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TETRAHEDRON: *ASYMMETRY*

Stereoselective reduction of chiral *trans*-3-acetyl-4-alkylpyrrolidin-2-ones

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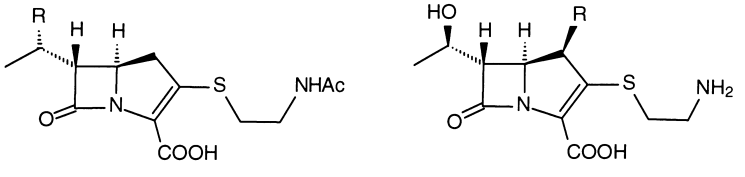
Abstract

A number of *trans*-3-acetyl-4-alkylpyrrolidin-2-ones **8a**–**d** and **11a**,**b** were prepared and reduction of the keto group, carried out with KBH_4 in CH_3OH, led mainly to 3-hydroxyethylpyrrolidin-2-ones **13a**–**d** and **19a**,**b** with high stereoselection. Configuration of the newly formed stereogenic centre on the hydroxyethyl chain was assigned by ^1H NMR data supported by molecular mechanic calculations and eventually confirmed by X-ray diffraction analysis of *p*-iodobenzoate derivative **15**.

1. Introduction

The continued interest for stereoselective synthesis of the β-lactam ring stems from a variety of antibiotics featuring a β-lactam moiety, in particular carbapenems[1] such as *epi*-thienamycin **1**,[2] (+)-PS-5, **2**,[3] thienamycin **3a**[4] and its 1β-methyl derivative **3b** (Scheme 1).[5]



1 R = OH, *Epi*-Thienamycin
2 R = H, (+)-PS-5

3a R = H, (+)-Thienamycin
3b R = CH_3, 1β-methyl Thienamycin

Scheme 1.

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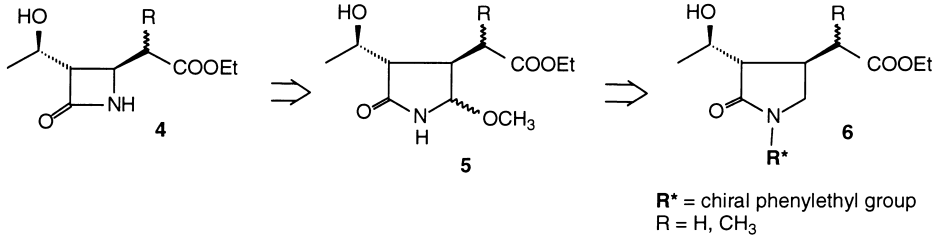
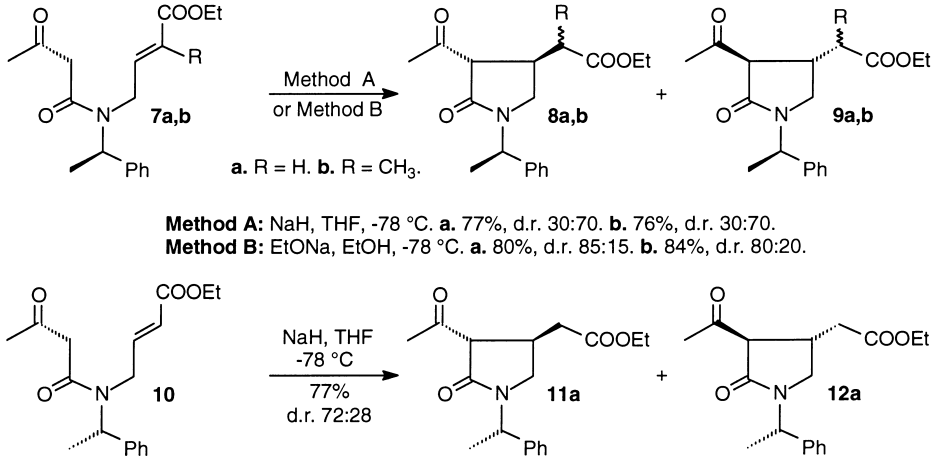
In the past few years we have investigated new procedures aimed at synthesising *trans*-3,4-disubstituted pyrrolidin-2-ones[6–8] and we report herein the stereoselective preparation of pyrrolidin-2-ones **6** bearing three contiguous stereogenic centres by reducing the carbonyl group at the 3-acetyl chain, leading to *trans*-3-hydroxyethyl-4-alkylpyrrolidin-2-ones,[9] and the structural assignment of the reduction products. These compounds could be precursors of substituted azetidinones **4**,[10] intermediates to carbapenems, through ring contraction of derivative **5**, which is currently being studied in our laboratory (Scheme 2).



Scheme 2.

2. Results and discussion

We recently discovered a stereoselective approach to *trans*-3,4-disubstituted pyrrolidin-2-ones by conjugate addition and this process was expected to be a highly attractive method for preparation of substrates having the same configuration as **4** at both C-3 and C-4.[8] Thus, amides **7a**,**b** were treated with NaH in THF at −78°C to give pyrrolidin-2-ones **8a**,**b** and **9a**,**b** in high yield and good diastereoselection but the major component of the reaction mixtures was product **9**, having opposite configurations at both C-3 and C-4 with respect to **4** (Scheme 3).[11] Moreover, both **8b** and **9b** resulted in 70:30 unseparability (*RS*) mixture at C-2 of the propanoate chain.[12] In addition, cyclisation of **10a**, carried out under the same conditions, led to a diastereomeric mixture of **11a** and **12a** in 70:30 d.r. and **11a** having the same configuration as **4** at both C-3 and C-4 (Scheme 3). *trans*-3,4-Disubstituted pyrrolidin-2-ones **8a**,**b**, **9a**,**b**, **11a** and **12a** were easily separated by silica gel chromatography and the absolute configuration of stereocentres on the heterocyclic ring was determined by ^{1}H NMR data supported by molecular mechanic calculations.[6–8]

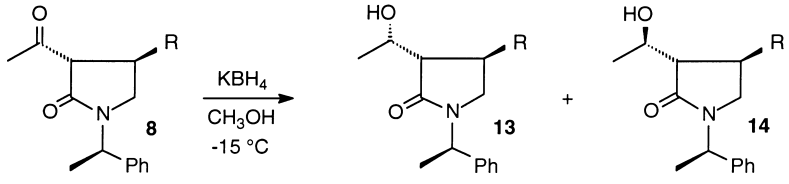


Scheme 3.

On the contrary, higher diastereoselection was observed when amides **7a**,**b** underwent cyclisation on treatment with sodium ethoxide in ethanol at −78°C, to give **8a**,**b** and **9a**,**b**, and the major component of the diastereomeric mixtures was product **8**, having the required configuration at both C-3 and C-4. This result was ascribed to a thermodynamic vs. kinetic control occurring at the cyclisation stage, and studies are currently underway in order to obtain a deeper insight about this stereodivergent cyclisation.

With pyrrolidin-2-ones **8a**,**b** in hand, we prepared 3-acetyl pyrrolidin-2-ones **8c**,**d** and **11b** by cyclisation of chiral acyclic amides induced by Mn(III) as previously reported,[7a,b] in order to check generality of the reduction outcome on a range of substrates.

Compounds **8a–d** were then treated with KBH_4 in CH_3OH at −15°C (Scheme 4), and 3-hydroxyethyl derivatives **13a–d** were obtained in good yield, together with minor amounts of their diastereomers **14a–d**, which were separated easily by silica gel chromatography. On the contrary, when the reaction was performed under the same conditions by using $NaBH_4$, mixtures of **13** and **14** were recovered in good yield but with 60:40 d.r.[13,14]



a. R = CH_2COOEt, 90%, d.r. 95:5. **b.** R = $CH(CH_3)COOEt$, 82%, d.r. 95:5.
c. R = $C(CH_3)=CH_2$, 85%, d.r. 96:4. **d.** R = $CH=CH_2$, 86%, d.r. 93:7.

Scheme 4.

Configuration of the newly formed stereogenic centre of both diastereomers **13a–d** and **14a–d** was assigned by means of ^1H NMR data supported by molecular mechanic calculations. In fact, in the minimum energy conformers of compounds **13a** and **14a** (**A** and **B**, respectively), a hydrogen bond links the hydroxy and the amidic carbonyl groups (Fig. 1).[15,16]

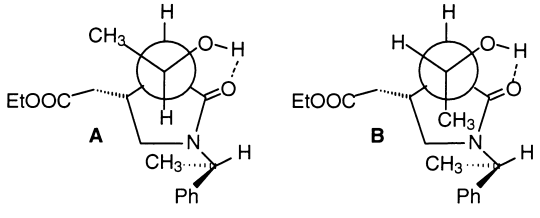


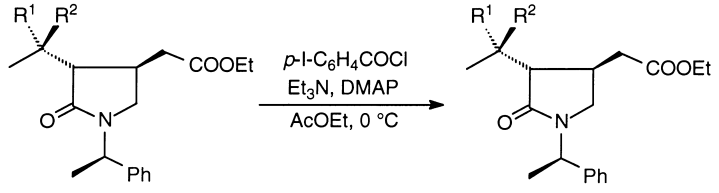
Figure 1. Minimum energy conformations of compounds **13a** (**A**) and **14a** (**B**)

Thus, in conformer **A**, H-3 and H-1′′ are antiperiplanar, in agreement with the large coupling constant observed in the ^1H NMR spectrum of **13a** (J=7.9 Hz). On the contrary, in conformer **B** they lie gauche, and accordingly the coupling constant observed for **14a** has a low value (3.5 Hz). In addition, the observed deshielding effect of the C*H*OH proton in **14a** with respect to **13a** can be ascribed to the presence of a minor conformer of **14a**, in which H-1′′ lies in the carbonyl plane.[17] The same trend was observed even for coupling constants and chemical shift values of compounds **13b–d** and **14b–d**, respectively (Table 1). Thus, on the basis of ^1H NMR data, the configuration of the newly introduced stereogenic centre at C-1′′ for the major diastereomers **13a–d** was assigned as *S*.[18,19]

Eventually, in order to obtain crystalline compounds suitable for X-ray diffraction analysis, the *p*-iodobenzoates **15** and **16** were prepared, and configuration of the stereogenic centre C-1′′ in **13a** was confirmed as *S* by X-ray diffraction analysis of **15** (Scheme 5; Fig. 2).[20,21]

Table 1
Selected coupling constants (J) and chemical shifts (δ) for the C*H*OH proton

Product	J	δ	Product	J	δ
13a	7.9	3.89	**14a**	3.5	4.17
13b	7.0	3.87	**14b**	3.7	4.10
13c	7.1	3.83	**14c**	3.6	4.21
13d	8.7	3.87	**14d**	3.5	4.25
19a	8.1	3.94	**20a**	4.0	4.19
19b	8.0	3.90	**20b**	4.1	4.28



13a. R^1 = OH, R^2 = H
14a. R^1 = H, R^2 = OH

15. R^1 = *p*-I-C_6H_4COO, R^2 = H, 78%
16. R^1 = H, R^2 = *p*-I-C_6H_4COO, 69%

Scheme 5.

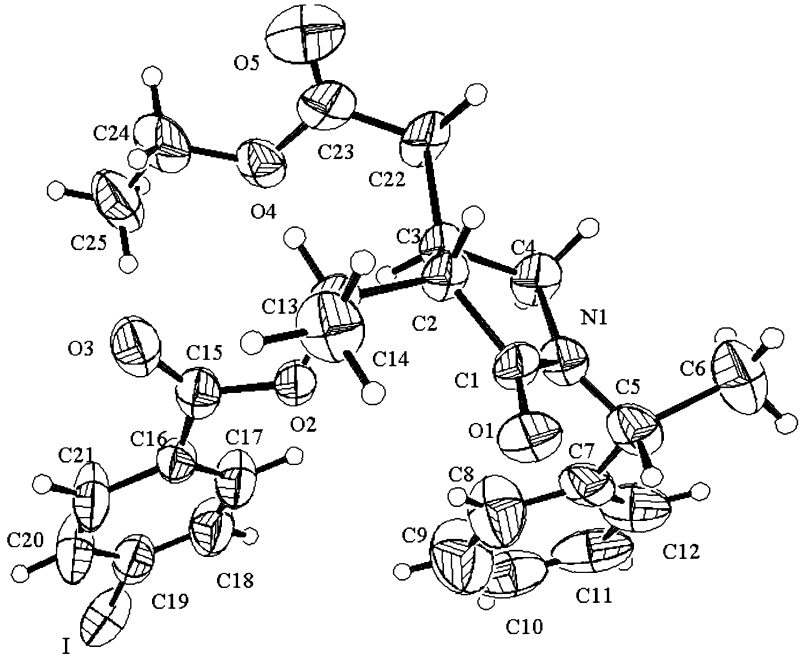


Figure 2. The ORTEP drawing of compound **15**

The vicinal coupling constants were not diagnostic for structural assignment of compounds **15** and **16**, their value being 2.8 and 3.5 Hz, respectively. This is in agreement with molecular mechanic calculations since, in the lowest energy conformation of both diastereomers, H-3 and H-1′′ lie gauche (Fig. 3). On the other hand, the chemical shifts showed the same trend observed for compounds **13a** and **14a**. In fact, by inspection of the most stable rotamers **A**′ and **B**′ of **15** and **16**, respectively, only in **B**′ is H-1′′ deshielded by the amidic carbonyl group (Fig. 4).[15,16,22] Thus, for both **15** and **16** configuration at C-1′′ can be assigned by inspection of the H-1′′ chemical shift value.

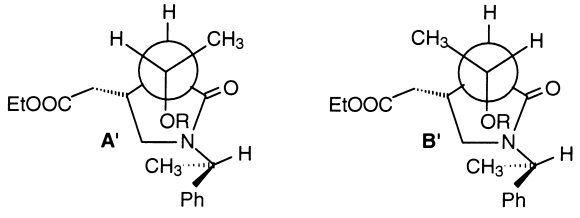


Figure 3. Minimum energy conformations of compounds **15** (**A**′) and **16** (**B**′) (R=*p*-I-C_6H_4CO)

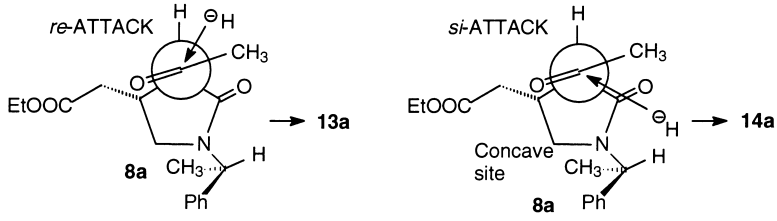
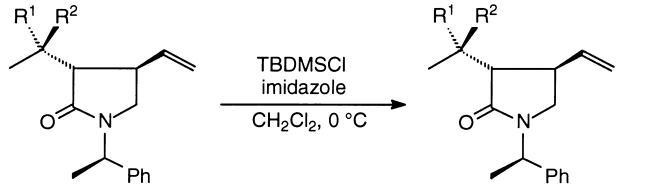


Figure 4. *re*- and *si*-Attack of the incoming hydride ion to **8a**

In order to extend the reliability of this assignment to other derivatives, TBDMS ethers **17** and **18** were prepared starting from **13d** and **14d**, respectively, and the same trend as for **15** and **16** was observed for both coupling constants and chemical shifts (Scheme 6).



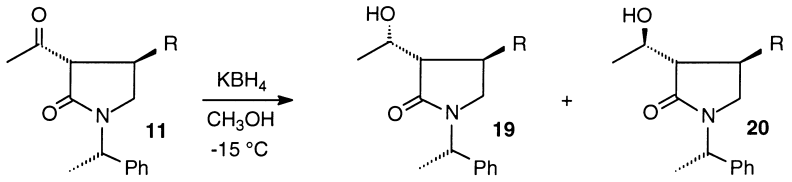
13d. R^1 = OH, R^2 = H
14d. R^1 = H, R^2 = OH

17. R^1 = TBDMSO, R^2 = H, 78%
18. R^1 = H, R^2 = TBDMSO, 79%

Scheme 6.

We then carried out the reduction reaction starting from pyrrolidin-2-ones **11a**,**b**, which only differs from **8a** and **8d**, respectively, by the configuration of the stereogenic centre at the phenethyl group. The reaction proceeded with high diastereoselection, leading mainly to **19a**,**b**, together with minor amounts of **20a**,**b** (Scheme 7).

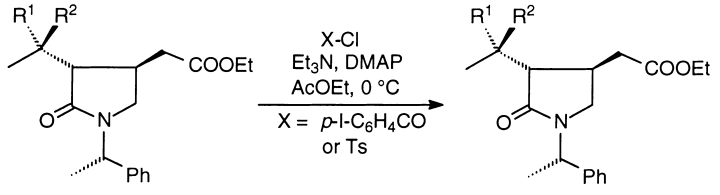
Minimum energy conformations for **19a** and **20a** confirmed the presence of an intramolecular hydrogen bond, as for both **13a** and **14a**.[15,16] Moreover, the vicinal coupling constants and chemical shifts of H-1′′ of compounds **19a**,**b** and **20a**,**b** showed the same trend observed for **13a**,**d** and **14a**,**d**, respectively (Table 1). The corresponding derivatives **21a**,**b** and **22a**,**b** were prepared, but crystals suitable for X-ray diffraction were not obtained, which could usefully result in unambiguous establishment of the configuration at 1′′. On the other hand, the values of both coupling constants and chemical shifts for **21a**,**b** and **22a**,**b** were in agreement with those observed for compounds **15**, **17** and **16**, **18**, respectively,



a. R = CH_2COOEt, 90%, d.r. 95:5. **b.** R = $CH{=}CH_2$, 90%, d.r. 95:5.

Scheme 7.

and it seemed reasonable to assume that the configuration at C-1′′ is *S* in the major products **19a**,**b**, the stereoselection of the reduction not being affected by configuration at C-1′′ of the phenethyl group (Scheme 8).



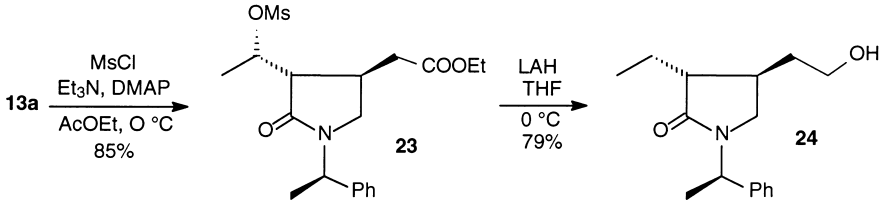
19a. R^1 = OH, R^2 = H
19a. R^1 = OH, R^2 = H
20a. R^1 = H, R^2 = OH
20a. R^1 = H, R^2 = OH

21a. R^1 = *p*-I-C_6H_4COO, R^2 = H, 66%
21b. R^1 =Ts, R^2 = H, 81%
22a. R^1 = H, R^2 = *p*-I-C_6H_4COO, 64%
22b. R^1 = H, R^2 = Ts, 81%

Scheme 8.

The stereoselection of the reduction process could eventually be understood by conformational analysis, since the carbonyl groups of compound **8a** lie *anti* to each other, the *anti* conformer result favoured by 2.89 kcal/mol over the *syn* conformer.[15,16] Thus, hydride ion approaches the keto group from the less hindered *re*-face, to preferentially give **13a**, where the new stereogenic centre has the *S* configuration at the hydroxyethyl chain (Fig. 4). On the contrary, when hydride ion approaches from the *si*-face of the keto group, leading to **14a**, a severe steric interaction occurs, where the attack proceeds from the concave site of a concave:convex shaped molecule.[23]

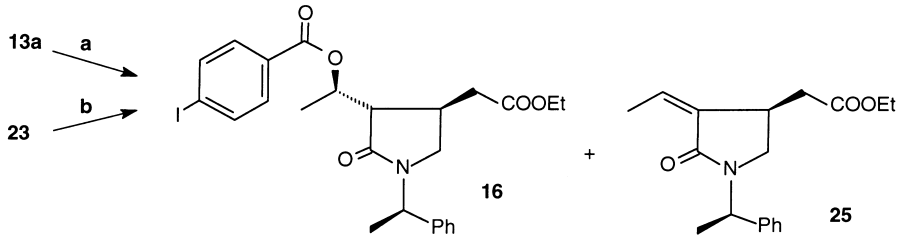
Since in carbapenem (+)-PS-5, **2**, an ethyl chain is present, we first studied removal of the hydroxy group starting from **13a**. The corresponding methanesulphonyl derivative **23** was prepared and then treated with LAH in THF to give 3-ethylpyrrolidin-2-one **24**, suitable for conversion into **2** after cleavage of the phenethyl group and ring contraction (Scheme 9).[24]



Scheme 9.

Although in pyrrolidin-2-one **13a** both the hydroxyethyl chain and the ring centres have the same configuration as in **1**,[25] the final task of this work was to invert the configuration at C-1′′ in order to obtain products having the same configuration at the hydroxyethyl chain as carbapenem **3a**. Thus, starting from **13a**, we first carried out an inversion reaction with DEAD–triphenylphosphine to give in good yield **16**,[26] in which the stereogenic centre at the hydroxyethyl chain has the required *R* configuration. Otherwise, the

inversion of the stereogenic centre in **13a** was performed by treating **21b** with the *p*-iodobenzoate anion on a polymeric support level.[27] In this case, however, **16** was obtained in a lower yield, owing to the formation of a minor amount of the side product **25**, derived from **16** by an *anti*-elimination process. The geometry of the double bond of **16**, established as *Z* by ^{1}H NMR data, further confirmed the structural assignment of **13a** (Scheme 10).



a. DEAD, *p*-iodobenzoic acid, TPP, THF, 0 °C, **16** (71% yield).
b. Amberlyst A 26 in the *p*-iodobenzoate form, refluxing benzene, **16** (65% yield), **25** (21% yield).

Scheme 10.

3. Conclusion

With the method in hand for construction of pyrrolidin-2-ones having three stereogenic centres with definite configuration, we are currently studying in our laboratory the contraction of the γ-lactam to the β-lactam ring proceeding via the functionalisation at C-5,[28] with the aim of obtaining intermediates suitable for conversion into both carbapenems **3a** and **3b**. In addition, further studies are currently underway in order to modify the stereochemical outcome of the reduction reaction[25] and to directly obtain compounds in which the stereogenic centre at the hydroxyethyl chain has *R* configuration.

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 ratios were determined by GC analysis using a Chrompack 9001 instrument equipped with a Chrompack 7720 capillary column (50 m×0.25 mm i.d.; stationary phase CP-Sil-5 CB). ^{1}H and ^{13}C NMR spectra were recorded at 200 MHz 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 hertz. Assignments were aided by decoupling and homonuclear two-dimensional experiments. Optical rotations were measured at 20°C on a Perkin–Elmer 241 polarimeter. Mass spectra (GC–MS) were obtained by electron impact at 70 eV on a Hewlett–Packard spectrometer 5890, series II, using an HP-5 capillary column (30 m×0.25 mm i.d.; stationary phase 5% phenyl methyl silicone). Flash chromatography was performed with silica gel 60 (230–400 mesh).

4.2. Materials

Compounds **8c**, **8d** and **11b** were prepared following the reported procedure.[7b]

4.3. (3S,4S,1′R)-3-Acetyl-1-(1′-phenylethyl)-4-(propen-2-yl)pyrrolidin-2-one **8c**

$[\alpha]_D$ 145.1 (c 1, $CHCl_3$). GC–MS: *m/z* 271 (M^+), 256, 228, 187, 172, 160, 124, 105, 91, 77. Anal. calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.20; H, 7.81; N, 5.12.

4.4. (3S,4R,1′R)-3-Acetyl-4-ethenyl-1-(1′-phenylethyl)pyrrolidin-2-one **8d**

$[\alpha]_D$ 163.3 (c 1, $CHCl_3$). GC–MS: *m/z* 257 (M^+), 242, 214, 200, 186, 173, 160, 132, 120, 105, 91, 77. Anal. calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.73; H, 7.4 1; N, 5.48.

4.5. Preparation of 3-oxobutanamides **7a**,**b** and **10**

A solution containing the appropriate amine (20 mmol) and *N*,*N*-dimethylaminopyridine (0.3 g) in dry THF (70 ml) at −15°C was slowly added to a solution containing diketene (1.8 g; 22 mmol) in dry THF (20 ml). After 1 h the solvent was removed under reduced pressure at 20°C and the residue purified by silica gel chromatography (cyclohexane:ethyl acetate, 7:3) to give amides **7a**,**b** or **10** (rotameric mixtures) as colourless oils.

4.6. (E,R)-N-(3-Ethoxycarbonyl-2-propenyl)-N-(1-phenylethyl)-3-oxobutanamide **7a**

The title compound was obtained in 77% yield as a colourless oil starting from (*E*,*R*)-*N*-(3-ethoxycarbonyl-2-propenyl)-*N*-(1-phenylethyl)amine.[8] IR: 1725, 1665 cm^{-1}. ^1H NMR: 1.24 (t, 3H, 40%, J=7.1), 1.27 (t, 3H, 60%, J=7.1), 1.50 (d, 3H, 60%, J=6.9), 1.60 (d, 3H, 40%, J=6.9), 2.28 (s, 3H, 60%), 2.31 (s, 3H, 40%), 3.48–3.94 (m, 2H), 3.50 (s, 2H, 60%), 3.71 (s, 2H, 40%), 4.14 (q, 2H, 40%, J=7.1), 4.16 (q, 2H, 60%, J=7.1), 5.05 (q, 1H, 40%, J=6.9), 5.77 (ddd, 1H, J=15.8, J=1.7, J=1.6), 6.08 (q, 1H, 60%, J=6.9), 6.65 (dt, 1H, 60%, J=15.8, J=4.8), 6.73 (dt, 1H, 40%, J=15.8, J=4.8), 7.18–7.42 (m, 5 ArH). ^{13}C NMR: 14.7, 16.7 (40%), 17.1 (60%) 30.3 (40%), 30.9 (60%), 44.1 (40%), 45.2 (60%), 50.7 (60%), 51.9 (40%), 56.8 (60%), 60.8 (40%), 61.2 (60%), 61.9 (40%), 122.7 (40%), 123.1 (60%), 127.1 (60%), 127.3 (40%), 128.0 (60%), 128.3 (40%), 128.5 (40%), 129.2 (60%), 140.0 (40%), 140.3 (60%), 144.2 (40%), 144.6 (60%), 166.1 (60%), 166.5 (40%), 167.1 (40%), 167.8 (60%), 172.1 (40%), 172.7 (60%). $[\alpha]_D$ 112.3 (c 1, $CHCl_3$). GC–MS: *m/z* 317 (M^+), 302, 274, 260, 246, 230, 188, 166, 155, 132, 105, 91, 77. Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.06; H, 7.22; N, 4.37.

4.7. (E,R)-N-[3-Ethoxycarbonyl-2-butenyl]-N-(1-phenylethyl)-3-oxobutanamide **7b**

Starting from (*E*,*R*)-*N*-[3-ethoxycarbonyl-2-buten-1-yl]-*N*-(1-phenylethyl)amine,[8] the title compound was obtained in 77% yield. IR: 1715, 1701, 1663, 1630 cm^{-1}. ^1H NMR: 1.22 (t, 3H, J=7.2, 30%), 1.23 (t, 3H, J=7.2, 70%), 1.49 (d, 3H, J=7.0, 70%), 1.57 (d, 3H, J=7.0, 30%), 1.66 (s, 3H, 70%), 1.92 (s, 3H, 30%), 2.25 (s, 3H, 70%), 2.28 (s, 3H, 30%), 3.46 (s, 2H, 70%), 3.55–3.84 (m, 2H), 3.68 (s, 2H, 30%), 4.10 (q, 2H, J=7.2, 30%), 4.12 (q, 2H, J=7.2, 70%), 5.05 (q, 1H, J=7.2, 30%), 6.05 (q, 1H, J=7.2, 70%), 6.29 (t, 1H, J=6.0, 70%), 6.43 (t, 1H, J=6.0, 30%), 7.15–7.41 (m, 5 ArH). ^{13}C NMR: 12.8 (30%), 12.9 (70%), 14.7 (70%), 16.8 (30%), 18.8 (30%), 22.6 (70%), 30.9, 41.6 (30%), 42.7 (70%), 50.7 (70%), 51.7

(30%), 56.6 (70%), 61.0 (30%), 61.2 (70%), 61.3 (30%), 127.2, 127.3, 127.5, 127.8, 128.0, 128.2, 128.4, 128.7, 129.0, 129.1, 129.3 (70%), 129.8 (30%), 138.6 (70%), 139.0 (30%), 140.0 (30%), 140.3 (70%), 167.1 (30%), 167.4 (70%), 176.3. $[\alpha]_D$ 93.6 (c 1, $CHCl_3$). GC–MS: *m/z* 331 (M^+), 316, 288, 230, 202, 180, 152, 126, 105, 77. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.81; H, 7.55; N, 4.18. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.83; H, 7.56; N, 4.33.

*4.8. (*E,S*)-*N*-(3-Ethoxycarbonyl-2-propenyl)-*N*-(1-phenylethyl)-3-oxobutanamide **10***

The title compound was obtained in 77% yield starting from (*E*,*S*)-*N*-(3-ethoxycarbonyl-2-propenyl)-*N*-(1-phenylethyl)amine.[8] $[\alpha]_D$ −111.9 (c 1, $CHCl_3$). Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.08; H, 7.18; N, 4.38.

*4.9. Cyclisation of the 3-oxobutanamides **7a**,**b** and **10** with NaH in THF (Method A)*[8]

4.9.1. General procedure

A solution containing amides **7a**,**b**, or **10** (10 mmol) in dry THF (30 ml) was slowly added at −78°C to a suspension of NaH (0.48 g; 10 mmol; 50% dispersion in mineral oil) in dry THF (20 ml). After 1 h solid NH_4Cl (5 g) was added and the temperature raised to 20°C. The mixture was poured into water (50 ml) and after extraction with ethyl acetate (2×100 ml) and drying (Na_2SO_4), the organic layer was evaporated under reduced pressure. The residue was chromatographed by silica gel chromatography (cyclohexane:ethyl acetate, 7:3) to give **8a**, **8b**, **9a**, **9b**, **11a** and **12a** as colourless oils.

*4.10. Ethyl (3*S,*4*R,*1′*R*)-[3-acetyl-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]acetate **8a** and its isomer (3*R,*4*S,*1′*R*) **9a***

Following cyclisation Method A, and starting from **7a**, compounds **8a** and **9a** were obtained in 77% overall yield as colourless oils. D.r. (3*S*,4*R*,1′*R*)-**8a**:(3*R*,4*S*,1′*R*)-**9a**, 30:70. Isomer (3*S*,4*R*,1′*R*)-**8a**: IR: 1735, 1668 cm^{-1}. ^1H NMR: 1.19 (t, 3H, J=6.5), 1.52 (d, 3H, J=7.1), 2.23 (dd, 1H, J=16.2, J=8.4), 2.35 (dd, 1H, J=16.2, J=7.2), 2.44 (s, 3H), 2.58 (dd, 1H, H_A, J_{AB}=9.7, J_{AX}=6.1), 3.14 (m, 1H, H_X), 3.39 (d, 1H, H_Y, J=7.2), 3.58 (dd, 1H, H_B, J_{AB}=9.7, J_{BX}=8.1), 4.06 (q, 2H, J=6.5), 5.45 (q, 1H, J=7.1), 7.21–7.42 (m, 5 ArH). ^{13}C NMR: 14.6, 16.6, 30.2, 30.8, 38.0, 46.5, 50.1, 61.2, 62.1, 127.6, 128.2, 129.1, 140.0, 168.9, 171.7. $[\alpha]_D$ 107.2 (c 1, $CHCl_3$). GC–MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.07; H, 7.27; N, 4.37. Isomer (3*R*,4*S*,1′*R*)-**9a**: IR: 1735, 1670 cm^{-1}. ^{1}NMR: 1.23 (t, 3H, J=6.5), 1.54 (d, 3H, J=7.2), 2.38 (dd, 1H, J=8.5, J=2.8), 2.45 (s, 3H), 2.47 (dd, 1H, J=8.5, J=2.2), 2.95 (dd, 1H, H_A, J_{AB}=8.8, J_{AX}=6.3), 3.07 (m, 1H, H_X), 3.25 (dd, 1H, H_B, J_{AB}=8.8, J_{BX}=7.5), 3.46 (d, 1H, H_Y, J_{XY}=7.4), 5.42 (q, 1H, J=7.2), 7.22–7.41 (m, 5 ArH). ^{13}C NMR: 14.6, 16.7, 30.3, 30.8, 38.1, 46.5, 50.0, 61.2, 61.9, 127.3, 128.1, 129.1, 139.9, 169.0, 171.7. $[\alpha]_D$ 130.6 (c 1, $CHCl_3$). GC–MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.16; H, 7.27; N, 4.45.

*4.11. Ethyl (2*RS,*3′*S,*4′*R,*1′′*R)-2-[3′-acetyl-2′-oxo-1′-(1′′-phenylethyl)pyrrolidin-4′-yl]propanoate **8b** and its isomer (2*RS,*3′*R,*4′*S,*1′′*R) **9b***

Following cyclisation Method A, and starting from **7b**, diastereomers **8b** and **9b** were obtained in 76% overall yield as colourless oils. D.r. (2*RS*,3′*S*,4′*R*,1′′*R*)-**8b**:(2*RS*,3′*S*,4′*R*,1′′*S*)-**9b**, 30:70. (2*RS*) ratio

(unassigned): 70:30. IR: 1725, 1710, 1668 cm^{-1}. Isomer (2*RS*,3′*S*,4′*R*,1′′*R*)-**8b**: ^{1}H NMR: 1.09 (d, 3H, 70%, J=7.1), 1.10 (d, 3H, 30%, J=7.0), 1.22 (t, 3H, 70%, J=7.1), 1.23 (t, 3H, 30%, J=7.1), 1.51 (d, 3H, 70%, J=7.1), 1.52 (d, 3H, 30%, J=7.1), 2.38–2.52 (m, 1H), 2.42 (s, 3H, 30%), 2.44 (s, 3H; 70%), 2.90–3.19 (m, 3H, H_A+H_B+H_X), 3.56 (d, 1H, H_Y, 30%, J=7.2), 3.61 (d, 1H, H_Y, 70%, J=7.2), 4.06 (q, 2H, 30%, J=7.1), 4.07 (q, 2H, 70%, J=7.2), 5.40 (q, 1H, 30%, J=7.1), 5.41 (q, 1H, 70%, J=7.1), 7.15–7.38 (m, 5 ArH). ^{13}C NMR: 14.6 (70%), 14.7 (30%), 14.9 (70%), 15.2 (30%), 16.6, 30.9 (30%), 31.0 (70%), 35.6 (30%), 36.1 (70%), 42.4 (30%), 43.0 (70%), 44.5 (30%), 44.8 (70%), 49.9 (70%), 50.0 (30%), 60.2 (30%), 60.5 (70%), 61.2 (30%), 61.3 (70%), 127.3, 128.1, 129.1, 139.9, 169.2 (30%), 169.3 (70%), 174.7, 203.7 (30%), 203.8 (70%). Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.81; H, 7.57; N, 4.20. Isomer (2*RS*,3′*R*,4′*S*,1′′*R*)-**9b**: ^{1}H NMR: 0.97 (d, 3H, J=7.0), 1.13 (t, 3H, 70%, J=7.1), 1.15 (t, 3H, 30%, J=7.1), 1.48 (d, 3H, 70%, J=7.2), 1.49 (d, 3H, 30%, J=7.2), 2.34 (dq, 1H, J=7.1, J=7.5), 2.42 (s, 3H, 30%), 2.45 (s, 3H, 70%), 2.63 (dd, 1H, H_A, 70%, J_{AX}=6.3, J_{AB}=9.9), 2.64 (dd, 1H, H_A, 30%, J_{AX}=6.8, J_{AB}=9.8), 2.87–3.20 (m, 1H, H_X), 3.43 (dd, 1H, H_B, 30%, J=8.6, J=9.8), 4.34 (dd, 1H, H_B, 30%, J_{BX}=8.6, J_{AB}=9.7), 3.47 (dd, 1H, H_B, 70%, J_{BX}=8.8, J_{AB}=9.8), 3.51 (d, 1H, H_Y, 70%, J=7.2), 3.55 (d, 1H, H_Y, 30%, J=7.2), 3.98 (q, 2H, 30%, J=7.1), 4.00 (q, 2H, 70%, J=7.1), 5.41 (q, 1H, 70%, J=7.2), 5.42 (q, 1H, J=7.2), 7.19–7.38 (m, 5 ArH). ^{13}C NMR: 14.6, 14.8 (30%), 14.9 (70%), 16.6, 31.0, 35.4 (70%), 36.0 (30%), 42.5 (70%), 42.8 (30%), 44.5 (30%), 44.9 (70%), 50.1 (30%), 50.2 (70%), 60.0 (70%), 60.7 (30%), 61.1 (30%), 61.2 (70%), 127.6, 128.2, 129.1, 139.9, 168.9 (70%), 169.2 (30%), 174.7, 203.7. GC–MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.79; H, 7.55; N, 4.19.

*4.12. Ethyl (3*S*,4*R*,1′S)-[3-acetyl-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]acetate **11a** and its isomer (3*R*,4*S*,1′*S*) **12a***

Following cyclisation Method A, and starting from **10**, compounds **11a** and **12a** were obtained as colourless oils, in 77% overall yield. D.r. (3*S*,4*R*,1′*S*)-**10a**:(3*R*,4*S*,1′*S*)-**11a**, 72:28. Isomer (3*S*,4*R*,1′*S*)-**11a**: $[\alpha]_D$ −129.2 (c 1, $CHCl_3$). Isomer (3*R*,4*S*,1′*S*)-**12a**: $[\alpha]_D$ −106.5 (c 1, $CHCl_3$). GC–MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.06; H, 7.26; N, 4.37.

*4.13. Cyclisation of amides **7a**,**b** with sodium ethoxide in ethanol (Method B)*

4.13.1. General procedure

To a solution containing amides **7a**,**b** (20 mmol) in dry ethanol (30 ml) was slowly added at −78° a solution containing sodium ethoxide [20 mmol; prepared by dissolving Na (480 mg; 20 mmol) in dry ethanol (20 ml)]. After 1 h, solid NH_4Cl (5.0 g) was added and the temperature raised to 20°C. After addition of water (50 ml), the mixture was extracted with ethyl acetate (3×100 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue purified by silica gel chromatography, to give pyrrolidin-2-ones **8a**,**b** and **9a**,**b** as colourless oils.

*4.14. Ethyl (3*S*,4*R*,1′R)-[3-acetyl-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]acetate **8a** and its isomer (3*R*,4*S*,1′*R*) **9a***

Following cyclisation Method B, and starting from **7a**, compounds **8a** and **9a** were obtained in 80% overall yield as colourless oils. D.r. (3*S*,4*R*,1′*R*)-**8a**:(3*R*,4*S*,1′*R*)-**9a**, 85:15. Isomer (3*S*,4*R*,1′*R*)-**8a**: $[\alpha]_D$ 107.2 (c 1, $CHCl_3$). GC–MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal.

calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.12; H, 7.30; N, 4.39. Isomer (3*R*,4*S*,1′*R*)-**9a**: $[\alpha]_D$ 130.6 (c 1, $CHCl_3$). GC–MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal. calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.15; H, 7.25; N, 4.38.

*4.15. Ethyl (2*RS,*3′*S,*4′*R,*1′′*R*)-2-[3′-acetyl-2′-oxo-1′-(1′′-phenylethyl)pyrrolidin-4′-yl]propanoate **8b** and its isomer (2*RS,*3′*R,*4′*S,*1′′*R) **9b***

Following cyclisation Method B, and starting from **7b**, diastereomers **8b** and **9b** were obtained in 84% overall yield as colourless oils. D.r. (2*RS*,3′*S*,4′*R*,1′′*R*)-**8b**:(2*RS*,3′*S*,4′*R*,1′′*S*)-**9b**, 80:20. (2*RS*) ratio (unassigned): 70:30. Isomer (2*RS*,3′*S*,4′*R*,1′′*R*)-**8b**: GC–MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.80; H, 7.58; N, 4.24. Isomer (2*RS*,3′*S*,4′*R*,1′′*S*)-**9b**: GC–MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77. Anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.82; H, 7.56; N, 4.20.

*4.16. Reduction of pyrrolidin-2-ones **8a–d** and **14a,b***

4.16.1. General procedure

To a solution containing pyrrolidin-2-ones **4a**–**d** or **11a**,**b** (10 mmol) in dry methanol (50 ml) at −15°C, KBH_4 (0.7 g; 10 mmol) was added and the mixture stirred for 1 h. Then solid NH_4Cl (2.0 g) and H_2O (40 ml) were added and the mixture extracted with ethyl acetate (3×100 ml). After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (ethyl acetate) to give diastereomeric alcohols **13** and **14** or **19** and **20** as colourless oils.

*4.17. Ethyl (3*S,*4*R,*1′*R,*1′′*S)-[3-(1′′-hydroxyethyl)-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]acetate **13a** and its (3*S,*4*R,*1′′*R,*1′′*R) isomer **14a***

By reduction of **8a**, a 95:5 diastereomeric mixture of **13a** and **14a** was obtained in 90% overall yield. GC–MS: *m/z* 319 (M^+), 304, 274, 260, 188, 132, 105, 91, 77. Isomer (3*S*,4*R*,1′*R*,1′′*S*)-**13a**: IR: 3415, 1725, 1673 cm^{-1}. ^1H NMR: 1.20 (d, 3H, J=6.2), 1.21 (t, 3H, J=7.0), 1.50 (d, 3H, J=7.0), 2.08–2.22 (m, 1H), 2.25–2.45 (m, 2H), 2.55–2.73 (m, 1H), 2.97 (dd, 1H, H_A, J_{AX}=6.2, J_{AB}=10.0), 3.24 (dd, 1H, H_B, J_{BX}=7.9, J_{AB}=10.0), 3.89 (dq, 1H, J=6.2, J=7.9), 4.70 (br s, 1H, OH), 5.45 (q,1H, J=7.0), 7.15–7.39 (m, 5 ArH). ^{13}C NMR: 14.6, 16.7, 21.2, 31.0, 39.3, 47.4, 49.5, 53.6, 61.3, 69.6, 127.4, 128.1, 129.1, 129.2, 140.1, 172.1, 175.4. $[\alpha]_D$ 108.8 (c 1, $CHCl_3$). Isomer (3*S*,4*R*,1′*R*,1′′*R*)-**14a**: IR: 3425, 1735, 1670 cm^{-1}. ^1H NMR: 1.23 (t, 3H, J=7.2), 1.24 (d, 3H, J=6.4), 1.51 (d, 3H, J=7.0), 2.25–2.66 (m, 3H), 2.98 (dd, 1H, H_A, J_{AX}=5.8, J_{AB}=10.3), 3.26 (dd, 1H, H_B, J_{BX}=7.5, J_{AB}=10.3), 3.75 (br s, 1H, OH), 4.11 (q, 2H, J=7.2), 4.17 (dq, 1H, J=6.4, J=3.5), 5.49 (q, 1H, J=7.0), 7.19–7.41 (m, 5 ArH). ^{13}C NMR: 14.8, 16.5, 20.8, 31.2, 39.6, 47.5, 50.0, 53.4, 61.2, 69.5, 127.4, 128.3, 129.1, 129.4, 140.2, 172.0, 175.6. $[\alpha]_D$ 98.6 (c 1, $CHCl_3$). Anal. calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.66; H, 7.83, N, 4.41.

*4.18. Ethyl (2*RS,*3′*S,*4′*S,*1′′*R,*1′′′*S)-2-[3′-(1′′′-hydroxyethyl)-1′-(1′′-phenylethyl)-2′-oxopyrrolidin-4′-yl]propanoate **13b** and its (2*RS,*3′*S,*4′*S,*1′′*R,*1′′′*R) isomer **14b***

By reduction of **8b**, compounds **13b** and **14b** were obtained in 82% overall yield and d.r. 95:5. The stereocentre at C-2 was present as unassigned configurational mixture *RS* 70:30. GC–MS: *m/z* 333 (M^+), 318, 288, 274, 214, 188, 172, 132, 120, 110, 105, 91. Isomer (2*RS*,3′*S*,4′*S*,1′′*R*,1′′′*S*)-**13b**: IR: 3418, 1722, 1670 cm^{-1}. ^1H NMR: 1.14 (d, 3H, 70%, J=7.1), 1.15 (d, 3H, 30%, J=7.1), 1.21 (d, 3H, J=6.3),

1.25 (t, 3H, J=7.1), 1.51 (d, 3H, 70%, J=7.1), 1.52 (d, 3H, 30%, J=7.1), 2.15–2.45 (m, 2H, H+H_Y), 2.51–2.73 (m, 1H, H_X), 2.98 (dd, 1H, 70%, H_B, J_{BX}=8.9, J_{AB}=10.1), 2.99 (dd, 1H, 70%, H_B, J_{BX}=8.9, J_{AB}=10.2), 3.11 (dd, 1H, 30%, H_A, J_{AX}=5.5, J_{AB}=10.2), 3.18 (dd, 1H, 70%, H_A, J_{AX}=5.5, J_{AB}=10.2), 3.87 (dq, 1H, J=6.3, J=7.0), 4.09 (q, 2H, 30%, J=7.1), 4.13 (q, 2H, 70%, J=7.1), 4.27 (br s, 1H, OH), 5.48 (q, 1H, J=7.1), 7.21–7.41 (m, 5 ArH). ^{13}C NMR: 12.7 (30%), 14.6 (30%), 14.7 (70%), 15.4 (70%), 16.3, 16.4, 21.1, 35.5 (30%), 36.7 (70%), 42.2 (70%), 42.5 (70%), 43.3 (30%), 44.3 (70%), 49.4, 52.2, 61.2, 69.4, 127.4, 128.1, 129.1, 140.0, 174.8, 175.1 (70%), 175.2 (30%). Isomer (2*RS*,3′*S*,4′*S*,1′′*R*,1′′′*R*)-**14b**: IR: 3418, 1722, 1670 cm^{-1}. ^{1}H NMR: 0.91 (d, 3H, 30%, J=7.0), 1.02 (d, 3H, 70%, J=7.0), 1.09 (t, 3H, 70%, J=7.1), 1.18 (t, 3H, 30%, J=7.1), 1.25 (d, 3H, J=6.3), 1.49 (d, 3H, 70%, J=7.2), 1.50 (d, 3H, 30%, J=7.2), 2.21–2.54 (m, 3H, H+H_X+H_Y), 2.71 (dd, 1H, H_A, J_{AX}=4.7, J_{AB}=10.1), 3.39 (dd, 1H, H_B, J_{BX}=8.6, J_{AB}=10.1), 3.87–4.06 (m, 3H), 4.10 (br s, 1H, OH), 5.44 (q, 1H, J=7.2), 7.18–7.39 (m, 5 ArH). ^{13}C NMR: 13.1 (30%), 14.5, 14.8 (70%), 16.4, 21.0, 35.4 (30%), 36.5 (70%), 42.2 (30%), 42.7 (70%), 42.9 (30%), 45.1 (70%), 49.7, 52.2 (70%), 52.4 (30%), 61.0, 69.2, 127.5, 128.1, 129.0, 139.9, 174.9, 175.0. Anal. calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.39; H, 8.14; N, 4.16.

*4.19. (3*S*,4*S*,1′*R*,1′′*S*)-3-(1′′-Hydroxyethyl)-1-(1′-phenylethyl)-4-(propen-2-yl)pyrrolidin-2-one **13c** and its (3*S*,4*S*,1′*R*,1′′*R*) isomer **14c***

By reduction of **8c**, diastereomers **13c** and **14c** were obtained in 85% overall yield and d.r. 96:4. GC–MS: *m/z* 273 (M^+), 258, 240, 189, 174, 162, 124, 105, 91, 77. Isomer (3*S*,4*S*,1′*R*,1′′*S*)-**13c**: IR: 3425, 1670, 900 cm^{-1}. ^{1}H NMR: 1.17 (d, 3H, J=6.2), 1.52 (d, 3H, J=7.2), 1.72 (s, 3H), 2.40–2.65 (m, 2H, H_X+H_Y), 2.95–3.11 (m, 2H, H_A+H_B), 3.83 (dq, 1H, J=6.2, J=7.1), 4.84 (m, 2H), 5.16 (br s, 1H, OH), 5.48 (q, 1H, J=7.2), 7.21–7.41 (m, 5 ArH). ^{13}C NMR: 16.6, 19.7, 21.0, 43.6, 46.2, 49.4, 51.0, 70.3, 114.3, 127.3, 128.1, 129.1, 140.2, 143.7, 176.0. $[\alpha]_D$ 89.7 (c 0.5, $CHCl_3$). Anal. calcd for $C_{17}H_{22}NO_2$: C, 74.97; H, 8.14; N, 5.14. Found: C, 74.93; H, 8.11; N, 5.10. Isomer (3*S*,4*S*,1′*R*,1′′*R*)-**14c**: IR: 3425, 1670, 915 cm^{-1}. ^{1}H NMR: 1.15 (d, 3H, J=6.2), 1.50 (d, 3H, J=7.2), 1.72 (s, 3H), 2.40–2.65 (m, 2H, H_X+H_Y), 2.95–3.11 (m, 2H, H_A+H_B), 4,21 (dq, 1H, J=6.2, J=3.6), 4.84 (m, 2H), 5.20 (br s, 1H, OH), 5.48 (q, 1H, J=7.2), 7.21–7.41 (m, 5 ArH). ^{13}C NMR: 16.7, 19.7, 21.2, 43.6, 46.4, 49.6, 51.2, 70.3, 114.5, 127.4, 128.3, 129.2, 140.4, 143.3, 176.7. $[\alpha]_D$ 92.1 (c 0.5, $CHCl_3$). Anal. calcd for $C_{17}H_{22}NO_2$: C, 74.97; H, 8.14; N, 5.14. Found: C, 74.91; H, 8.09; N, 5.08.

*4.20. (3*S*,4*R*,1′*R*,1′′*S*)-4-Ethenyl-3-(1′′-hydroxyethyl)-1-(1′-phenylethyl)pyrrolidin-2-one **13d** and its (3*S*,4*R*,1′*R*,1′′*R*) isomer **14d***

By reduction of **8d**, diastereomers **13d** and **14d** were obtained in 86% overall yield and d.r. 93:7. GC–MS: *m/z* 259 (M^+), 244, 226, 214, 200, 172, 132, 105, 91, 77. Isomer (3*S*,4*R*,1′*R*,1′′*S*)-**13d**: IR: 3352, 1665, 905 cm^{-1}. ^{1}H NMR: 1.20 (d, 3H, J=6.2), 1.53 (d, 3H, J=7.1), 2.28 (dd, 1H, J=8.8, J=8.7), 2.44–2.64 (m, 1H), 3.03 (dd, 1H, H_A, J_{AX}=9.9, J_{AB}=12.3), 3.07 (dd, 1H. H_B, J_{BX}=9.7, J_{AB}=12.3), 3.87 (dq, 1H, J=6.2, J=8.7), 4.55 (br s, 1H, OH), 5.04–5.16 (m, 2H), 5.46 (q, 1H, J=7.1), 5.75 (ddd, 1H, J=8.3, J=9.9, J=17.3), 7.22–7.43 (m, 5 ArH). ^{13}C NMR: 16.6, 21.7, 40.9, 46.9, 49.5, 53.6, 70.2, 118.0, 127.4, 128.2, 129.2, 138.8, 140.2, 176.1. $[\alpha]_D$ 153.1 (c 1, $CHCl_3$). Anal. calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.04, H, 8.12; N, 5.34. Isomer (3*S*,4*R*,1′*R*,1′′*R*)-**14d**: IR: 3350, 1668, 901 cm^{-1}. ^{1}H NMR: 1.24 (d, 3H, J=6.7), 1.53 (d, 3H, J=7.1), 2.59 (dd, 1H, J=3.5, J=9.5), 2.71–2.94 (m, 1H), 2.97–3.06 (m, 2H, H_A+H_B), 3.10 (br s, 1H, OH), 4.25 (dq, 1H, J=6.7, J=3.5), 5.15–5.03 (m, 2H), 5.49 (q, 1H, J=7.1), 5.77 (ddd, 1H, J=8.0, J=10.0, J=17.1), 7.21–7.42 (m, 5 ArH). ^{13}C NMR: 16.7, 20.1,

38.6, 46.8, 49.4, 54.0, 66.8,117.4, 127.3, 127.4, 127.6, 128.0, 129.1,138.9, 140.4, 174.7. $[\alpha]_D$ 130.3 (c 1, $CHCl_3$). Anal. calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.06; H, 8.20; N, 5.36.

*4.21. Ethyl (3S,4S,1′S,1′′S)-[3-(1′′-hydroxyethyl)-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]acetate **19a** and its (3S,4S,1′S,1′′R) isomer **20a***

By reduction of **11a**, diastereomers **19a** and **20a** were obtained in 90% overall yield and d.r. 95:5. GC–MS: *m/z* 319 (M^+), 304, 286, 274, 260, 188, 170,132, 105, 91, 77. Isomer (3*S*,4*S*,1′*S*,1′′*S*)-**19a**: IR: 3425, 1728, 1668 cm^{-1}. ^1H NMR: 1.20 (t, 3H, J=7.1), 1.25 (d, 3H, J=6.3), 1.53 (d, 3H, J=7.1), 2.01–2.31 (m, 2H), 2.34–2.48 (m, 1H, H_X), 2.51–2.68 (m, 2H, H_A+H_Y), 3.59 (dd, 1H, H_B, J_{BX}=8.0, J_{AB}=9.9), 3.94 (dq, 1H, J=6.3, J=8.1), 4.07 (q, 2H, J=7.1), 4.71 (br s, 1H, OH), 5.47 (q, 1H, J=7.1), 7.19–7.38 (m, 5 ArH). ^{13}C NMR: 14.6, 16.7, 21.2, 31.1, 39.2, 47.4, 49.7, 53.7, 61.2, 69.5, 127.6, 128.2, 129.1, 139.9, 172.1, 175.3. $[\alpha]_D$ −137.6 (c 1, $CHCl_3$). Isomer (3*S*,4*S*,1′*S*,1′′*R*)-**20a**: IR: 3433, 1725, 1665 cm^{-1}. ^1H NMR: 1.20 (t, 3H, J=7.1), 1.27 (d, 3H, J=6.5), 1.53 (d, 3H, J=7.1), 2.06 (br s, 1 H, OH), 2.25 (dd, 1H, J=8.8, J=16.3), 2.35–2.71 (m, 4H, H+H_A+H_X+H_Y), 3.57 (m, 1H, H_B), 4.07 (q, 2H, J=7.1), 4.19 (dq, 1H, J=4.0, J=6.5), 5.49 (q, 1H, J=7.1), 7.20–7.41 (m, 5 ArH). ^{13}C NMR: 14.6, 16.6, 20.4, 30.0, 39.3, 47.5, 49.7, 54.5, 61.2, 67.4, 127.6, 128.1, 128.8, 129.1, 140.0, 172.1, 174.6. $[\alpha]_D$ −148.3 (c 1, $CHCl_3$). Anal. calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.64; H, 7.81; N, 4.44.

*4.22. (3S,4R,1′S,1′′S)-4-Ethenyl-3-(1′′-hydroxyethyl)-1-(1′-phenylethyl)pyrrolidin-2-one **19b** and its (3S,4R,1′S,1′′R) isomer **20b***

By reduction of **11b**, diastereomers **19b** and **20b** were obtained in 90% overall yield and d.r. 95:5. GC–MS: *m/z* 259 (M^+), 244, 226, 214, 200, 172, 132, 105, 91, 77. Isomer (3*S*,4*R*,1′*S*,1′′*S*)-**19b**: IR: 3435, 1670, 903 cm^{-1}. ^1H NMR: 1.21 (d, 3H, J=6.5), 1.42 (br s, 1H, OH), 1.55 (d, 3H, J=7.0), 2.20 (dd, 1H, H_Y, J=8.1 J=9.2), 2.56–2.75 (m, 2H, H_X+H_A), 3.28–3.44 (m, 1H, H_B), 3.90 (dq, 1H, J=6.5, J=8.0), 5.02–5.18 (m, 2H), 5.48 (q, 1H, J=7.0), 5.66 (ddd, 1H, J=17.1, J=10.1, J=8.0), 7.21–7.42 (m, 5 ArH). ^{13}C NMR: 16.8. 21.6, 40.7, 46.8, 49.7, 53.7, 69.9, 117.7, 127.6, 128.2, 129.1, 138.8, 139.8, 175.9. $[\alpha]_D$ −103.6 (c 1, $CHCl_3$). Anal. calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.03; H. 8.11; N, 5.35. Isomer (3*S*,4*R*,1′*S*,1′′*R*)-**20b**: IR: 3430, 1675, 905 cm^{-1}. ^1H NMR: 1. 25 (d, 3H, J=6.5), 1.54 (d, 3H, J=7.0), 2.48 (dd, 1H, H_Y, J=9.1, J=3.4), 2.64 (dd, 1H, H_A, J_{AX}=8.0, J_{AB}=9.5), 2.81–3.01 (m, 1H, H_X), 3.14 (br s, 1H, OH), 3.37 (dd, 1H, H_B, J_{BX}=8.4, J_{AB}=9.5), 4.28 (dq, 1H, J=6.5, J=9.1), 4.98–5.16 (m, 2H), 5.50 (q, 1H, J=7.0), 5.67 (ddd, 1H, J=17.1, J=10.1, J=8.2), 7.21–7.42 (m, 5 ArH). ^{13}C NMR: 16.8, 20.6, 37.8, 46.9, 49.7, 54.7, 66.6, 116.8, 127.6, 128.1, 129.1, 139.5, 140.1, 174.7. $[\alpha]_D$ −114.3 (c 0.3, $CHCl_3$). Anal. calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.05; H. 8.13; N, 5.33.

4.23. Synthesis of p-*iodobenzoates **15**, **16**, **21a** and **22a***

4.23.1. General procedure

To a solution containing compounds **13a**, **14a**, **19a** or **20a** (5 mmol), triethylamine (0.7 ml) and DMAP (100 mg) in ethyl acetate (50 ml) at rt, was added a solution di *p*-iodobenzoyl chloride (1.4 g; 5 mmol) in ethyl acetate (20 ml). After 12 h the mixture was poured into H_2O (50 ml) and extracted with ethyl acetate (3×100 ml). After drying (Na_2SO_4) and removal of the solvent at reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate, 50:50) to give esters **15**, **16**, **21a** or **22a** as white solids.

4.24. *Ethyl (3S,4R,1′R,1′′S)-[3-(1′′-p-iodobenzoyloxyethyl)-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]-acetate* ***15***

The title compound was obtained in 78% yield starting from **13a**. M.p. 78–80°C. IR: 1718, 1663, 1654 cm^{-1}. ^1H NMR: 1.24 (t, 3H, J=7.2), 1.50 (d, 3H, J=6.5), 1.52 (d, 3H, J=7.2), 2.36–2.68 (m, 4H), 2.99 (dd, 1H, H_B, J_{BX}=5.4, J_{AB}=9.9), 3.24 (dd, 1H, H_A, J_{AX}=7.6, J_{AB}=9.9), 4.00 (q, 2H, J=7.2), 5.52 (dq, 1H, J=2.8, J=6.5), 5.54 (q, 1H, J=7.2), 7.32 (m, 5 ArH), 7.57 (d, 2ArH, J=8.5), 7.73 (d, 2 ArH, J=8.5). ^{13}C NMR: 14.6, 16.6, 17.4, 31.1, 39.0, 46.8, 49.4, 52.1, 61.3, 71.9, 101.3, 127.5, 128.1, 129.1, 130.1, 131.5, 138.2, 140.4, 165.8, 171.7, 171.9. $[\alpha]_D$ 126.3 (c 1, $CHCl_3$). GC–MS: *m/z* 549 (M^+), 504, 318, 286, 274, 231, 132, 105, 77. Anal. calcd for $C_{25}H_{28}NO_5I$: C, 54.65; H, 5.14; N, 2.55. Found: C, 54.61; H, 5.12; N, 2.53.

4.25. *X-Ray crystal structure analysis for* ***15***

Crystal data: $C_{25}H_{28}INO_5$, MW=549.91. Monoclinic. Space group $P2_12_12_1$(#19), *a*=7.973(1) Å, *b*=13.504(2) Å, *c*=23.192(2) Å, β=98.53(1)°, *V*=744.5(3) $Å^3$, *Z*=4, *D*(calc)=1.46 g/cm^3. Reflections (3439) were collected on a CAD4 Enraf–Nonius single crystal diffractometer at room temperature by ω scan technique using graphite-monochromated MoKα radiation (λ=0.71073 Å). The structure was solved using direct methods and refined through a full-matrix least-squares method with unit weights for 2382 observed reflections with $I \geq 3\sigma(I)$. Non-hydrogen atoms were treated anisotropically.[20] The hydrogen atoms were calculated from the carbon positions and added as fixed contributions with isotropic thermal parameters of 1.3 times the value of B_{eq} of the atoms to which they are attached. *R*=0.047 and *Rw*=0.040.[21] The ORTEP drawing is shown in Fig. 2 together with the atom numbering system.[29]

4.26. *Ethyl (3S,4R,1′R,1′′R)-[3-(1′′-p-iodobenzoyloxyethyl)-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]-acetate* ***16***

The title compound was obtained in 69% yield starting from **14a**. M.p. 88–90°C. IR: 1718, 1661, 1657 cm^{-1}. ^1H NMR: 1.24 (t, 3H, J=7.2), 1.45 (d, 3H, J=6.5), 1.48 (d, 3H, J=7.2), 2.46 (dd, 1H, H_Y, J=3.5, J=5.6), 2.47 (dd, 1H, J=8.3, J=16.1), 2.71–2.88 (m, 1H, H_X), 3.02 (dd, 1H, H_A, J_{AX}=4.6, J_{AB}=10.1), 3.30 (dd, 1H, H_B, J_{BX}=8.2, J_{AB}=10.1), 5.46 (q, 1H, J=7.2), 5.61 (dq, 1H, J=6.5, J=3.5), 6.98–7.24 (m, 5 ArH), 7.49 (d, 2H, J=8.5), 7.68 (d, 2H, J=8.5). ^{13}C NMR: 14.7, 16.4, 18.6, 29.5, 40.4, 47.4, 49.4, 53.5, 61.3, 71.5, 101.1, 127.4, 128.0, 128.9, 130.1, 131.4, 138.2, 139.9, 165.3, 172.0, 172.1. $[\alpha]_D$ 133.2 (c 1, $CHCl_3$). GC–MS: *m/z* 549 (M^+), 504, 318, 286, 274, 231, 132, 105, 77. Anal. calcd for $C_{25}H_{28}NO_5I$: C, 54.65; H, 5.14; N, 2.55. Found: C, 54.59; H, 5.10; N, 2.56.

4.27. *Ethyl (3S,4R,1′S,1′′S)-[3-(1′′-p-iodobenzoyloxyethyl)-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]-acetate* ***21a***

The title compound was obtained in 66% yield starting from **19a**. M.p. 78–80°C. IR: 1715, 1660, 1655 cm^{-1}. ^1H NMR: 1.18 (t, 3H, J=7.1), 1.53 (d, 3H, J=6.6), 1.54 (d, 3H, J=7.1), 2.28 (dd, 1H, J=8.5, J=16.1), 2.44–2.73 (m, 4H, H+H_A+H_X+H_Y), 3.52 (dd, 1H, H_B, J=7.2, J=9.3), 4.06 (q, 2H, J=6.6), 5.53 (dq, 1H, J=6.6, J=2.8), 5.55 (q, 1H, J=7.1), 7.22–7.41 (m, 5 ArH), 7.71 (d, 2H, J=8.5), 7.80 (d, 2H, J=8.5). ^{13}C NMR: 14.6, 16.7, 17.4, 31.2, 39.0, 46.9, 52.4, 61.2, 72.0, 101.4, 127.6, 128.2, 129.1, 131.5, 138.2, 140.5, 165.7, 171.6, 171.8. $[\alpha]_D$ −32.6 (c 1, $CHCl_3$). GC–MS: *m/z* 549 (M^+), 504, 318, 286, 274, 231, 132, 105, 77. Anal. calcd for $C_{25}H_{28}NO_5I$: C, 61.86; H, 5.81; N, 2.89. Found: C, 61.81; H, 5.77; N, 2.85.

4.28. *Ethyl (3S,4R,1′S,1′′R)-[3-(1′′-p-iodobenzoyloxyethyl)-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]-acetate* ***22a***

The title compound was obtained in 64% yield starting from **20a**. M.p. 87–89°C. IR: 1712, 1664, 1658 cm^{-1}. ^1H NMR: 1.18 (t, 3H, J=7.1), 1.48 (d, 3H, J=6.5), 1.51 (d, 3H, J=7.1), 2.24 (dd, 1H, J=8.5, J=16.3), 2.42–2.71 (m, 4H, $H+H_A+H_X+H_Y$), 3.57 (dd, 1H, H_B, J=7.2, J=9.2), 4.06 (q, 2H, J=6.6), 5.24 (q, 1H, J=7.1), 5.63 (dq, 1H, J=6.5, J=3.3), 7.21–7.42 (m, 5 ArH), 7.73 (d, 2H, J=8.6), 7.81 (d, 2H, J=8.6). ^{13}C NMR: 14.6, 16.5, 17.6, 30.5, 40.2, 47.3, 52.6, 62.3, 72.4, 101.6, 128.2, 128.4, 129.4, 130.9, 138.4, 141.2, 166.3, 171.4, 172.1. $[\alpha]_D$ −117.8 (c 1, $CHCl_3$). GC–MS: *m/z* 549 (M^+), 504, 318, 286, 274, 231, 132, 105, 77. Anal. calcd for $C_{25}H_{28}NO_5I$: C, 61.86; H, 5.81; N, 2.89. Found: C, 61.90; H, 5.75; N, 2.93.

4.29. *Preparation of* t-*butyldimethylsilyl ethers* ***17*** *and* ***18***

4.29.1. *General procedure*

To a solution containing either compound **13a** or **14a** (1.3 g; 5 mmol), triethylamine (0.5 g; 5 mmol) and imidazole (0.35 g; 5 mmol) in dichloromethane (20 ml) at 0°C, was added a solution of *t*-butyldimethylsilyl chloride (0.75 g; 5 mmol) in dichloromethane (10 ml). After 12 h the mixture was poured into H_2O (20 ml) and extracted with ethyl acetate (2×100 ml). The organic layer was dried (Na_2SO_4) and after removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate, 70:30) to give ethers **17** and **18**, respectively, as colourless oils.

4.30. *(3S,4R,1′R,1′′S)-3-(1′′-t-Butyldimethylsilyloxyethyl)-4-ethenyl-1-(1′-phenylethyl)pyrrolidin-2-one* ***17***

The title compound was obtained in 78% yield starting from **13a**. IR ($CHCl_3$): 1668, 904 cm^{-1}. ^1H NMR: 0.04 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.22 (d, 3H, J=6.4), 1.51 (d, 3H, J=7.0), 2.47 (dd, 1H, J=3.5, J=7.4), 2.81–3.01 (m, 1H), 3.02–3.06 (m, 2H), 4.27 (dq, 1H, J=3.5, J=6.4), 4.95–5.10 (m, 2H), 5.49 (q, 1H, J=7.0), 5.81 (ddd, 1H, J=6.7, J=9.5, J=17.1), 7.22–7.37 (m, 5 ArH). ^{13}C NMR: 16.4, 18.5, 20.5, 26.3, 37.7, 46.4, 49.1, 55.6, 68.2, 115.7, 127.5, 127.7, 127.9, 128.9, 140.1, 140.6, 173.3. $[\alpha]_D$ 88.4 (c 1, $CHCl_3$). GC–MS: *m/z* 374 (MH^+). 358, 316, 259, 212, 168, 105, 91,77. Anal. calcd for $C_{22}H_{35}NO_2Si$: C, 70.73; H, 9.44; N, 3.75. Found: C, 70.68; H, 9.41; N, 3.80.

4.31. *(3R,4S,1′S,1′′S)-3-(1′′-t-Butyldimethylsilyloxyethyl)-4-ethenyl-1-(1′-phenylethyl)pyrrolidin-2-one* ***13***

The title compound was obtained in 79% yield starting from **14a**. IR: 1668, 904 cm^{-1}. ^1H NMR: 0.00 (s, 3H), 0.06 (s, 3H), 0.82 (s, 3H), 1.17 (d, 3H, J=6.6), 1.50 (d, 3H, J=7.1), 2.27 (dd, 1H, J=1.8, J=8.3), 2.97 (dd, 1H, J=8.8, J=8.7), 3.07 (dd, 1H, J=9,3, J=8.7), 3.09–3.28 (m, 1H), 4.54 (dq, 1H, J=1.8, J=6.6), 4.99–5.15 (m, 2H), 5.44 (q, 1H, J=7.1), 5.82 (ddd, 1H, J=8.1, J=10.1, J=17.2), 7.22–7.38 (m, 5 ArH). ^{13}C NMR: −4.3, −4.0, 16.8, 23.1, 26.3, 35.9, 47.0, 49.8, 55.8, 67.0, 116.3, 127.7, 127.8, 128.9, 140.5, 141.0, 173.9. $[\alpha]_D$ 58.6 (c 1, $CHCl_3$). GC–MS: *m/z* 374 (MH^+), 358, 316, 259, 212, 168, 105, 91,77. Anal. calcd for $C_{22}H_{35}NO_2Si$: C, 70.73; H, 9.44; N, 3.75. Found: C, 70.76; H, 9.39; N, 3.71.

4.32. Preparation of p-toluenesulphonates **21b** and **22b**

4.32.1. General procedure

To a solution containing either compound **19a** or **20a** (1.6 g; 5 mmol) in pyridine (10 ml) at 0°C, was added a solution of *p*-toluenesulphonyl chloride (0.96 g; 5 mmol) in pyridine (5 ml). After 12 h the mixture was poured into H_2O (10 ml) and extracted with ethyl acetate (2×100 ml). The organic layer was subsequently washed with 2 M HCl and then dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate, 50:50) to give *p*-toluenesulphonates **21b** and **22b**, respectively, as colourless oils.

4.33. Ethyl (3S,4R,1′S,1′′S)-[2-oxo-1-(1′-phenylethyl)-3-(1′′-p-toluenesulphonyloxyethyl)pyrrolidin-4-yl]acetate **21b**

Starting from **19a**, the title product was obtained in 81% yield. IR: 1725, 1671 cm^{-1}. ^1H NMR: 1.21 (t, 3H, J=7.2), 1.26 (d, 3H, J=6.5), 1.47 (d, 3H, J=7.1), 2.22 (dd, 1H, J=8.7, J=16.5), 2.44 (s, 3H), 2.46–2.81 (m, 4H, H+H_A+H_X+H_Y), 3.55 (dd, 1H, H_B, J_{BX}=7.9, J_{AB}=9.8), 4.08 (q, 2H, J=7.2), 5.05 (dq, 1H, J=3.5, J=6.5), 5.44 (q, 1H, J=7.1), 7.18–7.38 (m, 5 ArH), 7.31 (d, 2H, J=8.5), 7.81 (d, 2H, J=8.5). ^{13}C NMR: 14.6, 16.6, 17.1, 22.2, 38.9, 46.9, 49.6, 52.8, 61.2, 79.8, 96.6, 127.6, 128.1, 128.3, 129.1, 130.4, 134.2, 139.9, 145.3, 171.1,172.0. $[\alpha]_D$ −62.3 (c 1, $CHCl_3$). GC–MS: *m/z* 302 (M^+–TsO^-), 234, 226, 198, 170, 133, 105, 91. Anal. calcd for $C_{25}H_{31}NO_6S$: C, 63.40; H, 6.60; N, 2.96. Found: C, 63.34; H, 6.55; N, 2.92.

4.34. Ethyl (3S,4R,1′S,1′′R)-[2-oxo-1-(1′-phenylethyl)-3-(1′′-p-toluenesulphonyloxyethyl)pyrrolidin-4-yl]acetate **22b**

Starting from **20a**, the title product was obtained in 80% yield. IR: 1728, 1670 cm^{-1}. ^1H NMR: 1.18 (t, 3H, J=7.1), 1.24 (d, 3H, J=6.4), 1.42 (d, 3H, J=7.0), 2.18–2.33 (m, 2H), 2.40–2.65 (m, 2H), 2.45 (s, 3H), 2.75 (m, 1H), 3.54 (dd, 1H, H_B, J_{BX}=7.9, J_{AB}=10.0), 4.05 (q, 2H, J=7.1), 5.08 (dq, 1H, J=4.3, J=6.4), 5.36 (q, 1H, J=7.0), 7.21–7.43 (m, 7 ArH), 7.83 (d, 2H, J=8.3). ^{13}C NMR: 14.6, 16.6, 17.1, 22.2, 38.9, 46.9, 49.6, 52.8, 61.2, 79.8, 96.6, 127.6, 128.1, 128.3, 129.1, 130.4, 134.2, 139.9, 145.3, 171.1, 172.0.]α]$_D$ −69.2 (c 1, $CHCl_3$). GC–MS: *m/z* 302 (M^+–TsO^-), 234, 226, 198, 170, 133, 105, 91. Anal. calcd for $C_{25}H_{31}NO_6S$: C, 63.40; H, 6.60; N, 2.96. Found: C, 63.33; H, 6.54; N, 2.91.

4.35. Ethyl (3S,4R,1′R,1′′S)-[3-(1′′-methanesulphonyloxyethyl)-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl] acetate **23**

To a solution containing pyrrolidin-2-one **13a** (1.6 g; 5 mmol), triethylamine (1 ml) and DMAP (100 mg) dry ethyl acetate (30 ml) at 0°C, was added a solution of methanesulphonyl chloride (0.6 g; 5 mmol) in ethyl acetate (5 ml). After 3 h the mixture was poured into H_2O (30 ml) and extracted with ethyl acetate (3×100 ml). After drying (Na_2SO_4) and removal of the solvent in vacuo, the residue was chromatographed on silica gel (cyclohexane:ethyl acetate, 50:50) to give **23** in 85% yield, as a colourless oil. IR: 1722, 1667 cm^{-1}. ^1H NMR: 1.99 (t, 3H, J=7.1), 1.39 (d, 3H, J=6.5), 1.47 (d, 3H, J=7.2), 2.25–2.51 (m, H), 2.54–2.75 (m, 2H), 2.91 (s, 3H), 2.89–3.04 (dd, 1H), 3.21 (dd, 1H, H_B, J_{BX}=7.3, J_{AB}=10.3), 4.08 (q, 2H, J=7.1), 5.19 (dq, 1H, J=6.5, J=3.0), 5.43 (q, 1H, J=7.2), 7.18–7.38 (m, 5 ArH). ^{13}C NMR: 14.6, 16.5, 17.9, 20.4, 30.3, 39.3, 46.8, 49.4, 52.8, 61.3, 79.3, 127.3, 127.5, 128.0, 129.1, 140.1, 171.0, 171.9. $[\alpha]_D$ 76.5 (c 1, $CHCl_3$). GC–MS: *m/z* 302 (M^+–MsO^-), 234, 226, 198, 170, 133, 105, 91. Anal. calcd for $C_{19}H_{27}NO_6S$: C, 57.41; H, 6.85; N, 3.53. Found: C, 57.35; H, 6.81; N, 3.50.

*4.36. (3*R,*4*R,*1′*R*)-3-Ethyl-4-(2′′-hydroxyethyl)-1-(1′-phenylethyl)pyrrolidin-2-one* ***24***

To a solution of compound **23** (1.3 g; 3.0 mmol) in dry THF (30 ml) under argon, $LiAlH_4$ (0.2 g; 5 mmol) was added and the reaction stirred for 1 h at rt. Then methanol (1 ml) and H_2O (30 ml) were added and the mixture extracted with ethyl acetate (2×100 ml). After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (ethyl acetate:cyclohexane, 80:20) to give **24** in 79% yield as colourless oil. IR: 3350, 1675 cm^{-1}. ^1H NMR: 0.94 (t, 3H, J=7.4), 1.48 (d, 3H, J=7.2), 1.58–1.84 (m, 3H), 1.95–2.17 (m, 1H, H_X), 2.23 (br s, 1H, OH), 2.90 (dd, 1H, H_A, J_{AX}=6.9, J_{AB}=9.8), 3.07 (dd, 1H, H_B, J_{BX}=7.9, J_{AB}=9.8), 5.46 (q, 1H, J=7.2), 7.18–7.38 (m, 5 ArH). ^{13}C NMR: 11.4, 16.5, 23.2, 34.0, 37.6, 47.1, 49.2, 50.0, 61.1, 127.4, 127.8, 129.0, 140.8, 176.2. $[\alpha]_D$ 126.3 (c 1, $CHCl_3$). GC–MS: *m/z* 261 (M^+), 246, 188, 170, 105, 91, 77. Anal. calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.49: H, 8.84; N, 5.33.

*4.37. Ethyl (3*S,*4*R,*1′*R,*1′′*R*)-[3-(1′′*-p-*iodobenzoyloxyethyl)-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]-acetate* ***16***

4.37.1. Method A

To a solution containing **13a** (1.3 g; 5 mmol), triphenylphosphine (2.6 g; 10 mmol), and 4-iodobenzoic acid (2.5 g; 10 mmol) in dry THF (50 ml), diethyl azodicarboxylate (0.17 g; 10 mmol) dissolved in dry THF (15 ml) was added at 20°C. After 1 h the solvent was removed under reduced pressure, the residue dissolved in ethyl acetate (100 ml) and the organic layer washed first with a saturated $NaHCO_3$ solution (100 ml), then with water (100 ml) and eventually dried (Na_2SO_4). The solvent was then evaporated and the residue purified by silica gel chromatography (cyclohexane:ethyl acetate, 70:30) to give *p*-iodobenzoate **16** in 71% yield as a white solid.

4.37.2. Method B

To a solution containing **23** (1.3 g; 3.0 mmol) in benzene (40 ml) ion exchange resin Amberlyst A 26 in the *p*-iodobenzoate form (5 g) was added and the mixture refluxed for 5 h. After filtration and removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (cyclohexane:ethyl acetate, 70:30) to give at first ethyl (*Z*,*4R*,*1′R*)-[3-ethyliden-2-oxo-1-(1′-phenylethyl)pyrrolidin-4-yl]acetate **25** in 21% yield as a colourless oil: IR: 1724, 1664 cm^{-1}. ^1H NMR: 1.21 (t, 3H, J=7.2), 1.53 (d, 3H, J=7.2), 2.18 (dd, 3H, J=7.3, J=1.8), 2.34 (dd, 1H, J=8.9, J=16.2), 2.53 (dd, 1H, J=4.8, J=16.2), 2.95 (dd, 1H, H_A, J_{AX}=3.9, J_{AB}=8.7), 2.90–3.15 (m, 1H, $H_{X)}$, 3.17 (dd, 1H, H_B, J_{BX}=7.5, J_{AB}=8.7), 4.08 (q, 2H, J=7.2), 5.53 (q, 1H, J=7.2), 5.89 (dq, 1H, J=7.3, J=1.9), 7.17–7.35 (m, 5 ArH). ^{13}C NMR: 13.7, 14.7, 16.5, 33.8, 40.2, 46.0, 49.1, 61.1, 127.7, 127.9, 129.0, 132.7, 134.1, 140.5, 168.0, 172.1. $[\alpha]_D$ 113.6 (c 1, $CHCl_3$). GC–MS: *m/z* 301 (M^+), 286, 258, 214, 197, 152, 110, 105, 91, 77. Anal. calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.68; H, 7.71; N, 4.61. By further elution, *p*-iodobenzoate **16** was obtained in 65% yield as a white solid.

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13. Reduction of pyrrolidin-2-ones **4a**–**d** performed with $NaBH_4$. To a solution containing pyrrolidin-2-one (10 mmol) in dry methanol (50 ml) at 0°C was added $NaBH_4$ (0.4 g; 10 mmol) and the mixture stirred for 1 h. Then solid NH_4Cl (2.0 g) and H_2O (40 ml) were added and the mixture extracted with ethyl acetate (3×100 ml). After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (ethyl acetate) to give products **13a**–**d** and **14a**–**d** as colourless oils in d.r. 60:40.
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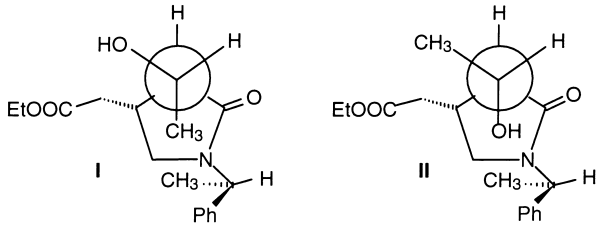
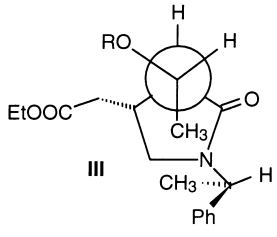
16. The search for low energy conformations was run using a BATCHMIN program included in MacroModel, Version 5.5. All calculations were carried out on a Silicon Graphics Indigo 2 R10000 workstation. For a reference, see: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Canfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem*. **1990**, *11*, 440–448.
17. Whereas conformer **I** of **13a** is practically missing (ΔE=2.44 kcal/mol with respect to **A**), conformer **II** of **14a** is significantly present (ΔE=0.64 kcal/mol with respect to **B**).



18. A number of stereoselective reductions of 3-acetyl azetidinones are reported in the literature. For examples see: (a) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem*. **1981**, *46*, 2208–2212; (b) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett*. **1982**, *23*, 2293–2296; (c) Chiba, T.; Nakai, T. *Chemistry Lett*. **1985**, 651–654; (d) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chemistry Lett*. **1985**, 1343–1346; (e) Chiba, T.; Nakai, T. *Tetrahedron Lett*. **1985**, *26*, 4647–4648; (f) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767–5790; (g) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron Lett*. **1986**, *27*, 6241–6244; (h) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron* **1988**, *44*, 2149–2165.
19. It is worth mentioning that for 3-hydroxyethyl azetidinones neither coupling constants or chemical shifts are useful tools for determining the configuration of the stereogenic centre in every case at the hydroxyethyl chain. See Ref. 18a.
20. All calculations were carried out on a VAX 2000 by using the program package *Molen, An Interactive Structure Solution Procedure*, Enraf-Nonius, Delft, The Netherlands, 1990.
21. Atom coordinates, anisotropic thermal parameters and tables of bond lengths and angles are deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.
22. Only in conformer **III** of compound **15** does H-1′′ lie on the plane of the carbonyl group, but this conformer is not significantly present (ΔE=6.23 kcal/mol with respect to **A**′).



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