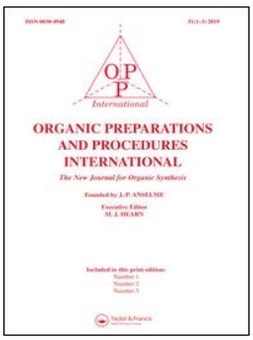

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EXPERIMENTAL PAPER

A Convenient Synthesis of Rivaroxaban from (*S*)-Epichlorohydrin

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Rivaroxaban **1** is an oxazolidinone derivative that is the first representative of a new series of anticoagulants,[1,2] and it was soon followed by apixaban, betrixaban and darexaban.[3–5] It is an oral, direct factor Xa inhibitor developed by Bayer and marketed as *Xarelto*. Factor Xa (FXa) is an essential blood coagulation factor that is responsible for the initiation of the coagulation cascade. Rivaroxaban **1** acts as an anticoagulant to prevent venous thromboembolism after major orthopaedic surgery in particular. It allows predictable anticoagulation with no need of dose adjustments and routine coagulation monitoring. Its pharmacological properties and therapeutic indications are amply summarized in the literature.[1,2,6–9]

Several synthetic methods were reported for the preparation of rivaroxaban **1**.[1,2,10–15] Three key structures can be used as advanced intermediates to prepare it (Figure 1). The first is derived from 4-(4-aminophenyl)morpholine-3-one **2a**, or its alkylated congener **2b** or a related carbamate **2c**. The second generally used building block for rivaroxaban is derived from 5-chlorothiophene-2-carboxylic acid **3a** or its functional derivatives such as chloride **3b** and amide **3c**. Both advanced intermediates, **2** and **3**, are available on the market and their syntheses have been fully described in the literature.[1,11,16–18]

A chiral building block is the third and very important advanced intermediate which is needed for rivaroxaban. The synthetic approaches for rivaroxaban differ especially in this crucial chiral building block, which is the source of the 2-oxo-1,3-oxazolidine moiety. Chiral building blocks which have already been used in the synthesis of rivaroxaban are (S)-glycidylphthalimide **4**, (*S*)-3-aminopropane-1,2-diol **5**, (*R*)-epichlorohydrin **6** and (*R*)-glycidyl butyrate **7** (Figure 1).[10–15]

The procedure mentioned in the basic patent has been carried out by means of (*S*)-glycidylphthalimide **4** as the chiral building block.[10] This process led to the required product **1** in four steps starting from the precursor **2a** (see Scheme 1). The second procedure has been carried out by means of (*S*)-3-aminopropane-1,2-diol **5** as the chiral building block.[11] This led to the desired product **1** in four steps starting from precursor **3b**. According to a number of other disclosures, rivaroxaban **1** could also be formed by means of (*R*)-epichlorohydrin **6** starting from substituted aniline **2a** in methods requiring three to five steps[12–14] (see Scheme 2). A more recent variation uses the (*R*)-glycidyl

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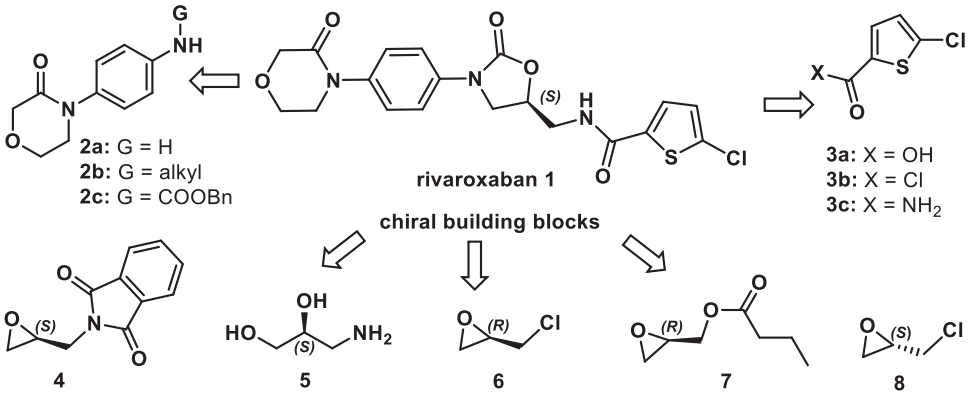
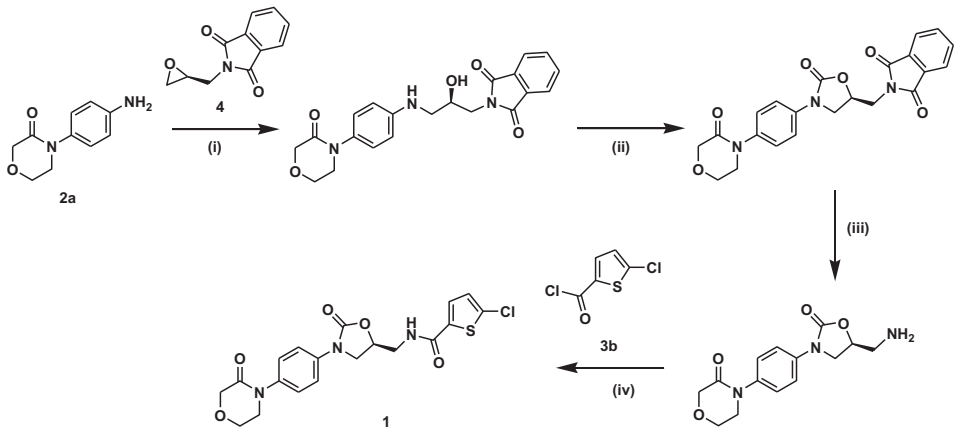


Figure 1. Retrosynthetic analysis for rivaroxaban **1**.



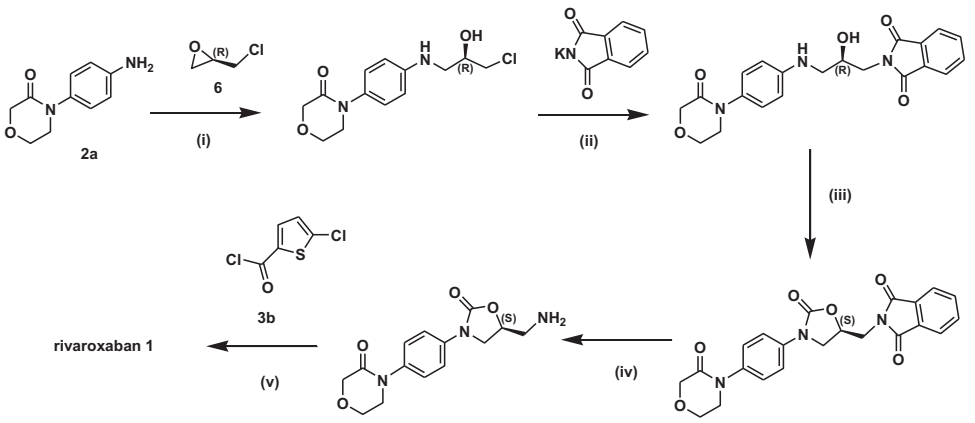
(i) EtOH, H_2O, **(ii)** CDI, DMAP, THF, **(iii)** CH_3NH_2, H_2O, EtOH, **(iv)** pyridine, THF

Scheme 1. The first method for preparation of rivaroxaban **1**.

butyrate **7** as the source of the chiral center.[15] This process led to **1** in five steps starting from carbamate **2c**.

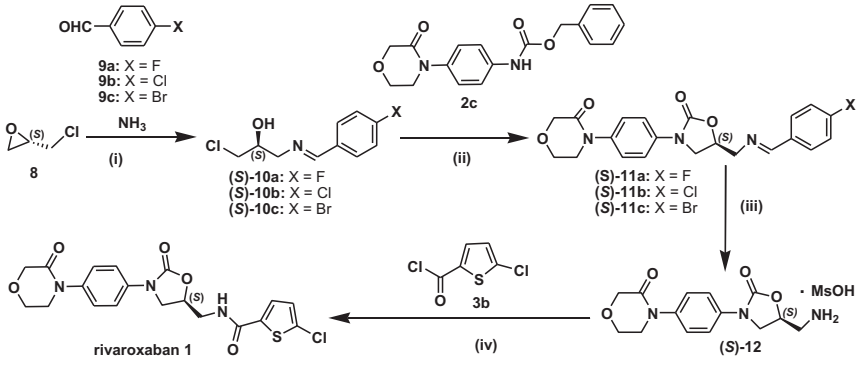
Commercially available chiral moieties have been sought for the manufacture of **1**. (*S*)-Epichlorohydrin **8** was found to be a suitable candidate for this purpose.[19–21] The important advantages of (*S*)-epichlorohydrin in the production of **1** are its good availability and price. As well, it has already been used in numerous industrial preparations of biologically active substances, and these preparations are well documented. For example, it is used in the production of L-carnitine or the antidiabetic sitagliptin.[22,23] The new and efficient method, whose details are presented in this paper, is based on **8** as a readily available chiral building block. It is suitable for scale-up for the active pharmaceutical ingredient (API).

The method is shown in Scheme 3. Commercially available (*S*)-epichlorohydrin **8** was first converted to (*S*)-1-(4-halobenzylideneamino)-3-chloropropan-2-ol **(*S*)-10** (X = F, Cl, Br) by treating with ammonia and 4-halobenzaldehyde **9** (X = F, Cl, Br) in yields from 51



(i) IPA, **(ii)** DMF, **(iii)** CDI, CH_2Cl_2, **(iv)** $NH_2NH_2.H_2O$, MeOH, **(v)** pyridine, THF

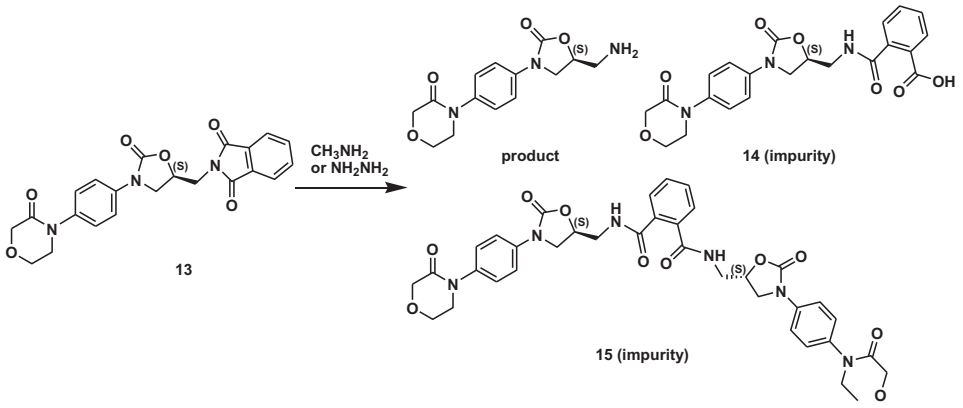
Scheme 2. The method for preparation of rivaroxaban **1** by means of (*R*)-epichlorohydrin **6**.



(i) THF, Hept., **(ii)** t-BuOLi, CH_2Cl_2, **(iii)** MsOH, EtOH, H_2O, **(iv)** MEK, H_2O, $KHCO_3$, EtOH

Scheme 3. The method for preparation of rivaroxaban **1** by means of (*S*)-epichlorohydrin.

to 70%, with chemical purities 99.0-99.4% (by GC) and contents of the unwanted enantiomer 0.10-0.55%. Coupling of **(*S*)-10** with benzyl 4-(3-oxomorpholine-4-yl)phenylcarbamate **2c** was done by lithium *tert*-butoxide in dichloromethane and led to oxazolidine **(*S*)-11** in high purity (optical 99.6-100%, chemical 99.3-100% by HPLC) and yields from 60 to 84%. High optical purity of the intermediate **(*S*)-11** is the key factor of our process because we were not able to improve this parameter for subsequent intermediates effectively. The easy deprotection of the benzylidene group by using methanesulfonic acid in ethanol gave the amine **(*S*)-12** as a crystalline methanesulfonate salt in almost quantitative yield and in high chemical and optical purities. The reaction of amine **(*S*)-12** with 5-chlorothiophene-2-carbonyl chloride **3b** in the final step led to target compound **1** (yield 96%, HPLC 99.95%, content of (*R*)-isomer less than 0.03%). The same process can be used for preparation of the (*R*)-enantiomer of rivaroxaban when (*R*)-epichlorohydrin is used as chiral building block.



Scheme 4. The common deprotection process.

The procedure in Scheme 3 (X = Cl) allows one to obtain rivaroxaban **1** reproducibly in overall yields of about 53%, with chemical purity higher than 99.8%, with individual impurity content below 0.1% (by HPLC) and with the content of the (*R*)-isomer less than 0.05% (according to HPLC). The chlorinated intermediates were preferred for larger-scale synthesis. The reason for that was both the overall yield of the process and the lower cost of 4-chlorobenzaldehyde. Two interesting features relating to the process were recognized. These are the selective deprotection step and the unusual chirality phenomenon which allows obtaining rivaroxaban from both optical isomers of epichlorohydrin.

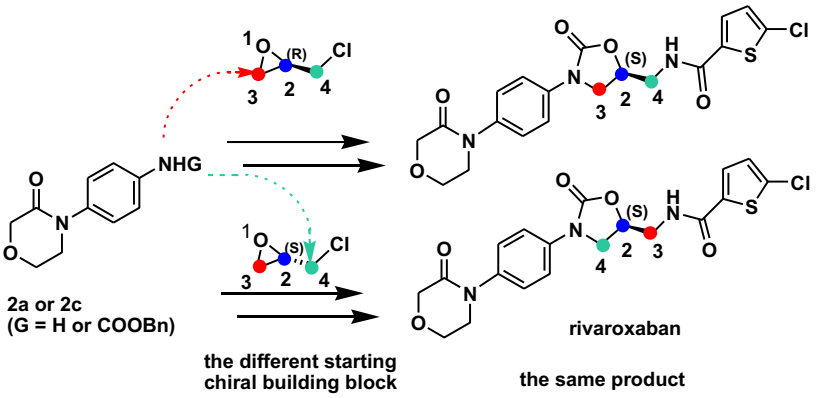
The method to perform the deprotection reaction leading to amine salts **(*S*)-12** is quite different from the previously described solutions.[1,2,10–15] The procedure is carried out hydrolytically under mild conditions and it is characterized by high yields (94-97%) (see Scheme 3). An aromatic aldehyde is liberated together with the target amine salt **(*S*)-12** during the deprotection. This favorable feature is consistent with the high solubility of aldehyde **9** in comparison with amine salts which are almost insoluble. This allows one to isolate chemically pure amine. On the other hand, the previous deprotection starting from intermediate **13** is characterized by production of critical impurities **14** and **15**[24] (see Scheme 4).

Another interesting feature is that rivaroxaban characterized by the configuration (*S*)- can be prepared by means of either (*R*)- or(*S*)- optical isomers of epichlorohydrin (see Scheme 5). This possibility is provided by the fact that epichlorohydrin contains two reactive centers that are capable of reacting with amines. This leads to a very interesting phenomenon; the resulting chirality depends on the order of reaction steps.

In conclusion, a novel and convenient four-step route has been developed for the synthesis of the antithrombotic drug rivaroxaban **1**. The process has the key features that (*S*)-epichlorohydrin is used as a readily-available chiral building block and that the easy deprotection of the benzylidene group from intermediate **(*S*)-11** leads to the salt with methanesulfonic acid **(*S*)-12**. The target product **1** was obtained in good overall yield and in excellent quality.

Experimental section

^{1}H and ^{13}C NMR spectra were measured with a Bruker Avance 500 spectrometer with the measuring frequencies of 500.131 MHz and 125.762 MHz respectively. The spectra



Scheme 5. Comparison of synthetic methods based on (*S*)- and (*R*)- epichlorohydrins.

were measured in DMSO-d_6 or in $CDCl_3$ solutions. ^1H chemical shifts were related to TMS (δ = 0.00 ppm) and ^{13}C chemical shifts to DMSO-d_6 (δ = 39.6 ppm) or $CDCl_3$ (δ = 77.6 ppm), respectively. The mass spectra were measured using a Sciex API 3000 Mass Spectrometer (Sciex, Canada) with positive atmospheric pressure ionization (TurboIonspray) or using an LTQ Orbitrap Hybrid Mass Spectrometer (ThermoFinnigan, USA) with direct injection into the APCI source in positive mode. Melting points were measured on a Kofler block with the sample heating speed of 10 °C (to 70 °C) and 4 °C (over 70 °C) per minute. HPLC chromatograms were measured with an Alliance 2695/2695XC HPLC device with PDA detector of the W2996/W2998 type. The HPLC method used to check the chemical purity of rivaroxaban was as follows: Stationary phase Ascentis Express RP-Amide, 100 x 3.0 mm, internal diameter 2.7 μm, column temperature 15 °C; mobile phase 0.01 M aqueous solution of ammonium acetate adjusted to pH 5.0 (A) and acetonitrile (B); gradient mode with flow rate of 0.6 ml/min; composition at the start was 90% of A and 10% of B; this composition was held for 2 min., then changed to 35% of A and 65% of B over 5 minutes, then changed to 25% of A and 75% of B over 4 min.; this composition was held for 2 min., than changed to 90% of A and 10% of B over 1 min. and this composition was held to the end (overall time 16 min.). Detection at the wavelength of 245 nm was used. Acetonitrile was used as the solvent for the preparation of the samples, 10-20 µl of the solution were used for the injection. This gradient HPLC method was used for checking the quality of the target substance **1** including its (*R*)-enantiomer. The HPLC method used to check the optical purity of rivaroxaban was as follows: stationary phase Chiralpak IA, 250 x 4.6mm; internal diameter 5µm, column temperature 40 °C; measurements were carried out in the isocratic mode; mobile phase: hexane (40%) and 2-butanol (60%). The flow rate of the mobile phase was 1 ml/min. Detection at 251 nm was used. The HPLC method to determine chemical purity of **(*S*/*R*)-11** was as follows: stationary phase Gemini-NX C18 110A, 100 x 4.6 mm, internal diameter 3 μm, column temperature 35 °C; measurements were carried out in the isocratic mode; mobile phase: 10 mM aqueous solution of triethylamine adjusted to pH 11.5 (60%) and methanol (40%); the flow rate of the mobile phase was 1.5 ml/min; detection at 250 nm was used. The HPLC method to determine the optical purity of **(*S*/*R*)-11** was as follows: stationary phase Lux 3u Amylose-2, 150 x 4.6 mm, internal diameter 3μm, column temperature 35 °C;

measurements were carried out in the isocratic mode; mobile phase: hexane (25%) and ethanol (75%) with addition of 0.2% diethylamine; the flow rate of the mobile phase was 1.5 ml/min.; detection at 252 nm was used. The HPLC method for chemical purity of **(*S*/*R*)-12**: **s**tationary phase Ascentis Express RP-Amide, 100 x 3.0 mm, internal diameter 2.7μm, column temperature 10 °C was used for analyses; mobile phase: 0.01 M aqueous solution of sodium octanesulfonate adjusted to pH 2.5 (A) and acetonitrile (B) was used. Gradient mode with the flow rate of mobile phase 0.5 ml/min was used. Composition at the start was 85% of A and 15% of B, this composition was held for 13 min., than changed to 50% of A and 50% of B over 5 minutes, this composition was held for 5 min., then changed to 85% of A and 15% of B over 2 min. and this composition was held to the end (overall time 30 min.). Detection at the wavelength of 245 nm was used. The HPLC method used to determine the optical purity of **(*S*/*R*)-12**: **s**tationary phase Lux 3u Cellulose-4, 150 x 4.6 mm, internal diameter 3 μm, column temperature 40 °C was used for analyses; measurements were carried out in the isocratic mode; mobile phase: hexane (10%) and ethanol (90%) with addition of 0.1% diethylamine. The flow rate of mobile phase was 1 ml/min. Detection at 245 nm was used. The HPLC method used to determine the optical purity of **(*S*/*R*)-10c**: stationary phase Chiralpak AD-3, 150 x 4.6 mm, internal diameter 3µm, column temperature 40 °C was used for analyses; measurements were carried out in the isocratic mode; mobile phase: hexane (85%) and ethanol (15%). The flow rate of mobile phase was 1.5 ml/min. Detection at 256 nm was used. GC chromatograms were measured with the Agilent technologies GC system 6890N and GC system 7890A with flame-ionization detector. The GC method used to determine chemical purity of **(*S*/*R*)-10**: stationary phase Rtx-5 Amine (30 m; 0.53 mm; 3.0 µm); temperature program: 60 °C (0 min.), 10 °C/min to 280 °C (8 min.); carrier gas: helium, constant flow 35 cm/s; injector temperature 250 °C, temperature at detector 290 °C. GC method used to determine optical purity of **(*S*/*R*)-10a** and **(*S*/*R*)-10b**: **s**tationary phase DB-1701 (30 m; 0.32 mm; 1.0 µm); temperature program: 200 °C (2 min), 5 °C/min to 280 °C (20 min); carrier gas: helium, constant flow 35 cm/s; injector temperature 250 °C, temperature at detector 300 °C. Analyzed compounds were reacted with (-)-(*R*)-menthylchlorformate in dichloromethane for 1 hour before the analysis. All reagents were from commercial sources.

Preparation of (S)-1-(4-chlorobenzylideneamino)-3-chloropropan-2-ol ((S)-10b))

An aqueous ammonia solution (2.0 L, 25-28%) was poured at ambient temperature into a stirred solution of 4-chlorobenzaldehyde (3.0 kg) in tetrahydrofuran (5.6 L). The mixture was stirred at room temperature for approx. 20 minutes. After that (*S*)-epichlorohydrin (2.0 L) and tetrahydrofuran (0.8 L) were added. The reaction mixture was stirred at approximately 33 °C for 2 hours, further at 55 °C for 4 hours and then gradually cooled to a temperature below 25 °C for another 10 hours. Then 65 L of toluene and 4.0 L of water were added and the separated organic layer was washed with brine (solution of 0.95 kg NaCl in 6.5 L water). The organic solution was concentrated by vacuum distillation; toluene (8.0 L) was poured into the residue and vacuum distillation was carried out once again. Heptane (13.0 L) and toluene (4.0 L) were poured into the obtained oil; the emulsion was stirred and heated at 60 °C to gain a clear solution. The solution was stirred while cooling

from a temperature of approx. 60 °C to approx. 10 °C for 1 hour and then stirred at 5 °C for another 1 hour. The precipitated crystalline product was collected by filtration, washed with heptanes (2x2.25 L) and dried. Off-white crystals were obtained (3.47 kg, yield 70%), m.p. 70-71 °C, purity by GC 99.3%, content of (*R*)- isomer by GC less than 0.10%. ^{1}H NMR (DMSO-d_6),δ(ppm): 3.60 (m, 2H); 3.73 (m, 2H); 3.95 (m, 1H); 5.26 (m, 1H); 7.51 (m, 2H); 7.77 (m, 2H); 8.34 (m, 1H).^{13}C NMR (DMSO-d_6), δ(ppm): 47.9; 63.6; 69.9, 128.7; 129.5; 134.8; 135.2; 161.3. MS (m/z): 232.0288 $(M+H)^+$. The following compounds **(*R*/*S*)-10** were prepared in an analogous manner.

Preparation of (R)-1-(4-chlorobenzylideneamino)-3-chloropropan-2-ol ((R)-10b))

Yield 51%, off-white crystals, m.p. 69-70 °C, purity by GC 99.4%, content of (*S*)- isomer by GC 0.09%. NMR and MS spectra correspond to **(*S*)-10b**.

Preparation of (S)-1-(4-fluorobenzylideneamino)-3-chloropropan-2-ol ((S)-10a))

Yield 51% off-white crystals, m.p. 59-61 °C, purity by GC 99.4%, content of (*R*)- isomer by GC 0.55%. ^{1}H NMR ($CDCl_3$), δ(ppm): 3.07 (bs, OH); 3.66 (m, 2H, CH_2); 3.78 (m, 2H, CH_2); 4.12 (pent, 1H, CH); 7.00-7.14 (m, 2H); 7.68-7.76 (m, 2H); 8.29 (s, 1H, CH).^{13}C NMR ($CDCl_3$), δ(ppm): 47.1; 63.1; 70.9; 115.7; 130.1; 131.9; 162.2; 164.5. MS (m/z): 216.0584 $(M+H)^+$.

Preparation of (R)-1-(4-fluorobenzylideneamino)-3-chloropropan-2-ol ((R)-10a))

Yield 56% off-white crystals, m.p. 55-58 °C, purity by GC 98.0%, content of (*S*)- isomer by GC 0.29%. NMR and MS spectra correspond to **(*S*)-10 (X = F)**.

Preparation of (S)-1-(4-bromobenzylideneamino)-3-chloropropan-2-ol ((S)-10c))

Yield 54% off-white crystals, m.p. 81.5-83.5 °C, purity by GC 99.0%, content of (*R*)- isomer by HPLC 0.18%. ^{1}H NMR ($CDCl_3$), δ (ppm): 2.78 (bs, OH); 3.65 (m, 2H, CH_2); 3.75 (m, 2H, CH_2); 4.13 (pent, 1H, CH); 7.34-7.58 (m, 4H); 8.29 (s, 1H, CH).^{13}C NMR ($CDCl_3$), δ (ppm): 47.1; 63.1; 70.8, 125.6; 129.6; 131.9; 134.6; 162.4.MS (m/z): 277.9782$(M+H)^+$.

Preparation of (R)-1-(4-bromobenzylideneamino)-3-chloropropan-2-ol ((R)-10c))

Yield 51% off-white crystals, m.p. 82-84 °C, purity by GC 99.5%, content of (*S*)- isomer by HPLC 0.75%. NMR and MS spectra correspond to **(*S*)-10 (X = Br)**.

Preparation of 4-{4-[(S)-5-[(((4-chlorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one ((S)-11b))

Lithium tert-butoxide (2.1 kg) and dichloromethane (32.0 L) were added into a stirred mixture of benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate (3.8 kg) and dichloromethane (2.0 L). The reaction mixture was stirred and heated at 40 °C for approx. 10 minutes, then

cooled below 35 °C. After that 3.3 kg of (*S*)-1-chloro-3-{[(4-chlorophenyl)methylene]amino}propan-2-ol and 11.5 L dichloromethane were added. The suspension was stirred and heated at 40-45 °C for 22 hours, then cooled below 25 °C, 34.0 L of water added, then vigorous stirring followed for 30 min. The organic layer was separated and dried over sodium sulfate. The mixture was heated to 40 °C and filtered. Ethanol (30.0 L) was poured into the filtrate and was distilled off under vacuum at 300-400 mbar and a bath temperature at 45 °C. Ethanol (27.0 L) was poured into the concentrated residue, the mixture heated at 50 °C for 15 minutes, then gradually cooled to 15 °C and stirred for 1.5 hours. The precipitated solid was collected by filtration, washed with cold ethanol (2x 4.0 L) and dried. A nearly white powder was obtained (4.04 kg, yield 84%), m.p. 143-144 °C, HPLC 99.3%, optical purity 100.0%, $[\alpha]_D^{25}$=-101.9° (CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 3.75 (m, 2H, CH_2); 3.88-3.99 (m, 2H, CH_2); 4.00-4.09 (m, 2H, CH_2); 4.09-4,21 (m, 2H, CH_2); 4.34 (s, 2H, CH_2); 4.97 (m, 1H, CH); 7.30-7.40 (m, 4H); 7.54-7.68 (m, 4H); 8.35 (m, 1H, CH).^{13}C NMR ($CDCl_3$), δ (ppm): 48.2; 49.7; 63.2; 64.1; 68.6; 71.8; 119.0; 126.1; 128.9; 129.5; 134.0; 137; 137.1; 137.3; 154.5;163.5; 166.7. MS (m/z): 414.1219 $(M+H)^+$. The following compounds **(*R/S*)-11** were prepared in an analogous manner.

Preparation of 4-{4-[(R)-5-[((4-chlorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one ((R)-11b))

Yield 73% off-white powder, m.p. 146-147 °C, purity by HPLC 100%, optical purity by HPLC 100%, $[\alpha]_D^{25} = +102.3°$ (CH_2Cl_2). NMR and MS spectra correspond to **(*S*)-11 (X = Cl).**

Preparation of 4-{4-[(S)-5-[((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one ((S)-11a))

Yield 78% off-white powder, m.p. 156-157 °C, purity by HPLC 99.3%, optical purity by HPLC 99.6%, $[\alpha]_D^{25}$ = -95.7° (CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ(ppm): 3.75 (m, 2H, CH_2); 3.88-3.99 (m, 2H, CH_2); 4.03 (m, 2H, CH_2); 4.09-4,19 (m, 2H, CH_2); 4.34 (s, 2H, CH_2); 4.97 (m, 1H, CH); 7.08 (m, 2H); 7.34 (m, 2H); 7.59 (m, 2H); 7.70 (m, 2H); 8.35 (m, 1H, CH).^{13}C NMR ($CDCl_3$), δ(ppm): 48.1; 49.7; 63.1; 64.1; 68.5; 71.8; 115.7; 119.0; 126.1; 130.3; 131.8; 137.0; 154.5; 163.3; 163.6; 165.6; 166.7.

Preparation of 4-{4-[(R)-5-[((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one ((R)-11a))

Yield 68% off-white powder, m.p. 156.5-157.5 °C, purity by HPLC 99.7%, optical purity by HPLC 100%, $[\alpha]_D^{25} = +95.2°$ (CH_2Cl_2). NMR spectra correspond to **(*S*)-11a**.

Preparation of 4-{4-[(S)-5-[((4-bromophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one ((S)-11c))

Yield 60% off-white powder, m.p. 150.5-151.5 °C, purity by HPLC 100%, optical purity by HPLC 100%, $[\alpha]_D^{25}$ = -95.6° (CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ(ppm): 3.68 (m, 2H, CH_2); 3.81-3.91 (m, 2H, CH_2); 3.96 (m, 2H, CH_2); 4.02-4.12 (m, 2H, CH_2); 4.27 (s, 2H,

CH_2); 4.90 (m, 1H, CH); 7.27 (m, 2H, 2xCH); 7.45-7.53 (m, 6H, 6xCH); 8.26 (m, 1H, CH).[13]C NMR ($CDCl_3$), δ(ppm): 48.1; 49.7; 63.2; 64.1; 68.6; 71.7; 119.0; 125.7; 126.1; 129.7; 131.9; 134.4; 137.0; 137.1; 154.5; 163.6; 166.8.

Preparation of 4-{4-[(R)-5-[(((4-bromophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one ((R)-11c))

Yield 55% off-white powder, m.p. 149-150 °C, purity by HPLC 99.9%, optical purity by HPLC 100%, $[\alpha]_D^{25} = +95.7°$ (CH_2Cl_2). NMR spectra correspond to **(*S*)-11 (X = Br).**

Preparation of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one methane-sulfonate salt ((S)-12))

4-{4-[(*S*)-5-[(((4-chlorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidine-3-yl]phenyl}morpholin-3-one (4.0kg) was added to ethanol (40 L) and this mixture was stirred and heated to 45 °C. After that a solution of methanesulfonic acid (0.64 L) in a mixture of 12.0 L of ethanol and 0.288 L of water was added at once, whereupon a cloudy solution was obtained. The crystalline product precipitated from the solution over approx. 1 minute. The suspension was stirred at 55 °C for 1 hour and then slowly cooled to 20 °C. The solid product was collected by filtration, washed with ethanol (3 x 4.0 L) and dried under vacuum. A nearly white powder was obtained (3.74 kg, yield 94%), m.p. 275-278 °C (decomp.), HPLC 99.8%, the content of (*R*)-isomer was under 0.03%. ^{1}H NMR (DMSO-d_6), δ (ppm):2.33 (s, 3H, CH_3); 3.28 (m, 2H, CH_2); 3.72 (m, 2H, CH_2); 3.87 a 4.22 (m, 2H, CH_2); 4.00 (m, 2H, CH_2); 4.20 (s, 2H, CH_2); 4.93 (m, 1H, CH); 7.44 (m, 2H); 7.54 (m, 2H); 8.13 (bs, 3H, -NH_2 + -SO_3H).[13]C NMR (DMSO-d_6), δ (ppm):39.8; 41.7; 47.2; 49.0; 63.5; 67.7; 69.5; 118.5; 125.9; 136.3; 137.2; 153.6; 166.0.Yields starting from **(*S*)-11a** and **(*S*)-11c** were 95-97%, HPLC over 99.5%, content of (*R*)-enantiomer 0.28-0.03%.

Preparation of 4-{4-[(5R)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one methane-sulfonate salt ((R)-12))

The synthetic process was the same as for **(*S*)-12**. Yields starting from **(*R*)-11** (X = F, Cl, Br) were 98-99%, HPLC over 99.5%, contents of (*S*)-enantiomer 0.21-0.03%. NMR spectra correspond to **(*S*)-12.**

Preparation of 5-chlorothiophene-2-carboxylic acid chloride (3b)

To a stirred suspension of 4.0 kg of 5-chlorothiophene-2-carboxylic acid in 8.0 L of toluene was added a solution of 2.0 L thionyl chloride in 4.0 L of toluene at 75 °C. The mixture was stirred and heated at reflux for 1 hour, then for another 1 hour at room temperature. The obtained solution was concentrated at atmospheric pressure by distilling off 12.0 L of liquid. One obtained approx. 10.0 L of slightly dark solution characterized by a concentration of 2.14 M of target chloride. This solution was used in the next step for the synthesis of rivaroxaban without further adjustments.

Preparation of Rivaroxaban 1

The methanesulfonate salt **(*S*)-12** (2.0 kg) was dissolved in a mixture of 5.0 L methyl ethyl ketone (MEK) and 10.0 L of water; we then added a solution of $KHCO_3$ (1.55 kg in 5.0 L of water), and the mixture was stirred and cooled to 15 °C. This was followed by the addition of a solution of the acid chloride of 5-chlorothiophene-2-carboxylic acid (13.9 L, 2.14 M in toluene) in 6.0 MEK and the reaction mixture was stirred at 20 °C for 15 minutes. Then ethanol (16.0 L) was added and stirred at 35 °C for 30 min. The mixture was stirred, heated to 50 °C for 30 min, filtered, the clear filtrate cooled to 5 °C and stirred for 2 hours. The separated product was collected by filtration, washed with hot water (2 x 2.5 L, 60 °C), ethanol (2 x 3.0 L) and dried under vacuum. Rivaroxaban (2.16 kg, yield 96%) was obtained in the form of a nearly white powder with m.p. 229.5-231 °C, HPLC 99.95%, the content of (*R*)- isomer was under 0.03%. ^{1}H NMR (DMSO-d_6), δ(ppm): 3.61 (t, 2H, CH_2); 3.71 (m, 2H, CH_2); 3.85 a 4.19 (m, 2x1H, CH_2); 3.97 (m, 2H, CH_2); 4.19 (s, 2H, CH_2); 4.84 (pent, 1H, CH); 7.18 (d, 1H); 7.40 (m, 2H); 7.56 (m, 2H); 7.68 (d, 1H); 8.95 (bt, 1H, NH).^{13}C NMR (DMSO-d_6), δ(ppm): 42.2; 47.4; 49.0; 63.4; 67.7; 71.3; 118.3; 125.9; 128.1; 128.4; 133.2; 136.4; 137.0; 138.4; 154.0; 160.8; 165.9.MS (m/z): 436.0729 $(M+H)^+$.

Preparation of (R)-5-chloro-N-({2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-thiophen-carboxamide (R-rivaroxaban)

The optical isomer of rivaroxaban with the configuration (*R*)- was obtained by the analogous procedure from methanesulfonate salt **(*R*)-12** from (*R*)-epichlorohydrin. The yield was 76% for the last step, HPLC 99.90%, the content of (*S*)-isomer was under 0.03%. NMR and MS spectra corresponded to rivaroxaban.

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