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New synthetic strategy for preparation of the anticoagulant drug Rivaroxaban *via* an asymmetric Henry reaction

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Keywords: Rivaroxaban; Anticoagulant drug; Henry reaction; Enantioselective catalysis

Abstract

A new synthetic approach towards the anticoagulant drug (*S*)-Rivaroxaban was described. This reaction sequence involved six steps overall, starting from commercially available and inexpensive *N*-(4-aminophenyl)morpholin-3-one. The stereogenic centre was introduced by an asymmetric Henry reaction catalysed by the complex of copper(II) acetate and (2*R*,5*S*)-2-(pyridine-2-yl)imidazolidine-4-one with 87% ee. The individual reaction steps proceeded with high yields and did not require any unusual or expensive reagents.

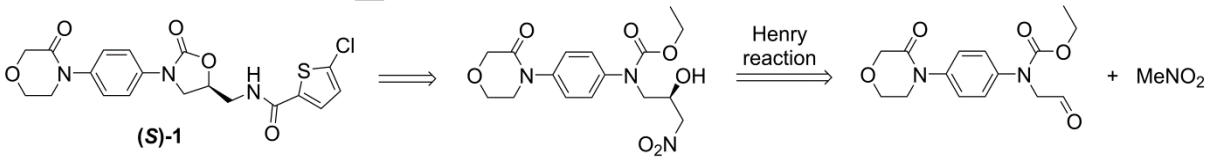
Introduction

Direct factor Xa inhibitors represent a class of anticoagulant drugs acting directly upon factor Xa, which is responsible for the conversion of prothrombin to thrombin through the prothrombinase complex.[1] The inhibition of factor Xa causes a decrease in thrombin production, which interrupts the pathways of the blood coagulation cascade, while favourable concentrations of thrombin remain unaffected.[1] (*S*)-Rivaroxaban (**1**), which was developed by Bayer HealthCare AG,[2] is such an inhibitor of factor Xa. It was approved by the FDA and EMEA in 2011 and has been sold under the tradename Xalerto® in Europe and USA.[3]

(*S*)-Rivaroxaban (**1**) has been prepared using various synthetic approaches, in which different chiral building blocks were utilised. From a pharmaceutical activity point of view, any synthesis of **1** must fulfil the fundamental requirement of installing the (*S*)-configuration of the target molecule, because only (*S*)-enantiomer is a powerful inhibitor of factor Xa.

Hence, according to a study of the anti-FXa potency *in vitro*, the inhibitory activity of (*S*)-enantiomer was IC_{50} = 0.7 nM, whereas the (*R*)-enantiomer was IC_{50} = 2300 nM.[2] Among the most often utilised chiral building blocks, (*S*)-glycidyl phthalimide,[2,4,5] (*R*)-epichlorohydrin,[6–10] (*S*)-epichlorohydrin,[11–15] (*R*)-glycidyl butyrate,[16] (*S*)-aminopropane-1,2-diol[17,18] and (*S*)-chloropropane-1,2-diol[9] are notable. The possible synthetic pathways were summarized in a recently published review.[19] Many of these syntheses possess disadvantages, e.g. the use of toxic reagents and/or hazardous solvents, the formation of by-product impurities, and low overall yields.[19] From this point of view, efforts to develop more convenient synthetic protocols for (*S*)-Rivaroxaban (**1**) production is still a worthy area of research.

A synthetic approach towards (*S*)-Rivaroxaban (**1**) *via* a catalytic asymmetric Henry reaction or other enantioselective catalysis step has not been reported. This fact challenged us to develop an alternative methodology for the preparation of (*S*)-Rivaroxaban (**1**), employing asymmetric catalysis for the introduction of its stereogenic centre. The stereogenic centre of (*S*)-Rivaroxaban (**1**) is located in a β-aminoethanolic moiety, which enables its potential construction *via* an asymmetric Henry reaction (Scheme 1). Recently, a straightforward synthesis of Linezolide was reported employing an asymmetric Henry reaction.[20] Inspired by this synthetic protocol, we decided to develop an appropriate method for (*S*)-Rivaroxaban (**1**).

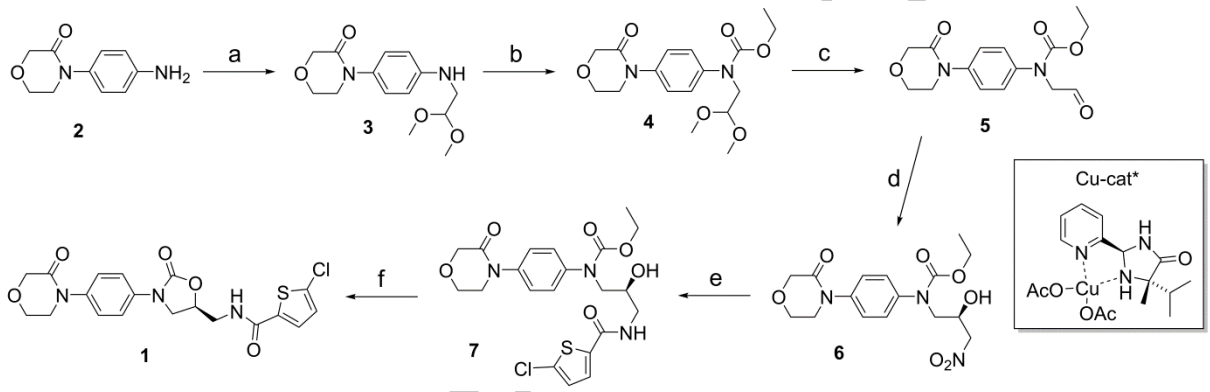


Scheme 1. The structure of (*S*)-Rivaroxaban (**1**) and its construction *via* an asymmetric Henry reaction.

Results and Discussion

The synthesis of **1** (Scheme 2) started from the commonly utilised intermediate, *N*-(4-aminophenyl)morpholin-3-one (**2**), which can be easily prepared from 2-(*N*-phenylamino)ethanol *via* a three-step synthesis, which proceeds in 52% overall yield.[21] Similar to the synthetic procedure for Linezolide,[20] aniline **2** was condensed with dimethoxyacetaldehyde in dry CH_2Cl_2 and the imine formed was reduced by $NaBH(OAc)_3$. The secondary amine **3** obtained in 94% yield was purified by column chromatography and

subsequently acylated with ethyl chloroformate (3 equiv.) in the presence of pyridine (1 equiv.). Under these conditions, carbamate **4** was isolated in high yield (86%). Reversing the sequence of these two steps, i.e. acylation of **2** with chloroformate and subsequent alkylation with bromoacetaldehyde dimethylacetal in the presence of different base (e.g. NaH, EtONa, K_2CO_3) was unsuitable due to the low reactivity of the corresponding carbamate. Aldehyde **5** was obtained from **4** by selective acid catalysed hydrolysis of the acetal group in 95% yield. Under the literature conditions,[20] acid catalysed hydrolysis of the morpholin-3-one ring or carbamate group did not take place.



Scheme 2. Synthesis of (*S*)-Rivaroxaban (**1**) *via* an asymmetric Henry reaction. Reagents and conditions: (a) $(MeO)_2CHCHO$, $NaBH(OAc)_3$, CH_2Cl_2, MS 4 Å, rt, 2 h, 94%; (b) $ClCO_2Et$ (3 equiv.), Py (1 equiv.), CH_2Cl_2, rt, 1.5 h, 86%; (c) HCl (aq), MeCN, rt, 18 h, 95%; (d) Cu-cat* (5 mol%), $MeNO_2$, IPA, 6 °C, 7 d, 72%, 87% ee; (e) H_2 (20 bar), Pd-C (10% wt), MeOH, rt, 24 h, then 5-Cl-thiophene-2-COCl, TEA, CH_2Cl_2, rt, 3 h, 70% over two steps; (f) K_2CO_3, MeOH, rt, 2 h, 97%.

Further, the asymmetric Henry reaction between aldehyde **5** and nitromethane was performed with the complex of copper(II) acetate and (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one.[22] Using the previously optimised reaction conditions,[22–24] this catalyst provided the corresponding nitroaldol product **6** with moderate chemical yield (72%) and satisfactory enantioselectivity (87% ee). The relatively long reaction time was necessary to achieve significant conversion. The ee was determined by chiral HPLC using a Chiralpak AS-H column. The absolute configuration of the major enantiomer (R_f = 38.7 min, see ESI) was determined by comparison of the specific rotation of **1** prepared by this method (negative value) with those found in the literature,[19] measured under the same conditions.

Next, nitroaldol **6** was reduced under a hydrogen atmosphere (20 bar) in the presence of palladium on carbon (10% wt) to give the corresponding aminoalcohol. The formed amine

was not isolated, and was immediately acylated with 5-chlorothiophene-2-carbonyl chloride. This manipulation of the amine did not lead to the undesired production of the cyclic urea derivative, which can be formed by intramolecular attack of the amine group onto the neighbouring carbamate group. The obtained amide **7** was purified by column chromatography with an overall yield of 70%. Finally, the ring-closure step was performed by treatment of derivative **7** with the K_2CO_3/MeOH system.[20] This base resulted in formation of the oxazolidinone ring in high yield (97%). The course of reaction can be observed by the precipitation of solid (*S*)-Rivaroxaban (**1**), which also simplified its separation from the reaction mixture in high purity. The characterization data of compound **1** were in accordance with those found in the literature.[2,4–19]

Conclusion

In conclusion, a new synthetic strategy for preparation of the anticoagulant drug (*S*)-Rivaroxaban was described. This method consists of a six-step synthesis, starting from relatively cheap chemicals, in which an overall 38% yield was achieved. The asymmetric Henry reaction represents the key step of the synthesis, which introduced a chiral centre into the molecule. In our case, the application of an enantioselective catalyst based on the copper(II) complex of a 2-(pyridine-2-yl)imidazolidine-4-one derivative led to (*S*)-Rivaroxaban (**1**) with high enantiomeric excess (87% ee).

Acknowledgment

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Supplementary data

The synthetic procedures and spectroscopic data are available in the "Supplementary data".

References

1. Comp, P. C. *Pharmacotherapy* **2003**, *23*, 772–778.
2. Roehrig, S.; Straub, A.; Pohlmann, J.; Lampe, T.; Pernerstorfer, J.; Schlemmer, K.-H.; Reinemer, P.; Perzborn, E. *J. Med. Chem.* **2005**, *48*, 5900–5908.
3. Highlights of Prescribing Information of XARELTO, Rivaroxaban, Extended-Release Tablets. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202439s001lbl.pdf Accessed 2011.
4. Mali, A. C.; Deshmukh, D. G.; Joshi, D. R.; Lad, H. D.; Patel, P. I.; Medhane, V.

J.; Mathad, V. T. *Sustain. Chem. Process.* **2015**, *3*, 11–22.

5. Straub, A.; Lampe, T.; Pohlmann, J.; Röhrig, S.; Perzborn, E.; Schlemmer, K.-H.; Pernerstorfer, J, WO 0147919 A9 (2001).
6. Yuan, J.; Liu, K.; Li, L.; Yuan, Y.; Liu, X.; Li, Y. *Molecules* **2014**, *19*, 14999–15004.
7. Li, C.; Liu, Y.; Zhang, Y.; Zhang, X. *J. Chem. Res.* **2011**, *35*, 400–401.
8. Zhang, X.; Li, C.; Zhang, Y.; Chen, Q., CN 102250076 A (2011).
9. Bodhuri, P.; Weeratunga, G., US 20110034465 A1 (2011).
10. Bodhuri, P.; Weeratunga, G., US 8101609 B2 (2012).
11. Hong, J., Zhang, Z.; Li, J.; Wang, J., CN 102702186 A.
12. Tang, B.; Xu, G.; Zhang, M., CN 102786516 A (2012).
13. Sipos, E.; Kovanyine Lax, G.; Havasi, B.; Volk, B.; Krasznai, G.; Ruzsics, G.; Barkoczy, J.; Toth Lauritz, M.; Lukacs, G.; Boza, A.; Hegedues, L. J.; Taborine Toth, M. J.; Pecsi, E., WO 2012153155 A1 (2012).
14. Prasangi, S.; Desireddy, S. R.; Rao, V. S.; Murthy, Y. L. N.; Palla, M. *Chem. Sci. Trans.* **2017**, *6*, 27–34.
15. Halama, A.; Kruliš, R.; Dammer, O.; Kalášek, S., WO 2013120465 A1 (2013).
16. Rafecas Jane, L.; Comely, A. C.; Ferrali, A.; Amela Cortes, C.; Pasto Aguila, M., WO 2011080341 (2011).
17. Thomas, C., WO 2004060887 A1 (2004).
18. Sturm, H.; De Souza, D.; Knepper, K.; Albert, M., WO 2011098501 A1 (2011).
19. Fattah, T. A.; Saeed, A. *Tetrahedron: Asymmetry* **2017**, *28*, 485–504.
20. Piccionello, A. P.; Pierro, P.; Accardo, A.; Buscemi, S.; Pace, A. *RSC Adv.* **2013**, *3*, 24946–24951.
21. Thomas, C.; Berwe, M.; Straub, A., WO 2005026135 A1 (2005).
22. Panov, I.; Drabina, P.; Padělková, Z.; Šimůnek, P.; Sedlák, M. *J. Org. Chem.* **2011**, *76*, 4787–4793.
23. Drabina, P.; Horáková, E.; Růžičková, Z.; Sedlák, M. *Tetrahedron: Asymmetry* **2015**, *26*, 141–147.
24. Panov, I.; Drabina, P.; Hanusek, J.; Sedlák, M. *Synlett* **2013**, *24*, 1280–1282.
25. Boruwa, J.; Gogoi, N.; Saikia, P.P.; Barua, N.C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326.
26. Drabina, P.; Harmand, L.; Sedlák, M. *Curr. Org. Synth.* **2014**, *11*, 879–888.
27. Alvarez-Casao, Y.; Marques-Lopez, E.; Herrera, R. P. *Symmetry* **2011**, *3*, 220–245.
28. Zhang, S.; Li, Y.; Xu, Y.; Wang, Z. *Chin. Chem. Lett.* **2018**, *29*, 873–883.

HIGHLIGHTS

- The anticoagulant drug (*S*)-Rivaroxaban was prepared by new synthetic method.
- The asymmetric Henry reaction was used for introduction of chiral centre.
- The individual reaction steps proceeded with high yields.
- High enantiomeric excess was obtained with the used chiral catalyst.