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Asymmetric synthesis of all four stereoisomers of 1-amino-3-hydroxy-cyclopentane-1-carboxylic acid

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ABSTRACT

An asymmetric synthesis of all four stereoisomers of 1-amino-3-hydroxy-cyclopentane-1-carboxylic acid based on a chiral glycine equivalent, oxazinone derivative is presented. The crucial point of the performed reactions is the alkylation of (*S*)- and (*R*)-glycine equivalent with the respective stereoisomers of 4-(2-iodoethyl)-1,3,2-dioxathiolan-2-oxide using phosphazenic base *t*-BuP_4.

1. Introduction

Non-proteinogenic, unnatural α-amino acids have increasingly attracted the attention of numerous disciplines in connection with the design and synthesis of enzyme inhibitors, pharmacologically active products, optically active starting materials and chiral catalysts. Moreover, they represent an array of diverse structural elements for the development of new peptidic and non-peptidic compounds.[1–4] Unnatural quaternary α-amino acids, especially with three-, four-, or five membered rings, play a special role in the design of peptides with improved properties. They possess a stereochemically stable quaternary carbon center, which after incorporation into peptides results in a significant conformational bias.[5–10]

Aminocycloalkanecarboxylic acids, e.g., α-*trans*-2,4-methanoglutamic acid (**1**) is an agonist of the NMDA receptor,[11] while 1,3-disubstituted cyclobutane derivative **2** is its antagonist.[12] It was found that (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (**3**) is a selective metabotropic glutamate receptor antagonist[13,14] (Fig. 1).

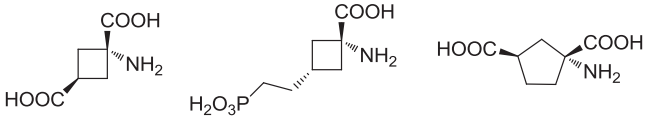

Fig. 1. Glutamate receptor agonist (**1**) and antagonists (**2**, **3**).

Currently, there are several strategies for the asymmetric synthesis of amino acids. They include the Strecker reaction, the asymmetric hydrogenation of dehydroamino acids using optically active catalysts, the nucleophilic and electrophilic amination of optically active carboxylic acid derivatives, nucleophilic and electrophilic substitution using chiral glycine equivalents (GEs) and biotechnological enzymatic processes.[15–36]

As a part of a study directed towards synthesis of chiral α-aminocycloalkanecarboxylic acids we developed the chiral GE **4** (Fig. 2),[37–39] which is easy to obtain and represents a very useful tool for the asymmetric construction of α,α-disubstituted amino acids. Compound **4** may be subjected repeatedly to deprotonation for alkylation reactions without risk of racemization as the chirality arises from a configurationally stable quaternary carbon. Moreover, its low molecular mass results in a favourable mass

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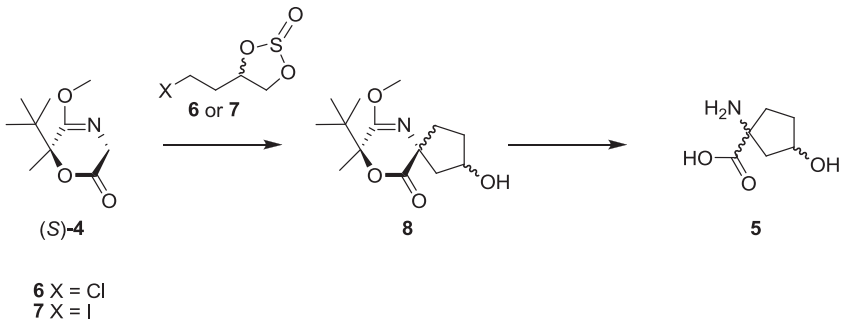


Fig. 2. The course of the planned synthesis exemplified for (*S*)-**4**.

balance for the overall synthetic sequence up to the free amino acids. With only a few signals being due to the chiral GE in the alkylation products the ^{1}H NMR spectra are in general very clear thus allowing a quick characterization of the alkylation products.

2. Results and discussion

The aim of the present study was to develop a synthesis for the construction of all four stereoisomers of 1-amino-3-hydroxycyclopentane-1-carboxylic acid (**5**) based on the chiral GEs (*S*)-**4** and (*R*)-**4**.

We focused our attention on the cyclic sulfites **6** and **7** as alkylating agents.[40–44] The course of our synthetic concept starting from (*S*)-**4** is presented in Fig. 2.

By subsequent stereoselective alkylation with 1,4-biselectrophiles such as **6** or **7** with the electrophilic moiety entering the molecule opposite to the *tert*-butyl group, the spirocyclic oxazine derivative **8** should form. Whereas the configuration of the spirocyclic stereocenter will be controlled by the asymmetric induction emerging from the glycine equivalent, the stereochemistry of the secondary alcohol will follow from the configuration of the alkylating agent, **6** or **7**, at the respective carbon. Hydrolysis of the thus formed double alkylation product should finally lead to the respective amino acid stereoisomer **5**.

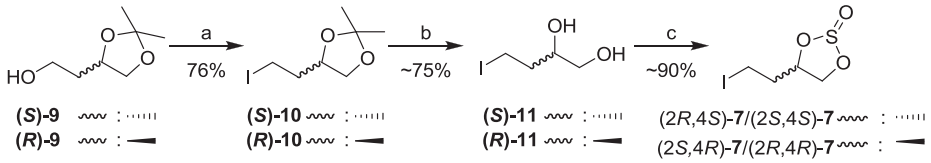
First attempts for the alkylation of compound (*S*)-**4** were undertaken with a mixture of the stereoisomers of **6** prepared according to the literature from racemic butan-1,2,4-triol.[45] However, despite using various bases (*s*-BuLi, NaN(SiMe$_3$)$_2$, *t*-BuP$_4$) (3.0 equiv), solvents (THF, DME), or temperature for the reaction (−50 °C to −30 °C) for the alkylation of the enolate of (*S*)-**4** the desired product **8** could not be obtained. In all cases only the starting material (*S*)-**4** was recovered.

Based on this result, it was decided to replace **6** by the analogous iodine derivative **7**. As starting materials for the synthesis of the mixtures of stereoisomers of 4-(2-iodoethyl)-1,3,2-dioxathiolan-2-oxide [(2*R*,4*S*)-**7**/(2*S*,4*S*)-**7**, (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7**], commercially available enantiomers of 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol, (*S*)-**9** or (*R*)-**9**, were used. Firstly, (*S*)-**9** or (*R*)-**9** were converted into iodo derivatives (*S*)-**10** or (*R*)-**10** using iodine, triphenylphosphine and imidazole. Then, deprotection to give compounds (*S*)-**11** or (*R*)-**11** was carried out in methanol in the presence of catalytic amounts of *para*-toluenesulfonic acid.[46] Finally, enantiomers of **11** were refluxed for 1 h with thionyl chloride in tetrachloromethane giving sulfites (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** or (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7** in 84% yield as a mixture of diastereomers (ds: 56:44 by ^{1}H NMR spectroscopy) (Fig. 3).

The thus prepared mixtures of diastereomers (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** or (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7** were used as the alkylating agents of GE (*S*)-**4** or (*R*)-**4**. The first series of reaction was performed with (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** and (*S*)-enantiomer of GE **4**. When (*S*)-**4** was treated at −30 °C with NaN(SiMe$_3$)$_2$, followed by (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** and NaN(SiMe$_3$)$_2$ (for the second deprotonation) (Table 1, entry 1), the obtained results were disappointing and starting material (*S*)-**4** was isolated from the reaction mixture. Similar results were obtained when *s*-BuLi was used as a deprotonation agent (Table 1, entries 2 and 3).

However, when (*S*)-**4** was treated at −78 °C with *t*-BuP$_4$, followed by (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** (1.5 equiv) and *t*-BuP$_4$, a clear improvement in the results was obtained and, as well as starting material (*S*)-**4**, a spirocyclic derivative **8a**/**b** was isolated with a low 15% yield (Table 1, entry 4). Finally, the best results were obtained when the necessary 2 equiv of *t*-BuP$_4$ were given at once at the beginning of the reaction sequence (Table 1, entry 5). In that case, the yield of **8a**/**b** rose to 42%, and the diastereoselectivity was quite high 94: 6 (**8a**:**8b**) (by ^{1}H NMR spectroscopy and HPLC).

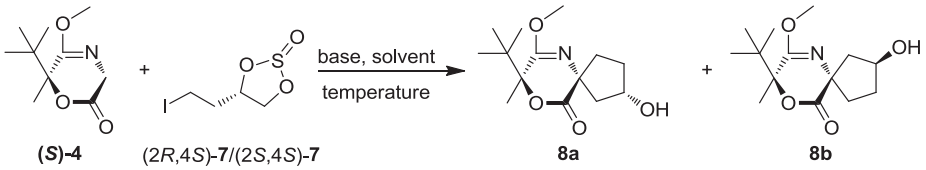
It is interesting to note that the stereoselectivity of the reaction strongly depends on the nature of the used reagents. When *t*-BuP$_4$ generated enolates of enantiomer (*S*)-**4** were subsequently treated with the electrophile (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7** the yield was 50% but the diastereoselectivity was significantly lower and amounted to 70:30 (**8e**:**8f**). As expected, this effect was also observed for (*R*)-**4**. In those cases, diastereoselectivities were 70:30 (**8c**:**8d**) for alkylation with



(a) I_2, Ph_3P, imidazole, Et_2O, 0°C-r.t., 18h; (b) *p*-TsOH, MeOH, r.t., 18h; (c) $SOCl_2$, CCl_4, reflux, 1h

Fig. 3. Synthesis of mixtures of diastereomers of 4-iodosulfites (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** or (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7**.

Table 1
The alkylation of glycine equivalent (*S*)-**4** with biselectrophil (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7**



No	Base/equiv	(2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** equiv	Temp	Solvent	Yield **8a**/**8b**	Recovered (*S*)-**4**	Ratio **8a**/**8b**
1.	$Na(SiMe_3)_2$/1.0+1.0	1.5	−30 °C	THF	0%	80%	—
2.	*s*-BuLi/1.0+1.0	1.5	−50 °C	THF	0%	68%	—
3.	*s*-BuLi/1.0+1.0	1.5	−50 °C	DME	0%	20%	—
4.	*t*-BuP_4/1.1+1.0	1.5	−78 °C	THF	15%	27%	94/6
5.	*t*-BuP_4/2.0	1.5	−65 °C	THF	42%	20%	94/6

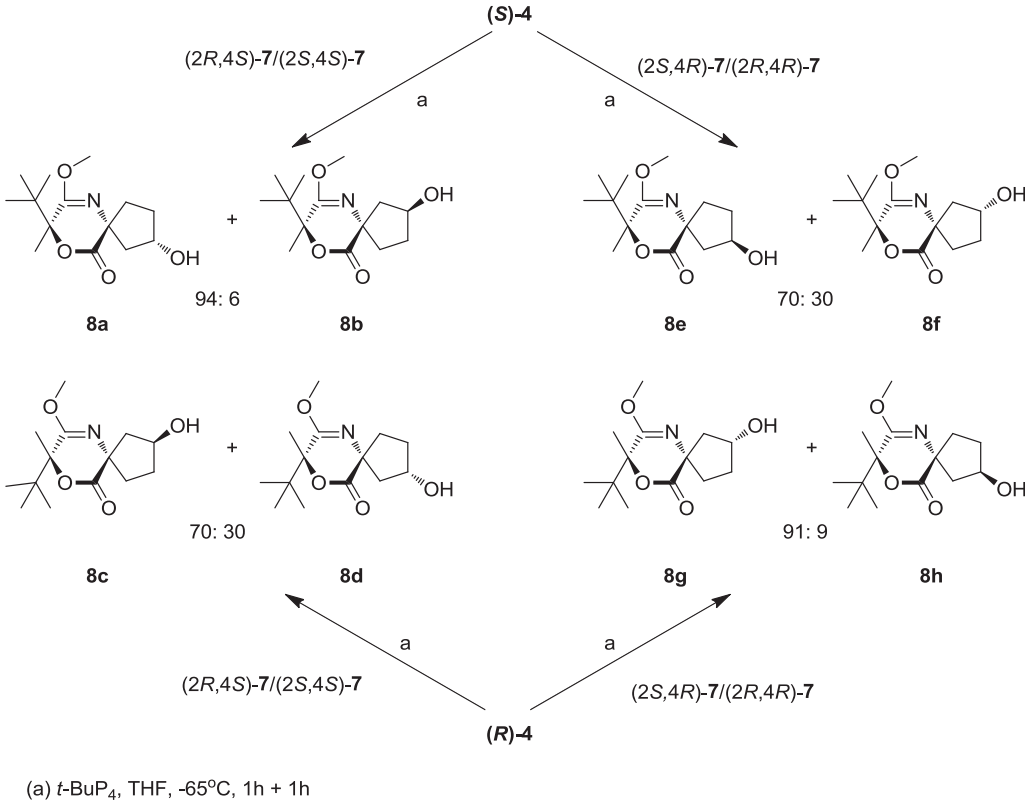


Fig. 4. The alkylation of enantiomeric glycine equivalents (*S*)-**4** and (*R*)-**4** with stereoisomeric iodosulfites (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** and (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7**.

(2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** and 91:9 (**8g**:**8h**) for reaction with (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7**, respectively (Fig. 4).

In the next step, the assignment of the absolute configuration of the major diastereomers **8** was performed. Those studies were based on finding that the absolute configurations of C-2 and C-8 carbon atoms were easily designated based on the knowledge of the absolute configuration of the starting materials, **4** and **7**. It was assumed that the required analysis could be accomplished by NMR experiments based on nuclear Overhauser effects (NOEs).[47]

The stereochemical assignment started with the spirocyclic derivative **8a**. However, due to strong signal overlap of the diagnostic protons of the cyclopentane moiety in 2D HSQC spectra, this methodology could not be applied directly for the required analysis (see Supplementary data).

Neither a change of solvent, nor addition of a chiral solvating agent such as (+)-(*R*)-α-methylbenzylamine, nor addition of the chemical shift reagent tris[3-(heptafluoropropyl-hydroxymethylene)camphorato]europium(III) resulted in separation of the diagnostic signals. In view of these findings, it was decided to assess the possibility of determining the absolute configuration at C-5 of stereoisomers **8** after their chemical transformation into the related ketones **9**.

The oxidation of major isomers of **8** was carried out with 2-iodoxybenzoic acid (IBX) in DMSO and yielded the desired ketone **9a** in 68% (from **8a**) and 60% (from **8e**) and **9b** in 60% (from **8c**) and 54% (from **8g**). The course of the performed reaction is presented in Fig. 5.

The NMR spectra of compound **9a** showed signals for the CH_2 protons of the cyclopentane fragment that were sufficiently

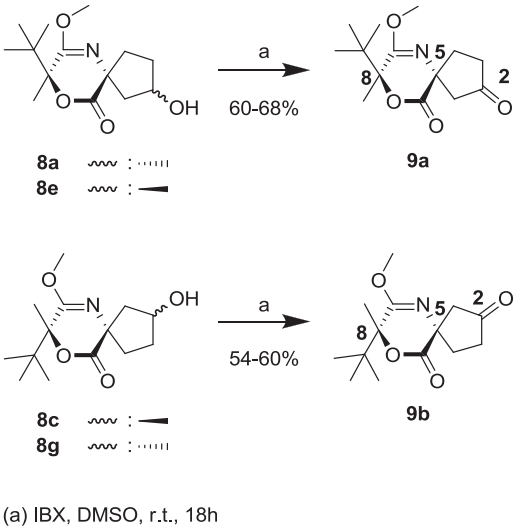


Fig. 5. The oxidation reaction of major stereoisomers of compounds **8**.

resolved to be used for NOE analysis (see Supplementary data). According to NOESY spectra, the *tert*-butyl group and the CH_2–CH_2– fragment of the cyclopentane moiety are on the same side of the 1,4-oxazine (see Supplementary data). Thus, with the absolute configuration at C-8 being known [(8*S*)], it was easy to conclude that the absolute configuration at C-5 must be (*R*) [(5*R*)]. Because the configuration of the asymmetric carbon atom at position C-5 of compounds **9a** and **8a** must be the same and configuration at C-2 is given from the fixed stereocenter of the biselectrophil (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7**, it was possible to assign absolute configuration of the precursor alcohol **8a** as (2*S*,5*R*,8*S*). As oxidation of compound **8e** had resulted in the same stereoisomer as obtained from oxidation of compound **8a**, the absolute configuration of alcohol **8e** has to be (2*R*,5*R*,8*S*).

Stereoisomeres **8c** and **8g** had yielded the same oxidation product, in this case **9b**. Using the same procedure for the assignment of the stereochemistry as for **8a** and **8e**, it was possible to determine the configuration for **8c** as (2*S*,5*S*,8*R*) and as (2*R*,5*S*,8*R*) for **8g**.

In the final stage, a two-step sequence hydrolysis of major diastereomers of compounds **8a**, **8c**, **8e** and **8g** was employed providing the free amino acids **5a**–**d**. The reactions were carried out in pressure tubes using microwave for heating. Firstly, the relevant diastereomers of compounds **8** were dissolved in a mixture of water and methanol (9:1) and were treated with TFA at 100 °C for 2 h. This resulted in complete cleavage of the imidate function. Then, the cleavage products thus obtained were treated with NaOH in methanol at 100 °C for 2 h to hydrolyze the remaining ester function. After workup with 2 M HCl and subsequent purification by ion exchange chromatography, the free cyclopentane derivatives **5a**–**d** were obtained 38–78% (Fig. 6).

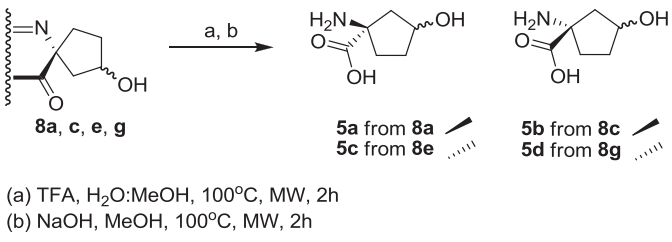


Fig. 6. Hydrolysis of 8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-aza-spiro [4.5]dec-6-en-10-one to the corresponding free amino acids.

3. Conclusions

In summary, an asymmetric synthesis of all four stereoisomers of 1-amino-3-hydroxy-cyclopentane-1-carboxylic acid, **5a**–**d**, based on the chiral glycine equivalents (*R*)-**4** and (*S*)-**4**, has been accomplished. The one-pot bis-alkylation of glycine equivalents **4** mediated by the phosphazenic base *t*-BuP_4 is to be considered the key step of the synthetic sequence. So far, this method has been used for the preparation of the free amino acids **5a**–**d**, but it should also easily provide access to related amino acids with different substituents in the 3-position of the cyclopentane ring.

4. Experimental

4.1. General

All experiments were carried out in oven-dried glassware under dry Ar atmosphere and standard vacuum techniques were used. Analytical grade chemicals were obtained from commercial sources and used without further purification. Solvents were dried under dry Ar atmosphere using standard methods and were freshly distilled before use. Thionyl chloride was distilled under low pressure up to three weeks before use. Chromatography was performed with silica gel (Merck Si_{60} 0.040–0.063 mm). For ion exchange chromatography demineralized water was used. Thin layer chromatography (TLC) was performed on precoated silica gel 60–F_{254} plates (Merck). The products were detected on the TLC plates by one of the following methods/detection reagents or a combination of them: UV light, ammonium cerium(IV)heptamolybdate solution, ninhydrin, or potassium permanganate. Reactions under microwave irradiation were carried out using a Discover LabMate (CEM Corporation). Optical rotation was measured on a polarimeter Jasco, model P-2000 using a sodium lamp, emitting light at a wavelength of 589 nm and a 10 cm polametric tube. Elemental analyses (C, H, N) were performed on an Elementar Vario EL III (Elementar Analysensystem, Hanau, Germany). NMR spectra were measured in $CDCl_3$ or in D_2O on a Varian Mercury-VX 300 spectrometer operating at 300.08 MHz (^{1}H) and 75.46 MHz (^{13}C). Chemical shifts (δ in parts per million) were referenced to the lock signal of the solvent. Coupling constants, *J*, are expressed in Hertz. Sample concentrations were in the range of 20 mg/ml. All spectra were acquired at ambient temperature, for each ^{1}H NMR spectrum, 16 scans were accumulated with spectral width of 4.2 kHz and 32 k data points. ^{13}C spectra were recorded with spectral width of 18 kHz and 64 k data points. All 2D experiments were performed using standard pulse sequences of spectrometer. Spectral widths of the ^{1}H and ^{13}C dimensions were 2.7 kHz and 13.5 kHz, respectively, data matrix for FT 1 k×1 k Mixing time for NOESY experiment was 500 ms. HPLC chromatography was performed using a Waters liquid chromatographic system consisting of a UV detector 486 and two gradient pumps 515 (*n*-heptane/ethyl acetate, 1.50 mL/min). Sample solutions were injected with a Waters valve loop injector. All measurements were carried out at ambient temperature. The HPLC columns were: LiChro-Cart® with LiChrospher® Si 60 cartridge (5 μm, 250 4 mm with precolumn 4 4 mm, Merck) (analytical) and a Hibar (prepacked) LiChrosorb® Si 60 (7 μm, 250 25 mm, Merck) (preparative). HR-MS: AutoSpec Premier (Waters). IR spectra were measured as KBr pellets on FT Jasco IR spectrometer (for solids) or as a film on Perkin Elmer FT-Infrared Spectrometer Paragon 1000 (for liquids).

4.2. (*S*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane ((*S*)-10)

To a solution of imidazole (2.98 g, 44.0 mmol) in diethyl ether (72 mL) at 0 °C triphenylposphine (5.60 g, 22.0 mmol), iodine (6.10 g, 24.0 mmol) and (*S*)-acetonide ((*S*)-**9**) (2.92 g, 20.0 mmol)

were added. The resulting mixture was warmed to room temperature and stirred for 18 h. Then solid $Na_2S_2O_3$ (5.00 g) was added and the resulting mixture was diluted with phosphate buffer pH=7.0 (72 mL). The aqueous phase was washed with diethyl ether (4×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuum. The crude product was purified by column chromatography (20% *tert*-butyl methyl ether/petroleum ether) to give the *title compound* (*S*)-**10** (3.97 g, 15.5 mmol, 76%) as orange oil; [Found: C, 32.94; H, 5.27. $C_7H_{13}O_2I$ (256.08) requires C, 32.83; H, 5.12%]; R_f (20% *tert*-butyl methyl ether/petroleum ether) 0.7; $[\alpha]_D^{20}$ −21.6 (*c* 1.100, MeOH) ($[\alpha]_D^{20}$ −22.3 (*c* 2.12, $CHCl_3$)[48]); δ_H (300 MHz, $CDCl_3$) 4.12–4.22 (1H, m, CH_2CHCH_2), 4.04–4.11 (1H, m, $CHCH_2O$), 3.57 (1H, dd, *J* 8.0, 6.4 Hz, $CHCH_2O$), 3.19–3.30 (2H, m, CH_2I), 1.97–2.13 (2H, m, CH_2CH_2CH), 1.40 (3H, s, CH_3C), 1.35 (3H, s, CH_3C); δ_C (75.5 MHz, $CDCl_3$) 109.2 (CH_3C), 75.7 (CH_2CHCH_2), 68.6 ($CHCH_2O$), 37.9 (CH_2CH_2CH), 27.0 (CH_3C), 25.5 (CH_3C), 1.2 (CH_2I).

4.3. (*R*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane ((*R*)-10)

This compound was obtained by the procedure described for the synthesis of (*S*)-**10**, from (*R*)-**9** (2.92 g, 20.0 mmol). Yield: 3.91 g (76%, 15.3 mmol) as orange oil. NMR data were identical to those of the enantiomer (*S*)-**10**; [Found: C, 32.95; H, 5.02. $C_7H_{13}O_2I$ (256.08) requires C, 32.83; H, 5.12%]; $[\alpha]_D^{20}$ +22.6 (*c* 1.054, MeOH) ($[\alpha]_D^{20}$ +23.0 (*c* 1.02, $CHCl_3$)[49]).

4.4. (*S*)-4-Iodobutan-1,2-diol ((*S*)-11))

To a stirred ice-cold solution of (*S*)-**10** (3.97 g, 15.5 mmol) in methanol (87 mL) was added *p*-TsOH×H_2O (0.60 g, 3.2 mmol). The mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched by addition solid sodium hydrogen carbonate (7 g). Solvent was removed in vacuum and the resulting residue was purified by column chromatography (ethyl acetate) to give the *title compound* (*S*)-**11** (2.14 g, 9.91 mmol, 64%) as a red oil. [Found: C, 22.39; H, 4.27. $C_4H_9O_2I$ (216.02) requires C, 22.24; H, 4.20%]; R_f (ethyl acetate) 0.4; $[\alpha]_D^{20}$ −33.9 (*c* 1.490, MeOH); δ_H (300 MHz, $CDCl_3$) 3.83–3.93 (1H, m, CH_2CHCH_2), 3.71 (1H, dd, *J* 11.0, 3.1 Hz, $CHCH_2O$), 3.52 (1H, dd, *J* 10.9, 7.0 Hz, $CHCH_2O$), 3.26–3.37 (2H, m, CH_2I), 1.91–1.97 (2H, m, CH_2CH_2CH); δ_C (75.5 MHz, $CDCl_3$) 71.9 (CH_2CHCH_2), 66.2 ($CHCH_2OH$), 36.4 (CH_2CH_2CH), 2.4 (CH_2I).

4.5. (*R*)-4-Iodobutan-1,2-diol ((*R*)-11))

This compound was obtained by the procedure described for the synthesis of (*S*)-**11**, from (*R*)-**10** (3.90 g, 15.2 mmol). Yield: 2.18 g (66%, 10.1 mmol) as red oil. NMR data were identical to those of the enantiomer (*S*)-**11**; [Found: C, 22.24; H 4.20. $C_4H_9O_2I$ (216.02) requires C, 22.38, H, 4.29%]; $[\alpha]_D^{20}$ −33.4 (*c* 1.678, MeOH).

4.6. (2*R*,4*S*)-4-(2-Iodoethyl)-1,3,2-dioxathiolan-2-oxide and (2*S*,4*S*)-4-(2-iodoethyl)-1,3,2-dioxathiolan-2-oxide ((2*R*,4*S*)-7/(2*S*,4*S*)-7)

Thionyl chloride (1.31 g, 0.8 mL, 11.0 mmol) was added to a suspension of (*S*)-**11** (2.06 g, 9.54 mmol) in tetrachloromethane (15 mL) and the solution was refluxed for 1 h. Then, the solvent was evaporated in vacuum and the remaining oil was purified by column chromatography (diethyl ether) to give the *title compound* (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** (2.17 g, 8.28 mmol, 87%) as a yellow oil, mixture of diastereomeres 56:44, determined by NMR; [Found: C, 18.53; H, 2.89; S, 12.31. $C_4H_7O_3SI$ (262.07) requires C, 18.33; H, 2.69; S, 12.24%]; R_f (diethyl ether) 0.88; $[\alpha]_D^{20}$ −57.8 (*c* 1.056, MeOH); ν_{max} (film) 1215, 1030, 960, 850 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.04–5.14 (1H, m, CH_2CHO), 4.78 (1H, dd, *J* 8.5, 6.2 Hz, $CHCH_2O$), 4.04 (1H, dd, *J* 8.5, 5.9 Hz, $CHCH_2O$), 3.17–3.29 (2H, m, ICH_2CH_2), 2.07–2.22 (2H, m, CH_2CH_2C) (for diastereoisomer 1); 4.64–4.74 (0.73H, m, $(CH_2)_2CHO$), 4.55–4.62 (0.76H, m, $CHCH_2O$), 4.38–4.45 (0.75H, m, $CHCH_2O$), 3.29–3.41 (1.58H, m, ICH_2CH_2), 2.21–2.35 (1.45H, m, CH_2CH_2C) (for diastereoisomer 2); δ_C (75.5 MHz, $CDCl_3$) 80.0 (CH_2CHCH_2), 70.7 ($CHCH_2O$), 36.5 (CH_2CH_2CH), −1.2 (ICH_2CH) (for diastereoisomer 1); 82.9 (CH_2CHCH_2), 70.0 ($CHCH_2O$), 37.8 (CH_2CH_2CH), 0.00 (ICH_2CH) (for diastereoisomer 2).

4.7. (2*R*,4*R*)-4-(2-Iodoethyl)-1,3,2-dioxathiolan-2-oxide and (2*S*,4*R*)-4-(2-iodoethyl)-1,3,2-dioxathiolan-2-oxide ((2*S*,4*R*)-7/(2*R*,4*R*)-7)

This compound was obtained by the procedure described for the synthesis of (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7**, from (*R*)-**11** (2.18 g, 10.1 mmol). Yield: 2.54 g (96%, 8.31 mmol) as yellow oil, mixture of diastereomeres 56:44, determined by NMR. NMR data were identical to the (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7**. [Found: C, 18.53, H, 2.89, S, 12.31. $C_4H_7O_3SI$ (262.07) requires C, 18.33; H, 2.69; S, 12.24%]; $[\alpha]_D^{20}$ +57.4 (1.230, MeOH); ν_{max} (film) 1210, 1034, 960, 850 cm^{-1}.

4.8. General procedure for the synthesis of the diastereoisomers of 8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (8a–h)

A solution of glycine equivalent (**4**) (0.20 g, 1.0 mmol) in THF (8 mL) was cooled to −65 °C, treated with *t*-BuP_4 (1 M in hexane, 2 mL, 2.0 mmol) and stirred for 1 h. Then, 4-(2-iodoethyl)-1,3,2-dioxathiolan-2-oxide (**7**) (0.40 mg, 1.5 mmol) was added and the stirring was continued for 2 h. Finally, the reaction was quenched by addition of phosphate buffer pH=7.0 (8 mL), and allowed to warm to room temperature. The inorganic layer was extracted with diethyl ether (4×10 mL). The combined organic layers was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The crude product was purified by column chromatography (50% petroleum ether/ethyl acetate) to give the *title compound* **8**.

4.9. (2*S*,5*R*,8*S*)-8-*tert*-Butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (8a) and (2*S*,5*S*,8*S*)-8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (8b)

From glycine equivalent (*S*)-**4** and (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** according to general procedure. Yield: 0.11 g (42%, 0.41 mmol) as a yellow oil. R_f (50% petroleum ether/ethyl acetate) 0.48. The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 1.50 mL/min): ds **8a**/**8b** 96:4. **8a**: t_{Ret} 11.03 min; **8b**: t_{Ret} 13.87 min. For analytical purposes a sample of **8a**/**8b** was separated by preparative HPLC (4% ethyl acetate/*n*-heptane; 15.0 mL/min): **8a**: t_{Ret} 17.51 min; **8b**: t_{Ret} 20.42 min [Found: C, 62.41; H, 8.63; N, 5.21. $C_{14}H_{23}NO_4$ requires C, 62.43; H, 8.61, N, 5.20%]; $[\alpha]_D^{20}$ +22.5 (*c* 0.875, MeOH); ν_{max} (film) 3473, 2949, 2859, 1707, 1332, 1104 cm^{-1}; HR-MS (EI): M^++1, found 270.1630 $C_{14}H_{23}NO_4$ requires 270.1627.

8a: δ_H (300 MHz, $CDCl_3$) 4.43–4.5 (1H, m, CCH_2CH), 3.67 (3H, s, CH_3O), 2.35–2.45 (2H, m, CCH_2CH), 2.21–2.31 (1H, m, CCH_2CH_2CH), 1.98–2.09 (3H, m, CCH_2CH_2CH), 1.54 (3H, s, CH_3), 1.03 (9H, s, $(CH_3)_3C$); δ_C (75.5 MHz, $CDCl_3$) 172.0 (C–COO), 158.8 (C–C(OCH_3)=N), 88.6 (C–C(OCH_3)=N), 75.2 (CH–OH), 66.4 (NCCOO), 52.9 (OCH_3), 51.2 (C–CH_2–CH), 40.4 ($C(CH_3)_3$), 36.7 (C–CH_2–CH_2–C=O), 35.7 (C–CH_2CH_2–C=O), 25.8 ($C(CH_3)_3$), 21.6 (C–CH_3).

8b: δ_H (300 MHz, $CDCl_3$) 4.44–4.56 (1H, m, CCH_2CH), 3.69 (3H, s, CH_3O), 2.41–2.48 (2H, m, CCH_2CH), 2.25–2.33 (1H, m, CCH_2CH_2CH), 1.88–1.99 (3H, m, CCH_2CH_2CH), 1.57 (3H, s, CH_3), 1.04 (9H, s, $(CH_3)_3C$); δ_C (75.5 MHz, $CDCl_3$) 172.1 (C–COO), 158.9 (C–C(OCH_3)=N), 88.6 (C–C(OCH_3)=N), 75.2 (CH–OH), 66.4 (NCCOO), 53.0

(OCH$_3$), 51.2 (C–CH$_2$–CH), 40.4 (C(CH$_3$)$_3$), 36.6 (C–CH$_2$–CH$_2$–C=O), 35.6 (C–CH$_2$CH$_2$–C=O), 25.8 (C(CH$_3$)$_3$), 21.7 (C–CH$_3$).

4.10. (2*S*,5*S*,8*R*)-8-*tert*-Butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (8c) and (2*S*,5*R*,8*R*)-8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-aza-spiro [4.5]dec-6-en-10-one (8d)

From glycine equivalent (*R*)-**4** and (2*R*,4*S*)-**7**/(2*S*,4*S*)-**7** according to general procedure. R_f (50% petroleum ether/ethyl acetate). Yield: 0.13 g (47%, 0.48 mmol) as a yellow oil. The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 1.50 mL/min): ds **8c**/**8d** 70:30. **8c**: t_{Ret} 12.47 min; **8d**: t_{Ret} 14.99 min. For analytical purposes a sample of **8c**/**8d** was separated by preparative HPLC (30% ethyl acetate/*n*-heptane; 15.0 mL/min): **8c**: t_{Ret} 16.48 min; **8d**: t_{Ret} 18.65 min.

[Found: C, 62.39; H, 8.62; N, 5.18. $C_{14}H_{23}NO_4$ requires C, 62.43; H, 8.61, N, 5.20%]; $[\alpha]_D^{20}$ −27.0 (*c* 0.935, MeOH); ν_{max} (film) 3438, 2947, 1734, 1331, 1220, 1105 cm^{-1}; HR-MS (EI): M$^+$+1, found 270.1625 $C_{14}H_{23}NO_4$ requires 270.1627.

8c: δ_H (300 MHz, CDCl$_3$) 4.44 (1H, br s, CCH$_2$C*H*OH), 3.66 (3H, s, C*H*$_3$O), 2.30–2.56 (2H, m, CC*H*$_2$CH), 2.07–2.20 (3H, m, CC*H*$_2$C*H*$_2$CH), 1.79–1.89 (1H, m, CC*H*$_2$CH$_2$CH), 1.52 (3H, s, C*H*$_3$), 1.01 (9H, s, (C*H*$_3$)$_3$C); δ_C (75.5 MHz, CDCl$_3$) 176.5 (C–COO), 158.6 (C–*C*(OCH$_3$)=N), 89.2 (*C*–C(OCH$_3$)=N), 74.3 (*C*H–OH), 64.9 (NCCOO), 52.7 (OCH$_3$), 52.5 (C–*C*H$_2$–CH), 41.2 (*C*(CH$_3$)$_3$), 38.5 (C–*C*H$_2$–CH$_2$–C=O), 36.1 (C–CH$_2$*C*H$_2$–C=O), 25.7 (C(*C*H$_3$)$_3$), 21.6 (C–*C*H$_3$).

8d: δ_H (300 MHz, CDCl$_3$) 4.44 (1H, br s, C*H*–OH), 3.67 (3H, s, C*H*$_3$O), 2.30–2.56 (2H, m, CC*H*$_2$C–OH), 2.07–2.20 (3H, m, CC*H*$_2$C*H*$_2$CH), 1.79–1.89 (1H, m, CC*H*$_2$CH$_2$CH), 1.54 (3H, s, C*H*$_3$), 1.03 (9H,s, (C*H*$_3$)$_3$C); δ_C (75.5 MHz, CDCl$_3$) 176.5 (C–COO), 158.6 (C–*C*(OCH$_3$)=N), 88.5 (*C*–C(OCH$_3$)=N), 75.1 (*C*H–OH), 66.2 (NCCOO), 52.7 (OCH$_3$), 52.5 (C–CH$_2$–CH), 42.2 (*C*(CH$_3$)$_3$), 38.5 (C–*C*H$_2$–CH$_2$–C=O), 35.5 (C–CH$_2$*C*H$_2$–C=O), 25.7 (C(*C*H$_3$)$_3$), 21.5 (C–*C*H$_3$).

4.11. (2*R*,5*R*,8*S*)-8-*tert*-Butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-aza-spiro[4.5]dec-6-en-10-one (8e) and (2*R*, 5*R*, 8*R*)-8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-aza-spiro [4.5]dec-6-en-10-one (8f)

From glycine equivalent (*S*)-**4** and (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7** according to general procedure. R_f (50% petroleum ether/ethyl acetate). Yield: 0.14 g (49%, 0.52 mmol) as a yellow oil, mixture of diastereomeres 91:9, **8e**:**8f**. The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 1.50 mL/min): ds **8e**/**8f** 91:9. **8e**: t_{Ret} 18.95 min; **8f**: t_{Ret} 20.74 min. For analytical purposes a sample of **8e**/**8f** was separated by preparative HPLC (9% ethyl acetate/*n*-heptane; 15.0 mL/min): **8e**: t_{Ret} 15.22 min; **8f**: t_{Ret} 17.98 min.

[Found: C, 62.40; H, 8.57; N, 5.22. $C_{14}H_{23}NO_4$ requires C, 62.43; H, 8.61; N, 5.20%]; $[\alpha]_D^{20}$ +23.4 (*c* 0.585, MeOH); ν_{max} (film) 3410, 2946, 1727, 1692, 1326, 1106 cm^{-1}; HR-MS (EI): M$^+$+1, found 270.1634 $C_{14}H_{23}NO_4$ requires 270.1627.

8e: δ_H (300 MHz, CDCl$_3$) 4.40–4.49 (m, 1H, C*H*–OH), 3.65 (s, 3H, C*H*$_3$O), 2.28–2.56 (m, 2H, CC*H*$_2$C–OH), 2.17–2.27 (m, 1H, CC*H*$_2$CH$_2$CH), 1.97–2.16 (m, 3H, CC*H*$_2$C*H*$_2$CH), 1.51 (s, 3H, C*H*$_3$), 1.01 (s, 9H, (C*H*$_3$)$_3$C); δ_C (75.5 MHz, CDCl$_3$) 176.5 (C–COO), 158.6 (C–*C*(OCH$_3$)=N), 89.1 (*C*–C(OCH$_3$)=N), 74.3 (*C*H–OH), 64.9 (NCCOO), 52.6 (OCH$_3$), 52.5 (C–*C*H$_2$–CH), 41.1 (*C*(CH$_3$)$_3$), 38.5 (C–*C*H$_2$–CH$_2$–C=O), 36.0 (C–CH$_2$*C*H$_2$–C=O), 25.8 (C(*C*H$_3$)$_3$), 21.6 (C–*C*H$_3$).

8f: δ_H (300 MHz, CDCl$_3$) 4.42–4.54 (1H, m, C*H*–OH), 3.70 (3H, s, C*H*$_3$O), 2.39–2.46 (2H, m, CC*H*$_2$C–OH), 2.30–2.35 (1H, m, CC*H*$_2$CH$_2$CH), 1.57 (3H, s, C*H*$_3$), 1.93–2.18 (3H, m, CC*H*$_2$C*H*$_2$CH), 1.05 (9H, s, (C*H*$_3$)$_3$C); δ_C (75.5 MHz, CDCl$_3$) 172.1 (C–COO), 158.0 (C–*C*(OCH$_3$)=N), 88.7 (*C*–C(OCH$_3$)=N), 75.4 (*C*H–OH), 66.6 (NCCOO), 53.0 (OCH$_3$), 51.3 (C–*C*H$_2$–CH), 40.5 (*C*(CH$_3$)$_3$), 38.8 (C–*C*H$_2$–CH$_2$–C=O), 35.7 (C–CH$_2$*C*H$_2$–C=O), 25.8 (C(*C*H$_3$)$_3$), 21.7 (C–*C*H$_3$).

4.12. (2*R*,5*S*,8*R*)-8-*tert*-Butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (8g) and (2*R*, 5*S*, 8*S*)-8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro [4.5]dec-6-en-10-one (8h)

From glycine equivalent (*R*)-**4** and (2*S*,4*R*)-**7**/(2*R*,4*R*)-**7** according to general procedure. Yield: 0.14 g (49%, 0.52 mmol) as a yellow oil, mixture of diastereomeres 70:30, **8g**:**8h**, R_f (50% petroleum ether/ethyl acetate) 0.49. The diastereoselectivity was determined by analytical HPLC (*n*-heptane/ethyl acetate, 1.50 mL/min): ds **8g**/**8h** 70:30. **8g**: t_{Ret} 15.29 min; **8h**: t_{Ret} 19.67 min. For analytical purposes a sample of **8g**/**8h** was separated by preparative HPLC (30% ethyl acetate/*n*-heptane, 15.0 mL/min): **8g**: t_{Ret} 19.04 min; **8h**: t_{Ret} 22.34 min.

[Found: C, 62.37; H, 8.60; N, 5.17. $C_{14}H_{23}NO_4$ requires C, 62.43; H, 8.61, N, 5.20%]; $[\alpha]_D^{20}$ −25.0 (*c* 0.655, MeOH); ν_{max} (film) 3457, 2961, 2850, 1716, 1694, 1336, 1100 cm^{-1}; HR-MS (EI): M$^+$+1, found 270.1623 $C_{14}H_{23}NO_4$ requires 270.1627.

8g: δ_H (300 MHz, CDCl$_3$) 4.39–4.51 (1H, m, CCH$_2$C*H*), 3.66 (3H, s, C*H*$_3$O), 2.34–2.42 (2H, m, CC*H*$_2$CH), 2.23–2.32 (1H, m, CC*H*$_2$CH$_2$CH), 1.99–2.08 (3H, m, CC*H*$_2$C*H*$_2$CH), 1.53 (3H, s, C*H*$_3$), 1.02 (9H, s, (C*H*$_3$)$_3$C); δ_C (75.5 MHz, CDCl$_3$) 172.0 (C–COO), 158.8 (C–*C*(OCH$_3$)=N), 88.5 (*C*–C(OCH$_3$)=N), 75.1 (*C*H–OH), 66.4 (NCCOO), 52.9 (OCH$_3$), 51.2 (C–CH$_2$–CH), 40.4 (*C*(CH$_3$)$_3$), 38.7 (C–*C*H$_2$–CH$_2$–C=O), 35.6 (C–CH$_2$CH$_2$–C=O), 25.8 (C(*C*H$_3$)$_3$), 21.6 (C–*C*H$_3$).

8h: δ_H (300 MHz, CDCl$_3$) 4.40–4.49 (1H, m, C*H*–OH), 3.66 (1H, s, C*H*$_3$O), 2.28–2.56 (2H, m, CC*H*$_2$C–OH), 2.17–2.27 (1H, m, CC*H*$_2$CH$_2$CH), 1.97–2.16 (3H, m, CC*H*$_2$C*H*$_2$CH), 1.53 (3H, s, C*H*$_3$), 1.02 (9H, s, (C*H*$_3$)$_3$C); δ_C (75.5 MHz, CDCl$_3$) 176.5 (C–COO); 159.0 (C–*C*(OCH$_3$)=N), 88.5 (*C*–C(OCH$_3$)=N), 75.0 (*C*H–OH), 66.2 (NCCOO), 52.6 (OCH$_3$), 52.5 (C–*C*H$_2$–CH), 42.2 (*C*(CH$_3$)$_3$), 39.0 (C–*C*H$_2$–CH$_2$–C=O), 35.5 (C–CH$_2$*C*H$_2$–C=O), 25.7 (C(*C*H$_3$)$_3$), 21.5 (C–*C*H$_3$).

4.13. General procedure for the synthesis of the diastereoisomers of 8-*tert*-butyl-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-2,10-dion (9a, b)

IBX (1.2 equiv) was dissolved in DMSO (2 mL for 0.1 mmol IBX), stirred for 10 min at room temperature and treated with a solution of 8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro [4.5]dec-6-en-10-one (1.0 equiv) (**8**) in DMSO (1 mL for 0.1 mmol **8**). After 18 h stirring at room temperature, the reaction mixture was diluted with diethyl ether (2 mL for 0.1 mmol **8**), cooled to 0 °C and quenched by addition of the same amount of water. The inorganic layer was diluted with brine and extracted with diethyl ether (2×5 mL). The combined organic layers were washed with saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous Na_2SO_4 and evaporated in vacuum. The crude product was purified by column chromatography (diethyl ether) to give the *title compound* **9**.

4.14. (5*R*,8*S*)-8-*tert*-Butyl-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-2,10-dion (9a)

From 0.12 g (0.44 mmol) (2*S*,5*R*,8*S*)-8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (**8a**) according to general procedure. Yield: 0.08 g (0.30 mmol, 68%) as a white solid.

From 0.10 g (0.37 mmol) (2*R*,5*R*,8*S*)-8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (**8e**)

according to general procedure. Yield: 0.06 g (0.22 mmol, 60%) as a white solid.

Mp=61 °C; [Found: C, 62.99; H, 7.81; N, 5.1. $C_{14}H_{21}NO$ (267.33) requires C, 62.90; H, 7.92; N, 5.24%]; R_f (diethyl ether) 0.8. $[\alpha]_D^{20}$ −40.6 (*c* 1.344, $CHCl_3$); ν_{max} (KBr) 2987, 2973, 2955, 1754, 1729, 1697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.66 (3H, s, CH_3O), 2.87 (1H, d, *J* 17.2 Hz, CCH_2CO), 2.50–2.64 (3H, m, CCH_2CH_2), 2.35 (1H, d, *J* 18.0 Hz, CCH_2CO), 2.11–2.19 (1H, m, CCH_2CH_2), 1.53 (3H, s, CH_3), 1.05 (9H, s, $(CH_3)_3C$); δ_C (75.5 MHz, $CDCl_3$) 215.0 (CH_2–(C=O)–CH_2), 171.2 (NCCOO), 159.8 (C–C(OCH_3)=N), 89.3 (C–C(OCH_3)=N), 62.6 (CH_2–C–CH_2–CH_2), 53.8 (C–CH_2–C=O), 53.0 (C–C(OCH_3)=N), 38.6 (C–C–C(OCH_3)=N), 36.7 (C–CH_2–CH_2–C=O), 35.7 (C–CH_2CH_2–C=O), 25.8 ($C(CH_3)_3$), 21.8 (C–CH_3).

4.15. (5*S*,8*R*)-8-*tert*-Butyl-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-2, 10-dion (9b)

From 0.11 g (0.41 mmol) (2*R*,5*S*,8*R*)-8-*tert*-Butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (**8g**) according to general procedure. Yield: 0.06 g (0.22 mmol, 54%) as a white solid.

From 0.10 g (0.41 mmol) (2*R*,5*S*,8*R*)-8-*tert*-butyl-2-hydroxy-7-methoxy-8-methyl-9-oxa-6-azaspiro[4.5]dec-6-en-10-one (**8e**) according to general procedure. Yield: 0.06 g (0.22 mmol, 60%) as a white solid.

Mp=74 °C; [Found: C, 63.12; H, 8.11; N, 5.34. $C_{14}H_{21}NO$ (267.33) requires C, 62.90; H, 7.92; N, 5.24%]; R_f (diethyl ether) 0.8. $[\alpha]_D^{20}$ +41.9 (*c* 1.018, $CHCl_3$); ν_{max} (KBr) 2987, 2973, 2955, 1755, 1730, 1696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.64 (3H, s, CH_3O), 2.84 (1H, d, *J* 17.18 Hz, CCH_2CO), 2.49–2.63 (3H, m, CCH_2CH_2), 2.33 (1H, d, *J* 16.4 Hz, CCH_2CO), 2.09–2.17 (1H, m, CCH_2CH_2), 1.51 (3H, s, CH_3), 1.03 (9H, s, $(CH_3)_3C$); δ_C (75.5 MHz, $CDCl_3$) 214.8 (CH_2–(C=O)–CH_2), 171.2 (NCCOO), 159.8 (C–C(OCH_3)=N), 89.3 (C–C(OCH_3)=N), 62.5 (CH_2–C–CH_2–CH_2), 53.7 (C–CH_2–C=O), 52.9 (C–C(OCH_3)=N), 38.6 (C–C–C(OCH_3)=N), 36.7 (C–CH_2–CH_2–C=O), 35.7 (C–CH_2CH_2–C=O), 25.8 ($C(CH_3)_3$), 21.8 (C–CH_3).

4.16. General procedure for the synthesis of the diastereoisomers of 1-amino-3-hydroxycyclopentane-1-carboxylic acid (5)

TFA (2.0 equiv) was added to a solution of **8** (0.40 equiv) in a mixture of water and methanol (9:1) (3 mL for 0.50 mmol **8**) and the reaction mixture was stirred for 2 h at 100 °C in a microwave. The solvent was then removed in vacuo and the residue was treated with methanol (3 mL for 0.50 mmol **8**) and NaOH (2.1 equiv) and stirred at 100 °C for 2 h in a microwave. The solvent was removed in vacuum, water was added (3 mL), and the alkaline solution was washed with diethyl ethyl (2×3 mL), adjusted to pH 2 by addition of 2 M HCl and again washed with diethyl ether (2×3 mL). The acidic aqueous solution was finally subjected to ion-exchange chromatography (Dowex 50 WX 8 cation exchange resin) to afford the *title compound* **5**.

4.17. (1*R*,3*S*)-1-Amino-3-hydroxycyclopentane-1-carboxylic acid (5a)

From 109 mg **8a** (0.40 mmol). Yield 38.0 mg (65%, 0.26 mmol) as a white solid, mp decomposition over 180 °C; [Found: C, 49.85; H, 7.71; N, 9.71. $C_6H_{11}NO_3$ (145.16) requires C, 49.65, H, 7.64, N, 9.65%]; $[\alpha]_D^{20}$ +5.1 (*c* 0.545, H_2O/EtOH 3:1); ν_{max} (KBr) 3024, 2930, 2643, 2517, 2360, 2342, 2029, 1607, 1477, 1402, 1340, 1328 cm^{-1}; δ_H (300 MHz, D_2O); 4.34–4.44 (m, 1H, CHOH), 2.22 (1H, dd, *J* 14.5, 4.7 Hz, CCH_2CH), 2.05–2.18 (1H, m, CCH_2CH_2), 1.87–2.00 (2H, m, $CHCH_2CH_2$), 1.71–1.84 (2H, m, $CHCH_2CH_2$); δ_C (75.5 MHz, D_2O) 177.3 (COOH), 73.0 (CHOH), 65.9 (CH_2CCH_2), 43.9 (CCH_2CH), 33.9 ($CHCH_2CH_2$), 33.5 ($CHCH_2CH_2$); t_{Ret}=5.67 min.

4.18. (1*S*,3*S*)-1-Amino-3-hydroxycyclopentane-1-carboxylic acid (5b)

From 141 mg **8c** (0.52 mmol). Yield 47.8 mg (63%, 0.33 mmol) as a white solid, mp decomposition over 180 °C; [Found: C, 49.70; H, 7.68; N, 9.69. $C_6H_{11}NO_3$ (145.16) requires C, 49.65, H, 7.64, N, 9.65%]; $[\alpha]_D^{20}$ −6.6 (*c* 0.595, H_2O/EtOH 3:1); ν_{max} (KBr) 3362, 3103, 2361, 2077, 1599, 1478, 1405, 1388 cm^{-1}; δ_H (300 MHz, D_2O) 4.23–4.32 (1H, m, CHOH), 2.18–2.27 (1H, m, CCH_2CH), 2.04–2.09 (1H, m, CCH_2CH_2), 1.87–2.01 (2H, m, $CHCH_2CH_2$), 1.70–1.82 (2H, m, $CHCH_2CH_2$); δ_C (75.5 MHz, D_2O) 177.8 (COOH), 72.3 (CHOH), 64.9 (CH_2CCH_2), 43.6 (CCH_2CH), 33.9 ($CHCH_2CH_2$), 33.8 ($CHCH_2CH_2$); t_{Ret}=4.92 min.

4.19. (1*S*,3*R*)-1-Amino-3-hydroxycyclopentane-1-carboxylic acid (5c)

From 93.4 mg **8e** (0.35 mmol). Yield 19.4 mg (0.13 mmol, 38%). [Found: C, 49.72; H, 7.68; N, 9.72. $C_6H_{11}NO_3$ (145.16) requires C, 49.65, H, 7.64, N, 9.65%]; $[\alpha]_D^{20}$ −5.4 (*c* 0.480, H_2O/EtOH 3:1); ν_{max} (KBr) 3024, 2930, 2643, 2516, 2360, 2341, 2028, 1607, 1477, 1404, 1340, 1328 cm^{-1}. Other analytical data were identical to those of the enantiomer **5a**.

4.20. (1*R*,3*R*)-1-Amino-3-hydroxycyclopentane-1-carboxylic acid (5d)

From 135 mg **8g** (0.50 mmol). Yield 51.6 mg (0.39 mmol, 78%). [Found: C, 49.87; H, 7.79; N, 9.73. $C_6H_{11}NO_3$ (145.16) requires C, 49.65, H, 7.64, N, 9.65%]; $[\alpha]_D^{20}$ +6.9 (*c* 0.620, H_2O/EtOH 3:1); ν_{max} (KBr) 3379, 3102, 2360, 2342, 2077, 1598, 1405, 1388 cm^{-1}. Other analytical data were identical to those of the enantiomer **5b**.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.12.013.

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