated to leave a volume of 4.32 L. toluene (10.8 kg) was charged to the reactor and the solution was distilled to leave a volume of 7.9 L. The reactor was heated until all of the solids had dissolved, without exceeding 120°C. The reaction was slowly allowed to cool to 25°C, and allowed to stir for 1 h. The solids were collected filtration via Büchner funnel and washed with toluene (2×0.5 kg). Additional (*S*)-**2** (170 g) was obtained from the mother liquor. The solids were combined and dried in vacuo to provide (*S*)-**2** (1.86 kg, 75%, 99.90% e.e.); $[\alpha]_D^{22}$ +85.4 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.76 (s, 1H), 2.83–2.96 (m, 4H), 3.43–3.55 (m, 2H), 3.64–3.78 (m, 2H), 4.32 (m, 1H), 4.50 (m, 1H), 4.90 (m, 1H), 6.86 (m, 4H); ^{13}C NMR: δ 43.2, 45.8, 46.4, 47.1, 65.2, 70.5, 117.2, 117.3, 121.5, 122.2, 142.5, 143.2, 164.8. E.e. was determined by HPLC (Chiralpak AD, 10 μm, 4.6 mm×25 cm, 80% hexane/10% EtOH/ 10% MeOH, 1.0 mL/min (*S*)-**2**: 15.5 min (*R*)-**2**: 18.9 min).

4.6. (*S*)-2-D-Tartrate

(±)-*N*-(1,4-Benzodioxan-2-carbonyl)piperazine (±)-**2** (50.0 g) was dissolved in acetonitrile (1130 mL) and methanol (97.5 mL) and treated at rt with a solution of D-tartaric acid (35.0 g) in water (227 mL). The reaction mixture was heated to 80°C, cooled to rt over 30 min and stirred at rt for 3 h. The precipitate was collected by filtration and washed with acetonitrile (150 mL), and dried to give **2**-D-tartrate (31.3 g, 39%). The diastereomeric ratio of the salt was determined by HPLC (Chiralpak AD column (4.6×250 mm) and a mixture of hexane/ethanol/methanol (9:1:1)) to be *S*:*R*=87:13). This wet cake (24.0 g) was further crystallized in a mixture of solvents (MeCN (318 mL); water (107 mL), and MeOH (64 mL)) to give the pure salt (12.0 g, 50% recovery); $[\alpha]_D^{22}$ −9.0 (*c*. 0.3, H_2O); ^{1}H NMR (DMSO-d_6): δ 3.02–3.08 (m, 4H), 3.65 (m, 2H), 3.77 (m, 2H), 4.06 (s, 2H), 4.20 (m, 1H), 4.41 (m, 1H), 5.23–5.26 (m, 1H), 6.91 (m, 4H), 6.0–7.5 (br s, 6H).

4.7. (*S*)-2 from (*S*)-2-D-tartrate

The above salt was treated with aqueous K_2CO_3 and extracted with dichloromethane. The organic phase was then separated and washed with brine, concentrated to give the (*S*)-**2** as free base (>99.3% e.e.); ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 1H), 2.80–2.96 (m, 4H), 3.48–3.78 (m, 4H), 4.26–4.40 (m, 1H), 4.46–4.51 (m, 1H), 4.80–4.84 (m, 1H), 6.85–6.92 (m, 4H).

4.8. Synthesis of (*S*)-doxazosin·HCl[3]

4-Amino-2-chloro-6,7-dimethoxyqunizoline (1.27 kg) and *N*-(1,4-benzodioxan-2-carbonyl)piperazine (*S*)-**2** (1.4 kg) were suspended in *n*-butanol (30 L). The mixture was heated under reflux for 4 h. The reaction mixture was cooled to 60°C. The slurry was collected by filtration. The wet cake was washed with ethyl acetate (500 mL) and dried at 50°C under vacuum to give product (2.5 kg, 99.2% chemical purity, and 99.80% e.e. as determined by chiral HPLC [Chiralcel OD-R, 10 μm, 4.6×25 cm, 0.5 M $NaClO_4$/acetonitrile (55:45), (*R*)-isomer: 17.4 min, (*S*)-isomer: 19.6 min].

4.9. Synthesis of (*S*)-doxazosin free base

(*S*)-Doxazosin·HCl (2.5 kg) was suspended in a mixture of DMF (7 kg) and water (3.6 kg) at 15–35°C and treated with K_2CO_3 (40% aq. 1.8 kg) to give a clear solution. The solution was diluted with water (30 kg) while (*S*)-doxazosin free base precipitated from the solution. The free base was collected by filtration and dried under vacuum to afford the title product (2.1 kg, 95%, 99.90% e.e., 99.7% chemical purity); $[\alpha]_D^{22}$ +25.4 (*c* 1, DMSO); ^{1}H NMR (DMSO-d_6): δ 3.66 (m, 8H), 3.79 (s, 3H), 3.83 (s, 3H), 4.21 (m, 1H), 4.41 (d, J=11.6 Hz, 1H), 5.24 (m, 1H), 6.84 (m, 5H), 7.17 (s, 2H), 7.44 (s, 1H); ^{13}C NMR: δ 41.57, 43.38, 43.99, 45.14, 55.44, 55.84, 64.79, 69.52, 103.04, 103.67, 105.28, 116.90, 117.10, 121.40, 121.51, 142.89, 143.08, 145.09, 148.77, 154.26, 158.29, 161.20, 164.91.

4.10. Synthesis of (*S*)-doxazosin mesylate

(*S*)-Doxazosin free base (2.1 kg) was suspended in MeOH (10 kg) at 25°C and treated with methanesulfonic acid (500 g). The reaction mixture was heated to 55°C for 30 min. The solution was slowly cooled to 25°C for 5 h to give (*S*)-doxazosin mesylate as a slurry. The (*S*)-doxazosin mesylate was collected by filtration and dried under vacuum to give the product (2.33 kg, 90%, 99.90% e.e., 99.7–99.8% chemical purity); $[\alpha]_D^{22}$ +69.6 (*c* 1, DMSO); ^{1}H NMR (DMSO-d_6): δ 2.46 (s, 3H), 3.70 (m, 8H), 3.82 (s, 3H), 3.88 (s, 3H), 4.20 (dd, J=11.7, 6.3 Hz, 1H), 4.47 (dd, J=11.7, 2.4 Hz, 1H), 5.32 (m, 1H), 6.84 (bs, 3H), 6.90 (m, 1H), 7.25 (s, 1H), 7.60 (s, 1H), 8.68 (s, 1H), 8.80 (s, 1H); ^{13}C NMR: δ 40.82, 44.09, 44.44, 56.15, 64.69, 69.47, 99.00, 101.54, 104.62, 116.92, 117.04, 121.44, 135.84, 142.86, 143.08, 146.82, 151.24, 155.32, 161.24, 165.29.

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10. Treatment of (*R*)-**2** (>99% e.e.) with a 20 mol% solution of potassium *tert*-butoxide in toluene at 90°C for 20 h yielded (*R*)-**2** in 10% e.e.