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Conformationally restricted analogues of both (*S*)-β-homoserine and (*S*)-aspartic acid from chiral 3-acylamino pyrrolidin-2-ones

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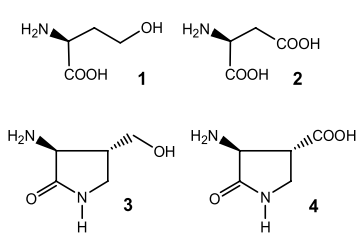
Abstract—Starting from chiral 3,4-*trans*-disubstituted pyrrolidin-2-ones **11a** and **11b**, obtained from a Baylis–Hillman adduct, conformationally restricted analogues of both (*S*)-β-homoserine, **17**, and (*S*)-aspartic acid, **21**, were synthesized, respectively, and these compounds are suitable either for introduction in peptidomimetics or for synthesis of novel β-foldamers.

1. Introduction

Properly substituted pyrrolidin-2-ones (γ-lactams) can be isosteres of natural amino acids. Thus, they can give rise to conformational constrictions useful to both restrict the flexibility of the peptide molecules and to provide informations on the topographical requirements of receptors,[1] when they are introduced in bioactive peptides. Moreover, the incorporation of these units in a peptide lead to analogues that display a lot of advantages such as increased biostability and bioselectivity against the natural biological target of the parent peptide. Therefore, they are interesting target compounds,[2] useful for the synthesis of both terminally constrained or internally constrained peptidomimetics[3] and their availability in an enantiomerically pure form is important for applications in medicinal chemistry.[4] In this field, our attention was focused to the pyrrolidin-2-ones **3** and **4**, that are constrained analogues of (*S*)-β-homoserine **1** and (*S*)-aspartic acid, **2**, respectively (Scheme 1).

2. Results and discussion

We already demonstrated the viability of the approach involving (C-3)–(C-4) bond formation for construction of the pyrrolidin-2-one ring, leading to conformationally restricted amino acids in the enantiomerically pure form.[5] As a further development, we recently, devised a conjugate addition/ring closure sequence starting from the Baylis–Hillman adduct **5** and (*S*)-phenylethylamine, leading to formation of both (N-1)–(C-5) and (N-1)–(C-2) bonds of the γ-lactam ring, and this synthetic approach was directed toward the synthesis of chiral 3-hydroxypyrrolidin-2-ones, intermediates for the preparation of an inhibitor of glycosidases.[6] Our previous investigations concerning the chemistry of Baylis–Hillman adducts disclosed a straightforward general procedure for the preparation of 3-acylamino-2-methylene alkanoates, by exploiting the corresponding acyl carbamates.[7] In this report, the acyl carbamates **7a**,**b** were prepared in quantitative yield by reaction of the adduct **5** and the appropriate acyl isocyanate **6a**,**b** (Scheme 2).[8] However, whereas treating the 1-naphthoyl carbamate **7b** with DABCO in DCM gave the corresponding 1-naphthoylamino derivative **8b** in good yield, the trichloroacetylamino derivative **8a** was obtained only in a disappointing 20% yield from **7a** under the same reaction conditions. The other products of this reaction were a complex, inseparable mixture of polar products. To overcome this problem, an alternative approach to compound **8a** was devised, starting from the trichloroacetimidate **9**. The preparation of this compound, however, turned



Scheme 1.

Keywords: Amino acids; Analogues; Baylis–Hillman; Peptidomimetics; Conformational constrictions.
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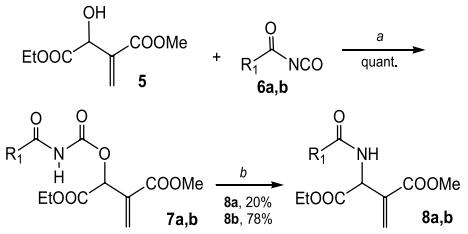
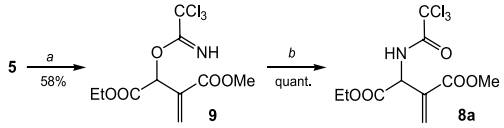


Scheme 2. Reagents and conditions: (a) DCM, rt (b) 10% DABCO, DCM, 0 °C; **8a**, $R_1=CCl_3$; **8b**, $R_1=$1-naphthyl.

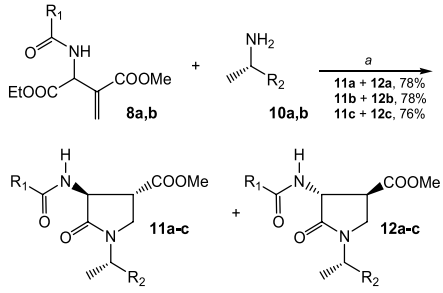


Scheme 3. Reagents and conditions: (a) CCl_3CN, DBU, −15 °C. (b) 10% DABCO, DCM, 0 °C, 2 min.

out to be far from routine. In fact, only traces of the desired product **9** were obtained by following the standard procedures.[9]

On the other hand, when the reaction was carried out by using CCl_3CN as the solvent and DBU as the base, the trichloroacetimidate **9** was obtained in moderate yield. Subsequent treatment with DABCO in DCM afforded the trichloroacetylamino derivative **8a** in quantitative yield (Scheme 3).[10]

By analogy with the synthesis of chiral hydroxypyrrolidin-2-ones from the Baylis–Hillman adduct **5**,[6] condensation of *N*-acylamino derivatives **8a**,**b** with (*S*)-phenylethylamine, **10a**, or (*S*)-4-MeO-phenylethylamine, **10b**, was carried out in MeOH from rt to 60 °C. Although a diastereomeric mixture of four 3,4-disubstituted pyrrolidin-2-ones was formed at first, as evidenced by the corresponding peaks for the methyl esters in the ^{1}H NMR spectrum of the crude reaction, direct treatment of the diastereomeric mixture with DBU in toluene at rt afforded in good yield the 3,4-*trans*-disubstituted derivatives **11a–c** and **12a–c**, exclusively, which were easily separated by flash chromatography on silica gel (Scheme 4).[11] The determination of the absolute configurations of 4-monosubstituted pyrrolidin-2-ones with nitrogen bearing a chiral phenylethyl group was described elsewhere.[5] Thus, ^{1}H NMR analysis was diagnostic for structural assignment at C-4 of **11a–c** and **12a–c**, as



Scheme 4. Reagents and conditions: (a) MeOH, rt to 60 °C, then DBU, toluene at rt. **a** $R_1=CCl_3$, $R_2=C_6H_5$; **b** $R_1=CCl_3$, $R_2=$4-$CH_3OC_6H_4$; **c** $R_1=$1-naphthyl, $R_2=C_6H_5$.

evidenced by the shielding effects on H-5 and H-5′ due to both the phenyl group and the substituent at C-4 (Table 1).

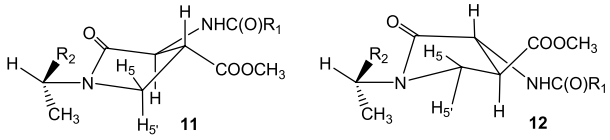
The configuration at C-3 was also assigned by ^{1}H NMR analysis, being significantly supported by the quite large $J_{3,4}$ coupling constant values ($J_{3,4}>9.0$ Hz) (Table 1), and further, confirmed by NOE difference data. In fact, by irradiation of H-3 only a very small enhancement (<1%) was observed to H-4, consistent with the *trans* relative stereochemistry. Eventually, compound **11a** was crystallized from methanol and from the single-crystal X-ray data its absolute configuration was definitely ascertained as (3*S*,4*R*,1′*S*), in full agreement with ^{1}H NMR spectral data (Fig. 1).[12,13]

Our first goal was to find a simple and straightforward access to the constrained β-homoserine derivative **3**,[14] but some difficulties arose in the removal of the naphthoyl group in both **11c** and **12c**. Therefore, since the trichloroacetyl group can be more easily cleaved, we considered as starting materials for further transformations the trichloroacetylamino derivatives **11a**,**b**, that are homochiral at C-3 with the same absolute configuration as the natural amino acids.

In fact, we treated the pyrrolidin-2-one **11a** with $NaBH_4$ in dry ethanol and we were pleased to obtain in good yield the corresponding *trans*-3-amino-4-hydroxymethyl derivative **13**, the reaction proceeding through simultaneous reduction of the methoxycarbonyl group and removal of the trichloroacetamido moiety (Scheme 5).

Prior to the removal of the phenylethyl group, both the

Table 1. Selected ^{1}H NMR data for compounds **11** and **12**



Entry	δ H-3 (ppm)	δ H-5 (ppm)	δ H-5′ (ppm)	$J_{3,4}$ (Hz)	$J_{4,5}$ (Hz)	$J_{4,5'}$ (Hz)
11a	4.65	3.45	3.28	9.5	9.1	8.7
12a	4.58	3.05	3.60	9.4	8.8	9.2
11b	4.65	3.43	3.28	9.6	9.2	8.7
12b	4.71	3.13	3.62	9.2	8.9	9.4
11c	4.84	—[a]	—[a]	9.2	—[a]	—[a]
12c	4.71	3.13	3.62	9.2	8.8	9.4

[a] H-5 and H-5′ give rise to a complex pattern, in agreement with a single shielding for each proton.

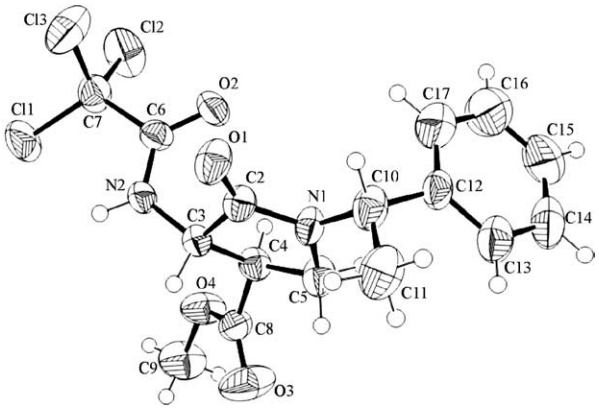
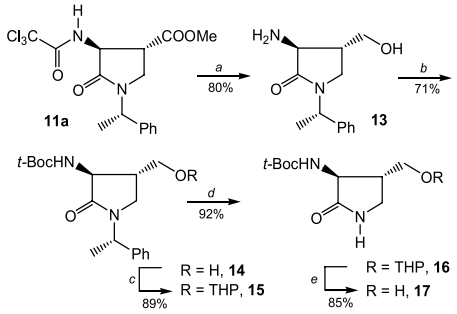


Figure 1. ORTEP drawing of compound **11a**.

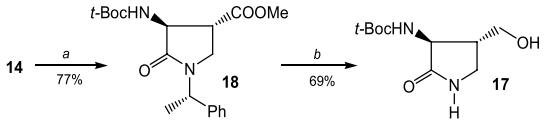


Scheme 5. Reagents and conditions: (a) $NaBH_4$ (4 equiv), dry EtOH, rt; (b) *t*-Boc_2O, MeOH, rt; (c) DHP, DCM, H 15, rt, (d) Li, NH_3, −78 °C; (e) Amberlyst H 15, MeOH, 40 °C.

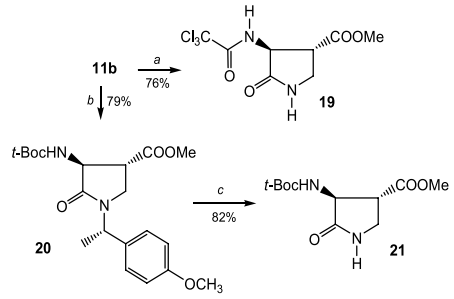
derivatives **14** and **15** were subsequently prepared. Cleavage of the phenylethyl group was easily performed by treating **15** with Li in liquid ammonia at −78 °C, leading to the unsubstituted pyrrolidin-2-one **16** in good yield. Eventually, removal of the THP group afforded **17**, the *N*-protected derivative of **3**, the analogue of β-homoserine (Scheme 5).[15,16]

Then, we started the synthesis of the analogue of the aspartic acid, **4**, but when compound **17** was treated with the Jones' reagent in order to obtain a carboxy group at C-5, only a complex mixture of products resulted from the reaction. In addition, when the compound **18**, easily prepared starting from **14**, underwent cleavage of the phenylethyl group with Li in liquid ammonia, compound **17** was exclusively obtained in moderate yield (Scheme 6).[17]

Thus, an alternative starting substrate to the compound **4** was pyrrolidin-2-one **11b**. In fact, by treatment with CAN in acetonitrile–water[18] this compound underwent rapid cleavage of the 4-methoxyphenylethyl group, to give in good yield the enantiomeric 3,4-*trans*-disubstituted pyrrolidin-2-one **19**, a diprotected form of the constrained analogue **4** (Scheme 7). In addition, the trichloroacetyl group was



Scheme 6. Reagents and conditions: (a) Jones' reagent, acetone, then CH_2N_2; (b) Li, NH_3, −78 °C.



Scheme 7. Reagents and conditions: (a) CAN, CH_3CN–H_2O; (b) 6 M NaOH; then *t*-Boc_2O, TEA, MeOH; then CH_2N_2, diethyl ether; (c) CAN, CH_3CN–H_2O.

removed from **11b** and the amino functionality at C-3 was protected as *t*-Boc derivative to give **20**. Eventually, by treatment with CAN in acetonitrile–water, the protected constrained analogue **21** was obtained in good yield.[19]

3. Conclusion

In summary, by reaction of either (*S*)-phenylethylamine **10a** or (*S*)-(4-methoxyphenyl)ethylamine **10b** and the acyl-amino derivatives **8a**,**b**, obtained from the Baylis–Hillman adduct **5**, the chiral 3,4-*trans*-disubstituted pyrrolidin-2-ones **11a**,**b** and **12a**,**b** were produced in good yield. Then, **17** and **21**, conformationally restricted analogues of (*S*)-β-homoserine and (*S*)-aspartic acid, were obtained starting from compounds **11a** and **11b**, respectively, and it is worth mentioning that both *ent*-**17** and *ent*-**21** can be accessible starting from **12a**,**b**. In addition, **21** and *ent*-**21** will be employed as units for the preparation of novel β-foldamers[20,21] having a constriction due to the sp^2 carbon of the pyrrolidin-2-one and work along this line is currently in progress in our laboratory.

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. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Varian Gemini 200 spectrometer, using $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (J) in Hz. Assignments were aided by decoupling and homonuclear two-dimensional experiments. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Mass spectra (MS) were obtained by electron impact on a Hewlett-Packard spectrometer 5890, series II. Column chromatography was performed with silica gel 60 (230–400 mesh). Compound **5** was synthesized as reported the literature.[22] Trichloroacetyl isocyanate **6a** was purchased from Aldrich, whereas 1-naphthoyl isocyanate **6b** was prepared according to a literature method starting from 1-naphthoyl chloride[8b] and used without purification.

4.2. General procedure for the preparation of acyl carbamates (7a,b)

To a solution containing the adduct **5** (1.9 g, 10 mmol) in dry DCM (50 mL), the appropriate acyl isocyanate **6** (12 mmol) dissolved in dry DCM (10 mL) was added at 0 °C and the mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (cyclohexane–ethyl acetate 80:20 as eluent) to give in quantitative yield the acyl carbamates **7a**,**b**.

4.2.1. 1-Ethyl 4-methyl 2-(1-trichloroacetylaminocarbonyloxy)-3-methylenebutanedioate (7a). According to the above reported procedure and starting from **5** and commercially available trichloroacetyl isocyanate **6a**, the compound **7a** was obtained as a viscous oil: IR ($CHCl_3$) ν 3355, 1741, 1724, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, $J=7.2$ Hz, 3H), 3.79 (s, 3H), 4.22 (q, $J=7.2$ Hz, 2H), 5.98 (s, 1H), 6.11 (s, 1H), 6.55 (s, 1H), 8.78 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 52.4, 62.3, 72.4, 91.4, 132.3, 133.7, 148.5, 157.5, 164.5, 166.7; MS: *m/z* 377–375 (2, M^+), 143 (22), 116 (40), 84 (100). Anal. Calcd for $C_{11}H_{12}Cl_3NO_7$: C, 35.08; H, 3.21; N, 3.72. Found: C, 35.02; H, 3.15; N, 3.64.

4.2.2. 1-Ethyl 4-methyl 2-(1-naphthoylaminocarbonyloxy)-3-methylenebutanedioate (7b). According to the above reported procedure and starting from **5** and 1-naphthoyl isocyanate **6b**, the compound **7b** was obtained as a viscous oil: IR ($CHCl_3$) ν 3350, 1734, 1724, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, $J=7.3$ Hz, 3H), 3.74 (s, 3H), 4.18 (q, $J=7.3$ Hz, 2H), 5.97 (s, 1H), 6.04 (s, 1H), 6.48 (s, 1H), 7.36–7.94 (m, 6 ArH), 8.21–8.29 (m, 1 ArH), 8.64 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 52.2, 62.0, 71.5, 124.3, 124.8, 125.9, 126.6, 127.6, 128.3, 128.4, 129.9, 131.7, 132.1, 133.5, 134.1, 149.5, 164.6, 166.9, 167.2; MS: *m/z* 385 (3, M^+), 197 (29), 155 (100), 127 (76), 83 (88), 43 (70). Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.27; H, 5.03; N, 3.59.

4.3. General procedure for the preparation of acylamino derivatives (8a,b)

To a solution containing **7** (15.0 mmol) in DCM (20 mL) at 0 °C, DABCO (0.2 g, 1.5 mmol) was added and the mixture was stirred for 15 min at 0 °C. The mixture was then diluted with ethyl acetate (150 mL) and the organic layer washed with 1 M HCl (30 mL) and brine (100 mL). After drying (Na_2SO_4), the solvents were removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 80:20 as eluent), to give pure compounds **8a**,**b**.

4.3.1. 1-Ethyl 4-methyl 2-trichloroacetylamino-3-methylenebutanedioate (8a). According to the above reported procedure and starting from **7a**, the title compound was obtained as a colorless oil (1.0 g; 20%), followed by a substantial amount of trichloroacetamide (1.8 g): IR ($CHCl_3$) ν 3351, 1732, 1722, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, $J=7.1$ Hz, 3H), 3.80 (s, 3H), 4.25 (q, $J=7.1$ Hz, 2H), 5.25 (d, $J=7.9$ Hz, 1H), 6.10 (s, 3H), 6.47 (s, 1H), 7.81 (d, $J=7.9$ Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 52.3, 56.0, 62.5, 92.0, 131.7, 134.1, 161.2, 165.3, 168.2; MS: *m/z* 334–332 (4, MH^+), 318–316 (12), 260 (22), 198 (18), 158 (44), 99 (100). Anal. Calcd for $C_{10}H_{12}Cl_3NO_5$: C, 36.12; H, 3.64; N, 4.21. Found: C, 36.16; H, 3.57; N, 4.16.

4.3.2. 1-Ethyl 4-methyl 2-(1-naphthoylamino)-3-methylenebutanedioate (8b). According to the above reported procedure and starting from **7b**, the title compound was obtained as a colorless oil (4.0 g, 78%): IR ($CHCl_3$) ν 3350, 1735, 1720, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, $J=7.4$ Hz, 3H), 3.75 (s, 3H), 4.25 (q, $J=7.4$ Hz, 2H), 5.72 (d, $J=8.5$ Hz, 1H), 6.19 (s, 1H), 6.48 (s, 1H), 7.14 (d, $J=8.5$ Hz, 1H, NH), 7.40–7.94 (m, 6 ArH), 8.31–8.42 (m, 1 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 52.2, 51.8, 62.2, 124.7, 125.4, 125.5, 126.4, 127.2, 128.3, 128.5, 130.2, 130.8, 131.0, 133.5, 136.0, 165.9, 168.7, 169.6; MS: *m/z* 341 (3, M^+), 268 (20), 155 (100), 127 (56), 43 (12). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.79; H, 5.57; N, 4.14.

4.3.3. 1-Ethyl 4-methyl 2-trichloroacetiminoxy-3-methylenebutanedioate (9). To a solution of the adduct **5** (2.8 g, 15 mmol) in CCl_3CN (7.5 g, 75.0 mmol), DBU (0.63 mL, 4.5 mmol) was directly added in three portions (every 15 min) at −15 °C under vigorous stirring. After 1 h the mixture was directly purified by silica gel chromatography (cyclohexane–ethyl acetate 95:5 as eluent) to give the trichloroacetimidate **9** (2.9 g; 58% yield) as a colorless oil: IR ($CHCl_3$) ν 3339, 1732, 1720, 1671 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, $J=7.3$ Hz, 3H), 3.82 (s, 3H), 4.25 (q, $J=7.3$ Hz, 2H), 6.12 (s, 1H), 6.13 (s, 1H), 6.55 (s, 1H), 8.53 (br s, 1H, =NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 53.0, 61.5, 73.4, 90.3, 129.7, 134.1, 160.8, 164.5, 166.8; MS: *m/z* 334 (MH^+, 5), 332 (MH^+, 5), 318 (6), 316 (6), 170 (32), 161 (24), 144 (100). Anal. Calcd for $C_{10}H_{12}Cl_3NO_5$: C, 36.12; H, 3.64; N, 4.21. Found: C, 36.06; H, 3.58; N, 4.27.

4.3.4. 1-Ethyl 4-methyl 2-trichloroacetylamino-3-methylenebutanedioate (8a). To a solution containing the trichloroacetimidate **9** (1.7 g, 5.0 mmol) in DCM (20 mL) at 0 °C, DABCO (65 mg, 0.5 mmol) was added and the mixture was stirred for 2 min at 0 °C. After dilution with ethyl acetate (150 mL), the organic layer was washed with 1 M HCl (30 mL) and brine (100 mL) and dried (Na_2SO_4). The solvents were removed under reduced pressure to give the pure trichloroacetylamino derivative **8a** (1.7 g; quantitative yield) as a colorless oil.

4.4. General procedure for the preparation of pyrrolidin-2-ones (11) and (12)

To a solution containing compound **8** (15 mmol) in methanol (20 mL), (*S*)-phenylethylamine **10a** or (*S*)-4-methoxyphenylethylamine **10b** (16 mmol) was added and the mixture was stirred for 12 h at rt and then for 2 h at 60 °C. Methanol was evaporated under reduced pressure, the residue was dissolved ethyl acetate (50 mL) and the organic layer washed with 1 M HCl (20 mL) and brine. After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was dissolved in toluene (20 mL), DBU (2.28 g, 15 mmol) was added and the

solution was stirred at rt for 12 h. After removal of the solvent, the residue was dissolved in ethyl acetate (40 mL) and the organic layer was washed with 2 M HCl (10 mL). After drying (Na_2SO_4) and removal of the solvent, the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 90:10), to give in equimolar amount pure separated diastereomers **11** and **12** as white crystalline solids.

4.4.1. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-1-(1′-phenylethyl)-3-trichloroacetylaminopyrrolidin-2-one (11a) and its (3*R*,4*S*,1′*S*)-isomer (12a). Starting from **8a** and **10a**, the diastereomers **11a** and **12a** were obtained after chromatographic separation in 78% overall yield according to the above reported procedure: IR ($CHCl_3$) ν 3347, 1725, 1670 cm^{-1}. Anal. Calcd for $C_{16}H_{17}Cl_3N_2O_4$: C, 47.14; H, 4.20; N, 6.87. Found: C, 47.06; H, 4.16; N, 6.82. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-1-(1′-phenylethyl)-3-trichloroacetylaminopyrrolidin-2-one (**11a**). Colorless crystals: mp 196–198 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (d, J=7.3 Hz, 3H), 3.09–3.21 (m, 1H), 3.28 (dd, J=8.7, 8.7 Hz, 1H), 3.45 (dd, J=8.7, 9.0 Hz, 1H), 3.75 (s, 3H), 4.65 (dd, J=5.6, 9.6 Hz, 1H), 5.50 (q, J=7.3 Hz, 1H), 7.25–7.48 (m, 6H, 5 ArH+NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2, 42.2, 44.0, 50.2, 52.7, 56.4, 127.0, 128.0, 128.8, 138.6, 162.3, 167.7, 171.6; $[\alpha]_D$ −75.0 (*c* 0.5, $CHCl_3$). MS: *m*/*z* 408 (4, M^+), 406 (4, M^+), 269 (4), 271 (4), 246 (8), 186 (18), 132 (21), 105 (100), 77 (25). (3*R*,4*S*,1′*S*)-4-Methoxycarbonyl-3-trichloroacetylamino-1-(1′-phenylethyl)pyrrolidin-2-one (**12a**). Colorless crystals: mp 138–140 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (d, J=7.0 Hz, 3H), 3.06 (dd, J=8.8, 9.2 Hz, 1H), 3.22–3.41 (m, 1H), 3.63 (dd, J=9.2, 9.2 Hz, 1H), 3.69 (s, 3H), 4.57 (dd, J=5.9, 9.1 Hz, 1H), 5.48 (q, J=7.0 Hz, 1H), 7.21–7.39 (m, 5 ArH), 7.84 (d, J=5.9 Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9, 42.2, 43.2, 50.3, 52.6, 56.2, 91.7, 126.8, 127.0, 128.0, 128.7, 138.6, 162.4, 167.9, 171.6; $[\alpha]_D$ −82.5 (*c* 1.06, $CHCl_3$); MS: *m*/*z* 408 (4, M^+), 406 (4, M^+), 269 (5), 271 (5), 246 (11), 186 (16), 132 (24), 105 (100), 77 (25).

4.4.2. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-3-trichloroacetylamino-1-[1′-(4″-methoxyphenyl)ethyl]pyrrolidin-2-one (11b) and its (3*R*,4*S*,1′*S*)-isomer (12b). Starting from **8a** and **10b**, the diastereomers **11b** and **12b** were obtained after chromatographic separation in 78% overall yield according to the above reported procedure: IR ($CHCl_3$) ν 3345, 1724, 1668 cm^{-1}. Anal. Calcd for $C_{17}H_{19}Cl_3N_2O_5$: C, 46.65; H, 4.38; N, 6.40. Found: C, 46.61; H, 4.34; N, 6.44. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-3-trichloroacetylamino-1-[1′-(4″-methoxyphenyl)ethyl]pyrrolidin-2-one (**11b**). Colorless crystals: mp 178–180 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (d, J=7.2 Hz, 3H), 3.06–3.31 (m, 1H), 3.28 (dd, J=8.7, 9.2 Hz, 1H), 3.43 (dd, J=9.2, 9.2 Hz, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 4.65 (dd, J=4.5, 9.6 Hz, 1H), 5.47 (q, J=7.2 Hz, 1H), 6.90 (d, J=8.7 Hz, 2 ArH), 7.26 (d, J=8.7 Hz, 2 ArH), 7.41 (d, J=4.5 Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3, 42.0, 43.9, 49.7, 52.7, 55.3, 56.5, 114.1, 128.2, 130.6, 159.2, 162.3, 167.6, 171.7; $[\alpha]_D$ −73.0 (*c* 0.6, $CHCl_3$); MS: *m*/*z* 436 (3, M^+), 434 (3, M^+), 301 (5), 299 (5), 216 (20), 162 (23), 135 (100), 77 (24). (3*R*,4*S*,1′*S*)-4-Methoxycarbonyl-3-trichloroacetylamino-1-[1′-(4″-methoxyphenyl)ethyl]pyrrolidin-2-one (**12b**). Colorless crystals: mp 46–48 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.58 (d, J=7.2 Hz, 3H), 3.05 (dd, J=8.8, 9.4 Hz, 1H), 3.20–3.56 (m, 1H), 3.60 (dd, J=9.2, 9.4 Hz, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 4.58 (dd, J=5.8, 9.4 Hz, 1H), 5.47 (q, J=7.2 Hz, 1H), 6.87 (d, J=8.6 Hz, 2 ArH), 7.21 (d, J=8.6 Hz, 2 ArH), 7.42 (d, 1H, NH, J=5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 42.1, 43.1, 49.8, 52.6, 55.2, 56.2, 91.7, 114.0, 128.2, 130.6. 159.2, 162.3, 167.7, 171.6; $[\alpha]_D$ −65.0 (*c* 2.0, $CHCl_3$); MS: *m*/*z* 436 (3, M^+), 434 (3, M^+), 301 (7), 299 (7), 216 (23), 162 (22), 135 (100), 77 (24).

4.4.3. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-3-(1″-naphthoylamino)-1-(1′-phenylethyl)pyrrolidin-2-one (11c) and its (3*R*,4*S*,1′*S*)-isomer (12c). Starting from **8b** and **10a**, the diastereomers **11c** and **12c** were obtained after chromatographic separation in 76% overall yield according to the above reported procedure: IR ($CHCl_3$) ν 3351, 1722, 1658 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.04; H, 5.87; N, 6.68. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-3-(1″-naphthoylamino)-1-(1′-phenylethyl)pyrrolidin-2-one (**11c**). Colorless crystals: mp 132–134 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.56 (d, J=7.0 Hz, 3H), 3.12–3.59 (m, 3H), 3.76 (s, 3H), 4.84 (dd, J=5.9, 9.2 Hz, 1H), 5.56 (q, J=7.0 Hz, 1H), 6.82 (d, J=5.9 Hz, 1H, NH), 7.21–7.73 (m, 9 ArH), 7.81–7.96 (m, 2 ArH), 8.31–8.48 (m, 1 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2, 42.2, 45.0, 50.0, 52.6, 56.1, 124.6, 125.4, 125.5, 125.6, 126.4, 127.0, 127.1, 127.8, 128.2, 128.3, 128.4, 128.8, 131.0, 133.2, 133.7, 139.1, 169.2, 170.1, 172.4; $[\alpha]_D$ −177.8 (*c* 0.6, MeOH); MS: *m*/*z* 416 (11, M^+), 261 (8), 245 (9), 186 (13), 172 (16), 155 (100), 127 (74), 105 (67). (3*R*,4*S*,1′*S*)-4-Methoxycarbonyl-3-(1″-naphthoylamino)-1-(1′-phenylethyl)pyrrolidin-2-one (**12c**). Colorless crystals: mp 176–178 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.58 (d, J=7.0 Hz, 3H), 3.13 (dd, J=8.8, 8.9 Hz, 1H), 3.35–3.51 (m, 1H), 3.62 (dd, J=9.4, 8.9 Hz, 1H), 3.73 (s, 3H), 4.71 (dd, J=6.2, 9.2 Hz, 1H), 5.50 (q, J=7.0 Hz, 1H), 6.89 (d, J=6.2 Hz, 1H), 7.22–7.72 (m, 9 ArH), 7.78–7.95 (m, 2 ArH), 8.34–8.44 (m, 1 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9, 42.3, 44.5, 50.2, 52.5, 55.9, 124.5, 125.3, 126.3, 127.0, 127.2, 127.8, 128.1, 128.7, 130.1, 130.9, 133.1, 133.5, 138.9, 169.2, 170.0, 172.2; $[\alpha]_D$ −115.2 (*c* 0.4, $CHCl_3$); MS: *m*/*z* 416 (15, M^+), 261 (8), 245 (7), 186 (10), 172 (18), 155 (100), 127 (75), 105 (67).

4.4.4. (3*S*,4*R*,1′*S*)-3-Amino-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (13). To a solution of **11a** (2.0 g; 5.0 mmol) in dry ethanol (10 mL) sodium borohydride (0.76 g; 20.0 mmol) was added at 0 °C. Then the ice-bath was removed and the reaction was stirred for 12 h at rt. Water (10 mL) was added, ethanol was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (2×70 mL). The combined organic phases were dried over sodium sulphate and filtered. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (ethyl acetate as eluent) to give **13** (0.94 g, 80%) as a viscous oil: IR ($CHCl_3$) ν 3350, 1671 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (d, J=7.0 Hz, 3H), 1.90–2.08 (m, 1H), 2.82 (br s, 3H, OH+NH_2), 2.97–3.02 (m, 2H), 3.38 (d, J=9.9 Hz, 1H), 3.70 (d, J=5.5 Hz, 2H), 5.40 (q, J=7.0 Hz, 1H), 7.17–7.38 (m, 5 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 41.6, 44.3, 49.3, 56.0, 62.3, 126.7, 126.8, 127.5, 128.5, 128.6, 139.6, 174.6; $[\alpha]_D$

−160.9 (*c* 0.5, $CHCl_3$). MS: *m/z* 218 (2, M^+-NH_2), 217 (4), 203 (4), 187 (5), 122 (11), 106 (13), 85 (18), 82 (48) 70 (100). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.59; H, 7.69; N, 12.02.

4.4.5. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (14). To the compound **13** (0.94 g, 4.0 mmol) dissolved in methanol (10 mL), di-*tert*-butyl dicarbonate (0.96 g, 4.4 mmol) was added and the mixture was stirred at rt for 12 h. Removal of the solvent and purification of the residue by chromatography on silica gel (cyclohexane–ethyl acetate 50:50 as eluent) gave the product **14** (0.95 g, 71%) as a colorless oil: IR ($CHCl_3$) ν 3345, 1730, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.54 (d, $J=7.0$ Hz, 3H), 2.07–2.25 (m, 1H), 2.98 (dd, $J=5.8$, 7.2 Hz, 1H), 3.05 (dd, $J=7.2$, 7.2 Hz, 1H), 3.63–3.76 (m, 2H, 1H+OH), 4.02–4.15 (m, 1H), 4.21 (dd, $J=5.4$, 10.3 Hz, 1H), 5.41 (d, $J=5.4$ Hz, 1H, NH), 5.49 (q, $J=7.0$ Hz, 1H), 7.22–7.43 (m, 5 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2, 28.2, 41.4, 45.8, 49.7, 55.4, 61.6, 80.7, 126.8, 127.7, 128.6, 139.4, 157.5, 171.0; $[\alpha]_D$ −141.3 (*c* 1.5, $CHCl_3$); MS: *m/z* 335 (2, MH^+), 279 (48), 218 (15), 187 (46), 156 (32), 134 (30), 106 (100), 70 (44), 58 (87). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.59; H, 7.79; N, 8.42.

4.4.6. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-1-(1′-phenyl-ethyl)-4-tetrahydropyranyloxymethylpyrrolidin-2-one (15). To a solution of **14** (1.0 g; 3.0 mmol) and DHP (0.5 g; 6.0 mmol) in DCM (20 mL), acidic resin H 15 (1.0 g) was added at 0 °C.[23] After 3 h at 0 °C, the resin was filtered off, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 70:30 as eluent) to give the title compound (1.12 g, 89%) as a colorless oil: IR ($CHCl_3$) ν 3341, 1728, 1666 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.41–1.79 (m, 6H), 1.45 (d, $J=7.0$ Hz, 3H), 2.18–2.39 (m, 1H), 3.01–3.22 (m, 2H), 3.38–3.56 (m, 2H), 3.62–4.02 (m, 2H), 4.16 (dd, $J=5.3$, 10.1 Hz, 1H), 4.54 (m, 1H), 5.03 (d, $J=5.3$ Hz, 1H, NH), 5.46 (q, $J=7.0$ Hz, 1H), 7.21–7.36 (m, 5 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 19.4 (50%), 19.5 (50%), 25.1, 28.1, 30.3, 41.2 (50%), 41.5 (50%), 42.3 (50%), 42.8 (50%), 49.3, 54.4 (50%), 54.7 (50%), 62.2 (50%), 62.4 (50%), 66.9 (50%), 67.5 (50%), 79.4, 98.8 (50%), 99.4 (50%), 126.7, 127.3, 128.3, 139.5, 155.6, 171.0 (50%), 171.1 (50%).

4.4.7. (3*S*,4*R*)-3-*t*-Butoxycarbonylamino-4-tetrahydropyranyloxymethylpyrrolidin-2-one (16). After NH_3 (40 mL) was condensed in a three-necked flask at −78 °C, Li shots (140 mg, 20.0 mmol) were added and the blue solution was stirred at this temperature for 20 min. Then compound **15** (1.25 g, 3.0 mmol) was dissolved in a mixture of THF (9 mL) and *t*-BuOH (1 mL), and the solution was added in one portion. After 3 min, the reaction mixture was quenched by addition of solid NH_4Cl (2 g) and warmed to rt. Ammonia was removed, ethyl acetate (40 mL) and water (10 mL) were added, the mixture was extracted with ethyl acetate (2×50 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (cyclohexane–ethyl acetate 40:60 as eluent) to give the compound **16** (0.87 g; 92%) as a colorless oil: IR ($CHCl_3$) ν 3341, 1728, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35–1.82 (m, 6H), 1.41 (s, 9H), 2.47–2.71 (m, 1H), 3.15–3.29 (m, 1H), 3.38–3.71 (m, 3H), 3.74–4.16 (m, 3H), 4.59 (m, 1H), 5.10 (br s, 1H, NH), 6.65 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0 (50%), 19.2 (50%), 25.1, 28.0, 30.2, 42.0 (50%), 42.5 (50%), 42.8 (50%), 43.1 (50%), 53.2 (50%), 53.6 (50%), 61.8 (50%), 62.2 (50%), 66.6 (50%), 66.9 (50%), 79.3, 98.4 (50%), 99.1 (50%), 155.6, 175.4 (50%), 175.5 (50%).

4.4.8. (3*S*,4*R*)-3-*t*-Butoxycarbonylamino-4-hydroxymethylpyrrolidin-2-one (17). Compound from **16** (0.79 g, 2.5 mmol) was dissolved in MeOH (20 mL), acidic resin Amberlyst H 15 (1.0 g) was added and the mixture was heated at 45 °C for 3 h.[23] After filtration, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 30:70 as eluent) to give title compound (0.49 g, 85% yield) as a white solid: mp 128–130 °C: IR ($CHCl_3$) ν 3345, 1728, 1671 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.32–2.52 (m, 1H), 3.13 (m, 1H), 3.36 (m, 1H), 3.65 (dd, $J=6.1$, 12.1 Hz, 1H), 3.77 (dd, $J=4.3$, 12.1 Hz, 1H), 4.14 (dd, $J=5.9$, 10.3 Hz, 1H), 5.31 (d, $J=5.9$ Hz, 1H, NH), 6.36 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.2, 41.1, 47.5, 54.3, 61.7, 80.8, 157.4, 175.0; $[\alpha]_D$ −49.2 (*c* 0.6, MeOH); MS: *m/z* 230 (1, M^+), 203 (3), 174 (5), 149 (17), 81 (45), 69 (88), 57 (51), 43 (100). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.11; H, 7.85; N, 12.21.

4.4.9. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-methoxycarbonyl-1-(1′-phenylethyl)pyrrolidin-2-one (18). To a solution containing compound **14** (1.0 g, 3.0 mmol) in acetone (10 mL), the Jones' reagent (1.5 mL) was added at 0 °C and the mixture was stirred for 5 min. Then ethyl acetate (20 mL) and subsequently saturated aqueous Na_2CO_3 solution (15 mL) were added at 0 °C. After extraction of the aqueous phase with ethyl acetate (50 mL), organics were discarded and pH of the aqueous layer raised to 2 by slow addition of 1 M HCl under stirring. Then, extraction with ethyl acetate (2×50 mL) followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure gave a residue which was dissolved in methanol (5 mL). This solution was treated with an ethereal solution of CH_2N_2 in ether [CAUTION: Diazomethane is an explosive and a highly toxic gas. Explosions may occur if the substance is dry and undiluted. All operations involving diazomethane should be carried out in an efficient fumehood following appropriate precautions] until nitrogen evolution ceased. Then, the solvent was evaporated under reduced pressure, to give a residue which was purified by silica gel chromatography (cyclohexane–acetate 70:30 as eluent) affording the ester **18** (0.84 g, 77% yield) as a colorless oil: IR ($CHCl_3$) ν 3341, 1733, 1725, 1664 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.40 (s, 9H), 1.51 (d, $J=7.2$ Hz, 3H), 2.93–3.12 (m, 1H), 3.15 (dd, $J=8.8$, 9.3 Hz, 1H), 3.39 (dd, $J=9.2$, 9.3 Hz, 1H), 3.69 (s, 3H), 4.43 (dd, $J=6.5$, 9.5 Hz, 1H), 5.31 (d, $J=6.5$ Hz 1H, NH), 5.46 (q, $J=7.2$ Hz, 1H), 7.21–7.35 (m, 5 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 28.1, 41.6, 45.3, 49.7, 52.2, 56.3, 80.0, 126.9, 127.6, 128.5, 139.0, 155.2, 169.3, 172.3; $[\alpha]_D$ −53.8 (*c* 1.0, $CHCl_3$); MS: *m/z* 363 (2, MH^+), 306 (26, MH^+-57), 245 (6), 186 (25), 133 (20), 105 (93), 69 (57), 57 (100). Anal. Calcd for

$C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.94; H, 7.19; N, 7.69.

4.4.10. (3*S*,4*R*)-3-*t*-Butoxycarbonylamino-4-hydroxymethylpyrrolidin-2-one (17). After NH_3 (30 mL) was condensed in a three-necked flask at −78 °C, Li shots (70 mg, 10.0 mmol) were added and the blue solution was stirred at this temperature for 20 min. Then compound **18** (0.38 g, 1.0 mmol) was dissolved in a mixture of THF (4 mL) and *t*-BuOH (1 mL), and the solution was added in one portion. After 3 min, the reaction mixture was quenched by addition of solid NH_4Cl (2 g) and warmed to rt. After removal of ammonia, ethyl acetate (40 mL) and water (10 mL) were added, the mixture was extracted with ethyl acetate (2×50 mL) and the combined organic layers were dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was purified by silica gel chromatography (cyclohexane–ethyl acetate 30:70 as eluent) to give the compound **17** (0.18 g; 69%) as a white solid: mp 128–130 °C; $[\alpha]_D$ −49.2 (*c* 0.6, MeOH); MS: *m/z* 230 (1, M^+), 203 (3), 174 (5), 149 (17), 81 (45), 69 (88), 57 (51), 43 (100). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.11; H, 7.85; N, 12.21.

4.4.11. (3*S*,4*R*)-3-Trichloroacetylamino-4-methoxycarbonylpyrrolidin-2-one (19). A solution of **11b** (1.31 g, 3.0 mmol) in CH_3CN (5 mL) was treated at rt with cerium ammonium nitrate (CAN) (3.3 g, 6.0 mmol) dissolved in water (10 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–EtOAc 80:20 as eluent) on silica gel to give **19** (0.7 g, 76%) as a white solid: mp 73–75 °C: IR ($CHCl_3$) ν 3347, 1728, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.39–3.57 (m, 2H), 3.59–3.71 (m, 1H), 3.76 (s, 3H), 4.62 (dd, J=7.3, 9.1 Hz, 1H), 7.43 (s, 1H, NH), 8.12 (d, J=7.3 Hz 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.7, 45.1, 52.8, 55.0, 91.7, 162.6, 171.6, 172.2; $[\alpha]_D$ −46.1 (*c* 1.9, $CHCl_3$); MS: *m/z* 302 (3, M^+), 304 (3, M^+), 269 (34), 267 (34), 185 (45), 141 (56), 110 (82), 82 (100), 55 (80). Anal. Calcd for $C_8H_9Cl_3N_2O_4$: C, 31.66; H, 2.99%; N, 9.23. Found: C, 31.63; H, 2.26; N, 9.18.

4.4.12. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-methoxy-carbonyl-1-[1′-(4-methoxyphenyl)ethyl]pyrrolidin-2-one (20). In a flask containing compound **11b** (0.5 g, 1.14 mmol), 6 M NaOH (5 mL) was added at rt and the resulting mixture was stirred for 24 h. The pH of the homogeneous solution was adjusted to 7 by addition of 6 M HCl, then water was removed under reduced pressure and methanol (10 mL) was added in order to precipitate the salts that were removed by filtration and filter was washed with methanol (5 mL). The combined filtrates were partially evaporated under reduced pressure and Boc_2O (0.33 g, 1.5 mmol) and TEA (0.4 mL, 3.0 mmol) were added at rt. After 12 h water (5 mL) was added, methanol was removed in vacuo and the solution was acidified with 1 M HCl (0.3 mL). After extraction with ethyl acetate (3×10 mL), the organic layer was dried (Na_2SO_4) and removal of the solvent under reduced pressure gave a residue that was taken off in methanol (5 mL). Subsequent esterification by excess diazomethane in ethyl ether [CAUTION: Diazomethane is an explosive and a highly toxic gas. Explosions may occur if the substance is dry and undiluted. All operations involving diazomethane should be carried out in an efficient fumehood following appropriate precautions] followed by removal of the solvent and purification of the residue by silica gel chromatography (cyclohexane–ethyl acetate 70:30 as eluent) gave compound **20** (0.36 g, 79%) as a viscous oil: IR ($CHCl_3$) ν 3341, 1731, 1725, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.50 (d, J= 7.2 Hz, 3H), 2.91–3.10 (m, 1H), 3.16 (dd, J=8.8, 9.5 Hz, 1H), 3.38 (dd, J=9.3, 9.5 Hz, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 4.43 (dd, J=6.3, 9.6 Hz, 1H), 5.20 (d, J=6.3 Hz, 1H, NH), 5.44 (q, J=7.2 Hz, 1H), 6.86 (d, J=8.8 Hz, 2 ArH), 7.22 (d, J=8.8 Hz, 2 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 28.1, 41.5, 45.2, 49.2, 52.2, 55.1, 56.3, 79.9, 113.8, 128.1, 131.0, 155.2, 160.0, 169.2, 172.3; $[\alpha]_D$ −117.1 (*c* 1.9, $CHCl_3$); MS: *m/z* 393 (1, MH^+), 336 (19, MH^+-57), 321 (10), 275 (7), 216 (33), 135 (100), 69 (42), 57 (67). Anal. Calcd for $C_{20}H_{28}N_2O_6$: C 61.21; H 7.19; N 7.14. Found: C, 61.24; H, 7.16; N, 7.09.

4.4.13. (3*S*,4*R*)-3-*t*-Butoxycarbonylamino-4-methoxycarbonylpyrrolidin-2-one (21). A solution of **20** (0.39 g, 1.0 mmol) in CH_3CN (5 mL) was treated at rt 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 **21** (0.21 g, 82%) as white solid: mp 131–133 °C: IR ($CHCl_3$) ν 3340, 1733, 1725, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.24–3.65 (m, 3H), 3.75 (s, 3H), 4.31 (dd, J=7.3, 9.2 Hz, 1H), 5.44 (d, J= 7.3 Hz, 1H, NH), 7.12 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.2, 31.3, 46.6, 52.4, 55.1, 80.3, 155.4, 172.2, 173.5; $[\alpha]_D$ −36.7 (*c* 0.6, $CHCl_3$); MS: *m/z* 258 (1, M^+), 202 (16, MH^+-57), 185 (10), 143 (13), 81 (28), 69 (56), 57 (100), 43 (98). Anal. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.16; H, 7.02; N, 10.85. Found: C, 51.12; H, 6.97; N, 10.79.

4.5. Crystal data for 11a

$C_{16}H_{17}Cl_3N_2O_4$: Mw=407.67, colorless crystal 0.35× 0.28×0.15 mm, a=8.594(4) Å, b=8.188(3) Å, c= 19.262(6) Å, α=90.00(3)°, β=90.00(3)°, γ=90.00(3)°, V=1841.5(11) $Å^3$, D_{calc}=1.470 mg/m^3, α=0.095 mm^{-1}, Z=4, Orthorhombic, space group $P2_12_12_1$, λ=0.71069 Å, T=223 K, ω and ϕ scans, 11413 reflections collected, 2245 independent (R_{int}=0.0251), 242 refined parameters, $R1/wR2$ [$I \geq 2\sigma(I)$]=0.0499/0.1308 and $R1/wR2$ (all data)=0.0516/0.1329, maximum (minimum) residual electron density 0.497 (−0.392) e $Å^{-3}$.

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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.2005.03.129

Crystallographic data for the structural analysis of compound **11a** have been deposited at the Cambridge Crystallographic Data Centre. The CCDC no. 261070 has been assigned for the compound **11a**. 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).

^{1}H and ^{13}C NMR spectra of compounds **11a–c**, **12a–c**, **17**, **19** and **21**, can be found, in the online version, at doi:10.1016/j.tet.2005.03.129.

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