ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 5, pp. 663–667. © Pleiades Publishing, Ltd., 2013.
Original English Text © A.N. Reznikov, E.V. Golovin, Yu.N. Klimochkin, 2013, published in Zhurnal Organicheskoi Khimii, 2013, Vol. 49, No. 5, pp. 682–686.

Dedicated to Full Member of the Russian Academy of Sciences
I.P. Beletskaya on occasion of her jubilee

Enantioselective Synthesis of γ-Aminobutyric Acid Derivatives by Ni(II)-Catalyzed Reaction of Diethyl Malonate with Nitroalkenes

A. N. Reznikov, E. V. Golovin, and Yu. N. Klimochkin

Samara State Technical University, ul. Molodogvardeiskaya 244, Samara, 443001 Russia
e-mail: orgphosphorus@yandex.ru

Received December 30, 2012

Abstract—A new synthetic approach to (3*R*)-4-amino-3-methylbutyric acid and [(4*R*)-2-oxo-4-phenylpyrrolidin-1-yl]acetamide [(*R*)-phenotropil] has been developed. Asymmetric center with a required configuration has been generated via enantioselective addition of diethyl malonate to 1-nitropropene and β-nitrostyrene, catalyzed by Ni(II) complexes with (*R*,*R*)- and (*S*,*S*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine.

DOI: 10.1134/S1070428013050047

γ-Aminobutyric acid (GABA) was found in the mammalian brain as early as 1950. It is the main inhibitory neurotransmitter in the mammalian central nervous system. GABA and its derivatives are used in the treatment of nervous system disorders such as logopathy, memory impairment, cerebral atherosclerosis, and mental deficiency in children. GABAergic compounds can improve cerebral circulation and its autoregulation, prevent peroxide lipid oxidation, enhance the activity of antioxidant systems, exhibit membrane protecting effect, improve glucose utilization, and level energy deficiency [1]. Some GABA derivatives show nootropic activity; they improve learning ability, mental activity, and memory. Therapeutic effects of numerous GABA derivatives and analogs have been studied up to now [2].

Among new-generation nootropic drugs, a cyclic GABA derivative, (2-oxo-4-phenylpyrrolidin-1-yl)acetamide (phenotropil, phenylpiracetam, carphedon), should be noted. Numerous studies have shown that phenotropil enhances cerebral metabolism and blood circulation, stimulates redox reactions, increases the energy potential via glucose utilization, and improves blood circulation in ischemic brain regions [3]. The (*R*) isomer of phenotropil was found to produce more profound muscle relaxant and analgesic effects as compared to its (*S*) enantiomer [4]; therefore, development of new enantioselective syntheses of (*R*)-phenotropil is an important problem.

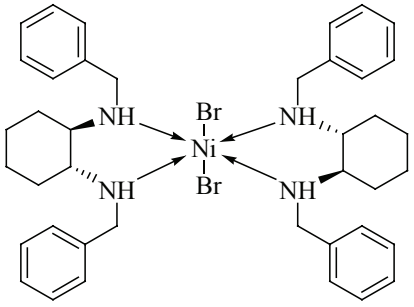
(3*R*)-4-Amino-3-methylbutanoic acid is a synthetic precursor of dipeptidyl peptidase-IV (DPP-IV) inhibitors that are promising for the treatment of type II diabetes mellitus [5]; it may also be used as intermediate product in the synthesis of a structural fragment of the antiasthmatic drug Zeneca ZD 3523 [6].

The known methods for the synthesis of (*R*)-phenotropil [4, 7] and (3*R*)-4-amino-3-methylbutanoic acid [8] are based on chemoenzymatic separation of intermediate compounds. An alternative synthetic route to (3*R*)-4-amino-3-methylbutanoic acid implies radical cyclization of (*S*)-*N*-allyl-2-bromo-*N*-(1-phenylethyl)acetamide or *S*-(2-{allyl[(*S*)-1-phenylethyl]amino}-2-oxoethyl) *O*-ethyl dithiocarbonate in the presence of an equimolar amount of tributylstannane [9], which complicates the overall synthesis procedure and is inadmissible from the viewpoints of environmental safety and purity of pharmaceutical substances.

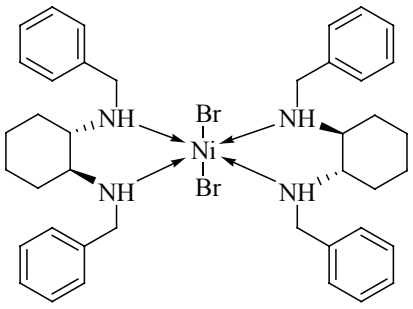
A very promising synthetic approach to nonracemic 3-substituted GABA derivatives is based on enantioselective addition of 1,3-dicarbonyl compounds to nitroalkenes in the presence of transition metal complexes [10]. The addition of malonates to nitrostyrene derivatives can be

catalyzed by chiral nickel [11], cobalt, and manganese complexes [12] with various diamines.

In continuation of our previous studies, in the present article we report on the synthesis of (3*R*)-4-amino-3-methylbutanoic acid and (*R*)-phenotropil via enantioselective addition of diethyl malonate to 1-nitropropene and β-nitrostyrene in the presence of chiral nickel complexes **Ia** and **Ib**.



(*R*,*R*)-**Ia**



(*S*,*S*)-**Ib**

The addition of diethyl malonate (**III**) to 1-nitropropene (**II**) was catalyzed by 2 mol % of **Ia**. The reaction was enantioselective, and (*R*)-nitro ester **IV** with an *ee* value of more than 79% was obtained (Scheme 1). The hydrogenation of **IV** over Raney nickel was accompanied by pyrrolidine ring closure to give ester **V** which was subjected to acid hydrolysis. After recrystallization from ethanol, (3*R*)-4-amino-3-methylbutanoic acid (**VI**) with *ee* 98% (according to the HPLC data) was isolated.

Alkaline hydrolysis of ester **V**, followed by decarboxylation of acid **VII**, afforded (4*R*)-4-methylpyrrolidin-2-one (**VIII**) (Scheme 2).

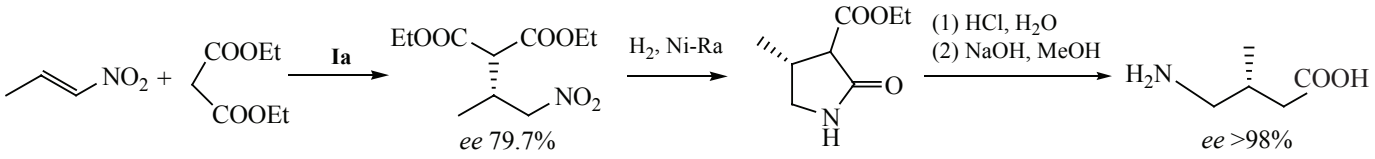
The addition of diethyl malonate (**III**) to β-nitrostyrene (**IX**) in the presence of 0.2 mol % of complex **Ib** in toluene gave (*R*)-nitro ester **X** with *ee* 92.3% (HPLC). (4*R*)-4-Phenylpyrrolidin-2-one (**XII**) was synthesized from ester (**XI**) in a way similar to the synthesis of **VIII** (Scheme 3).

Thus the use of a low-cost and readily accessible Ni(II) complex as catalyst in enantioselective Michael addition as the key step ensures preparation of (3*R*)-4-amino-3-methylbutanoic acid and (*R*)-phenotropil with high enantiomeric excess.

EXPERIMENTAL

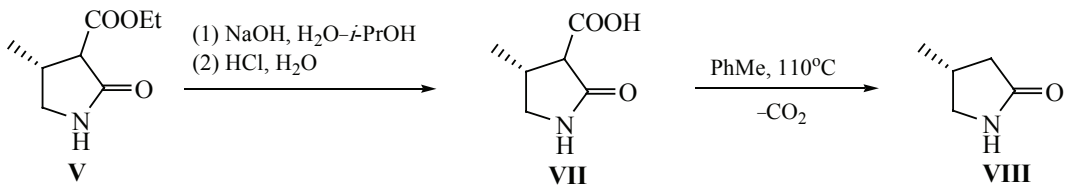
The ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-ECX400 instrument at 399.78 and 100.53 MHz, respectively, from solutions in $CDCl_3$ using the residual proton signal and carbon signal of the solvent as reference. The mass spectra were obtained on a Finnigan Trace

Scheme 1.



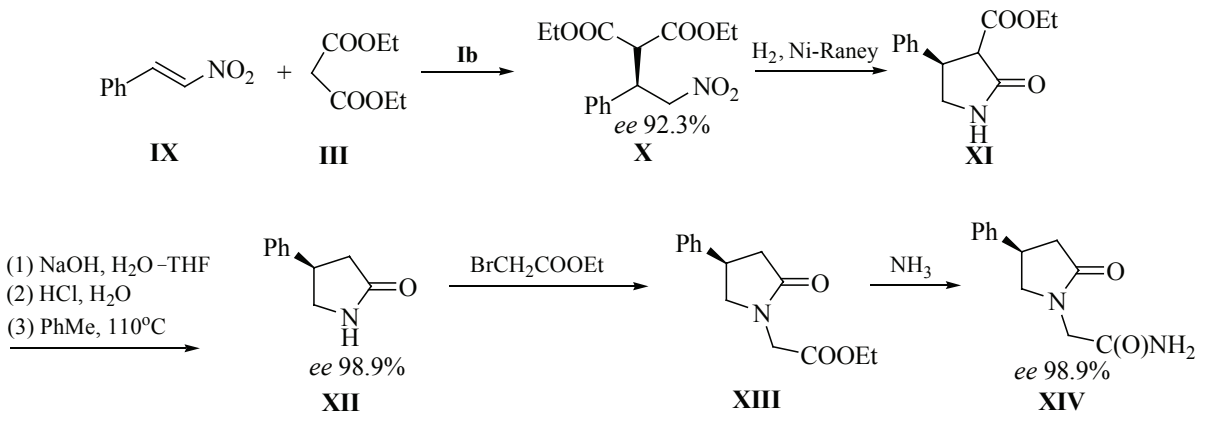
II **III** **IV** **V** **VI**

Scheme 2.



V **VII** **VIII**

Scheme 3.



IX III X XI XII XIII XIV

DCQ GC–MS system (SGE BPX-5 capillary column; 30 m × 0.32 mm; electron impact, 70 eV).

Enantiomeric purity of the products was estimated by HPLC on a Waters liquid chromatograph equipped with a Waters 2487 UV detector and a Waters 2414 refractive index detector; analysis conditions: **IV**: Chiralcel OD-3 column, eluent hexane–propan-2-ol (95 : 5), flow rate 1.0 ml/min; **X**, **XII**: Chiralcel AD, hexane–propan-2-ol (95:5), 1.0 ml/min; **XIV**: Lux Amylose-2 (150×4.6 mm; 5 μm), hexane–ethanol (70:30), 2.0 ml/min. (3*R*)-4-Amino-3-methylbutanoic acid (**VI**) was preliminary derivatized by treatment with D-Marfey reagent; HPLC conditions: YMC Pack Pro C18 (150×3.0 mm, 3 μm), formate buffer (pH 3.0) in methanol (4:6)–methanol (70:30), 0.6 ml/min. The elemental compositions were determined on a EuroVector EA 3000 analyzer. The optical rotatins were measured on a Rudolph Research Analytical polarimeter.

Chiral nickel complexes **Ia** and **Ib** were synthesized according to the procedure reported in [10].

Diethyl 2-[(2*R*)-1-nitropropan-2-yl]propanedioate (IV). Nickel complex **Ia**, 6.1 g (7.5 mmol, 1.02 mol %), was added to a mixture of 63.8 g (0.733 mol) of 1-nitropropene (**II**) and 269.7 g (1.686 mol) of diethyl malonate (**III**), and the mixture was kept for 48 h at 50°C. Ester **IV** was isolated by vacuum distillation. Yield 173.0 g (96%), bp 105–112°C (3.8×10^{-2} mm), *ee* = 79.7% (HLPC); retention time, min: (*R*)-**IV** 8.9, (*S*)-**IV** 10.5; $[\alpha]_D^{20}$ = +12.12° (*c* = 0.025 g ml^{-1}, chloroform). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 d (3H, CH_3, $^3J_{HH}$ = 6.8 Hz), 1.24 t (6H, CH_3, $^3J_{HH}$ = 7.1 Hz), 2.99 m (1H, C**H**CH_3), 3.44 d [1H, C**H**$(COOEt)_2$, $^3J_{HH}$ = 6.6 Hz], 4.18 m (4H, CH_2O, mixture of rotamers), 4.42 d.d (1H, CH_2NO_2, J_{HH} = 7.9, 2.7 Hz), 4.60 d.d (1H, CH_2NO_2, J_{HH} = 5.0, 12.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.05 (CH_3), 15.53 (CH_3), 32.01 (**C**HCH_3), 54.17 [**C**$H(COOEt)_2$], 61.88 and 61.92 (CH_2O, mixture of rotamers), 78.58 (CH_2NO_2), 167.68 and 167.72 (C=O, mixture of rotamers). Mass spectrum *m*/*z* (I_{rel}, %): 186 (5) $[M-CH_3NO_2]^+$, 168 (32), 140 (17), 113 (27), 80 (25), 69 (100). Found, %: C 48.62; H 6.89; N 5.71. $C_{10}H_{17}NO_6$. Calculated, %: C 48.58; H 6.93; N 5.67.

Ethyl (4*R*)-4-methyl-2-oxopyrrolidine-3-carboxylate (V). A high-pressure reactor was charged with a solution of 173.0 g (0.700 mol) of ester **IV** in 350 ml of propan-2-ol, 5 g of Raney nickel was added, and the mixture was heated for 20 h at 50°C under a hydrogen pressure of 10–15 atm. The solvent was distilled off under reduced pressure, the residue was dissolved in 300 ml of chloroform, the solution was filtered through a 3-cm layer of silica gel (filter diameter 20 cm), the sorbent was washed with 500 ml of chloroform, and the solvent was distilled off under reduced pressure. Yield 111.6 g (93%), $[\alpha]_D^{20}$ = +39.45° (*c* = 0.0236 g ml^{-1}, chloroform). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.05 d (3H, CH_3, J_{HH} = 6.8 Hz), 1.18 t (3H, CH_3, J_{HH} = 6.8 Hz), 2.74 m (1H, CH), 2.85 m (2H, CH_2), 3.44 t (1H, CH, J_{HH} = 9.1 Hz), 4.12 q (2H, CH_2O, J_{HH} = 6.8 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 171 (75) $[M]^+$, 126 (40), 125 (32), 98 (20), 97 (40), 87 (65), 69 (100), 57 (40). Found, %: C 56.20; H 7.69; N 8.25. $C_8H_{13}NO_3$. Calculated, %: C 56.13; H 7.65; N 8.18. *M* 171.19.

(3*R*)-4-Amino-3-methylbutanoic acid (VI). A mixture of 111.6 g (0.652 mol) of ester **V**, 107 ml of concentrated aqueous HCl, and 107 ml of water was heated for 18 h at the boiling point. The mixture was cooled and extracted with ethyl acetate (2 × 100 ml) to remove neutral impurities, and the aqueous phase was evaporated under

reduced pressure. The residue, amino acid hydrochloride, 88.9 g, was dissolved in 250 ml of methanol, a solution of 28.0 g (0.700 mol) of sodium hydroxide in 1 l of methanol was added under stirring and cooling until pH 7, the mixture was evaporated to a volume of 500 ml, 500 ml of ethyl acetate was added, and the mixture was filtered through a 3-cm layer of silica gel (filter diameter 20 cm). The solvent was distilled off under reduced pressure, and the residue was recrystallized from 700 ml of ethanol. Yield 43.5 g (57%), mp 191–193°C, *ee* = 98% (HPLC), $[\alpha]_D^{25}$ = –8.36° (*c* = 0.052 g ml^{-1}, water; published data [8]: $[\alpha]_D^{25}$ = –7.34° (*c* = 0.052 g ml^{-1}, water); retention time, min: (*S*)-**VI** 6.0, (*R*)-**VI** 7.8 min. ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.02 d (3H, CH_3, $^3J_{HH}$ = 6.9 Hz), 2.15 m (1H, CH), 2.27 d (2H, CH_2, $^3J_{HH}$ = 6.7 Hz), 2.86 d (2H, CH_2, $^3J_{HH}$ = 6.7 Hz), 4.96 br.s (3H, NH_3^+). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 17.58 (CH_3), 29.48 (CH), 43.69 (CH_2), 45.37 (CH_2), 179.17 (COO^-). Found, %: C 51.32; H 9.42; N 11.91. $C_5H_{11}NO_2$. Calculated, %: C 51.26; H 9.46; N 11.96.

(4*R*)-4-Methyl-2-oxopyrrolidine-3-carboxylic acid (VII). A solution of 106 g (2.65 mol) of sodium hydroxide in 212 ml of water was added to a solution of 39.0 g (0.228 mol) of compound **V** in 106 ml of propan-2-ol, and the mixture was stirred for 1.5 h at room temperature. The precipitate of carboxylic acid sodium salt was filtered off, washed with propan-2-ol (20 ml), and dried. The salt, 32.8 g, was dissolved in 25 ml of water, 25 ml of 35% aqueous HCl was added on cooling, and the the precipitate was filtered off, washed with 15 ml of water, and dried. Yield 24.1 g (74%), mp 135–137°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.00 d (3H, CH_3, J_{HH} = 6.8 Hz), 2.60 m (1H, CH), 2.73 t (1H, CH), 2.82 d (1H, CH), 3.30 t (1H, CH), 7.78 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.19 (CH_3), 34.77 (**C**HCH_3), 47.41 (CH_2N), 56.25 (**C**HCOOH), 171.90 (C=O), 173.02 (COOH). Found, %: C 50.42; H 6.31; N 9.72. $C_6H_9NO_3$. Calculated, %: C 50.35; H 6.34; N 9.79.

(4*R*)-4-Methylpyrrolidin-2-one (VIII). A solution of 24.1 g (0.168 mol) of acid **VII** in 370 ml of toluene was heated for 1.5 h under reflux, and the solvent was removed under reduced pressure. Yield 16.2 g (97%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.91 d (3H, CH_3, $^3J_{HH}$ = 6.8 Hz), 1.74 d.d (1H, $^3J_{HH}$ = 6.6, $^2J_{HH}$ 16.3 Hz), 2.26 d.d (1H, $^3J_{HH}$ = 8.7, $^2J_{HH}$ = 16.2 Hz), 2.31 m (1H), 2.75 d.d (1H, $^3J_{HH}$ = 6.0, $^2J_{HH}$ = 9.8 Hz), 3.31 d.d (1H, $^3J_{HH}$ = 7.8, $^2J_{HH}$ = 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.54 (CH_3), 29.24 (CH), 38.60 (CH_2), 49.81 (CH_2), 179.28 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 99 (100) $[M]^+$, 69 (30), 56 (55). Found, %: C 60.61; H 9.09; N 14.05. C_5H_9NO. Calculated, %: C 60.58; H 9.15; N 14.13. *M* 99.13.

Diethyl 2-[(1*R*)-2-nitro-1-phenylethyl]propanedioate (X). Complex **Ib**, 325 mg (0.402 mmol), was added to a solution of 30.0 g (0.201 mol) of β-nitrostyrene (**IX**) and 36.6 ml (38.7 g, 0.241 mmol) of diethyl malonate in 68 ml of toluene, and the mixture was stirred for 6 h at 50°C. The solvent was distilled off under reduced pressure, and the residue was subjected to chromatography on Kieselgel 60 using chloroform as eluent. Yield 48.1 g (77%), mp 45–46°C, *ee* = 92% (HPLC), $[\alpha]_D^{30}$ = –6.62° (*c* = 0.015 g ml^{-1}, $CHCl_3$); published data [13]: mp 43–45°C; retention time, min: (*R*)-**X** 18.5, (*S*)-**X** 43.1. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.03 t (3H, CH_3, $^3J_{HH}$ = 7.1 Hz), 1.24 t (3H, CH_3, $^3J_{HH}$ = 7.1 Hz), 3.80 d [1H, C**H**$(COOEt)_2$, $^3J_{HH}$ = 9.2 Hz], 3.99 q (2H, CH_2O, $^3J_{HH}$ = 7.1 Hz), 4.21 m (3H, CH_2O, C**H**Ph), 4.88 m (2H, CH_2NO_2), 7.23–7.30 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.79 (CH_3), 14.02 (CH_3), 43.06 (**C**HPh), 55.08 [**C**H$(COOEt)_2$], 61.93 and 62.21 (CH_2O), 78.68 (CH_2NO_2), 128.11 (C^o), 128.41 (C^m), 128.99 (C^p), 136.36 (C^i), 166.90 and 167.53 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 309 $[M]^+$, 263 (12), 218 (12), 190 (13), 189 (100), 171 (58), 161 (56), 145 (30), 133 (22), 131 (20), 117 (28), 115 (70), 105 (15), 104 (55), 103 (34), 91 (26), 78 (15), 77 (20). Found, %: C 58.29; H 6.14; N 4.49. $C_{15}H_{19}NO_6$. Calculated, %: C 58.25; H 6.19; N 4.53. *M* 309.31

Ethyl (4*R*)-2-oxo-4-phenylpyrrolidine-3-carboxylate (XI). A high-pressure reactor was charged with 75 g (0.242 mol) of nitro ester **X** in 200 ml of propan-2-ol, 5 g of Raney nickel was added, and the mixture was heated at 50°C under a hydrogen pressure of 30 atm. The mixture was filtered, the filtrate was evaporated under reduced pressure, and the oily residue was crystallized from petroleum ether–toluene. Yield 48.05 g (85%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 t (3H, CH_3, $^3J_{HH}$ = 7.1 Hz), 3.40 m (1H), 3.52 m (1H), 3.79 m (1H), 4.09 m (1H), 4.22 q (2H, CH_2, $^3J_{HH}$ = 7.1 Hz), 7.24–7.33 m (5H, Ph), 7.44 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.23 (CH_3), 44.51 (CH), 47.99 (CH_2), 61.89 (CH), 127.10 (C^o), 127.63 (C^m), 129.08 (C^p), 140.03 (C^i), 169.48 (C=O), 173.36 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 233 $[M]^+$, 187 (10), 160 (100), 130 (68), 115 (37), 103 (72), 91 (33), 77 (70). Found, %: C 67.02; H 6.42; N 5.92. $C_{13}H_{15}NO_3$. Calculated, %: C 66.94; H 6.48;

N 6.00. *M* 233.26.

(4*R*)-4-Phenylpyrrolidin-2-one (XII). A solution of 40.5 g (0.174 mol) of ester **XI** in 380 ml of THF was cooled to 0°C, 190 ml of 15% aqueous potassium hydroxide was added, the mixture was stirred for 3 h, 500 ml of water was added, and the mixture was extracted with diethyl ether (2 × 200 ml) to remove neutral impurities. The aqueous phase was acidified with concentrated aqueous HCl until a colorless solid separated. The mixture was cooled with an ice bath for complete precipitation, and the precipitate was filtered off and dried in air. Yield of 2-oxo-4-phenylpyrrolidine-3-carboxylic acid 25.5 g (71%). The product, 25.5 g (0.124 mol), was heated for 6 h in 100 ml of boiling toluene, the mixture was washed with a 30% solution of Na_2CO_3 (2 × 100 ml) and with water, the solvent was distilled off under reduced pressure, and the residue was recrystallized from petroleum ether–toluene. Yield 12.8 g (64%), mp 86–89°C, *ee* = 99% (HPLC), $[\alpha]_D^{20}$ = –36° (*c* = 0.01 g ml^{-1}, chloroform); retention time, min: (*R*)-**XII** 6.2, (*S*)-**XII** 6.9. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.43 d.d (1H, 3-H, $^3J_{HH}$ = 6.8, $^2J_{HH}$ = 16.8 Hz), 2.65 d.d (1H, 3-H, $^3J_{HH}$ = 8.8, $^2J_{HH}$ = 16.8 Hz), 3.36 d.d (1H, 5-H, $^3J_{HH}$ = 8.4, $^2J_{HH}$ = 8.8 Hz), 3.64 m (1H, 4-H), 3.72 d.d (1H, 5-H, $^3J_{HH}$ = 8.4, $^2J_{HH}$ = 8.8 Hz), 7.20–7.27 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 38.35 (C^3), 40.11 (C^4), 49.50 (C^5), 126.52 (C^o), 126.91 (C^m), 128.60 (C^p), 142.02 (C^i), 178.21 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 161 $[M]^+$, 104 (100), 78 (10). Found, %: C 74.56; H 6.81; N 8.61. $C_{10}H_{11}NO$. Calculated, %: C 74.51; H 6.88; N 8.69. *M* 161.20.

Ethyl [(4*R*)-2-oxo-4-phenylpyrrolidin-1-yl]acetate (XIII) [4]**.** A solution of 345 mg (2.14 mmol) of compound **XII** in 30 ml of 1,4-dioxane was added under argon to a suspension of 93 mg (2.35 mmol) of 60% sodium hydride in 1,4-dioxane. The mixture was stirred for 30 min at 80°C and cooled to room temperature, 0.393 g (2.37 mmol) of ethyl bromoacetate was added, and the mixture was heated for 6 h under reflux. The solvent was removed under reduced pressure, the residue was diluted with 50 ml of ethyl acetate, the solution was washed with 5% aqueous HCl (2 × 10 ml) and brine (10 ml), the organic phase was separated and dried over sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by flash chromatography on silica gel using chloroform–methanol (95 : 5) as eluent. Yield 354 mg (67%), $[\alpha]_D^{20}$ = +4.6° (*c* = 3.0, MeOH). ^{1}H NMR spectrum, δ, ppm: 1.28 t (3H, CH_3, $^3J_{HH}$ = 7.1 Hz), 2.59 d.d (1H, 3-H, $^3J_{HH}$ = 8.4, $^2J_{HH}$ = 17.0 Hz), 2.87 d.d (1H, 3-H, $^3J_{HH}$ = 8.4, $^2J_{HH}$ = 17.0 Hz), 3.54 m (1H, 5-H), 3.64 m (1H, 4-H), 3.83 m (1H, 5-H), 4.11 d.d (2H, N**C**H_2CO, $^3J_{HH}$ = 16.3, $^2J_{HH}$ = 33.0 Hz), 4.20 q (2H, CH_2O, $^3J_{HH}$ = 7.1 Hz), 7.20–7.39 m (5H, Ph). Found, %: C 68.08; H 6.87; N 5.62. $C_{14}H_{17}NO_3$. Calculated, %: C 68.00; H 6.93; N 5.66.

2-[(4*R*)-2-Oxo-4-phenylpyrrolidin-1-yl]acetamide [(*R*)-phenotropil] (XIV) [4]**.** Gaseous ammonia was bubbled over a period of 5 h through a solution of 0.25 g (1.01 mmol) of ester **XIII** in 30 ml of methanol at room temperature. The solvent was distilled off under reduced pressure, and the residue was purified by flash chromatography on silica gel using chloroform–methanol as eluent (gradient elution, 5–10% of methanol). Yield 0.19 g (87%), mp 107–108°C, *ee* = 99.8% (HPLC), $[\alpha]_D^{20}$ = +8.5° (*c* = 3.0, MeOH); retention time, min: (*R*)-**XIV** 12.9, (*S*)-**XIV** 16.2. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.59 d.d (1H, 3-H, $^3J_{HH}$ = 8.4, $^2J_{HH}$ = 17.0 Hz), 2.81 d.d (1H, 3-H, $^3J_{HH}$ = 8.4, $^2J_{HH}$ = 17.0 Hz), 3.53 m (1H, 5-H), 3.63 m (1H, 4-H), 3.85 m (1H, 5-H), 3.97 d.d (2H, NCH_2CO, $^3J_{HH}$ = 16.3, $^2J_{HH}$ = 33.0 Hz); 6.24 br.s and 6.66 br.s (1H each, NH_2), 7.22–7.31 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 37.48 (C^3), 38.54 (C^4), 46.25 (C^5), 55.55 (N**C**H_2CO), 126.89 (C^m), 127.27 (C^p), 129.01 (C^o), 141.97 (C^i), 170.78 (C=O), 175.03 ($CONH_2$). Found, %: C 66.10; H 6.41; N 12.79. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.04; H 6.47; N 12.84.

ACKNOWLEDGMENTS

This study was performed under financial support by the Ministry of Education and Science of the Russian Federation (state contract no. 11.519.11.2012).

REFERENCES

1. *Malaya meditsinskaya entsiklopediya* (Concise Medical Encyclopedia), Moscow: Sovetskaya Entsiklopediya, 1991, vol. 1.
2. Berestovitskaya, V.M., Zobacheva, M.M., and Vasil'eva, O.S., *Izv. Ross. Gos. Ped. Univ. imeni A.I. Gertsena*, 2002, no. 2, p. 133.
3. Samotrueva, M.A., Tyurenkov, I.N., Serezhnikova, T.K., Grazhdantseva, N.N., Khlebtsova, E.B., Berestovitskaya, V.M., and Vasil'eva, O.S., *Farmatsiya*, 2011, no. 1, p. 28.
4. Veinbergs, G., Vorona, M., Dambrova, M., Karina, L., Zvejniece, L., Kalvinš, I., and Cernobrovijs, A., WO Pat-

ent no. 2007 104 780, 2007; Veinberg, G., Vorona, M., Zvejniece, L., Chernobrovijs, A., Kalvinsh, I., Karina, L., and Dambrova, M., EP Patent no. 2 013 166, 2009.

5. Koo, K.D., Jung, H., Lee, C.S., Lee, I.S., Yeo, D.J., Kwon, O.H., Kim, K.-H., Lim, D., Kim, Y.H., Chang, M., Kim, J.Y., and Koh, J.S., WO Patent no. 2008 093 960, 2008.
6. Jacobs, R.T., Bernstein, P.R., Cronk, L.A., Vacek, E.P., Newcomb, L.F., Aharony, D., Buckner, C.K., and Kusner, E.J., *J. Med. Chem*., 1994, vol. 37, p. 1282.
7. Vorona, M., Veinberg, G., Vikainis, S., Kuznetsov, E., Lebedev, A., Ponomarev, Yu., Chernobrovijs, A., Zvejniece, L., and Dambrova, M., *Chem. Heterocyclic. Compd*., 2012, vol. 48, p. 720.
8. Andruszkiewicz, R., Barrett, A.G.M., and Silverman, R., *Synth. Commun*., 1990, vol. 20, p. 159.
9. Rodriguez, V., Sanchez, M., Quintero, L., and Sartillo-Piscill, F., *Tetrahedron*, 2004, vol. 60, p. 10809.
10. Evans, D.A., Mito, S., and Seidel, D., *J. Am. Chem. Soc*., 2007, vol. 129, p. 11583.
11. Reznikov, A.N. and Klimochkin, Yu.N., *Russ. J. Org. Chem*., 2012, vol. 48, p. 1526.
12. Reznikov, A.N., Golovin, E.V., and Klimochkin, Yu.N., *Russ. J. Gen. Chem*., 2012, vol. 82, p. 1827.
13. Liu, J.-M., Wang, X., Ge, Z.M., Sun, Q., Cheng, T.-M., and Li, R.-T., *Tetrahedron*, 2011, vol. 67, p. 636.