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A novel conformationally restricted analogue of 3-methylaspartic acid via stereoselective methylation of chiral pyrrolidin-2-ones

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ABSTRACT

Conformationally restricted analogues of β-methylaspartic acid were easily prepared starting from chiral *N*-protected *trans*-3-amino-4-methoxycarbonyl pyrrolidin-2-ones. The key step of the synthesis was the methylation reaction at C-4, proceeding with high diastereoselection *syn* to the protected amino group lying at C-3 of the pyrrolidin-2-one ring.

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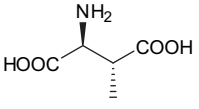
1. Introduction

The binding affinity of bioactive peptides to their receptors and subsequent biological transduction relies on both the backbone conformation of the peptides, and the side-chain orientation of key pharmacophore groups.[1] Moreover, topographical considerations are an important approach for exploring the stereochemical requirements for receptor recognition and for signal transduction,[1,2] so that novel designed amino acids having constrained a side chain are incorporated into peptide templates. In fact, the use of enantiomerically pure β-substituted amino acids into bioactive peptide ligands at key pharmacophore residues was proven to be a powerful tool for understanding ligand–receptor binding interactions and in peptidomimetic design.[3]

In recent years we synthesized a range of novel conformationally constrained amino acids by using asymmetric synthetic strategies with the aim to obtain mimetics of bioactive oligopeptides[4] and neurotransmitter analogues.[5] Within this topic, (2*S*,3*R*)-3-methyl aspartic acid, **1**, and its (2*S*,3*S*)-diastereomer, **2**, were compounds of particular interest.



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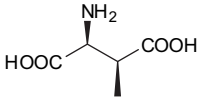


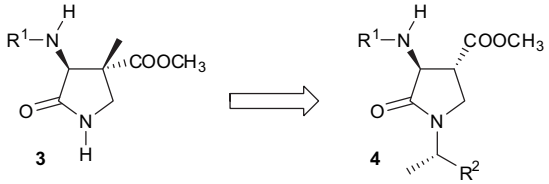
2

In fact, they display a toxic action on *Escherichia coli* being antimetabolites of aspartic acid, and interfere with the functioning of this acid in the formation of pyrimidine precursors.[6] In addition, they are involved in metabolic pathways such as the reversible isomerization of (*S*)-glutamic acid to (2*S*,3*S*)-3-methyl aspartic acid catalysed by glutamate mutase.[7] (2*S*,3*R*)-3-Methyl aspartic acid was recently found to be precursor of the unit C of cryptophycin I, a potent anticancer agent from *Nostoc* cyanobionts,[8] and a component of lipodepsipeptides.[9]

Eventually, a series of side-chain-constrained RGD peptides containing both (2*S*,3*R*)-**1** and (2*S*,3*S*)-3-methylaspartic acid **2** within the RGD sequence have been assayed for binding to the integrin receptors $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$ and the results demonstrated the importance of the side-chain orientation of this particular residue within the RGD sequence.[10]

2. Results and discussion

Initially, we considered the lactams **3a**,**b**, protected analogues of β-methylaspartic acid, in which the conformational restriction arising from the presence of the lactam ring could be derived from compounds **4a**–**c**, recently prepared in our laboratory in enantiomerically pure form.[11a]



a. $R^1 = CCl_3CO$
b. R^1 = *t*-Boc

a. $R^1 = CCl_3CO$, R^2 = PMP
b. R^1 = t-Boc, R^2 = PMP
c. $R^1 = CCl_3CO$, R^2 = Ph

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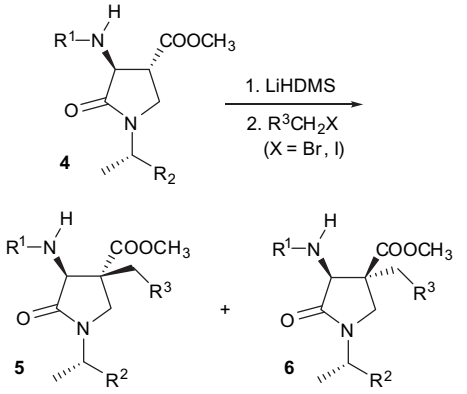
We were delighted to find that treatment of compound **4a** with LiHMDS (3.0 equiv) at 0 °C, followed by alkylation at −78 °C with CH_3I (2.5 equiv) furnished in an excellent 77% yield a 90:10 diastereomeric mixture of **5a** and **6a** (Table 1). Crystallisation allowed isolation of the major diastereomer **5a**, whose stereochemistry was first assigned as (3*S*,4*R*,1′*S*) by comparison of chemical shifts of minor diastereomer.[11] The relative stereochemistry was confirmed as *syn* for the Cl_3CONH and methyl groups by NOE experiments (Fig. 1) and eventually single crystal X-ray analysis allowed unambiguous assignment of the configuration, as reported in Figure 2.[12–14]

Table 1
Alkylation of pyrrolidin-2-ones **4**



Entry	R^1	R^2	R^3	Yield[a] % (dr)
a	CCl_3CO	PMP	H	77 (90:10)
b	*t*-Boc	PMP	H	75 (85:15)
c	CCl_3CO	PMP	Ph	60 (60:40)
d	CCl_3CO	Ph	H	77 (89:11)
e	CCl_3CO	Ph	$(CH_3)_2CH$	51 (80:20)
f	CCl_3CO	Ph	CH_2=CH	94 (60:40)
g	CCl_3CO	Ph	Ph	75 (60:40)

[a] Determined from ^1H NMR spectra of reaction mixtures.

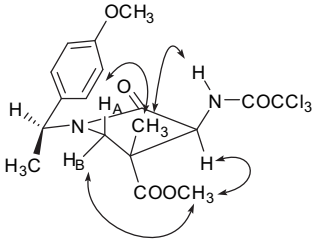


Figure 1. Selected NOE enhancements for compound **5a**.

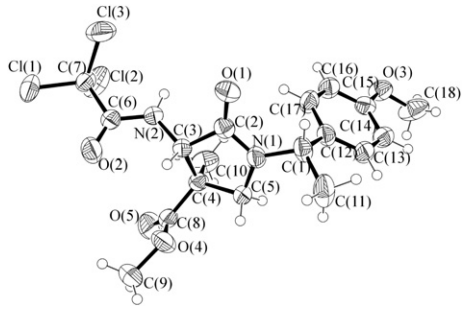
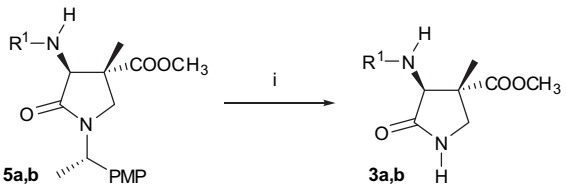


Figure 2. ORTEP drawing of compound **5a** (50% probability).

An analogous trend was observed for methylation of **4b** and **4c**, this latter containing (*S*)-phenylethylamine as the chiral inducer (Table 1).

Next, compounds **5a**,**b** were treated with CAN in acetonitrile–water.[15] Under these conditions cleavage of the 4-methoxyphenylethyl group occurred, to give in good yield the enantiomerically pure 3,4,4-trisubstituted pyrrolidin-2-ones **3a**,**b**, both protected forms of a conformationally restricted analogue of β-methylaspartic acid, **1** (Scheme 1).



Scheme 1. *Reagents and conditions:* **i** CAN, CH_3CN–H_2O; **a**, R^1=CCl_3CO, 83%; **b**, R^1=*t*-C_4H_9OCO, 82%.

Having established that the methylation of pyrrolidin-2-ones **4a–c** proceeds with good stereoselection, leading contrary to the expectations[16] to products where the methyl group lies *syn* to the amide group,[17] we envisaged that this method can disclose the access to a lot of chiral pyrrolidin-2-ones having a quaternary centre at C-4.

However, when halides other than methyl iodide were employed, the reaction proceeded with decreased stereoselection. In addition, diastereomeric mixtures were difficult to separate, an efficient separation being obtained only when (*S*)-4-methoxyphenylethylamine was the chiral inducer (Table 1, entries **a**–**c**).[18] On the other hand it is worth mentioning that well defined signal patterns were always observed in the ^1H NMR spectra, and the chemical shifts allowed a straightforward assignment of the configuration of diastereomers. In fact, for all compounds the shielding effect due to the aryl group of the chiral inducer was instrumental in the structural assignment (Table 2).[14]

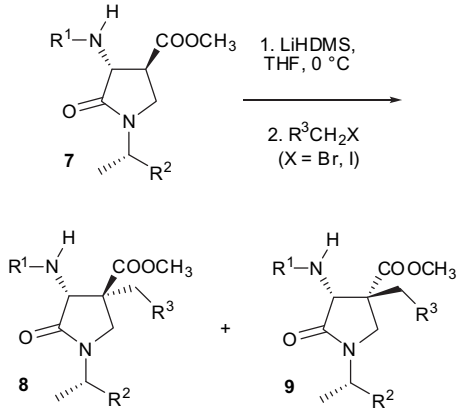
Table 2
Significant chemical shifts for compounds **5**, **6** and **8**, **9**

Compound	(C-4)–CH_2–R	(C-4)–$COOCH_3$
5a	0.93	3.78
6a	1.53	3.43
5b	2.08 and 3.16	3.76
6b	3.27	3.46
5c	0.86	3.69
6c	1.44	3.40
5d	0.92	3.78
6d	1.46	3.41
5e	0.81–0.99	3.67
6e	1.21–1.34	3.49
5f	1.68 and 2.44	3.77
6f	2.57	3.43
5g	2.06 and 3.13	3.78
6g	3.30	3.42
8a	1.22	3.72
9a	1.09	3.76
8b	3.20 and 3.31	3.74
9b	2.95 and 3.60	3.82
8c	2.15–2.67	3.70
9c	2.44–2.55	3.73

With the aim to ascertain if a matching/mismatching effect takes place owing to the contemporary presence of the centres at both C-3 and C-1′, we carried out the alkylation reactions starting from pyrrolidin-2-ones **7a**,**b**, diastereomers of **4a**,**c**.[11a] Under the same reaction conditions, however, similar stereoselection levels were observed. That is, when methyl iodide was the alkylating reagent, **4a** afforded a mixture of compounds **5a** and **6a** in 90:10 dr (matched case) whereas starting from **7a** compounds **8a** and **9a** were obtained in 89:11 dr (mismatched case). Thus, the configuration at C-1′ seems to be independent, the asymmetric induction clearly depending upon the configuration of C-3, which directs the

alkylation outcome. Thus, the ratio of the diastereomers seems to be controlled by the inherent bias of the diastereomeric transition states, not by the position of the phenyl group of the chiral inducer. There was no effect also for alkylation of compounds **7a** and **7b** carried out with benzyl bromide and allyl bromide, respectively, thus confirming that the C-1′ configuration has very low impact on these reactions (Table 3).

Table 3
Alkylation of pyrrolidin-2-one **7a**,**b**



Entry	R^1	R^2	R^3	Yield[a] % (dr)
a	CCl_3CO	PMP	H	73 (89:11)
b	CCl_3CO	PMP	Ph	77 (60:40)
c	CCl_3CO	Ph	CH_2=CH	90 (60:40)

[a] Determined from ^{1}H NMR spectra of reaction mixtures.

The results we obtained could be rationalised as follows. In 4-alkyl substituted pyrrolidin-2-ones the attack of the electrophile to the enolate anion was previously found to proceed on the less hindered side, leading to a 3,4-*trans*-relationship,[16] so that the alkylation of the anion of **4** would be expected to occur *anti* to the bulky trichloroacetylamino group leading to **6**. However, the preferential formation of compound **5** could be explained by a chelation effect between the lithium bonded to nitrogen of the dianion and the halogen of the halide. In the presence of overwhelming factors such as bulkiness of the electrophile, control of the chelation was less effective, and the electrophile was able to attack the enolate on the less hindered side, opposite to the trichloroacetylamino group. Eventually, the chiral inducer did not appear to be involved in diastereoselection, probably due to the distance occurring between the reacting centre and the phenyl group of the inducer. In fact, no significant effect was observed when the alkylation was carried out starting from the pyrrolidin-2-ones **7** having the opposite configuration at both C-3 and C-4 with respect to **4**.

3. Conclusions

In summary, enantiomerically pure 3,4,4-trisubstituted pyrrolidin-2-ones **5a**–**c** were produced in good yield and **5a**,**b** gave **3a** and **3b**, conformationally restricted protected analogues of (*S*)-β-methylaspartic acid, **1**. These resulting unnatural amino acid derivatives are new and versatile intermediates possessing orthogonally functionalized substituents with a wide range of applications in medicinal chemistry where aspartates are involved.[19]

Moreover, it is worth noting that compounds **5**, having a quaternary carbon, are suitable for preparing novel β-foldamers tethered on a pyrrolidin-2-one ring.[20] The constriction due to this centre, according to the Thorpe–Ingold effect[21] observed for α-amino acids,[22] can give rise to a new class of polypeptide helices, allowing modulation of the helix in analogy with the behaviour of hybrid sequences containing α- and β-residues.[23] Work along this line is currently in progress in our laboratory, in particular towards modulation of the secondary structure of amphiphilic β-foldamers, and will be reported in due course.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal IA 9000 apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. Diastereomeric purity was determined by GC analysis using an instrument equipped with a capillary column (50 m×0.25 mm i.d.; stationary phase CP-Sil-5 CB). ^{1}H NMR spectra were recorded at 200 and 400 MHz, whereas ^{13}C NMR spectra were recorded at 50 or 100 MHz, using $CDCl_3$ as a solvent, unless otherwise reported. Chemical shifts (δ) are reported in parts per million relative to TMS and coupling constants (J) in hertz. Assignments were aided by decoupling and homonuclear two-dimensional experiments. Optical rotations were measured using a 1 dm path length cell. The samples were analysed with a liquid chromatography Agilent Technologies HP1100 equipped with a Zorbax Eclipse XDB-C8 Agilent and Technologies column (flow rate 0.5 mL/min) and equipped with a diode-array UV detector (220 and 254 nm). Acetonitrile and methanol for HPLC were purchased from a commercial supplier. All the samples were prepared by diluting 1 mg in 5 mL of a 1:1 mixture of H_2O and acetonitrile in pure acetonitrile or in pure methanol. The MSD1100 mass detector was utilized under the following conditions: mass range 100–2500 uma, positive scanning, energy of fragmentor 50 V, drying gas flow (nitrogen) 10.0 mL/min, nebulizer pressure 45 psig, drying gas temperature 350 °C, capillary voltage 4500 V. Column chromatography was performed with silica gel 60 (230–400 mesh). Compounds **4a**–**c** and **7a**,**b** were prepared as already reported.[11a]

4.2. General procedure for alkylation of pyrrolidin-2-ones 4a–c and 7

To a solution of pyrrolidin-2-ones **4a**–**c** or **7**[11a] (2.0 mmol) in dry THF (6 mL), LiHDMS (1 M in hexanes; 6 mL; 6.0 mmol) was added under argon at 0 °C and the mixture was stirred for 1 h at 0 °C. Then the mixture was cooled to −78 °C and solution of the appropriate halide (5 mmol) dissolved in dry THF (5 mL) was added. After 2 h, H_2O (100 mL) was added and the mixture extracted with ethyl acetate (3×20 mL). After drying (Na_2SO_4) the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 1:1) to give **5**, **6** or **8**, **9** as diastereomeric mixtures.

4.2.1. (3S,4R,1′S)-4-Methoxycarbonyl-1-[1′-(4-methoxyphenyleth-1′-yl)]-4-methyl-3-trichloroacetylaminopyrrolidin-2-one, ***5a****, and its (3S,4S,1′S)-isomer,* ***6a****.* The title compounds were obtained from **4a** in 77% yield as a diastereomeric mixture (dr 90:10), which was easily separated by crystallisation. ESI-MS: m/z 450.1 $[M]^+$, 473.2 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{21}Cl_3N_2O_5$: C, 47.86; H, 4.69; N, 6.20. Found: C, 47.75; H, 4.74; N, 6.14. **Isomer-(3*S*,4*R*,1′*S*)**, **5a**: white crystals: mp 151–153 °C; ν_{max} 3342, 1747, 1705, 1652 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.93 (3H, s, CH_3), 1.54 (3H, d, J 7.2, 1′-CH_3), 2.77 (1H, d, J 9.9, pro-*R* H-5), 3.72 (1H, d, J 9.9, pro-*S* H-5), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.93 (1H, d, J 4.8, H-3), 5.48 (1H, q, J 7.2, H-1′), 6.88 (2 ArH, d, J 8.5), 7.15 (1H, d, J 4.8, NH), 7.23 (2 ArH, d, J 8.5); δ_C (50 MHz, $CDCl_3$) 15.3, 16.2, 47.9, 49.5, 50.2, 52.9, 55.2, 60.1, 91.7, 114.0, 128.3, 130.5, 159.3, 162.5, 167.6, 173.5; $[\alpha]_D$ −40.0 (c 1.0, $CHCl_3$). **Isomer-(3*S*,4*S*,1′*S*)**, **6a**: colourless oil: ν_{max} 3345, 1744, 1708, 1660 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.53 (3H, s, CH_3), 1.54 (3H, d, J 7.2,

1′-CH_3), 3.18 (1H, d, *J* 10.5, pro-*R* H-5), 3.21 (1H, d, *J* 10.5, pro-*S* H-5), 3.43 (3H, s, $COOCH_3$), 3.75 (3H, s, OCH_3), 4.68 (1H, d, *J* 8.2, H-3), 5.46 (1H, q, *J* 7.2, H-1′), 6.88 (2 ArH, d, *J* 8.5), 7.23 (2 ArH, d, *J* 8.5), 7.79 (1H, d, *J* 8.2, NH); δ_C (50 MHz, $CDCl_3$) 14.3, 15.9, 48.1, 49.6, 50.1, 50.5, 52.6, 59.8, 91.9, 114.2, 128.0, 128.3, 128.8, 129.0, 139.0, 163.6, 168.6, 179.6; $[\alpha]_D$ −21.7 (*c* 0.5, $CHCl_3$).

4.2.2. (3S,4R,1′S)-3-t-Butoxycarbonylamino-4-methoxycarbonyl-4-methyl-1-[1′-(4-methoxyphenyleth-1′-yl) pyrrolidin-2-one, ***5b****, and its (3S,4S,1′S)-isomer,* ***6b****.* The title compounds were obtained in 75% yield as an easily separable diastereomeric mixture (dr 85:15). ESI-MS: *m*/*z* 406.2 $[M]^+$, 429.2 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.05; H, 7.44; N, 6.89. Found: C, 61.94; H, 7.33; N, 6.93. **Isomer-(3*S*,4*R*,1′*S*)**, **5b**: colourless oil: ν_{max} 3345, 1724, 1710, 1655 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.86 (s, 3H, CH_3), 1.38 (s, 9H, 3×CH_3), 1.47 (3H, d, *J* 7.2, 1′-CH_3), 2.65 (1H, d, *J* 9.8, pro-*R* H-5), 3.65 (1H, d, *J* 9.8, pro-*S* H-5), 3.69 (3H, s, $COOCH_3$), 3.76 (3H, s, OCH_3), 4.73 (1H, d, *J* 6.5, H-3), 5.05 (1H, d, *J* 6.5, NH), 5.43 (1H, q, *J* 7.2, H-1′), 6.82 (2 ArH, d, *J* 8.8), 7.17 (2 ArH, d, *J* 8.8); δ_C (50 MHz, $CDCl_3$) 15.5, 15.9, 26.1, 47.9, 49.0, 49.2, 52.5, 55.1, 59.9, 79.8, 113.8, 128.2, 130.9, 155.3, 159.1, 168.8, 174.2; $[\alpha]_D$ -56.3 (*c* 1.6, $CHCl_3$). **Isomer-(3*S*,4*S*,1′*S*)**, **6b**: colourless oil: ν_{max} 3347, 1728, 1711, 1658 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.38 (3×CH_3, s, 9H), 1.44 (3H, s, CH_3), 1.48 (3H, d, *J* 7.2, 1′-CH_3), 3.18 (1H, d, *J* 8.8, pro-*R* H-5), 3.21 (1H, d, *J* 8.8, pro-*S* H-5), 3.40 (3H, s, $COOCH_3$), 3.73 (3H, s, OCH_3), 4.68 (1H, d, *J* 6.4, H-3), 5.15 (1H, d, *J* 6.4, NH), 5.48 (1H, q, *J* 7.2, H-1′), 6.81 (2 ArH, d, *J* 8.8), 7.19 (2 ArH, d, *J* 8.8); δ_C (50 MHz, $CDCl_3$) 15.6, 16.0, 26.0, 47.5, 48.8, 49.1, 52.4, 55.4, 59.6, 79.8, 113.6, 128.1, 130.7, 155.1, 159.3, 168.5, 174.1; $[\alpha]_D$ −47.1 (*c* 0.5, $CHCl_3$).

4.2.3. (3S,4R,1′S)-4-Benzyl-4-methoxycarbonyl-1-[1′-(4-methoxyphenyleth-1′-yl)]-3-trichloroacetylaminopyrrolidin-2-one, ***5c****, and its (3S,4S,1′S)-isomer,* ***6c****.* The title compounds were obtained in 60% yield as an easily separable diastereomeric mixture (dr 60:40). ESI-MS: *m*/*z* 526.1 $[M]^+$, 549.2 $[M+Na]^+$. Anal. Calcd for $C_{24}H_{25}Cl_3N_2O_5$: C, 54.61; H, 4.77; N, 5.31. Found: C, 54.55; H, 4.71; N, 5.39. **Isomer-(3*S*,4*R*,1′*S*)**, **5c**: colourless oil: ν_{max} 3361, 1731, 1712, 1681 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.52 (3H, d, *J* 7.2, 1′-CH_3), 2.08 (1H, d, *J* 13.4, CHPh), 3.00 (1H, d, *J* 14.7, pro-*R* H-5), 3.16 (1H, d, *J* 13.4, CHPh), 3.67 (1H, d, *J* 14.7, pro-*S* H-5), 3.76 (s, 3H, $COOCH_3$), 3.86 (s, 3H, OCH_3), 5.00 (1H, d, *J* 7.8, H-3), 5.57 (1H, q, *J* 7.2, H-1′), 6.22 (1H, d, *J* 7.8, NH), 6.94–7.15 (5 ArH, m), 7.21–7.35 (4 ArH, m); δ_C (50 MHz, $CDCl_3$) 16.0, 33.9, 42.9, 49.6, 52.7, 52.8, 55.6, 59.9, 92.2, 114.4, 127.1, 128.4, 129.2, 130.0, 131.1, 134.9, 159.9, 162.7, 167.1, 172.0; $[\alpha]_D$ −14.3 (*c* 0.7, $CHCl_3$). **Isomer-(3*S*,4*S*,1′*S*)**, **6c**: colourless oil: ν_{max} 3355, 1734, 1711, 1685 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.44 (3H, d, *J* 7.0, 1′-CH_3), 3.06 (1H, d, *J* 13.8, pro-*R* H-5), 3.18 (1H, d, *J* 13.8, pro-*S* H-5), 3.27 (2H, s, CH_2Ph), 3.46 (3H, s, $COOCH_3$), 3.79 (3H, s, OCH_3), 4.84 (1H, d, *J* 9.2, H-3), 5.38 (1H, q, *J* 7.0, H-1′), 6.78–6.89 (2 ArH, d, *J* 8.2), 7.04–7.41 (7 ArH, m), 8.01 (1H, d, *J* 9.2, NH); δ_C (50 MHz, $CDCl_3$) 16.0, 39.8, 47.5, 49.1, 52.7, 54.6, 55.5, 57.7, 92.4, 113.9, 114.3, 127.6, 128.5, 128.9, 129.7, 131.2, 134.8, 159.3, 162.7, 168.1, 173.5; $[\alpha]_D$ −38.5 (*c* 0.52, $CHCl_3$).

4.2.4. (3S,4R,1′S)-4-Methoxycarbonyl-4-methyl-1-(1′-phenyleth-1′-yl)-3-trichloroacetylaminopyrrolidin-2-o-ne, ***5d****, and its (3S,4S,1′S)-isomer,* ***6d****.* The title compounds were obtained in 77% yield as a diastereomeric inseparable mixture (dr 89:11). ν_{max} 3352, 1734, 1709, 1655 cm^{-1}; ESI-MS: *m*/*z* 420.1 $[M]^+$, 443.1 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{19}Cl_3N_2O_4$: C, 48.42; H, 4.54; N, 6.64. Found: C, 48.35; H, 4.49; N, 6.71. **Isomer-(3*S*,4*R*,1′*S*)**, **5d**: δ_H (200 MHz, $CDCl_3$) 0.92 (3H, s, CH_3), 1.56 (3H, d, *J* 7.2, 1′-CH_3), 2.76 (1H, d, *J* 12.5, pro-*R* H-5), 3.74 (1H, d, *J* 12.5, pro-*S* H-5), 3.78 (3H, s, $COOCH_3$), 4.94 (1H, d, *J* 6.2, H-3), 5.51 (1H, q, *J* 7.2, H-1′), 7.18 (1H, d, *J* 6.2, NH), 7.24–7.41 (5 ArH, m); δ_C (50 MHz, $CDCl_3$) 15.4, 16.1, 48.1, 50.2, 50.5, 53.1, 60.2, 91.8, 127.3, 128.0, 128.6, 128.8, 128.9, 138.8, 162.6, 167.9, 173.6. **Isomer-(3*S*,4*S*,1′*S*)**, **6d**: δ_H (200 MHz, $CDCl_3$) 1.46 (3H, s, CH_3), 1.53 (3H, d, *J* 7.1, CH_3), 3.18 (1H, d, *J* 12.4, pro-*R* H-5), 3.23 (1H, d, *J* 12.4, pro-*S* H-5), 3.41 (3H, s, $COOCH_3$), 4.88 (1H, d, *J* 8.6, H-3), 5.48 (1H, q, *J* 7.1, H-1′), 7.22–7.42 (5 ArH, m), 7.71 (1H, d, *J* 7.6, NH); δ_C (50 MHz, $CDCl_3$) 14.3, 15.9, 48.1, 49.6, 50.1, 52.6, 59.8, 91.8, 127.3, 128.0, 128.3, 128.8, 129.0, 139.0, 163.3, 168.6, 173.6.

4.2.5. (3S,4R,1′S)-4-Methoxycarbonyl-4-(2″-methyl-prop-1″-yl)-1-(1′-phenyleth-1′-yl)-3-trichloroacetylaminopyrrolidin-2-one, ***5e****, and its (3S,4S,1′S)-isomer,* ***6e****.* The title compounds were obtained in 51% yield as a diastereomeric inseparable mixture (dr 80:20). ν_{max} 3353, 1740, 1709, 1651 cm^{-1}; ESI-MS: *m*/*z* 462.1 $[M]^+$, 485.2 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{25}Cl_3N_2O_4$: C, 51.80; H, 5.43; N, 6.04. Found: C, 51.72; H, 5.48; N, 6.12. **Isomer-(3*S*,4*R*,1′*S*)**, **5e**: δ_H (200 MHz, $CDCl_3$): 0.45 (3H, d, *J* 7.0, CH_3), 0.58 (3H, d, *J* 7.0, CH_3), 0.81–0.99 (2H, m, CH_2), 1.49–1.61 (1H, m, CH), 1.56 (3H, d, *J* 7.2, 1′-CH_3), 3.01 (1H, d, *J* 13.2, pro-*R* H-5), 3.67 (3H, s, $COOCH_3$), 3.74 (1H, d, *J* 13.2, pro-*S* H-5), 4.86 (1H, d, *J* 7.4, H-3), 5.53 (1H, q, *J* 7.2, H-1′), 7.00 (1H, d, *J* 7.4, NH), 7.21–7.37 (5 ArH, m); δ_C (50 MHz, $CDCl_3$) 15.8, 21.9, 24.0, 24.6, 36.0, 43.7, 49.9, 51.4, 52.4, 59.7, 92.3, 127.5, 127.6, 127.9, 128.6, 128.9, 139.0, 162.5, 167.6, 173.1. **Isomer-(3*S*,4*S*,1′*S*)**, **6e**: δ_H (200 MHz, $CDCl_3$) 0.77 (3H, d, *J* 7.0, CH_3), 0.85 (3H, d, *J* 7.0, CH_3), 1.21–1.34 (2H, m, CH_2), 1.51–1.61 (1H, m, CH), 1.52 (3H, d, *J* 7.2, 1′-CH_3), 3.15 (1H, d, *J* 12.4, pro-*R* H-5), 3.27 (1H, d, *J* 12.4, pro-*S* H-5), 3.49 (3H, s, $COOCH_3$), 4.73 (1H, d, *J* 9.4, H-3), 5.51 (1H, q, *J* 7.2, H-1′), 7.21–7.37 (5 ArH, m), 8.22 (1H, d, *J* 9.4, NH); δ_C (50 MHz, $CDCl_3$) 15.4, 22.3, 25.5, 29.8, 36.0, 44.3, 49.7, 51.4, 53.1, 58.8, 92.6, 127.3, 127.6, 127.9, 128.4, 128.9, 139.2, 162.7, 168.6, 174.5.

4.2.6. (3S,4R,1′S)-4-Allyl-4-methoxycarbonyl-1-(1′-phenyleth-1′-yl)-3-trichloroacetylaminopyrrolidin-2-one, ***5f****, and its (3S,4S,1′S)-isomer,* ***6f****.* The title compounds were obtained in 94% yield as a diastereomeric inseparable mixture (dr 60:40). ν_{max} 3349, 1736, 1712, 1674 cm^{-1}; ESI-MS: *m*/*z* 446.1 $[M]^+$, 469.2 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{21}Cl_3N_2O_4$: C, 50.97; H, 4.73; N, 6.26. Found: C, 51.04; H, 4.68; N, 6.32. **Isomer-(3*S*,4*R*,1′*S*)**, **5f**: δ_H (200 MHz, $CDCl_3$) 1.57 (3H, d, *J* 7.2, 1′-CH_3), 1.68 (1H, dd, *J* 9.6, *J* 13.7, C*H*$_2$–CH=), 2.44 (1H, dd, *J* 5.0, *J* 13.7, C*H*$_2$–CH=), 3.06 (1H, d, *J* 10.3, pro-*R* H-5), 3.75 (1H, d, *J* 10.3, pro-*S* H-5), 3.77 (3H, s, $COOCH_3$), 4.71–4.81 (2H, m, CH=C*H*$_2$), 4.96 (1H, d, *J* 6.4, H-3), 5.15–5.35 (1H, m, C*H*=CH_2), 5.53 (1H, q, *J* 7.2, H-1′), 7.08 (1H, d, *J* 6.4, NH), 7.21–7.38 (5 ArH, m); δ_C (50 MHz, $CDCl_3$) 15.8, 33.3, 45.1, 50.1, 50.8, 52.9, 59.8, 91.9, 120.3, 127.0, 127.2, 127.5, 128.3, 128.8, 131.8, 138.6, 162.6, 167.3, 172.5. **Isomer-(3*S*,4*S*,1′*S*)**, **6f**: δ_H (200 MHz, $CDCl_3$) 1.52 (3H, d, *J* 7.2, 1′-CH_3), 2.57 (2H, d, *J* 7.3, C*H*$_2$–CH=), 3.18 (1H, d, *J* 10.5, pro-*R* H-5), 3.26 (1H, d, *J* 10.5, pro-*S* H-5), 3.43 (3H, s, $COOCH_3$), 4.77 (1H, d, *J* 8.8, H-3), 5.04–5.18 (2H, m, CH=C*H*$_2$), 5.51 (1H, q, *J* 7.2, H-1′), 5.51–5.81 (1H, m, C*H*=CH_2), 7.21–7.38 (5 ArH, m), 7.85 (1H, d, *J* 8.8, NH); δ_C (50 MHz, $CDCl_3$) 15.7, 38.2, 47.3, 49.5, 52.5, 53.6, 57.9, 92.3, 120.4, 126.9, 127.9, 128.3, 128.5, 128.8, 131.2, 138.9, 162.4, 168.4, 173.0.

4.2.7. (3S,4R,1′S)-4-Benzyl-4-methoxycarbonyl-1-(1′-phenyleth-1′-yl)-3-trichloroacetylaminopyrrolidin-2-o-ne, ***5g****, and its (3S,4S,1′S)-isomer,* ***6g****.* The title compounds were obtained in 75% yield as a diastereomeric inseparable mixture (dr 60:40). ν_{max} 3347, 1736, 1708, 1668 cm^{-1}; ESI-MS: *m*/*z* 496.1 $[M]^+$, 522.1 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{23}Cl_3N_2O_4$: C, 55.49; H, 4.66; N, 5.63. Found: C, 55.42; H, 4.59; N, 5.69. **Isomer-(3*S*,4*R*,1′*S*)**, **5g**: δ_H (200 MHz, $CDCl_3$) 1.57 (3H, d, *J* 7.2, 1′-CH_3), 2.06 (1H, d, *J* 13.4, C*H*Ph), 3.00 (1H, d, *J* 14.5, pro-*R* H-5), 3.13 (1H, d, *J* 13.4, C*H*Ph), 3.70 (1H, d, *J* 14.5, pro-*S* H-5), 3.78 (3H, s, $COOCH_3$), 5.02 (1H, d, *J* 7.4, H-3), 5.63 (1H, q, *J* 7.2, H-1′), 6.18 (1H, d, *J* 7.4, NH), 6.94–7.35 (10 ArH, m); δ_C (50 MHz, $CDCl_3$) 16.0, 33.9, 42.9, 49.6, 52.7, 52.8, 55.6, 59.9, 91.9, 120.3, 127.0, 127.2, 127.5, 128.3, 128.8, 131.8, 138.6, 162.6, 167.3, 172.5. **Isomer-(3*S*,4*S*,1′*S*)**, **6g**: δ_H (200 MHz, $CDCl_3$) 1.48 (3H, d, *J* 7.0, 1′-CH_3), 3.11 (1H, d, *J* 13.6, pro-*R* H-5), 3.17 (1H, d, *J* 13.6, pro-*S* H-5), 3.30 (2H, s, C*H*$_2$Ph), 3.42 (3H, s, $COOCH_3$), 4.86 (1H, d, *J* 9.2, H-3), 5.41 (1H, q, *J* 7.0, H-1′), 6.98–7.41 (10 ArH, m), 8.04 (1H, d, *J* 9.2, NH); δ_C (50 MHz, $CDCl_3$) 16.0, 29.8,

39.8, 47.5, 49.1, 52.7, 54.6, 55.5, 57.7, 92.4, 92.3, 120.4, 126.9, 127.9, 128.3, 128.5, 128.8, 131.2, 138.9, 162.4, 168.4, 173.0.

4.2.8. (3R,4S,1′S)-4-Methoxycarbonyl-1-[1′-(4-methoxyphenyleth-1′-yl)]-4-methyl-3-trichloroacetylaminopyrrolidin-2-one, ***8a****, and its (3R,4R,1′S)-isomer,* ***9a****.* The title compounds were obtained in 73% yield as an easily separable diastereomeric mixture (dr 89:11). ESI-MS: *m*/*z* 450.1 $[M]^+$, 473.2 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{21}Cl_3N_2O_5$: C, 47.86; H, 4.69; N, 6.20. Found: C, 47.78; H, 4.60; N, 6.16. **Isomer-(3*R*,4*S*,1′*S*)**, **8a**: white solid: mp 122–123 °C; ν_{max} 3355, 1735, 1712, 1661 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.22 (3H, s, CH_3), 1.51 (3H, d, *J* 7.2, 1′-CH_3), 3.03 (1H, d, *J* 10.4, pro-*R* H-5), 3.35 (1H, d, *J* 10.4, pro-*S* H-5), 3.72 (3H, s, $COOCH_3$), 3.79 (3H, s, OCH_3), 4.87 (1H, d, *J* 5.2, H-3), 5.43 (1H, q, *J* 7.2, H-1′), 6.86 (2 ArH, d, *J* 8.8), 7.18 (2 ArH, d, *J* 8.8), 7.38 (1H, d, *J* 5.2, NH); δ_C (100 MHz, $CDCl_3$) 15.8, 15.9, 47.7, 49.7, 50.7, 52.9, 55.2, 60.0, 91.7, 114.1, 128.2, 130.4, 159.3, 162.5, 167.7, 173.3. $[\alpha]_D$ −27.6 (*c* 1.0, $CHCl_3$). **Isomer-(3*R*,4*R*,1′*S*)**, **9a**: colourless oil: ν_{max} 3351, 1737, 1710, 1665 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, s, CH_3), 1.46 (3H, d, *J* 7.2, 1′-CH_3), 2.77 (1H, d, *J* 10.4, pro-*R* H-5), 3.52 (1H, d, *J* 10.4, pro-*S* H-5), 3.69 (3H, s, OCH_3), 3.76 (3H, s, $COOCH_3$), 4.56 (1H, d, *J* 8.4, H-3), 5.43 (1H, q, *J* 7.2, H-1′), 6.86 (2 ArH, d, *J*=8.8), 7.18 (2 ArH, d, *J* 8.8), 7.68 (1H, d, *J* 8.4, NH); δ_C (100 MHz, $CDCl_3$) 14.8, 15.6, 47.7, 49.4, 50.6, 50.7, 52.6, 59.7, 91.9, 114.2, 127.9, 130.6, 159.4, 163.5, 168.7, 173.8. $[\alpha]_D$ −22.1 (*c* 0.5, $CHCl_3$).

4.2.9. (3R,4S,1′S)-4-Benzyl-4-methoxycarbonyl-1-[1′-(4-methoxyphenyleth-1′-yl)]-3-trichloroacetylaminopyrrolidin-2-one, ***8b****, and its (3R,4R,1′S)-isomer,* ***9b****.* The title compounds were obtained in 77% yield as an easily separable diastereomeric mixture (dr 60:40). ESI-MS: *m*/*z* 526.1 $[M]^+$, 549.2 $[M+Na]^+$. Anal. Calcd for $C_{24}H_{25}Cl_3N_2O_5$: C, 54.61; H, 4.77; N, 5.31. Found: C, 54.53; H, 4.73; N, 5.37. **Isomer-(3*R*,4*S*,1′*S*)**, **8b**: colourless oil: ν_{max} 3348, 1737, 1709, 1681 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* 7.2, 1′-CH_3), 2.58 (1H, d, *J* 14.0, pro-*R* H-5), 3.20 (1H, d, *J* 10.8, C*H*Ph), 3.31 (1H, d, *J* 10.8, C*H*Ph), 3.40 (1H, d, *J* 14.0, pro-*S* H-5), 3.74 (3H, s, $COOCH_3$), 3.78 (3H, s, OCH_3), 4.92 (1H, d, *J* 7.2, H-3), 5.40 (1H, q, *J* 7.2, 1′-H), 6.84 (2 ArH, d, *J* 8.8), 7.15 (2 ArH, d, *J* 8.8,), 7.20–7.30 (5 ArH, m), 7.47 (1H, d, *J* 8.8, NH); δ_C (100 MHz, $CDCl_3$) 16.5, 26.9, 34.7, 44.5, 50.1, 52.1, 55.2, 60.0, 92.0, 114.1, 128.2, 128.7, 129.8, 130.8, 135.4, 159.3, 162.7, 167.6, 172.2. $[\alpha]_D$ −19.4 (*c* 0.5, $CHCl_3$). **Isomer-(3*R*,4*R*,1′*S*)**, **9b**: colourless oil: ν_{max} ($CHCl_3$) 3350, 1735, 1709, 1678 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 7.2, 1′-CH_3), 2.95 (1H, d, *J* 10.4, C*H*Ph), 3.05 (1H, d, *J* 14.0, pro-*R* H-5), 3.17 (1H, d, *J* 14.0, pro-*S* H-5), 3.60 (1H, d, *J* 10.4, C*H*Ph), 3.75 (3H, s, OCH_3), 3.82 (3H, s, $COOCH_3$), 4.73 (1H, d, *J* 8.4, H-3), 5.40 (1H, q, *J* 7.2, H-1′), 6.86 (2 ArH, d, *J* 8.8), 7.14 (2 ArH d, *J* 8.8), 7.20–7.30 (5 ArH, m), 7.83 (1H, d, *J* 8.8, NH); δ_C (100 MHz, $CDCl_3$) 15.8, 26.8, 30.1, 43.4, 47.6, 49.5, 57.5, 58.6, 92.8, 113.7, 114.0, 127.4, 128.3, 128.6, 129.3, 129.7, 131.0, 133.0, 159.0, 162.7, 168.1, 173.7. $[\alpha]_D$ −27.5 (*c* 0.44, $CHCl_3$).

4.2.10. (3R,4S,1′S)-4-Allyl-4-methoxycarbonyl-1-(1′-phenyleth-1′-yl)-3-trichloroacetylaminopyrrolidin-2-one, ***8c****, and its (3R,4R,1′S)-isomer,* ***9c****.* The title compounds were obtained in 90% yield as a diastereomeric inseparable mixture (dr 55:45). ν_{max} 3352, 1736, 1711, 1682 cm^{-1}; ESI-MS: *m*/*z* 446.1 $[M]^+$, 469.2 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{21}Cl_3N_2O_4$: C, 50.97; H, 4.73; N, 6.26. Found: C, 50.93; H, 4.78; N, 6.22. **Isomer-(3*R*,4*S*,1′*S*)**, **8c**: δ_H (400 MHz, $CDCl_3$) 1.53 (3H, d, *J* 7.2, 1′-CH_3), 2.15 (1H, dd, *J* 9.2, *J* 14.4, CH_2–C=), 2.67 (1H, dd, *J* 5.6, *J* 14.4, CH_2–C=), 3.20 (1H, d, *J* 10.4, pro-*R* H-5), 3.35 (1H, d, *J* 10.4, pro-*S* H-5), 3.70 (3H, s, $COOCH_3$), 4.92 (1H, d, *J* 6.4, H-3), 5.02–5.10 (1H, m, CH=CH_2), 5.10–5.15 (1H, m, CH=CH_2), 5.45 (1H, q, *J* 7.2, 1′-H), 5.63–5.76 (1H, m, C*H*=CH_2), 7.20–7.40 (5 ArH, m), 7.71 (1H, d, *J* 6.4, NH); δ_C (100 MHz, $CDCl_3$) δ 15.8, 34.1, 46.0, 50.3, 52.8, 53.4, 59.6, 91.7, 120.1, 126.9, 127.9, 128.3, 128.6, 128.7, 132.6, 138.5, 162.6, 167.6, 172.4. **Isomer-(3*R*,4*R*,1′*S*)**, **9c**: δ_H (400 MHz, $CDCl_3$) 1.51 (3H, d, *J* 7.2, 1′-CH_3), 2.44–2.55 (2H, m, CH_2–C=), 2.85 (1H, d, *J* 10.4, pro-*R* H-5), 3.58 (1H, d, *J* 10.4, pro-*S* H-5), 3.73 (3H, s, $COOCH_3$), 4.67 (1H, d, *J* 8.4, H-3), 5.05 (1H, m, CH=CH_2), 5.12–5.17 (1H, m, CH=CH_2), 5.48 (1H, q, *J* 7.2, 1′-H), 5.53–5.64 (1H, m, C*H*=CH_2), 7.20–7.40 (5 ArH, m), 7.94 (1H, d, *J* 8.4, NH); δ_C (100 MHz, $CDCl_3$) 15.5, 30.1, 38.1, 47.3, 50.0, 52.6, 58.3, 92.1, 120.0, 126.9, 127.0, 127.4, 127.8, 128.7, 131.2, 138.7, 162.4, 168.1, 172.5.

5. General procedure for removal of the 4-methoxyphenylethyl group from 5a,b

A solution of **5a** or **5b** (1.0 mmol) in CH_3CN (5 mL) was treated at room temperature with cerium ammonium nitrate (CAN) (1.1 g, 2.0 mmol) dissolved in H_2O (5 mL), and the reaction mixture was stirred for 3 h. The aqueous layer was extracted with ethyl acetate (3×25 mL), the organic layers were combined, washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure provided a crude residue, which was purified by silica gel chromatography (cyclohexane–ethyl acetate 30:70) to give compound **3a** or **3b**.

5.1. (3*S*,4*R*)-4-Methoxycarbonyl-4-methyl-2-trichloroacetylaminopyrrolidin-2-one, 3a

Compound **3a** (0.26 g, 83%) was obtained as white solid: mp 86–88 °C. ν_{max} 3351, 1736, 1711, 1664 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30 (3H, s, CH_3), 3.23 (1H, dd, *J* 10.0, *J* 1.8, H-5 pro-*R*), 3.82 (3H, s, OCH_3), 3.87 (1H, d, *J* 10.0, H-5 pro-*S*), 4.92 (1H, d, *J* 5.2, H-3), 6.50 (1H, br s, NH), 7.24 (1H, d, *J* 5.2, NH); δ_C (50 MHz, $CDCl_3$) 6.1, 49.8, 50.2, 53.0, 58.8, 91.7, 162.6, 171.8, 173.4; $[\alpha]_D$ -75.9 (*c* 0.4, $CHCl_3$); ESI-MS: *m*/*z* 315.9 $[M]^+$, 338.1 $[M+Na]^+$. Anal. Calcd for $C_9H_{11}Cl_3N_2O_4$: C, 34.04; H, 3.49; N, 8.82. Found: C, 33.96; H, 3.44; N, 8.76.

5.2. (3*S*,4*R*)-2-*t*-Butoxycarbonylamino-4-methoxycarbonyl-4-methylpyrrolidin-2-one, 3b

Compound **3b** (0.22 g, 82%) was obtained as white solid: mp 108–110 °C. ν_{max} 3348, 1741, 1710, 1655 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.22 (3H, s, CH_3), 1.38 (9H, s, 3×CH_3), 3.09 (1H, dd, *J* 10.0, *J* 1.7, H-5 pro-*R*), 3.72 (3H, s, $COOCH_3$), 3.78 (1H, d, *J* 10.0, H-5 pro-*S*), 4.71 (1H, d, *J* 7.0, H-3), 5.20 (1H, d, *J* 7.0, NH), 7.16 (1H, br s, NH); δ_C (50 MHz, $CDCl_3$) 16.4, 28.3, 49.5, 49.9, 52.7, 58.9, 80.1, 155.6, 173.5, 174.3; $[\alpha]_D$ 46.3 (*c* 1.08, $CHCl_3$); ESI-MS: *m*/*z* 272.1 $[M]^+$, 295.2 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.29. Found: C, 52.86; H, 7.33; N, 10.21.

6. Single crystal X-ray investigation of 5a

Compound **5a**: colourless crystals, $C_{18}H_{21}Cl_3N_2O_5$, *M*=1806.87, crystal size 0.45×0.35×0.25 mm, orthorhombic, $P2_12_12_1$ (No. 19): *a*=9.8532(14) Å, *b*=11.0667 (15) Å, *c*=18.769(3) Å, *V*=2046.6(5) $Å^3$, *Z*=4, *ρ* (calcd)=1.46 mg m^{-3}, *F*(000)=936, *μ*=0.48 mm^{-1}, 23,251 reflections ($2\theta_{max}$=57°) measured on a Bruker Apex II CCD detector diffractometer at 293 K using Mo Kα radiation (*λ*=0.71073 Å), 4822 unique [R_{int}=0.018], used for structure solution (Direct Methods, SHELXS-97)[12] and refinement (full-matrix least-squares on F^2, SHELXL-97)[13] with 253 parameters, H atoms found in difference Fourier and refined with a riding model, R_1 ($I>2\sigma(I)$=0.036, wR_2=0.107, *S*=0.93, largest diff. peak and hole 0.39 and −0.29 e $Å^{-3}$ in the vicinity of the Cl atoms. The absolute configuration was determined reliably by using the Flack parameter [0.01(5)] for the correct absolute structure). ORTEP-3 was used for graphics.[14,24]

The molecular structure of compound **5a** is reported in Figure 2 together with the crystallographic labelling. Hydrogen atoms bear the same labelling as the C or N atom to which they are attached. Bond lengths and angles fall within the normal range of values and will not be discussed here. The assignment of chirality to the stereogenic centres at C(1), S, C(3), *S*, and C(4), *R*, has been made unambiguously by using the Flack parameter. The pentacyclic ring

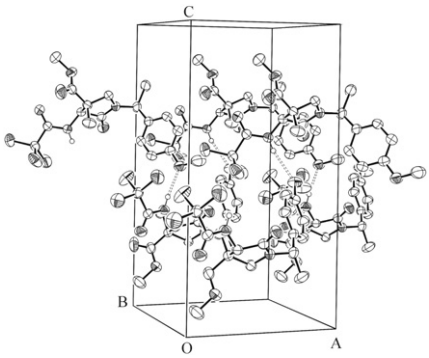


Figure 3. Packing of **5a** (50% probability) showing the network of N–H···O bonding (broken lines) along the *a* axis, which connects the molecules in a infinite chain; the remaining H atoms are omitted for clarity.

exhibits an envelope conformation with C(4) 0.5 Å out of the plane comprising the other four atoms. A strong network of inter-molecular H-bonding interactions occurs, which involves N(2)–H(2) and O(3) [symmetry operation 0.5+*x*, 0.5−*y*, 2−*z*] with a D···A distance of 3.170(2) and a DHA angle of 165°. A second H-bonding interaction involves C(13)–H(13)···O(5) [symm. op. −1+*x*, *y*, *z*] with D···A distance of 3.131(3) Å and DHA angle of 130°, while a second CH···O interaction occurs between C(3)–H(3) and O(5) [symm. op. 1−*x*, 0.5+*y*, 1.5−*z*] with D···A distance of 3.228(3) Å and DHA angle of 130°. Finally, a further H-bonding interaction is formed between C(18)–H(18A) and O(1) [symm op −0.5+*x*, 0.5−*y*, 2−*z*] with D···A distance of 3.299(4) Å and DHA angle of 145(3)°.[24,25] Interestingly, the N–H···O interaction connects the molecules related by the binary screw axis parallel to ***a***, thus forming an infinite chain of hydrogen bonded molecules wrapped in a helix along the 100 direction (Fig. 3).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.004.

References and notes

1. (a) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolymers (Pept. Sci.)* **1997**, *43*, 219–266; (b) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366–1375; (c) Hanessian, S.; Auzzas, L. *Acc. Chem. Res.* **2008**, *41*, 1241–1251.
2. Hruby, V. J.; Boteju, L. W. *Molecular Biology and Biotechnology*; VCH: New York, NY, 1995, pp 658–664.
3. (a) Hruby, V. J. *Biopolymers* **1993**, *33*, 1073–1082; (b) Martin, S. F.; Dorsey, G. O.; Gane, T.; Hillier, M. C.; Kessler, H.; Baur, M.; Mathä, B.; Erickson, J. W.; Bhat, T. N.; Munshi, S.; Gulnik, S. V.; Topol, I. A. *J. Med. Chem.* **1998**, *41*, 1581–1597; (c) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305–1318; (d) Wang, S.; Tang, X.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 1307–1310; (e) Hruby, V. J.; Balse, P. M. *Curr. Med. Chem.* **2000**, *7*, 945–970.
4. (a) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Org. Lett.* **2004**, *6*, 2571–2574; (b) Galeazzi, R.; Martelli, G.; Marcucci, E.; Mobbili, G.; Natali, D.; Orena, M.; Rinaldi, S. *Eur. J. Org. Chem.* **2007**, 4402–4407; (c) Galeazzi, R.; Marcucci, E.; Martelli, G.; Natali, D.; Orena, M.; Rinaldi, S. *Amino Acids* **2008**, *34*, 333–336.
5. See, for an example: Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3353–3358 and references cited herein.
6. Woolley, D. V. *J. Biol. Chem.* **1960**, *235*, 3238–3241.
7. Madhavapeddi, P.; Marsh, E. N. G. *Chem. Biol.* **2001**, *8*, 1143–1149.
8. (a) Chaganty, S.; Golakoti, T.; Heltzel, C.; Moore, R. E.; Yoshida, W. Y. *J. Nat. Prod.* **2004**, *67*, 1403–1406; (b) Magarvey, N. A.; Beck, Z. Q.; Golakoti, T.; Ding, Y.; Huber, U.; Hemscheidt, T. K.; Abelson, D.; Moore, R. E.; Sherman, D. H. *ACS Chem. Biol.* **2006**, *1*, 766–779.
9. Baltz, R. H.; Miao, V.; Wrigley, S. K. *Nat. Prod. Rep.* **2005**, *22*, 717–741.
10. Schabbert, S.; Pierschbacher, M. D.; Mattern, R.-H.; Goodman, M. *Bioorg. Med. Chem.* **2002**, *10*, 3331–3337.
11. (a) Galeazzi, R.; Martelli, G.; Orena, M.; Rinaldi, S.; Sabatino, P. *Tetrahedron* **2005**, *61*, 5465–5473; (b) Galeazzi, R.; Martelli, G.; Natali, D.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1779–1787.
12. Sheldrick, G. M. *SHELXS97*; University of Gottingen: Germany, 1997.
13. Sheldrick, G. M. *SHELXL97*; University of Gottingen: Germany, 1997.
14. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
15. Hokhura, H.; Handa, M.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2002**, *67*, 2692–2695.
16. (a) Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2529–2532; (b) Varea, T.; Dufour, M.; Micouin, L.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 1035–1038; (c) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Panagiotaki, M. *Heterocycles* **2003**, *60*, 2485–2498.
17. For an alkylation proceeding *syn* to a hydroxy group, see: Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Harling, J. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2293–2296; For stereoselective alkylations of aspartic acid derivatives, see: Hanessian, S.; Margarita, R.; Hall, A.; Luo, X. *Tetrahedron Lett.* **1998**, *39*, 5883–5886.
18. Interestingly, the ratio of isomers did not change when the nature of the cation was varied from Li to K, although the yields decreased accordingly.
19. (a) Parr, I. B.; Boehlein, S. K.; Dribben, A. B.; Schuster, S. M.; Richards, N. G. J. *J. Med. Chem.* **1996**, *39*, 2367–2378; (b) Karginov, V. A.; Mamaev, S. V.; An, H.; Van Cleve, M. D.; Hecht, S. M.; Komatsoulis, G. A.; Abelson, N. Z. *J. Am. Chem. Soc.* **1997**, *119*, 8166–8176.
20. Galeazzi, R.; Mammi, S.; Martelli, G.; Menegazzo, I.; Orena, M.; Rinaldi, S. *Chem. Commun.* **2006**, 4915–4917.
21. (a) Sagan, S.; Karoyan, P.; Lequin, O.; Chassaing, G.; Lavielle, S. *Curr. Med. Chem.* **2004**, *11*, 2799–2822; (b) Yeh, M.-Y.; Luh, T.-Y. *Chem. Asian J.* **2008**, *3*, 1620–1624.
22. (a) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers* **2001**, *60*, 396–419; (b) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxtermann, Q. B. *Synlett* **2006**, 1295–1310.
23. (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232; (b) Sanford, A. R.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649–1659; (c) Baldauf, C.; Günther, R.; Hofmann, H.-J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1594–1597; (d) Ananda, K.; Vasudev, P. G.; Sengupta, A.; Raja, K. M. P.; Shamala, N.; Balaram, P. *J. Am. Chem. Soc.* **2005**, *127*, 16668–16674.
24. Crystallographic data for the structural analysis of compound **5a** have been deposited at the Cambridge Crystallographic Data Centre. The CCDC no. 652268 has been assigned to the compound **5a**. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).
25. Steiner, T. *Crystallogr. Rev.* **1996**, *6*, 1–51.