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Practical synthesis of a peptidomimetic thrombin inhibitor

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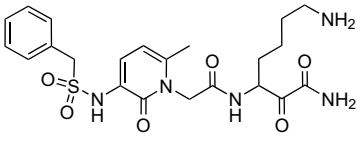
ABSTRACT

Compound **1** is a low molecular weight thrombin inhibitor developed for treatment of deep vein thrombosis and cardiovascular diseases. We herein report our efforts to develop a robust, efficient and reproducible process suitable for large-scale synthesis of compound **1**.

1. Introduction

Compound **1** is a low molecular weight thrombin inhibitor with a high selectivity ratio in the inhibition of factor Xa.[1] The compound is a peptidomimetic containing a transition state analogue, which forms a complex with Ser195 of thrombin, inducing prolonged coagulation time and inhibition of platelet aggregation.[2] Developed for treatment of deep vein thrombosis and arterial indications, the hydrochloride salt of **1** was selected development candidate as a racemate, since the active (*S*)-enantiomer rapidly racemizes in solution. A hydrogen/deuterium exchange experiment performed at pH 7.4 for 1 day shows that 72% of αC–H is converted into αC–D.



(+/-)-1.HCl

We herein report our process development efforts to scale-up an alternative route of synthesis of compound **1** suitable for further development. The medicinal chemistry route (Scheme 1) goes through two building blocks **3** and **8**, which are readily available from commercially available raw materials. Intermediate **3** is synthesized in three steps from *Z*-Lys(Boc)OH **4** by using known in-house procedure,[3] while intermediate **5** is synthesized in three steps from 2-hydroxy-6-methyl-pyridine-3-carboxylic acid **2** according to the literature prescription.[4]

2. Results and discussions

The process starting from building blocks **3** and **5** as described in Scheme 1, was not deemed suitable for larger-scale production for several reasons: (a) the Dess–Martin reagent must be avoided on large scale because of safety concerns; (b) aminolysis of α-enol ester **6** upon treatment with ammonia is not suitable for scaling-up. The reaction is hampered by a major solubility issue, which may result in stirring problem; (c) the reverse phase chromatography prescription to purify crude material **1** lacks robustness for an application to large scale; (d) the overall yield of this process over the last seven steps (12%) is rather low; (e) moreover, preliminary development work raises an additional issue: Synthesis of intermediate **6** by using described reaction conditions resulted in the formation of two main impurities, **9** and **10** (Fig. 1).

Impurity **9**, identified as a bis-hydroxy derivative is formed by reaction of **6** with excess free amine **5**. Compound **10** a bis-sulfonamide impurity, originates from the esterification of **3** with alcohol **6**. These impurities amount up to 30% in the reaction mixture and any efforts failed to wash them from hydroxy ester **6**.

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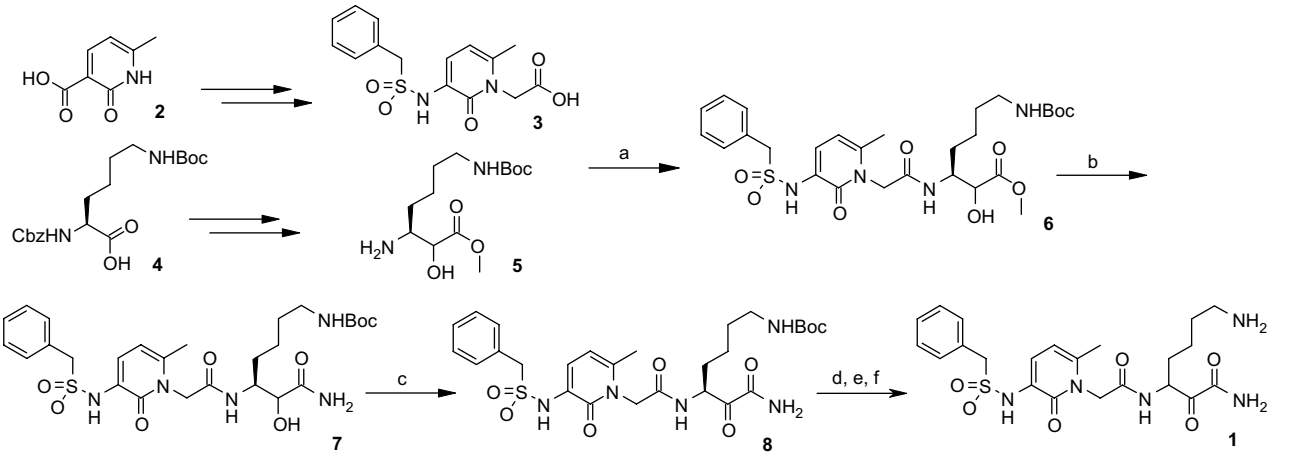


Scheme 1. Medicinal chemistry route. Reagents and conditions: (a) *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimine (EDC), hydroxybenzotriazole (HOBt), *N*,*N*-diisopropylethylamine, DMF; (b) methanol, NH_3; (c) Dess–Martin periodinane, dichloromethane; (d) TFA, dichloromethane; (e) phosphate buffer pH 8; (f) (1) purification by reverse phase chromatography, (2) ion exchange chromatography.

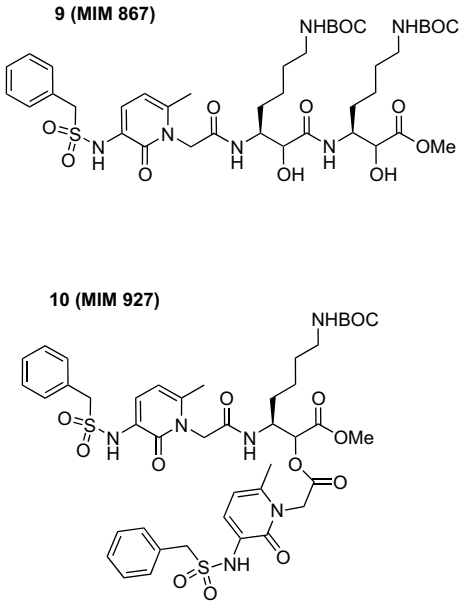
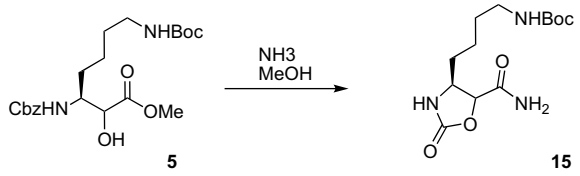


Figure 1. Identified impurities.

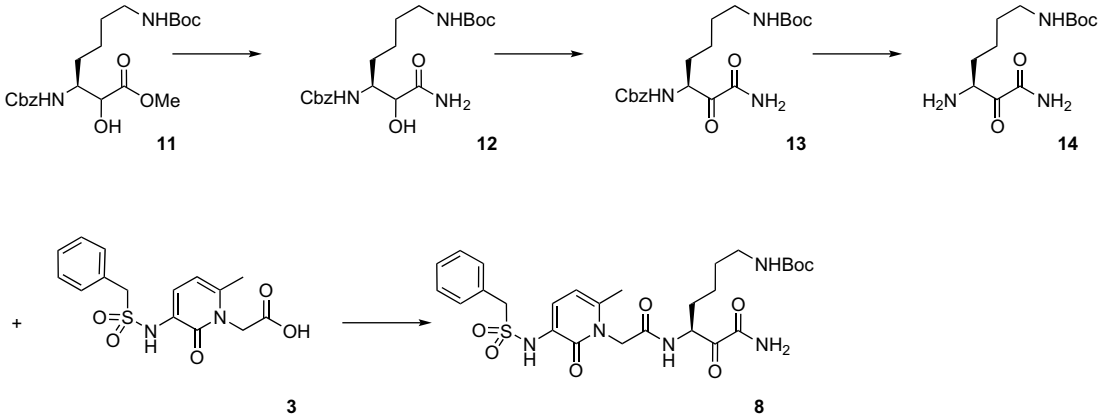
A first alternative route was sought to circumvent the issues described above. This approach (Scheme 2) makes the synthesis route more convergent, as three steps instead of five remains after peptidic coupling reaction.

When **11** was submitted to the Medicinal Chemistry procedure for amide formation (15N ammonia solution in MeOH or 15N methanolic ammonia solution), the solubility issue was not encountered, but a major impurity identified by NMR as the oxazolidinone structure **15** (Scheme 3) was detected up to 20%. Formation of **15** can be rationalized by intramolecular cyclization of the hydroxyl with the carbamate protecting group.

Removal of this impurity by crystallization from diisopropylether gave **12** in 81% yield and 99% HPLC purity. In addition, the reaction proved to be sluggish and doesn't go to completion even after three days. Prolonged reaction time and processing time seriously limit the throughput of this step. A modified Weinreb procedure ($AlMe_3$, NH_3, CH_2Cl_2/THF)[5] was tested to speed up the reaction, which has resulted in a complete conversion within 12 h at 40 °C, without side product formation. Presumably, ammonia trapped as an aluminate complex act as a deactivated nucleophile,



Scheme 3. Formation of impurity **15**.

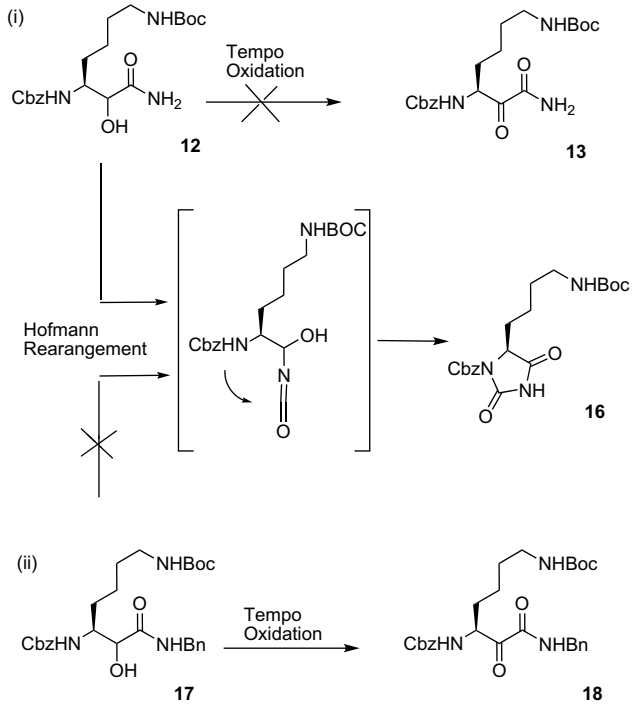


Scheme 2. First alternative route.

which is unable to promote the cyclization. Compound **12** was isolated in very high purity (>99%) by precipitation in water and a single crystallization from isopropylether.

With the hydroxyl amide **12** available, we turned our attention to the key oxidation step. The choice for the mild Dess–Martin reagent in Medicinal Chemistry originates from the intention to synthesize a chiral product. But with the aim to deliver a racemate, the oxidation methods available are not limited to mild reagents.

Based on good in-house experience, our first choice was to use the nitroxyl radical TEMPO as a catalyst in a biphasic reaction mixture of dichloromethane and aqueous sodium hypochlorite as co-oxidant.[6] A single product was isolated in 77% yield and 95% purity. Amazingly, analysis by LC–MS and NMR showed that the isolated product was the hydantoin compound **16** rather than the desired keto amide **13**. We reasoned that the presence of bromide in the reaction mixture promotes a Hoffman type rearrangement,[7] giving an isocyanate as an intermediate, which in turn, is trapped by the nitrogen in δ-position leading to the hydantoin structure **16** (Scheme 4, (i)).

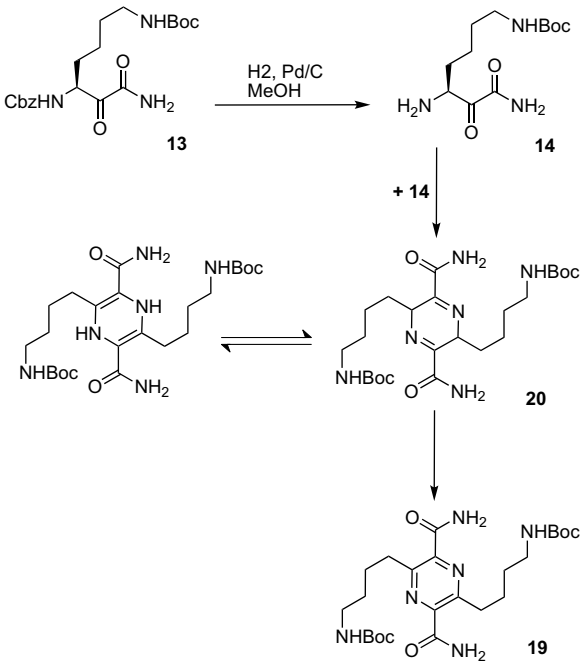


Scheme 4. Formation of hydantoin **18**—proposed mechanism.

In order to confirm the validity of this mechanism, the same sequence was carried out with benzylamine (Scheme 4, (ii)) since Hoffmann rearrangement do not take place with substituted amides. In that case no rearrangement was observed, leading to the expected oxidation product **18** in 81% yield. To the best of our knowledge, this is the first example in the literature of a chiral hydantoin synthesis via a TEMPO-catalyzed mechanism.

Among other tested oxidation conditions, Ru-oxidation by using tetrapropylammonium perruthenate (TPAP) reagent[8] has resulted mainly in degradation. The best result was obtained with a Moffat-type oxidation. When a combination of DMSO, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimine (EDC) and catalytic amount of dichloroacetic acid (DCAA)[9] have been used, **13** was isolated in 95% yield and >90% purity. The low solubility of hydroxyl amide **12** was in addition nicely circumvented by using DMSO as reagent.

In order to release the free amine for coupling reaction with building block **3**, keto amide **13** was submitted to hydrogenolysis conditions (H_2, Pd/C) in methanol. Only 11% of the desired amine **14** was produced next to two main products (Scheme 5). The structures of **19** (MIM 510, 5%) and **20** (MIM 508, 75%) were elucidated by LC–MS and NMR. The reaction leading to **19** and **20** can be explained by dimerization of amino ketone **14** via diimine formation, and afterwards Pd catalyzed aromatization.

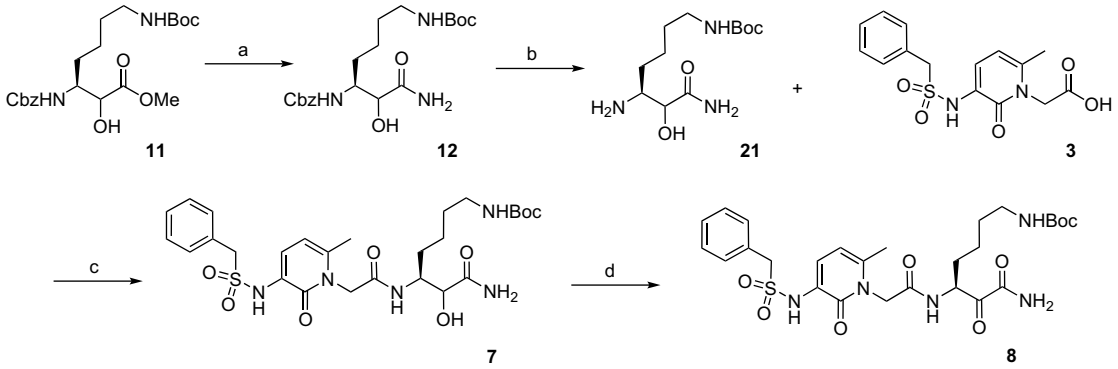


Scheme 5. Dimerization impurities **21** and **22**.

It has been observed that ketone **13** promptly equilibrate to the hemiacetal form at 0 °C in MeOH. Suspecting this behaviour to promote dimerization, the reaction was repeated in THF, but again a mixture of **19** and **20** was isolated. In view of these results and the evidence that **14** is not stable and promptly dimerizes, it has been decided to establish the α-keto side chain after peptidic coupling reaction (Scheme 6).

The free amine was then released one step earlier at the stage of the α-hydroxy amide **12** by conventional hydrogenation in methanol. Amine **21**, which isolation proved to be troublesome, was used as such in the next step. Subsequent peptide coupling reaction was performed according to Medicinal Chemistry prescription (EDC, HOBt) by using diisopropylamine as base and DMF as solvent. A satisfying 91% LC–MS purity was achieved, with as a main contaminant esterification product **22** (Fig. 2). Attempts to purify the coupling product **7** revealed to be more difficult than expected because of the different behaviour in crystallization of the two diastereoisomers (44:56). A first crystallization from ethyl acetate provided **7** in 30% yield (20:80 mixture of isomers). Recovery of the remaining product from the mother liquors was accomplished by two additional crystallizations from ethyl acetate/diisopropylether. By using this procedure **7** has been isolated in a disappointingly low 67% combined yield. When the reaction was performed at large scale, the purity of **7** measured by LC–MS dropped to 71%, contaminated by three main impurities **22**, **23** and **24** (Fig. 2). Impurities **23** and **24** are the result of a polymerization mechanism, by addition of acid monomers **3** to sulfonamide functionality.

To circumvent the formation of these impurities, other peptidic coupling conditions were screened. It turned out that when the reaction was performed in *N*-methyl-2-pyrrolidinone (NMP), together with 4-methylmorpholine (NMM) as a base, the reaction took place without side products formation. Reproducibility was demonstrated upon scaling-up: compound **7** was isolated in 91%



Scheme 6. Selected alternative route. Reagents and condition: (a) NH_3, $AlMe_3$, CH_2Cl_2/THF, recrystallization from *i*-Pr_2O, 75%; (b) H_2, Pd/C, 98%; (c) EDCI, HOBt, NMM, NMP, 91%; (d) DMSO, EDC, dichloroacetic acid, THF, recrystallization from AcOEt, 74%.

yield with a purity of 94% and thus engaged without any purification into the next step. By using such a 'one-pot procedure', loss of material due to difference in crystallization behaviour of the diastereoisomers could be avoided.

Oxidation of hydroxy amide **7** by using a catalytic TEMPO, sodium hypochlorite and potassium bromide system[10] gave a lot of degradation. With a catalytic ruthenium oxide/sodium periodate system[11] or by using Swern oxidation,[12] no reaction took place. Again, the Moffat oxidation was the most effective.[13] To optimize yield and impurity profile, a screening of the parameters, which may influence the oxidation reaction was undertaken. Results are summarized in (Table 1).

THF is the solvent of choice as can be seen from (entries 2 and 3) and EDC the best reagent (entries 3 and 6). Dichloroacetic acid (DCAA) is the best additive but to achieve complete conversion, 0.75 equiv is required (entries 1 and 3). Phosphoric acid (H_3PO_4) was identified as a potential alternative catalyst, though the quality of the isolated product was lower (entry 7). As a last observation, 10 equiv of DMSO is required to consume all starting material (entries 3 and 5).

On large scale, the Moffat oxidation was complete within 3 h at 20 °C. The crude reaction mixture was crystallized from ethyl acetate, and **8** isolated as an off-white solid in 80% yield and >95% purity. The content of precursor **7** in keto amide **8** is a critical quality attribute as there is no way to purge it by the end of the synthesis. Hence, stringent specification was set at this stage.

The process developed thus far was reproduced in our kilo-lab facilities starting from 465 g of building block **11**. The synthesis proved to be robust and reproducible as no major difference with the optimized process was noted. The four steps sequence starting from **11** was performed in an overall 51% yield delivering 328 g of keto amide **8** with the desired high quality level.

To finalize the synthesis of **1**, Boc-deprotection and racemization remains to be done (Scheme 7).[14] In order to change costly and cumbersome reverse phase purification into normal phase purification, racemization of **8** was envisioned prior to Boc-deprotection. Unfortunately, any attempts to racemize **8** were not successful, presumably due to the poor solubility of **8** in water and in most organic solvents. By using organic bases in DMF or DMSO, degradation takes place while racemization was partly observed when basic buffers were used. Compound **8** was thus deprotected with TFA in dichloromethane. The TFA salt of the deprotected amine was isolated quantitatively after precipitation from *tert*-butyl methyl ether in 94% HPLC purity. Racemization was investigated on the TFA salt with phosphate buffers at different pH, controlling the enantiomeric excess by capillary electrophoresis. Complete racemization was observed between pH=7.5 and pH=8.0. At higher pH, degradation occurs. The process was reproduced at 300 g scale and resulted in a clean and complete racemization in 24 h.

Purification of the resulting racemate was accomplished successfully by reverse phase chromatography. Optimization of the Medicinal Chemistry procedure led to a streamlined approach where desalting of the phosphate solution and purification were

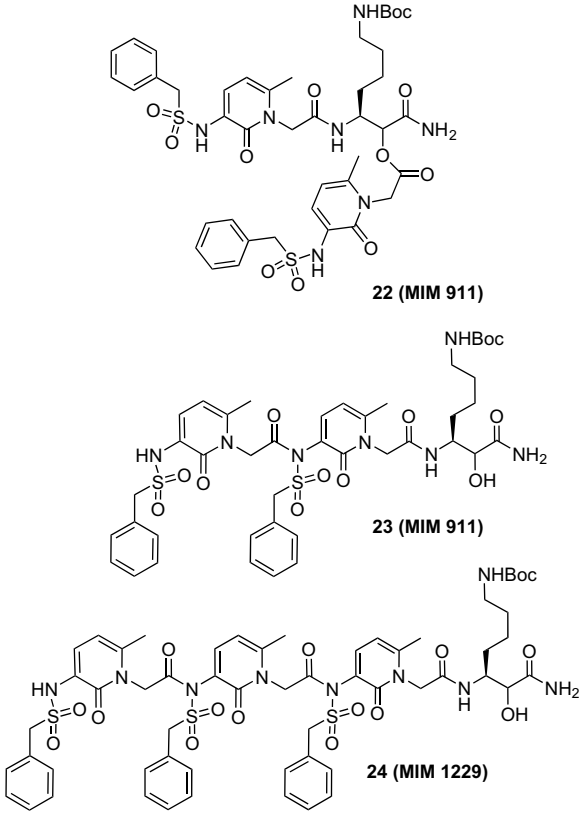
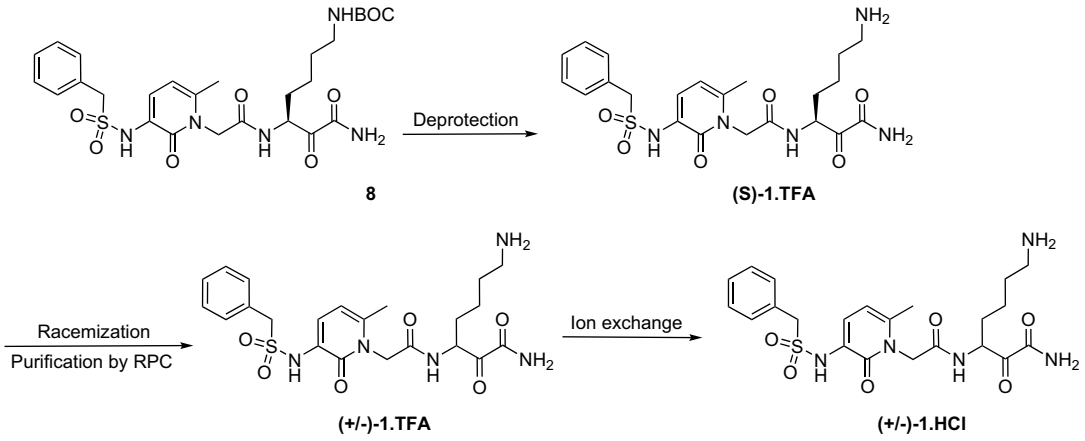


Figure 2. Peptidic coupling reaction—structure of main impurities.

Table 1
Oxidation of α-hydroxy amide **7**—design of experiment

Entry	Reagents[a]	Catalyst[b]	Solvent	**7**[e]	**8**[e]
1	10 equiv/10 equiv	0.5 equiv	THF	16%	54%
2	30 equiv/10 equiv	0.5 equiv	CH_2Cl_2	14%	14%
3	10 equiv/10 equiv	0.75 equiv	THF	0%	89%
4	7.5 equiv/10 equiv	0.75 equiv	THF	0.4%	86%
5	5 equiv/10 equiv	0.75 equiv	THF	3%	83%
6	10 equiv/10 equiv[d]	0.5 equiv	THF	4%	33%
7	10 equiv/10 equiv	0.5 equiv[c]	THF	2%	64%

[a] Reagents=DMSO/EDC.
[b] Catalyst=DCAA.
[c] Catalyst=H_3PO_4.
[d] Reagent=DMSO/DCC.
[e] Yield determined by LC–MS.



Scheme 7. Racemization and purification process of **1**.

Table 2
Ion exchange in purification process

	Small scale	Large scale
HPLC purity	>98.0% a/a	>95.0% a/a
TFA anion	<0.1% w/w	11.6% w/w
Chlorine anion	6.6% w/w	2.7% w/w

both accomplished in a single run by using acetonitrile and an aqueous HCl buffer solution as eluent.

TFA displacement by the HCl buffer used for purification was demonstrated on small scale. Unfortunately this was not reproducible on large scale as only 40% of the ion exchange occurred (Table 2).

The ion exchange experiment was performed in batch with two different resins. By using the low loaded Q Sepharose resin (0.2 equiv Cl^-/g) 0.25% w/w of TFA salt remained, but when the higher loaded resin, AG 1X8 (1.2 equiv Cl^-/g) was used, the exchange was complete.

On large scale, the purification of crude (+/−)-**1**·**TFA**, was performed on a 110 mm column filled with Delta-Pack C18. After ion exchange chromatography on AG 1X8 resin, the solution was filtered dust free and lyophilized to give 140 g of (+/−)-**1**·**HCl**. The isolated off-white amorphous powder was of suitable quality for toxicological and first into human evaluation. The measured HPLC purity was >97% without single impurity above the qualification level as defined by the ICH guidelines.

3. Conclusion

In summary, we have developed an efficient process for the preparation of the anti-hypertensive compound **1**, in high purity (>97%) with an improved overall yield of 23% versus 11% in the earlier route. The new process is amenable to large-scale preparation and successfully overcomes the drawbacks of a troublesome aminolysis and a Dess–Martin oxidation. The improved robustness of the new route was demonstrated by the synthesis of a batch of 140 g of compound **1**. A particular attention has been dedicated to the identification of impurities in order to get better knowledge and understanding of the processes to help in the decision making to develop alternative pathway. Additionally, the process developed in the end, for the purification of compound **1**, has contributed to a much lower cost of the overall synthesis even though a chromatography is still required.

4. Experimental

4.1. General

The NMR spectra were recorded with a Brucker DRX-500 instrument at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The electronspray ionization (ESI) mass spectra were obtained using an API 165 Sciex mass spectrometer. All the reactions were performed under a positive pressure of nitrogen. Commercial grade anhydrous solvents and reagents were used without further purification. HPLC was conducted with an Agilent Technologies HP 1100 on a Symmetry C18 (5 μm, 150 mm×2.1 mm) an Hypersil-Phenyl (5 μm, 250 mm×4.6 mm) and a Supelcosil LC-18-DB column (5 μm, 250 mm×4.6 mm), with purities being determined by peak area % at the UV detector wavelength of 210 nm. The enantiomeric purities were determined by capillary electrophoresis with a HP3^{D}CE equipment (Agilent Technologies) using sulphopropyl-β-cyclodextrine as chiral selector at the UV detector wavelength of 200 nm.

4.2. *N*-((1*S*)-1-{4-[(*tert*-Butoxy)carbonylamino]butyl}-2-carbamoyl-2-hydroxyethyl)(phenylmethoxy)-carboxamide (12)

To CH_2Cl_2 (3 L) cooled at −30 °C was added NH_3 (500 g, 27.5 mol) under gentle stirring. $AlMe_3$ (0.7 L, 1.4 mol) was slowly added and the solution aged for 1 h at −30 °C, then warmed to 0 °C. A solution of **11** (465 g, 1.1 mol) in THF (3.5 L) was added slowly. The mixture was aged 5 h at 40 °C and 16 h at rt before quenching with 0.01 M aqueous HCl (12 L). After concentration of the volatiles in vacuo, the mixture was diluted with water and the pH was adjusted to 7 by using 0.01 M aqueous HCl. The precipitate was filtered off and washed with heptane. The white solid was poured in hot methanol (10 L) and stirred for 1 h. The precipitate containing insoluble aluminium salts was filtered through a pad of Celite. The filtrate was concentrated in vacuo at 40 °C to give a white solid, which was recrystallized from diisopropylether (8 L). The white crystals were filtered and dried in vacuo to yield **12** (334 g, 75%). MS (ESI) *m*/*z* 410 (M^++H); HPLC (Symmetry C18) 98.4% pure; ^{1}H NMR (DMSO-d_6) (assignments with asterisk are related to the signals of a second diastereoisomer): δ ~1.35 (m, 2H), 1.53–1.05 (m, 2H), 1.42 (m, 2H), 1.36 (s, 9H), 2.86 (m, 2H), ~3.78 (m, 1H), 3.90 (dd, 1H), 3.82* (dd, 1H), 5.01 (m, 2H), 5.56 (d, 1H, *J*=5.7 Hz), 5.41* (d, 1H, *J*=6.2 Hz), 6.92 (d, 1H, *J*=8.5 Hz), 6.57* (d, 1H, *J*=9.4 Hz), 6.73 (t, 1H), 7.23–7.15 (2br s, 2H), 7.39–7.28 (m, 5H).

4.3. *N*-((5*S*)-5-Amino-6-carbamoyl-6-hydroxyhexyl)-(*tert*-butoxy)carboxamide (21)

A mixture of **12** (330 g, 0.81 mol) and 5% Pd–/C (33 g, 10 mol %) in methanol (7 L) was introduced in an autoclave and put under hydrogen pressure (4 bar) at RT for 3 h. The reaction mass was filtered over a layer of Celite and the catalyst was washed with methanol (4 L). The combined filtrate was concentrated. The residual solid was submitted to three azeotropic distillations with

toluene at 50 °C, to remove all trace of water and methanol to give **21** (217 g, 98%). MS (ESI) *m*/*z* 276 (M^++H); ^{1}H NMR (DMSO-d_6) (assignments with asterisk are related to the signals of a second diastereoisomer): δ 1.29–1.16 (m, 2H), 1.34 (m, 2H), 1.37 (s, 9H), 1.41 (m, 2H), 1.85 (br s, 2H), 2.79 (m, 1H), 2.88 (m, 2H), 3.71 (d, 1H, *J*=3.8 Hz), 3.64* (d, 1H, *J*=3.1 Hz), 5.41 (br s, 1H), 6.74 (t, 1H), 7.19/7.11 (2br s, 2H).

4.4. *N*-((1*S*)-1-{4-[(*tert*-Butoxy)carbonylamino]butyl}-2-carbamoyl-2-hydroxyethyl)-2-(6-methyl-2-oxo-3-{[benzylsulfonyl]amino}hydropyridyl)acetamide (7)

To a stirred suspension of **21** (230 g, 0.79 mol) in NMP (8.5 L) at 10 °C was added **3** (280 g, 0.79 mol). The mixture was aged for 30 min to reach rt at which HOBt (118 g, 0.87 mol), EDCI (167 g, 0.87 mol) and NMM (88 g, 0.87 mol) were added successively. The resulting mixture was aged at rt for 16 h until all starting material has been consumed. The reaction mixture was poured into water at a temperature below 25 °C. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layer was concentrated in vacuo to give **7** as a white-brown solid (468 g, 91%). MS (ESI) *m*/*z* 594 (M^++H); HPLC (Hypersil-Phenyl) 99.3% pure; ^{1}H NMR (DMSO-d_6) (assignments with asterisk are related to the signals of a second diastereoisomer): δ 1.37 (s, 9H), 1.59–1.08 (m, 6H), 2.23 (s, 3H), 2.20* (s, 3H), 2.87 (m, 2H), 3.88 (dd, 1H), 3.84* (dd, 1H), 4.08 (m, 1H), 4.02* (m, 1H), 4.51 (s, 2H), 4.52*/4.49* (d/d, 2H), 4.77 (s, 2H), 4.83*/4.66* (d/d, 2H), 5.68 (d, 1H, *J*=5.6 Hz), 5.56* (d, 1H, *J*=5.6 Hz), 6.08 (d, 1H, *J*=6.6 Hz), 6.07* (d, 1H, *J*=6.6 Hz), 6.74 (t, 1H), 6.73* (t, 1H), 7.12 (~d, 1H), 7.21/7.15 (s/s, 2H), 7.39–7.27 (m, 5H), 8.02 (d, 1H, *J*=8.8 Hz), 7.79* (d, 1H, *J*=8.8 Hz), 8.54 (s, 1H).

4.5. *N*-((1*S*)-1-{4-[(*tert*-Butoxy)carbonylamino]butyl}-2-carbamoyl-2-oxoethyl)-2-(6-methyl-2-oxo-3-{[benzylsulfonyl]amino}hydropyridyl)acetamide (8)

To a stirred solution of **7** (444 g, 0.74 mol) in THF (5 L) and DMSO (531 mL, 7.4 mol) at rt, was added EDCI (716 g, 3.7 mol). The resulting heterogeneous mixture was aged for 20 min and dichloroacetic acid (46 mL, 0.56 mol) was added. The reaction was monitored by HPLC and complete conversion was observed after 5 h at rt. About 90% of the solvent was concentrated in vacuo and water was added to the suspension. The solid was filtered, washed three times with water and heptane and dried in vacuo. The crude product was recrystallized from ethyl acetate (1.5 L). The white precipitate was filtered and washed once with ethyl acetate at 0 °C then dried in vacuo to give **8** (328 g, 74%). MS (ESI) *m*/*z* 592 (M^++H); HPLC (Hypersil-Phenyl) 95.2% pure; ^{1}H NMR (DMSO-d_6): δ 1.35 (m, 2H), 1.37 (s, 9H), 1.38 (m, 2H), 1.75/1.50 (m/m, 2H), 2.22 (s, 3H), 2.89 (m, 2H), 4.51 (s, 2H), 4.90/4.73 (d/d, 2H), 5.00 (m, 1H), 6.07 (d, 1H, *J*=7.7 Hz), 6.77 (t, 1H), 7.11 (d, 1H, *J*=7.7 Hz), 7.39–7.28 (m, 5H), 8.02/7.77 (s/s, 2H), 8.56 (s, 1H), 8.67 (d, 1H, *J*=6.9 Hz).

4.6. *N*-[1-(4-Aminobutyl)-2-carbamoyl-2-oxoethyl]-2-(6-methyl-2-oxo-3-{[benzylsulfonyl]amino}hydropyridyl)-acetamide (+/−)-**1**·HCl

To a stirred solution of **11** (300 g, 0.507 mol) in dichloromethane (0.6 L) at rt, TFA (2.4 L) was added and the mixture aged for 2 h. TBME (18 L) was added at 10 °C to crystallize the TFA salt. The white solid was filtered off and washed two times with TBME (since the compound is very hygroscopic, it was not filtered to dryness). The wet crystals still containing residual TBME were dried in vacuo to give (*S*)-**1**·**TFA**. To a stirred solution of (*S*)-**1**·**TFA** in water (34 L), phosphate buffer (8 L, 0.2 M, pH 7.9) was added dropwise to adjust the pH to 7.5 and the reaction mixture was stirred at rt for 24 h at which point the racemization was complete. The pH was then adjusted to 3 with a concentrated HCl and filtered 'dust free'. The solution of (+/−)-**1**·**TFA** was purified on reverse phase silica (Deltapack C18 15 μm) at a flow rate of 0.5 L/min by using ACN/H_2O pH 3 as eluent. The fractions with purity higher than 97% were collected and ACN was concentrated in vacuo. The resulting water solution was freeze-dried to give pure (+/−)-**1**·**TFA** (186 g). The solid was dissolved in water (1.86 L) and charged in a glass reactor containing an ion exchange resin (Biorad AG 1X8) conditioned at pH 3.4. The solution was aged for 1 h, filtered and freeze-dried to give (+/−)-**1**·**HCl** (132.6 g, 45%). MS (ESI) *m*/*z* 492 (M^++H); HPLC (Supelcosil) 97.8% purity; CE enantiomeric ratio 1.06; ^{1}H NMR (D_2O): δ 1.33 (m, 1H), 1.48 (m, 2H), 1.64 (m, 2H), 1.74 (m, 1H), 2.28 (s, 3H), 2.93 (m, 2H), 4.16 (dd, 1H, hydrate form), 4.57 (dd, 2H), 4.84 (dd, 2H), 5.17 (dd, 1H, keto form), 6.25 (dd, 1H), 7.40–7.29 (m, 6H).

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References and notes

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14. Analysis of a sample of **8** by ^{1}H NMR using Pirckle's alcohol as chiral chelating agent, showed an enantiomeric purity of 80% meaning that the compound partly racemizes over the four steps sequence.