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α-Quaternary Proline Derivatives by Intramolecular Diastereoselective Arylation of *N*-Carboxamido Proline Ester Enolates

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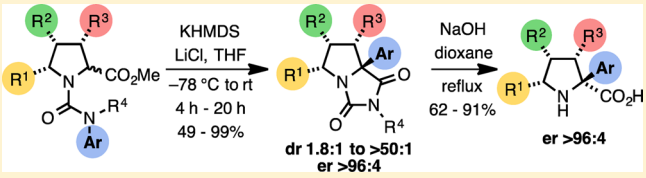
Supporting Information

ABSTRACT: Pyrrolidine-2-carboxylate esters substituted in the 3-, 4- or 5-positions were converted to their *N*′-aryl urea derivatives. Deprotonation at the 2-position to form a potassium enolate led to migration of the *N*′-aryl substituent to the 2 position of the pyrrolidine ring, followed by cyclization of the resulting urea to give bicyclic α-aryl hydantoin derivatives of substituted prolines. Depending on the substitution pattern of the starting material, high diastereoselectivity was observed in the aryl migration, allowing formation of the products in enantiomerically enriched form, despite the intermediacy of a planar enolate. The hydrolysis of the bicyclic hydantoins under basic conditions gave a range of enantiopure and enantioenriched quaternary α-aryl proline derivatives.



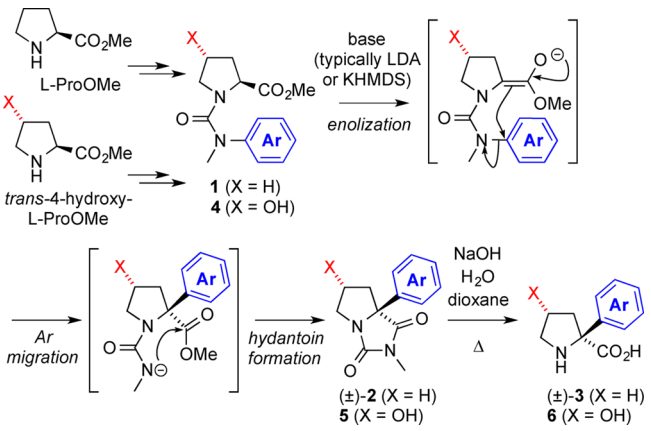
INTRODUCTION

The structural uniqueness of proline as the only genetically coded secondary amino acid gives it particular importance as a starting point for the synthesis of natural[1] and non-natural biologically active compounds.[2] Proline derivatives have been explored not only in peptide chemistry,[3,4] where conformational rigidity promotes polyproline-type secondary structures and induces important biological effects,[5] but also in the design of new chiral auxiliaries[3,4a] and organocatalysts[6] for asymmetric synthesis, where proline's status as the most readily available chiral pyrrolidine gives it central importance.

Cα-quaternary proline derivatives are of particular interest in medicinal chemistry,[3] and their stereoselective synthesis has been achieved by methods including "self-regeneration of stereocenters",[7] diastereoselective alkylations,[8] chirality transfer via cyclic ammonium ylides[9] or 1,3-dipolar cycloaddition.[10] However, methods allowing the synthesis of α-aromatic proline derivatives are few in number and limited in scope. De novo construction of α-aryl proline scaffolds has been achieved using 1,3-dipolar cycloaddition reactions of azomethine ylides,[11] by 1,4 addition reactions with acrylates,[12] or by lithiation-substitution of *N*-Boc-2-phenylpyrrolidine.[13] Methods for direct enantioselective α-arylation of prolines (oxidative nucleophilic substitution of hydrogen in nitroarenes[14] and rearrangement of proline sulfonamides[15]) are limited to arylation with electron-deficient rings.

In recent years we have reported that anionic derivatives of lithiated ureas,[16] carbamates[17] and thiocarbamates[18] may be α-arylated by rearrangements involving the intramolecular nucleophilic aromatic substitution of *N*-aryl rings, both electron-rich and electron-poor. By such methods, racemic[19] or (when a pseudoephedrine chiral auxiliary is used) enantioenriched[20] hydantoins and quaternary amino acids may be formed by rearrangement of the urea derivatives of amino esters, amino nitriles, amino amides and amino acids. The reported[19b] racemic arylation of proline derivative **1** by this method is shown in Scheme 1: formation of an enolate with base leads to aryl migration and hydantoin formation. Hydrolysis of the racemic hydantoin **2** yields the racemic α-arylproline **3**.

Scheme 1. α-Arylation of Proline[19b] and Hydroxyproline



We now show that by making use of enantiomerically enriched compounds containing stereogenic centers at the 3, 4 or 5-position of a substituted proline ring, similar rearrangements can be induced to proceed diastereoselectively, allowing the general synthesis of valuable and otherwise inaccessible

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enantiopure α-quaternary α-aryl proline derivatives, despite the intermediacy of a planar enolate.

RESULTS AND DISCUSSION

We started the study with readily available *trans*-4-hydroxy-L-proline, which was converted to the hydroxyproline ureas **4a–d** (Scheme 1 and Table 1; full details in SI). Treatment with base under optimized conditions [KHMDS (3.5 equiv), LiCl (3.5 equiv), −78 °C to rt, 4 h] led to rearrangement in each case, giving the hydantoins as mixtures of diastereoisomers **5** and **5′** (Table 1).

Table 1. Arylation of *trans*-4-Hydroxy-L-proline by Rearrangement and Hydrolysis

entry	SM	Ar	**5**, yield (%)	d.r.[a]	**6**, yield (%)
1	**4a**	C_6H_5	**5a** 70, **5′a** 9	7.7:1	**6a** 89
2	**4b**	3-$MeOC_6H_4$	**5b** 57, **5′b** 10	4.7:1	**6b** 91, **6′b** 83
3[b]	**4c**	1-naphthyl	(**5c** + **5′c**)[b] 89	2:1	–
4	**4d**	3-BrC_6H_4	**5d** 67, **5′d** 26	2:1	**6d** 89, **6′d** 91

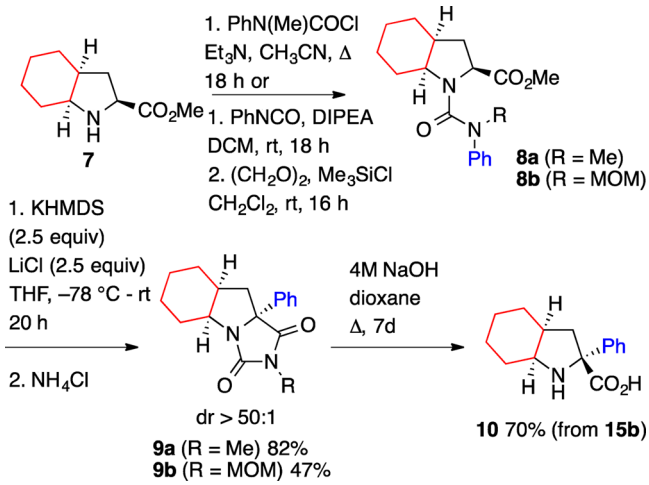
[a]Diastereoisomeric ratio, determined by ^{1}H NMR of the crude reaction mixture. [b]The diastereoisomers **5c** + **5′c** could not be separated.

The relative configuration of the major diastereoisomers was deduced from the X-ray crystal structure of **5a**, in which the hydroxyl group occupied the *endo* face of the bicyclic hydantoin structure (Figure 1). The relative configuration of the other major products was assigned by analogy, supported by the fact that they all show a NOESY correlation between a C-*H* signal of the aryl ring and $C^3H_AH_B$, and have distinguishing features in their NMR spectra such as the chemical shift separation between H_A and H_B in the $C^3H_AH_BC^4H_XOH$ spin system and the chemical shift of the O–H signal. Furthermore, the major diastereoisomers are dextrorotatory while the minor diastereoisomers are laevorotatory.

Presumably, the diastereoselectivity results from migration of the ring to the less hindered face of the enolate (Scheme 1). The best diastereoselectivity was obtained during the phenyl ring migration from **4a**; the other rings migrated with lower selectivity. Nonetheless, in most cases the diastereoisomers were separable, giving access to quaternary hydantoins **5** in enantiopure form. Both diastereoisomers of the hydantoin products **5** were readily hydrolyzed under basic conditions [NaOH (4 M)/Dioxane, reflux, 72 h] to give enantiomerically pure quaternary 4-hydroxyprolines **6** and **6′** in excellent yields (Table 1).

Greater diastereoselectivity was observed using an alternative available proline derivative, the bicyclic perhydroindoline ester **7** (a precursor of the ACE inhibitor perindopril). Conversion of **7** either to the N-Me or N-MOM urea **8a** or **8b** gave substrates for rearrangement that were treated under the same conditions: KHMDS + LiCl in THF, warming from −78 °C to rt. In both cases, a single diastereoisomer of the hydantoin product **9a** and **9b** was obtained (Scheme 2). The relative stereochemistry of the product **9a** was determined by X-ray crystallography (Figure 1). The *N*-methyl hydantoin **9a** was resistant to hydrolysis, but the N-MOM hydantoin **9b** gave, after extended treatment with 4 M NaOH in dioxane, the α-arylated bicyclic amino acid **10**.

Scheme 2. Arylation of a Perindopril Precursor Amino Ester



The diastereoselective arylation of proline derivatives substituted at other positions of the ring was investigated by synthesizing the starting materials by diastereoselective

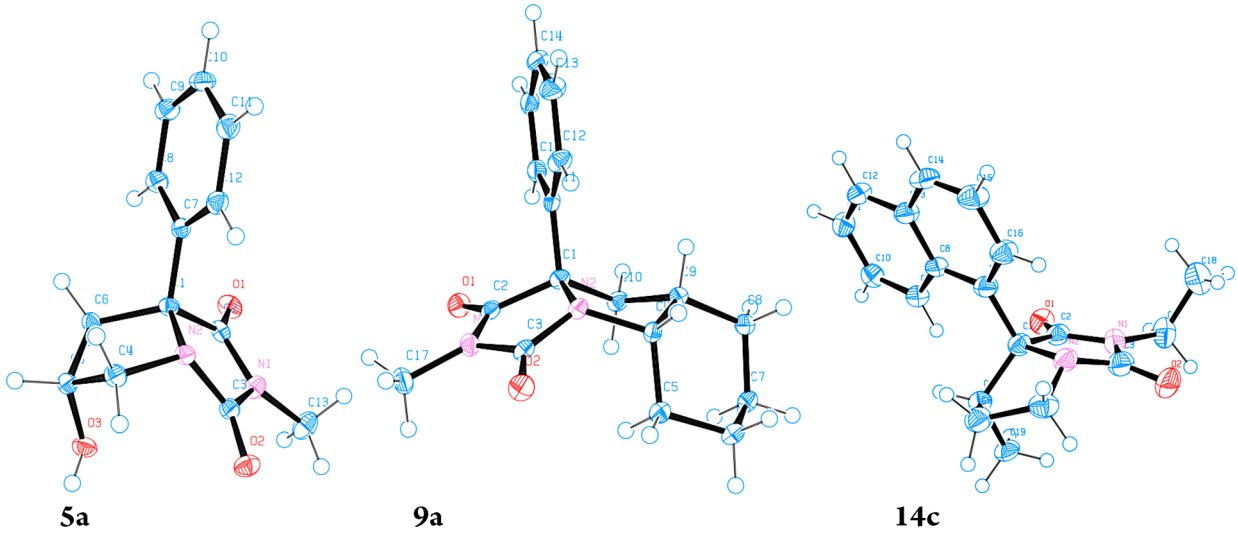


Figure 1. X-ray crystal structures of **5a**, **9a** and **14c**.[21] Ellipsoids are shown at the 50% probability level.

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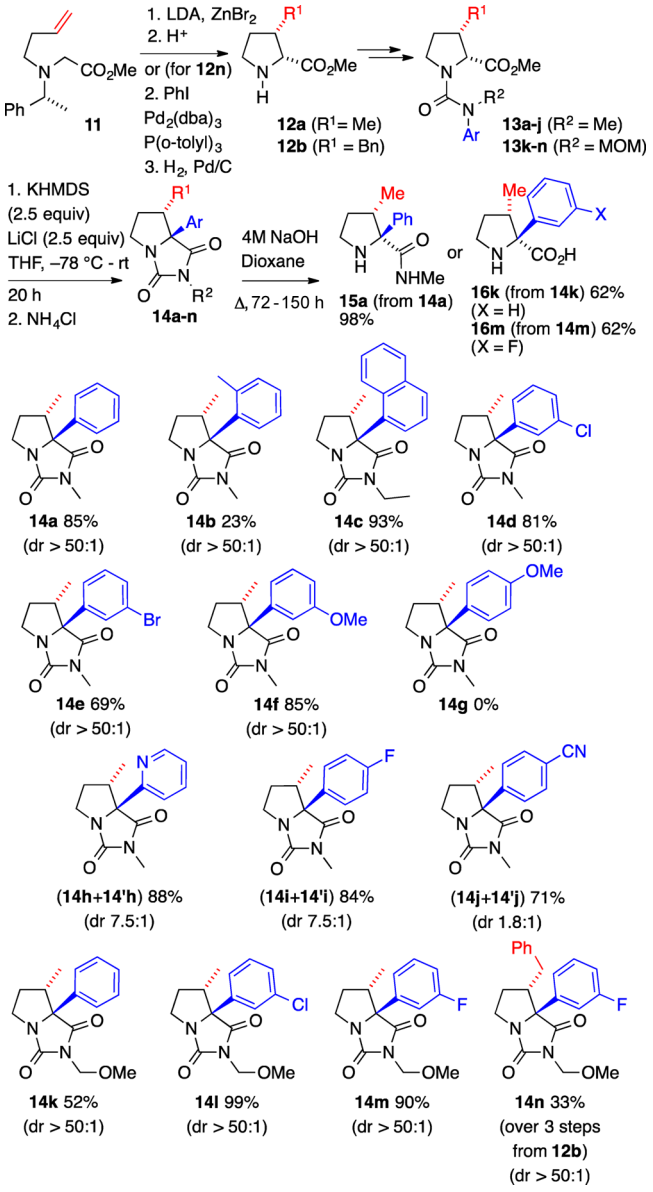
cyclization reactions of acyclic precursors. Proline derivatives **13** with a substituent at the 3-position were made in enantiomerically enriched form by the intramolecular carbozincation reaction of **11** to give **12** as shown in Scheme 3.[22]

Scheme 3. Scope of the Reaction of Proline Derivatives Substituted in Position 3[a]



[a]Diastereoisomeric ratios determined by NMR of the crude reaction mixture.

Conversion of **12** to the ureas **13a–j** gave an initial set of enantiopure (e.r. > 96:4 by HPLC) starting materials for rearrangement to **14**. Under optimized conditions (2.5 equiv KHMDS, 2.5 equiv LiCl, −78 °C to rt, 20 h), the hydantoins **14a–j** shown in Scheme 3 were obtained.[23]

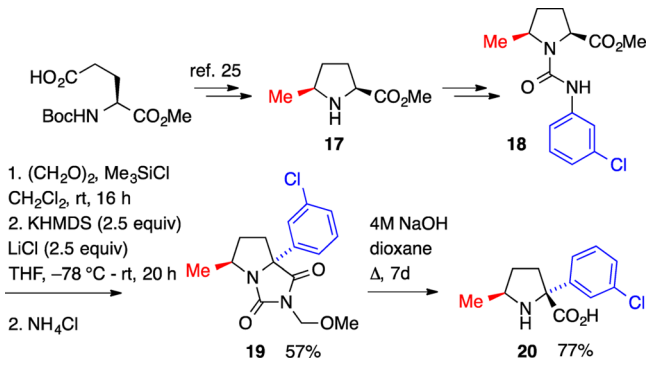
The 3-substituted proline analogues **14a–f** were formed with essentially complete diastereoselectivity. The relative configuration of the major diastereoisomer of **14c** was assigned from its X-ray crystal structure (Figure 1), and the other hydantoins **14** assigned by similarities in their NOESY spectra, the sign of $[\alpha]_D$, and the chemical shift of the quaternary carbon C2 in the ^{13}C NMR (around 80–78 ppm for **14** and around 76–74 ppm for **14′**).

The aryl migrations were successful with hindered and with electron-rich aromatic rings; only the rearrangement of the *p*-methoxyphenyl-substituted of **3g** failed. Hydantoins **14h–j**, which bear electron-withdrawing 2-pyridyl, 4-fluoro and 4-cyano groups, were formed with lower diastereoselectivity. This may be due to the known[24] reversibility of the intramolecular arylation step with electron-deficient rings. This fact, combined with the likelihood cyclization of the minor diastereoisomer to the less hindered *exo* substituted bicyclic system of **14′** is faster than cyclization to the *endo* substituted bicyclic system of **14**, could lead to the observed product ratios that differ from the selectivity of the migration itself.

Hydrolysis of the hydantoin **14a** led not to the desired amino acid but instead to the proline methyl amide **15a** (Scheme 3) which proved resistant to further hydrolysis even under powerfully forcing conditions. A new set of substrates **13k–n** were therefore made with a base-stable but more readily removable N-substituent (Scheme 3). Methoxymethyl ether (MOM) protection has previously been shown to be compatible with related intramolecular arylations,[19a] and MOM-protected ureas **13k–n** rearranged under the same conditions to give hydantoins **14k–n** (Scheme 3) in good yields and with complete diastereoselectivity. The hydrolysis under basic conditions [NaOH (4 M)/Dioxane, reflux, 7 days] of hydantoins **14k** and **14m** resulted in the direct formation of Cα quaternary 3-alkylprolines in enantiomerically enriched form.

The arylation of 5-substituted proline derivatives was explored using enantiopure 5-substituted N-MOM protected urea derivative **18** of 5-methylproline ester **17**, itself formed by a reported method from the *N*-Boc-L-glutamic acid methyl ester (Scheme 4).[25] Urea **18** rearranged to a single diastereoisomer

Scheme 4. Arylation of a 5-Substituted Proline Derivative



of **19**, whose relative configuration was proved by NOESY and COSY spectroscopy. Hydrolysis of the hydantoin product afforded the amino acid **20** in 77% yield.

In summary, prolines substituted in positions 3 or 5 may be Cα-arylated to form bicyclic or tricyclic hydantoin derivatives with high diastereoselectivity (d.r. > 50:1) by rearrangement of their *N*-carboxamido (urea) derivatives. Hydrolysis of the resulting hydantoins leads to enantiopure quaternary proline derivatives of potential utility as scaffolds for medicinal chemistry.

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EXPERIMENTAL SECTION

General Information. All reactions were performed under a nitrogen or argon atmosphere in flame-dried apparatus. All reagents and chemicals were bought from chemical suppliers and used without further purification (unless otherwise stated). Tetrahydrofuran (THF) was distilled under nitrogen from sodium wire using benzophenone as an indicator. Diisopropylamine (DiPA) and dichloromethane (DCM) were obtained by distillation from calcium hydride under nitrogen. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was distilled under reduced pressure from calcium hydride and stored over molecular sieves. Trimethylsilyl chloride (TMSCl) was distilled under reduced pressure from calcium hydride and stored under argon. Triethylamine was stored over KOH. All solvents were removed under vacuum using a rotary evaporator. Pet. Ether indicates fractions of petroleum ether boiling at 40−60 °C. Lithium chloride (LiCl) was dried in the oven and used directly. KHMDS was used as a solution in THF (1.0 M) and NaHMDS was used as a solution in THF (1.0 M) and LDA was used as a solution in THF/heptane/ethylbenzene (2.0 M). They were titrated prior to use with *N*-benzylbenzamide in anhydrous THF.[26] Acetone/dry ice cooling baths were used to obtain −78 °C. Thin layer chromatography (TLC) was performed using commercially available precoated plates. Visualization was by UV light (at 254 nm) or by staining with phosphomolybdic acid or "Seebach" dip (2.50 g phosphomolybdic acid hydrate, 1.00 g cerium(IV) sulfate tetrahydrate, 3.20 mL conc. H_2SO_4, 90.50 mL H_2O) then heating. Flash column chromatography used chromatography grade silica, 60 Å particle size, well 40−63 μm, and compounds were loaded as saturated solutions in the correct solvents. Capillary melting points were determined on a melting point apparatus and are uncorrected. Optical rotations $[\alpha]_\lambda^T$ were recorded on a polarimeter using a cell with a path length of 0.25 dm at 18−22 °C with the solvent and concentration (c) quoted in g/100 mL. Nuclear magnetic resonance (NMR) spectra (1H NMR and 13C NMR) were recorded on either 300, 400, or 500 MHz spectrometers. The residual solvent peak for $CDCl_3$ (δ_H: 7.26 ppm; δ_C: 77.16 ppm), CD_3OD (δ_H: 3.31 ppm; δ_C: 49.00 ppm) were used as internal standards when assigning NMR spectra.[27] Chemical shifts, δ, are quoted in parts per million (ppm) downfield of trimethylsilane. Coupling constants (J) are reported to the nearest 0.1 Hz. The splitting patterns for the spectra assignment are abbreviated to singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), septet (sept.), multiplet (m), broad (br.) and some as a combination of these. Infrared spectra were recorded on a FT-IR spectrometer, with absorption of most relevance quoted as ν in cm^{-1} and the samples were run as solids or evaporated films. High resolution mass spectra (HRMS) were recorded using the mass spectrometer, the QTOF or the LTQ Orbitrap. Enantiomeric and diastereomeric ratios were determined by HPLC with UV detection at 254, 230, and 210 nm. A Daicel Chiralcel OD-H column with hexane:2-propanol (IPA) as the eluent for all separations, unless otherwise stated. The separation was performed at 25 °C.

General Experimental Procedures. *Procedure **1**: Urea Formation Using Isocyanates (**13k−m** and **18**).* The proline derivative (1.0 equiv), anhydrous dichloromethane (0.2 M) and diisopropylethylamine (DIPEA) (1.2 equiv) were combined and stirred for 10 min under nitrogen at room temperature. The isocyanate (1.0 equiv) was added. The reaction mixture was stirred for 5 h at room temperature and quenched with water. The organic layer was removed and the aqueous layer extracted twice with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

*Procedure **2**: Urea Formation Using Carbamoyl Chlorides (**4a−d**, **8a** and **13a−j**).* The proline derivative (1.0 equiv), anhydrous acetonitrile (0.4 M) and triethylamine (1.3 equiv) were combined and stirred for 10 min under nitrogen at room temperature. The carbamoyl chloride (1.3 equiv) was added. The reaction mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was removed and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with 1 M HCl and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

*Procedure **3**: MOM Protection (**8b**, **13k−m** and **19**).* Commercially available TMSCl (6.0 equiv) was added to a mixture of the urea derivative (1.0 equiv) and paraformaldehyde (6.0 equiv) in dichloromethane at 0 °C and stirred overnight at room temperature. The mixture was cooled to 0 °C and methanol (1.5 mL/mmol of urea) was added. The mixture was stirred for 30 min at 0 °C, then poured into saturated aqueous $NaHCO_3$ solution at 0 °C. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

*Procedure **4**: Rearrangement to Hydantoin (Hydroxyproline Derivatives **5a−d** and **5′a-d**).* Anhydrous LiCl (3.5 equiv) and anhydrous THF (0.1 M) were added to the proline ester derivative **4a−d** (1.0 equiv). The reaction mixture was cooled to −78 °C and KHMDS (3.5 equiv) was added dropwise. After stirring at −78 °C for 30 min the reaction mixture was allowed to warm to room temperature and stirred for 4 h, quenched with NH_4Cl and stirred for 15 min. The mixture was extracted three times with ethyl acetate, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

*Procedure **5**: Rearrangement to Hydantoin (**9a−b**, **14a−n** and **14′h-14′j**).* Anhydrous LiCl (2.5 equiv) and anhydrous THF (0.1 M) were added to the proline ester derivative (1.0 equiv). The reaction mixture was cooled to −78 °C. KHMDS (2.5 equiv) was added dropwise to the reaction mixture. After stirring at −78 °C for 30 min the reaction mixture was allowed to warm to room temperature and stirred for 20 h quenched with NH_4Cl and stirred for 15 min. The mixture was extracted three times with ethyl acetate, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

*Procedure **6**: Hydrolysis to Amino Acid.* A solution of hydantoin (1.0 equiv), aqueous NaOH (4.0 M) and dioxane (1.2 M) was stirred at 100 °C for 3 d (for **5a**, **5b**, **5′b**, **5d**, **5′d**, **14a**) and 150 °C for 7 d (**9b**, **14k**, **14m**, **19**). The reaction mixture was cooled to room temperature, extracted twice with diethyl ether, acidified with conc. HCl (pH = 1) and concentrated under reduced pressure. The amino acid was obtained by filtration on acidic Dowex ion exchange column.

Methyl (2*S*,4*R*)-4-hydroxy-1-[methyl(phenyl)carbamoyl]-pyrrolidine-2-carboxylate (4a). Following general procedure 2, *N*-methyl-*N*-phenyl carbamoyl chloride (0.93 g), *trans*-4-hydroxy-L-proline methyl ester (1.10 g), DMAP (one spatula end) and Et_3N (1.77 mL) in dichloroethane (13.8 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the title compound as a solid (1.23 g, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.32−7.17 (4H, m, 4 × CH_{Ar}), 7.12−7.04 (1H, m, CH_{Ar}), 4.68 (1H, dd, J = 10.0 and 7.4, NC*H*), 4.16 (1H, brd, J = 2.9, C*H*OH), 3.70 (3H, s, OCH_3), 3.15 (3H, s, NCH_3), 2.92 (1H, brd, J = 6.9, NCH_AH_B), 2.81 (1H, d, J = 4.1, O*H*), 2.67 (1H, dd, J = 11.5 and 3.7, NCH_AH_B), 2.22−2.11 (1H, m, CH_AH_B), 1.74 (1H, ddd, J = 13.7, 10.2 and 4.1, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.8, 159.6, 145.6, 129.6, 125.6, 125.2, 70.6, 58.7, 57.6, 52.3, 39.6, 37.7. mp 150−151 °C. $[\alpha]_D^{20}$ = +186 (c = 1.00; $CHCl_3$). IR (film, cm^{-1}) ν_{max} = 3364, 3004, 2947 (C−H), 1746 (C═O), 1641 (C═O). HRMS (ESI^+) m/z calcd for $C_{14}H_{18}N_2O_4Na$ $[M + Na]^+$ 301.1164, found 301.1170.

Methyl (2*S*,4*R*)-1-[(3-bromophenyl)(methyl)carbamoyl]-4-hydroxypyrrolidine-2-carboxylate (4b). Following general procedure 2, *N*-methyl-*N*-(3-methoxyphenyl)carbamoyl chloride (200 mg), *trans*-4-hydroxy-L-proline methyl ester (200 mg), DMAP (one spatula end) and Et_3N (321 μL) in dichloroethane (2.50 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the title compound as a solid (212 mg, 63%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.22 (1H, t, J = 8.1, CH_{Ar}), 6.93−6.84 (2H, m, 2 × CH_{Ar}), 6.73−6.62 (1H, m, CH_{Ar}), 4.73 (1H, dd, J = 9.9 and 7.5, NC*H*), 4.21 (1H, brs, C*H*OH), 3.78 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.18 (3H, s, NCH_3), 3.14 (1H, brs, O*H*), 3.02 (1H, brd, J = 11.3,

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NCH_AH_B), 2.79 (1H, dd, J = 11.5 and 3.7, NCH_AH_B), 2.29−2.16 (1H, m, CH_AH_B), 1.79 (1H, ddd, J = 13.7, 10.2 and 4.1, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 160.5, 159.6, 146.8, 130.1, 117.6, 111.1, 111.0, 70.5, 58.7, 57.4, 55.5, 52.3, 39.4, 37.8. mp 104−106 °C. $[\alpha]_D^{20}$ = +119 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{20}N_2O_5Na$ $[M + Na]^+$ 331.1270, found 331.1259.

Methyl (2*S*,4*R*)-4-hydroxy-1-[methyl(naphthalene-1-yl)-carbamoyl]pyrrolidine-2-carboxylate (4c). Following general procedure 2, *N*-ethyl-*N*-(naphthalen-1-yl)carbamoyl chloride (234 mg), *trans*-4-hydroxy-L-proline methyl ester (200 mg), DMAP (one spatula end) and Et_3N (321 μL) in dichloroethane (2.50 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the title compound as as a solid (302 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (1H, d, J = 8.2, CH_{Ar}), 7.90 (1H, d, J = 7.8, CH_{Ar}), 7.83−7.74 (1H, m, CH_{Ar}), 7.63−7.39 (4H, m, 4 × CH_{Ar}), 4.88−4.44 (1H, brs, NC*H*), 4.18−4.00 (1H, brs, C*H*OH), 3.95−3.82 (1H, brs, H_A of AB, NCH_2CH_3), 3.77 (3H, brs, OCH_3), 3.60−3.24 (1H, brs, H_B of AB, NCH_2CH_3), 2.77−2.56 (1H, m, NCH_AH_B), 2.21−1.95 (1H, brs, O*H*), 2.24−2.21 (1H, brs, NCH_AH_B), 1.75 (1H, ddd, J = 13.2, 9.5 and 4.1, CH_AH_B), 1.55−1.42 (1H, m, CH_AH_B), 1.15 (3H, t, J = 7.0, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.8, 159.8, 139.4, 134.8, 130.4, 128.8, 127.4, 127.0, 126.6, 126.5, 125.9, 123.3, 70.8, 58.9, 56.5, 52.3, 46.3, 37.5, 13.3. mp 80−82 °C. $[\alpha]_D^{20}$ = +120 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{19}H_{23}N_2O_4$ $[M + H]^+$ 343.1658, found 343.1673.

Methyl (2*S*,4*R*)-1-[(3-bromophenyl)(methyl)carbamoyl]-4-hydroxypyrrolidine-2-carboxylate (4d). Following general procedure 2, *N*-methyl-*N*-(3-bromophenyl)carbamoyl chloride (249 mg), *trans*-4-hydroxy-L-proline methyl ester (200 mg), DMAP (one spatula end) and Et_3N (321 μL) in dichloroethane (2.50 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the title compound as as a solid (371 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43−7.34 (1H, m, CH_{Ar}), 7.26−7.09 (4H, m, 4 × CH_{Ar}), 4.69 (1H, dd, J = 9.9 and 7.6, NC*H*), 4.20 (1H, brs, C*H*OH), 3.71 (3H, s, OCH_3), 3.14 (3H, s, NCH_3), 2.96 (1H, brd, J = 11.3, NCH_AH_B), 2.83 (1H, brd, J = 3.0, O*H*), 2.74 (1H, dd, J = 11.4 and 3.8, NCH_AH_B), 2.26−2.14 (1H, m, CH_AH_B), 1.78 (1H, ddd, J = 13.6, 10.2 and 4.1, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5, 159.2, 146.9, 130.8, 128.1, 128.0, 123.8, 122.9, 70.5, 58.7, 57.7, 52.4, 39.3, 37.7. mp 100−102 °C. $[\alpha]_D^{20}$ = +126 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{17}N_2O_4BrNa$ $[M + Na]^+$ 379.0269, found 379.0262.

(6*R*,7a*R*)-6-Hydroxy-2-methyl-7a-phenyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (5a). Following general procedure 4, KHMDS (1.26 mL), urea **4a** (100 mg), LiCl (53 mg) and THF (3.60 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 50:50 Pet. Ether:EtOAc), **5a** and **5′a** as solids (63 mg, 70% and 11 mg, 12%, respectively). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60−7.52 (2H, m, 2 × CH_{Ar}), 7.42−7.36 (2H, m, 2 × CH_{Ar}), 7.33−7.28 (1H, m, CH_{Ar}), 4.50 (1H, brs, C*H*OH), 4.09 (1H, dd, J = 12.7 and 1.1, NCH_AH_B), 3.21 (1H, dd, J = 12.7 and 2.7, NCH_AH_B), 2.96 (3H, s, NCH_3), 2.87 (1H, brs, O*H*), 2.78 (1H, dt, J = 14.1 and 1.5, CH_AH_B), 2.30 (1H, dd, J = 14.1 and 4.4, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.3, 163.6, 139.7, 129.0, 128.4, 125.3, 73.5, 73.4, 56.0, 45.6, 25.7. mp 149−150 °C. $[\alpha]_D^{20}$ = +57 (c = 1.00; $CHCl_3$). IR (film, cm^{-1}) ν_{max} = 3457 (OH), 3058, 2935 (C−H), 1772, 1702 (C═O). HRMS (ESI$^+$) m/z calcd for $C_{13}H_{15}N_2O_3$ $[M + H]^+$ 247.1083, found 247.1084.

(6*R*,7a*R*)-6-Hydroxy-2-methyl-7a-phenyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (5′a). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66−7.57 (2H, m, 2 × CH_{Ar}), 7.47−7.29 (3H, m, 3 × CH_{Ar}), 4.65 (1H, brs, C*H*OH), 4.24 (1H, dd, J = 12.7 and 6.4, NCH_AH_B), 3.33 (1H, dd, J = 12.8 and 2.6, NCH_AH_B), 2.97 (3H, s, NCH_3), 2.57 (1H, dd, J = 12.8 and 1.1, CH_AH_B), 2.42 (1H, dd, J = 13.8 and 6.4, CH_AH_B), 1.55 (1H, brd, J = 5.5, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.3, 160.1, 137.8, 129.1, 128.7, 125.8, 74.0, 73.8, 54.5, 45.4, 25.5. HRMS (ESI$^+$) m/z calcd for $C_{13}H_{14}N_2O_3Na$ $[M + Na]^+$ 269.0902, found 269.0913.

(6*R*,7a*S*)-6-Hydroxy-7a-(3-methoxyphenyl)-2-methyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (5b). Following general procedure 4, KHMDS (1.14 mL), urea **4b** (100 mg), LiCl (48 mg) and THF (3.24 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 50:50 Pet. Ether:EtOAc), **5b** and **5′b** as oils (51 mg, 57% and 9 mg, 10%, respectively). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33−7.24 (1H, m, CH_{Ar}), 7.19−7.07 (2H, m, 2 × CH_{Ar}), 6.88−6.81 (1H, m, CH_{Ar}), 4.50 (1H, brs, C*H*OH), 4.10 (1H, brd, J = 12.7, NCH_AH_B), 3.81 (3H, s, OCH_3), 3.21 (1H, dd, J = 12.7 and 2.5, NCH_AH_B), 2.96 (3H, s, NCH_3), 2.79−2.73 (1H, m, CH_AH_B), 2.66 (1H, brs, O*H*), 2.30 (1H, dd, J = 14.2 and 4.3, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.1, 163.5, 160.0, 141.3, 130.1, 117.6, 113.8, 111.0, 73.5, 73.3, 56.0, 55.5, 46.6, 25.7. $[\alpha]_D^{20}$ = +117 (c = 1.00; $CHCl_3$). IR (film, cm^{-1}) ν_{max} = 3472 (OH), 2949 (C−H), 1772, 1705 (C═O), 1289, 1038 (C−O). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{16}N_2O_4Na$ $[M + Na]^+$ 299.1008, found 299.1011.

(6*R*,7a*R*)-6-Hydroxy-7a-(3-methoxyphenyl)-2-methyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (5′b). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (1H, t, J = 7.9, CH_{Ar}), 7.23−7.09 (2H, m, 2 × CH_{Ar}), 6.93−6.84 (1H, m, CH_{Ar}), 4.70−4.58 (1H, m, C*H*OH), 4.23 (1H, dd, J = 12.8 and 6.4, NCH_AH_B), 3.83 (3H, s, OCH_3), 3.33 (1H, dd, J = 12.8 and 2.6, NCH_AH_B), 2.97 (3H, s, NCH_3), 2.58 (1H, dd, J = 13.8 and 1.5, CH_AH_B), 2.39 (1H, dd, J = 13.8 and 6.3, CH_AH_B), 1.50 (1H, d, J = 6.9, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 160.2, 160.0, 139.3, 130.3, 118.1, 114.1, 111.7, 74.1, 73.8, 55.5, 54.5, 45.3, 25.5. $[\alpha]_D^{20}$ = −122 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{16}N_2O_4Na$ $[M + Na]^+$ 299.1008, found 299.1004.

(6*R*,7a*R*)-6-Hydroxy-2-ethyl-7a-(naphthalene-1-yl)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (5c) and (6*R*,7a*S*)-6-Hydroxy-2-ethyl-7a-(naphthalene-1-yl)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (5′c). Following general procedure 4, KHMDS (1.02 mL), urea **4c** (100 mg), LiCl (43 mg) and THF (2.92 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 50:50 Pet. Ether:EtOAc), a mixture of **5c** and **5′c** as an oil (77 mg, 89%; d.r. 2:1). Maj ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65−8.54 (1H, m, CH_{Ar}), 7.92−7.76 (3H, m, 3 × CH_{Ar}), 7.64−7.57 (1H, m, CH_{Ar}), 7.55−7.48 (1H, m, CH_{Ar}), 7.47−7.37 (1H, m, CH_{Ar}), 4.44 (1H, brs, C*H*OH), 4.15 (1H, dd, J = 12.9 and 1.7, NCH_AH_B), 3.62−3.43 (2H, m, NCH_2), 3.17−3.05 (2H, m, NCH_AH_B and CH_AH_B), 2.55 (1H, dd, J = 14.3 and 4.5, CH_AH_B), 2.46 (1H, brs, O*H*), 1.20−1.11 (3H, m, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.2, 162.5, 135.8, 135.3, 130.3, 129.8, 128.9, 127.6, 126.0, 125.1, 122.7, 74.2, 73.4, 54.3, 46.4, 34.6, 13.0. Min ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65−8.54 (1H, m, CH_{Ar}), 7.92−7.76 (3H, m, 3 × CH_{Ar}), 7.64−7.57 (1H, m, CH_{Ar}), 7.55−7.48 (1H, m, CH_{Ar}), 7.47−7.37 (1H, m, CH_{Ar}), 4.65−4.55 (1H, brs, C*H*OH), 4.32 (1H, dd, J = 12.7 and 6.8, NCH_AH_B), 3.62−3.43 (2H, m, NCH_2), 3.25 (1H, dd, J = 12.6 and 4.4, NCH_AH_B), 2.94 (1H, dd, J = 13.9 and 3.2, CH_AH_B), 2.81 (1H, dd, J = 13.8 and 7.2, CH_AH_B), 1.74 (1H, brs, O*H*), 1.20−1.11 (3H, m, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 159.1, 135.8, 134.2, 130.4, 130.1, 129.0, 127.7, 126.1, 126.0, 125.2, 123.5, 74.5, 73.2, 52.4, 45.0, 34.5, 13.3. HRMS (ESI$^+$) m/z calcd for $C_{18}H_{18}N_2O_3Na$ $[M + Na]^+$ 333.1215, found 333.1215.

(6*R*,7a*S*)-7a-(3-Bromophenyl)-6-hydroxy-2-methylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (5d). Following general procedure 4, KHMDS (0.98 mL), urea **4d** (100 mg), LiCl (42 mg) and THF (2.80 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 50:50 Pet. Ether:EtOAc), **5d** and **5′d** as an oil (61 mg, 67% and 24 mg, 26%, respectively). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (1H, m, CH_{Ar}), 7.55−7.41 (2H, m, 2 × CH_{Ar}), 7.31−7.20 (1H, m, CH_{Ar}), 4.52 (1H, brs, C*H*OH), 4.11 (1H, brd, J = 12.7, NCH_AH_B), 3.20 (1H, dd, J = 12.7 and 2.5, NCH_AH_B), 2.97 (3H, s, NCH_3), 2.77 (1H, d, J = 14.2, CH_AH_B), 2.47 (1H, brs, O*H*), 2.25 (1H, dd, J = 14.2 and 4.3, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.7, 163.5, 142.0, 131.6, 130.6, 128.3, 124.3, 123.1, 73.5, 72.9, 56.2, 45.7, 25.8. $[\alpha]_D^{20}$ = +146 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{13}H_{14}N_2O_3Br$ $[M + H]^+$ 325.0188, found 325.0188.

(6*R*,7a*R*)-7a-(3-Bromophenyl)-6-hydroxy-2-methylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (5′d). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.714 (1H, m, CH_{Ar}), 7.57−7.42 (2H, m, 2 ×

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CH_{Ar}), 7.34−7.23 (1H, m, CH_{Ar}), 4.66 (1H, brs, CHOH), 4.21 (1H, dd, J = 12.8 and 6.3, NCH_AH_B), 3.31 (1H, dd, J = 12.7 and 2.7, NCH_AH_B), 2.96 (3H, s, NCH_3), 2.51 (1H, dd, J = 13.8 and 1.6, CH_AH_B), 2.40 (1H, dd, J = 13.8 and 6.2, CH_AH_B), 1.63 (1H, brs, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.9, 160.0, 140.3, 131.7, 130.5, 128.8, 124.7, 123.1, 73.7, 73.4, 54.5, 45.3, 25.6. $[\alpha]_D^{20}$ = −140 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{13}H_{14}N_2O_3Br$ $[M + H]^+$ 325.0188, found 325.0176.

(2*S*,4*R*)-4-Hydroxy-2-phenylpyrrolidine-2-carboxylic acid (6a). Following general procedure 6, hydantoin **5a** (40 mg) gave **6a** (30 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54−7.49 (2H, m, 2 × CH_{Ar}), 7.45−7.34 (3H, m, 3 × CH_{Ar}), 4.63−4.65 (1H, m, CHOH), 3.51−3.39 (2H, m, NCH_2), 3.05−2.96 (1H, m, CH_AH_B), 2.63 (1H, dd, J = 13.8 and 5.0, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.9, 139.6, 129.9, 129.7, 127.5, 76.4, 70.7, 54.4, 43.6. $[\alpha]_D^{20}$ = +73 (c = 1.00; MeOH). HRMS (ESI$^+$) m/z calcd for $C_{11}H_{13}N_1O_3Na$ $[M + Na]^+$ 230.0793, found 230.0803.

(2*S*,4*R*)-4-Hydroxy-2-(3-methoxyphenyl)pyrrolidine-2-carboxylic acid (6b). Following general procedure 6, hydantoin **5b** (37 mg) gave **6b** (29 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (1H, t, J = 8.0, CH_{Ar}), 7.11−7.03 (2H, m, 2 × CH_{Ar}), 6.98−6.90 (1H, m, CH_{Ar}), 4.60 (1H, brs, CHOH), 3.81 (3H, s, OCH_3), 3.57−3.39 (2H, m, NCH_2), 2.99 (1H, d, J = 13.7, CH_AH_B), 2.61 (1H, dd, J = 13.8 and 5.0, CH_AH_B). ^{13}C NMR (100 MHz, CD_3OD) δ = 174.8, 161.4, 140.7, 131.0, 119.5, 115.1, 113.5, 76.4, 70.7, 55.8, 55.4, 43.4. $[\alpha]_D^{20}$ = +66 (c = 1.00; MeOH). HRMS (ESI$^+$) m/z calcd for $C_{12}H_{15}N_1O_4Na$ $[M + Na]^+$ 260.0899, found 260.0902.

(2*R*,4*R*)-4-Hydroxy-2-(3-methoxyphenyl)pyrrolidine-2-carboxylic acid (6′b). Following general procedure 6, hydantoin **5′b** (7 mg) gave **6′b** (5 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (1H, t, J = 8.0, CH_{Ar}), 7.19−7.08 (2H, m, 2 × CH_{Ar}), 6.98−6.86 (1H, m, CH_{Ar}), 4.63−4.55 (1H, m, CHOH), 3.83 (3H, s, OCH_3), 3.53 (1H, dd, J = 11.8 and 6.3, NCH_AH_B), 3.15 (1H, dd, J = 13.7 and 6.2, CH_AH_B), 3.12 (1H, dd, J = 10.9 and 4.1, NCH_AH_B), 2.40 (1H, dd, J = 13.4 and 5.8, CH_AH_B). ^{13}C NMR (100 MHz, CD_3OD) δ = 175.2, 161.3, 141.4, 130.7, 119.7, 114.9, 113.5, 76.0, 70.2, 55.8, 53.4, 43.6. $[\alpha]_D^{20}$ = −37 (c = 1.00; MeOH). HRMS (ESI$^+$) m/z calcd for $C_{12}H_{16}N_1O_4$ $[M + H]^+$ 238.1079, found 238.1090.

(2*S*,4*R*)-2-(3-Bromophenyl)-4-hydroxypyrrolidine-2-carboxylic acid (6d). Following general procedure 6, hydantoin **5d** (42 mg) gave **6d** (33 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (1H, brs, CH_{Ar}), 7.57−7.51 (1H, m, CH_{Ar}), 7.47−7.44 (1H, m, CH_{Ar}), 7.33 (1H, t, J = 7.9, CH_{Ar}), 4.57 (1H, brs, CHOH), 3.51−3.38 (2H, m, NCH_2), 2.99 (1H, d, J = 13.7, CH_AH_B), 2.55 (1H, dd, J = 13.8 and 5.0, CH_AH_B). ^{13}C NMR (100 MHz, CD_3OD) δ = 174.4, 142.3, 132.7, 131.6, 130.7, 126.4, 123.7, 75.9, 70.7, 54.5, 43.7. $[\alpha]_D^{20}$ = +59 (c = 1.00; MeOH). HRMS (ESI$^+$) m/z calcd for $C_{11}H_{12}N_1O_3NaBr$ $[M + Na]^+$ 307.9898, found 307.9909.

(2*R*,4*R*)-2-(3-Bromophenyl)-4-hydroxypyrrolidine-2-carboxylic acid (6′d). Following general procedure 6, hydantoin **5′d** (21 mg) gave **6′d** (17 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (1H, brs, CH_{Ar}), 7.55−7.46 (2H, m, 2 × CH_{Ar}), 7.30 (1H, t, J = 7.9, CH_{Ar}), 4.58−4.49 (1H, m, CHOH), 3.46 (1H, dd, J = 11.6 and 6.1, NCH_AH_B), 3.11 (1H, dd, J = 13.5 and 6.19, CH_AH_B), 3.06 (1H, dd, J = 11.7 and 3.9, NCH_AH_B), 2.30 (1H, dd, J = 13.4 and 5.5, CH_AH_B). ^{13}C NMR (100 MHz, CD_3OD) δ = 175.7, 143.8, 132.1, 131.3, 130.8, 126.5, 123.4, 75.3, 70.5, 53.8, 44.1. $[\alpha]_D^{20}$ = −68 (c = 1.00; MeOH). HRMS (ESI$^+$) m/z calcd for $C_{11}H_{12}N_1O_3Br$ $[M - H]^+$ 283.9922, found 283.9909.

Methyl (2*S*,3a*S*,7a*S*)-1-[methyl(phenyl)carbamoyl]-octahydro-1*H*-indole-2-carboxylate (8a). Following general procedure 2, *N*-methyl-*N*-(2-methylphenyl)carbamoyl chloride (200 mg), perhydroindoline ester **7** (200 mg) and Et_3N (292 μL) in acetonitrile (2.30 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the title compound as an oil (283 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32−7.18 (2H, m, 2 × CH_{Ar}), 7.13−6.99 (3H, m, 3 × CH_{Ar}), 4.30 (1H, t, J = 7.4, NCH), 3.66 (3H, s, OCH_3), 3.34 (1H, dt, J = 11.2 and 6.3, NCH), 3.04 (3H, s, NCH_3), 2.12−1.99 (1H, m, CH), 1.96−1.78 (1H, m, CH_2), 1.62−1.48 (1H, m, CH_AH_B), 1.47−1.32 (1H, m, CH_2), 1.30−1.20 (1H, m, CH_AH_B), 1.18−0.98 (3H, m, CH_AH_B and CH_2), 0.89−0.63 (1H, m, CH_AH_B). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 160.1, 146.8, 129.5, 125.4, 125.1, 59.8, 59.3, 52.1, 40.3, 37.4, 30.8, 26.4, 25.8, 24.0, 20.2. $[\alpha]_D^{20}$ = +60.8 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{18}H_{24}N_2O_3Na$ $[M + Na]^+$ 339.1685, found 339.1686.

Methyl (2*S*,3a*S*,7a*S*)-1-[(methoxymethyl)(phenyl)-carbamoyl]-octahydro-1*H*-indole-2-carboxylate (8b). Following general procedure 1, phenyl isocyanate (99 μL), perhydroindoline ester **7** (200 mg) and DIPEA (186 μL) in dichloromethane (4.55 mL) gave a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the urea as an oil (275 mg, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42−7.34 (2H, m, 2 × CH_{Ar}), 7.30−7.21 (2H, m, 2 × CH_{Ar}), 7.06−6.93 (1H, m, CH_{Ar}), 6.43 (1H, brs, NH), 4.46 (1H, dd, J = 9.5 and 8.0, NCH), 3.92−3.80 (1H, m, NCH), 3.78 (3H, s, OCH_3), 2.50−2.38 (1H, m, CH), 2.24−2.01 (3H, m, CH_AH_B and CH_2), 1.85−1.48 (5H, m, CH_AH_B, CH_2 and CH_2), 1.43−1.36 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.3, 153.7, 139.0, 129.0, 123.1, 119.7, 59.4, 57.5, 52.6, 37.5, 33.6, 28.5, 26.0, 23.8, 20.5. mp 108−109 °C. $[\alpha]_D^{20}$ = −68 (c = 1.00; $CHCl_3$). IR (film, cm^{-1}) ν_{max} = 2925, 2853 (C−H), 1749 (C═O), 1647 (C═O). HRMS (ESI$^+$) m/z calcd for $C_{17}H_{22}N_2O_3Na$ $[M+ Na]^+$ 325.1528, found 325.1537.

Following general procedure 3, TMSCl (207 μL), urea (82 mg) and paraformaldehyde (49 mg) in dichloromethane (1.36 mL) gave the title compound as an oil (78 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42−7.10 (5H, m, 5 × CH_{Ar}), 5.05 (1H, d, J = 10.4, H_A of AB, NCH_2O), 4.86 (1H, d, J = 10.4, H_B of AB, NCH_2O), 4.46−4.24 (1H, m, NCH), 3.73 (3H, s, OCH_3), 3.47−3.26 (4H, m, NCH and OCH_3), 2.21−1.82 (3H, m, CH_2 and CH), 2.24−2.01 (7H, m, CH_AH_B, CH_2, CH_2 and CH_2), 0.93−0.63 (1H, m, CH_AH_B), 1.43−1.36 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.9, 158.8, 144.1, 129.5, 125.9, 125.2, 82.7, 59.9, 59.5, 56.3, 52.2, 37.3, 30.8, 26.4, 25.8, 24.0, 20.1. $[\alpha]_D^{20}$ = +11.6 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{19}H_{27}N_2O_4$ $[M + H]^+$ 347.1971, found 347.1986.

(4a*S*,8a*S*,9a*R*)-2-Methyl-9a-phenyl-decahydro-1*H*-imidazolidino[1,5-*a*]indole-1,3-dione (9a). Following general procedure 5, KHMDS (1.31 mL), urea **8a** (166 mg), LiCl (56 mg) and THF (5.25 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc), **9a** as an oil (123 mg, 82%).^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65−7.57 (2H, m, 2 × CH_{Ar}), 7.41−7.29 (3H, m, 3 × CH_{Ar}), 3.92−3.82 (1H, m, NCH), 2.91 (3H, s, NCH_3), 2.71−2.60 (1H, m, CH_AH_B), 2.44−2.27 (2H, m, CH_AH_B and CH_AH_B), 2.18−2.05 (1H, m, CH_AH_B), 1.79−1.41 (4H, m, 2 × CH_2), 1.35−1.12 (3H, m, CH_2 and CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6, 158.0, 140.0, 128.6, 128.3, 125.7, 74.2, 57.2, 38.6, 37.5, 26.2, 26.2, 25.2, 23.2, 21.4. $[\alpha]_D^{20}$ = −71 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{17}H_{20}N_2O_2Na$ $[M + Na]^+$ 307.1422, found 307.1425.

(4a*S*,8a*S*,9a*R*)-2-(Methoxymethyl)-9a-phenyldecahydro-1*H*-imidazolidino[1,5-*a*]indole-1,3-dione (9b). Following general procedure 5, KHMDS (0.40 mL), urea **8b** (55 mg), LiCl (17 mg) and THF (1.60 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **9b** as an oil (24 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66−7.54 (2H, m, 2 × CH_{Ar}), 7.43−7.28 (3H, m, 3 × CH_{Ar}), 4.82 (1H, d, J = 10.6, H_A of AB, NCH_2O), 4.78 (1H, d, J = 10.6, H_B of AB, NCH_2O), 3.95−3.83 (1H, m, NCH), 3.27 (3H, s, OCH_3), 2.73−2.60 (1H, m, CH_AH_B), 2.46−2.32 (2H, m, CH_AH_B and CH_AH_B), 2.23−2.09 (1H, m, CH_AH_B), 1.79−1.40 (4H, m, 2 × CH_2), 1.38−1.13 (3H, m, CH_2 and CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.3, 157.0, 139.7, 128.7, 128.5, 125.6, 74.1, 69.9, 57.3, 57.2, 38.5, 37.6, 26.2, 26.2, 23.1, 21.4. $[\alpha]_D^{20}$ = −74 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{18}H_{22}N_2O_3Na$ $[M + Na]^+$ 337.1528, found 337.1535.

(2*R*,3a*S*,7a*S*)-2-Phenyl-octahydro-1*H*-indole-2-carboxylic acid (10). Following general procedure 6, hydantoin **9b** (28 mg) gave **10** (15 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57−7.49 (2H, m, 2 × CH_{Ar}), 7.47−7.33 (3H, m, 3 × CH_{Ar}), 3.71 (1H, q, J = , NCH), 2.79 (1H, dd, J = 13.8 and 7.1, CH_AH_B), 2.71 (1H, dd, J = 13.7 and 6.3, CH_AH_B), 2.49 (1H, sex, J = 6.4, CH), 1.94−1.81 (2H, m, CH_2),

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1.75−1.57 (4H, m, 2 × CH_2), 1.55−1.33 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.5, 140.4, 130.0, 129.7, 127.6, 75.9, 60.7, 39.1, 26.2, 26.0, 23.0, 22.3. $[\alpha]_D^{20}$ = −16 (c = 1.00; MeOH). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{20}N_1O_2$ $[M + H]^+$ 246.1494, found 246.1489.

3-Methyl proline methyl ester **12a** and 3-methyl proline methyl ester **12b** were synthesized by intramolecular carbozincation[22] followed by hydrogenation.[28]

Methyl (2*R*,3*S*)-3-methyl-1-[methyl(phenyl)carbamoyl]-pyrrolidine-2-carboxylate (13a). Following general procedure 2, *N*-methyl-*N*-phenylcarbamoyl chloride (585 mg), 3-methyl proline methyl ester **12a** (380 mg) and Et_3N (481 μL) in acetonitrile (6.60 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 60:40 Pet. Ether:EtOAc) to yield the title compound as a white solid (530 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38−7.30 (2H, m, 2 × CH_{Ar}), 7.28−7.22 (2H, m, 2 × CH_{Ar}), 7.18−7.11 (1H, m, CH_{Ar}), 4.42 (1H, d, J = 7.5, $C_\delta H$), 3.75 (3H, s, OCH_3), 3.22 (3H, s, NCH_3), 2.95−2.86 (1H, m, $C_\alpha H_A H_B$), 2.81−2.70 (1H, m, $C_\alpha H_A H_B$), 2.40 (1H, hept, J = 7.0, $C_\gamma H$), 1.78 (1H, ddt, J = 12.3, 7.4 and 6.1, $C_\beta H_A H_B$), 1.77 (1H, dtd, J = 12.1, 7.6 and 6.9, $C_\beta H_A H_B$), 0.87 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 159.6, 146.0, 129.5, 125.7, 125.2, 64.7, 51.8, 47.9, 39.8, 35.1, 32.5, 14.9. mp 88−90 °C. $[\alpha]_D^{20}$ = −56 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{21}N_2O_3$ $[M + H]^+$ 277.1547, found 277.1551.

Methyl (2*R*,3*S*)-3-methyl-1-[methyl(2-methylphenyl)-carbamoyl]pyrrolidine-2-carboxylate (13b). Following general procedure 2, *N*-methyl-*N*-(2-methylphenyl)carbamoyl chloride (217 mg), 3-methyl proline methyl ester **12a** (130 mg) and Et_3N (165 μL) in acetonitrile (2.30 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 50:50 Pet. Ether:EtOAc) to yield the title compound as an oil (231 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24−7.11 (4H, m, 4 × CH_{Ar}), 4.36 (1H, d, J = 7.6, $C_\delta H$), 3.73 (3H, s, OCH_3), 3.08 (3H, s, NCH_3), 3.08−2.86 (1H, m, $C_\alpha H_A H_B$), 2.76−2.56 (1H, m, $C_\alpha H_A H_B$), 2.38−2.24 (4H, m, $ArCH_3$ and $C_\gamma H$), 1.78−1.68 (1H, m, $C_\beta H_A H_B$), 1.65−1.53 (1H, m, $C_\beta H_A H_B$), 0.87 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 159.7, 144.3, 135.4, 131.3, 128.0, 127.3, 126.9, 64.9, 51.6, 47.3, 38.9, 35.1, 32.5, 17.9, 14.7. $[\alpha]_D^{20}$ = −42.3 (c = 1.00; $CHCl_3$). IR (film, cm^{-1}) ν_{max} = 2964, 2883, 1741, 1641. HRMS (ESI$^+$) m/z calcd for $C_{16}H_{23}N_2O_3$ $[M + H]^+$ 291.1703, found 291.1701.

Methyl (2*R*,3*S*)-3-methyl-1-[methyl(naphthalene-1-yl)-carbamoyl]pyrrolidine-2-carboxylate (13c). Following general procedure 2, *N*-ethyl-*N*-(naphthalen-1-yl)carbamoyl chloride (318 mg), 3-methyl proline methyl ester **12a** (150 mg) and Et_3N (101 μL) in acetonitrile (2.62 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the title compound as an oil (295 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21−7.93 (1H, m, CH_{Ar}), 7.89 (1H, m, CH_{Ar}), 7.78 (1H, d, J = 8.4, CH_{Ar}), 7.63−7.49 (2H, m, 2 × CH_{Ar}), 7.48−7.29 (2H, m, 2 × CH_{Ar}), 4.65−4.18 (1H, m, $C_\delta H$), 4.08−3.20 (2H, m, CH_2CH_3), 3.73 (3H, s, OCH_3), 3.02−2.45 (1H, m, $C_\alpha H_A H_B C_\gamma H$), 2.39−2.11 (2H, m, $C_\alpha H_A H_B$ and $C_\gamma H$), 1.73−1.39 (2H, m, $C_\beta H_2$), 1.14 (3H, t, J = 7.0, CH_3CH_2), 0.81 (3H, d, J = 6.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.7, 159.7, 139.6, 134.8, 130.7, 128.6, 127.3, 126.8, 126.4, 126.2, 125.7, 123.4, 64.9, 51.6, 47.4, 46.5, 35.0, 32.3, 14.5, 13.3. $[\alpha]_D^{20}$ = +11.2 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{20}H_{24}N_2O_3Na_1$ $[M + Na]^+$ 363.1679, found 363.1686.

Methyl (2*R*,3*S*)-1[(3-chlorophenyl)(methyl)carbamoyl]-3-methylpyrrolidine-2-carboxylate (13d). Following general procedure 2, *N*-methyl-*N*-(3-chlorophenyl)carbamoyl chloride (241 mg), 3-methyl proline methyl ester **12a** (130 mg) and Et_3N (165 μL) in acetonitrile (2.30 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 60:40 Pet. Ether:EtOAc) to yield the title compound as an oil (220 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30−7.23 (2H, m, 2 × CH_{Ar}), 7.20−7.14 (1H, m, CH_{Ar}), 7.14−7.09 (1H, m, CH_{Ar}), 4.44 (1H, d, J = 7.5, $C_\delta H$), 3.75 (3H, s, OCH_3), 3.21 (3H, s, NCH_3), 3.01−2.91 (1H, m, $C_\alpha H_A H_B$), 2.89−2.78 (1H, m, $C_\alpha H_A H_B$), 2.45 (1H, hept, J = 6.9, $C_\gamma H$), 1.83 (1H, ddt, J = 12.1, 7.4 and 6.2, $C_\beta H_A H_B$), 1.66−1.54 (1H, m, $C_\beta H_A H_B$), 0.89 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 159.3, 147.3, 135.0, 130.5, 125.3, 125.1, 123.3, 64.7, 51.8, 47.9, 39.5, 35.1, 32.5, 14.9. $[\alpha]_D^{20}$ = −48.4 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}N_2O_3ClNa$ $[M + Na]^+$ 333.0982, found 333.0975.

Methyl (2*R*,3*S*)-1[(3-bromophenyl)(methyl)carbamoyl]-3-methylpyrrolidine-2-carboxylate (13e). Following general procedure 2, *N*-methyl-*N*-(3-bromophenyl)carbamoyl chloride (181 mg), 3-methyl proline methyl ester **12a** (80 mg) and Et_3N (101 μL) in acetonitrile (1.4 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the title compound as an oil (190 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45−7.39 (2H, m, 2 × CH_{Ar}), 7.29−7.25 (1H, m, CH_{Ar}), 7.23−7.19 (2H, m, 2 × CH_{Ar}), 4.45 (1H, d, J = 7.4, $C_\delta H$), 3.76 (3H, s, OCH_3), 3.21 (3H, s, NCH_3), 3.01−2.90 (1H, m, $C_\alpha H_A H_B$), 2.89−2.80 (1H, m, $C_\alpha H_A H_B$), 2.46 (1H, hept, J = 6.9, $C_\gamma H$), 1.88−1.79 (1H, m, $C_\beta H_A H_B$), 1.65−1.54 (1H, m, $C_\beta H_A H_B$), 0.89 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 159.2, 147.4, 130.7, 128.2, 128.0, 123.7, 122.9, 64.7, 51.9, 47.9, 39.5, 35.1, 32.5, 14.9. $[\alpha]_D^{20}$ = −46.8 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}N_2O_3BrNa$ $[M + Na]^+$ 377.0477, found 377.0485.

Methyl (2*R*,3*S*)-1[(3-methoxyphenyl)(methyl)carbamoyl]-3-methylpyrrolidine-2-carboxylate (13f). Following general procedure 2, *N*-methyl-*N*-(3-methoxyphenyl)carbamoyl chloride (236 mg), proline (130 mg) and Et_3N (165 μL) in acetonitrile (2.30 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 60:40 Pet. Ether:EtOAc) to yield the title compound as an oil (205 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25−7.19 (1H, m, CH_{Ar}), 6.88−6.80 (2H, m, 2 × CH_{Ar}), 6.73−6.66 (1H, m, CH_{Ar}), 4.44 (1H, d, J = 7.5, $C_\delta H$), 3.80 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.21 (3H, s, NCH_3), 3.02−2.91 (1H, m, $C_\alpha H_A H_B$), 2.89−2.79 (1H, m, $C_\alpha H_A H_B$), 2.41 (1H, hept, J = 7.1, $C_\gamma H$), 1.80 (1H, ddt, J = 12.2, 7.5 and 6.1, $C_\beta H_A H_B$), 1.62−1.51 (1H, m, $C_\beta H_A H_B$), 0.87 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 160.6, 159.6, 147.3, 130.1, 117.7, 111.0, 64.6, 55.5, 51.8, 47.7, 39.7, 35.1, 32.5, 14.9. $[\alpha]_D^{20}$ = −51.2 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{16}H_{22}N_2O_4Na$ $[M + Na]^+$ 329.1477, found 329.1476.

Methyl (2*R*,3*S*)-1[(4-methoxyphenyl)(methyl)carbamoyl]-3-methylpyrrolidine-2-carboxylate (13g). Following general procedure 2, *N*-methyl-*N*-(4-methoxyphenyl)carbamoyl chloride (188 mg), 3-methyl proline methyl ester **12a** (104 mg,) and Et_3N (132 μL) in acetonitrile (1.82 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 40:60 Pet. Ether:EtOAc) to yield the title compound as an oil (156 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20−7.12 (2H, m, 2 × CH_{Ar}), 6.90−6.83 (2H, m, 2 × CH_{Ar}), 4.40 (1H, d, J = 7.5, $C_\delta H$), 3.80 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 2.95−2.83 (1H, m, $C_\alpha H_A H_B$), 2.79−2.67 (1H, m, $C_\alpha H_A H_B$), 2.38 (1H, hept, J = 7.0, $C_\gamma H$), 1.78 (1H, ddt, J = 12.4, 7.3 and 6.2, $C_\beta H_A H_B$), 1.77 (1H, dtd, J = 12.3, 7.7 and 7.1, $C_\beta H_A H_B$), 0.86 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5, 159.8, 157.2, 139.0, 127.3, 114.6, 64.7, 55.6, 51.8, 47.9, 40.3, 35.0, 32.5, 14.8. $[\alpha]_D^{20}$ = −30 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{16}H_{22}N_2O_4Na_1$ $[M + Na]^+$ 329.1477, found 329.1476.

Methyl (2*R*,3*S*)-3-methyl-1-[methyl(pyridin-2-yl)carbamoyl]-pyrrolidine-2-carboxylate (13h). Following general procedure 2, *N*-methyl-*N*-(pyridin-2-yl)carbamoyl chloride (232 mg), 3-methyl proline methyl ester **12a** (150 mg) and Et_3N (101 μL) in acetonitrile (2.62 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 20:80 Pet. Ether:EtOAc) to yield the title compound as an oil (90 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (1H, dd, J = 4.9 and 1.1, CH_{Ar}), 6.62 (1H, td, J = 8.3 and 2.0, CH_{Ar}), 7.32 (1H, brd, J = 8.2, CH_{Ar}), 7.32 (1H, ddd, J = 7.2, 5.0 and 0.7, CH_{Ar}), 4.54 (1H, d, J = 7.5, $C_\delta H$), 3.76 (3H, s, OCH_3), 3.35 (3H, s, NCH_3), 3.21−3.01 (2H, m, $C_\alpha H_2$), 2.54 (1H, hept, J = 7.0, $C_\gamma H$), 1.90 (1H, ddt, J = 12.2, 7.1 and 6.4,

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$C_\beta H_A H_B$), 1.64 (1H, dq, J = 13.8, 7.1 and 7.1, $C_\beta H_A H_B$), 0.93 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.0, 158.9, 157.2, 148.6, 137.9, 118.3, 116.4, 64.4, 51.9, 47.6, 36.0, 35.3, 32.4, 15.0. $[\alpha]_D^{20}$ = −56 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{20}N_3O_3$ $[M + H]^+$ 278.1499, found 278.1491.

Methyl (2*R*,3*S*)-1[(4-fluorophenyl)(methyl)carbamoyl]-3-methylpyrrolidine-2-carboxylate (13i). Following general procedure 2, *N*-methyl-*N*-(4-fluorophenyl)carbamoyl chloride (238 mg), 3-methyl proline methyl ester **12a** (139 mg) and Et_3N (176 μL) in acetonitrile (2.43 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 50:50 Pet. Ether:EtOAc) **13i** as a white solid (210 mg, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25−7.19 (2H, m, 2 × CH_{Ar}), 7.09−6.98 (2H, m, 2 × CH_{Ar}), 4.42 (1H, d, J = 7.4, $C_\delta H$), 3.74 (3H, s, OCH_3), 3.18 (3H, s, NCH_3), 2.93−2.83 (1H, m, $C_\alpha H_A H_B$), 2.82−2.73 (1H, m, $C_\alpha H_A H_B$), 2.41 (1H, hept, J = 7.0, $C_\gamma H$), 1.83−1.73 (1H, ddt, J = 12.2, 7.1 and 6.2, $C_\beta H_A H_B$), 1.77 (1H, dq, J = 12.2 and 7.3, $C_\beta H_A H_B$), 0.86 (3H, d, J = 7.0, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 160.2 (d, $^1J_{C-F}$ = 245.2), 159.7, 142.1 (d, $^4J_{C-F}$ = 2.9), 127.5 (d, $^3J_{C-F}$ = 8.3), 116.3 (d, $^2J_{C-F}$ = 22.6), 64.7, 51.8, 47.9, 40.1, 35.0, 32.5, 14.9. mp 116−118 °C. $[\alpha]_D^{20}$ = −5.5 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{20}N_2O_3F_1$ $[M + H]^+$ 295.1452, found 295.1445.

Methyl (2*R*,3*S*)-1[(4-cyanophenyl)(methyl)carbamoyl]-3-methylpyrrolidine-2-carboxylate (13j). Following general procedure 2, *N*-methyl-*N*-(4-cyanophenyl)carbamoyl chloride (265 mg), 3-methyl proline methyl ester **12a** (150 mg) and Et_3N (181 μL) in acetonitrile (2.60 mL) gave, after 20 h heating at reflux, a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 30:70 Pet. Ether:EtOAc) to yield the title compound as an oil (277 mg, 88%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.65−7.58 (2H, m, 2 × CH_{Ar}), 7.37−7.30 (2H, m, 2 × CH_{Ar}), 4.49 (1H, d, J = 7.5, $C_\delta H$), 3.76 (3H, s, OCH_3), 3.27 (3H, s, NCH_3), 3.07−2.90 (2H, m, $C_\alpha H_2$), 2.52 (1H, hept, J = 6.9, $C_\gamma H$), 1.89 (1H, ddt, J = 12.4, 7.4 and 6.5, $C_\beta H_A H_B$), 1.62 (1H, dq, J = 12.6 and 7.0, $C_\beta H_A H_B$), 0.90 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.8, 158.7, 149.8, 133.6, 123.4, 118.9, 107.0, 64.6, 52.0, 47.8, 38.4, 35.1, 32.4, 15.0. $[\alpha]_D^{20}$ = −153 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{16}H_{19}N_3O_3Na_1$ $[M + Na]^+$ 324.1324, found 324.1321.

Methyl (2*R*,3*S*)-1-[(methoxymethyl)(phenyl)carbamoyl]-3-methylpyrrolidine-2-carboxylate (13k). Following general procedure 1, phenyl isocyanate (114 μL), 3-methyl proline methyl ester **12a** (150 mg) and DIPEA (214 μL) in dichloromethane (5.25 mL) gave a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 75:25 Pet. Ether:EtOAc) to yield the unprotected urea as an oil (241 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43−7.35 (2H, m, 2 × CH_{Ar}), 7.31−7.22 (2H, m, 2 × CH_{Ar}), 7.06−6.97 (1H, m, CH_{Ar}), 6.25 (1H, brs, NH), 4.48 (1H, brd, J = 8.3, NCH), 3.79−3.67 (4H, m, NCH_AH_B and OCH_3), 3.54−3.42 (1H, m, NCH_AH_B), 2.62−2.48 (1H, m, CH), 2.19−2.07 (1H, m, CH_AH_B), 2.03−1.88 (1H, m, CH_AH_B), 1.06 (3H, d, J = 6.9, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 153.6, 138.8, 129.0, 123.2, 119.7, 63.2, 52.0, 45.9, 36.3, 32.3, 14.8. $[\alpha]_D^{20}$ = +3.2 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{18}N_2O_3Na$ $[M + Na]^+$ 285.1215, found 285.1206.

Following general procedure 3, TMSCl (610 μL) was added to a mixture of this urea (210 mg) and paraformaldehyde (144 mg) in dichloromethane (4.00 mL) to give the title compound as an oil (230 mg, 94%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38−7.28 (4H, m, 4 × CH_{Ar}), 7.21−7.13 (1H, m, CH_{Ar}), 5.13 (1H, d, J = 10.3, H_A of AB, NCH_2O), 4.97 (1H, d, J = 10.3, H_B of AB, NCH_2O), 4.44 (1H, brd, J = 7.5, NCH), 3.74 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 3.03−2.89 (1H, m, NCH_AH_B), 2.84−2.71 (1H, m, NCH_AH_B), 2.42 (1H, hept, J = 7.3, CH), 1.85−1.74 (1H, m, CH_AH_B), 1.67−1.53 (1H, m, CH_AH_B), 0.89 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 158.7, 143.7, 129.5, 125.5, 125.2, 82.1, 64.8, 56.0, 51.8, 48.0, 35.1, 32.4, 14.8. HRMS (ESI$^+$) m/z calcd for $C_{16}H_{22}N_2O_4Na$ $[M + Na]^+$ 329.1477, found 329.1477.

Methyl (2*R*,3*S*)-1-[(3-chlorophenyl)(methoxymethyl)-carbamoyl]-3-methylpyrrolidine-2-carboxylate (13l). Following general procedure 1, 3-chlorophenyl isocyanate (116 μL), 3-methyl proline methyl ester **12a** (137 mg) and DIPEA (196 μL) in dichloromethane (4.80 mL) gave a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the unprotected urea as an oil (123 mg, 43%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.55 (1H, brs, CH_{Ar}), 7.25−7.20 (1H, m, CH_{Ar}), 7.15 (1H, t, J = 7.9, CH_{Ar}), 7.00−6.94 (1H,m, CH_{Ar}), 6.38 (1H, brs, NH), 4.45 (1H, brd, J = 8.3, NCH), 3.74 (3H, s, OCH_3), 3.71−3.62 (1H, m, NCH_AH_B), 3.50−3.38 (1H, m, NCH_AH_B), 2.52 (1H, oct, J = 6.8, CH), 2.15−2.04 (1H, m, CH_AH_B), 2.00−1.84 (1H, m, CH_AH_B), 1.04 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5, 153.4, 140.1, 134.6, 129.9, 123.1, 119.7, 117.6, 63.2, 52.0, 45.8, 36.3, 32.3, 14.7. $[\alpha]_D^{20}$ = +22.8 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{17}N_2O_3ClNa$ $[M + Na]^+$ 319.0825, found 319.0832.

Following general procedure 3, TMSCl (295 μL) was added to a mixture of unprotected urea (115 mg) and paraformaldehyde (70 mg) in dichloromethane (1.94 mL) gave the title compound as an oil (108 mg, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38−7.31 (1H, m, CH_{Ar}), 7.30−7.18 (2H, m, 2 × CH_{Ar}), 7.16−7.09 (1H, m, CH_{Ar}), 5.11 (1H, d, J = 10.4, H_A of AB, NCH_2O), 4.94 (1H, d, J = 10.4, H_B of AB, NCH_2O), 4.45 (1H, brd, J = 7.5, NCH), 3.74 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.06−2.92 (1H, m, NCH_AH_B), 2.92−2.78 (1H, m, NCH_AH_B), 2.46 (1H, hept, J = 7.1, CH), 1.84 (1H, ddt, J = 12.2, 7.3 and 6.1, CH_AH_B), 1.86−1.74 (1H, dq, J = 12.2 and 7.5, CH_AH_B), 0.90 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.8, 158.2, 145.0, 135.0, 130.3, 125.4, 124.6, 122.7, 81.9, 64.8, 56.0, 51.8, 48.1, 35.0, 32.3, 14.8. $[\alpha]_D^{20}$ = −20.5 (c = 1.00; $CHCl_3$). IR (film, cm^{-1}) ν_{max} = 2950, 2888, 1743, 1655. HRMS (ESI$^+$) m/z calcd for $C_{16}H_{21}N_2O_4ClNa$ $[M + Na]^+$ 363.1088, found 363.1077.

Methyl (2*R*,3*S*)-1-[(3-fluorophenyl)(methoxymethyl)-carbamoyl]-3-methylpyrrolidine-2-carboxylate (13m). Following general procedure 1, 3-fluorophenyl isocyanate (120 μL), 3-methyl proline methyl ester **12a** (150 mg) and DIPEA (213 μL) in dichloromethane (5.25 mL) gave a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 75:25 Pet. Ether:EtOAc) to yield the urea as an oil (248 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44−7.34 (1H, m, CH_{Ar}), 7.24−7.12 (1H, m, CH_{Ar}), 7.06−6.98 (1H, m, CH_{Ar}), 6.79−6.67 (1H, m, CH_{Ar}), 6.31 (1H, brs, NH), 4.47 (1H, brd, J = 8.3, NCH), 3.83−3.63 (4H, m, NCH_AH_B and OCH_3), 3.55−3.42 (1H, m, NCH_AH_B), 2.60−2.41 (1H, m, CH), 2.19−2.07 (1H, m, CH_AH_B), 2.03−1.86 (1H, m, CH_AH_B), 1.06 (3H, d, J = 6.9, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5, 162.0 (ArC_{Ar}), 153.3, 140.5 (d, $^3J_{C-F}$ = 10.7), 130.0 (d, $^3J_{C-F}$ = 9.6), 114.6 (d, $^4J_{C-F}$ = 2.8), 109.8 (d, $^2J_{C-F}$ = 21.3), 107.0 (d, $^2J_{C-F}$ = 26.7), 63.2, 52.1, 46.9, 36.3, 32.3, 14.7. $[\alpha]_D^{20}$ = +3.6 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{17}N_2O_3FNa$ $[M + Na]^+$ 303.1121, found 303.1129.

Following general procedure 3, TMSCl (630 μL) was added to a mixture of urea (232 mg) and paraformaldehyde (149 mg) in dichloromethane (4.14 mL) gave the title compound as an oil (259 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33−7.28 (1H, m, CH_{Ar}), 7.15−7.03 (2H, m, 2 × CH_{Ar}), 6.87 (1H, ddt, J = 8.3, 2.5 and 0.8, CH_{Ar}), 5.12 (1H, d, J = 10.4, H_A of AB, NCH_2O), 4.96 (1H, d, J = 10.4, H_B of AB, NCH_2O), 4.46 (1H, brd, J = 7.5, NCH), 3.75 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 3.10−2.97 (1H, m, NCH_AH_B), 2.93−2.80 (1H, m, NCH_AH_B), 2.46 (1H, hept, J = 7.1, CH), 1.89−1.79 (1H, m, CH_AH_B), 1.63 (1H, dq, J = 12.2 and 7.8, CH_AH_B), 0.91 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.8, 163.3 (d, $^1J_{C-F}$ = 246.7), 158.3, 145.4 (d, $^3J_{C-F}$ = 9.7), 130.5 (d, $^3J_{C-F}$ = 9.3), 120.2 (d, $^4J_{C-F}$ = 3.1), 112.2 (d, $^2J_{C-F}$ = 21.1), 111.8 (d, $^2J_{C-F}$ = 23.3), 82.0, 64.8, 56.0, 51.9, 48.0, 35.1, 32.4, 14.8. $[\alpha]_D^{20}$ = −3.2 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{16}H_{21}N_2O_4FNa$ $[M + Na]^+$ 347.1383, found 347.1369.

(7*S*,7a*S*)-2,7-Dimethyl-7a-phenyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14a). Following general procedure 5, KHMDS (0.89 mL), urea **13a** (98 mg), LiCl (38 mg) and THF (3.55 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14a** as an oil (74 mg, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63−7.53 (2H, m, 2 × CH_{Ar}), 7.43−7.30 (3H, m, 3 × CH_{Ar}), 3.84 (1H, ddd, J = 10.7, 10.0 and 8.2,

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$C_\alpha H_A H_B$), 3.42 (1H, ddd, J = 11.3, 9.5 and 2.2, $C_\alpha H_A H_B$), 2.95 (3H, s, NCH_3), 2.65 (1H, br quint, J = 6.9, $C_\gamma H$), 2.02 (1H, dtd, J = 13.2, 9.5 and 6.2, $C_\beta H_A H_B$), 1.77 (1H, ddt, J = 12.9, 7.8 and 1.3, $C_\beta H_A H_B$), 1.01 (3H, d, J = 7.1, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5, 160.2, 138.2, 128.7, 128.4, 125.7, 78.7, 43.2, 42.6, 33.0, 25.0, 15.5. $[\alpha]_D^{20}$ = +228 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{16}N_2O_2Na$ $[M + Na]^+$ 267.1109, found 267.1098.

(7*S*,7a*S*)-2,7-Dimethyl-7a-(2-methylphenyl)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14b). Following general procedure 5, KHMDS (0.82 mL), urea **13b** (95 mg), LiCl (35 mg) and THF (3.33 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14b** as an oil (19 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51−7.40 (1H, m, CH_{Ar}), 7.29−7.11 (3H, m, 3 × CH_{Ar}), 3.85 (1H, td, J = 9.9 and 8.6, $C_\alpha H_A H_B$), 3.36 (1H, ddd, J = 11.4, 9.8 and 2.2, $C_\alpha H_A H_B$), 3.03−2.92 (4H, m, $C_\gamma H$ and NCH_3), 2.73 (3H, s, ArCH_3), 2.27 (1H, dtd, J = 13.2, 9.8 and 6.5, $C_\beta H_A H_B$), 1.86−1.75 (1H, m, $C_\beta H_A H_B$), 1.03 (3H, d, J = 7.2, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 159.5, 136.7, 135.7, 133.3, 128.5, 126.5, 126.0, 80.1, 42.1, 40.0, 33.2, 25.0, 21.9, 15.4. $[\alpha]_D^{20}$ = +192 (c = 1.00; $CHCl_3$). IR (film, cm^{-1}) ν_{max} = 2958, 2900, 2875, 1769, 1708. HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}N_2O_2$ $[M + H]^+$ 259.1447, found 259.1452.

(7*S*,7a*S*)-2,7-Dimethyl-7a-(naphthalen-1-yl)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14c). Following general procedure 5, KHMDS (0.81 mL), urea **13c** (110 mg), LiCl (34 mg,) and THF (3.23 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14c** as a white solid (93 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.71 (1H, d, J = 8.7, CH_{Ar}), 7.85 (1H, dd, J = 14.7 and 8.1, CH_{Ar}), 7.65 (1H, d, J = 7.3, CH_{Ar}), 7.60 (1H, td, J = 7.3 and 1.0, CH_{Ar}), 7.51 (1H, t, J = 7.8, CH_{Ar}), 7.41 (1H, t, J = 7.6, CH_{Ar}), 3.91 (1H, dt, J = 10.4 and 9.0, $C_\alpha H_A H_B$), 3.59−3.42 (3H, m, $C_\alpha H_A H_B$ and CH_2CH_3), 3.30 (1H, br quint, J = 6.9, $C_\gamma H$), 1.98−1.84 (1H, m, $C_\beta H_A H_B$), 1.83−1.72 (1H, m, $C_\beta H_A H_B$), 1.18 (3H, t, J = 7.2, CH_3CH_2), 1.17 (3H, d, J = 7.2, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 159.3, 135.3, 133.8, 130.4, 129.9, 128.8, 128.0, 125.9, 125.6, 125.0, 124.3, 80.4, 41.7, 40.8, 34.3, 33.0, 15.3, 13.4. $[\alpha]_D^{20}$ = +274 (c = 1.00; $CHCl_3$). mp 174−176 °C. HRMS (ESI$^+$) m/z calcd for $C_{19}H_{20}N_2O_2Na$ $[M + Na]^+$ 331.1422, found 331.1431.

(7*S*,7a*S*)-7a-(3-Chlorophenyl)-2,7-dimethyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14d). Following general procedure 5, KHMDS (0.80 mL), urea **13d** (100 mg), LiCl (34 mg) and THF (3.22 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14d** as an oil (73 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59−7.54 (1H, m, CH_{Ar}), 7.51−7.45 (1H, m, CH_{Ar}), 7.34−7.27 (2H, m, 2 × CH_{Ar}), 3.85 (1H, ddd, J = 11.0, 9.9 and 7.9, $C_\alpha H_A H_B$), 3.43 (1H, ddd, J = 11.4, 9.3 and 2.4, $C_\alpha H_A H_B$), 2.97 (3H, s, NCH_3), 2.63 (1H, dquint, J = 7.1 and 1.2, $C_\gamma H$), 2.03 (1H, dtd, J = 13.2, 9.5 and 6.2, $C_\beta H_A H_B$), 1.79 (1H, dddd, J = 10.0, 7.9, 2.1 and 1.7, $C_\beta H_A H_B$), 1.01 (3H, d, J = 7.1, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 160.1, 140.4, 134.8, 130.0, 128.7, 126.0, 124.1, 78.4, 43.4, 42.8, 33.0, 25.2, 15.5. $[\alpha]_D^{20}$ = +130.5 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{16}N_2O_2Cl$ $[M + H]^+$ 279.0900, found 279.0911.

(7*S*,7a*S*)-7a-(3-Bromophenyl)-2,7-dimethyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14e). Following general procedure 5, KHMDS (0.70 mL), urea **13e** (100 mg), LiCl (30 mg) and THF (2.82 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14e** as an oil (63 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79−7.68 (1H, m, CH_{Ar}), 7.60−7.45 (2H, m, 2 × CH_{Ar}), 7.33−7.22 (1H, m, CH_{Ar}), 3.94−3.79 (1H, m, $C_\alpha H_A H_B$), 3.54−3.39 (1H, m, $C_\alpha H_A H_B$), 2.97 (3H, s, NCH_3), 2.65 (1H, brquint, J = 6.9, $C_\gamma H$), 2.14−1.98 (1H, m, $C_\beta H_A H_B$), 1.87−1.75 (1H, m, $C_\beta H_A H_B$), 1.03 (3H, d, J = 7.1, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 160.1, 140.6, 131.6, 130.3, 128.9, 124.6, 122.9, 78.3, 43.4, 42.8, 33.0, 25.2, 15.5. $[\alpha]_D^{20}$ = +237 (c = 1.00; $CHCl_3$). IR (film, cm^{-1}) ν_{max} = 2967, 2902, 1771, 1708. HRMS (ESI$^+$) m/z calcd for $C_{14}H_{15}N_2O_2BrNa$ $[M + Na]^+$ 345.0215, found 345.0283.

(7*S*,7a*S*)-7a-(3-Methoxyphenyl)-2,7-dimethyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14f). Following general procedure 5, KHMDS (0.82 mL), urea **13f** (100 mg), LiCl (35 mg) and THF (3.26 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14f** as an oil (53 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30−7.27 (1H, m, CH_{Ar}), 7.18−7.14 (1H, m, CH_{Ar}), 7.12−7.08 (H, m, CH_{Ar}), 6.88−6.83 (H, m, CH_{Ar}), 3.89−3.74 (4H, m, OCH_3 and $C_\alpha H_A H_B$), 3.43 (1H, ddd, J = 11.4, 9.4 and 2.4, $C_\alpha H_A H_B$), 2.96 (3H, s, NCH_3), 2.65 (1H, dquint, J = 7.0 and 1.0, $C_\gamma H$), 2.05 (1H, dtd, J = 13.1, 9.5 and 6.2, $C_\beta H_A H_B$), 1.76 (1H, dddd, J = 12.9, 7.9, 2.2 and 1.7, $C_\beta H_A H_B$), 1.00 (3H, d, J = 7.1, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 160.2, 159.9, 139.9, 129.8, 118.1, 113.8, 111.6, 78.7, 55.5 (CH_3O), 43.2, 42.6, 33.1, 25.1, 15.5. $[\alpha]_D^{20}$ = +141.2 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{18}N_2O_3Na$ $[M + Na]^+$ 297.1215, found 297.1204.

(7*S*,7a*S*)-2,7-Dimethyl-7a-(pyridine-2-yl)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14h). Following general procedure 5, KHMDS (0.64 mL), urea **13h** (71 mg), LiCl (27 mg) and THF (2.56 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 30:70 Pet. Ether:EtOAc) **14h** as a white solid and **14′h** as an oil (50 mg, 80% and 6.5 mg, 10%, respectively). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.70 (1H, brd, J = 4.2, CH_{Ar}), 7.69 (1H, td, J = 7.8 and 1.7, CH_{Ar}), 7.54 (1H, brd, J = 7.9, CH_{Ar}), 7.25 (1H, ddd, J = 7.4, 5.0 and 0.6, CH_{Ar}), 4.54 (1H, td, J = 10.1 and 8.9, $C_\alpha H_A H_B$), 3.39 (1H, ddd, J = 11.4, 9.5 and 2.4, $C_\alpha H_A H_B$), 3.22 (1H, br quint, J = 7.0, $C_\gamma H$), 2.99 (3H, s, NCH_3), 1.98 (1H, dtd, J = 13.1, 9.5 and 6.3, $C_\beta H_A H_B$), 1.84−1.74 (1H, m, $C_\beta H_A H_B$), 1.03 (3H, d, J = 7.2, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 160.4, 156.2, 150.1, 137.1, 123.3, 120.5, 80.3, 43.4, 40.3, 33.2, 25.2, 15.4. $[\alpha]_D^{20}$ = +156 (c = 1.00; $CHCl_3$). mp 88−90 °C. HRMS (ESI$^+$) m/z calcd for $C_{13}H_{16}N_3O_2$ $[M + H]^+$ 246.1237 found 246.1240.

(7*S*,7a*R*)-2,7-Dimethyl-7a-(pyridine-2-yl)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14′h). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.68−8.61 (1H, m, CH_{Ar}), 7.91−7.82 (1H, m, CH_{Ar}), 7.75−7.66 (1H, m, CH_{Ar}), 7.30−7.21 (1H, m, CH_{Ar}), 3.86−3.70 (2H, m, $C_\alpha H_2$), 3.01 (3H, s, NCH_3), 2.33−2.18 (2H, m, $C_\gamma H$ and $C_\beta H_A H_B$), 2.00−1.84 (1H, m, $C_\beta H_A H_B$), 0.94 (3H, d, J = 7.1, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.9, 159.6, 153.6, 149.6, 136.1, 123.3, 122.2, 76.3, 45.3, 42.4, 34.6, 25.2, 14.5. $[\alpha]_D^{20}$ = −33.6 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{13}H_{15}N_3O_2Na_1$ $[M + Na]^+$ 268.1056, found 268.1061.

(7*S*,7a*S*)-7a-(4-Fluorophenyl)-2,7-dimethyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14i). Following general procedure 5, KHMDS (0.85 mL), urea **13i** (100 mg), LiCl (36 mg) and THF (3.40 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14i** as an oil (66 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61−7.48 (2H, m, 2 × CH_{Ar}), 7.12−7.00 (2H, m, 2 × CH_{Ar}), 3.84 (1H, ddd, J = 10.9, 10.2 and 8.1, $C_\alpha H_A H_B$), 3.42 (1H, ddd, J = 11.4, 9.4 and 2.3, $C_\alpha H_A H_B$), 2.96 (3H, s, NCH_3), 2.61 (1H, quint, J = 7.0, $C_\gamma H$), 2.03 (1H, dtd, J = 13.2, 9.6 and 6.1, $C_\beta H_A H_B$), 1.78 (1H, ddt, J = 13.0, 7.8 and 1.6, $C_\beta H_A H_B$), 1.00 (3H, d, J = 7.1, CH_3CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 162.9 (d, $^1J_{C-F}$ = 247.5), 160.2, 134.1 (d, $^4J_{C-F}$ = 3.2), 127.6 (d, $^3J_{C-F}$ = 8.2), 115.6 (d, $^2J_{C-F}$ = 21.8), 78.3, 43.3, 42.8, 33.0, 25.2, 15.5. $[\alpha]_D^{20}$ = +169 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{16}N_2O_2F_1$ $[M + H]^+$ 263.1190, found 263.1185.

4-[(7*S*,7a*S*)-2,7-Dimethyl-1,3-dioxo-hexahydro-1*H*-pyrrolo-[1,2-*c*]imidazolidine-7a-yl]benzonitrile (14j). Following general procedure 5, KHMDS (0.72 mL), **13j** (87 mg), LiCl (31 mg) and THF (2.89 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 40:60 Pet. Ether:EtOAc) **14j** and **14′j** as an oil (35 mg, 46% and 20 mg, 25%, respectively). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75−7.65 (4H, m, 4 × CH_{Ar}), 3.88 (1H, td, J = 10.0 and 9.2, $C_\alpha H_A H_B$), 3.43 (1H, br t, J = 9.6, $C_\alpha H_A H_B$), 2.98 (3H, s, NCH_3), 2.65 (1H, br quint, J = 6.6, $C_\gamma H$), 2.07−1.92 (1H, m, $C_\beta H_A H_B$), 1.87−1.75 (1H, m, $C_\beta H_A H_B$), 1.04 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5, 160.1, 143.6, 132.5, 126.7, 118.5, 112.5, 78.6, 43.6, 43.1, 33.0, 25.3, 15.5. $[\alpha]_D^{20}$ = +151 (c = 1.00; $CHCl_3$). HRMS

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(ESI$^+$) m/z calcd for $C_{15}H_{15}N_3O_2$ $[M + Na]^+$ 292.1062, found 292.1070.

4-[(7*S*,7a*R*)-2,7-Dimethyl-1,3-dioxo-hexahydro-1*H*-pyrrolo-[1,2-*c*]imidazolidine-7a-yl]benzonitrile (14′j). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79−7.72 (2H, m, 2 × CH_{Ar}), 7.71−7.64 (2H, m, 2 × CH_{Ar}), 3.78 (1H, td, J = 11.3 and 7.9, $C_\alpha H_A H_B$), 3.59 (1H, td, J = 10.6 and 1.5, $C_\alpha H_A H_B$), 2.98 (3H, s, NCH_3), 2.33−2.20 (2H, m, $C_\beta H_A H_B$ and $C_\gamma H$), 1.67−1.55 (1H, m, $C_\beta H_A H_B$), 1.01 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.8, 159.9, 139.0, 131.9, 128.2, 118.5, 112.6, 74.7, 45.3, 42.2, 34.2, 25.4, 14.5. $[\alpha]_D^{20}$ = −27.4 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{15}N_3O_2$ $[M + Na]^+$ 292.1062, found 292.1070.

(7*S*,7a*S*)-2-(Methoxymethyl)-7-methyl-7a-phenyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14k). Following general procedure 5, KHMDS (0.65 mL), urea **13k** (79 mg), LiCl (27 mg) and THF (2.58 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14k** as an oil (37 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62−7.52 (2H, m, 2 × CH_{Ar}), 7.44−7.30 (3H, m, 3 × CH_{Ar}), 4.85 (2H, s, NCH_2O), 3.94−3.83 (1H, m, NCH_AH_B), 3.52−3.41 (1H, m, NCH_AH_B), 3.32 (3H, s, OCH_3), 2.71 (1H, br quint, J = 6.7, CH), 2.14−1.97 (1H, m, CH_AH_B), 1.86−1.73 (1H, m, CH_AH_B), 1.06 (3H, d, J = 7.1, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 159.2, 137.9, 128.8, 128.6, 125.7, 78.6, 70.1, 57.5, 43.1, 42.6, 32.8, 15.6. $[\alpha]_D^{20}$ = +78.8 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{18}N_2O_3Na_1$ $[M + Na]^+$ 297.1215, found 297.1208.

(7*S*,7a*S*)-7a-(3-Chlorophenyl)-2-(methoxymethyl)-7-methyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14l). Following general procedure 5, KHMDS (0.72 mL), **13l** (98 mg), LiCl (31 mg) and THF (2.88 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14l** as an oil (88 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60−7.52 (1H, m, CH_{Ar}), 7.50−7.43 (1H, m, CH_{Ar}), 7.36−7.27 (2H, m, 2 × CH_{Ar}), 4.83 (2H, s, NCH_2O), 3.94−3.80 (1H, m, NCH_AH_B), 3.52−3.40 (1H, m, NCH_AH_B), 3.32 (3H, s, OCH_3), 2.66 (1H, br quint, J = 6.8, CH), 2.05 (1H, dtd, J = 13.4, 9.6 and 6.2, CH_AH_B), 1.86−1.74 (1H, m, CH_AH_B), 1.05 (3H, d, J = 7.1, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 159.0, 140.1, 134.9, 130.1, 128.8, 126.0, 124.0, 78.2, 70.2, 57.6, 43.3, 42.8, 32.8, 15.5. $[\alpha]_D^{20}$ = +88 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{17}N_2O_3Na_1Cl_1$ $[M + Na]^+$ 331.0825, found 331.0811.

(7*S*,7a*S*)-7a-(3-Fluorophenyl)-2-(methoxymethyl)-7-methyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14m). Following general procedure 5, KHMDS (0.96 mL), urea **13m** (125 mg), LiCl (41 mg) and THF (3.85 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) **14m** as an oil (101 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39−7.33 (2H, m, 2 × CH_{Ar}), 7.30−7.27 (1H, m, CH_{Ar}), 7.07−7.00 (1H, m, CH_{Ar}), 4.84 (2H, s, NCH_2O), 3.89 (1H, ddd, J = 11.1, 9.8 and 8.0, NCH_AH_B), 3.45 (1H, ddd, J = 11.6, 9.4 and 2.4, NCH_AH_B), 3.32 (3H, s, OCH_3), 2.67 (1H, quintd, J = 7.1 and 1.1, CH), 2.05 (1H, dtd, J = 13.2, 9.3 and 6.2, CH_AH_B), 1.80 (1H, dddd, J = 10.1, 7.9, 2.2 and 1.7, CH_AH_B), 1.06 (3H, d, J = 7.1, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 163.0 (d, $^1J_{C-F}$ = 246.9), 159.0, 140.5 (d, $^3J_{C-F}$ = 7.1), 130.4 (d, $^3J_{C-F}$ = 8.1), 121.4 (d, $^4J_{C-F}$ = 2.9), 115.5 (d, $^2J_{C-F}$ = 21.2), 113.1 (d, $^2J_{C-F}$ = 23.3), 78.3 (d, $^4J_{C-F}$ = 1.8, C), 70.2, 57.6, 43.3, 42.7, 32.8, 15.5. $[\alpha]_D^{20}$ = +94.4 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{17}N_2O_3NaF$ $[M + Na]^+$ 315.1121, found 315.1122.

(7*S*,7a*S*)-7-Benzyl-7a-(3-fluorophenyl)-2-(methoxymethyl)-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3-dione (14n). Following general procedure 1, 3-fluorophenyl isocyanate (15 μL), 3-benzyl proline methyl ester **12b** (29 mg) and DIPEA (28 μL) in dichloromethane (0.66 mL) gave a crude used in the next reaction. Following general procedure 3, TMSCl was added to a mixture of unprotected urea and paraformaldehyde in dichloromethane gave a crude urea **13n**, which used in the next reaction. Following general procedure 5, KHMDS (0.17 mL), urea **13n** (26 mg), LiCl (7 mg) and THF (0.68 mL) gave, after purification by flash column chromatography (SiO_2, 100:0 to 85:15 Pet. Ether:EtOAc) **14n** as an oil (16 mg, 33% in three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47−7.20 (6H, m, 6 × CH_{Ar}), 7.19−7.12 (2H, m, 2 × CH_{Ar}), 7.09−7.01 (1H, m, CH_{Ar}), 4.90 (2H, s, NCH_2O), 3.99−3.83 (1H, m, NCH_AH_B), 3.57−3.42 (1H, m, NCH_AH_B), 3.35 (3H, s, OCH_3), 3.22−3.10 (1H, m, $PhCH_AH_B$), 2.84−2.68 (1H, m, CH), 2.09 (1H, t, J = 12.9, $PhCH_AH_B$), 1.92−1.69 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.7, 163.0 (d, $^1J_{C-F}$ = 246.9), 158.9, 140.5 (d, $^3J_{C-F}$ = 7.1), 138.1 (C_{Ar}), 130.6 (d, $^3J_{C-F}$ = 8.1), 129.1, 128.9, 127.0, 121.4 (d, $^4J_{C-F}$ = 2.9), 115.7 (d, $^2J_{C-F}$ = 21.2), 113.1 (d, $^2J_{C-F}$ = 23.3), 78.0 (d, $^4J_{C-F}$ = 1.8, C), 70.3, 57.7, 49.8, 43.2, 34.6, 28.5. $[\alpha]_D^{20}$ = +154.4 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{21}H_{22}N_2O_3F_1$ $[M + H]^+$ 369.1614, found 369.1603.

(2*S*,3*S*)-*N*,3-Dimethyl-2-phenylpyrrolidine-2-carboxamid (15a). Following general procedure 6, hydantoin **14a** (45 mg) gave **15a** (39 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (1H, brs, NH), 7.47−7.35 (2H, m, 2 × CH_{Ar}), 7.31−7.22 (2H, m, 2 × CH_{Ar}), 7.22−7.12 (1H, m, CH_{Ar}), 3.03 (1H, ddd, J = 10.0, 7.6 and 4.8, NCH_AH_B), 2.91 (1H, dt, J = 9.9 and 7.6, NCH_AH_B), 2.74 (3H, d, J = 5.0, NCH_3), 2.66 (1H, sext, J = 7.0, CH), 2.09 (1H, brs, NH), 1.91 (1H, dddd, J = 12.3, 7.5, 6.8 and 4.8, CH_AH_B), 1.48 (1H, ddt, J = 14.9, 12.4 and 7.5, CH_AH_B), 1.12 (3H, d, J = 7.0, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.3, 144.2, 128.6, 127.3, 126.2, 74.3, 44.6, 42.7, 34.2, 26.1, 17.0. $[\alpha]_D^{20}$ = +102 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{13}H_{19}N_2O_1$ $[M + H]^+$ 219.1497, found 219.1495.

(2*S*,3*S*)-3-Methyl-2-phenylpyrrolidine-2-carboxylic acid (16k). Following general procedure 6, hydantoin **14k** (13 mg) gave **16k** (6 mg, 62%). ^{1}H NMR (400 MHz, MeOH) δ = 7.59−7.50 (2H, m, 2 × CH_{Ar}), 7.48−7.31 (3H, m, 3 × CH_{Ar}), 3.51 (1H, ddd, J = 11.6, 9.3 and 3.3, NCH_AH_B), 3.14 (1H, dt, J = 11.4 and 8.5, NCH_AH_B), 3.01 (1H, dtd, J = 16.6, 9.8 and 6.7, NCH_AH_B), 2.30 (1H, dddd, J = 12.7, 8.3, 6.6 and 3.3, CH_AH_B), 1.88 (1H, ddt, J = 12.8, 9.8 and 9.3, CH_AH_B), 1.34 (3H, d, J = 6.9, CH_3CH). ^{13}C NMR (100 MHz, MeOH) δ = 172.9, 138.6, 130.0, 129.9, 128.2, 79.1, 44.1, 39.6, 33.0, 16.2. $[\alpha]_D^{20}$ = +22 (c = 1.00; MeOH). HRMS (ESI$^+$) m/z calcd for $C_{12}H_{16}N_1O_2$ $[M - H]^+$ 206.1181, found 206.1183.

(2*S*,3*S*)-2-(3-Fluorophenyl)-3-methylpyrrolidine-2-carboxylic acid (16m). Following general procedure 6, hydantoin **14m** (91 mg) gave **16m** (43 mg, 62%). ^{1}H NMR (400 MHz, MeOH) δ = 7.49−7.42 (1H, m, CH_{Ar}), 7.38−7.32 (1H, m, CH_{Ar}), 7.32−7.26 (1H, m, CH_{Ar}), 7.19−7.11 (1H, m, CH_{Ar}), 3.53 (1H, ddd, J = 11.7, 9.2 and 3.4, NCH_AH_B), 3.18 (1H, dt, J = 11.4 and 8.1, NCH_AH_B), 2.96 (1H, dtd, J = 16.7, 6.8 and 6.8, NCH_AH_B), 2.29 (1H, dddd, J = 12.7, 7.5, 6.6 and 3.4, CH_AH_B), 1.88 (1H, ddt, J = 12.8, 9.7 and 9.4, CH_AH_B), 1.33 (3H, d, J = 6.9, CH_3CH). ^{13}C NMR (100 MHz, MeOH) δ = 172.1, 164.3 (d, $^1J_{C-F}$ = 245.3), 141.2 (d, $^3J_{C-F}$ = 7.4), 131.8 (d, $^3J_{C-F}$ = 8.3), 124.1 (d, $^4J_{C-F}$ = 2.8), 116.7 (d, $^2J_{C-F}$ = 21.0), 115.5 (d, $^2J_{C-F}$ = 23.5), 78.7, 44.3, 40.1, 32.5, 16.2. $[\alpha]_D^{20}$ = +105.2 (c = 1.00; MeOH). HRMS (ESI$^+$) m/z calcd for $C_{12}H_{13}F_1N_1O_2$ $[M - H]^+$ 222.0930, found 222.0929.

Methyl (2*S*,5*S*)-1-[(3-chlorophenyl)carbamoyl]-5-methylpyrrolidine-2-carboxylate (18). Following general procedure 1, 3-chlorophenyl isocyanate (45 μL), proline **17** (130 mg) and DIPEA (154 μL) in dichloromethane (2.71 mL) gave a crude product that was purified by flash column chromatography (SiO_2, 100:0 to 70:30 Pet. Ether:EtOAc) to yield the title compound as an oil (110 mg, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57−7.48 (1H, m, CH_{Ar}), 7.23−7.14 (2H, m, 2 × CH_{Ar}), 7.03−6.97 (1H, m, CH_{Ar}), 6.95 (1H, brs, NH), 4.50−4.38 (1H, m, NCH), 4.14−3.99 (1H, m, NCH), 3.81 (3H, s, OCH_3), 2.28−2.09 (3, m, CH_2 and CH_AH_B), 1.82−1.69 (1H, m, CH_AH_B), 1.36 (3H, d, J = 6.3, CH_3CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 154.0, 140.3, 134.6, 129.9, 123.0, 119.6, 117.5, 60.6, 54.3, 52.9, 32.9, 28.0, 21.0. $[\alpha]_D^{20}$ = +7.8 (c = 1.00; $CHCl_3$). HRMS (ESI$^+$) m/z calcd for $C_{14}H_{16}N_2O_3Cl$ $[M - H]^+$ 295.0849, found 295.0858.

(5*S*,7a*R*)-7a-(3-Chlorophenyl)-2-(methoxymethyl)-5-methyl-hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-1,3 dione (19). Following general procedure 3, TMSCl (257 μL) was added to a mixture of urea **18** (100 mg) and paraformaldehyde (61 mg) in dichloromethane (1.69 mL) gave the MOM urea as an oil (quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28−7.22 (1H, m, CH_{Ar}), 7.20−7.17 (1H, m, CH_{Ar}), 7.16−7.11 (1H, m, CH_{Ar}), 7.09−7.03 (1H, m, CH_{Ar}), 5.18

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(1H, d, J = 10.4, H_A of AB, NCH_2O), 4.77 (1H, d, J = 10.4, H_B of AB, NCH_2O), 4.40−4.28 (1H, m, NCH), 3.72−3.62 (1H, m, NCH), 3.59 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 2.06−1.81 (3, m, CH_2 and CH_AH$_B$), 1.66−1.52 (1H, m, CH$_A$$H_B$), 1.23 (3H, d, J = 6.2, CH_3CH). ^{13}C NMR (100 MHz, CDCl$_3$) δ = 173.0, 158.1, 144.6, 134.9, 130.4, 125.6, 125.0, 123.0, 82.4, 61.9, 56.4, 55.4, 52.2, 32.2, 29.2, 20.1. IR (film, cm^{-1}) ν_{max} = 3313, 2973, 2951, 1747, 1643. HRMS (ESI$^+$) m/z calcd for $C_{16}H_{21}N_2O_4ClNa_1$ [M + Na]$^+$ 363.1088, found 363.1077.

Following general procedure 5, KHMDS (0.84 mL), MOM urea (0.34 mmol), LiCl (36 mg) and THF (3.40 mL) gave, after purification by flash column chromatography (SiO$_2$, 100:0 to 70:30 Pet. Ether:EtOAc), **19** as an oil (59 mg, 57% from **18**) ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.58−7.52 (1H, m, CH_{Ar}), 7.49−7.42 (1H, m, CH_{Ar}), 7.36−7.27 (2H, m, 2 × CH_{Ar}), 4.84 (1H, d, J = 10.6, H_B of AB, NCH_2O), 4.79 (1H, d, J = 10.6, H_B of AB, NCH_2O), 4.07−3.93 (1H, m, NCH), 3.29 (3H, s, OCH_3), 2.35−2.23 (1H, m, CH_2), 2.19−2.04 (1H, m, CH_AH$_B$), 1.86−1.75 (1H, m, CH$_A$$H_B$), 1.55 (3H, d, J = 6.6, CH_3CH). ^{13}C NMR (100 MHz, CDCl$_3$) δ = 173.8, 155.8, 140.3, 134.9, 130.2, 128.8, 125.8, 123.9, 75.1, 70.0, 57.4, 54.0, 34.7, 33.8, 17.7. $[\alpha]_D^{20}$ = −52 (c = 1.00; CHCl$_3$). HRMS (ESI$^+$) m/z calcd for $C_{15}H_{17}N_2O_3Na_1Cl_1$ [M + Na]$^+$ 331.0825, found 331.0834.

(2*S*,5*S*)-2-(3-Chlorophenyl)-5-methylpyrrolidine-2-carboxylic acid (20). Following general procedure 6, hydantoin **19** (53 mg) gave **20** (32 mg, 77%). ^{1}H NMR (400 MHz, MeOH) δ = 7.58−7.49 (1H, m, CH_{Ar}), 7.47−7.36 (3H, m, 3 × CH_{Ar}), 3.84−3.71 (1H, m, NCH), 2.99−2.87 (1H, m, CH_AH$_B$), 2.43−2.25 (2H, m, CH_AH$_B$ and CH$_A$$H_B$), 1.75−1.60 (1H, m, CH$_A$$H_B$), 1.53 (3H, d, J = 6.6, CH_3CH). ^{13}C NMR (100 MHz, MeOH) δ = 174.0, 141.2, 135.7, 131.4, 129.7, 127.8, 126.9, 77.1, 58.3, 35.0, 32.7, 18.9. $[\alpha]_D^{20}$ = −40 (c = 1.00; MeOH). IR (film, cm^{-1}) ν_{max} = 3137, 3047, 2819, 1626. HRMS (ESI$^+$) m/z calcd for $C_{12}H_{14}N_1O_2NaCl$ [M + Na]$^+$ 262.0622, found 262.0611.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01912.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds; optimization experiments; chromatograms demonstrating enantiomeric enrichment. (PDF)

Crystallographic data. (CIF)

Crystallographic data. (CIF)

Crystallographic data. (CIF)

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Notes

The authors declare no competing financial interest.

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