SYNTHESIS OF SOME N-SUBSTITUTED DERIVATIVES OF 1-(1H-PYRROLE-1-YLMETHYL)-10-OXA-4-AZATRICYCLO[5.2.1.$0^{2,6}$]DEC-8-ENE-3,5-DIONE WITH AN EXPECTED ANXIOLYTIC ACTIVITY

JERZY KOSSAKOWSKI and MAGDALENA PAKOSIŃSKA-PARYS

Medical University, Department of Medical Chemistry, 3 Oczki Str., 02-007 Warsaw

The anxiolytics of second generation (buspirone, gepirone, ipsapirone, tandospirone and others) are 1-arylpiperazine derivatives with a high affinity to the 5-HT_{1A} receptor (1-3). Therefore, they are widely used in the treatment of psychotic and neurotic disorders. This paper is a continuation of our research in the field of 4-aryl/heteroaryl piperazinylalkyl derivatives (4, 5) of 1-(1H-pyrrole-1-ylmethyl)-10-oxa-azatricyclo[5.2.1.$0^{2,6}$] dec-8-ene-3,5-dione. Here we describe the synthesis of a series of isoindole-modified analogs related to tandospirone (Figure 1).

Our starting material was isoindole **I** (Scheme 1), obtained in the Diels-Alder reaction of 1-(2-furylmethyl)-1H-pyrrole with maleimide. By alkylation of the imide **I** with 1,4-dibromobutane, respectively, N-4-bromobutyl substituted derivative **II** was obtained. Next, compound **II** was condensed with appropriate amines to give derivatives **III** – **X**. The structures of compounds **I-X** have been established on the basis of ^{1}H NMR spectra and elemental analysis.

EXPERIMENTAL

Chemistry. Melting points were determined in a capillary Kofler's apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker DMX400

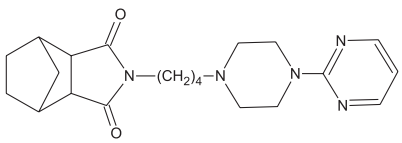
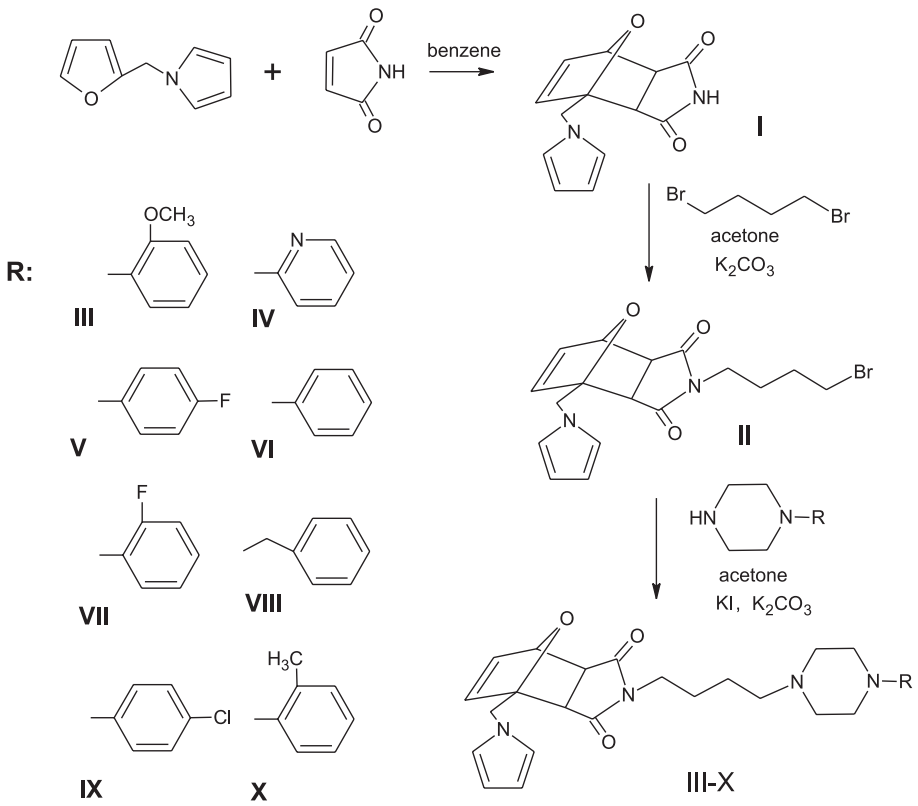


Figure 1. Tandospirone.



Scheme 1. Method of preparation of the reported compounds.

spectrometer, operating at 400.13 MHz for ^{1}H or on a Varian UNITYplus-200 spectrometer, operating at 199.97 MHz for ^{1}H. The chemical shift values, expressed in ppm, were references downfield to TMS at ambient temperature. All values of microanalysis were within ± 0.4% of the calculated compositions. Column flash chromatography and TLC were performed on silica gel 60 (Merck) using chloroform or chloroform/methanol (9:1, v/v) mixture as eluent.

1-(1H-pyrrole-1-ylmethyl)-10-oxa-4-azatricyclo [5.2.1.$0^{2,6}$] dec-8-ene-3,5-dione **I**

A mixture of 1-(2-furylmethyl)-1H-pyrrole (1 g, 0.0067 mol) and maleimide (0.7 g, 0.0072 mol) was refluxed in benzene (15 mL) for 1 h. The product (**I**) was filtered off and the residue was crystallized from benzene.

I. Yield 98%, m.p. 150^{o}C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 7.87 (s, 1H, NH), 6.84 (s, 2H, $CH_{pyrrole}$), 6.47 (d, *J* = 5,2 Hz, 1H, CH=), 6.17 (m, 3H, CH=, $CH_{pyrrole}$), 5.3 (s, 1H, CH-O), 4.72 (d, 1H, *J* = 15,2 Hz, CH-C=O), 4.40 (d, 1H, *J* = 15,2 Hz, CH-C=O), 3.0 (d, 1H, *J* = 6,4 Hz, CH_2), 2.9 (d, 1H, *J* = 6,4 Hz, CH_2). For $C_{13}H_{12}N_2O_3$ (244.24) calc.: 63.52% C, 4.92% H, 11,45% N; found: 62.35% C, 4.82% H, 11.32% N.

4-(4-bromobutyl)-1-(1*H*-pyrrol-1-ylmethyl)-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione **II**

A mixture of compound **I** (0.5 g, 0.002 mol), 1,4-dibromobutane (1.29 g, 0.006 mol) and anhydrous K_2CO_3 (0.5 g) was stirred on magnetic stirrer at ambient temperature for 15 h in acetone (50 mL). When reaction was completed (confirmed by TLC on silica gel, developing system: chloroform-methanol), the inorganic precipitate was filtered off and the solvent was evaporated.

II. Yield 70%, oil, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 6.84 (s, 2H, $CH_{pyrrole}$), 6.47 (d, *J* = 4.8 Hz, 1H, CH=), 6.17 (m, 3H, CH=, $CH_{pyrrole}$), 5.26 (s, 1H, CH-O), 4.71 (d, 1H, *J* = 15.2 Hz, CH-C=O), 4.33 (d, 1H, *J* = 15.6 Hz, CH-C=O), 3.56 (m, 2H, CH_2), 3.42 (m, 2H, CH_2), 2.98 (d, 1H, *J* = 6.4 Hz, CH_2), 2.90 (d, 1H, *J* = 6.4 Hz, CH_2), 1.85 (m, 4H, CH_2). For $C_{17}H_{19}BrN_2O_3 \times 1/2\ H_2O$ (388.24) calc.: 52.58% C, 5.19% H, 7.21% N; found: 52.51% C, 4.94% H, 7.08% N.

General procedure for preparation of 4-[4-(4-arylo/heteroarylopipererazyn-1-ylo)-butylo]-1-(1H-pyrrole-1-ylmethyl)-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-diones **III-X**

A mixture of compound **II** (0.2 g, 0.00053 mol), anhydrous K_2CO_3 (0.2 g), KI (0.2 g) and the corresponding N-substituted piperazine (0.17 g, 0.001 mol) was stirred on magnetic stirrer at ambient temperature for 40 h in acetone (50 mL). When the reaction was completed (as found by TLC on silica gel, developing system: chloroform-methanol) the mixture was filtered off and the solvent was evaporated.

III. Yield 60%, m.p. 168^{o}C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 6.88 (m, 6H $CH_{arom,}$ $CH_{pyrrole}$), 6.48 (d, *J* = 5.2 Hz, 1H, CH=), 6.18 (d, 3H, *J* = 5.6 Hz, CH=, $CH_{pyrrole}$), 5.27 (s, 1H, CH-O), 4.73 (d, 1H, *J* = 15.2 Hz, CH-C=O), 4.34 (d, 1H, *J* = 15.6 Hz, CH-C=O), 3.77 (s, 3H, O-CH_3), 3.57 (t, 2H, *J* = 6.8 Hz, CH_2), 3.10 (s, 4H, $CH_{2piper.}$), 2.98 (d, 1H, *J* = 6.4 Hz, CH_2), 2.91 (d, 1H, *J* = 6.4 Hz, CH_2), 2.61 (m, 4H, $CH_{2piper.}$), 2.44 (m, 2H, CH_2), 1.67 (m, 4H, CH_2). For $C_{28}H_{35}ClN_4O_4$ (527.048) calc.: 63.81% C, 6.69% H, 10.62% N; found: 63.79% C, 6.68% H, 10.61% N.

IV. Yield 62%, m.p. 167^{o}C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 8.20 (d, 1H, J=3.2Hz $H_{\beta pirydyl}$), 7.48 (m, 1H, $H_{\alpha pirydyl}$), 6.85 (m, 3H, $CH_{pyrrole}$), 6.64 (d, 2H, *J* = 8.4 Hz, $H_{\beta pirydyl}$), 6.48 (d, 1H, *J* = 5.6 Hz, CH=), 6.18 (m, 3H, $H_{\gamma pirydyl}$, $CH_{pyrrole}$), 5.27 (s, 1H, CH-O), 4.73 (d, 1H, *J* = 15.2 Hz, CH-C=O), 4.33 (d, 1H, *J* = 15.6 Hz, CH-C=O), 3.58 (m, 6H, CH_2, $CH_{2piper.}$), 2.96 (m, 2H, CH_2), 2.55 (m, 4H, $CH_{2piper.}$) 2.42 (m, 2H, CH_2), 1.67 (m, 4H, CH_2). For $C_{28}H_{34}Cl_3N_5O_3 \times 2.5\ H_2O$ (615.96) calc.: 50.69% C, 6.38% H, 11.37% N; found: 50.57% C, 6.30% H, 11.04% N.

V. Yield 70%, m.p. 140^{o}C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 6.9 (t, 2H, *J* = 8.6 Hz, $CH_{arom.}$), 6.86 (m, 4H, $CH_{pyrrole,}$ CH_{arom}), 6.46 (d, 1H, *J* = 4.8 Hz, CH=), 6.17 (d, 1H, *J* = 6.4 Hz, CH=, CH_{arom}), 5.27 (s, 1H, CH-O), 4.71 (d, 1H, *J* = 15.2 Hz, CH-C=O), 4.33 (d, 1H, *J* = 15.2 Hz, CH-C=O), 3.56 (t, 2H, *J* = 7 Hz, CH_2), 3.12 (m, 4H, $CH_{2piper.}$), 2.97 (d, 1H, *J* = 6.4 Hz, CH_2), 2.90 (d, 1H, *J* = 6.4 Hz, CH_2), 2.61 (s, 4H, $CH_{2piper.}$) 2.43 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.55 (m, 2H, CH_2). For $C_{27}H_{32}Cl_3FN_4O_3 \times H_2O$ (533.032) calc.: 60.80% C, 6.42% H, 10.5% N; found: 60.41% C, 6.42% H, 10.34% N.

VI. Yield 64%, m.p. 162^{o}C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 7.23 (m, 3H, $CH_{arom.}$), 6.92 (d, 2H, *J* = 8.4 Hz, $CH_{pyrrole,}$ CH_{arom}), 6.85 (m, 3H, $CH_{pyrrole,}$ CH_{arom}), 6.46 (d, 1H, *J* = 5.2 Hz, CH=), 6.17 (d, 3H, *J* = 5.2 Hz, CH=, CH_{arom}), 5.26 (s, 1H, CH-O), 4.71 (d, 1H, *J* = 15.6 Hz, CH-C=O), 4.34 (d, 1H, *J* = 15.2 Hz, CH-C=O), 3.56 (t, 2H, *J* = 7 Hz, CH_2), 3.20 (m, 4H, $CH_{2piper.}$), 2.97 (d, 1H, *J* = 6.4 Hz, CH_2), 2.90 (d, 1H, *J* = 6.4 Hz, CH_2), 2.60 (m, 4H, $CH_{2piper.}$) 2.42 (m, 2H, CH_2), 1.63 (m, 4H, CH_2). For $C_{27}H_{34}Cl_2N_4O_3 \times 1.5\ H_2O$ (560.50) calc.: 57.85% C, 6.65% H, 9.99% N; found: 57.81% C, 6.48% H, 9.96% N.

VII. Yield 71%, m.p. 130^{o}C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 7.1 (m, 4H, $CH_{arom.}$), 6.80 (s, 2H, $CH_{pyrrole}$), 6.46 (d, 1H, *J* = 5.2 Hz, CH=), 6.10 (m, 3H, CH=, CH_{arom}), 5.26 (s, 1H, CH-O), 4.70 (d, 1H, *J* = 15.2 Hz, CH-C=O), 4.34 (d, 1H, *J* = 15.2 Hz, CH-C=O), 3.90 (m, 2H, CH_2), 3.6 (m, 4H, $CH_{2piper.}$), 3.49 (m, 2H, CH_2), 3.35 (m, 2H, $CH_{2piper.}$) 3.1 (m, 4H, CH_2 $CH_{2piper.}$), 2.68 (m, 2H, CH_2), 1.76 (m, 2H, CH_2). For $C_{27}H_{32}ClFN_4O_3 \times 2H_2O$ (551.048) calc.: 58.85% C, 6.21% H, 10.16% N; found: 59.14% C, 6.54% H, 10.13% N.

VIII. Yield 65%, m.p. 174^{o}C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 7.77 (m, 2H, $CH_{arom.}$), 7.49 (m, 3H, $CH_{arom.}$), 6.82 (s, 2H, $CH_{pyrrole}$), 6.47 (d, 1H, *J* = 5.2 Hz, CH=), 6.12 (m, 3H, CH=, $CH_{pyrrole}$), 5.27 (s, 1H, CH-O), 4.71 (d, 1H, *J* = 15.6 Hz, CH-C=O), 4.35 (d, 1H, *J* = 15.2 Hz, CH-C=O), 4.31 (m, 2H, CH_2), 3.56 (m, 6H, $CH_{2piper.}$), 3.22 (m, 2H, $CH_{2piper.}$) 3.07 (m, 2H, CH_2), 1.77 (m, 8H, CH_2). For $C_{28}H_{36}Cl_2N_4O_3 \times 9.5\ H_2O$ (698.048) calc.: 48.17% C, 7.6% H, 8.02% N; found: 48.35% C, 7.20% H, 8.01% N.

IX. Yield 69%, m.p. 175^{o}C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 7.22 (m, 4H, $CH_{arom.}$), 6.83 (s, 2H, $CH_{pyrrole}$), 6.47 (d, 1H, *J* = 5.2 Hz, CH=), 6.17 (m, 3H, CH=, CH_{arom}), 5.26 (s, 1H, CH-O), 4.70 (d, 1H, *J* = 15.6 Hz, CH-C=O), 4.33 (d, 1H, *J* = 15.2 Hz, CH-C=O),

4.04 (m, 2H, CH_2), 3.58 (m, 6H, $CH_{2piper.}$), 3.48 (m, 2H, $CH_{2piper.}$) 3.10 (m, 4H, CH_2), 1.96 (m, 2H, CH_2), 1.77 (m, 2H, CH_2). For $C_{27}H_{33}Cl_3N_4O_3 \times 2H_2O$ (603.96) calc.: 53.69% C, 6.17% H, 9.27% N; found: 54.01% C, 6.12% H, 9.17% N.

X. Yield 72%, m.p. 168°C, ^{1}H NMR (400.13 MHz, $CDCl_3$) δ (ppm): 7.23 (m, 4H, $CH_{arom.}$), 6.83 (s, 1H, $CH_{pyrrole}$), 6.47 (d, 2H, *J* = 5.2 Hz, CH=, $CH_{pyrrole}$), 6.16 (m, 3H, CH=, $CH_{pyrrole}$), 5.26 (s, 1H, CH-O), 4.70 (d, 1H, *J* = 15.2 Hz, CH-C=O), 4.30 (d, 1H, *J* = 15.2 Hz, CH-C=O), 3.97 (m, 2H, CH_2), 3.60 (m, 6H, $CH_{2piper.}$), 3.30 (m, 2H, $CH_{2piper.}$) 3.14 (m, 2H, CH_2), 3.01 (m, 2H, CH_2) 2.45 (s, 3H, CH_3), 1.98 (m, 2H, CH_2), 1.78 (m, 2H, CH_2). For $C_{28}H_{35}ClN_4O_3 \times 2.5\ H_2O$ (552.092) calc.: 60.47% C, 7.20% H, 10.07% N; found: 60.53% C, 6.97% H, 10.06% N.

CONCLUSION

Ten new compounds derivatives of 1-(1H-pyrrole-1-ylmethyl)-10-oxa-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione were obtained.

REFERENCES

1. Riblet L.A., Taylor D.P., Edison M.S., Stanton H.C.: J. Clin. Psychiatry 43, 11 (1982).
2. Turło J., Zawadowski T.: Farmaco 51, 815 (1996).
3. Ishizumi K., Kojma A., Antoku F.: Chem. Pharm. Bull. 39, 2288 (1991).
4. Kossakowski J., Jarocka M.: Farmaco 56, 785 (2001).
5. Kossakowski J., Raszkiewicz A., Bugno R., Bojarski A.J.: Pol. J. Pharmacol., 56, 843 (2004).

AN APPROACH TO ENANTIOSELECTIVE ACTIVATION OF N-BENZOYL-α-METHYLSERINE WITH CHIRAL N-TRIAZINYLAMMONIUM CHLORIDE

BEATA KOLESIŃSKA[1], TOSHIFUMI MIYAZAWA[2], JANINA E. KAMIŃSKA[3], SEBASTIAN OLCZYK[3] and ZBIGNIEW J. KAMIŃSKI*[1]

[1] Institute of Organic Chemistry, Łódź University of Technology, Żeromskiego 116, 90-924 Łódź, Poland
[2] Department of Chemistry, Konan University, 8-9-1 Okamoto, Higashinada-ku, Kobe 658-8501, Japan
[3] Institute of General Food Chemistry, Łódź University of Technology, B. Stefanowskiego 4/10, 90-924 Łódź, Poland

Enantiomerically homogeneous α-methylserine was identified as component of several antibiotics (1–4) and found applications in contemporary pharmacology. Recently α-methylserine has also been applied as an expedient building block in syntheses of complex natural products (5–8) and substrate in the peptide synthesis (9).

Other α-substituted serine analogues are also easily accessible in racemic form (10, 11), however, only a few of them have been resolved (12–15) or obtained as pure enantiomers in asymmetric syntheses (16).

Due to the presence of two side chains attached to the α-carbon atom, α-methylserine, (chimera of serine and alanine) belongs simultaneously to L and D family of amino acids (see Figure 1). This ambigous stereogenic relation may cause severe problems in case of any enantioselective transformation including an application of enzymes for the resolution of α-methylserine (as well as any other readily accessible racemic α-substituted serines), chromatography on chiral stationary phase as well as enantioselective reactions. Therefore, an application of chimeric amino acids as substrates in enantioselective processes could be challenging goal when both side chains are relatively equivalent. Moreover, the results obtained (even in the case of small ee) would be valuable tool for verification of a mechanism of molecular recognition.

The preliminary studies on enantioselective activation (17) of an easily accessible racemic N-benzoyl α-substituted serines with chiral condensing reagents shown the low ee in all experiments involving α-methylserine (bearing relatively equivalent in size methyl and hydroxymethyl side chains at C_α). Herein, an approach is presented leading to diversification of

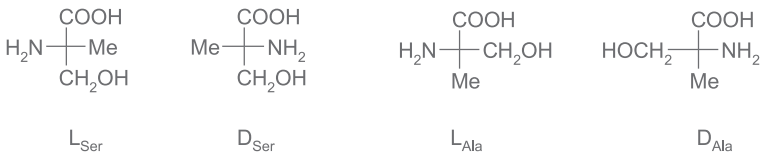


Figure 1. α-Methylserine, chimera of serine and alanine, belongs simultaneously to L and D amino acid family.

* Corresponding author: Z.J. Kamiński, Institute of Organic Chemistry, Politechnika Łódzka, ul. Żeromskiego 116, 90-924 Łódź, Poland, e-mail: kaminsz@mail.p.lodz.pl, phone: 42-631-31-51

side chains of α-methylserine based on the temporary modification of the hydroxymethyl substituent C_α.

EXPERIMENTAL

N-Benzoyl-α-substituted serines (10) (**4a-c**) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) have been prepared according to procedure previously described. THF, N-methylmorpholine and pyridine (reagent grade) were stored over potassium hydroxide. All other reagents were obtained from commercial sources and used as received.

Activation of *rac*-N-benzoyl-α-methylserine (*rac*-4) (typical procedure)

A vigorously stirred suspension of brucine (**2b**) (394 mg, 1 mmol) in THF (10 mL) was cooled to 0-5°C and treated with CDMT (**1**) (175.5 mg, 1 mmol) for 30 min. Then, *rac*-N-benzoyl-α-methylserine (***rac*-4**) (446 mg, 2 mmol) was added and stirring at 0-5°C have been continued overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL). The organic solution was washed with 0,5 M sodium bicarbonate solution (4 × 10 mL) and aqueous extracts were collected. Organic phase was washed thoroughly with cold 1 M $NaHSO_4$, water, and dried with $MgSO_4$. After filtration, the solvent was removed under reduced pressure yielding 2-phenyl-4-hydroxymethyl-4-methyl-1,3-oxazolin-5-one (**5**) (158 mg, yield 77%) as oily product.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.47 (s, 3H, $\underline{CH_3}$); 3.92 (AB system, 2H, *J* = 11 Hz, $\underline{CH_2}$-OH); 7.61-7.44 (m, 3H, $C_6\underline{H_5}$-C=N); 8.00-7.96 (m, 2H, $C_6\underline{H_5}$-C=N-).

IR (film) ν (cm^{-1}): 3375 (-OH); 2952 (C-H_{ar}); 2875 (C-H_{alk}); 1824 (C=O); 1656 (C=N).

The combined sodium bicarbonate extracts were washed with dichloromethane (10 mL) cooled to 5°C and aqueous phase was acidified to pH 3 with 1 M $NaHSO_4$. Then, the suspension was thoroughly extracted with ethyl acetate (4 × 10 mL) and combined organic extracts were washed with brine (10 mL), dried, filtered and organic solvent was removed under reduced pressure yielding N-benzoyl-α-methylserine (**4**) (129 mg, yield 58%) as crystalline solid, m.p. = 144-146°C, lit (12). m.p. = 137-139°C.

^{1}H-NMR (D_2O) δ (ppm): 1.51 (s, 3H, $C\underline{H_3}$); 3.99 (AB system, 2H, *J* = 11 Hz, $C\underline{H_2}$-OH); 7.64-7.47 (m, 3H, $C_6\underline{H_5}$CONH); 7.81-7.76 (m, 2H, $C_6\underline{H_5}$CONH).

2-Phenyl-4-methyl-4-hydroxymethyl-1,3-oxazolin-5-one (*rac*-5)

A vigorously stirred solution of CDMT (**1**) (16,7 g, 95 mmol) in dichloromethane (80 mL) was cooled to 0°C, N-methylmorpholine (10.4 mL, 95 mmol) was added dropwise, then ***rac*-4** (21.2 g, 95 mM) was added and stirring was continued for 3 h at 0-5°C and for 21 h at room temperature. The suspension was cooled again to 0°C, then thoroughly washed with water, 1 M aq. $NaHSO_4$, water, 1 M $NaHCO_3$, dried with $MgSO_4$, filtered and filtrate was concentrated under reduced pressure. The solid residue was dried and recrystallized from ethyl acetate/hexane yielding ***rac*-5** (13.8 g; yield 71%), m.p. 121-2°C.

Analysis for $C_{11}H_{11}NO_3$ (205,23): calculated: C 64.38%; H 5.40%; N 6.83%; found: C 64.28%; H 5.45%; N 7.03%.

IR (KBr) ν (cm^{-1}): 3264 (OH); 2952 (alifat.); 1832 (C=O); 1644 (C=N) [cm^{-1}].

2-Phenyl-4-methyl-4-trimethylacetyloxymethyl-1,3-oxazolin-5-one (*rac*-8)

A vigorously stirred solution of ***rac*-5** (7.18 g; 0.035 mmol) in dichloromethane (20 mL) was cooled to 0°C, then trimethylacetyl (pivaloyl) chloride (6.46 mL, 0.053 mmol). was added followed by dropwise addition of triethylamine (7.3 mL) and catalytic amount of DMAP. The stirring was continued at r.t. for 24 h. The suspension was diluted with dichloromethane (30 mL) and washed with 1 M aq. $NaHSO_4$, water, 1 M $NaHCO_3$, water again, dried with anh. $MgSO_4$, filtered and filtrate was concentrated under reduced pressure and then purified on silica column using chloroform for elution. Product crystallized slowly when treated with hexane affording ***rac*-8** as crystalline solid (3.33 g; yield 32 %), m.p. 80-82°C.

IR (KBr) ν (cm^{-1}): 2976 (C-H); 1828 (C=O); 1632 (C=N).

^{1}H-NMR (CD_3COCD_3) δ (ppm): 1.0 (s, 9H, -C-($C\underline{H_3}$)$_3$); 1.55 (s, 3H, $C\underline{H_3}$-CN-); 4.25, 4.48 (AB system, 2H, *J* = 11 Hz, -C-$C\underline{H_2}$-O-); 7.55-7.68 (m, 3H, $C_6\underline{H_5}$-CN-); 7.98-8.02 (m, 2H, $C_6\underline{H_5}$-CN-).

N-benzoyl-O-trimethylacetyl-α-methylserine (*rac*-7)

A solution of 2-phenyl-4-methyl-4-trimethylacetyloxymethyl-1,3-oxazolin-5-one (***rac*-8**) (3.325 g, 11 mmol) in THF 30 mL) was cooled to 0°C then 1 M LiOH was added in small portions until **rac-8** was not detected by TLC (12 mL). The solution was neutralized with 1 M $NaHSO_4$, organic solvent was evaporated and the aqueous residue was acidified with 1 M HCl to pH 2. Product was extracted with ethyl acetate (3 × 15 mL). Combined organic extracts were washed with brine, dried with $MgSO_4$, filtered and the solvent was removed yielding N-benzoyl-O-trimethylacetyl-α-methylserine, (***rac*-7**), m.p. 86-88°C.

^{1}H-NMR (CD_3COCD_3) δ (ppm): 1.15 (s, 9H, -C-($C\underline{H_3}$)$_3$); 1.67 (s, 3H, $C\underline{H_3}$-CN-); 4.58,4.70 (AB system, 2H, *J* = 11 Hz, -C-$C\underline{H_2}$-O-); 7.46-7.54 (m, 3H, $C_6\underline{H_5}$-CONH-); 7.84-7.88 (m, 2H, $C_6\underline{H_5}$-CONH-).

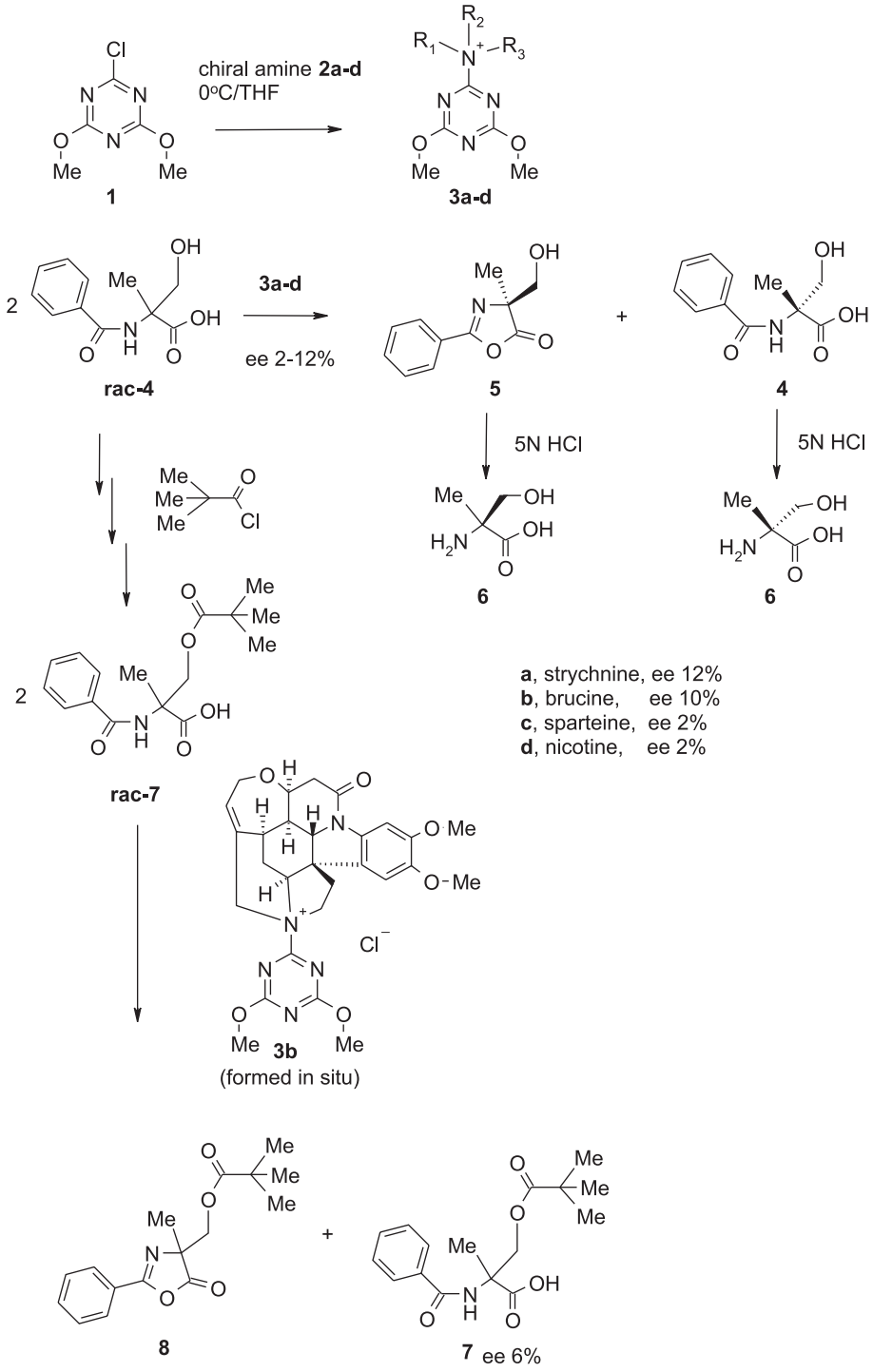
Activation of N-benzoyl-O-trimethylacetyl-α-methylserine (*rac*-7)

A standard procedure was applied. Brucine (**2b**) (394 mg, 1 mmol) in THF (10 mL), CDMT (**1**) (175.5 mg, 1 mmol), and N-benzoyl-O-trimethylacetyl-α-methylserine (***rac*-7**) (614 mg; 2 mmol) were used in the reaction. The neutral product was isolated and identified as 2-phenyl-4-trimethylacetyloxymethyl-4-methyl-1,3-oxazolin-5-one (**8**) (185 mg) as an oil.

^{1}H-NMR (CD_3COCD_3) δ (ppm) 1 (s, 9H, -C-($C\underline{H_3}$)$_3$); 1.55 (s, 3H, $C\underline{H_3}$-CN-); 4.25, 4.48 (AB system, 2H, *J* =11 Hz, -C-$C\underline{H_2}$-O-); 755-7.68 (m, 3H, $C_6\underline{H_5}$-CN-); 7.98-8.02 (m, 2H, $C_6\underline{H_5}$-CN-).

From the aqueous sodium bicarbonate extracts oily N-benzoyl-O-trimethylacetyl-α-methylserine (**7**) was isolated (309 mg).

^{1}H-NMR (CD_3COCD_3) δ (ppm): 1.15 (s, 9H, -C-($C\underline{H_3}$)$_3$); 1.67 (s, 3H, $C\underline{H_3}$-CN-); 4.58,4.70 (AB system,



Scheme 1. Enantioselective activation of *rac*-N-benzoyl-2-methylserine (***rac*-4**) and *rac*-N-benzoyl-O-trimethyloacetyl-α-methylserine (**rac-7**) with chiral coupling reagents prepared *in situ* from triazine **1** and chiral tertiary amines **2a-d**.

2H, *J* = 11 Hz, -C-C$\underline{H}_2$-O-); 7.46-7.54 (m, 3H, $C_6\underline{H}_5$-CONH-); 7.84-7.88 (m, 2H, $C_6\underline{H}_5$-CONH-).

The enantiomeric composition of N-benzoyl-2-O-trimethylacetyloxymethylalanine (**7**) was determined (47:53) using Dionex HPLC apparatus equipped with UV-diode-array detector, at oven temperature 25°C on S,S-Whelk-01 (250 × 4.6 mm) column with chiral stationary phase derived from 4-(3,5-dinitrobenzamido)-tetrahydrophenanthrene covalently bound to silica (Regis Technologies). The mixture hexane/isopropanol (8:2, v/v) with 0.01 M ammonium acetate was used as mobile phase. Analyses were conducted at flow rate 2.0 mL/min with UV detection at 225 nm.

RESULTS AND DISCUSSION

An activation of racemic N-benzoyl-α-methylserine (***rac*-4**) by means of chiral coupling reagents **3a-d**

prepared *in situ* by treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (**1**) with chiral tertiary amine: strychnine (**2a**), brucine (**2b**), nicotine (**2c**) or sparteine (**2d**) gave enantiomerically enriched 2-phenyl-4-hydroxymethyl-4-substituted-1,3-oxazolin-5-one (**5**) with 10-12% ee (for brucine and strychnine, respectively) and an intact excess of N-benzoylated substrate (**4**).

In order to differentiate the size of C^{α} substituents ***rac*-4** has been O-acylated with bulky trimethylacetyl group. The synthetic procedure involved cyclo-dehydratation of ***rac*-4** to appropriate ***rac*-5**, selective O-trimethylacetylation with trimethylacetyl chloride in the presence of triethylamine to 2-phenyl-4-trimethyl-acetyloxymethyl-4-methyl-1,3-oxazol-5-one followed by selective hydrolysis with aq. LiOH to ***rac*-7**. An attempts to prepare even more bulky O-triethylsilyl derivative of ***rac*-4** failed because of insufficient stability of triethylsililyl group in the presence of carboxylic function.

In all experiments neutral oxazolinones **5, 8** were isolated by extraction of products of enantioselective activation of ***rac*-4** or ***rac*-7** with ethyl acetate and subsequent washing of organic phase with diluted acids to remove chiral amine and triazine side-products, then washing with aqueous bicarbonate solution to isolate unreacted **6** and **7**, respectively. This simplified isolation procedure gave both **5, 8** and **6, 7** sufficiently pure for further studies by chromatography on chiral stationary phase, avoiding changes of enantiomeric composition caused by intensive purification procedure.

Enantiomeric purity of isolated products **5** and **6** were determined after acidic hydrolysis to appropriate α-methylserine and subsequent resolution of scalemic mixture into enantiomers on ligand-exchange column packed with octadecylsilanized silica coated with N,S-dioctyl-D-penicillamine as a chiral ligand-exchange phase (Sumichiral OA-5000) (18). The configuration of the faster eluted enantiomer of 2-methylserine (**4**) was established as R, based on the experiment involving enantiomerically homogeneous sample obtained by racemate resolution (19). Enantiomeric purity of **7** and **8** (6% ee) was determined by direct resolution into enantiomers on chiral SS-Whelk 01 stationary phase.

CONCLUSIONS

The studies shown, that activation of N-benzoyl-α-methylserine with chiral coupling reagents proceeds substantially less enantioselectively (6-12% ee) than in the case of amino acids substituted with single side chain at C_{α} atom (98% ee). Structural modification of chiral auxiliary **2a-d** used for synthesis of enantioselective coupling reagents **3a-d** caused small changes of ee. O-Trimethylacetylation of N-benzoyl-α-methylserine what considerably increased the difference between the size of both C_{α} side chains also did not enhanced ee. This suggests that in case of α-methylserine, the relative difference of the bulk of the side chains is not the crucial factor for increase of enantioselectivity. Therefore, further search for a general and efficient method of α-methylserine enantioselective activation requires re-designing of the chiral auxiliary structure by introducing into the auxiliary molecule of fragment, which is prone to recognize hydroxymethyl group by hydrogen bonding, but not the size of the side chains.

Acknowledgments

The study was supported by the Polish State Committee for Scientific Research under the Project 4-T09A 189 25.

REFERENCES

1. for review see: a) Riego E., Hernandez D., Albericio F., Alvarez M.: Synthesis, 1907 (2005); b) Wipf P., Venkatraman S.: Synlett **1**, 1 (1997); c) Hamada Y., Shioiri T.: Chem. Rev. 105, 4441 (2005).
2. a) Haskell T.H. et al.: J. Am. Chem. Soc. 80, 743 (1958); b) Latosińska J.N., Seliger J., Grechishkin V.S., Spychała J.: Magn. Reson. Chem. 37, 881 (1999).
3. Snider B.B., Duvall J.R.: Tetrahedron Lett. 44, 3067 (2003).
4. Matsukawa Y., Isobe M., Kotsuki H., Ichikawa Y.: J. Org. Chem. 70, 5339 (2005).
5. Smith N.D., Goodman M.: Org. Lett. 5, 1035 (2003).
6. a) Fukuyama T., Xu L.: J. Am. Chem. Soc. 115, 8449 (1993); b) Smith N.D., Wohlrab A.M., Goodman, M.: Org. Lett. 7, 255 (2005); c) Wipf P., Venkatraman S., Miller C.P.: Tetrahedron Lett. 36, 3639 (1995).
7. a) Hatakeyama S., Fukuyama H., Mukugi Y., Irie H.: Tetrahedron Lett. 37, 4047 (1996); b) Enders D., Bartsch M., Runsink J.: Synthesis 243 (1999); c) Kovacs-Kulyassa A., Herczegh P., Sztaricskai F.: Tetrahedron 53, 13883 (1997); d) Matsukawa Y., Isobe M., Kotsuki H., Ichikawa Y.: J. Org. Chem. 70, 5339 (2005); e) Horikawa M., Nakajima T., Ohfune Y.: Synlett 609 (1998).
8. Avenoza A., Peregrina J.M., San Martin E.: Tetrahedron Lett. 44, 6413 (2003).
9. a) Eid C.N., Nicas T.I., Mullen D.L., Loncharich R.J., Paschal J.W.: Bioorg. Med. Chem. Lett. **7,** 2087 (1997); b) Chen M-H., Steiner M.G., et al.: Bioorg. Med. Chem. Lett. 6, 2163 (1996).
10. Kamiński Z.J., Leplawy M.T.: Synthesis 292 (1974).
11. Kamiński Z.J., Leplawy M.T., Zabrocki J.: Synthesis 792 (1973).
12. Leplawy M.T., Olma A.: Pol. J. Chem. 53, 353 (1979).
13. a) Horikawa M., Nakajima T., Ohfune Y.: Synlett 253 (1997); b) Chen S.: Amino Acids **27**, 277 (2004).
14. Shiraiva T., Suzuki M., Sakai Y., Nagasawa H., Takatani K., Noshi D., Yamanashi K.: Chem. Pharm. Bull. 50, 1362 (2002).
15. Chenault H.K., Dahmer J., Whitesides G.M.: J. Am. Chem. Soc. 111, 6354 (1989).
16. for review see Ohfune Y., Shinada T.: Eur. J. Org. Chem. 5127 (2005).
17. Kamiński Z.J., Kolesińska B., Kamińska J.E., Góra J.: J. Org. Chem. 63, 4248 (2001).
18. Miyazawa T., Minowa H., Shindo Y., Yamada, T.: J. Liq. Chromatogr. Relat. Technol. 23, 1061 (2000).
19. Olma A., Pol. J. Chem. 70, 1442 (1996).