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The asymmetric Henry reaction as synthetic tool for production of drugs Linezolid and Rivaroxaban

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Abstract

The human drugs – antibiotic Linezolid (**1**) and anticoagulant Rivaroxaban (**2**) – belongs among modern pharmaceutics, which contain oxazolidine-2-one moiety bearing stereogenic centre. The chirality of these drugs is fundamental attribute of their biological activity. Herein, one of the efficient asymmetric syntheses of those drugs was studied in detail. High enantioselective catalysts were tested in the key step of the synthetic procedure, i.e. asymmetric Henry reaction, under different reaction conditions, using several starting aldehydes. The corresponding nitroaldols as chiral intermediates of those drugs were obtained in high yields and enantiomeric excess up to 91% ee.

Keywords: Asymmetric Henry reaction; Enantioselective catalysis; Linezolid; Oxazolidine-2-one derivatives; Rivaroxaban

Introduction

Oxazolidine-2-one derivatives belong among important branch of pharmaceutical substances [1,2]. This class includes for instance many of oxazolidine-type antibiotics – e.g. Linezolid (**1**) [3] (sold under the trade name Zyvox® (Chart. 1), Tedizolid [4], Radezolid [5]) and the anticoagulant Rivaroxaban (**2**) [6,7] (Chart. 1), the member of DOACs (direct oral anticoagulants). All these human drugs can be considered as modern medicaments, which were developed and approved during past three decades [8]. Chirality of the mentioned oxazolidine-2-ones is crucial factor of their therapeutic effect, because only single enantiomer affords desired biological activity. Hence, only *S*-enantiomer of Rivaroxaban (**2**) (sold under trade name Xarelto®) exhibits strong inhibitory activity against coagulant factor Xa, whereas *R*-enantiomer is almost inactive (IC_{50} = 0.7 nM for *S*- vs. 2300 nM for *R*-) [7]. Similarly, in the case of the oxazolidine-2-one antibiotics only *S*-enantiomers are able to block the bacterial ribosomes, what leads to the prevention of translation processes in bacteria [9,10]. With regards to these facts, high enantiomeric purity is one of the fundamental requirements in the production of such pharmaceutical substances, because the reduction of abundance of undesirable stereoisomer to a minimum can supress possible side effects.

The oxazolidine-2-one-type drugs are usually prepared according to the synthetic methods, that utilizes available chiral building blocks (e.g. epichlorohydrine, glycidol, 3-chloropropane-1,2-diol etc.) [11]. Beside this, the approaches in which the asymmetric synthesis takes place are also applicable. Recently, the utilization of asymmetric Henry reaction for the preparation of two oxazolidine-type drugs – Linezolid (**1**) and Rivaroxaban (**2**) – was described [12,13]. These published papers confirmed that the application of asymmetric Henry reaction represents the promising alternative route for feasible production of these compounds. Nevertheless, these studies gave only preliminary results, because it was included only one enantioselective catalyst

in the case of preparation of Rivaroxaban (**1**) [12] and the study of the Linezolid (**2**) synthesis used only commercially unavailable and poor enantioselective catalysts (max ee 72%) [13].

In this paper, we focused on the application of asymmetric Henry reaction for the preparation of oxazolidine-2-one-type drugs Linezolid (**1**) and Rivaroxaban (**2**) in detail. The main aim of this study was the evaluation of catalytic activity and enantioselectivity of several established enantioselective catalysts applicable to the asymmetric Henry reaction, which were used for the preparation of chiral intermediates of these drugs. Various highly efficient catalysts based on copper complexes of different types of chiral ligands – 2-(pyridine-2-yl)imidazolidine-4-ones **I–III** bis-oxazolines **IV–VII**; or diamine **VIII** were chosen for the study. Furthermore, the modification of the structure of prochiral aldehyde intermediate **15** and **19** was also performed with the aim to increase of enantiomeric purity of corresponding nitroaldol products **21–26**. The structural modification consisted in the introduction of different alkyl moiety to carbamate functional group of aldehyde intermediate **15**–**20**. The bulky and/or chiral alkyl group, i.e. *tert*-butyl, L-menthyl and (–)-bornyl) were considered.

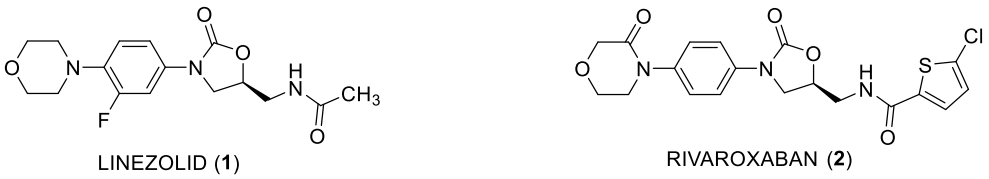
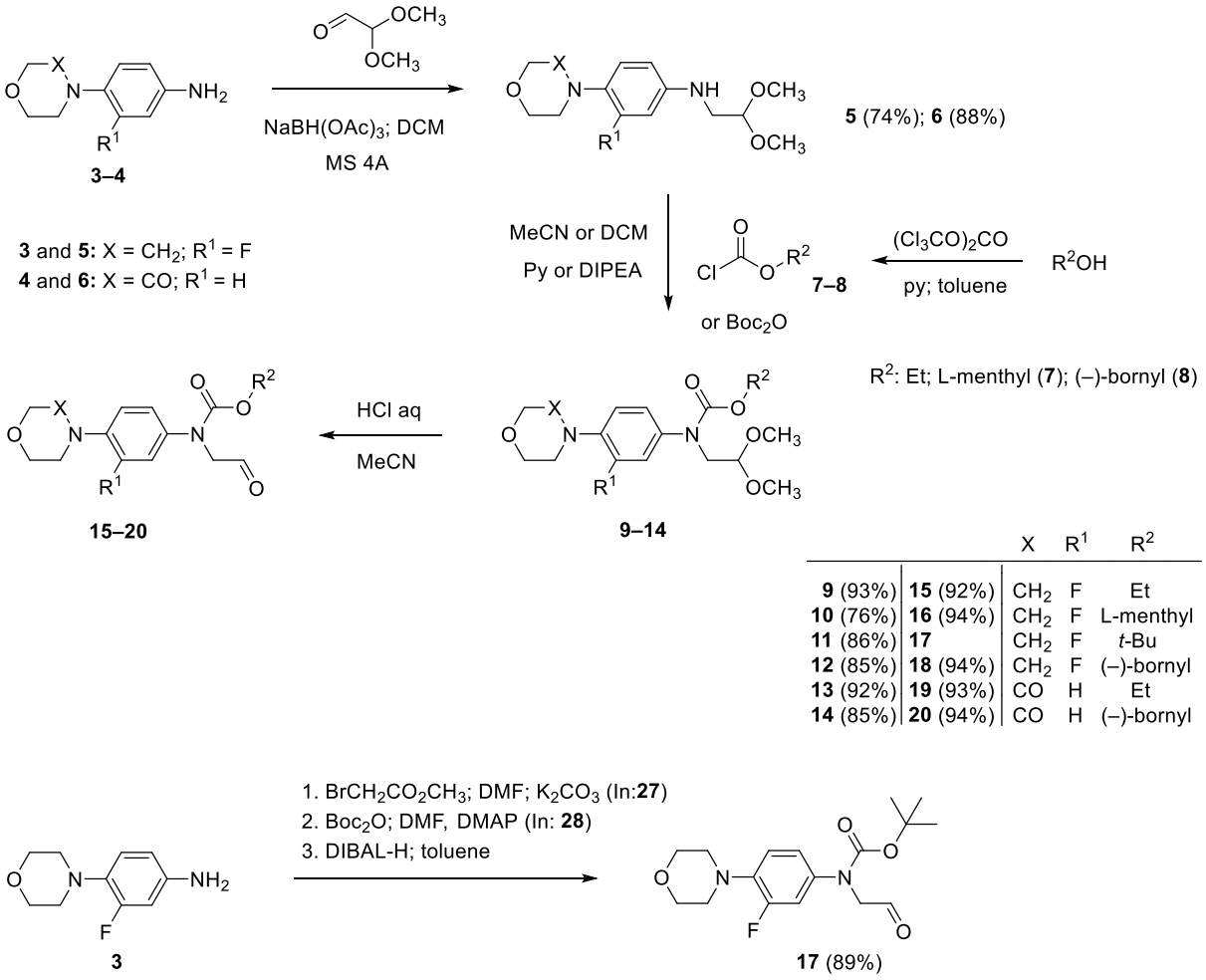


Chart. 1 The structure of oxazolidine-2-one drugs Linezolid (**1**) and Rivaroxaban (**2**)

Results and discussion

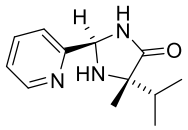
The aldehydes **15**–**20** were prepared by analogical methods, which were described previously [12,13]. The starting L-menthyl (**7**) and (–)-bornyl chloroformate (**8**) were obtained according to the modified synthetic procedure [14]. Here, it was included the chromatographic purification of final chloroformates, what led to removing of corresponding alkyl chlorides formed as by-

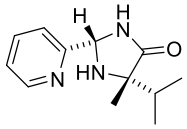
products. The aldehyde **17** was prepared by different way, because the acid-catalysed hydrolysis of its acetal intermediate **11** was accompanied with simultaneous cleavage of Boc group. Herein, the attempts of selective deacetalation of **11** by treatment of several reagents (e.g. I_2/acetone [15]; $FeCl_3 \cdot 6H_2O$/acetaldehyde [16]; $Ce(OTf)_3$ [17]) were unsuccessful. Therefore, the alternative synthesis [18] was utilized, which consisted of alkylation of aniline **3** by methyl bromoacetate, followed by introduction of Boc-group into intermediate **27** and final reduction of **28** with DIBAL-H (Scheme 1).

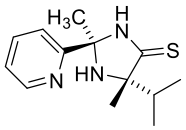


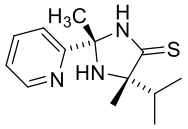
Scheme 1. The syntheses of aldehydes **15–20**

For the catalytic study of the asymmetric Henry reaction of aldehydes **15**–**20** with nitromethane were chosen highly enantioselective catalysts based on copper(II) complexes of chiral nitrogen ligands. Generally, the chiral complexes of copper possess many advantages valuable for pharmaceutical industry, e.g. low toxicity, low-cost, possibility of recycling [19]. Therefore, they represent very useful tool for many of asymmetric transformations, including Henry reaction. The pilot study of the synthesis Rivaroxaban via asymmetric Henry reaction [12] described the application of only one copper complex of 2-(pyridine-2-yl)imidazolidin-4-one derivative. In this work, we extent the series of catalysts with the copper complexes of another six 2-(pyridine-2-yl)imidazolidin-4-ones **Ia,b–IIIa,b** [20–22], four bis-oxazolines **IV–VII** [23,24] and chiral diamine – alkaloid (+)-sparteine **VIII** [25] (Chart 2). All Henry reactions were performed on sub-millimolar scale. The obtained products **21**–**26** were separated from starting aldehydes **15**–**20** by column chromatography. The reaction conditions (i.e. temperature, reaction time, amount of catalyst, solvent) were adopted from the pilot study [12] for relevant comparison of catalyst's characteristics. Subsequently, the reaction temperature and loading of catalyst was tuned using aldehyde **15** to achieve satisfactory chemical yields and ee in nitroaldol **21** (Table 1).


Ia


Ib


IIa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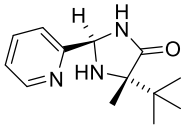
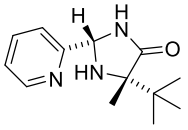
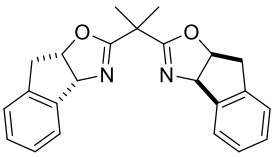

IIIa


IIIb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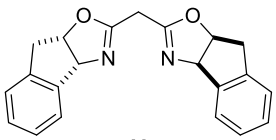
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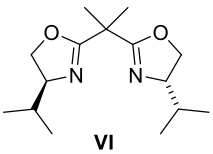
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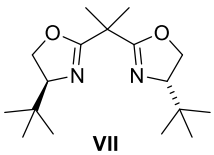

VII

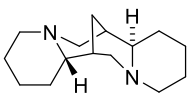
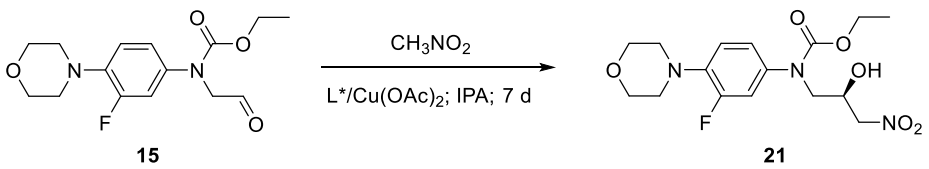

VIII

Chart 2. The survey of chiral ligands used for the study of the asymmetric Henry reaction

Table 1. The survey of the performed attempts of the asymmetric Henry reactions of aldehyde **15** with nitromethane under various conditions



15 **21**

Ligand	Cat. loading [mol %]	Temperature [°C]	Yield[a] [%]	ee[b] [%]
Ia	5	6	**55**	**88 (*R*)**
Ia	10	6	**78**	**88 (*R*)**
Ia	5	20	**94**	**85 (*R*)**
Ib	5	20	**65**	**68 (*S*)**
IIa	5	6	**37**	**80 (*R*)**
IIa	10	6	**47**	**86 (*R*)**
IIa	5	20	**69**	**68 (*R*)**
IIb	5	6	**21**	**40 (*S*)**
IIb	10	6	**26**	**69 (*S*)**
IIb	5	20	**67**	**66 (*S*)**
IIIa	5	6	**45**	**77 (*R*)**
IIIa	10	6	**70**	**86 (*R*)**
IIIa	5	20	**87**	**81 (*R*)**
IIIb	5	20	**31**	**38 (*S*)**
IV	5	6	**78**	**85 (*R*)**
IV	5	20	**46**	**88 (*R*)**
IV	10	6	**55**	**89 (*R*)**
V	5	6	**10**	**–**
V	5	20	**29**	**45 (*R*)**
VI	5	6	**40**	**80 (*S*)**
VI	5	20	**82**	**78 (*S*)**
VII	5	6	**43**	**46 (*S*)**
VII	5	20	**46**	**54 (*S*)**
VIII	5	6	**40**	**9 (*S*)**

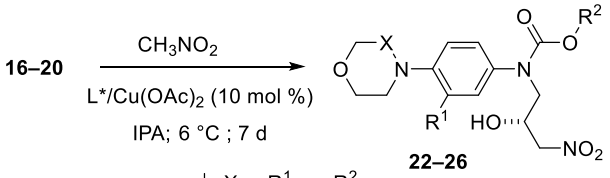
[a] The yield was determined by ^{1}H NMR analysis of crude product.

[b] The enantiomeric excess was determined by chiral HPLC.

From the obtained results summarized in Table 1 was found out, that the highest enantioselectivity exhibit the copper(II) complexes of ligands **Ia**, **IIa**, **IIIa** and **IV**. Fortunately, these catalysts provide the *R*-enantiomer of nitroaldol **21** as a major product, which can be subsequently transformed to *S*-Linezolid (**1**) (the active stereoisomer). On the other hand, the catalysts derived from 2-(pyridine-2-yl)imidazolidine-4-ones **Ib–IIIb**, bis-oxazoline ligands **V–VII** and (+)-sparteine (**VIII**) show only insufficient enantioselectivity, therefore, they were excluded for further catalytic study. Obviously, the higher catalyst loading does not affect enantioselectivity, however, it enables the achievement of high chemical yield. Performing of the reaction at room temperature also increases the yield, nevertheless, the certain drop of ee was observed, especially in the case of catalyst **IIa**. From this point of view, the 10 mol % of catalyst derived from ligands **Ia**, **IIa**, **IIIa** and **IV** and reaction temperature 6 °C were evaluated as optimal reaction conditions for studied asymmetric Henry reaction.

Further, the asymmetric Henry reaction of the other aldehydes **16**–**20** was studied (Table 2). The bulky (R^2 = *t*-Bu) or chiral (R^2 = L-menthyl or (–)-bornyl) alkoxy group was introduced into the carbamate moiety instead of ethyl group in aldehydes **15** and **19**. Of note, the nitroaldols **22**, **24** and **26** were formed as a pair of epimers, therefore, possible separation of the individual stereoisomers of these compounds was assumed. Hence, it should be noted that the R^2O- part of the carbamate group does not modify the structure of Linezolid (**1**), because this molecular moiety is cleaved by intramolecular nucleophilic substitution within the final reaction step (Scheme 2). The catalysts derived from ligands **Ia**, **IIa**, **IIIa** and **IV** were also tested in asymmetric Henry reaction using two substrates **19**–**20**, which afford the chiral intermediates **25**–**26** applicable for Rivaroxaban (**2**) synthesis.

Table 2. The survey of the performed attempts of the asymmetric Henry reactions of aldehydes **16–20** with nitromethane catalysed by copper(II) complexes of **Ia**, **IIa**, **IIIa** and **IV**



	X	R^1	R^2
22	CH_2	F	L-menthyl
23	CH_2	F	*t*-Bu
24	CH_2	F	(–)-bornyl
25	CO	H	Et
26	CO	H	(–)-bornyl

Nitroaldol R^2	Ligand	Yield[a] [%]	ee[b,c] [%]
22	**Ia**	**63**	**89 (*R*)**
22	**IIa**	**49**	**87 (*R*)**
22	**IIIa**	**38**	**83 (*R*)**
22	**IV**	**72**	**89 (*R*)**
23	**Ia**	**80**	**85 (*R*)**
23	**IIa**	**62**	**85 (*R*)**
23	**IIIa**	**72**	**86 (*R*)**
23	**IV**	**73**	**87 (*R*)**
24	**Ia**	**70**	**87 (*R*)**
24	**IIa**	**63**	**88 (*R*)**
24	**IIIa**	**62**	**88 (*R*)**
24	**IV**	**79**	**90 (*R*)**
25	**Ia**	**91**	**86 (*R*)**
25	**IIa**	**72**	**83 (*R*)**
25	**IIIa**	**55**	**86 (*R*)**
25	**IV**	**80**	**90 (*R*)**
26	**Ia**	**65**	**86 (*R*)**
26	**IIa**	**44**	**83 (*R*)**
26	**IIIa**	**44**	**88 (*R*)**
26	**IV**	**67**	**91 (*R*)**

[a] The yield was determined by ^{1}H NMR analysis of crude product.

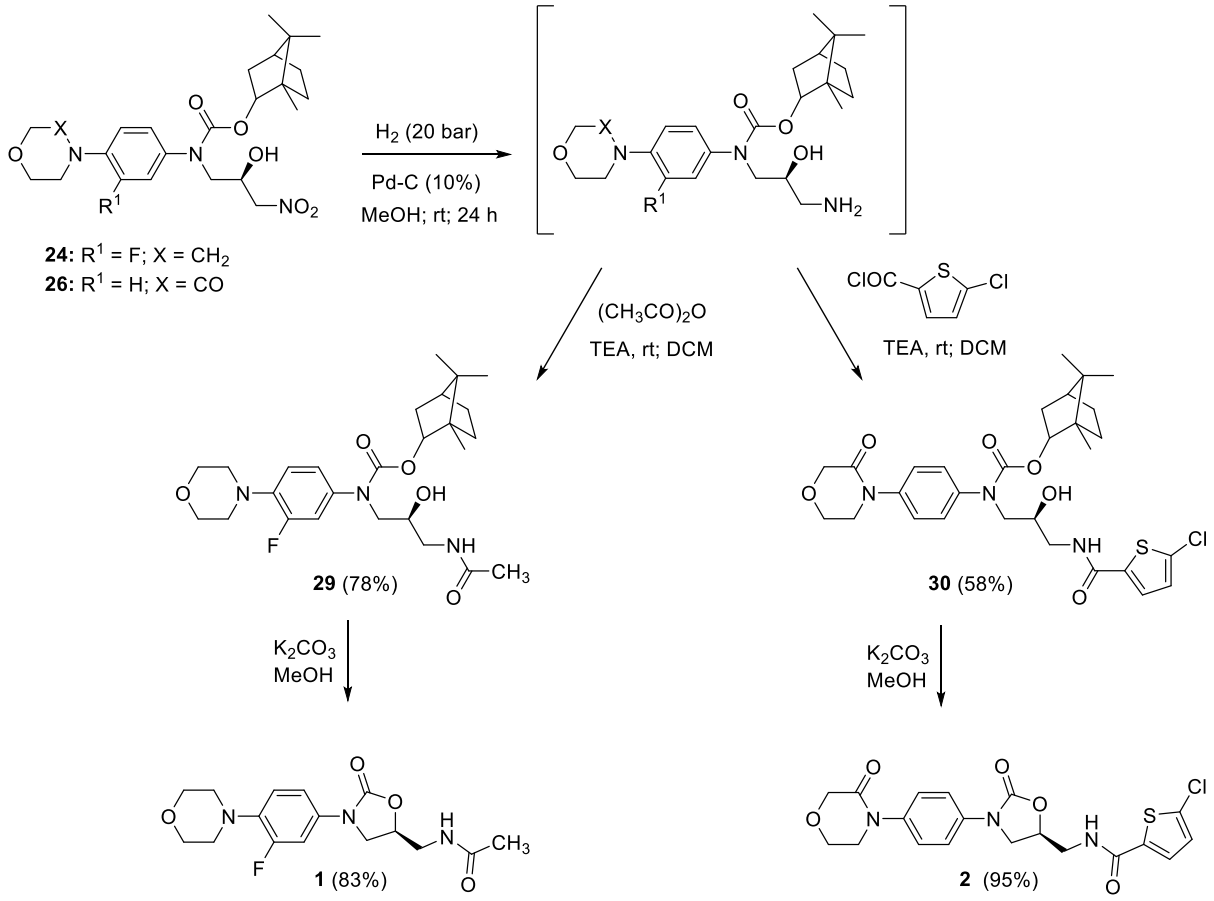
[b] The enantiomeric excess was determined by chiral HPLC.

[c] The values for nitroaldols **22**, **24** and **26** represent de nor ee

From the results summarized in Table 2 follows, that carbamate substituent in the aldehydes **16**–**20** does not affect the enantioselectivity. All nitroaldol products **22**–**26** were obtained with values of ee in the range of 83–91%. This observation was confirmed with the attempt, where the aldehyde **16** bearing substituent R^2 = D-menthyl (opposite sense of chirality) was applied. This substrate was transformed to the corresponding nitroaldol **22** by the action of the complex $Cu(OAc)_2$/**Ia** with practically identical ee of 88%. On the other hand, the interpretation of chemical yields is rather indistinct. Generally, the copper(II) complexes of ligands **Ia** and **IV** exhibit higher catalytic activity than the catalysts derived from **IIa** and **IIIa**. Thus, the yields achieved by **Ia** and **IV** can be considered as satisfactory almost for all nitroaldols **21**–**26**. The influence of R^2- substitution differs in the type of substrate. In the cases of nitroaldols **21**–**24** leading to Linezolid (**1**) were found higher chemical yields for derivatives **22** (R^2 = *t*-Bu) and **23** (R^2 = (–)-bornyl) (62–80%) than derivatives **21** (R^2 = Et) and **24** (R^2 = L-menthyl) (38–78%). However, in the cases of nitroaldols **25–26**, affording subsequently Rivaroxaban (**2**), were obtained higher chemical yields for derivative **25** (R^2 = Et) (55–91%) than **26** (R^2 = (–)-bornyl) (44–67%). For these findings we do not have any reliable explanation.

Next, the synthetic method [12,13] of the preparation of the target oxazolidine-2-one drugs **1** and **2** from new chiral intermediates was verified (Scheme 2). For this study, the bornyl-derivatives **24** and **26** were chosen. The reductions of nitro group in **24** and **26** via hydrogenation procedure proceeded smoothly with almost quantitative yields; the amine intermediates were immediately used in the next step. Hence, their acylations were performed by the action of corresponding acylating reagent (1.0 equiv.) in DCM and the presence of TEA (1.1 equiv.). The amides **29**–**30** were obtained with moderate yields (78 % for **29** and 58 % for **30**), what are values comparable with those described for analogous ethyl-derivatives previously [12,13]. Finally, the base-catalysed intramolecular re-esterification (cyclisation) led to the desired

products **1** and **2**. In the case of amides **29**–**30**, the reaction conditions of the cyclisation were slightly modified, i.e. the reaction time was prolonged to 24 h and the product precipitated was washed with hexane to remove traces of borneol. No changes in the enantiomeric excess and the presence of the major *S*-enantiomer in drugs **1** and **2** was confirmed by chiral HPLC analysis.



Scheme 2. The synthesis of Linezolid (**1**) and Rivaroxaban (**2**) from nitroaldols **24** or **26**

Moreover, an enhancement of the abundance of the major epimer in the nitroaldols **22**, **24** and **26** as well as the amides **29**–**30** was examined. Generally, epimers represent the pair of stereoisomers more easily separable by standard techniques than enantiomers. In particular, an exploration of convenient chromatographic conditions was performed. Unfortunately, none of

the conditions were discovered even though all derivatives were tested. Subsequently, the possibility of separation of epimers by recrystallisation was tested. For this reason, the nitroaldols **24** and **26** were prepared in 10 mmol scale (ca. 4 g) using the catalyst $Cu(OAc)_2$/**IV** (10 mol %; 20 °C). The nitroaldols **24** and **26** were obtained in these scale up experiments with the value of de 84% for **24** and 88% for **26**. Nevertheless, they were isolated as oil/waxy solid material, what made the attempts of recrystallisation impossible. On the other hand, the corresponding amides **29**–**30** are fine crystalline solids. Their crystallisation was successfully performed from several solvents. However, the isolated crystals kept the value of de at the practically same level as starting material in all cases. The separation via kinetic resolution in final reaction step was also examined. The course of re-esterification was stopped at conversion of ca 50 % and the values of de were determined. Unfortunately, no difference between the values of de of starting amides **29**–**30** and final drugs **1**–**2** were found.

Conclusion

In conclusion, the synthetic approach to the production of the antibiotic Linezolid (**1**) and the anticoagulant Rivaroxaban (**2**) based on the asymmetric Henry reaction was studied in detail. The series of 11 efficient enantioselective catalysts was tested to obtain the corresponding nitroaldol **21** in the enantiomeric excess as high as possible. Four of them based on chiral ligands **Ia**, **IIa**, **IIIa** and **IV** were evaluated as the most effective catalysts. They exhibit the mutually comparable enantioselectivity in the range of 83–91% ee. It was found out, that the enantioselectivity does not vary with the substitution in the carbamate group of used aldehydes **15**–**20**. However, all nitroaldols **21**–**24** prepared as chiral intermediates suitable for the Linezolid (**1**) synthesis were obtained with higher ee (83–90%) than in the previously published study (up to 72% ee) [13]. The introduction of chiral moiety into the structure of aldehydes **16**, **18** and **20** led to the formation of nitroaldols **22**, **24** and **26** as pair of epimers. Unfortunately,

the attempts of separation of minor epimer were unsuccessful. Nevertheless, the abundance of inactive stereoisomer (*R*-) in final Linezolid (**1**) or Rivaroxaban (**2**) can be considered as low enough (5–8%) to discontinue the effort of its separation due to economic reasons.

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