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SYNTHESIS OF 1,2,3,4-TETRAHYDROPYRIDO-[2,3-*b*]PYRAZINE-2,3-DIONE DERIVATIVES WITH A CHIRAL SUBSTITUENT AT THE NITROGEN ATOM*

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The sequence of steps including nucleophilic substitution of the chlorine atom in 2-chloro-3-nitropyridine by esters of optically active phenylalanine, reduction of the nitro group, acylation with ethyl oxalyl chloride, and intramolecular cyclization, leads to the synthesis of derivatives of 1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-2,3-dione with a chiral substituent at the nitrogen atom. It was established that, depending on the conditions of carrying out the cyclization, the parallel formation of derivatives of imidazo[4,5-b]pyridine is possible. Conditions were found for selectively carrying out the cyclization under with only structures of pyrazines or imidazole condensed with pyridine were formed.

Keywords: *tert*-butyl ester of imidazo-[4,5-*b*]pyridine-2-carboxylic acid, 2-chloro-3-nitropyridine, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-2,3-diones, chiral substituent at the nitrogen atom, esters of optically active phenylalanine, nucleophilic substitution.

Derivatives of 1,2,3,4-tetrahydro-2,3-dioxoquinoxalines, based on their affinity towards the AMPA receptor, are used as medicinal agents suitable for the treatment of illnesses caused by the hyperactivity of exciting amino acids such as glutamic or aspartic for example [1]. Such illnesses include Parkinson's disease, Alzheimer's disease, Huntington's chorea, etc. Particular attention has been paid recently to derivatives of 1,4-dihydropyrido[2,3-*b*]pyrazines, since replacement of the benzene fragment in the quinoxaline molecule by pyridine significantly strengthens the biological action of such preparations due to the high affinity to the benzodiazepine receptors as well. Consequently such compounds may be used for the prophylaxis of post-ischemic cell death, the death of cells after trauma of the brain, on insult, hypoxia, anoxia, and hypoglycemia, and also epilepsy, and muscular spasms [2]. In addition the clearly marked tendency in contemporary medical practice to use chiral enantiomerically pure compounds as drug substances must be considered.

In this connection the aim of our investigation was the development of methods of synthesis of derivatives of 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinediones with a chiral substituent at the nitrogen atom. As a source of chirality we used enantiomerically pure esters of phenylalanine **1a-c**. To obtain the desired derivatives of 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazines **7** we proposed the following synthetic route.

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* Dedicated to Academician J. Stradins in connection with his 75th jubilee.

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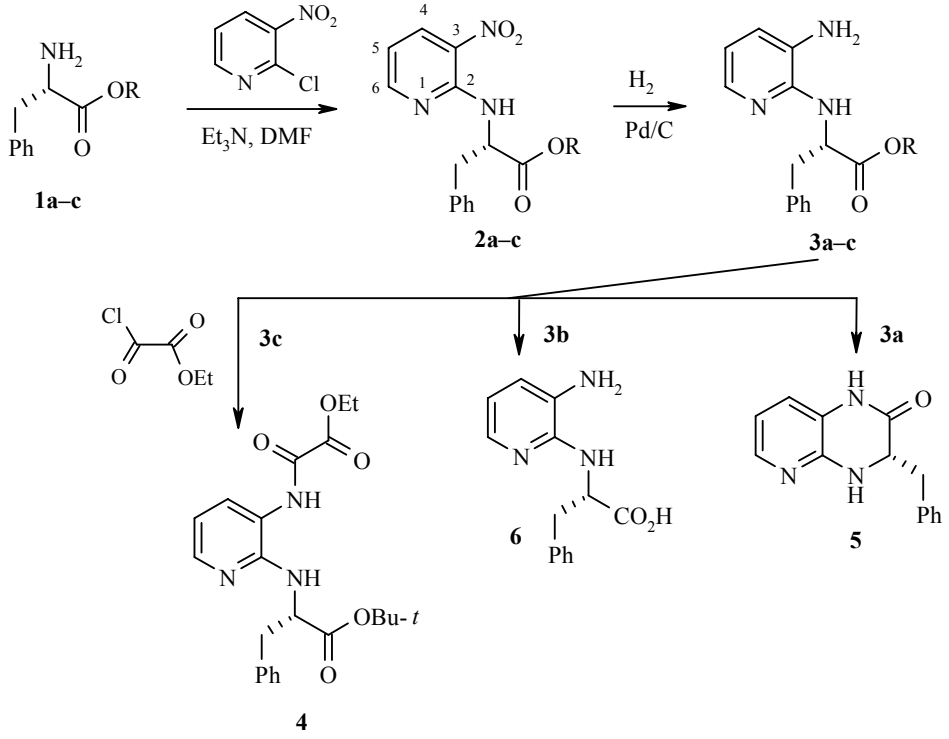
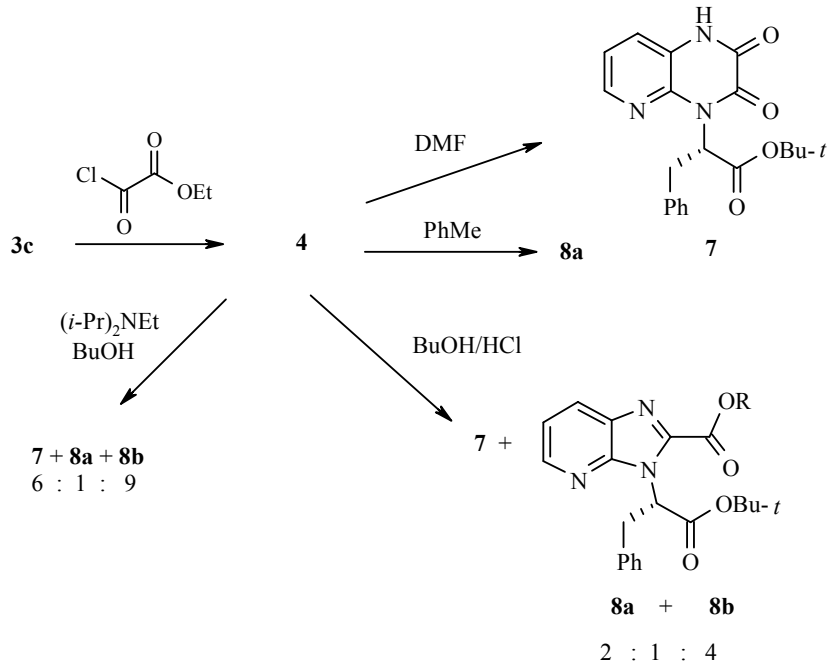
Nucleophilic substitution of the chlorine atom in 2-chloro-3-nitropyridine with esters of L-phenylalanine **1a-c** on heating in DMF in the presence of triethylamine leads to the formation of esters of N-(3-nitro-2-pyridyl)-L-phenylalanine **2a-c** in moderate yield. Initial experiments on the catalytic hydrogenation of ethyl ester **2a** showed that it is accompanied by spontaneous cyclization into 3-benzyl-1,2,3,4-tetrahydropyrido-[2,3-*b*]pyrazin-2-one (**5**) in quantitative yield. Based on literature data [3] we proposed that the use of the benzyl (**2b**) or *tert*-butyl (**2c**) esters may prevent the spontaneous cyclization on reduction of the nitro group. However, according to data of chromato-mass spectrometry (LCMS) on hydrogenation of the benzyl ester **2b** a complex mixture is formed containing, together with compound **5**, acid **6** (~30%) the product of debenzylation of the initial ester, consequently the most convenient subject for further investigation proved to be the *tert*-butyl ester **3c**. The L-phenylalanine *tert*-butyl ester (**2c**) necessary for obtaining ester **3c** was synthesized by us by a modification of the procedure of [4] from L-phenylalanine and isobutene in an autoclave in the presence of sulfuric acid.



2, 3 a R = Et, **b** R = Bn, **c** R = *t*-Bu

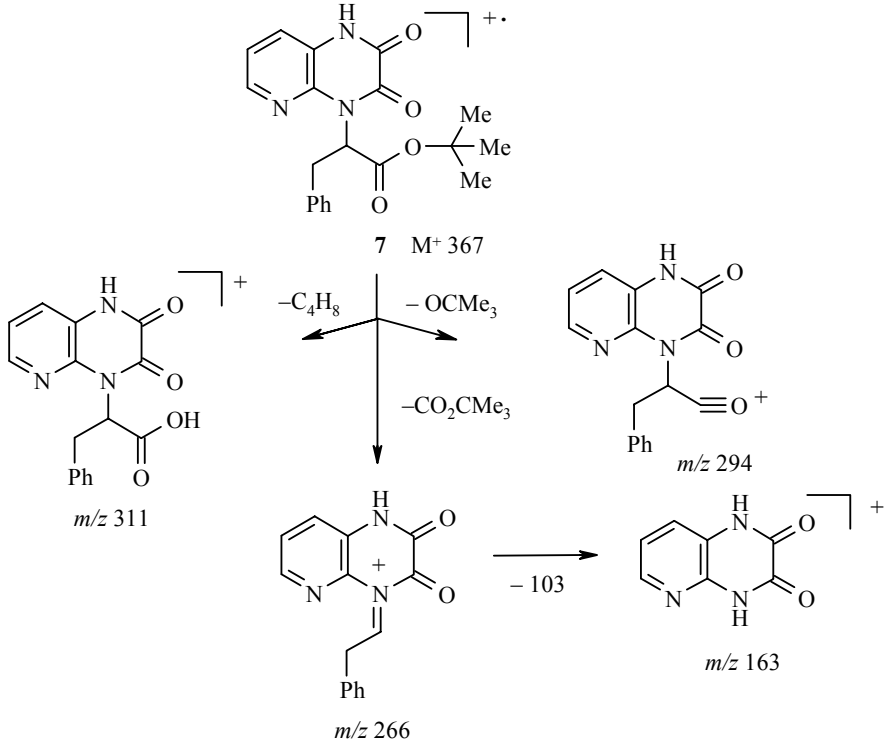
There are two electrophilic centers in the polyfunctional compound **4** resulting on acylation with monoethyl oxalyl chloride, an ester and an amide carbonyl group. Attack by the amino group in position 2 at the ester group of the oxalyl fragment must lead to the desired piperazine derivative **7**, while on reaction involving the amide carbonyl the imidazole compound **8** must be formed.

The formation of piperazinones under conditions of acid catalyzed cyclization was reported in [5]. Our attempts to use this procedure and carry out the cyclization of compound **4** in the presence of HCl in butanol led to the parallel formation of both compounds, with the preferential formation of imidazoles **8a,b** (70%) (the process is accompanied by transesterification with the formation of the butyl ester **8b**). An analogous picture was also observed on using a basic catalyst. On carrying out cyclization in the presence of diisopropylethylamine in butanol the preferential formation (60%) of compounds **8a,b** was also observed.

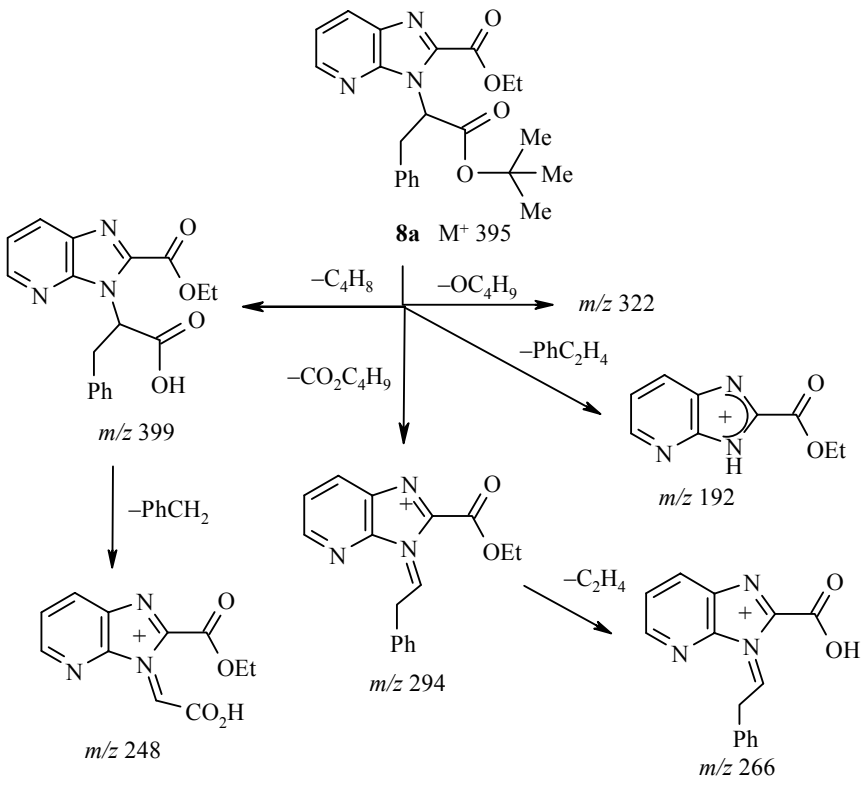


8 a R = Et, **b** R = Bu

Peaks were observed in the mass spectra of compounds **7** and **8** corresponding to the molecular ions of the proposed structures, and this was confirmed by the character of their fragmentation. The mass spectral decomposition of piperazine structure **7** is linked mainly with the fragmentation of the N-alkyl substituent, and one of the most intense peaks in the spectrum is that of the ion with *m/z* 163, having the structure of the unsubstituted pyridopyrazinone.



The fragmentation of the molecular ion of compound **8a** is also linked with the primary decomposition of the N-alkyl substituent, but the peak of the 2-ethoxycarbonylimidazo[4,5-*b*]pyridine ion (*m/z* 192, *I* 100%) is the maximum in the mass spectrum.



It turned out that the direction of thermal cyclization depends to a very high degree on the solvent used in the reaction. We successfully chose conditions in which each process may selectively be carried out separately. In reality carrying out the cyclization in a nonpolar solvent (toluene) leads selectively to the formation of imidazole **8a**, while the use of a polar aprotic solvent (DMF) enables the desired piperazine structure **7** to be obtained exclusively

It should be noted that all the stages of the proposed synthetic route proceed without affecting the asymmetric center, which enabled us to obtain enantiomerically pure (*ee* 100%) pyridopiperazinedione **7** with a chiral substituent at the nitrogen atom.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DPX (400 MHz) instrument in $CDCl_3$ (if no other solvent is indicated), internal standard was TMS, and ^{13}C NMR spectra on a Bruker AMX 400 (100 MHz) instrument. Chromato-mass spectral investigations of reaction mixtures and isolated compounds were carried out using a Shimadzu Analytical HPLC SCL10Avp liquid chromatograph and a PE SCIX API 150 mass spectrometer (electrospray, positive ionization).

A check on the progress of reactions and the purity of the compounds obtained was carried out by TLC on Sorbfil plates (sorbent was STKh-1VE silica gel) in the system hexane–ethyl acetate, 10:1, or by liquid chromatography with the mass spectral detector.

Commercial 2-chloro-3-nitropyridine and L-phenylalanine ethyl ester hydrochloride (Aldrich) were used, L-phenylalanine benzyl ester was obtained by the procedure of [6].

L-Phenylalanine *tert*-Butyl Ester. L-Phenylalanine (5 g, 0.03 mol) was suspended in dioxane (100 ml) in a 250 ml autoclave and conc. H_2SO_4 (3.3 g, 33 mmol) was added. The obtained solution was cooled to -15°C, liquid isobutene (50 ml) was added to the resulting solid mass, and the mixture was stirred in the sealed autoclave at 50°C for 12 h. The contents of the autoclave, cooled to ~20°C were poured into a cooled (~0°C) mixture of ether (100 ml) and 1 N NaOH solution (300 ml), extracted with ether (3×100 ml), the extract dried with sodium sulfate, evaporated, and the *tert*-butyl ester (2 g, 30%) was obtained as a colorless liquid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.43 (9H, s, $3CH_3$); 2.84 (1H, dd, *J* = 13.5, *J* = 6.2, CH_2Ph); 3.03 (1H, dd, *J* = 13.5, *J* = 6.2, CH_2Ph); 3.61 (1H, m, NH_2CHCO); 7.23 (3H, m, H Ph); 7.30 (2H, m, H Ph).

N-(3-Nitropyrid-2-yl)-L-phenylalanine Esters 2a-c (General Method). 2-Chloro-3-nitropyridine (11.1 g, 0.07 mol) was added to a solution of phenylalanine ester hydrochloride (0.07 mol) in DMF (100 ml), and triethylamine (14.85 g, 0.147 mol) was poured in. The reaction mixture was stirred at 100°C for 10 h (check by TLC, hexane–ethyl acetate, 10:1), poured into water, and extracted with ethyl acetate (3×100 ml). The extract was dried over sodium sulfate, and evaporated. The residue was chromatographed on a column of silica gel in hexane–ethyl acetate, 10:1.

N-(3-Nitropyrid-2-yl)-L-phenylalanine Ethyl Ester (2a). Yield 50%; mp 66-68°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 3.22 (1H, dd, *J* = 13.8, *J* = 7.4, CH_2Ph); 3.33 (1H, dd, *J* = 13.8, *J* = 7.4, CH_2Ph); 4.20 (2H, q, *J* = 7.2, CH_2CH_3); 5.13 (1H, m, NHCHCO); 6.70 (1H, m, NH); 7.26 (3H, m, H Ph); 7.35 (2H, m, H Ph); 8.36 (1H, dd, *J* = 4.5, *J* = 1.8, H-5); 8.41 (1H, dd, *J* = 8.4, *J* = 1.8, H-6); 8.45 (1H, m, H-4). Found, %: C 60.99; H 5.32; N 13.37. $C_{16}H_{17}N_3O_4$. Calculated, %: C 60.94; H 5.43; N 13.33.

N-(3-Nitropyrid-2-yl)-L-phenylalanine Benzyl Ester (2b). Yield 45%; mp 120-122°C. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 3.22 (1H, dd, *J* = 13.8, *J* = 7.4, CH_2Ph); 3.33 (1H, dd, *J* = 13.8, *J* = 7.4, CH_2Ph); 5.17 (3H, m, NHCHCO, CH_2Ph); 6.68 (1H, m, NH); 7.20 (2H, d, *J* = 6.6, H Ph); 7.27 (5H, m, H Ph); 7.35 (3H, m, H Ph); 8.29 (1H, dd, *J* = 4.5, *J* = 1.4, H-5); 8.40 (1H, dd, *J* = 8.3, *J* = 1.4, H-6); 8.43 (1H, m, H-4). Found, %: C 67.04; H 4.97; N 11.31. $C_{21}H_{19}N_3O_4$. Calculated, %: C 66.83; H 5.07; N 11.13.

N-(3-Nitropyrid-2-yl)-L-phenylalanine *tert*-Butyl Ester (2c). Yield 70%; mp 137-139°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (9H, s, $3CH_3$); 3.25 (2H, m, CH_2Ph); 5.04 (1H, m, NHCHCO); 6.70 (1H, m, NH); 7.28 (5H, m, H Ph); 8.37 (1H, d, *J* = 4.5, H-5); 8.41 (1H, d, *J* = 8.3, H-6); 8.48 (1H, m, H-4). Found, %: C 63.11; H 6.12; N 12.21. $C_{18}H_{21}N_3O_4$. Calculated, %: C 62.96; H 6.16; N 12.24.

(3*S*)-3-Benzyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-2-one (5). 10 % Pd/C (5 wt.%) was added to a solution of compound **2a** (0.95 g, 3 mmol) in methanol (50 ml), the mixture was purged with argon, and then with hydrogen. The mixture was hydrogenated in an atmosphere of hydrogen at room temperature (check by TLC). The reaction mixture was filtered, the filtrate was heated to 50°C, and the methanol evaporated. The residue was washed with ether and compound **5** (0.70 g, 95%) was obtained having mp 265-267°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.97 (2H, m, CH_2Ph); 4.30 (1H, d, *J* = 1.3, NHCHCO); 6.43 (1H, dd, *J* = 7.5, *J* = 5.1, H-5); 6.68 (1H, s, NH); 6.75 (1H, dd, *J* = 7.5, *J* = 1.1, H-6); 7.20 (5H, m, H Ph); 7.54 (1H, dd, *J* = 5.1, *J* = 1.1, H-4); 10.28 (1H, s, NHCO). Found, %: C 70.25; H 5.42; N 17.61. $C_{14}H_{13}N_3O$. Calculated, %: C 70.28; H 5.48; N 17.56.

(2*S*)-2-(1,4-Dihydro-2,3-dioxopyrido[2,3-*b*]pyrazin-4-yl)-3-phenylpropionic Acid *tert*-Butyl Ester (7). 10% Pd/C was added to a solution of compound **2c** (1.00 g, 3 mmol) in ether (50 ml), the mixture was purged with argon and then with hydrogen. The mixture was hydrogenated in an atmosphere of hydrogen at room temperature (check by TLC). The reaction mixture was filtered. Triethylamine (0.48 g, 4.8 mmol) was added to the filtrate containing compound **3c**, the solution was cooled to 0°C, ethyl oxalyl chloride (0.57 g, 4.2 mmol) was added dropwise, giving a white precipitate. The mixture was stirred at room temperature for 1 h. The solid was filtered off, and the filtrate evaporated. Compound **4** was obtained as a yellow oily liquid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (9H, s, $3CH_3$); 1.41 (3H, t, *J* = 7.1, CH_3); 3.16 (2H, m, CH_2Ph); 4.39

(2H, q, J = 7.1, C<u>H</u>$_2$CH$_3$); 4.88 (2H, m, N<u>H</u>C<u>H</u>CO); 6.70 (1H, m, H-5); 7.21 (3H, m, H Ph); 7.26 (2H, m, H Ph); 7.71 (1H, dd, J = 7.7, J = 1.5, H-6); 8.03 (1H, dd, J = 5.1, J = 1.4, H-4). ^{13}C NMR spectrum, δ, ppm: 13.5, 27.5, 37.9, 55.3, 63.3, 66.6, 113.6, 117.4, 126.3, 127.9, 129.1, 131.4, 136.5, 145.3, 150.5, 154.7, 160.0, 171.7.

A solution of the obtained compound **4** (without further purification) in DMF (20 ml) was stirred at 120°C (check by TLC), then poured into water, and extracted with ethyl acetate (3×50 ml). The extract was dried over sodium sulfate, and evaporated. The residue was chromatographed on a column of silica gel in ethyl acetate. Piperazine **7** (0.6 g, 50%) was obtained having mp 212-214°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.41 (9H, s, C(CH$_3$)$_3$); 3.63 (2H, m, CH$_2$Ph); 6.28 (1H, m, NCHCO); 7.05 (5H, m, H Ph); 7.12 (1H, m, H-5); 7.65 (1H, d, J = 7.5, H-6); 8.21 (1H, d, J = 4.6, H-4); 11.78 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 368 $[M + 1]^+$ (0.4), 311 (1.0), 294 (7.2), 266 (14.4), 163 (72.0), 57 (100). Found, %: C 65.41; H 5.81; N 11.48. $C_{20}H_{21}N_3O_4$. Calculated, %: C 65.38; H 5.76; N 11.44.

3-[(1*S*)-1-Benzyl-*tert*-butoxycarbonylmethyl]-3H-imidazo[4,5-*b*]pyridine-2-carboxylic Acid Ethyl Ester (8a). A solution of compound **4** obtained as indicated in the previous procedure was evaporated. Toluene (30 ml) was added to the obtained yellow oily liquid, the mixture boiled for 10 h (check by TLC), and the toluene distilled off in vacuum. The residue was chromatographed on a column of silica gel in the system hexane–ethyl acetate, 10:1. Imidazole **8a** (0.6 g, 55%) was obtained as a yellow oily liquid. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.40 (12H, m, 3CCH$_3$, CH$_2$C<u>H</u>$_3$); 3.73 (2H, m, CH$_2$Ph); 4.41 (2H, m, C<u>H</u>$_2$CH$_3$); 6.36 (1H, dd, J = 10.4, J = 5.5, NCHCO); 6.85 (2H, dd, J = 6.6, J = 2.7, H Ph); 7.01 (3H, m, H Ph); 7.25 (1H, dd, J = 8.2, J = 4.6, H-5); 8.10 (1H, dd, J = 8.2, J = 1.5, H-6); 8.43 (1H, dd, J = 4.6, J = 1.3, H-4). Mass spectrum, *m/z* (I_{rel}, %): 396 $[M + 1]^+$ (0.2) , 339 (0.2), 294 (16.6), 266 (4.2), 248 (10.4), 192 (73.9), 57 (100). Found, %: C 66.86; H 6.40; N 10.67. $C_{22}H_{25}N_3O_4$. Calculated, %: C 66.82; H 6.37; N 10.63.

Cyclization of N-[3-(Ethoxyoxalylamino)pyrid-2-yl]-L-phenylalanine *tert*-Butyl Ester (4).

A. In the presence of hydrochloric acid. Hydrochloric acid (2 drops) was added to a solution of compound **4** in butanol (10 ml), and the mixture boiled for 10 h (check by chromato-mass spectrometry). A mixture of compounds **7**, **8a**, and **8b** in a ratio of 2:1:4 was obtained.

B. In the presence of diisopropylethylamine. Diisopropylethylamine (2 drops) was added to a solution of compound **4** in butanol (10 ml) and the mixture boiled for 10 h (check by chromato-mass spectrometry). A mixture of compounds **7**, **8a**, and **8b** in a ratio of 6:1:9 was obtained.

3-[(1*S*)-1-Benzyl-2-*tert*-butoxycarbonylmethyl]-3H-imidazo[4,5-*b*]pyridine-2-carboxylic Acid Butyl Ester (8b) was isolated chromatographically on a column of silica gel in the system hexane–CH_2Cl_2–MeOH, 1:4:(from 0 to 25). ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.95 (3H, t, J = 7.1, CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); 1.37 (11H, m, 3CCH$_3$, CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$); 1.76 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$); 3.74 (2H, m, CH$_2$Ph); 4.34 (2H, m, C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$); 6.36 (1H, dd, J = 10.4, J = 5.5, NCHCO); 6.84 (2H, m, H Ph); 7.00 (3H, m, H Ph); 7.23 (1H, dd, J = 8.2, J = 4.6, H-5); 8.09 (1H, dd, J = 8.2, J = 1.5, H-6); 8.43 (1H, dd, J = 4.6, J = 1.3, H-4). Mass spectrum, *m/z* (I_{rel}, %): 424 $[M + 1]^+$ (80.9), 368 (100), 312 (4.2), 268 (6.8), 220 (4.7), 120 (1.1).

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