Enantiospecific Synthesis of All Four Stereoisomers of Novel Bicyclic Arylacetamides as κ-Opioid Agonists

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Conformationally constrained bicyclic derivatives of the potent and selective κ-opioid receptor agonist 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[(1*S*)-1-phenyl-2-(1-pyrrolidinyl)-ethyl] acetamide (3, ICI-199, 441) were designed to explore the effect of the conformational restriction and stereochemistry of the pharmacophoric ethylenediamine incorporated into the pyrrolidine on the affinity and κ-selectivity. A facile enantiospecific synthetic route was established to afford all four stereoisomers starting from readily available amino acids through mild cyclization and amide formation.

Keywords κ-opioid receptor agonist, bicyclic arylacetamide, conformational restriction, enantiospecific synthesis

κ-Opioid agonists produce a variety of pharmacological effects including antinociception in animals and analgesia in man.[1,2] Since selective κ-opioid agonists are devoid of the abuse potential and the adverse side effects associated with morphine-like analgesics (which act via μ-receptor activation), there has been considerable interest in identifying and developing such a compound as an effective and safe pain relieving agent. During the past decade, several pharmaceutical research groups have discovered potent κ-agonist analgesics (Fig. 1), most of which were derived from the lead structure U-50, 488 (**1**)[3] including annulated compounds (*e.g.* **2**)[4] and simplified ligands (*e.g.* **3**)[5] as well as heterocyclic analogues (*e.g.* **4**, **5**).[6,7] However, sedation, dysphoria, and strong diuresis usually accompany their applications.[8]

The present study was undertaken to produce novel derivatives by joining two κ-pharmacophoric elements of ethylenediamine[9] and pyrrolidine[10] into a fused bicyclic structure to gain safer biological profiles. Conformational restriction of flexible drugs has proved invaluable in medicinal chemistry in determining drug-receptor steric requirements and in the identification of new structures with greater efficacy and selectivity as well as completely new pharmacological profiles. Previous efforts on the conformational restriction of κ-agonist turned out promising but were applied to the κ-pharmacophore sequence N-C-C-N (sp2) only, leaving pyrrolidine unit pendent (*e.g.* **2**). We were intrigued to restrict pyrrolidine unit with ethylenediamine framework to investigate the effect of the different conformational change on its κ-agonist activity and selectivity. Thus from the structural prototype of κ-agonist ICI-199, 441 (**3**), a novel class of bicyclic arylacetamides of general formula **6** was designed and synthesized, featuring a cyclic bridged structure of 1,4-diazabicyclo[4.3.0]nonane in the basic amino functionality.

According to the structure/κ-receptor affinity relationship studies,[3-7,10-12] the κ-receptor affinity and selectivity of these monoacylated ethylenediamines are strongly dependent on the stereochemistry. Take the methyl substituted analogs of **5** as an example: a significant κ-receptor affinity was observed for the racemic *threo*-isomer **5** [(±)-*threo*-**5**: $K_i = 0.60$ nmol/L], but only low κ-receptor affinity was found for the corresponding *erythro*-isomer of **5** [(±)-*erythro*-**5**: $K_i = 1000$ nmol/L].[7] For our novel bicyclic arylacetamide structures, there are two

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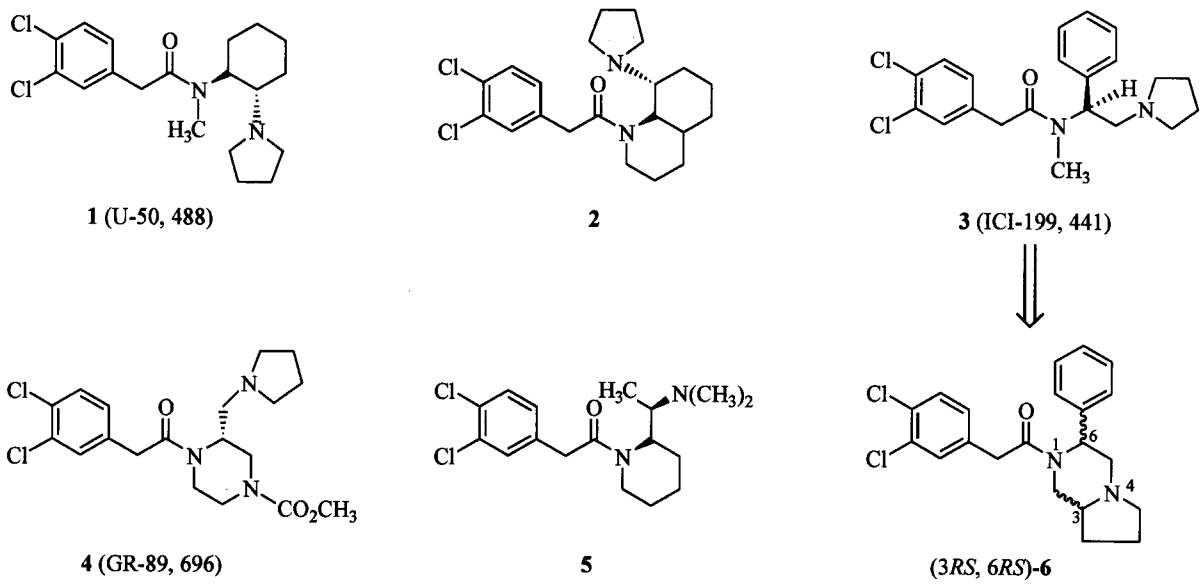


Fig. 1 Selected typical κ-agonists and designed bicyclic analogs.

chiral carbon atoms which produce four possible diastereomers, namely, (3*S*,6*R*)-(−)-1-*N*-[2-(3,4-dichlorophenyl)] acetyl-6-phenyl-1, 4-diazabicyclo [4.3.0]-nonane (**6a**), (3*R*,6*S*)-(+)-1-*N*-[2-(3,4-dichlorophenyl)] acetyl-6-phenyl-1, 4-diazabicyclo [4.3.0]-nonane (**6b**), (3*S*,6*S*)-(−)-1-*N*-[2-(3,4-dichlorophenyl)] acetyl-6-phenyl-1, 4-diazabicyclo [4.3.0]-nonane (**6c**) and (3*R*,6*R*)-(+)-1-*N*-[2-(3,4-dichlorophenyl)] acetyl-6-phenyl-1, 4-diazabicyclo [4.3.0]-nonane (**6d**). The chirality would surely make a great impact on the activity. It would be interesting and valuable to get all stereoisomers of this novel conformationally constrained structure and examine their κ-affinity and selectivity.

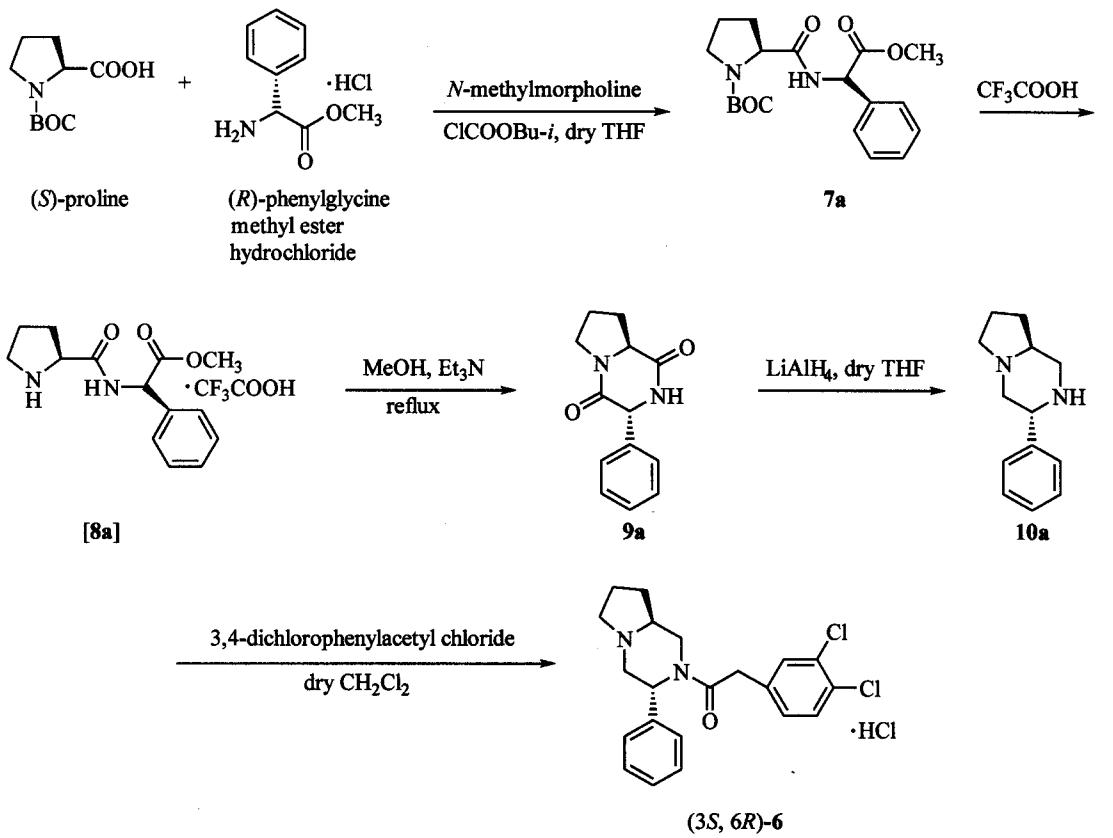
As outlined in Scheme 1, a chiral pool synthesis was employed for the preparation of the substituted bicyclic analogs **6**. Four stereoisomers **6a—d** of general formula **6** can be obtained enantioselectively from corresponding starting materials, *i.e.*, *S*- or *R*-amino acids. Coupling of BOC-protected (*S* or *R*)-proline with (*S* or *R*)-phenylglycine methyl ester hydrochloride afforded **7a—d** respectively.[5] The *tert*-butoxycarbonyl group of **7a—d** was removed with aid of CF_3COOH to produce **8a—d**. Cyclization[13] of **8a—d** by treatment with excess Et_3N provided **9a—d**, which was followed by reduction with $LiAlH_4$ to give **10a—d**. Condensation of optically pure **10a—d** with 3,4-dichlorophenylacetyl chloride furnished products **6a—d** respectively. The yields and physical properties of **6a—d** were indicated in the experimental section. The related biological evaluation of the four novel κ-agonists is under way in this laboratory and will be reported in due course.

In summary, a new class of conformationally constrained bicyclic arylacetamides was designed and synthesized for the purpose to seek κ-agonist analgesics with safer pharmacological profiles. The κ-pharmacophoric ethylenediamine was incorporated into the pyrrolidine unit to investigate the effect of conformation and chirality on the κ-selectivity and activity. All four stereoisomers were directly and conveniently obtained via an enantiospecific synthesis approach from the corresponding amino acids.

Experimental

Melting points (uncorrected) were determined on a Buchi-610 capillary apparatus. Specific rotations (uncorrected) were determined on a Perkin-Elmer 241 polarimeter. Elemental analyses were determined to be within ± 0.4% of the theoretical values for elements C, H and N. ^1H NMR spectra were obtained from either $CDCl_3$ solutions or DMSO-d_6 solutions using a Bruker AM-400 spectrometer. Chemical shifts are reported as δ values relative to internal Me_4Si. IR spectra were recorded on a DTGS spectrometer in KBr pellets. Low and high resolution mass spectra were determined on MAT-95 mass spectrometer. TLC was performed on 0.25 mm HSGF 254 silica

Scheme 1



gel plates. All final products were characterized by NMR, IR, MS and elemental analysis.

D-Phenylglycine, *D*- and *L*-proline were purchased from GL Biochem Ltd. (Shanghai, China). *L*-phenylglycine was purchased from Aldrich (Milwaukee, WI, USA). Specific rotations were indicated as follows: *D*-proline $[\alpha]_D^{20}$ + 83— + 85 (*c* 1, H_2O); *L*-proline $[\alpha]_D^{20}$ − 84.5— − 86.0 (*c* 1, H_2O); *D*-phenylglycine $[\alpha]_D^{20}$ − 158.5 (*c* 1, 1 mol/L HCl); *L*-phenylglycine $[\alpha]_D^{20}$ + 155 (*c* 1, 1 mol/L HCl).

[(S)-N-(tert-Butoxycarbonyl)prolyl]-(R)-phenylglycine methyl ester (**7a**)

To a stirred cold solution of *N*-(*tert*-butoxycarbonyl)-*L*-proline (3.3 g, 15 mmol) in 30 mL of dry THF was added *N*-methylmorpholine (3.5 mL, 31 mmol). After stirring for 5 min, isobutyl chloroformate (2.06 g, 15 mmol) was added dropwise, and the mixture was stirred at 0 ℃ for 0.5 h. Then (*R*)-phenylglycine methyl ester hydrochloride (3.03 g, 15 mmol) was added. After 0.5 h at 0 ℃, the stirring was continued at r.t. overnight. The mixture was diluted with water (100 mL) and extracted with EtOAc (200 mL). The organic phase was washed with 1 mol/L HCl (200 mL), 10% aqueous K_2CO_3 (200 mL) and brine (100 mL) successively, dried over $MgSO_4$, filtered and evaporated to give light yellow oil. Recrystallization from EtOAc/petroleum (60—90 ℃) gave 5.0 g of **7a** in yield of 92% as a colorless crystalline solid. M. p. 101—103 ℃, $[\alpha]_D^{18}$ − 146.10 (*c* 0.23, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (s, 6H, two CH_3 of *t*-Bu), 1.51 (s, 3H, one CH_3 of *t*-Bu), 1.94—2.32 (m, 4H), 3.35—3.52 (m, 2H), 3.74 (s, 3H, $COOCH_3$), 4.18—4.34 (m, 1H), 5.55—5.65 (m, 1H), 6.96 (brs, 1H, CONH), 7.36 (brs, 5H, ArH); IR (KBr) ν: 3326, 1747, 1700, 1652, 1390, 740, 702 cm^{-1}; MS (EI) *m/z*: 362 (M^+). Anal. calcd for $C_{19}H_{26}N_2O_5$: C 62.97, H 7.23, N 7.73; found C 63.15, H 7.17, N 7.69.

[(R)-N-(tert-Butoxycarbonyl)prolyl]-(S)-phenylglycine methyl ester (**7b**)

Compound **7b** was prepared from BOC-protected (*R*)-proline and (*S*)-phenylglycine methyl ester hydrochloride analogously to compound **7a**: 90% yield, m. p. 104—106 ℃, $[\alpha]_D^{25}$ + 146.18 (*c* 1.08, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.27 (s, 6H, two CH_3 of *t*-Bu), 1.49 (s, 3H, one CH_3 of *t*-Bu), 1.89—2.36 (m, 4H), 3.32—3.51 (m, 2H), 3.72 (s, 3H, $COOCH_3$), 4.22—4.38 (m, 1H), 5.52—5.63 (m, 1H), 6.97 (brs, 1H, CONH), 7.35 (brs, 5H, ArH); IR (KBr) ν: 3326, 1747, 1700, 1652, 1390, 786, 740, 702 cm^{-1}; MS (EI) *m/z*: 362 (M^+). Anal. calcd for $C_{19}H_{26}N_2O_5$: C 62.97, H 7.23, N 7.73; found C 63.00, H 7.17, N 7.65.

[(S)-N-(tert-Butoxycarbonyl)prolyl]-(S)-phenylglycine methyl ester (**7c**)

Compound **7c** was prepared from BOC-protected (*S*)-proline and (*S*)-phenylglycine methyl ester hydrochloride following the same procedure described for compound **7a**: 94% yield, m. p. 62—64 ℃, $[\alpha]_D^{21}$ +57.00 (*c* 0.30, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.43 (s, 9H, *t*-Bu), 1.84—2.34 (m, 4H), 3.33—3.43 (m, 2H), 3.72 (s, 3H, $COOCH_3$), 4.25—4.41 (m, 1H), 5.55 (m, 1H), 6.99 (brs, 1H, CONH), 7.33 (brs, 5H, ArH); IR (KBr) ν: 3293, 1753, 1699, 1664, 1367, 703 cm^{-1}; MS (EI) *m/z*: 362 (M^+). Anal. calcd for $C_{19}H_{26}N_2O_5$: C 62.97, H 7.23, N 7.73; found C 62.91, H 7.07, N 7.65.

[(R)-N-(tert-Butoxycarbonyl)prolyl]-(R)-phenylglycine methyl ester (**7d**)

Compound **7d** was prepared from BOC-protected (*R*)-proline and (*R*)-phenylglycine methyl ester hydrochloride using the same procedure of compound **7a**: 93% yield, m. p. 58—60 ℃, $[\alpha]_D^{25}$ - 60.57 (*c* 1.008, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.44 (s, 9H, *t*-Bu), 1.84—2.33 (m, 4H), 3.31—3.45 (m, 2H), 3.72 (s, 3H, $COOCH_3$), 4.24—4.42 (m, 1H), 5.54 (m, 2H), 6.99 (brs, 1H, CONH), 7.34 (brs, 5H, ArH); IR (KBr) ν: 3297, 1745, 1699, 1670, 1367, 702 cm^{-1}; MS (EI) *m/z*: 362 (M^+). Anal. calcd for $C_{19}H_{26}N_2O_5$: C 62.97, H 7.23, N 7.73; found C 62.66, H 7.10, N 7.62.

N-[(S)-Prolyl]-(R)-phenylglycine methyl ester (**8a**)

A solution of **7a** (4.8 g, 16.8 mmol) in CF_3COOH (18 mL) was stirred at r.t. until the reaction completed (1.5 h). The solvent was evaporated *in vacuo* to give **8a** as a colorless CF_3COOH salt which was used directly for the next step without further purification.

N-[(R)-Prolyl]-(S)-phenylglycine methyl ester (**8b**)

Compound **8b** was prepared from **7b** analogously to compound **8a**.

N-[(S)-Prolyl]-(S)-phenylglycine methyl ester (**8c**)

Compound **8c** was prepared from **7c** analogously to compound **8a**.

N-[(R)-Prolyl]-(R)-phenylglycine methyl ester (**8d**)

Compound **8d** was prepared from **7d** analogously to compound **8a**.

(3S,6R)-(-)-6-Phenyl-1,4-diazabicyclo[4.3.0]*-nonane-2,5-dione* (**9a**)

The crude product **8a** was dissolved in MeOH (80 mL) and treated with Et_3N (11.6 mL, 82.5 mmol). The reaction mixture was refluxed overnight. The solvent was removed by evaporation. The oily residue was diluted with $CHCl_3$ (200 mL) and washed successively with 1 mol/L HCl (100 mL), 10% aqueous K_2CO_3 (140 mL) and water (50 mL). After usual work-up, the residue was recrystallized from hot 2-propanol (15 mL) to afford 1.78 g of pure **9a** in yield of 46%. M. p. 208—210 ℃; $[\alpha]_D^{18}$ - 82.2 (*c* 0.23, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.76—1.84 (m, 1H), 1.96—2.09 (m, 2H), 2.32—2.39 (m, 1H), 3.42—3.48 (m, 1H), 3.62—3.68 (m, 1H), 3.97—4.06 (m, 1H), 5.18 (s, 1H), 6.86 (brs, 1H, NH), 7.26—7.48 (m, 5H, ArH); IR (KBr) ν: 3263, 1656, 1633, 715, 692 cm^{-1}; MS (EI) *m/z*: 230 (M^+). Anal. calcd for $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17;

found C 67.56, H 6.20, N 12.12.

(3*R*,6*S*)-(+)-6-*Phenyl*-1,4-*diazabicyclo* [4.3.0]-*nonane*-2,5-*dione* (**9b**)

Compound **9b** was prepared from **8b** following the same procedure described for compound **9a**: 48% yield, m.p. 204—206 ℃, $[\alpha]_D^{25}$ + 80.1 (*c* 0.23, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.77—1.83 (m, 1H), 1.98—2.14 (m, 2H), 2.35—2.42 (m, 1H), 3.45—3.52 (m, 1H), 3.64—3.71 (m, 1H), 3.98—4.05 (m, 1H), 5.15 (s, 1H), 6.55 (brs, 1H, NH), 7.31—7.48 (m, 5H, ArH); IR (KBr) ν: 3264, 1656, 1633, 715 cm^{-1}; MS (EI) *m/z*: 230 (M^+). Anal. calcd for $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17; found C 67.83, H 6.03, N 12.01.

(3*S*,6*S*)-(−)-6-*Phenyl*-1,4-*diazabicyclo* [4.3.0]-*nonane*-2,5-*dione* (**9c**)

Compound **9c** was prepared from **8c** analogously to compound **9a**: 56% yield, m.p. 209—211 ℃, $[\alpha]_D^{21}$ − 80.0 (*c* 0.33, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.79—1.84 (m, 1H), 1.98—2.14 (m, 2H), 2.32—2.38 (m, 1H), 3.42—3.48 (m, 1H), 3.62—3.69 (m, 1H), 3.97—4.06 (m, 1H), 5.06 (s, 1H), 7.04 (brs, 1H, NH), 7.32—7.48 (m, 5H, ArH); IR (KBr) ν: 3263, 1652, 1633, 715 cm^{-1}; MS (EI) *m/z*: 230 (M^+). Anal. calcd for $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17; found C 67.51, H 6.17, N 12.12.

(3*R*,6*R*)-(+)-6-*Phenyl*-1,4-*diazabicyclo* [4.3.0]-*nonane*-2,5-*dione* (**9d**)

Compound **9d** was prepared from **8d** analogously to compound **9a**: 52% yield, m.p. 207—209 ℃, $[\alpha]_D^{25}$ + 80.7 (*c* 1.09, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.74—1.86 (m, 1H), 1.99—2.12 (m, 2H), 2.34—2.41 (m, 1H), 3.44—3.51 (m, 1H), 3.63—3.70 (m, 1H), 3.98—4.08 (m, 1H), 5.15 (s, 1H), 6.84 (brs, 1H, NH), 7.32—7.49 (m, 5H, ArH); IR (KBr) ν: 3264, 1656, 1633, 715, 692 cm^{-1}; MS (EI) *m/z*: 230 (M^+). Anal. calcd for $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17; found C 67.82, H 6.17, N 12.08.

(3*S*,6*R*)-(−)-6-*Phenyl*-1,4-*diazabicyclo* [4.3.0]-*nonane* (**10a**)

9a (0.9 g, 3.91 mmol) was added portionwise into a stirred suspension of $LiAlH_4$ (0.59 g, 15.7 mmol) in dry THF (30 mL) at 0 ℃. The reaction mixture was refluxed for 1.5 h and then cooled down to 0 ℃, treated carefully with water (0.59 mL), 15% aqueous NaOH (0.59 mL), and water (1.8 mL). The mixture was filtered through celite, and the filter cake was washed with Et_2O for several times. The combined filtrate was evaporated to give an oily residue, which was redissolved in Et_2O (150 mL), and extracted with 1.5 mol/L HCl (100 mL). The acidic aqueous phase was basified to pH 12 with solid NaOH, and reverse-extracted with Et_2O (150 mL). After drying over $MgSO_4$, the Et_2O was removed to give 0.71g of **10a** as a clear yellow oil in yield of 90%. $[\alpha]_D^{23}$ − 18.68 (*c* 1.009, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) (* one active hydrogen is not observed.) δ: 1.41—1.49 (m, 1H), 1.72—1.86 (m, 3H), 2.22—2.31 (m, 3H), 2.64—2.75 (m, 1H), 3.08—3.24 (m, 3H), 3.94—4.02 (m, 1H), 7.28—7.42 (m, 5H, ArH); IR (KBr) ν: 3257, 757, 696 cm^{-1}; MS (EI) *m/z*: 202 (M^+). HRMS calcd for $C_{13}H_{18}N_2$ 202.1470, found 202.1480.

(3*R*,6*S*)-(+)-6-*Phenyl*-1,4-*diazabicyclo* [4.3.0]-*nonane* (**10b**)

Compound **10b** was prepared from **9b** following the same procedure described for compound **10a**: 89% yield, $[\alpha]_D^{23}$ + 20.75 (*c* 1.074, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) (* one active hydrogen is not observed.) δ: 1.40—1.51 (m, 1H), 1.68—1.84 (m, 3H), 2.08—2.24 (m, 3H), 2.69—2.75 (m, 1H), 3.09—3.22 (m, 3H), 3.93—4.01 (m, 1H), 7.24—7.41 (m, 5H, ArH); IR (KBr) ν: 3257, 757, 698 cm^{-1}; MS (EI) *m/z*: 202 (M^+). HRMS calcd for $C_{13}H_{18}N_2$ 202.1470, found 202.1477.

(3*S*,6*S*)-(−)-6-*Phenyl*-1,4-*diazabicyclo* [4.3.0]-*nonane* (**10c**)

Compound **10c** was prepared from **9c** analogously to compound **10a**: 90% yield, $[\alpha]_D^{23}$ − 20.73 (*c* 1.004,

CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) (* one active hydrogen is not observed.) δ: 1.38—1.44 (m, 1H), 1.72—1.84 (m, 3H), 2.11—2.24 (m, 3H), 2.65—2.74 (m, 1H), 3.09—3.26 (m, 3H), 3.89—3.96 (m, 1H), 7.24—7.31 (m, 5H, ArH); IR (KBr) ν: 3257, 756, 696 cm^{-1}; MS (EI) *m/z*: 202 (M^+). HRMS calcd for $C_{13}H_{18}N_2$ 202.1470, found 202.1448.

(3R,6R)-(+)-6-Phenyl-1,4-diazabicyclo[4.3.0]-nonane (**10d**)

Compound **10d** was prepared from **9d** analogously to compound **10a**: 87% yield, $[\alpha]_D^{23}$ + 22.55 (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) (* one active hydrogen is not observed.) δ: 1.42—1.48 (m, 1H), 1.73—1.82 (m, 3H), 2.16—2.26 (m, 3H), 2.68—2.74 (m, 1H), 3.08—3.26 (m, 3H), 3.91—3.98 (m, 1H), 7.24—7.39 (m, 5H, ArH); IR (KBr) ν: 3257, 756, 696 cm^{-1}; MS (EI) *m/z*: 202 (M^+). HRMS calcd for $C_{13}H_{18}N_2$ 202.1470, found 202.1474.

(3S,6R)-(−)-1-N-[2-(3,4-Dichlorophenyl)]acetyl-6-phenyl-1,4-diazabicyclo[4.3.0]nonane hydrochloride salt (**6a**)

To a solution of **10a** (0.2 g, 0.99 mmol) in dry CH_2Cl_2 (10 mL) was added 3, 4-dichlorophenylacetyl chloride (0.22 g, 0.99 mmol) in dry CH_2Cl_2 (10 mL) and the mixture was stirred at r.t. for 1 h, then evaporated *in vacuo*. The residue was dissolved in water (50 mL), basified to pH 11 with 2 mol/L NaOH aqueous solution and extracted with ether (150 mL). After usual work-up, the viscous yellow oily residue was treated with ethereal HCl and recrystallized from EtOAc/petroleum (60—90 ℃) to afford 0.39 g of **6a** in yield of 92% as a white solid. M. p. 166—168 ℃, $[\alpha]_D^{25}$ − 61.7 (*c* 0.78, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.64—2.32 (m, 4H), 2.72—2.92 (m, 3H), 3.42—3.74 (m, 5H), 4.28—4.31 (m, 1H), 5.08—5.20 (m, 1H), 6.94—7.42 (m, 8H, ArH), 12.94 (brs, 1H, HN^+); IR (KBr) ν: 1646, 698 cm^{-1}; MS (EI) *m/z*: 390 [(M − HCl) + 1]$^+$. Anal. calcd for $C_{21}H_{23}Cl_3N_2O$: C 59.24, H 5.44, N 6.58; found C 59.23, H 5.42, N 6.74.

(3R,6S)-(+)-1-N-[2-(3,4-Dichlorophenyl)]acetyl-6-phenyl-1,4-diazabicyclo[4.3.0]nonane hydrochloride salt (**6b**)

Compound **6b** was prepared from **10b** analogously to compound **6a**: 90% yield, m.p. 166—168 ℃, $[\alpha]_D^{25}$ + 58.46 (*c* 1.19, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.72—2.32 (m, 4H), 2.44—2.58 (m, 3H), 3.39—3.58 (m, 4H), 3.64—3.76 (m, 1H), 4.20—4.30 (m, 1H), 5.04—5.19 (m, 1H), 6.96—7.44 (m, 8H, ArH), 12.86 (brs, 1H, HN^+); IR (KBr) ν: 1646, 711 cm^{-1}; MS (EI) *m/z*: 390 [(M − HCl) + 1]$^+$. Anal. calcd for $C_{21}H_{23}Cl_3N_2O$: C 59.24, H 5.44, N 6.58; found C 59.21, H 5.51, N 6.62.

(3S,6S)-(−)-1-N-[2-(3,4-Dichlorophenyl)]acetyl-6-phenyl-1,4-diazabicyclo[4.3.0]nonane hydrochloride salt (**6c**)

Compound **6c** was prepared from **10c** analogously to compound **6a**: 91% yield, m.p. 183—185 ℃, $[\alpha]_D^{25}$ − 61.4 (*c* 1.07, CH_3OH); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.63—1.78 (m, 1H), 1.80—2.04 (m, 2H), 2.18—2.36 (m, 1H), 2.64—2.96 (m, 2H), 3.38—3.58 (m, 5H), 3.62—3.74 (m, 1H), 4.12—4.26 (m, 1H), 5.06—5.31 (m, 1H), 6.94—7.32 (m, 8H, ArH), 12.74 (brs, 1H, HN^+); IR (KBr) ν: 1646, 698 cm^{-1}; MS (EI) *m/z*: 390 [(M − HCl) + 1]$^+$. Anal. calcd for $C_{21}H_{23}Cl_3N_2O$: C 59.24, H 5.44, N 6.58; found C 59.23, H 5.23, N 6.83.

(3R, 6R)-(+)-1-N-[2-(3,4-Dichlorophenyl)]-acetyl-6-phenyl-1,4-diazabicyclo[4.3.0]nonane hydrochloride salt (**6d**)

Compound **6d** was prepared from **10d** analogously to compound **6a**: 89% yield, m.p. 182—184 ℃, $[\alpha]_D^{25}$ + 64.3 (*c* 1.04, CH_3OH); ^1H NMR ($CDCl_3$) δ: 1.64—1.78 (m, 1H), 1.95—2.12 (m, 2H), 2.24—2.38 (m, 1H), 2.80—2.96 (m, 2H), 3.38—3.56 (m, 5H), 3.62—3.76 (m, 1H), 4.17—4.32 (m, 1H), 5.04—5.28 (m, 1H), 6.92—7.41 (m, 8H, ArH), 12.82 (brs, 1H, HN^+); IR (KBr) ν: 1648, 746, 698 cm^{-1}; MS (EI) *m/z*: 390 [(M − HCl) +

1]$^+$. Anal. calcd for $C_{21}H_{23}Cl_3N_2O$: C 59.24, H 5.44, N 6.58; found C 58.97, H 5.53, N 6.66.

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