Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1779–1787

Chiral 3-hydroxypyrrolidin-2-ones. Part 2: Stereodivergent synthesis of conformationally restricted analogues of β-homoserine☆

Roberta Galeazzi,[a] Gianluca Martelli,[a] Desiré Natali,[b] Mario Orena[a,*] and Samuele Rinaldi[a]

[a]*Dipartimento di Scienze dei Materiali e della Terra, Università Politecnica delle Marche, Via Brecce Bianche, I-60121 Ancona, Italy*
[b]*Istituto di MorfologiaUmana Normale, Universtà Politecnica delle Marche, Via Tronto 10/A, I-60131 Ancona, Italy*

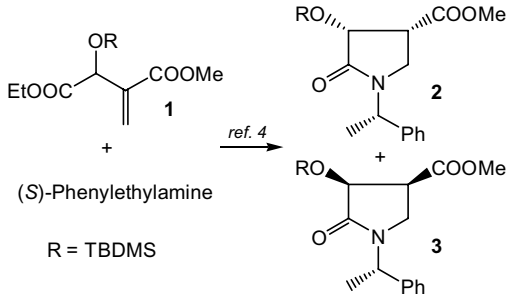
Received 18 February 2005; accepted 2 March 2005
Available online 23 March 2005

Abstract—Starting from the homochiral 3-*t*-butyldimethylsilyloxypyrrolidin-2-one **2**, a stereodivergent synthetic route was developed leading to both 3,4-*trans*- and 3,4-*cis*-3-amino-4-hydroxymethyl pyrrolidin-2-ones, **19** and **28**, that are conformationally restricted analogues of β-homoserine **4**. In addition, with a large number of 3,4-disubstituted pyrrolidin-2-ones in hand, a trend was observed for both H-3 chemical shifts and $J_{3,4}$ values, allowing the configuration to be assigned to either 3-hydroxy or 3-amino derivatives.

1. Introduction

In recent years, the need to replace natural amino acids in peptides with nonproteinogenic counterparts in order to obtain new medicinal agents, exhibiting better binding to specific receptors and more potent inhibition of target enzymes, has stimulated a great deal of innovation in synthetic methods.[1] In addition, developments in new bioorganic methodologies, such as site-directed mutagenesis using expanded genetic codes, total- or semi-synthesis of enzymes, and protein splicing, have enabled incorporation of unnatural amino acids and their constrained derivatives into the framework of native proteins, with the aim of providing more drug-like peptidomimetics, which have improved physiological and physiochemical properties, such as binding affinity and metabolic stability.[2]

Over the course of a study directed at developing procedures for the preparation of pyrrolidin-2-ones (γ-lactams) in high yield and a high degree of stereochemical control,[3] we recently reported a convenient approach to homochiral 3-hydroxypyrrolidin-2-ones **2** and **3** starting from the Baylis–Hillmans adduct **1** (Scheme 1).[4]



Scheme 1.

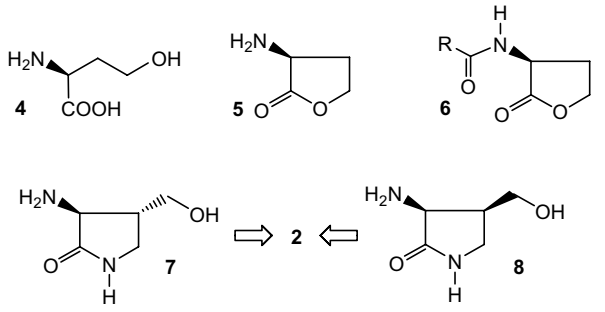
A closer inspection of the structure of compound **2** suggested that it would constitute as a suitable precursor to pyrrolidin-2-ones **7** and **8**, the conformationally constrained isosteres of (*S*)-β-homoserine **4**,[5] an amino acid involved in physiologically important biotransformations.[6] In fact, this compound has received particular attention since *N*-acyl (*S*)-β-homoserine lactones **6**, prepared starting from (*S*)-β-homoserine lactone **5**, are effectors of prokaryotic gene expression and are cell-density-dependent (quorum sensing) signal molecules.[7]

☆ Ref. 4 is considered to be Part 1.

* Corresponding author. Tel.: +39 071 2204720; fax: +39 071 2204714; e-mail: m.orena@univpm.it

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.03.003

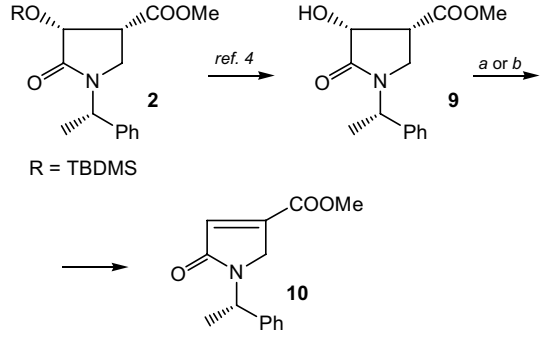
Thus, the preparation of the heterocycles **7** and **8** is of remarkable interest, due to their potential biological activity in this field.[8] Starting from **2** we report herein the stereodivergent synthesis of these analogues for use alone or in solid phase peptide synthesis (Scheme 2).



Scheme 2.

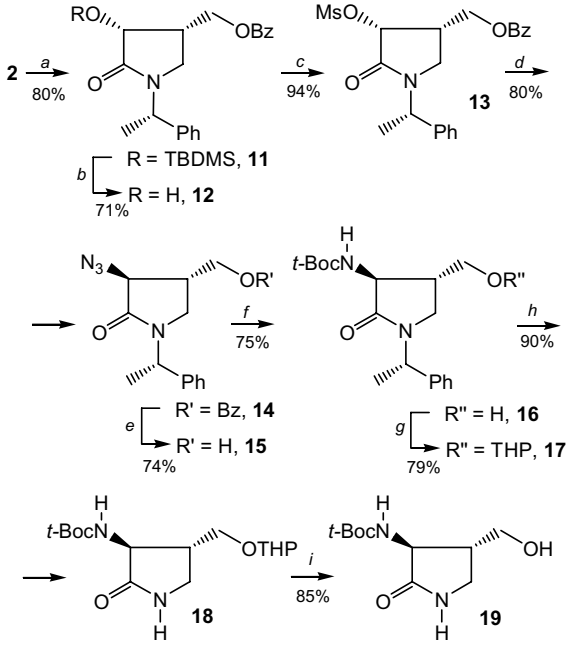
2. Results and discussion

At first, the placement of an amino group at the 3-position of **2** was investigated, but conversion of the alcohol moiety into a nitrogen-containing functionality was not trivial. In fact, owing to an elimination reaction, treatment of compound **9**[4] with diphenylphosphoryl azide (DPPA)[9] led to the exclusive formation of the α,β-unsaturated lactam **10**, instead of the expected azido derivative. Similar results were obtained even upon heating the methanesulfonyl derivative of **9** in DMSO in the presence of sodium azide. In fact at rt, there was no reaction at all, whereas at 80 °C, fast elimination occurred (Scheme 3).



Scheme 3. Reagents and conditions: (a) DPPA, toluene, 67%; (b) methanesulfonyl chloride, Et_3N, DCM, 0 °C; then NaN_3, DMSO, from rt to 80 °C, 78%.

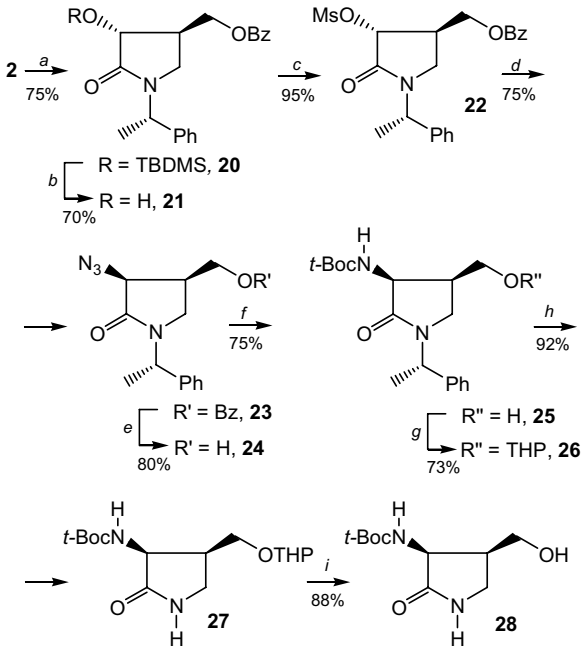
Thus, by reaction with $LiAlH_4$, compound **2** gave the corresponding alcohol that was directly converted into ester **11** in 80% overall yield by reaction with benzoyl chloride. Through such a process the relative configuration remained unchanged, as determined by NOE (irradiation of H-4 resulted in a 11% enhancement on H-3). Subsequent removal of the TBDMS group, carried out with 6 M HCl in methanol, afforded **12** in 71% yield. After activation of the alcohol moiety as a mesylate, intramolecular nucleophilic displacement carried out with sodium azide in DMSO led to the azido derivative **14** in 80% yield. In order to avoid amide formation as a side reaction during the reduction of the azido group, the benzoate ester was cleaved with anhydrous Na_2CO_3 in methanol, to give the alcohol **15**. The next step of the synthesis was the straightforward conversion of the azido group at C-3 into a *t*-butoxycarbonylamino group. Thus, **15** was treated with Zn and saturated aqueous NH_4Cl to give the corresponding amino derivative, which was immediately converted into **16** by reaction with Boc_2O. Eventually, the hydroxy function was protected as THP ether to give **17**, which was treated with Li in liquid NH_3 in order to remove the chiral phenylethyl group. The corresponding pyrrolidin-2-one **18** was recovered in very good yield and final removal of the THP ether allowed us to obtain **19**, the *t*-Boc protected form of **7**, the constrained isostere of (*S*)-β-homoserine having a 3,4-*trans*-disubstitution pattern (Scheme 4).



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt; then BzCl, TEA, DCM; (b) 6 M HCl, MeOH, rt; (c) methanesulfonyl chloride, TEA, DCM, rt; (d) NaN_3, DMSO, rt; (e) anhydrous Na_2CO_3, MeOH, rt; (f) Zn, MeOH, NH_4Cl, then $(Boc)_2O$, MeOH; (g) DHP, H 15, DCM, rt; (h) Li, NH_3, −78 °C; (i) H 15, MeOH, 40 °C.

Having successfully demonstrated the feasibility of using pyrrolidin-2-one **2** for the synthesis of **19**, the *N*-*t*-Boc derivative of the isostere **7**, we turned our attention to the preparation of an *N*-protected form of the 3,4-*cis*-disubstituted isostere **8**, once again starting from the pyrrolidin-2-one **2**. This latter compound was treated with $NaBH_4$ in anhydrous ethanol[10] and the alcohol acylated with benzoyl chloride under standard conditions to give ester **20** in 75% overall yield. We were pleased to observe that the reduction reaction led to the 3,4-*trans*-disubstituted product exclusively, the epimerization at C-4 prior to reduction probably being

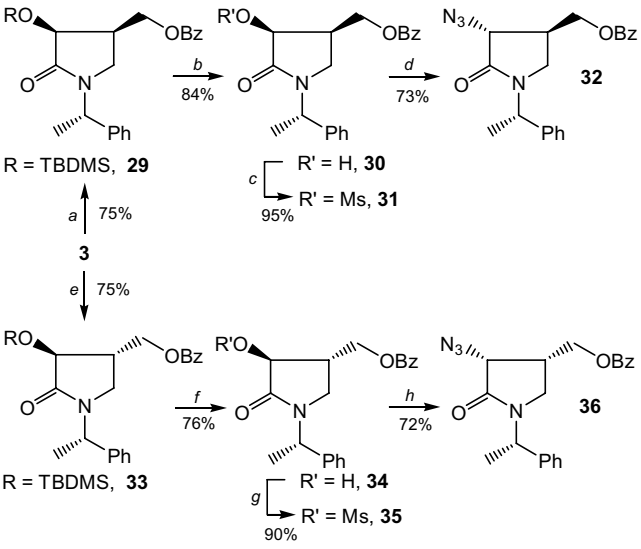
due to the presence of a small amount of sodium ethoxide in the reaction mixture. In fact, the configurational assignment of **20** was established first by NOE difference experiments (irradiation of H-3 resulted in a 10% enhancement of CH_2OBz), and then by comparison between the values for $J_{3,4}$ of both diastereomers **11** and **20** (6.8 vs 8.0 Hz), that were reasonably explained by inspection of molecular models. The subsequent transformation of **20** to **28** was accomplished by the same set of reactions used in the preparation of compound **19**, a small change being exclusively introduced in the conversion of the mesylate **22** into the azido derivative **23**, that required heating and a longer reaction time, clearly owing to the steric hindrance of the bulky group at C-4 that lies on the same side of the incoming azide ion (Scheme 5).



Scheme 5. Reagents and conditions: (a) $NaBH_4$, EtOH, rt; then BzCl, TEA, DCM; (b) 6 M HCl, MeOH, rt; (c) methanesulfonyl chloride, TEA, DCM, 0 °C; (d) NaN_3, DMSO, 65 °C; (e) anhydrous Na_2CO_3, MeOH, rt; (f) Zn, MeOH, NH_4Cl, then $(Boc)_2O$, MeOH; (g) DHP, H 15, DCM, rt; (h) Li, NH_3, −78 °C; (i) H 15, MeOH, 40 °C.

Eventually, the same reaction sequences reported above were carried out starting from compound **3**, with the aim of preparing intermediates useful for the synthesis of *ent*-**19** and *ent*-**28**. In this case, azido derivatives **32** and **36** were obtained in comparable and reproducible overall yields, with respect to compounds **14** and **23** (Scheme 6).

Then, with a relatively large number of 3,4-disubstituted pyrrolidin-2-ones in hand, by considering the trend of the ^1H NMR coupling constants and chemical shifts of H-3, we were able to develop a concrete criterion for the structural assignment of 3,4-*cis* and 3,4-*trans* disubstituted pyrrolidin-2-ones.[11] In fact, $J_{3,4\text{-}cis}$ are significantly smaller than the corresponding $J_{3,4\text{-}trans}$ (the difference in their values is about 1.0 Hz), with only



Scheme 6. Reagents and conditions: (a) $LiAlH_4$, THF, rt, then BzCl, TEA, DCM; (b) 6 M HCl, MeOH; (c) methanesulfonyl chloride, TEA, DCM, 0 °C; (d) NaN_3, DMSO, rt; (e) $NaBH_4$, EtOH, rt, then BzCl, TEA, DCM; (f) 6 M HCl, MeOH; (g) methanesulfonyl chloride, TEA, DCM, 0 °C; (h) NaN_3, DMSO, 65 °C.

the exception being mesylate **22** ($J_{3,4\text{-}trans}$ = 7.5 Hz).[12,13] In addition, the signal of H-3 of the *cis*-isomers usually appears somewhat shielded with respect to the analogous signal of the *trans*-isomers, due to the effect of the group at C-4 (Table 1).

Table 1. H-3 chemical shifts and $J_{3,4}$ values for 3,4-disubstituted pyrrolidin-2-ones

3,4-*cis*	δ	$J_{3,4}$	3,4-*trans*	δ	$J_{3,4}$
11	4.41	6.8	**20**	4.23	8.0
29	4.46	6.5	**33**	4.32	8.4
12	4.55	7.7	**21**	4.36	8.6
30	4.55	7.7	**34**	4.44	9.2
13	5.35	7.8	**22**	5.21	7.5
31	5.39	7.6	**35**	5.27	8.2
23	4.36	7.3	**14**	4.18	8.8
36	4.32	8.1	**32**	4.11	8.4
24	4.35	8.1	**15**	4.19	9.0
25	4.41	8.0	**16**	4.21	10.3
28	4.41	7.4	**19**	4.14	10.3

3. Conclusion

In summary, pyrrolidin-2-ones **2** and **3**, with the appropriate choice of the reaction sequence, can lead in a straightforward manner to all four stereoisomers of a conformationally restricted analogue of β-homoserine, **7**, **8**, *ent*-**7** and *ent*-**8**. Moreover it is worth mentioning that, owing to the easy elaboration of the hydroxymethyl group at C-4, the latter compounds might return a convenient access to a lot of conformationally constrained analogues of proteinogenic amino acids whose synthesis is currently underway in our laboratory, directed towards the preparation of constrained, bioactive oligopeptides.

4. Experimental

4.1. General

Melting points were measured on a hot stage apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ using NaCl cells. 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). ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, using $CDCl_3$ as a solvent unless otherwise reported. Chemical shifts (δ) are reported in ppm 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. Mass spectra (MS) were obtained by electron impact at 70 eV. Column chromatography was performed with silica gel 60 (230–400 mesh). Compounds **2**, **3** and **9** were prepared as described in Ref. 4.

4.2. (1′*S*)-4-Methoxycarbonyl-1,5-dihydro-1-(1′-phenylethyl)-2*H*-pyrrol-2-one 10

4.2.1. Method A. To a solution containing **9** (1.2 g, 4.5 mmol) and diphenylphosphoryl azide (1.5 g, 5.5 mmol) in toluene (15 mL), DBU (0.84 g, 5.5 mmol) was added at 0 °C and the reaction stirred at room temperature for 6 h. The mixture was poured in ethyl acetate (50 mL) and the organic layer washed with 2 M HCl (20 mL) and brine. After drying over Na_2SO_4 and removal of the solvent, the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 80:20 as eluent), to give **10** (0.74 g, 67%) as a clear oil: IR ($CHCl_3$) ν 1724, 1648 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.64 (d, J = 7.1 Hz, 3H), 3.36 (d, J = 1.9 Hz, 2H), 3.71 (s, 3H), 5.44 (q, J = 7.1 Hz, 1H), 7.26–7.43 (m, 5ArH + 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.1, 36.7, 50.1, 51.3, 108.9, 126.6, 128.1, 128.9, 139.9, 140.7, 163.4, 175.4; $[\alpha]_D = -64.3$ (c 1.0, $CHCl_3$); MS: m/z 245 (9, M^+), 149 (16), 129 (14), 105 (100), 69 (42), 43 (65). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.51; H, 6.12; N, 5.75.

4.2.2. Method B. The alcohol **9** (1.1 g, 4.0 mmol) was dissolved in dry dichloromethane (10 mL) containing triethylamine (0.51 g, 5.0 mmol) and methanesulfonyl chloride (0.57 g, 5.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and subsequently poured onto crushed ice containing 1 M HCl (15 mL). After extraction with ethyl acetate (2 × 30 mL), washing with dilute HCl, and drying (Na_2SO_4), evaporation of the solvent under reduced pressure gave the crude mesylate as an oil. To this product DMSO (5 mL) and solid sodium azide (0.33 g, 5.0 mmol) were subsequently added and the mixture was stirred first at 0 °C for 3 h and then for 1 h at 80 °C. Water (10 mL) was added to the reaction mixture and, after extraction with ethyl acetate (2 × 40 mL), the organic layers were combined and washed with brine, dried (Na_2SO_4) and evaporated. Purification of the residue by silica gel chromatography (cyclohexane–ethyl acetate 80:20 as eluent) gave **10** (0.76 g, 78%) as a colourless oil. MS: m/z 245 (9, M^+), 149 (16), 129 (14), 105 (100), 69 (42), 43 (65). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.51; H, 6.12; N, 5.75.

4.3. (3*R*,4*S*,1′*S*)-4-Benzoyloxymethyl-3-*t*-butyldimethylsilyloxy-1-(1′-phenylethyl)pyrrolidin-2-one 11

To a solution containing compound **2**[4] (2.3 g, 6.0 mmol) in dry THF (15 mL), $LiAlH_4$ (0.23 g, 6.0 mmol) was added at 0 °C. After 3 h methanol (1 mL) was added followed by a saturated solution of Seignette salt (20 mL). The mixture was then extracted with ethyl acetate (3 × 50 mL), the organic layer dried over Na_2SO_4 and eventually removed under reduced pressure. The residue was dissolved in dry dichloromethane (15 mL) containing triethylamine (0.6 g, 6.0 mmol), and benzoyl chloride (0.84 g, 6.0 mmol) then added at 0 °C. The reaction mixture was stirred for 4 h and then concentrated. Water (15 mL) and ethyl acetate (70 mL) were added and the resulting organic solution washed with brine, dried and concentrated. Purification of the residue by silica gel chromatography (cyclohexane–ethyl acetate 90:10 as eluent) afforded **11** (2.2 g, 80%) as a colourless oil: IR ($CHCl_3$) ν 1735, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.18 (s, 3H), 0.22 (s, 3H), 0.92 (s, 9H), 1.52 (d, J = 7.0 Hz, 3H), 2.63–2.80 (m, 1H), 3.10 (dd, J = 7.0, 9.9 Hz, 1H), 3.26 (dd, J = 5.1, 9.9 Hz, 1H), 4.34 (dd, J = 7.7, 11.2 Hz, 1H), 4.41 (d, J = 6.8 Hz, 1H), 4.57 (dd, J = 5.9, J = 11.2 Hz, 1H), 5.48 (q, J = 7.0 Hz, 1H), 7.22–7.73 (m, 8ArH), 7.95–8.05 (m, 1ArH), 8.12–8.19 (m, 1ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4, −4.5, 15.8, 18.3, 25.7, 37.4, 42.4, 49.3, 62.7, 71.9, 127.0, 127.5, 128.3, 128.5, 128.8, 129.5, 130.5, 133.0, 134.4, 139.8, 162.3, 166.4, 171.9; $[\alpha]_D = -24.4$ (c 1.03, $CHCl_3$); MS: m/z 396 (21 M^+-57), 292 (10), 179 (17), 105 (100), 77 (19), 57 (12), 43 (15). Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.79; H, 7.81; N, 3.07.

4.4. (3*R*,4*S*,1′*S*)-4-Benzoyloxymethyl-3-hydroxy-1-(1′-phenylethyl)pyrrolidin-2-one 12

To a solution of compound **11** (1.36 g, 3.0 mmol) in methanol (10 mL), 6 M HCl (7 mL) was added and the solution stirred at room temperature for 2 h. Then water (10 mL) was added, methanol removed under reduced pressure and the mixture was extracted with ethyl acetate (2 × 40 mL). After drying over Na_2SO_4 and evaporation of the solvent, the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 70:30 as eluent), to give compound **12** (0.72 g, 71%) as a colourless oil: IR ($CHCl_3$) ν 3345, 1736, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.49 (d, J = 7.1 Hz, 3H), 2.55 (br s, 1H, OH), 2.77–2.94 (m, 1H), 3.08 (dd, J = 6.7, 10.3 Hz, 1H), 3.32 (dd, J = 3.3, 10.3 Hz, 1H), 4.42 (dd, J = 7.4, 11.4 Hz, 1H), 4.55 (d, J = 7.7 Hz, 1H), 4.69 (dd, J = 4.8, 11.4 Hz, 1H), 5.48 (q, J = 7.1 Hz, 1H), 7.21–7.62 (m, 8ArH), 7.97–8.05 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.6, 36.3, 42.7, 49.6, 62.6, 70.7, 127.0, 127.7, 128.3, 128.6, 129.5, 129.6, 129.9, 133.0, 139.4, 166.5, 173.5; $[\alpha]_D = -97.5$ (c 1.0, $CHCl_3$); MS: m/z 219 (3, MH^+-121), 188 (11),

149 (6), 105 (32), 91 (24), 69 (25), 43 (67), 40 (100). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.72; H, 6.28; N, 4.08.

4.5. (3*S*,4*R*,1′*S*)-3-Azido-4-benzoyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 14

Alcohol **12** (1.2 g, 3.6 mmol) was dissolved in dry dichloromethane (10 mL) containing triethylamine (0.84 g, 5.4 mmol) after which methanesulfonyl chloride (0.45 mL, 5.4 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and subsequently poured onto crushed ice containing dilute HCl. After extraction with ethyl acetate (2 × 30 mL), washing with dilute HCl and drying over Na_2SO_4, evaporation of the solvent under reduced pressure gave the crude *(3R,4S,1′S)-4-benzoyloxymethyl-3-methanesulfonyloxy-1-(1′-phenylethyl)pyrrolidin-2-one* **13** (1.41 g, 94%) as a pale yellow oil that was used without further purification: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.53 (d, J = 7.1 Hz, 3H), 2.89–3.04 (m, 1H), 3.14 (dd, J = 6.7, 10.3 Hz, 1H), 3.34 (dd, J = 5.3, 10.3 Hz, 1H), 3.35 (s, 3H), 4.49 (dd, J = 6.5, 11.4 Hz, 1H), 4.58 (dd, J = 5.8, 11.4 Hz, 1H), 5.35 (d, J = 7.8 Hz, 1H), 5.48 (q, J = 7.1 Hz, 1H), 7.22 (m, 7ArH), 7.99–8.07 (m, 2ArH). Then, the methanesulfonyl derivative **13** (0.84 g, 2.0 mmol) was taken up in DMSO (5 mL) and solid sodium azide (0.38 g, 6.0 mmol) added. (**Caution!**: Although these experiments have proceeded without incident, extreme caution should be exercised in the handling of organic azides, particularly with manipulations that involve heating of neat liquids or solid residues). The mixture was stirred at room temperature for 4 h and then poured into water (10 mL)–ethyl acetate (20 mL). After extraction with ethyl acetate (2 × 40 mL), the organic layers were combined and washed with brine, dried over Na_2SO_4 and evaporated. Purification by silica gel chromatography (cyclohexane–ethyl acetate 80:20 as eluent) gave **14** (0.58 g, 80%) as a colourless oil: IR ($CHCl_3$) ν 2107, 1728, 1665 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55 (d, J = 7.2 Hz, 3H), 2.36–2.55 (m, 1H), 3.13–3.17 (m, 2H), 4.18 (d, J = 8.8 Hz, 1H), 4.44 (d, J = 5.5 Hz, 2H), 5.51 (q, J = 7.2 Hz, 1H), 7.24–7.65 (m, 8ArH), 7.96–8.05 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0, 38.7, 42.0, 49.7, 61.9, 63.5, 126.9, 127.8, 128.5, 128.6, 128.7, 129.3, 129.6, 133.4, 138.9, 166.1, 169.4; $[\alpha]_D = -271.2$ (c 1.0, $CHCl_3$); MS: m/z 365 (3, MH^+), 322 (6), 214 (26), 146 (10), 105 (100), 77 (67), 51 (23). Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.88; H, 5.49; N, 15.41.

4.6. (3*S*,4*R*,1′*S*)-3-Azido-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 15

A mixture of **14** (1.29 g, 3.5 mmol) and anhydrous sodium carbonate (0.27 g, 2.5 mmol), in dry methanol (7 mL) was stirred at room temperature for 5 h. After filtration, methanol was removed under reduced pressure and the residue purified by silica gel chromatography (cyclohexane–ethyl acetate 60:40 as eluent) to give **15** (0.69 g, 74%) as a viscous oil: IR ($CHCl_3$) ν 2107, 1722, 1670 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.53 (d, J = 7.1 Hz, 3H), 2.09–2.28 (m, 1H), 2.85 (br s, 1H, OH), 3.03 (dd, J = 8.4, 9.9 Hz, 1H), 3.18 (dd, J = 8.4, 9.9 Hz, 1H), 3.73 (dd, J = 6.6, 9.2 Hz, 1H), 3.76 (dd, J = 5.2, 9.2 Hz, 1H), 4.19 (d, J = 9.0 Hz, 1H), 5.45 (q, J = 7.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0, 41.3, 41.7, 49.7, 60.8, 61.5, 126.9, 127.8, 128.6, 139.0, 170.1; $[\alpha]_D = -373.8$ (c 1.1, $CHCl_3$); MS: m/z 218 (12, M^+-42), 201 (16), 146 (9), 132 (7), 105 (100), 77 (34). Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.94; H, 6.15; N, 21.47.

4.7. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 16

To a solution of compound **15** (0.78 g, 3.0 mmol) in MeOH (5 mL), Zn powder (0.39 g, 6.0 mmol) and an aqueous saturated solution of NH_4Cl (1 mL) were subsequently added and the mixture was stirred for 15 min at rt. Then a saturated Na_2CO_3 solution (15 mL) was added and the mixture extracted with DCM (3 × 50 mL). After drying over Na_2SO_4 and removal of the solvent under reduced pressure, the residue was dissolved in methanol (10 mL) after which di-*t*-butyl dicarbonate (0.78 g, 3.3 mmol) was added and the mixture stirred at room temperature for 12 h. Removal of the solvent and purification of the residue by chromatography on silica gel (cyclohexane–ethyl acetate 70:30 as eluent) gave **16** (0.75 g, 75%) as a colourless oil: IR ($CHCl_3$) ν 3345, 1730, 1668 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.54 (d, J = 7.0 Hz, 3H), 2.07–2.21 (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, 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, 5ArH); ^{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 (MH^+, 2), 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.

4.8. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-tetrahydropyranyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 17

To a solution of compound **16** (1.0 g, 3.0 mmol) and DHP (0.5 mL, 6.0 mmol) in DCM (20 mL), resin H 15 (1 g) was added and the mixture was stirred for 3 h at rt. The resin was then filtered off and the solvent removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 70:30 as eluent), to give compound **17** (1.0 g, 79%) as a colourless oil: IR ($CHCl_3$) ν 3341, 1728, 1666 cm^{-1}; ^{1}H 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, 1H, NH, J = 5.3 Hz), 5.46 (q, J = 7.0 Hz, 1H), 7.21–7.36 (m, 5ArH); ^{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).

4.9. (3*R*,4*S*)-3-*t*-Butoxycarbonylamino-4-hydroxymethylpyrrolidin-2-one 19

Ammonia (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 **17** (1.25 g, 3.0 mmol) was dissolved in a mixture of THF (9 mL) and *t*-BuOH (1 mL), and the solution added in one portion. After 3 min, the reaction mixture was quenched by the addition of solid NH_4Cl (2 g) and warmed to room temperature. Then ammonia was removed, ethyl acetate (40 mL) and water (10 mL) added, the mixture extracted with ethyl acetate (2 × 50 mL) and the combined organic layers dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was purified by silica gel chromatography (cyclohexane–ethyl acetate 40:60 as eluent) to give *(3S,4R)-3-t-butoxycarbonylamino-4-tetrahydropyranyloxymethylpyrrolidin-2-one* **18** (0.85 g, 90%) as a colourless oil: IR ($CHCl_3$) *v* 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). This product was dissolved in methanol (20 mL), H 15 (1 g) then added and the mixture heated to 45 °C for 1 h. The resin was filtered off, the solvent removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 30:70 as eluent) to give **19** (0.53 g, 85%) as a white solid: mp 128–130 °C; IR ($CHCl_3$) *v* 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, 12.14.

4.10. (3*R*,4*R*,1′*S*)-4-Benzoyloxymethyl-3-*t*-butyldimethylsilyloxy-1-(1′-phenylethyl)pyrrolidin-2-one 20

To a solution containing compound **2** (2.3 g, 6.0 mmol) in dry ethanol (15 mL), $NaBH_4$ (0.96 g, 24.0 mmol) was added at room temperature. After 6 h, the reaction mixture was poured in water (30 mL) and extracted with ethyl acetate (3 × 50 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure. The residue was dissolved in dry DCM (15 mL) containing triethylamine (0.6 g, 6.0 mmol) and benzoyl chloride (0.84 g, 6.0 mmol) was added at 0 °C. The reaction mixture was stirred for 4 h and then concentrated. Water (15 mL) and ethyl acetate (70 mL) were added and the resulting organic solution washed with brine, dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel chromatography (cyclohexane–ethyl acetate 90:10 as eluent) afforded **20** (2.0 g, 75%) as a colourless oil: IR ($CHCl_3$) *v* 1724, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.16 (s, 3H), 0.24 (s, 3H), 0.93 (s, 9H), 1.57 (d, J = 7.3 Hz, 3H), 2.52–2.73 (m, 1H), 2.76 (dd, J = 8.1, 9.4 Hz, 1H), 3.46 (dd, J = 7.8, 9.4 Hz, 1H), 4.23 (d, J = 8.0 Hz, 1H), 4.29 (dd, J = 6.6, 11.2 Hz, 1H), 4.42 (dd, J = 4.3, 11.2 Hz, 1H), 5.51 (q, J = 7.3 Hz, 1H), 7.22–7.72 (m, 6ArH), 7.87–7.95 (m, 2ArH), 8.08–8.21 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.2, −4.1, 15.9, 18.2, 25.7, 41.5, 41.8, 49.5, 63.6, 73.1, 127.0, 127.6, 128.4, 128.6, 128.8, 129.5, 129.6, 130.1, 130.5, 133.1, 134.4, 139.6, 166.1, 172.0; $[\alpha]_D$ = −29.8 (*c* 2.4, $CHCl_3$); MS: *m/z* 396 (21, M^+−57), 292 (10), 179 (17), 105 (100), 77 (19), 57 (12), 43 (15). Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.81; H, 7.83; N, 3.04.

4.11. (3*R*,4*R*,1′*S*)-4-Benzoyloxymethyl-3-hydroxy-1(1′-phenylethyl)pyrrolidin-2-one 21

Starting from **11** (1.36 g, 3.0 mmol), the title compound (0.71 g, 70%) was prepared as a colourless oil as described for **12**: IR ($CHCl_3$) *v* 3347, 1726, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.58 (d, J = 7.1 Hz, 3H), 2.64–2.81 (m, 1H), 2.82 (dd, J = 8.5, 8.9 Hz, 1H), 3.50 (dd, J = 7.7, 8.9 Hz, 1H), 4.36 (d, J = 8.6 Hz, 1H), 4.41 (dd, J = 6.2, 11.4 Hz, 1H), 4.53 (dd, J = 4.3, 11.4 Hz, 1H), 5.52 (q, J = 7.1 Hz, 1H), 7.23–7.61 (m, 8ArH), 7.91–7.98 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.8, 40.6, 41.9, 49.6, 63.9, 71.9, 126.9, 127.6, 128.3, 128.5, 129.4, 129.6, 133.0, 139.1, 166.1, 173.8; $[\alpha]_D$ = −71.1 (*c* 1.6, $CHCl_3$); MS: *m/z* 219 (3, MH^+−121), 188 (11), 149 (6), 105 (32), 91 (24), 69 (25), 43 (67), 40 (100). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.68; H, 6.24; N, 4.13. Found: C, 70.61; H, 6.19; N, 4.17.

4.12. (3*R*,4*R*,1′*S*)-4-Benzoyloxymethyl-3-methanesulfonyloxy-1-(1′-phenylethyl)pyrrolidin-2-one 22

Starting from **21** (1.2 g, 3.0 mmol), the title compound (1.44 g, 95%) was prepared as a colourless oil as described for **13**: ^1H NMR (200 MHz, $CDCl_3$): δ 1.61 (d, J = 7.1 Hz, 3H), 2.84 (dd, J = 8.5, 8.9 Hz, 1H), 2.86–3.06 (m, 1H), 3.37 (s, 3H), 3.58 (dd, J = 7.7, 8.9 Hz, 1H), 4.44 (d, J = 4.2 Hz, 2H), 5.21 (d, J = 7.5 Hz, 1H), 5.49 (q, J = 7.1 Hz, 1H), 7.21–7.65 (m, 8ArH), 7.91–7.99 (m, 2ArH).

4.13. (3*S*,4*S*,1′*S*)-3-Azido-4-benzoyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 23

Starting from **22** (0.84 g, 2.0 mmol), the title compound (0.55 g, 75%) was prepared as a colourless oil as described for **14**, but heating of the reaction mixture to 70 °C for 4 h was required. (**Caution!**: Although these experiments have proceeded without incident, extreme caution should be exercised in the handling of organic azides, particularly with manipulations that involve heating of neat liquids or solid residues): IR ($CHCl_3$) *v*

2104, 1726, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.56 (d, J = 7.2 Hz, 3H), 2.79–2.96 (m, 2H), 3.40 (dd, J = 8.8, 11.8 Hz, 1H), 4.10 (dd, J = 7.4, 11.6 Hz, 1H), 4.36 (d, J = 7.3 Hz, 1H), 4.44 (dd, J = 5.8, 11.6 Hz, 1H), 5.50 (q, J = 7.2 Hz, 1H), 7.21–7.63 (m, 8ArH), 7.87–7.96 (m, 2ArH); ^{13}C NMR: 16.1, 35.1, 42.9, 49.8, 61.3, 62.2, 127.0, 127.8, 128.4, 128.7, 129.6, 133.1, 138.8, 166.0, 169.2; $[\alpha]_D = -302.0$ (c 0.5, $CHCl_3$); MS: m/z 365 (3, MH^+), 322 (6), 214 (26), 146 (10), 105 (100), 77 (67), 51 (23). Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.96; H, 5.47; N, 15.34.

4.14. (3*R*,4*R*,1′*S*)-3-Azido-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 24

Starting from **23** (1.29 g, 3.5 mmol), the title compound (0.73 g, 80%) was prepared as a colourless oil as described for **15**: IR ($CHCl_3$) ν 3346, 2110, 1666 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.51 (d, J = 7.2 Hz, 3H), 2.49–2.78 (m, 1H), 2.80 (dd, J = 4.3, 10.2 Hz, 1H), 3.33 (dd, J = 7.4, 10.2 Hz, 1H), 3.45 (dd, J = 5.7, 11.4 Hz, 1H), 3.62 (dd, J = 6.8, 11.4 Hz, 1H), 4.35 (d, J = 8.1 Hz, 1H), 5.46 (q, J = 7.2 Hz, 1H), 7.21–7.44 (m, 5ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.1, 36.9, 42.7, 49.7, 61.0, 61.6, 127.0, 127.8, 128.6, 139.0, 169.6; $[\alpha]_D = -278.0$ (c 2.0, $CHCl_3$); MS: m/z 218 (12, M^+-42), 201 (16), 146 (9), 132 (7), 105 (100), 77 (34). Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.95; H, 6.17; N, 21.55.

4.15. (3*S*,4*S*,1′*S*)-3-*t*-Butoxycarbonylamino-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 25

Starting from **24** (0.78 g, 3.0 mmol), the title compound (0.75 g, 75%) was prepared as a colourless oil as described for **16**: IR ($CHCl_3$) ν 3455, 1722, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.52 (d, J = 7.2 Hz, 3H), 1.93 (br s, 1H, OH), 2.62–2.77 (m, 1H), 2.93 (dd, J = 1.5, 10.3 Hz, 1H), 3.30 (dd, J = 6.1, 11.2 Hz, 1H), 3.38 (dd, J = 6.8, 10.3 Hz, 1H), 3.49 (dd, J = 4.7, 11.2 Hz, 1H), 4.41 (dd, J = 5.6, 8.0 Hz, 1H), 5.24 (d, J = 5.6 Hz, 1H, NH), 5.46 (q, J = 7.2 Hz, 1H), 7.23–7.36 (m, 5ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.1, 28.3, 37.8, 42.6, 49.7, 54.4, 61.0, 80.1, 127.1, 127.7, 128.5, 139.5, 156.4, 171.0; $[\alpha]_D = -83.0$ (c 1.4, $CHCl_3$); 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, 64.58; H, 7.81; N, 8.34.

4.16. (3*S*,4*S*,1′*S*)-3-*t*-Butoxycarbonylamino-4-tetrahydropyranyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 26

Starting from **25** (1.0 g, 3.0 mmol), the title compound (0.92 g, 73%) was prepared as a colourless oil as described for **17**: IR ($CHCl_3$) ν 3344, 1721, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28–1.55 (m, 6H), 1.38 (s, 9H, 50%), 1.40 (s, 9H, 50%), 1.48 (d, J = 7.2 Hz, 3H), 2.75–2.90 (m, 1H), 3.00 (dd, J = 8.3, 9.6 Hz, 1H) 3.12–3.48 (m, 4H), 3.09–3.44 (m, 4H), 3.49–3.66 (m, 1H), 3.87 (m, 1H, 50%), 4.34 (m, 1H, 50%), 4.55 (dd, J = 6.4, 7.2 Hz, 1H), 5.39 (d, J = 6.4 Hz, 1H, NH), 5.44 (q, J = 7.2 Hz, 1H), 7.18–7.35 (m, 5ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.9 (50), 16.1 (50), 19.0 (50), 19.2 (50), 25.0 (50), 25.1 (50), 26.7, 28.1, 30.0 (50), 30.1 (50), 35.0 (50), 35.1 (50), 41.1 (50), 42.4 (50), 49.5 (50), 50.0 (50), 53.8 (50), 54.3 (50), 61.7 (50), 62.0 (50), 65.0 (50), 65.2 (50), 79.6 (50), 79.8 (50), 98.6 (50), 99.4 (50), 127.0, 127.1, 127.3, 127.5, 129.4 (50), 132.8 (50), 139.5, 156.0 (50), 156.1 (50), 170.6 (50), 170.8 (50).

4.17. (3*S*,4*S*,1′*S*)-3-*t*-Butoxycarbonylamino-4-tetrahydropyranyloxymethylpyrrolidin-2-one 27

Starting from **26** (1.25 g, 3.0 mmol), the title compound (0.87 g, 92%) was prepared as a colourless oil as described for **18**: IR ($CHCl_3$) ν 3350, 1725, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 1.41–1.82 (m, 6H), 2.74–2.99 (m, 1H), 3.21–3.53 (m, 4H), 3.60–3.85 (m, 2H), 4.40 (dd, J = 7.2, 7.4 Hz, 1H), 5.09 (d, J = 7.2 Hz, 1H, NH, 50%), 5.33 (d, J = 7.2 Hz, 1H, NH, 50%), 4.45–4.58 (m, 1H), 6.82 (d, J = 6.5 Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2 (50), 19.6 (50), 25.2 (50), 25.3 (50), 28.2, 30.4 (50), 30.5 (50), 37.6, 42.5 (50), 42.7 (50), 52.8 (50), 52.9 (50), 62.1 (50), 62.6 (50), 65.8, 79.8, 99.4, 156.1, 175.0.

4.18. (3*S*,4*S*,1′*S*)-3-*t*-Butoxycarbonylamino-4-hydroxymethylpyrrolidin-2-one 28

Starting from **27** (0.85 g, 2.7 mmol), the title compound (0.55 g, 88%) was prepared as a white solid as described for **19**: mp 150–152 °C; IR ($CHCl_3$) ν 3347, 1721, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.15 (br s, 1H, OH), 2.81–2.89 (m, 1H), 3.40 (dd, J = 10.2, 10.2 Hz, 1H), 3.53 (dd, J = 6.9, 10.2 Hz, 1H), 3.66 (dd, J = 4.0, 10.6 Hz, 1H), 3.73 (dd, J = 4.0, 10.6 Hz, 1H), 4.41 (dd, J = 5.6, 7.4 Hz, 1H), 5.30 (d, J = 5.6 Hz, 1H, NH), 6.14 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 39.5, 42.8, 53.0, 61.1, 80.0, 156.5, 175.8; $[\alpha]_D = +21.5$ (c 1.4, 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, 52.13; H, 7.84; N, 12.20.

4.19. (3*S*,4*R*,1′*S*)-4-Benzoyloxymethyl-3-*t*-butyldimethylsilyloxy-1-(1′-phenylethyl)pyrrolidin-2-one 29

Starting from **3** (2.3 g, 6.0 mmol), the title compound (2.0 g, 75%) was prepared as a colourless oil as described for **11**: IR ($CHCl_3$) ν 1718, 1667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.18 (s, 3H), 0.23 (s, 3H), 0.93 (s, 9H), 1.55 (d, J = 7.1 Hz, 3H), 2.74–2.87 (m, 1H), 2.95 (dd, J = 5.3, 9.9 Hz, 1H), 3.33 (dd, J = 6.8, 9.9 Hz, 1H), 4.15 (dd, J = 8.3, 11.3 Hz, 1H), 4.46 (d, J = 6.5 Hz, 1H), 4.52 (dd, J = 6.1, 11.3 Hz, 1H), 5.50 (q, J = 7.1 Hz, 1H), 7.20–7.65 (m, 8ArH), 7.89–8.18 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.4, −4.5, 16.1, 18.3, 25.7, 37.5, 42.0, 49.0, 52.3, 72.1, 126.9, 127.5, 128.3, 128.4, 129.5, 129.9, 130.1, 133.0, 133.4, 139.4, 166.2, 172.0; $[\alpha]_D = -77.8$ (c 0.6, $CHCl_3$); MS: m/z 396 (21, M^+-57), 292 (10), 179 (17), 105 (100), 77 (19), 57 (12), 43 (15). Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.78; H, 7.74; N, 3.06.

4.20. (3*S*,4*R*,1′*S*)-4-Benzoyloxymethyl-3-hydroxy-1-(1′-phenylethyl)pyrrolidin-2-one 30

Starting from **29** (1.36 g, 3.0 mmol), the title compound (0.85 g, 84%) was prepared as a colourless oil as described for **12**: IR ($CHCl_3$) ν 3344, 1721, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.54 (d, J = 7.1 Hz, 3H), 2.85–3.04 (m, 2H + OH), 3.38 (dd, J = 6.7, 10.5 Hz, 1H), 4.05 (dd, J = 8.5, 11.5 Hz, 1H), 4.55 (d, J = 7.7 Hz, 1H), 4.56 (dd, J = 4.8, 11.5 Hz, 1H), 5.47 (q, J = 7.1 Hz, 1H), 7.15–7.61 (m, 8ArH), 7.81–7.91 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.9, 36.2, 42.0, 49.5, 62.0, 72.8, 126.1, 127.6, 128.1, 128.4, 129.4, 129.8, 132.7, 138.7, 166.0, 173.6; $[\alpha]_D = -112.3$ (c 3.5, $CHCl_3$); MS: m/z 219 (3, MH^+-121), 188 (11), 149 (6), 105 (32), 91 (24), 69 (25), 43 (67), 40 (100). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.68; H, 6.24; N, 4.13. Found: C, 70.63; H, 6.20; N, 4.09.

4.21. (3*S*,4*R*,1′*S*)-4-Benzoyloxymethyl-3-methanesulfonyloxy-1-(1′-phenylethyl)pyrrolidin-2-one 31

Starting from **30** (1.2 g, 3.6 mmol), the title compound (1.4 g, 95%) was prepared as a colourless oil as described for **13**: ^1H NMR (200 MHz, $CDCl_3$): δ 1.57 (d, J = 7.1 Hz, 3H), 2.95–3.15 (m, 2H), 3.32 (s, 3H), 3.46 (dd, J = 6.7, 10.5 Hz, 1H), 4.24 (dd, J = 7.1, 11.4 Hz, 1H), 4.45 (dd, J = 5.6, 11.4 Hz, 1H), 5.39 (d, J = 7.6 Hz, 1H), 5.47 (q, J = 7.1 Hz, 1H), 7.18–7.29 (m, 5ArH), 7.38–7.49 (m, 2ArH), 7.51–7.63 (m, 1ArH), 7.89–7.95 (m, 2ArH).

4.22. (3*R*,4*S*,1′*S*)-3-Azido-4-benzoyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 32

Starting from **31** (0.84 g, 2.0 mmol), the title compound (0.53 g, 73%) was prepared as a colourless oil as described for **14**. (**Caution!**: Although these experiments have proceeded without incident, extreme caution should be exercised in the handling of organic azides, particularly with manipulations that involve heating of neat liquids or solid residues): IR ($CHCl_3$) ν 2109, 1724, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.59 (d, J = 7.3 Hz, 3H), 2.47–2.65 (m, 1H), 2.81 (dd, J = 7.8, 9.9 Hz, 1H), 3.48 (dd, J = 8.5, 9.9 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 4.35 (d, J = 5.5 Hz, 2H), 5.52 (q, J = 7.3 Hz, 1H), 7.23–7.54 (m, 5ArH), 7.38–7.51 (m, 2ArH), 7.53–7.64 (m, 1ArH), 7.87–7.95 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.9, 38.2, 42.0, 50.0, 61.8, 63.4, 126.9, 127.8, 128.4, 128.6, 129.3, 129.5, 133.2, 139.0, 165.9, 169.4; $[\alpha]_D = -39.4$ (c 2.0, $CHCl_3$); MS: m/z 365 (3, MH^+), 322 (6), 214 (26), 146 (10), 105 (100), 77 (67), 51 (23). Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.87; H, 5.48; N, 15.32.

4.23. (3*S*,4*S*,1′*S*)-4-Benzoyloxymethyl-3-*t*-butyldimethylsilyloxy-1(1′-phenylethyl)pyrrolidin-2-one 33

Starting from **3** (2.3 g, 6.0 mmol), the title compound (2.0 g, 75%) was prepared as a colourless oil as described for **20**: IR ($CHCl_3$) ν 1724, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.17 (s, 3H), 0.24 (s, 3H), 0.94 (s, 9H), 1.51 (d, J = 7.1 Hz, 3H), 2.41–2.60 (m, 1H), 3.08 (dd, J = 9.7, 12.3 Hz, 1H), 3.12 (dd, J = 9.2, 12.3 Hz, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.8 (dd, J = 6.3, 11.4 Hz, 1H), 4.50 (dd, J = 4.2, 11.4 Hz, 1H), 5.49 (q, J = 7.1 Hz, 1H), 7.28–7.72 (m, 8ArH), 7.95–8.21 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.1, −4.1, 16.1, 18.2, 25.7, 26.9, 41.3, 42.0, 49.2, 63.5, 73.0, 127.0, 127.6, 128.4, 128.5, 128.6, 129.5, 129.6, 130.1, 133.2, 139.5, 166.3, 172.0; $[\alpha]_D = -230.7$ (c 1.3, $CHCl_3$); MS: m/z 396 (21, M^+-57), 292 (10), 179 (17), 105 (100), 77 (19), 57 (12), 43 (15). Anal. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found: C, 68.79; H, 7.72; N, 3.13.

4.24. (3*S*,4*S*,1′*S*)-4-Benzoyloxymethyl-3-hydroxy-1(1′-phenylethyl)pyrrolidin-2-one 34

Starting from **33** (1.36 g, 3.0 mmol), the title compound (0.77 g, 76%) was prepared as a colourless oil as described for **12**: IR ($CHCl_3$) ν 3347, 1724, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.54 (d, J = 7.2 Hz, 3H), 2.49–2.71 (m, 1H), 2.98 (br s, 1H, OH), 3.12–3.24 (m, 2H), 4.44 (d, J = 9.2 Hz, 1H), 4.47 (dd, J = 6.3, 11.6 Hz, 1H), 4.57 (dd, J = 4.7, 11.6 Hz, 1H), 5.51 (q, J = 7.2 Hz, 1H), 7.27–7.65 (m, 8ArH), 7.95–8.17 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.1, 41.1, 42.0, 49.7, 63.8, 72.0, 127.0, 127.9, 128.3, 128.7, 128.8, 129.6, 130.1, 133.2, 133.3, 138.9, 166.3, 174.0; $[\alpha]_D = -181.7$ (c 1.2, $CHCl_3$); MS: m/z 219 (3, MH^+-121), 188 (11), 149 (6), 105 (32), 91 (24), 69 (25), 43 (67), 40 (100). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.73; H, 6.19; N, 4.08.

4.25. (3*S*,4*S*,1′*S*)-4-Benzoyloxymethyl-3-methanesulfonyloxy-1-(1′-phenylethyl)pyrrolidin-2-one 35

Starting from **34** (1.2 g, 3.6 mmol), the title compound (1.35 g, 90%) was prepared as a colourless oil as described for **13**: ^1H NMR (200 MHz, $CDCl_3$): δ 1.53 (d, J = 7.2 Hz, 3H), 2.71–2.90 (m, 1H), 3.16 (dd, J = 7.9, 10.0 Hz, 1H), 3.23 (dd, J = 8.8, 10.0 Hz, 1H), 3.37 (s, 3H), 4.48 (dd, J = 5.6, 11.8 Hz, 1H), 4.54 (dd, J = 5.1, 11.8 Hz, 1H), 5.27 (d, J = 8.2 Hz, 1H), 5.47 (q, J = 7.2 Hz, 1H), 7.24 (m, 8ArH), 7.96–8.07 (m, 2ArH).

4.26. (3*R*,4*R*,1′*S*)-3-Azido-4-benzoyloxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one 36

Starting from **35** (0.84 g, 2.0 mmol), the title compound (0.52 g, 72%) was prepared as a colourless oil as described for **23**. (**Caution!**: Although these experiments have proceeded without incident, extreme caution should be exercised in the handling of organic azides, particularly with manipulations that involve heating of neat liquids or solid residues): IR ($CHCl_3$) ν 2108, 1723, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.52 (d, J = 7.1 Hz, 3H), 2.71–2.89 (m, 1H), 3.10 (dd, J = 7.1, 10.1 Hz, 1H), 3.25 (dd, J = 5.1, 10.1 Hz, 1H), 4.32 (d, J = 8.1 Hz, 1H), 4.33 (dd, J = 6.8, 11.4 Hz, 1H), 4.53 (dd, J = 5.8, 11.4 Hz, 1H), 5.50 (q, J = 7.1 Hz, 1H), 7.23–7.63 (m, 8ArH), 7.96–8.05 (m, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.7, 34.8,

42.9, 49.6, 61.0, 62.5, 126.8, 127.7, 128.3, 128.6, 129.5, 133.1, 139.1, 166.1, 169.1; $[\alpha]_D = -21.7$ (*c* 0.75, $CHCl_3$); MS: *m/z* 365 (3, MH^+), 322 (6), 214 (26), 146 (10), 105 (100), 77 (67), 51 (23). Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.85; H, 5.48; N, 15.41.

Acknowledgements

This research was supported by MIUR (Rome, Italy, PRIN 2004) and Università Politecnica delle Marche (Italy).

References

1. (a) Wilken, J.; Kent, S. B. H. *Curr. Opin. Biotechnol.* **1998**, *9*, 412–426; (b) Cotton, G. J.; Muir, T. W. *Chem. Biol.* **1999**, *6*, 247–256; (c) Hamachi, I.; Eboshi, R.; Watanabe, J.; Shinkai, S. *J. Am. Chem. Soc.* **2000**, *122*, 4530–4531; (d) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629–8659; (e) Suat, K. K.; Jois, S. D. S. *Curr. Pharm. Des.* **2003**, *9*, 1209–1224; (f) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342–351.
2. (a) Marshall, G. R. *Tetrahedron* **1993**, *49*, 3547–3558; (b) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bos, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039–3049; (c) Adang, A. E. P.; Hermkens, P. H. H.; Linders, J. T. M.; Ottenheijm, H. C. J.; van Staveren, C. J. *Rec. Trav. Chim. Pays Bas* **1994**, *113*, 63–78; (d) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720; (e) Synthesis of Peptides and Peptidomimetics. In *Houben-Weyl, Methods in Organic Chemistry*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme: Stuttgart, New York, 2003; Vol. E22c.
3. (a) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M. *Synlett* **1995**, 1159–1160; (b) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069–1084; (c) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 79–88; (d) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 3573–3584; (e) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1997**, *8*, 133–137; (f) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 261–270; (g) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 4029–4042; (h) Fava, C.; Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3697–3703; (i) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3353–3358; (j) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Panagiotaki, M. *Heterocycles* **2003**, *60*, 2485–2498.
4. Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2004**, *15*, 3249–3256.
5. (a) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1996**, *7*, 721–728; (b) Hammer, K.; Rømming, C.; Undheim, K. *Tetrahedron* **1998**, *54*, 10837–10850; (c) Hammer, K.; Undheim, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2359–2368; (d) Krikstolaityte, S.; Sackus, A.; Rømming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2001**, *12*, 393–398.
6. (a) Barclay, F.; Chrystal, E.; Gani, D. *J. Chem. Soc., Chem. Commun.* **1994**, 815–816; (b) Barclay, F.; Chrystal, E.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 683–690.
7. (a) Telford, G.; Wheeler, D.; Williams, P.; Tomkins, P. T.; Appleby, P.; Sewell, H.; Stewart, G. S. A. B.; Bycroft, B. W.; Pritchard, D. I. *Infect. Immun.* **1998**, *66*, 36–42; (b) Lawrence, R. N.; Dunn, W. R.; Bycroft, B. W.; Camara, M.; Chhabra, S. R.; Williams, P.; Wilson, V. G. *Br. J. Pharmacol.* **1999**, *128*, 845–848; (c) Chhabra, S. R.; Harty, C.; Hooi, D. S. W.; Daykin, M.; Williams, P.; Telford, G.; Pritchard, D. I.; Bycroft, B. W. *J. Med. Chem.* **2003**, *46*, 97–104.
8. (a) Olsen, J. A.; Severinsen, R.; Rasmussen, T. B.; Hentzer, M.; Givskov, M.; Nielsen, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 325–328; (b) Reverchon, S.; Chantegrel, B.; Deshayes, C.; Doutheau, A.; Cotte-Pattat, N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1153–1157; (c) Castang, S.; Chantegrel, B.; Christian, D.; Dolmazon, R.; Gouet, P.; Haser, R.; Reverchon, S.; Nasser, W.; Hugouvieux-Cotte-Pattat, N.; Doutheau, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5145–5149.
9. Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.
10. (a) Mandal, S. B.; Achari, B.; Chattopadhyay, S. *Tetrahedron Lett.* **1992**, *33*, 1647–1650; (b) Tsuboi, S.; Furutani, H.; Ansari, M. H.; Sakai, T.; Utaka, M.; Takeda, A. *J. Org. Chem.* **1993**, *58*, 486–492; (c) Bonini, B. F.; Carboni, P.; Gottarelli, G.; Masiero, S.; Spada, G. P. *J. Org. Chem.* **1994**, *59*, 5930–5936; (d) Boger, D. L.; Honda, T.; Menezes, R. F.; Colletti, S. L.; Dang, Q.; Yang, W. *J. Am. Chem. Soc.* **1994**, *116*, 82–92.
11. For similar compounds, see: (a) Kametani, T.; Kigawa, Y.; Ihara, M. *Tetrahedron* **1979**, *35*, 313–316; (b) Ma, D.; Jiang, J. *Tetrahedron: Asymmetry* **1998**, *9*, 575–579; (c) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993–996.
12. (a) Molecular mechanics calculations were carried out on **22** both using the implementation of an Amber all-atom force field (AMBER*) and MM2* within the framework of MACROMODEL version 5.5, both in vacuo and using the implicit chloroform GB/SA solvation model and the torsional space was randomly varied with the usage-directed Monte Carlo conformational search. Six conformations were found to lie between 0.0 and 0.46 kcal/mol: Conformation 1: $E_n = 0.0$, torsion angle (H-3)–(C-3)–(C-4)–(H-4) = −165.3°; Conformation 2: $E_n = 0.1$, torsion angle (H-3)–(C-3)–(C-4)–(H-4) = −162.9°; Conformation 3: $E_n = 0.13$, torsion angle (H-3)–(C-3)–(C-4)–(H-4) = −165.9°; Conformation 4: $E_n = 0.21$, torsion angle (H-3)–(C-3)–(C-4)–(H-4) = −163.4°; Conformation 5: $E_n = 0.41$, torsion angle (H-3)–(C-3)–(C-4)–(H-4) = −163.4°; Conformation 6: $E_n = 0.46$, torsion angle (H-3)–(C-3)–(C-4)–(H-4) = −164.1°. In the lowest energy conformation the torsion angle (H-3)–(C-3)–(C-4)–(H-4) was −165.3°, in agreement with the observed $J_{3,4}$ value, so that in **22** additional and specific interactions must occur between the substituents altering the geometry. On the other hand, it is worth noting that for all the other pyrrolidin-2-ones, the calculated torsion angles were in agreement with the observed $J_{3,4}$ values. For references, see: Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *4*, 230–252; (b) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134; (c) Mahamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–452; (d) Still, W. C.; Tempczyk, A.; Hawley, R.; Hendrickson, C. T. *J. Am. Chem. Soc.* **1990**, *112*, 6127–6129; (e) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386; (f) Goodman, J. M.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110–1116.
13. Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.