

Stereoselective synthesis of α -hydroxy- β -amino acids: the chiral pool approach*

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Abstract: A method for the stereoselective homologation of α -amino acids into *syn*- α -hydroxy- β -amino acids is described, based on the conversion of stereoisomeric cyanohydrins into *trans*-oxazolines. The synthetic potential of the method is illustrated in the enantioselective formal synthesis of Bestatin.

Keywords: amino acids, cyanohydrins, bestatin, AHPA, oxazoline.

INTRODUCTION

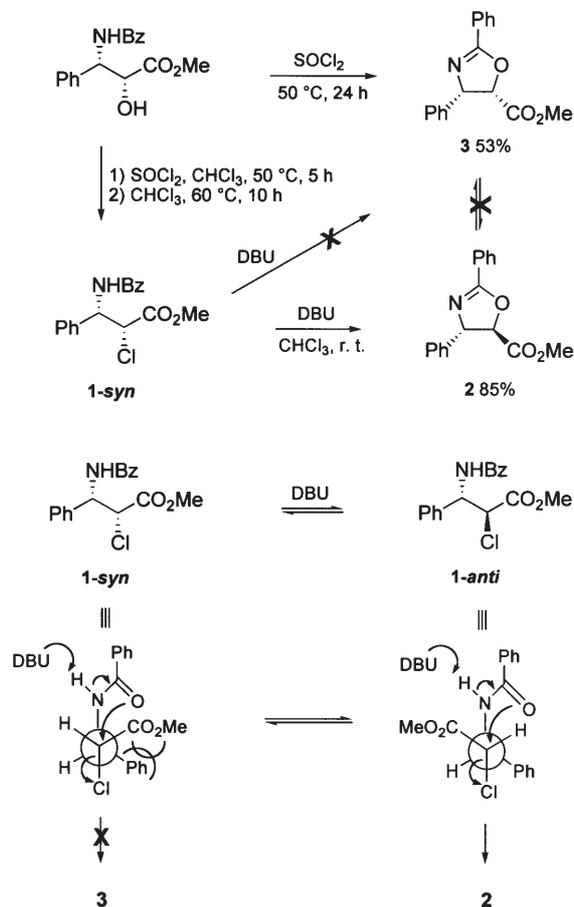
Within a large family of β -amino acids,¹ α -hydroxy- β -amino acids occupy an especially important place.² These compounds are known as constituents of several clinically approved drugs and natural products that show important biological activities: Taxol³ and Taxotere⁴ (antimitotics), Bestatin (Ubenimex, immunostimulant),⁵ KRI-1314 (a renin inhibitor),⁶ Microginin (an ACE inhibitor),⁷ KNI 272 and R-87366 (HIV-protease inhibitors),⁸ dideoxykanamycin A (antibacterial),⁹ to name just a few. Therefore, this class of compounds has attracted considerable interest of organic chemists and numerous methods for their enantioselective synthesis have been devised. However, room still exists for the improvement of the existing methodology.

RESULTS AND DISCUSSION

We sought to develop a semisynthetic approach to α -hydroxy- β -amino acids based on the homologation of α -amino acids. The ready availability and low cost of the optically pure α -amino acids recommend them as a suitable chiral pool for the targeted transformation.¹⁰ A one carbon homologation of α -amino acids has

* Dedicated to Professor Živorad Čeković, with the sentiments of gratitude and respect, on the occasion of his 70th birthday.

Serbian Chemical Society active member.



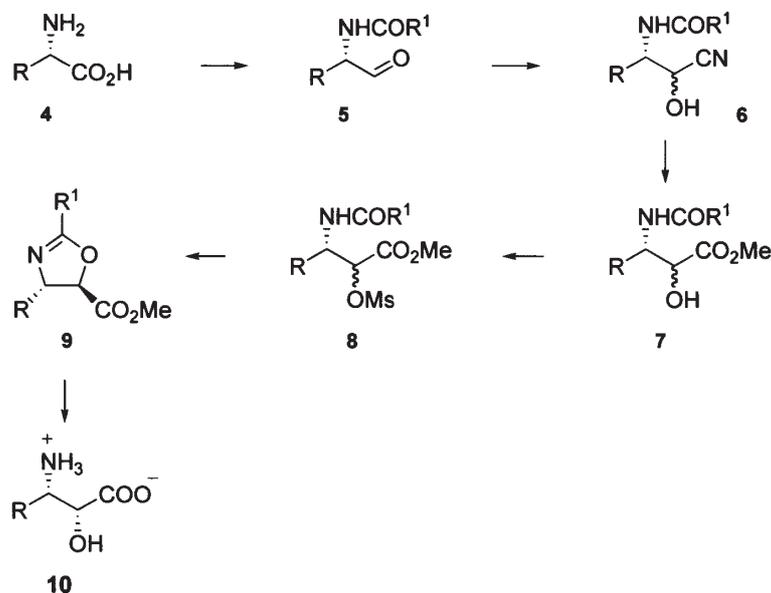
Scheme 1.

been performed *via* the corresponding amino aldehydes,¹¹ using the addition of vinylmetals¹² or of the acetylde anion¹³ as latent carboxylic groups, followed by subsequent oxidative deprotection. Amino aldehydes have also been homologated by the cyanohydrin reaction,¹⁴ where trimethylsilyl cyanide,¹⁵ tributylstannyl cyanide,¹⁶ with or without added Lewis acids, as well as diethylaluminum cyanide (Nagata's reagent),¹⁷ are the most often used reagents for this reaction. The stereoselectivity of the reaction varies and usually a careful choice of reagents and reaction conditions is needed in order to achieve good diastereoselectivity. In our approach, we considered performing the cyanohydrin reaction under operationally simple conditions, with cheap and environmentally the least harmful sodium cyanide. Such a reaction would not be expected to be diastereoselective; therefore, an additional means was needed in order to secure stereocontrolled product formation.

Some time ago, we found that chloroester **1-syn** can be transformed into *trans*-oxazoline **2** on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),

in a smooth reaction that formally represents an intramolecular S_N2 substitution with the retention of configuration (Scheme 1).¹⁸ No equilibrium was established between the *cis*- and *trans*-oxazolines under the reaction conditions, which ruled-out the intermediacy of the former isomer. Performing the reaction in a NMR tube, with spectral monitoring, revealed that the addition of DBU causes rapid epimerization of **1-syn**, with the formation of an equimolar mixture of **1-syn** and **1-anti**; during the course of the reaction, the concentrations of both epimers decrease proportionally to the increase in the concentration of the *trans*-oxazoline product **2**. No other intermediates were detected in the reaction mixture, which indicated the mechanism represented in Scheme 1, where the rapidly equilibrating mixture of isomers is funnelled into a single product, through the application of the Curtin-Hammett principle.

Subsequently, it was found by others¹⁹ and us¹⁸ that a similar transformation is also feasible when the more easily available mesylates are substituted for the chlorides. This allowed us to conceive a process for the stereoselective conversion of α -amino acids **4** into *trans*-oxazolines – the synthetic equivalents of α -hydroxy- β -amino acids – as delineated in Scheme 2. After the addition of cyanide to amido aldehyde **5**, which is expected to be stereorandom, the mixture of stereoisomeric cyanohydrins **6** would be first converted into the corresponding esters **7** and then mesylated. Treatment of **8** with DBU should bring about the rectification of stereochemistry at C-2 in **9**, obviating the need for a tedious chromatographic separation of diastereoisomers. However, this reaction sequence hides a potential pit-fall: the easy racemization of the amido aldehyde **5**, both under the conditions of



Scheme 2.

oxidation and nucleophilic addition. Indeed, oxidations of α -amino alcohols, as well as nucleophilic additions to α -amino aldehydes, were successfully performed when the amino group was protected as a tertiary amine or carbamate, while the α -amido aldehydes are known to be very sensitive towards racemization.

We decided to test the feasibility of this reaction sequence by applying it in the synthesis of (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid (also known as allophenylnorstatine; abbreviated as (2*S*,3*R*)-AHPA, (2*S*,3*R*)-AHPBA, or Apns).²⁰ This important acid is a constituent of several aminopeptidase inhibitors: Bestatin,⁵ Phebestin²¹ and Probestin²² (Fig. 1).^{23,13} The suitable starting compound for the synthesis would be D-phenylalanine.

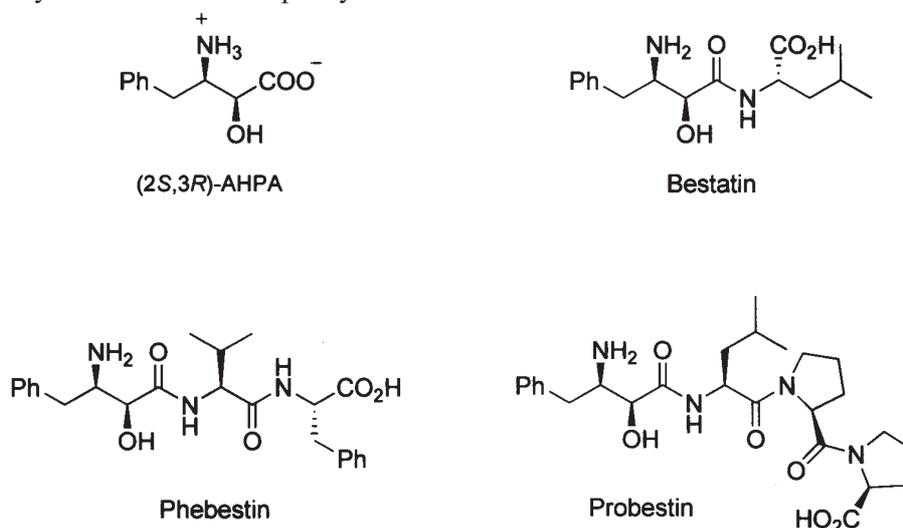
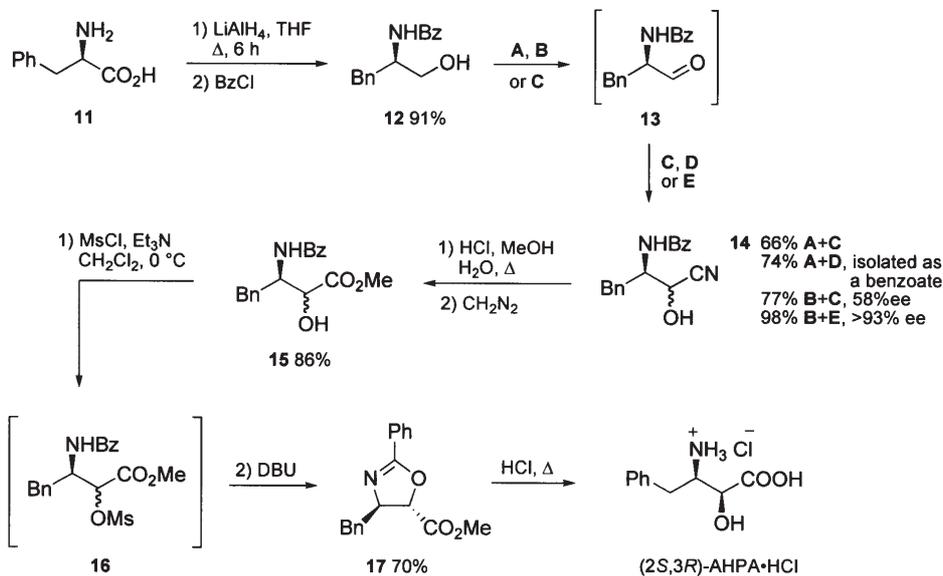


Figure 1.

The synthesis, represented in Scheme 3, started with the reduction of D-phenylalanine **11** with lithium aluminum hydride, followed by *in situ* benzoylation to give the known α -amido alcohol **12**.²⁴ The oxidation/cyanide addition sequence was tried with several reagents, the efficiencies of which were compared in terms of the product yield and optical purity. To determine the optical purity of the product cyanhydrin **14**, this compound was reduced with sodium borohydride back into the starting alcohol **12**, the optical rotation of which was compared to the original values. The combination of the Swern oxidation and cyanide addition using potassium cyanide in the presence of benzyltriethylammonium chloride (TEBA) afforded cyanohydrin **14** in 66 % yield. Quenching the reaction mixture with benzoyl chloride afforded a somewhat higher yield of the corresponding benzoate (74 %),²⁵ but this compound turned out to be less suitable for the subsequent transformations. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) mediated oxidation,²⁶ followed by potassium cyanide/TEBA treatment, gave **14** in 77 % yield. The attractive feature of this method is its operational simplicity. However, the optical purity of **14** was unsat-

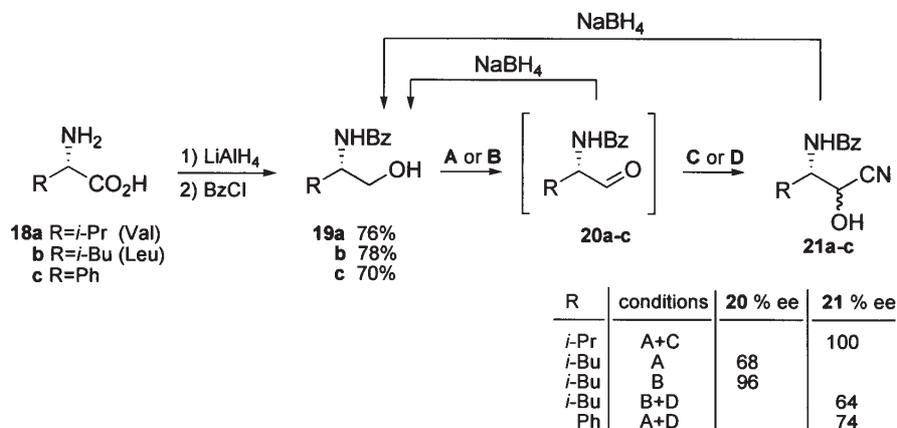


A: Swern; B: TEMPO, NaOCl; C: KCN, TEBA; D: KCN, TEBA, BzCl; E: HCN

Scheme 3.

isfactory (58 % ee). With the presumption that partial racemization may have occurred in the second step, under the influence of the relatively basic “naked” cyanide anion, the experimental procedure was modified in that the cyanohydrin reaction was accomplished with *in situ* generated hydrogen cyanide. Gratifyingly, **14** was obtained in almost quantitative yield, with an optical purity exceeding 93 %. Methanolysis of **14** produced a mixture of the desired ester **15** and the corresponding acid, which was converted into **15** with diazomethane (86 % from **14**). The mesylation of **15** and the oxazoline formation were envisaged to be accomplished as a one pot transformation. Treatment of **15** with mesyl chloride, in the presence of triethylamine, led to almost instantaneous formation of mesylate **16**. Addition of DBU to the reaction mixture then promoted the isomerization/cyclization sequence which yielded the *trans*-oxazoline **17** in 70 % yield (accompanied with 1.7 % of the *cis*-oxazoline). Hydrolysis of **17** was accomplished with refluxing hydrochloric acid, to give (2*S*,3*R*)-AHPA in 88 % yield. The optical rotation of the product ($[\alpha]_{\text{D}} = +29.3^\circ$) corresponded well with the literature value for the optically pure compound ($[\alpha]_{\text{D}} = +27.4^\circ$).^{23f} Thus, starting from D-phenylalanine, the synthesis of (2*S*,3*R*)-AHPA was accomplished in 7 steps and in 48 % overall yield.

The successful accomplishment of the above synthesis demonstrated that at least some α -amido aldehydes can survive the oxidation/addition sequence without isomerization. However, the proclivity of these compounds towards racemization is known to vary and to be structure dependent. To test the generality of



A: TEMPO, NaOCl; **B:** DMP; **C:** KCN, TEBA; **D:** HCN

Scheme 4.

the procedure, several other α -amido alcohols were prepared from the corresponding α -amino acids, and then submitted to the oxidation/cyanide addition sequence. The optical purity of the α -amido aldehydes **20** and cyanohydrins **21** was determined by their reduction with sodium borohydride into the starting alcohols **19** and comparison of the optical rotation values of the original sample and the reduction product. The results of these experiments are represented in Scheme 4. In the case of valinol **19a**, the oxidation with TEMPO/sodium hypochlorite, followed by the addition of a cyanide (potassium cyanide/TEBA), afforded the optically pure cyanohydrin **21a**. With leucinol **19b** the situation was more complicated. TEMPO-mediated oxidation of **19b** afforded the optically enriched aldehyde **20b** with 68 % ee. Recently, it was shown that sensitive α -amido aldehydes can racemize under the reaction conditions employed for the TEMPO-mediated oxidation. It was suggested that the highest level of optical purity of the α -amido aldehyde products can be attained when Dess-Martin periodinane (DMP) is used as the oxidant, under modified experimental conditions.²⁷ Indeed, when the oxidation of **19b** was performed according to this procedure, the optical purity of **20b** was 96 % ee! However, the cyanohydrin **21b** was obtained with a low degree of optical purity (64 %), indicating that **20b** isomerized under the experimental conditions, even though the cyanohydrin reaction was effected with hydrogen cyanide – the mildest reagent for this type of transformation. Thus, the high proclivity of the leucine derived α -amidoaldehyde **20b** towards isomerization prevents its use as an intermediate in the homologation protocol. Similarly, when the same sequence of reactions – oxidation/addition – was applied to the phenylglycinol derivative **19c**, the cyanohydrin **21c** was obtained with an optical purity not exceeding 75 % ee.

To conclude, stereoselective conversion of a stereoisomeric mixture of cyano-

hydrin mesylates into *trans*-oxazoline allows for a stereoselective synthesis of α -hydroxy- β -amino acids starting from α -amino acids. In all cases the transformation is diastereoselective and gives *syn*-products. However, the enantioselectivity of the reaction sequence depends on the substrate structure. While phenylalanine and valine derived α -hydroxy- β -amino acids are obtained with excellent optical purity, with phenylglycine and leucine partial racemization occurs. Further investigations are needed in order to establish the scope and limitations of this reaction sequence.

EXPERIMENTAL

General experimental

All reactions were performed in dried glassware under an inert (Ar) atmosphere. Petroleum ether refers to the fraction with the distillation range 70–90 °C. All chromatographic separations²⁸ were performed on Silica, 10–18, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents.²⁹ NMR Spectra were recorded on a Varian Gemini 200 instrument, ¹H-NMR at 200 MHz, ¹³C-NMR at 50 MHz, for samples in deuterated chloroform. Chemical shifts are expressed in ppm using tetramethylsilane as the internal standard, coupling constants (*J*) are in Hz. IR Spectra were recorded on a Perkin-Elmer 457 grating FT instrument, and are expressed in cm⁻¹. Mass spectra were obtained on a Finnigan ITDS 700 instrument. Microanalyses were performed at the Vario EL III instrument CHNOS Elemental Analyzer, Elementar Analysensysteme GmbH, Hanau-Germany. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

(R)-(+)-N-benzoylphenylalaninol (**12**). This compound was obtained according to the previously described procedure for the preparation of its enantiomer,¹² in 91 % yield. White crystals, mp 176 °C (lit.²⁴ mp 169–170.5 °C, lit.¹² mp 179–180 °C); Anal. calcd. for C₁₆H₁₇NO₂: C 75.27, H, 6.71; N 5.49, found: C 75.21, H 6.66, N 5.59, [α]_D = +82.4° (*c* 0.5, MeOH), lit.²⁴ [α]_D +93.4°, *c* 0.97, MeOH, lit.¹² for the *ent*-**12** [α]_D = -18°, *c* 1.5, MeOH); IR_(KBr): 3308, 1640; ¹H-NMR (DMSO-*d*₆): 2.88 (*dd*, *J* = 13.4, *J* = 9.3, 1H), 3.03 (*dd*, *J* = 13.4, *J* = 5.2, 1H); 3.59 (*m*, *J* = 9.3, *J* = 5.2, *J* = 2.5, 1H), 3.90 (*d*, *J* = 2.5, 1H); 7.31 (*m*, 5H), ¹³C-NMR (DMSO-*d*₆): 35.6 (CH₂); 54.1, 67.6, 127.7, 129.3, 129.9 (CH), 136.4, 173.2 (C).

(R)-(+)-N-benzoylphenylalaninal cyanohydrin (**14**). To a cold (0 °C), rapidly stirred two-phase mixture of **12** (1 g, 3.92 mmol), sodium bromide (8.1 mg, 78 μ mol), TEMPO free radical (12.3 mg, 78 μ mol), THF (12 mL), dichloromethane (12 mL) and water (2 mL), was added a solution of sodium hypochlorite 2.9 mL of 11 % solution, 4.3 mmol containing sodium bicarbonate (1.68 g, 20 mmol), over a period of 15 min and stirred for an additional 10 min. The layers were separated, the aqueous layer was extracted with dichloromethane, the combined organic extract was washed with a solution of sodium iodide (0.58 g) in 10 % aqueous sodium hydrogensulfate, then with 10 % aqueous sodium thiosulfate and finally with 7 % aqueous sodium bicarbonate. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude aldehyde **13** was dissolved in dichloromethane (13 mL), cooled (0 °C), and a solution of hydrogen cyanide in methanol (prepared by the addition of acetic acid (640 mg, 10.7 mmol) to a solution of potassium cyanide (644 mg, 9.9 mmol) in methanol (5.25 mL)) was added in one portion under vigorous stirring. After 5 min, the reaction was quenched by the addition of diethyl ether (26 mL) and a mixture of brine (20 mL) and saturated aqueous sodium bicarbonate (5 mL). The organic phase was separated, the aqueous phase was extracted with diethyl ether, the combined organic extract was washed with brine/sodium bicarbonate mixture, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 1.08 g (98 %) of the crude title compound **14**, as a mixture of stereoisomers in the ratio 1:1.23.

The optical purity of **14** was determined in the following manner: to a solution of **14** (60 mg, 0.214 mmol) in ethanol (1 mL) was added sodium borohydride (40 mg, 1.06 mmol), at r.t., with stirring. After completion of the reaction the mixture was acidified with 1.5 M hydrochloric acid, diluted with water and extracted with ethyl acetate. The combined organic extract was washed with saturated aqueous sodium bicarbonate, water, brine, dried over anhydrous magnesium sulfate, the solvent was evaporated under the reduced pressure and the residue was purified by dry-flash chromatography (eluent: petroleum ether/acetone = 4/1). The optical rotation value for the product was $[\alpha]_D^{25} = +77.2^\circ$ (c 0.5, MeOH), which corresponds to 93.4 % ee.

Spectral data for the mixture of isomers: IR_{KBr} : 3314, 1647, 1631, 1530, 1491, 1449, 1082; ^1H-NMR : 2.29–3.22 (m), 3.28 (dd , $J_1 = 14.0$, $J_2 = 6.2$, $\delta 2.97$ – $\delta 3.22 + \delta 3.28 = 2H$), 4.29 (m), 4.51–4.75 (m , $\delta 4.29 + \delta 4.51$ – $\delta 4.75 = 2H$), 5.57 (d , $J = 5.7$), 6.12 (d , $J = 7.4$, $\delta 5.57 + \delta 6.12 = 1H$), 6.47 ($br. d$), 6.61 (d , $J = 5.0$, $\delta 6.47 + \delta 6.61 = 1H$), 7.20–7.65 (m , 10H); $^{13}C-NMR$ ($CDCl_3 + CD_3OD$): 35.13 (CH_2), 35.53 (CH_2), 54.39 (CH), 54.57 (CH), 61.95 (CH), 63.91 (CH), 118.43 (CN), 118.87 (CN), 126.89 (CH), 127.04 (CH), 127.09 (CH), 128.50 (CH), 128.69 (CH), 128.78 (CH), 129.00 (CH), 129.02 (CH), 131.90 (CH), 132.00 (CH), 133.30 (C), 133.43 (C), 136.11 (C), 136.68 (C), 168.60 (C), 169.35 (C).

(3*R*)-*N*-benzoyl-3-amino-2-hydroxy-4-phenylbutanoic acid methyl ester, mixture of (2*R*)- and (2*S*)-isomers (**15**). A cold (0 °C) solution of **14** (1.02 g, 3.64 mmol) in a mixture of diethyl ether/methanol (51 mL of the $Et_2O/MeOH = 3/1$) was saturated with gaseous hydrogen chloride. The reaction mixture was stirred for 24 h at a temperature below 5 °C, then water (11 mL) was added and stirring was continued for 24 h at the same temperature, followed by 24 h at r. t. The reaction mixture was evaporated to dryness and the residue was taken up in tetrahydrofuran (20 mL). Diazomethane solution in diethyl ether was added dropwise, until the yellow colour persisted. After 15 min the solvent was evaporated and the crude product was purified by dry-flash chromatography (eluent: petroleum ether/acetone = 4/1), to give 0.98 g (86.4 %) of the title compound **15** as a mixture of isomers in 1.1:1 ratio.

IR_{KBr} (for the mixture of isomers): 3420, 1741, 1639, 1535, 1326, 1112; ^1H-NMR (less polar isomers): 3.0 (dd , $J_1 = 13.4$, $J_2 = 9.0$, 1H), 3.10 (dd , $J_1 = 13.4$, $J_2 = 6.8$, 1H), 3.60 (s , 3H), 4.20 (d , $J = 1.9$, 1H), 4.80 (m , 1H), 6.53 (d , $J = 9.3$, 1H), 7.20–7.53 (m , 8H), 7.65–7.69 (m , 2H); $^{13}C-NMR$ (less polar isomer): 37.63 (CH_2), 52.67 (CH or CH_3), 53.40 (CH_3 or CH), 70.16 (CH), 126.64 (CH), 126.91 (CH), 128.40 (CH), 128.52 (CH), 129.32 (CH), 131.48 (CH), 134.11 (C), 137.26 (C), 167.39 (C), 174.07 (C); ^1H-NMR (more polar isomer): 2.90 (dd , $J_1 = 14.3$, $J_2 = 6.8$, 1H), 3.01 (dd , $J_1 = 14.3$, $J_2 = 7.6$, 1H), 3.59 (s , 3H), 4.44 (d , $J = 3.6$, 1H), 4.86 (m , 1H), 6.50 (d , $J = 8.4$), 7.10–7.57 (m , 8H), 7.62–7.70 (m , 2H); $^{13}C-NMR$ (more polar isomer): 35.34 (CH_2), 52.63 (CH or CH_3), 53.34 (CH_3 or CH), 72.14 (CH), 126.81 (CH), 126.94 (CH), 128.56 (CH), 128.67 (CH), 129.42 (CH), 131.67 (CH), 134.08 (C), 136.84 (C), 167.47 (C), 173.05 (C).

(4*R*,5*S*)-methyl 4-benzyl-4,5-dihydro-2-phenyloxazole-5-carboxylate (**17**). To a cold (0 °C) solution of **15** (526 mg, 1.68 mmol) and triethylamine (0.35 mL, 2.52 mmol) in dichloromethane (11 mL) was added mesyl chloride (0.16 mL, 2.02 mmol), with vigorous stirring, under an argon atmosphere. After 10 min DBU (0.75 mL, 5.04 mmol) was added and the reaction mixture was stirred at r.t. for 6 h. The solution was washed with 1 M hydrochloric acid, aqueous sodium bicarbonate and water, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum ether/acetone = 95/5) afforded 350 mg (71 %) of the *trans*-oxazoline **17** as a viscous oil, followed by 8.5 mg (1.7 %) of the *cis*-oxazoline.

Anal. calcd. for $C_{18}H_{17}NO_3$, C 73.20 %, H 5.80 %, N 4.74 %, found: C 73.63, H 5.73 %, N 4.35 %; $[\alpha]_D^{25} = -31.4^\circ$ (c 1, CH_2Cl_2); IR_{film} : 3030, 2955, 2920, 1757, 1657, 1495, 1452, 1438, 1288, 1213, 1082, 1059; ^1H-NMR : 2.96 (dd , $J_1 = 6.6$, 1H), 3.18 (dd , $J_1 = 14.0$, $J_2 = 5.8$, 1H), 3.69 (s , 3H), 4.64 (dd , $J_1 = 11.8$, $J_2 = 6.1$, 1H), 4.74 (d , $J = 6.1$, 1H), 7.16–7.58 (m , 8H), 7.95–8.03 (m , 2H); $^{13}C-NMR$: 41.32 (CH_2), 52.47 (CH_3), 72.67 (CH), 79.50 (CH), 126.75 (CH), 128.37 (CH), 128.47 (CH), 128.50 (CH), 129.67 (CH), 131.69 (CH), 136.62 (C), 163.24 (C), 170.88 (C).

(2*S*,3*R*)-AHPA-HCl. A solution of **17** (330.6 mg, 1.12 mmol) in 10 % hydrochloric acid (15 mL) was refluxed (110 °C) for 8 h. The reaction mixture was evaporated to dryness, dry ethanol was

added (2×5 mL) and evaporated to dryness again. Diethyl ether (7 mL) was added to the solid residue, heated to reflux for 10 min, and the hot solvent was decanted (this procedure was repeated two more times). The crude product was recrystallized from isopropanol/diethyl ether, to give 229.6 mg (88.5 %) of (2S,3R)-АНРА hydrochloride.

White crystals, mp 185–186 °C; Anal. calcd. for $C_{10}H_{14}ClNO_3$: C 51.84 %, H 6.09 %, N 6.05 %; found: C 51.54 %, H 6.31 %, N 6.19 %; $[\alpha]_D^{25} = +29.3^\circ$ (c 0.43, 1 M HCl); (lit.^{23f} $[\alpha]_D^{25} = +27.4^\circ$ (c 0.43, 1 M HCl)); 1H -NMR (DMSO- d_6): 2.88 (dd, $J_1 = 13.4$, $J_2 = 9.3$, 1H), 3.03 (dd, $J_1 = 13.4$, $J_2 = 5.2$, 1H), 3.59 (m, 1H), 3.90 (d, $J = 2.5$, 1H), 7.31 (m, 5H); ^{13}C -NMR (DMSO- d_6): 35.62 (CH₂), 54.06 (CH), 67.58 (CH), 127.68 (CH), 129.32 (CH), 129.91 (CH), 136.45 (C), 173.18 (C).

ИЗВОД

СТЕРЕОСЕЛЕКТИВНЕ СИНТЕЗЕ α -ХИДРОКСИ- β -АМИНОКИСЕЛИНА ИЗ ПРИРОДНИХ ХИРАЛНИХ ПРЕКУРСОРАГОРАДАНА ТАСИЋ,¹ РАДОМИР МАТОВИЋ² и РАДОМИР Н. САИЧИЋ^{2,3}

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Описана је метода за стереоселективну синтезу α -хидрокси- β -аминокиселина суп-конфигурације, полазећи од α -аминокиселина, као природних хиралних прекурсора. Енантиоселективност процеса зависи од структуре полазне аминокиселине, као и реакционих услова. Примена ове методе илустрована је у синтези (2S,3R)-3-амино-2-хидрокси-4-фенилбутанске киселине, конституента неколико важних биолошки активних једињења.

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