Ring closure reactions of bicyclic prolinol and prolin ester enantiomers

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Dedicated to Professor Henk van der Plas on the occasion of his 80th birthday

Abstract
Starting from the of bicyclic proline ester, ethyl *exo*-2-azabicyclo[2.2.1]heptane-3-carboxylate (+)-**5** several hydantoines and thiohydantoines were prepared by acidic ring closure of the corresponding urea or thiourea derivatives. Enantiomer (-)-**5** was reduced to 2-azanorbornylmethanol **12**, which was transformed to 5,8-methanooxazolo- and thiazolo[3,4-*a*]pyridine derivatives. The structures, stereochemistry and relative configurations of the synthesized compounds were proved by NMR.

Keywords: Bicyclic prolinol, enantioselective synthesis, epimerisation, ring closure, 1,3-heterocycles

Introduction

α-Amino acids, both natural and unnatural, play a central part in biology and chemistry.[1] They are fundamental constituents of proteins and other biologically important compounds and one of the most frequently used sources of chiral starting materials for organic synthesis. The synthesis and application of bicyclic α-amino acids have received much attention of recent years. Many of these amino acids are carriers of pharmaceutical activities,[2,3] and they have been used as building blocks for the synthesis of conformationally constrained peptides.[4] Among them *exo*-2-azabicyclo[2.2.1]heptane-3-carboxylic acid has received attention as a conformationally more rigid substitute for prolin in biologically active peptides[5-7] and in the design of chiral ligands used in asymmetric catalysis.[8,9]

Ester derivatives of prolin exhibit interesting pharmacological effects: the L-proline ester of 2,6-diisopropylphenol (Propofol) derivative was synthetized by Trapini et al. This prolinate highly soluble and stable in water at physiological pH and rapidly hydrolyzed in plazma, could have potential as a water-soluble propofol prodrug for parenteral administration.[10] Analogues of (*N*-glyoxyl)propyl proline esters and chiral bicyclic proline esters have good binding affinity toward FKBP12, suggesting their potential therapeutic utility in treating degenerative disorders of the nervous system.[11] Prolin esters and prolinol are widely used for the preparation of bicyclic oxazolidine,[9, 12-18] but its 2-azanorbornane derivatives[19,20] have not been extensively investigated.

Amino ester **5** can be used as a starting substance for the preparation of other bifunctional compounds, *e.g.* amino acids, 1,2-aminoalcohols[21,22] and 1,2-diamines[23] and it has a few applications in the syntheses of other heterocycles.[24,25]

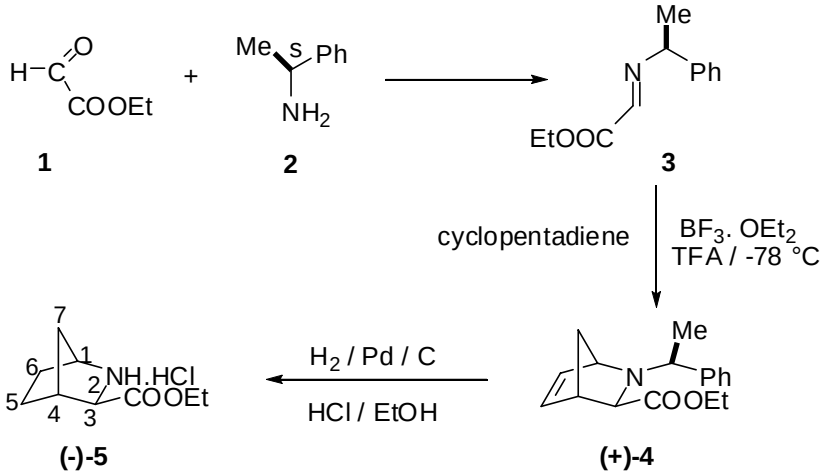
The synthesis and stereochemistry of bicyclic saturated heterocycles with condensed skeleton containing two heteroatoms have been the subject of our study for a long time.[26] Previously several methods have been published for the preparation of *cis*- or *trans*-cycloalkane-fused 1,3-heterocycles.[26] As a continuation of this work our aim was to prepare enantiomeric bicyclic prolin esters (–)-**5** and (+)-**5** and prolinol derivatives and to synthesize some 2-azanorbornane-fused heterocycles.

Results and Discussion

Amino ester (–)-**5** and (+)-**5** were prepared according to reported methods with small modifications. The syntheses of the key intermediate **4**, is based on the finding that chiral imines with cyclopentadiene gives the [4+2]-cycloadduct. In spite of the reaction is highly *exo*-selectivity, the separation of the major *exo*-isomer in the reaction from its diastereomers was accomplished by flash chromatography[27, 28]. Multigram scale synthesis of the aza-Diels Alder adducts ethyl and methyl (1*R*,3*R*,4*S*)-2-[(1*S*)-1-phenylethyl]-azabicyclo[2.2.1]hept-5-ene-3-carboxylate has been performed by Andersson *et al*.[9] In this new protocol no purification of the intermediates, ethyl and methyl glyoxylate and the imine used for the Diels-Alder reaction, was necessary. The authors found that the methyl ester analogue of **4** could be easily recrystallized from pentane to afford diastereomerically pure adduct in 56 % yield. The ethyl ester **4** have been separated from its diastereomers by column chromatography.

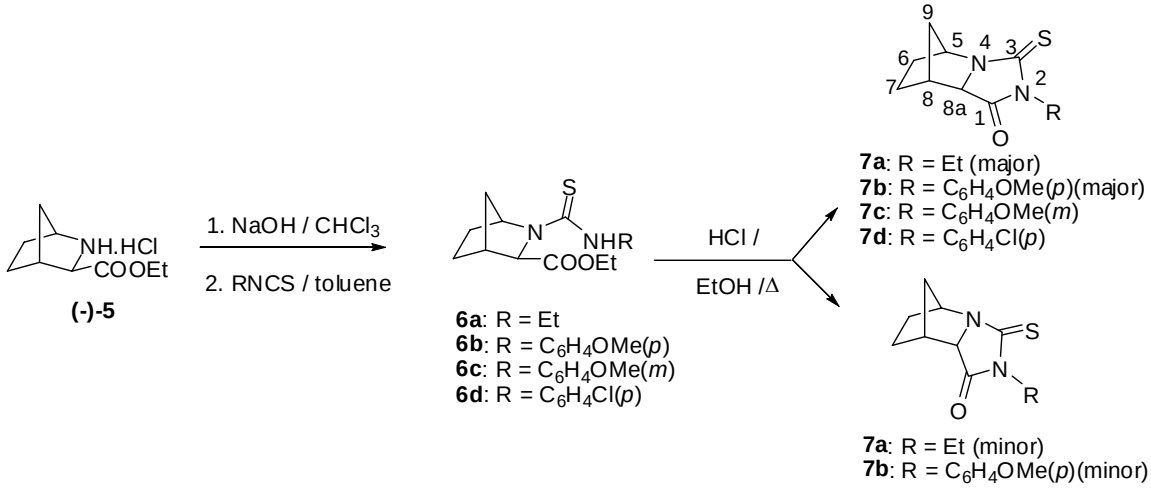
Our synthetic route to amino ester **5** is shown in Scheme 1. The synthesis started with oxidative cleavage of diethyl L-tartarate with sodium periodate, yielding the product, ethyl glyoxylate **1** in 1 h.[24] The aza-Diels-Alder reaction between **3** (derived from ethyl glyoxylate **1** and (*S*)-(-)-1-phenylethylamine **2**) and cyclopentadiene, in the presence of trifluoroacetic acid and boron trifluoride diethyl etherate, have been performed in a one-step procedure.[9] The crude hetero Diels-Alder adduct **4** could not crystallized from pentane, it was purified by column chromatography. Hydrogenation of the double bond of **4** and concomitant removal of the phenylethyl groups by hydrogenolysis in the presence of $Pd(OH)_2/C$ afforded amino ester **(–)-5**.

The α-amino acid ester **(+)-5** was prepared from (*R*)-(+)-1-phenylethylamine by the same method. The enantiomeric purity of amino esters **5** were checked (*ee* > 99%) by chiral gas chromatography.



Scheme 1

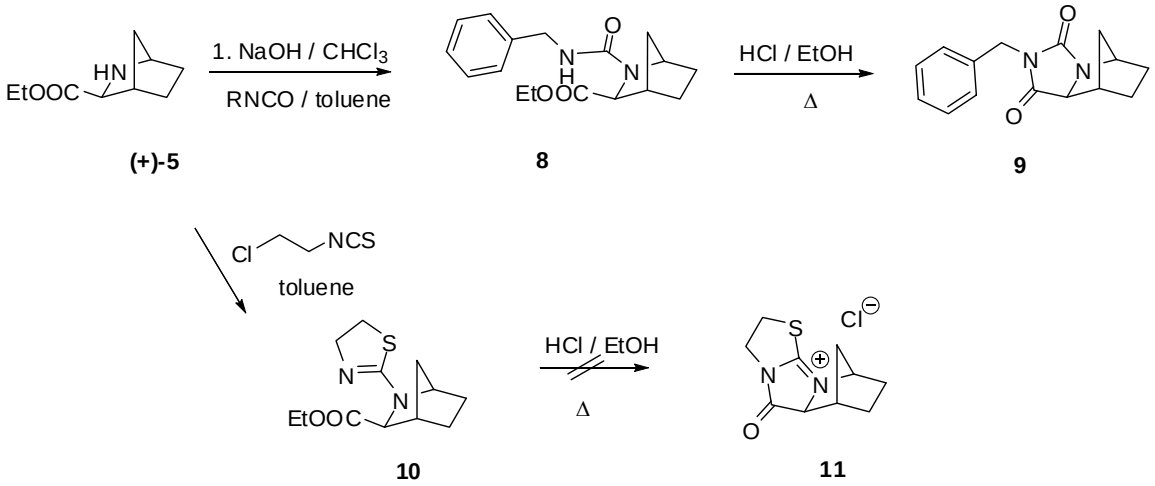
Reaction of isothiocyanates with amino ester base **(–)-5** resulted in the corresponding thioureas **6a-d**. Thioureas **6a-d** were cyclised with ethanolic hydrogen chloride or with aqueous hydrochloric acid, resulting in tricyclic 2-thioxo-imidazolidinone **7a-d**. When **6a,b** were boiled in acidic solution, partial isomerization took place resulting in *exo*-**7a,b** as the main products, which were separated from the *endo*-**7a,b** by column chromatography. The *m*-methoxy and *p*-chloro-substituted thioureas **7c,d** resulted in only the *exo*-2-thioxo-imidazolidinone **7c,d**, no formation of the *endo* isomer was observed (Scheme 2).



Scheme 2

When benzylisocyanate was reacted ester base **(+)-5** the corresponding urea **8** was formed which was cyclised with ethanolic hydrogen chloride to hydantoin **9**. Some related bicyclic hydantoins and thiohydantoins has been designed and synthesized in an enantiomeric manner by Salvati *et al*.[29] Some of the compounds are potent antagonist to the androgen receptor.[30-32]

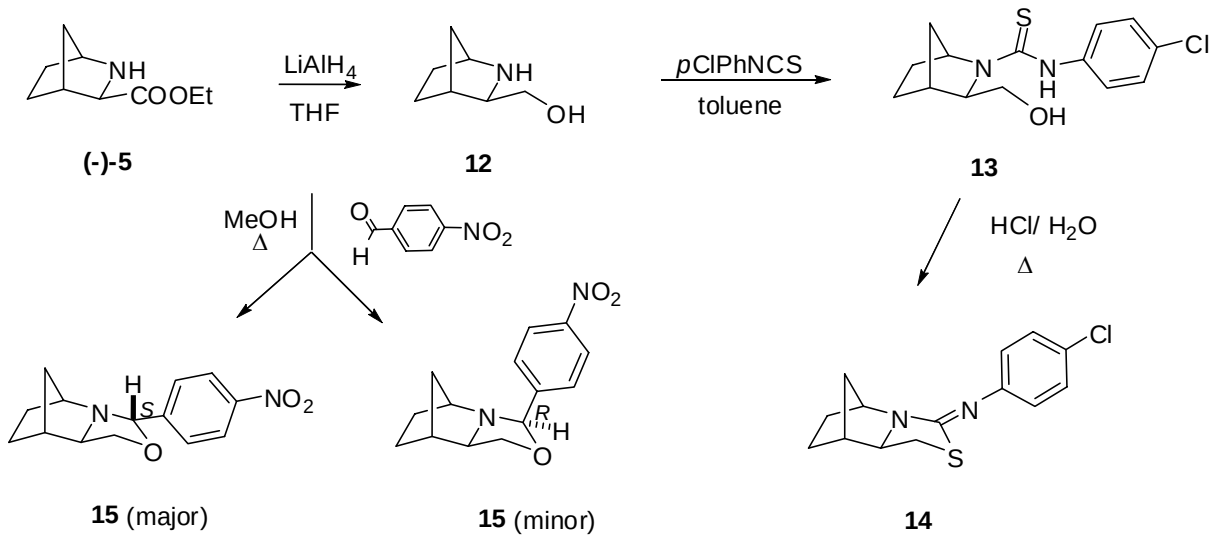
When amino ester base (+)-**5** was reacted with 2-chloroethyl isothiocyanate, *N*-thiazoline derivative **10** was formed. This intermediate was attempted to cyclise with ethanolic hydrogen chloride but the formation of the tetracyclic **11** was not observed.



Scheme 3

The amino alcohol **12** was prepared from amino ester **(–)-5** by $LiAlH_4$ reduction.[28] **12** can be used as a chiral ligand for asymmetric transfer hydrogenation of ketones,[28] and as a starting material for ring-closure reactions.[19,20] The synthesis of heterocycle **14** started from the *p*-chlorophenyl isothiocyanate adduct of **12**. Treatment of thiourea **13** with ethanolic hydrogen chloride under reflux provided thiazolidine **14** (Scheme 4). The possible Z-E isomerism of **14** was not investigated.

When amino alcohol **12** was condensed with *p*-nitrobenzaldehyde in methanol, the reaction reached completion within a few hours. After evaporation of the solvent the formation of two epimeric oxazolo[1,5-*a*]pyridine derivatives **15** was observed, of which the two epimers could be separated by crystallization. As the NMR spectra indicated, in the major epimer **15** H-3 locates on the same side as the bridge carbon C-9 of the norbornene skeleton.



Scheme 4

The ^{1}H and ^{13}C NMR signals of **6a-d**, **7a-d**, **8–10**, and **12**–**15** were assigned with the help of dqf-COSY, multiplicity-edited HSQC and HMBC experiments. The relative stereochemistry of the products was deduced mainly from NOESY experiments and proton-proton coupling constants. Many of the proton and carbon NMR signals were quite broad at 298 K in DMSO-d_6 (and even more so in $CDCl_3$) due to some fast-intermediate chemical exchange processes such as hindered rotation of the substituents and because of the presence of small, unresolved proton-proton couplings within the ^{1}H spin system of the 2-azanorbornane moiety. The reaction intermediates, e.g. compounds **6**, generally displayed broader NMR lines than the ring-closed products. In the NMR spectra of each product, only one set of signals was observed indicating that any thermodynamically favoured dynamic processes were either relatively fast on the NMR time scale at the applied experimental conditions (in DMSO at 298 K at the field of a 500 MHz instrument), or slow enough so that additional form(s) do not become clearly detectable in the sample within a few hours after dissolution in DMSO. However, many of the ^{1}H NMR signals were quite broad possibly due to some fast-intermediate chemical exchange process such as hindered rotation of the substituents, and due to the presence of small, unresolved proton-proton couplings within the ^{1}H spin system of the 2-azanorbornane moiety. In every case, the NMR spectra were consistent with the expected structures.

The ethoxycarbonyl substituent is in an *exo* position in the starting 2-azanorbornanes **(–)-5** and (+)-**5** yielding products that are *exo* substituted at C-8a if the configuration is retained during the synthesis. Compounds **6a-d**, **7a,b** (major products), **7c,d**, **8**, **9** and **15** (minor product) were indeed found to be *exo* substituted/fused, as deduced from the NOE cross peak between H-8a (or H-3 for the intermediates) and the *endo*-proton at C-7 (C-5 for the intermediates), and from the lack of such a cross peak between H-8a (H-3) and the *syn*-proton at the methylene bridge carbon C-9 (C-7). Remarkably, the minor products of **7a** and **7b** did have the inverted configuration at

C-8a resulting in and *endo*-fused imidazolidine ring, as proven by the NOE correlation between H-8a and H-9*syn* in the NOESY spectra of these compounds.

Product **15** exhibited two epimers with respect to the asymmetric carbon C-3, of which the major and the minor form could be separated pure by crystallisation. The major and minor epimers of **15** were again identified by their NOE correlations. For the major form a strong NOE is observed between protons H-9*syn* and H-3, as well as between H-5 and H-3. Therefore the major epimer is the one in which H-3 locates on the same side as the bridge carbon C-9 of the norbornene skeleton. In case of the minor epimer of **15** the *ortho* protons of the *p*-nitrophenyl group (7.70 ppm) displayed and NOE correlation with H-9*syn* (1.47 ppm) whereas H-3 (5.34 ppm) was NOE correlated with H-8a (3.28 ppm). This establishes that in the minor epimer the aryl group is on the same face of the tricyclic skeleton as the methylene bridge.

Experimental Section

General Procedures. Melting points were determined with a Koffler apparatus and are not corrected. Merck Kieselgel 60F254 plates were used for TLC: the eluent was toluene-MeOH 4:1. Column chromatography was performed on silica gel (Merck 60, 70-230 mesh). NMR-spectra were acquired using Bruker Avance 400 and 500 spectrometers (equipped with BBI-5mm-Zgrad-ATM and BBO-5mm-Zgrad probes) operating at 399.75 and 500.13 MHz for ^{1}H and 100.53 and 125.77 MHz for ^{13}C, respectively. No sample spinning was used. DMSO-d_6 was used as solvent with tetramethylsilane (TMS) as an internal standard (δ_{TMS} = 0.00 ppm for both ^{1}H and ^{13}C), and the probe temperature was set at 298 K. Spectra were processed by a PC with Windows XP operating system and XWin-NMR software. ^{1}H NMR spectra were acquired with single-pulse excitation using a 30° flip angle, 2.3 μs (BBI) or 3.0 μs (BBO) pulse width, 10.3 kHz spectral width and 3.17 s acquisition time, and processed with 0.3 Hz exponential weighing prior to Fourier transform. ^{13}C NMR spectra were acquired with single-pulse excitation and broadband proton decoupling (waltz-16) using a 30° flip angle, 4.2 μs (BBI) or 2.3 μs (BBO) pulse width, 30.0 kHz spectral width and 1.09 s acquisition time, and processed with 1.0 Hz exponential weighing prior to Fourier transform. The gradient-selected dqf-COSY, NOESY, multiplicity-edited HSQC and HMBC 2D NMR experiments were acquired using vendor-provided pulse programs (cosygpmfqf, noesygpph, hsqcedetgpsisp2 and hmbcgplpndqf, respectively). The NOESY mixing time was set at 0.3 s, and the HSQC and HMBC experiments were optimized for a one-bond C,H coupling constant of 145 Hz and long-range coupling constants of 10 Hz.

The electron ionization (EI) mass spectra were recorded on a VG ZABSpec mass spectrometer (VG Analytical, Division of Fisons, Manchester, UK), that was equipped with Opus V3.3X program package (Fisons Instruments, Manchester, UK). The ionization energy was 70 eV and source temperature 160 °C. Small samples dissolved in methanol were placed into a quartz capillary tube and methanol was evaporated with hot air. Thereafter the sample was taken into

the ionization chamber via the solid insertion probe. Perfluorokerosine (PFK) was used for calibration of the mass scale. The elemental compositions of the molecular ions were determined by peak matching (10% valley definition) using 10000 resolution.

Cyclopentadiene was obtained from its dimer by heating at 200 °C. The *ee* values of the esters (+)-**5** and (–)-**5** were determined by gas chromatography on a Chrompack CP Chiracel-Dex CB column (25 m). Amino esters **(–)-5** and **(+)-5** were derivatised with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) and pyridine (P) before the gas chromatographic analysis. To a solution of ester **5** (1 mg in 0,1 mL CH_2Cl_2) 15 μL DMAP/P (1:9) and 15 μL Ac_2O was added; [80 °C for 5 min →130 °C (rate of temperature rise 20 °C/min; 70 kPa, carrier gas N_2, $T_{inj.}$ 250 °C, $T_{det.}$ 270 °C), retention times (min): **(–)-5**: 12.42; **(+)-5**: 12.71]. Optical rotations were measured with a Perkin-Elmer 341 polarimeter.

Ethyl (1*S*,3*R*,4*R*)-2-azabicyclo[2.2.1]heptane-3-carboxylate hydrochloride (–)-5 and ethyl (1*R*,3*S*,4*S*)-2-azabicyclo[2.2.1]heptane-3-carboxylate hydrochloride (+)-5.

To a magnetically stirred aqueous solution of diethyl L-(+)-tartrate (6.8 g, 33 mmol in 50 mL), one equivalent of $NaOI_4$ was added at 0 ºC during 15 min. The mixture was stirred for one hour at the same temperature and evaporated. The residue was dissolved in CH_2Cl_2, dried (Na_2SO_4) and evaporated. The produced ethyl glyoxylate (5.1 g 50 mmol) was dissolved in CH_2Cl_2, molecular sieves (2 g, 4Å) were added under argon atmosphere and the mixture was cooled to 4 °C. (*S*)-(–)-1-Phenylethylamine (6.2 g, 51 mmol) was added and the mixture was stirred for 1 h. The water bath was replaced with a dry ice/isopropanol bath with an external cooler and the reaction mixture was cooled to −78 °C. A solution of imine **3** was sequentially treated with CF_3COOH (4 mL, 52 mmol), $BF_3.Et_2O$ (6.6 mL, 52 mmol) and with freshly distilled cyclopentadiene (5.1 mL). When the addition was complete the reaction mixture was stirred for 8 h at −75 °C and the mixture was thereafter allowed to warm to ambient temperature. When the room temperature was reached the mixture, it was poured into a saturated aqueous solution of Na_2CO_3. The resulting mixture was stirred for 2 h and filtered then through a pad of Celite and the residue washed with CH_2Cl_2 (2x 50 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2x 50 mL). The organic phases was dried ($MgSO_4$), and evaporated to give the crude Diels-Alder adduct **4**, which was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (9:1) (6.86 g, 52 %) $[\alpha]_D^{25}$ = +86.0 (c 1, MeOH). The major diastereomer **4** (6 g, 22 mmol) was hydrogenated over $Pd(OH)_2/C$ (5%, 0.5 g) in abs. EtOH (100 mL) at 50 bar initial H_2 pressure. After 3 days the mixture was filtered off and the residue washed with abs. EtOH. To the filtrate ethanolic HCl (5 mL, 22%) was added and the mixture was then evaporated. The residue was crystallized with Et_2O and recrystallized from EtOH/Et_2O. (–)-**5**: White crystals mp 148-149 ºC yield 3.0 g, (66%) Lit mp[28]: 153-154 ºC $[\alpha]_D^{25}$ = –15.9 (c 1, MeOH) Lit $[\alpha]_D^{25}$ = –16.3 (c 1, MeOH) [27] The (+)-**5** amino ester hydrochloride was prepared from (*R*)-(+)-1-phenylethylamine by the same method. White crystals mp 148-149 ºC Lit mp[28] 153-154 ºC $[\alpha]_D^{25}$ = +18.8 (c 1, MeOH) Lit $[\alpha]_D^{25}$ = +16.2 (c 1, MeOH)[28] ^{1}H NMR (DMSO-d_6) δ (ppm): 1.25 (3H, t, *J* = 7.1 Hz, OCH_2CH_3,), 1.54-1.70 (5H, m, H-5, H-6, H-7), 1.93 (1H, brt, *J* = 10.3

Hz, H-6), 2.87 (1H, brd, *J* = 3.4 Hz, H-4), 4.02 (1H, s, H-3), 4.05 (1H, brs, H-1), 4.23 (2H, m, OC*H*$_2$CH$_3$). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 13.8 (OCH$_2$*C*H$_3$), 24.3 (C-6), 26.1 (C-7), 34.7 (C-5), 39.8 (C-4), 58.2 (C-1), 61.6 (C-3), 62.3 (O*C*H$_2$CH$_3$), 168.3 (C=O). $M^{+\bullet}$(6) $C_9H_{15}NO_2^{+\bullet}$ Calcd 169.1103 Obsd 169.1104 Other ions *m/z* (%): 96(100), 68(66), 67(11), 41(11)

General procedure the synthesis of urea and thiourea derivatives 6a-d and 8

One equivalent of the corresponding isothiocyanate or isocyanate was added to 0.5 g (2.96 mmol) (+)-**5** or (−)-**5** bases, dissolved in 20 mL toluene. The mixture was stirred overnight then was evaporated, *n*-hexane was added, and the crystalline products **6b-d** and **8** were filtered off and recrystallized. The oily **6a** was purified by column chromatography.

Ethyl (1*S*,3*R*,4*R*)-2-ethylthiocarbamoyl-2-azabicyclo[2.2.1]heptane-3-carboxylate (6a). Oil, (*n*-hexane/EtOAc = 3:1); yield 0.48 g, (64 %); $[\alpha]_D^{25}$ = +135.7 (c 1, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.08 (3H, t, *J* = 6.9 Hz, NCH$_2$*CH*$_3$), 1.18 (3H, t, *J* = 7.0 Hz, OCH$_2$*CH*$_3$,), 1.39-1.44 (2H, m, H-5, H-7), 1.49 (1H, brm, H-6), 1.60 (1H, brm, H-6), 1.72 (1H, m, H-5), 1.92 (1H, brm, H-7), 2.54 (1H, brs, H-4), 3.46 (2H, brm, NCH$_2$CH$_3$), 4.07 (2H, brq, *J* = 7.0 Hz, OCH$_2$CH$_3$), 4.22 (1H, brs, H-3), 4.55 (1H, brs, H-1), 7.61 (1H, brs, NH). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 14.0 (OCH$_2$*C*H$_3$), 14.5(NCH$_2$*C*H$_3$), 27.2(C-5), 28.8 (C-6), 35.2 (C-7), 39.5 (N*C*H$_2$CH$_3$), 40.9 (C-4), 57.3 (C-1), 60.0 (O*C*H$_2$*C*H$_3$), 69.0 (C-3), 170.0 (C=O), 178.3 (C=S). $M^{+\bullet}$(100) $C_{12}H_{20}N_2O_2S^{+\bullet}$ Calcd 256.1246 Obsd 256.1256 Oher ions *m/z* (%): 210(14), 183(16), 169(15), 144(13), 140(29), 96(65), 95(12), 68(45), 67(10), 60(15), 44(2)

Ethyl (1*S*,3*R*,4*R*)-2-(4-methoxyphenylthiocarbamoyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (6b). White crystals, mp 185-186 ºC (EtOAc); yield 0.63 g, (64 %); $[\alpha]_D^{25}$ = +80.3 (c 0.5, EtOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.19 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$,), 1.48 (1H, Br d, *J* = 9.9 Hz, H-7*anti*), 1.51(1H, m, H-5*endo*), 1.63-1.73 (2H, m, H-6*exo*, H-6endo), 1.77 (1H, m, H-5*exo*), 2.02 (1H, m, H-7*syn*), 2.61 (1H, brs, H-4), 3.74 (3H, s, *p*-OCH$_3$) 4.08 (2H, q, J = 7.0 Hz, OC*H*$_2$CH$_3$), 4.31 (1H, brs, H-3), 4.82 (1H, brs, H-1), 6.87 (2H, m, *m*-Ar), 7.22 (2H, m, *o*-Ar), 9.16 (1H, brs, N*H*). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 14.0 (OCH$_2$*C*H$_3$), 27.2 (C-5), 29.2 (C-6), 35.4 (C-7), 41.0 (C-4), 55.1 (*p*-OCH$_3$), 58.4 (C-1), 60.1 (O*C*H$_2$*C*H$_3$), 69.4 (C-3), 113.1 (*m*-Ar), 127.6 (*o*-Ar), 1331. (*i*-Ar), 156.5 (*p*-Ar), 169.8 (C=O), 178,5 (C=S). $M^{+\bullet}$(87) $C_{17}H_{22}N_2O_3S^{+\bullet}$ Calcd 334.1351; Obsd 334.1353.Other ions *m/z* (%): 301(13), 289(12), 288(40), 212(30), 195(11), 184(11), 167(14), 166(20), 165(100), 150 (26), 140 (51), 138(14), 125(11.5), 123(26), 122(22), 108(18), 96(90), 95(11), 79(29), 68(41), 67(17), 41(12)

Ethyl (1*S*,3*R*,4*R*)-2-(3-methoxyphenylthiocarbamoyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (6c). White crystals, mp 102-104 ºC (EtOAc); yield 0.73 g, (74 %); $[\alpha]_D^{25}$ = +82.4 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.19 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 1.48 (1H, brd, *J* = 9.9 Hz, H-7*anti*), 1.51 (1H, m, H-5*endo*), 1.62-1.73 (2H, m, H-6*exo*, H-6*endo*), 1.78 (1H, m, H-5*exo*), 2.02 (1H, m, H-7*syn*), 2.62 (1H, brs, H-4), 3.73 (3H, s, *m*-OCH$_3$), 4.09 (2H, q, *J* = 7.0 Hz, OC*H*$_2$CH$_3$), 4.33 (1H, brs, H-3), 4.86 (1H, brs, H-1), 6.70 1H, m, *p*-Ar), 6.98 (1H, m, *o*'-Ar), 7.04 (1H, brs, *o*-Ar), 7.20 (1H, t, *J* = 8.1 Hz, *m*'-Ar), 9.24 (1H,

brs, N*H*). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 14.0 (OCH$_2$*C*H$_3$), 27.2 (C-5), 29.4 (C-6), 35.4 (C-7), 41.0 (C-4), 55.0 (*m*-OCH$_3$), 58.8 (C-1), 60.1 (O*C*H$_2$CH$_3$), 69.3 (C-3), 110.1 (*o*-Ar), 111.1 (*p*-Ar), 117.6 (*o*'-Ar), 128.5 (*m*'-Ar), 141.3 (*i*-Ar), 158.8 (*m*-Ar), 169.7 (C=O), 177.9 (C=S). M$^{+\bullet}$(100) $C_{17}H_{22}N_2O_3S^{+\bullet}$ Calcd 334.1351; Obsd 334.1356. Other ions *m/z* (%): 333(15), 301(10), 289(7), 288(9), 261(7), 212(20), 195(8), 184(5.5), 169(10), 166(14.5), 165(23), 140(17), 138(6), 123(15), 96(60), 95(7), 79(14), 77(13), 68(29), 67(9), 41(7)

Ethyl (1*S*,3*R*,4*R*)-2-(4-chlorophenylthiocarbamoyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (6d). White crystals, mp 60-62 ºC (EtOAc); yield 0.66 g, (68 %); $[\alpha]_D^{25}$ = +92.9 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.19 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H$_3$*), 1.49 (1H, brd, *J* = 10.0 Hz, H-7*anti*), 1.51 (1H, m, H-5*endo*), 1.62-1.73 (2H, m, H-6*exo*, H-6*endo*), 1.78 (1H, m, H-5*exo*), 2.03 (1H, m, H-7*syn*), 2.63 (1H, br~s, H-4), 4.09 (2H, q, *J* = 7.0 Hz, OC*H$_2$*CH$_3$), 4.31 (1H, brs, H-3), 4.86 (1H, brs, H-1), 7.35 (2H, m, *m*-Ar), 7.42 (2H, m, *o*-Ar), 9.35 (1H, brs, N*H*). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 14.0 (OCH$_2$*C*H$_3$), 27.1 (C-5), 29.4 (C-6), 35.4 (C-7), 41.0 (C-4), 58.9 (C-1), 60.2 (O*C*H$_2$CH$_3$), 69.4 (C-3), 127.2 (*o*-Ar), 127.7 (*m*-Ar), 128.5 (*p*-Ar), 139.2 (*i*-Ar), 169.6 (C=O), 177.9 (C=S). M$^{+\bullet}$: 340(24); 338(64) Calcd 338.0856; Obsd 338.0860. Other ions *m/z* (%): 305(5.5), 292(24), 265(6), 212(33), 171(24), 169/73.5), 140 (18), 138(11.5), 127(19.5), 111(24), 96(100), 95(18), 79(21), 75(13), 68(57), 67(19), 41(13)

Ethyl (1*R*,3*S*,4*S*)-2-(benzylcarbamoyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (8). White crystals, mp: 92-94 ºC (*n*-hexane/EtOAc), yield 0.61 g, (69 %); $[\alpha]_D^{25}$ = –82.6 (c 0.5, EtOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.18 (3H, t, *J* = 7.2 Hz, OCH$_2$C*H$_3$*), 1.31 (1H, brd, *J* = 9.6 Hz, H-7), 1.43 (1H, m, H-5), 1.52-1.61 (2H, m, H-6), 1.69 (1H, m, H-5), 1.74 (1H, brm, H-7), 2.58 (1H, brs, H-4), 3.78 (1H, brs, H-3), 4.01-4.11 (2H, m, OC*H$_2$*CH$_3$), 4.16 (1H, dd, *J* = 15.5, 5.7 Hz, NC*H$_2$*), 4.26-4.30 (2H, m, H-1, NC*H$_2$*), 6.96 (1H, brs, N*H*), 7.20 (1H, m, *p*-Ar), 7.24 (2H, m, *o*-Ar), 7.30 (2H, m, *m*-Ar). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 14.0 (OCH$_2$*C*H$_3$), 27.3 (C-5), 29.7 (C-6), 35.0 (C-7), 41.2 (C-4), 43.0 (N*C*H$_2$), 55.7 (C-1), 60.0 (O*C*H$_2$CH$_3$), 63.7 (C-3), 126.3 (*p*-Ar), 126.7 (*o*-Ar), 128.0 (*m*-Ar), 140.9 (*i*-Ar), 155.8 (NH-C=O), 170.9 (O-C=O). M$^{+\bullet}$(22) $C_{17}H_{22}N_2O_3^{+\bullet}$ Calcd 302.1630 Obsd 302.1639 Other ions *m/z* (%): 256(38), 229(17), 228(11), 106(12), 96(100), 91(58), 68(44), 67(22), 65(11), 54(11), 41(12)

General procedure of thiohydantoines 7a-d and hydantoine 9

Compound **6a-d** or **8** (2.5 mmol) was refluxed in 25 mL EtOH containing 20% dry HCl for 5 h. The reaction mixture was evaporated, diethyl ether was added, and the crystalline products **7c, d** were filtered off and recrystallized. The epimers of **7a** and **7b** were separated by column chromatography (*n*-hexane/EtOAc 5:1).

5,8,8a-Hexahydro-2-ethyl-3-thioxo-5,8-methanoimidazo[1,5-*a*]pyridine-1(5*H*)-one (7a). (5*S*,8*R*,8a*R*)-7a (major epimer). oil (EtOAc), yield 0.21 g, (41%); $[\alpha]_D^{25}$ = +109.0 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.09 (3H, t, *J* = 7.1 Hz, NCH$_2$C*H$_3$*), 1.10 (1H, brm, H-9*syn*), 1.32 (1H, brd, *J*= 10.6 Hz, H-9*anti*), 1.64-1.72 (3H, m, H-7, H-7, H-6), 1.80 (1H, m, H-6), 2.81 (1H, brs, H-8), 3.68 (2H, q, *J* = 7.2 Hz, NC*H$_2$*), 3.95 (1H, s, H-8a), 4.64 (1H, brd, *J* = 3.5 Hz, H-5). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 12.3 (NCH$_2$*C*H$_3$), 26.4 (C-6), 28.3 (C-7), 34.8 (C-9),

36.3 (N*C*H$_2$), 39.1 (C-8), 65.2 (C-5), 67.3 (C-8a), 174.4 (C-1), 192.3 (C-3). M$^{+\bullet}$(100) $C_{10}H_{14}N_2OS^{+\bullet}$ Calcd 210.0827 Obsd 210.0836 Other ions *m/z*(%): 144(11), 141(27), 96(12), 95(10), 68(24), 67(20), 54(14), 41(11)

(5*S*,8*R*,8a*S*)-7a (minor epimer). White crystals, mp 62-63 ºC, yield 57 mg, (11%); $[\alpha]_D^{25}$ = +100.1 (c, 0.5 MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 0.97 (1H, m, H-7*endo*), 1.10 (3H, t, *J* = 7.1 Hz, NCH$_2$*C*H$_3$), 1.53 (1H, m, H-6*exo*), 1.64 (1H, m, H-7*exo*), 1.80 (1H, m, H-9*anti*), 2.05-2.11 (2H, m, H-6*endo*, H-9), 2.85 (1H, brs, H-8), 3.63-3.73 (2H, m, NC*H$_2$*), 4.36 (1H, brs, H-5), 4.54 (1H, dd, *J* = 3.6, 1.4 Hz, H-8a). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 12.6 (NCH$_2$*C*H$_3$), 21.3 (C-7), 27.2 (C-6), 36.0 (N*C*H$_2$), 37.6 (C-8), 39.7 (C-9), 61.9 (C-5), 70.4 (C-8a), 172.9 (C-1), 187.8 (C-3). M$^{+\bullet}$(56) $C_{10}H_{14}N_2OS^{+\bullet}$ Calcd 210.0827 Obsd 210.0830 Other ions *m/z*(%): 144(100), 141(6), 96(5), 68(15), 67(16), 41(8)

5,8,8a-Hexahydro-2-(4-methoxyphenyl)-3-thioxo-5,8-methanoimidazo[1,5-*a*]pyridine-1(5*H*)-one (7b).

(5*S*,8*R*,8a*R*)-7b (major epimer). White crystals, mp 183-184 ºC (EtOAc), yield 0.42 g, (58 %);$[\alpha]_D^{25}$ = +63.4 (c 0.5, EtOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.38-1.44 (2H, m, H-9*syn*, H-9*anti*), 1.69-1.76 (3H, m, H-7, H-7, H-6), 1.85 (1H, m, H-6), 2.91 (1H, brs, H-8), 3.80 (3H, s, *p*-OCH$_3$), 4.13 (1H, s, H-8a), 4.72 (1H, brd, *J* = 3.6 Hz, H-5), 7.02 (2H, m, *m*-Ar), 7.19 (2H, m, *o*-Ar). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 26.4 (C-6), 28.3 (C-7), 35.3 (C-9), 39.4 (C-8), 55.3 (*p*-OCH$_3$), 65.5 (C-5), 67.7 (C-8a), 114.0 (*m*-Ar), 126.2 (*i*-Ar), 129.5 (*o*-Ar), 159.2 (*p*-Ar), 174.2 (C-1), 192.6 (C-3). M$^{+\bullet}$(91) $C_{15}H_{15}N_2O_2S^{+\bullet}$ Calcd 288.0932 Obsd 288.0943 Other ions *m/z* (%): 255(10), 222(5), 166(11), 165(100), 150(17), 149(15), 134(13), 133(6), 122(9), 67(8)

(5*S*,8*R*,8a*S*)-7b (minor epimer). White crystals, mp 105-107 ºC (EtOAc), yield 86 mg, (12 %); $[\alpha]_D^{25}$ = –57.0 (c 0.5, EtOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm) 1.25 (1H, m, H-7*endo*), 1.60 (1H, m, H-6*exo*), 1.73 (1H, m, H-7*exo*), 1.85 (1H, m, H-9*anti*), 2.15 (1H, m, H-9*syn*), 2.25 (1H, m, H-6*endo*), 2.92 (1H, m, H-8), 3.80 (3H, s, *p*-OCH$_3$), 4.43 (1H, brs, H-5), 4.72 (1H, dd, *J* = 3.6, 1.4 Hz, H-8a), 7.02 (2H, m, *m*-Ar), 7.17 (2H, m, *o*-Ar). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 21.5 (C-7), 27.4 (C-6), 37.8 (C-8), 39.9 (C-9), 55.3 (*p*-OCH$_3$), 62.3 (C-5), 70.8 (C-8a), 114.0 (*m*-Ar), 126.0 (*i*-Ar), 129.6 (*o*-Ar), 159.2 (*p*-Ar), 172.8 (C-1), 188.1 (C-3). M$^{+\bullet}$(76) $C_{15}H_{15}N_2O_2S^{+\bullet}$ Calcd 288.0932 Obsd 288.0944 Other ions *m/z* (%): 255(3) 222(100), 166(8), 165(54), 150(17), 149(12.5), 134(12), 133(10), 122(10), 67(10)

(5*S*,8*R*,8a*R*)-5,8,8a-Hexahydro-2-(3-methoxyphenyl)-3-thioxo-5,8-methanoimidazo[1,5-*a*]pyridine-1(5*H*)-one (7c). White crystals, mp 126-127 ºC (EtOAc), yield (0.53 g, (73%); $[\alpha]_D^{25}$ = +42.6 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm):): 1.40 (1H, brd, *J* = 10.6 Hz, H-9*anti*), 1.46 (1H, m, H-9*syn*), 1.69-1.76 (3H, m, H-7, H-7, H-6), 1.85 (1H, m, H-6), 2.92 (1H, brs, H-8), 3.76 (3H, s, *m*-OCH$_3$), 4.13 (1H, s, H-8a), 4.73 (1H, br d, *J* = 3.4 Hz, H-5), 6.84 (1H, m, *o*'-Ar), 6.89 (1H, m, *o*-Ar), 7.02 (1H, m, *p*-Ar), 7.39 (1H, t, *J* = 8.1 Hz, *m*'-Ar). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 26.4 (C-6), 28.3 (C-7), 35.3 (C-9), 38.9-39.9 (C-8, under DMSO), 55.3 (*m*-OCH$_3$), 65.6 (C-5), 67.8 (C-8a), 114.2 (*o*-Ar), 114.3 (*p*-Ar), 120.4 (*o*'-Ar), 129.5 (*m*'-Ar), 134.7 (*i*-Ar), 159.4 (*m*-Ar), 173.9 (C-1), 192.0 (C-3). M$^{+\bullet}$(100) $C_{15}H_{16}N_2O_2S_2^{+\bullet}$ Calcd 288.0932 Obsd 288.0942 Other ions *m/z* (%): 287(6), 254(5), 222(9), 166(14), 166(11), 165(98), 95(20), 77(10), 67(10.5)

(5*S*,8*R*,8a*R*)-5,8,8a-Hexahydro-2-(4-chlorophenyl)-3-thioxo-5,8-methanoimidazo[1,5-*a*]pyridine-1(5*H*)-one (7d). White crystals, mp 155-157 ºC (EtOAc), yield 0.49 g, (67%); $[\alpha]_D^{25}$ = +48.2 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.40 (1H, brd, *J* = 10.5 Hz, H-9*anti*), 1.48 (1H, m, H-9*syn*), 1.70-1.76 (3H, m, H-7, H-7, H-6), 1.86 (1H, m, H-6), 2.92 (1H, brs, H-8), 4.15 (1H, s, H-8a), 4.73 (1H, brd, *J* = 3.2 Hz, H-5), 7.36 (2H, m, *o*-Ar), 7.57 (2H, m, *m*-Ar). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 26.4 (C-6), 28.3 (C-7), 35.4 (C-9), 38.9-39.9 (C-8, under DMSO), 65.6 (C-5), 67.9 (C-8a), 128.9 (*m*-Ar), 130.3 (*o*-Ar), 132.5 (*p*-Ar), 133.4 (*i*-Ar), 173.8 (C-1), 191.6 (C-3). $M^{+\bullet}$(100) $C_{15}H_{16}N_2O_2S_2^{+\bullet}$ Calcd 292.0437 Obsd 292.0444 Other ions *m/z* (%): 229(12), 226(10), 171(29), 169(79), 111(12.5), 95(45.5), 68(17), 67(19), 54(10), 41(10)

(5*R*,8*S*,8a*S*)-5,8,8a-tetrahydro-2-benzyl-5,8-methanoimidazo[1,5-*a*]pyridine-1,3(2*H*,5*H*)-dione (9). White crystals, mp 85-86 ºC (EtOAc), yield 0.47 g, (73%); $[\alpha]_D^{25}$ = –78.1 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.07 (1H, m, H-9), 1.30 (1H, brd, *J*= 10.7 Hz, H-9), 1.50-1.58 (2H, m, H-6, H-7), 1.63 (1H, m, H-7), 1.70 (1H, m, H-6), 2.75 (1H, brd, *J*= 2.8 Hz, H-8), 3.82 (1H, br s, H-8a), 4.22 (1H, brd, *J*= ~2.4 Hz, H-5), 4.51 (1H, d, *J*= 15.2 Hz, N*CH*$_2$), 4.54 (1H, d, *J*= 15.2 Hz, N*CH*$_2$), 7.24 (2H, m, *o*-Ar), 7.28 (1H, m, *p*-Ar), 7.33 (2H, m, *m*-Ar). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 27.0 (C-6), 27.7 (C-7), 34.5 (C-9), 38.8 (C-8), 41.8 (N*CH*$_2$), 60.4 (C-5), 65.8 (C-8a), 127.3 (*o*-Ar), 127.5 (*p*-Ar), 128.5 (*m*-Ar), 136.2 (*i*-Ar),163.2 (C-3), 173.9 (C-1). $M^{+\bullet}$(100) $C_{15}H_{16}N_2O_2^{+\bullet}$ Calcd 256.1222 Obsd 256.1212 Other ions *m/z* (%): 228(22), 132(11), 96(18), 95(12), 91(57), 68(19), 678189, 54(14)

Ethyl (1*R*,3*S*,4*S*)-2-(4,5-dihydro-thiazol-2-yl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (10). It was prepared from base (+)-**5** (0.5 g, 2.96 mmol) in 20 mL with one equivalent of the chloroethylisothiocyanate[33] as described for **6**. The oily product was purified by column chromatography. Oil, (toluene: methanol = 4:1), yield 0.64 g, (85%); $[\alpha]_D^{25}$ = –193.1 (c 1, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.22, (3H, t, *J* = 7.1, OCH$_2$C*H*$_3$), 1.52 (1H, brd, *J* = 11.0, H-7), 1.62 (1H, brm, H-5), 1.65-1.70 (2H, brm, H-6), 1.75 (1H, brm, H-7), 1.77 (1H, brm, H-5), 2.86 (1H, brd, *J* = 2.8, H-4), 3.58 (2H, brm, C*H*$_2$S), 3.92 (2H, brt, *J*=7.3Hz, N*CH*$_2$), 4.12 (1H, brs, H-1), 4.17 (3H, q, *J* = 7.1, OC*H*$_2$CH$_3$), 4.21 (1H, brs, H-3). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 13.8 (OCH$_2$*C*H$_3$), 25.8 (C-5), 28.9 (C-6), 32.5 (*C*H$_2$S), 35.1 (C-7), 42.0 (C-4), 50.8 (CH$_2$N), 61.4 (O*C*H$_2$CH$_3$, 68.0 and 68.3 (C-1 and C-3), 176.8 (C=O). $M^{+\bullet}$(27) $C_{12}H_{18}N_2O_2S^{+\bullet}$ Calcd 254.1089 Obsd 254.1083 Other ions *m/z* (%): 182(21), 181(100), 153(62)

(1*S*,3*R*,4*R*)-3-Hydroxymethyl-2-azabicyclo[2.2.1]heptane (12). To a slurry of LiAlH$_4$ (1.5 g, 39.55 mmol) in 50 mL of dry THF, amino ester base **(–)-5** (4.25 g, 25 mmol) in 20 mL of THF was added dropwise at room temperature. After stirring one hour, the mixture was decomposed with 2 mL of water under ice cooling. The inorganic material was filtered off and washed with THF. After drying and evaporation, the resulting oil was crystallized from *n*-hexane and recrystallized. White crystals, mp 126-127 ºC (*i*Pr$_2$O) yield (1.8 g, 57%; $[\alpha]_D^{25}$ = –61.9 (c 0.5, MeOH) Lit: $[\alpha]_D^{25}$ = –62.9 (c 1, CHCl$_3$)[28] ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.39, (1H, td, *J* = 9.0, 1.9 Hz, H-5,) 1.47 (1H, d *J* = 10.9 Hz, H-7), 1.61 (1H, dd, *J* = 3.3, *J* = 12.2 Hz, H-6), 1.66 (1H, dd, *J* = 3.5, *J* = 12.2 Hz, H-6), 1.75 (2H, m, H-5, H-7), 2.41 (1H, brs, H-4), 3.16 (1H, dd, *J* = 5.5,

J = 7.9 Hz, H-3), 3.39 (1H, dd, *J* = .2, *J*= 11.6 Hz, C*H*$_2$OH), 3.66 (1H, dd, *J* = 5.5, *J* = 11.6 Hz, C*H*$_2$OH), 3.89 (1H, brs, H-1), 8.70 (1H, brs, N*H*). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 25.0 (C-6), 27.1 (C-5), 34.4 (C-7), 37.0 (C-4), 56.8 (C-1), 60.2 (*C*H$_2$OH), 64.2 (C-3). M$^{+\bullet}$(3.5) $C_7H_{13}NO^{+\bullet}$ Calcd 127.0997 Obsd 127.0991 Other ions *m/z* (%): 95(84), 68(100), 67(11), 41(16)

(1*S*,3*R*,4*R*)-1-(4-Chlorophenyl)-3-(3-hydroxymethyl-bicyclo[2.2.1]hept-2-yl thiourea (13). It was prepared from amino alcohol **12** (0.4 g, 3.14 mmol in 20 mL), with *p*-chlorophenylisothiocyanate as described for **6**. White crystals, mp 189-190 ºC (EtOAc) yield 0.61 g, (66%); $[\alpha]_D^{25}$ = +198.5 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.2-2.0 (6H, m, H-5, H-6, H-7), 3.17 (1H, d *J* = 5.0, Hz, H-4), 3.61 (1H, m, H-3), 3.61-3.66 (2H, m, C*H*$_2$OH), 4.83 (1H, brs, H-1), 7.33 (2H, m, *m*-Ar), 7.49 (2H, brd, *J* = 7.6 Hz, *o*-Ar). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 27.1 (C-6), 28.7 (C-5), 35.0 (C-7), 41.1 (C-4), 62.7 (C-1), 65.3 (*C*H$_2$OH), 70.0 (C-3), 125.2 (*o*-Ar), 127.9 (*p*-Ar), 128.4 (*m*-Ar), 139.9 (*i*-Ar), 179.0 (C=S). M$^{+\bullet}$(19) $C_{14}H_{17}N_2OSCl^{+\bullet}$ Calcd 296.0750 Obsd 296.0756 Other ions *m/z* (%): 278(12), 171(38), 169(100), 127(33), 113(11), 111(39), 96(53), 75(21), 68(63), 67(18)

(5*S*,8*R*,8a*R*)-3-(4-Chlorophenylimino)-perhydro-5,8-methanothiazolo[3,4-*a*]pyridine (14). It was prepared from **13** (2 mmol) as described for tiohydantoines **7**. White crystals, mp 184-185 ºC (EtOH) yield 0.3 g, (55 %); $[\alpha]_D^{25}$ = +394.0 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.50 (2H, brm, H-6, H-9), 1.63 (1H, brm, H-6), 1.70-1.75 (2H, m, H-7), 1.81 (1H, brm, H-9), 2.59 (1H, brs, H-8), 3.23 (1H, brt, *J* = 12.1 Hz, H-1), 3.62 (1H, brdd, *J* = 6.5 ,12.1 Hz, H-1), 4.06 (1H, brm, H-8a), 4.80 (1H, brs, H-5), 7.33, (2H, brm, *o*-Ar), 7.59 (2H, brd, *J* = 8.0 Hz, *m*-Ar). ^{13}C NMR (DMSO-d$_6$) δ (ppm): 26.8 (C-7), 27.1 (C-6), 37.0 (C-9), 37.5 (C-1), 39.9 (C-8), 64.3 (C-5) 71.6 (C-8a), 125.4 (*o*-Ar), 129.3 (*m*-Ar), 131.1 (*p*-Ar), 139.0 (*i*-Ar) , 170.0 (C-3). M$^{+\bullet}$(100) $C_{14}H_{15}N_2SCl^{+\bullet}$ Calcd 278.0644 Obsd 278.0644 Other ions *m/z* (%): 277(28), 211(10), 169(15), 41(10)

3-(4-Nitrophenyl)-perhydro-5,8-methanooxazolo[3,4-*a*]pyridine (15). To a solution of the amino alcohol **12** (300 mg, 2.36 mmol) in 20 mL methanol, *p*-nitrobenzaldehyde (389 mg, 2.36 mmol) was added, and the mixture was refluxed for 10 hours. The solvent was then evaporated off. The product proved to be a mixture of epimers, of which the two epimers could be separated by crystallization from *n*-hexane.

(3*S*,5*S*,8*R*,8a*R*)-15 (major epimer). Yellow crystals, mp 101-102 ºC (*n*-hexane) yield 0.25 g, (41 %); $[\alpha]_D^{25}$ = –86,7 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm): 1.10 (1H, brd, *J* = 9.8 Hz, H-9*anti*), 1.20-1.60 (4H, m, H-7, H-6), 1.67 (1H, dm, *J* = 9.8 Hz, H-9*syn*), 2.30 (1H, brs, H-8), 3.14 (1H, dd, *J* = 4.8, 7.4 Hz, H-8a), 3.42 (1H, brs, H-5), 3.47 (1H, dd, *J* = 4.8, 8.9 Hz, H-1), 3.69 (1H, dd, *J* = 7.4, 8.9 Hz, H-1), 5.54 (1H, brs, H-3), 7.68, (2H, m, *o*-Ar), 8.19 (2H, m, *m*-Ar) ^{13}C NMR (DMSO-d$_6$) δ (ppm): 26.6 (C-7), 30.1 (C-6), 31.9 (C-9), 40.6 (C-8), 62.0 (C-5), 67.7 (C-8a), 69.3 (C-1), 95.7 (C-3), 123.1 (*m*-Ar), 127.8 (*o*-Ar), 147.0 (*p*-Ar), 149.2 (*i*-Ar).

(3*R*,5*S*,8*R*,8a*R*)-15 (minor epimer). Yellow crystals, mp 94-195 ºC (*n*-hexane) yield 0.21 g, (35 %); $[\alpha]_D^{25}$ = –80,2 (c 0.5, MeOH) ^{1}H NMR (DMSO-d$_6$) δ (ppm):): 0.89 (1H, brd, *J* = 9.5 Hz, H-9*anti*), 1.21-1.32 (3H, m, H-7, H-6, H-6), 1.39 (1H, m, H-7), 1.47 (1H, m, H-9*syn*), 2.36 (1H, brd, *J* = 4.0 Hz, H-8), 2.61 (1H, brm, H-5), 3.28 (1H, dd, *J* = 7.7, 2.9 Hz, H-8a), 3.70 (1H, dd, *J*

= 8.8, 3.0 Hz, H-1), 3.75 (1H, dd, *J* = 8.8, 7.7 Hz, H-1), 5.34 (1H, brs, H-3), 7.70 (2H, m, *o*-Ar), 8.29 (2H, m, *m*-Ar). ^{13}C NMR (DMSO-d_6) δ (ppm): 26.3 (C-7), 30.4 (C-6), 33.5 (C-9), 41.4 (C-8), 56.3 (C-5), 67.9 (C-8a), 69.6 (C-1), 94.2 (C-3), 123.4 (*m*-Ar), 128.0 (*o*-Ar), 143.6 (*i*-Ar), 147.2 (*p*-Ar). $M^{+\bullet}$(100) $C_{14}H_{16}N_2O_3^{+\bullet}$ Calcd 260.1161 Obsd 260.1173 Other ions *m/z* (%): 259(15), 231(27), 230(92), 202(21), 138(32), 109(30), 108(38), 94(27), 89(1), 81(36), 80(33), 77(15), 68(27), 67(39), 66(20), 55(12), 54(43), 53(15), 42(11), 41(37), 39(19)

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