PAPER　　　　　　　　www.rsc.org/obc | Organic & Biomolecular Chemistry

2,5-Disubstituted pyrrolidines: synthesis by enamine reduction and subsequent regioselective and diastereoselective alkylations†

## Syed Raziullah Hussaini and Mark G. Moloney*

Methodology for the diastereoselective synthesis of 2,5-disubstituted pyrrolidines by reduction of enamines derived from pyroglutamic acid is reported; the nature of nitrogen protection was found to be critical for the stereochemical control of the reaction outcome. Regioselective manipulation of the C-2 and C-5 substituents is possible, providing access to differently substituted pyrrolidines for a limited number of cases.

The pyrrolidine ring nucleus forms the core of many natural products, and exhibits wide-ranging biological activity.[1–6] In order to provide rapid access to these systems, we[7,8] have been interested in the development of reliable chemistry for the stereocontrolled manipulation of any or all ring positions of pyroglutamic acid.[9,10] In particular, 2,5-disubstituted pyrrolidines **1** are compounds of considerable importance,[11] and reliable diastereoselective access to these systems continues to generate interest.[12,13] Our focus has more recently turned to manipulation of the lactam carbonyl of pyroglutamate **2a** as a route to these systems, and of particular value is the Eschenmoser ring contraction,[14,15] involving condensation of thiolactam **2b** with an α-bromoester. This reaction can occur under particularly mild conditions, especially when the bromo component is substituted with two electron withdrawing groups, and is tolerant of a range of other functional groups, and as a result has been extensively applied by Rapoport[16] and others.[17–19] However, it is known that reduction of the enaminone products from the Eschenmoser contraction is highly substrate and reagent dependent, being particularly easy for β-enamino (mono)esters, and that *cis*-stereocontrol with catalytic hydrogenation and *trans*-stereocontrol with metal hydrides is possible;[20] an exhaustive review of the chemistry of enaminone systems has recently appeared,[21] and a detailed analysis of the push–pull effect which operates in these systems reported.[22] Our plan was to further examine the scope of this process, with the specific aim of defining enabling methodology for the preparation of 2,5-disubstituted pyrrolidines **1** by chain extension at either or both of the 2 and 5 positions of pyroglutamate **2a** (Scheme 1); some of this work has appeared in preliminary form.[23,24]

(i) Lawesson's reagent (82%); (ii) (EtO₂C)₂CHBr, NaHCO₃ (100%)
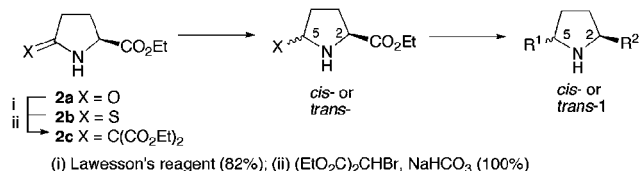
Scheme 1

The Department of Chemistry, Chemistry Research Laboratory, The University of Oxford, Mansfield Road, Oxford, UK OX1 3TA
† Electronic supplementary information (ESI) available: Copies of selected ¹H NMR spectra. See DOI: 10.1039/b604183c

Results and discussion

The key step of the sequence is activation of the lactam carbonyl of pyroglutamic acid ethyl ester **2a**[25] as the thiocarbonyl derivative **2b**, achieved using either P_2S_5 or Lawesson's reagent; we found that this was most reliably achieved with crude ester **2a** using commercially available HPLC-grade dichloromethane at room temperature for only 1.5 h using our published method.[24] Excellent yields (82%) of the corresponding product **2b** were obtained which could be readily purified by a single chromatographic step on up to a 12 g scale. Thiolactam **2b** could be readily converted to enamine **2c** in quantitative yield under standard Eschenmoser coupling conditions, thus securing the necessary starting material for further studies.

Reductions selectively leading to *trans*-pyrrolidines

Lactams **2c** and **3** (as a 1 : 2 mixture of *E/Z* geometric isomers, prepared by Eschenmoser contraction of **2b** with ethyl 2-bromo-3-oxo-3-phenylpropionate[26]) were subjected to reduction conditions which had been successfully applied to related enamine substrates substituted with a single ester function (Scheme 2).[20] However, the enamine function proved to be particularly resistant to reduction and reaction of **3** and **2c** could only be achieved with sodium borohydride to give alcohols **4a,b** (yields 71 and 80% respectively), resulting from C-2 ester reduction and not enamine reduction. An attempt to activate this system by protection of the nitrogen function of **2c** and **3** as the corresponding BOC derivatives required forcing conditions, but gave **5a** and **5b** in 73 and 23% yield respectively. However, this enamine function still proved to be unreactive, since for example reaction of **5a** with $NaBH_4$ gave only enamine **6** from C-2 ester reduction and debenzoylation (11%). Interestingly, application of conditions (nBuLi, CuI, Et_2O) to **3** and **5a** recently reported to be successful for conjugate additions to lactam-derived enamine systems[19] was not successful, illustrating the lack of reactivity of this enamine system.

Because of the complications of chemoselectivity in the differently substituted enamine substrate **3**, reductions of diester **2c** were examined in more detail (Scheme 2). Sodium cyanoborohydride in ethanol at pH 3–5[27] gave product **7a**, although this product could not be separated from an unidentified impurity. Catalytic hydrogenation (H_2, Pt/C or Pd/C, 4.5 atm) also returned unreacted

This journal is © The Royal Society of Chemistry 2006
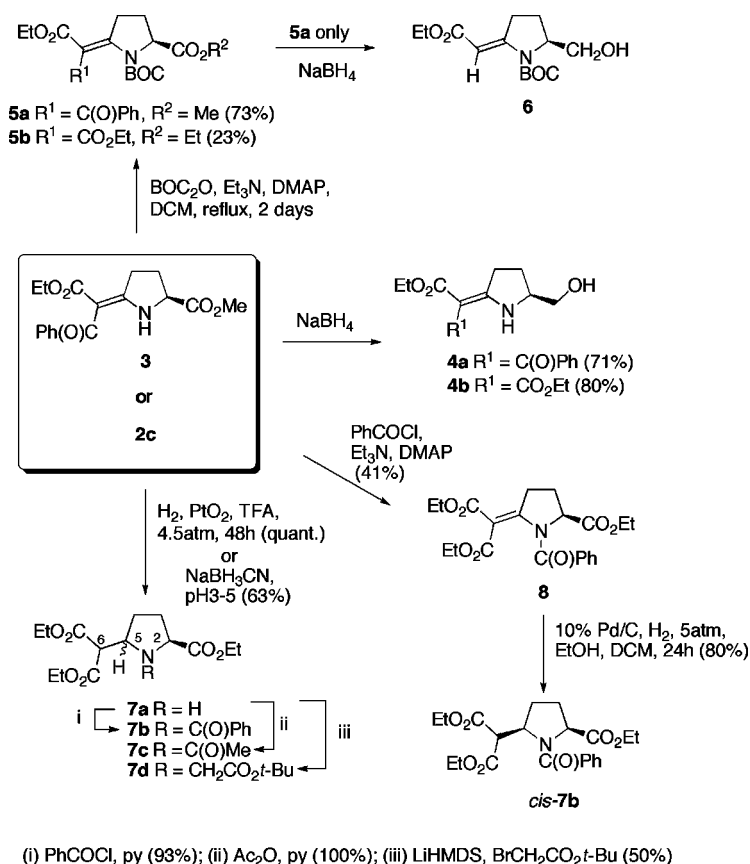
Scheme 2

starting material, indicating a substantial lowering of reactivity of β-enamino diesters relative to their β-enamino monoester counterparts, but application of more forcing conditions (H$_2$, PtO$_2$.H$_2$O,‡ TFA–HOAc (1 : 3), 4.5 atm, 48 h)[26] gave a quantitative yield of a 1 : 2 ratio of an inseparable *cis*- : *trans*-product mixture **7a** (this stereochemical assignment was established subsequently on the benzoyl derivative **7b**, *vide infra*). This approach provides a convenient solution to the problem of the difficult reduction of β-enamino esters which has been noted in the literature.[17,26–28] Benzoylation of the amine nitrogen of **7a** (PhCOCl, py, 30–40 °C) proceeded without difficulty to give a separable mixture of *cis*- and *trans*-**7b** in excellent yield but variable *cis*- : *trans*-ratio, suggesting the possibility of equilibration during the acylation reaction. Acetylation (Ac$_2$O, py) proceeded in good yield and gave a mixture of *cis*- and *trans*-**7c**.

The assignment of relative stereochemistry in these systems proved to be of particular difficulty but was of considerable importance. Since useful correlations of stereostructure and ^{1}H NMR spectroscopic data had previously been established in our pyroglutamate systems[29,30] it seemed feasible that a similar analysis might prove fruitful in this case; however, rotameric equilibria, not present for the pyroglutamates, proved to be a serious complication for these pyrrolidines, as might be expected. Although the two

different diastereomers of **7b** could be readily distinguished (in the ^{1}H NMR spectrum of compounds *cis*- and *trans*-**7b** (in CDCl$_3$), all 3 ester methylene, H-2 and H-6 signals were co-incident at about δ 4.1–4.4 for the *cis*-product, but in the *trans*-compound, one of the ester methylenes was upfield from the others by 0.3 ppm, and H-2 and H-6 (which were almost co-incident ($\Delta\delta$ 0.05 ppm)) were downfield by $\Delta\delta$ 0.2 ppm of the remaining two ester methylenes), direct assignment of relative stereochemistry was not possible. Furthermore, the ^{1}H NMR spectrum exhibited overlapped signals and extensive broadening for *cis*-**7b**, presumably as a result of rotameric equilibration, but those of *trans*-**7b** did not.§ A better spread of chemical shift values was possible in C$_6$D$_6$, but not enough to enable stereochemical assignment, and rotameric effects were still evident. However, variable temperature (VT) analysis (373 K in d$_6$-DMSO) resulted in significant sharpening of all signals, and enabled acquisition of NOE data (Fig. 1). For *cis*-**7b**, irradiation of both C(2)H and C(5)H, in addition to a weak mutual enhancement, gave clear enhancements at C(3)H and C(4)H, and the stereochemistry of *trans*-**7b** was indicated by C(2)H enhancements at C(3)H and C(3)H′ and by C(5)H enhancements at C(3)H′ and C(4)H′, with no C(2)H–C(5)H enhancements. Independent stereochemical assignment was possible by single crystal X-ray analysis of pyrrolidine *cis*-**7b**,[23] which confirmed these NOE

‡ PtO$_2$ obtained from BDH proved to give shortest reaction times and to be the most reliable.

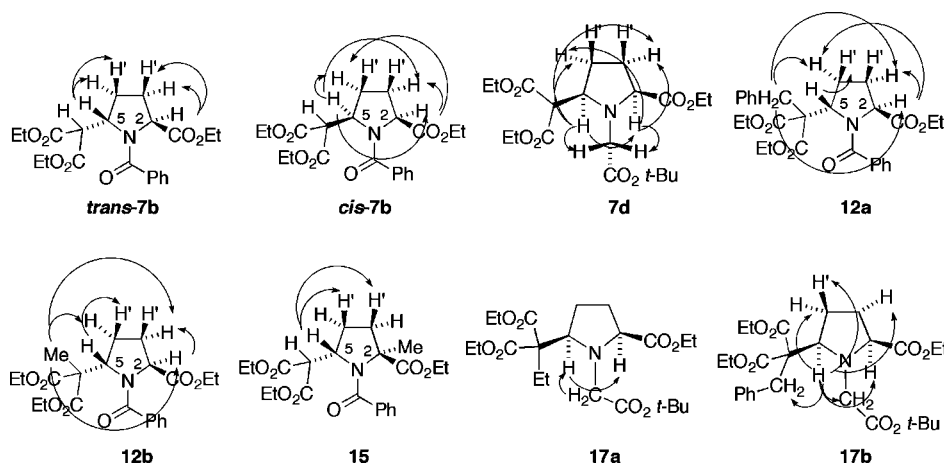§ Copies of selected ^{1}H NMR spectra are available in electronic form (see accompanying ESI data).†

This journal is © The Royal Society of Chemistry 2006

Org. Biomol. Chem., 2006, **4**, 2600–2615 | 2601

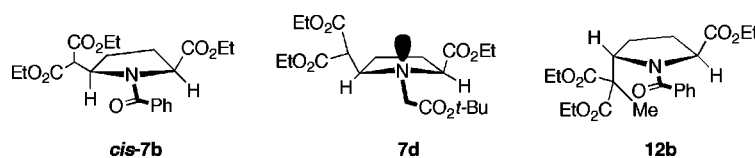**Fig. 1** NOESY data for selected compounds.

Fig. 2 Preferred conformations in 2,5-disubstituted pyrrolidines.

results; the crystal structure indicated a conformation in which the C-2 substituent was pseudoaxial, the C-5 group pseudoequatorial, the C-3 was out of plane of the remaining ring atoms, and the nitrogen was slightly pyramidalised (Fig. 2). Presumably this arrangement minimises eclipsing interactions in the ring which would arise in a di(pseudoequatorial) conformer. Unfortunately, a similar crystallographic analysis was not possible for *trans*-**7b**, since it was an oil. Further investigation of pyrrolidines **7b** indicated that the pure *cis*-isomer could be converted (NaH–DMF–0 °C → RT) to a *cis*- : *trans*-product mixture (1.7 : 1), and that treatment of the pure *trans*-**7b** with LDA at low temperature also gave recovered starting material in which the *trans*-isomer predominated (5.7 : 1). This clearly indicates that equilibration of the two isomers is possible; we presume that initial β-elimination, favoured by a highly acidic C(6)H and good *N*-benzoyl leaving group followed by ring re-closure, is responsible for this outcome under these conditions (Scheme 3, *a* and *b*). Unexpected retro-Michael additions of cyclic β-aminoesters have been observed previously.[31]

Reductions selectively leading to *cis*-pyrrolidines

We subsequently found that reversal of the order of steps leading to the intermediate benzamide **7b** permitted reduction under milder conditions and consequent isolation of the *cis*-isomer. Thus, protection of the enamine function[21] of **2c** under forcing conditions (PhC(O)Cl, Et$_3$N, DCM, DMAP, 2 days at reflux) gave *N*-benzoyl derivative **8** in 41% yield (Scheme 2), whose structure

Scheme 3

(i) NaH, MeI (19%), or NaH, EtOTf (58%) or LiHMDS, BrCH₂CO₂*t*-Bu (27%)
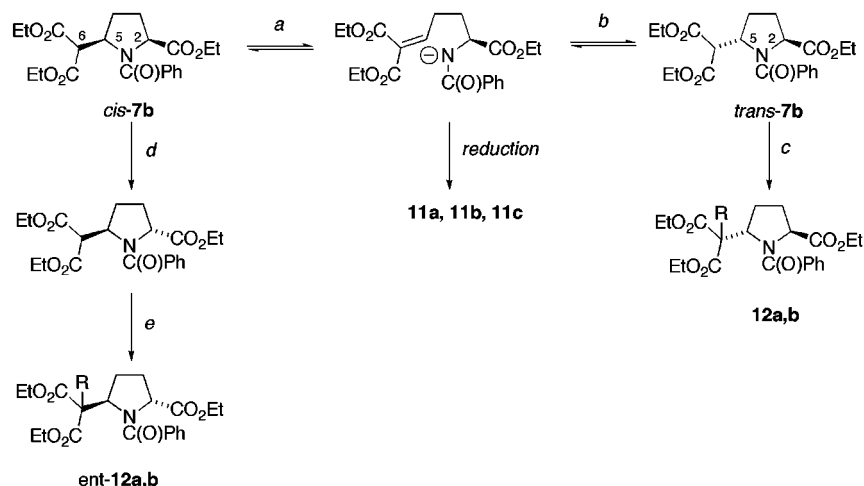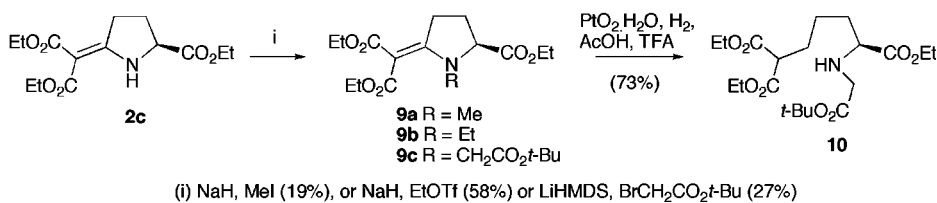
Scheme 4

was confirmed by single crystal X-ray analysis,¶ and this was susceptible to reduction under significantly milder conditions than enamine **2c** (10% Pd–C, H₂, 5 atm, 24 h, EtOH : DCM = 10 : 1) to give pyrrolidine **7b**, this time as a 9 : 1 mixture of *cis* : *trans*-isomers in 80% yield. However, since we later found (*vide supra*) that alkylation of the enolate derived from *cis*-**7b** gave only the corresponding *trans*-products, due to the same facile ring opening–ring closing equilibration illustrated in Scheme 3, this compound was of limited synthetic utility for our purpose.

Since the crucial equilibration process of Scheme 3a,b leading to *trans*-products **7b** seemed likely to depend on the good leaving ability of the *N*-benzoyl groups of **7b**, it was of interest to apply an amine protecting group which did not withdraw electron density from the nitrogen. However, protection of the amine group of compounds like **2c** and **7a** is difficult due either to the delocalised nature of the amine lone pair or the hindered nature of the amine function, respectively, and a further complication for derivatives of **7a** is their highly basic and polar characteristics which makes for difficult isolation. Although it was possible to alkylate enamine **2c** giving compounds **9a** and **9b** (Scheme 4), these compounds could not be subsequently reduced by catalytic hydrogenation; in the case of **9c**, ring cleavage resulted very efficiently, giving heptanedioate **10**. On the other hand, attempts at introducing *N*-Me or *N*-Bn groups into **7a** by standard alkylation-type approaches gave recovered starting material and/or low yield of product, and attempted reductive amination with benzaldehyde gave no identifiable material. Deprotonation of amine **7a** (*cis* : *trans* = 1 : 2) with LiHMDS at 0 °C followed by reaction with *tert*-butyl bromoacetate was successful, however, and gave the desired adduct **7d** in 50% yield (Scheme 2), as the *cis*-isomer exclusively; this isomer is likely to be favoured since an all *anti*-conformational arrangement of contiguous substituted ring positions is possible (similar conformational preference for the *anti*-substitution pattern in related acylated oxazolidines has been demonstrated).[32–35] Significantly, this tertiary amine could be readily purified by chromatography on silica, unlike related compounds which required distillation.[36] Noteworthy also was that the ¹H NMR spectrum of this compound at room temperature gave well resolved signals, unlike the *N*-benzoyl protected **7b** which required VT analysis at 373 K to give useful spectra,[23] and its stereochemical assignment was based on careful NOE
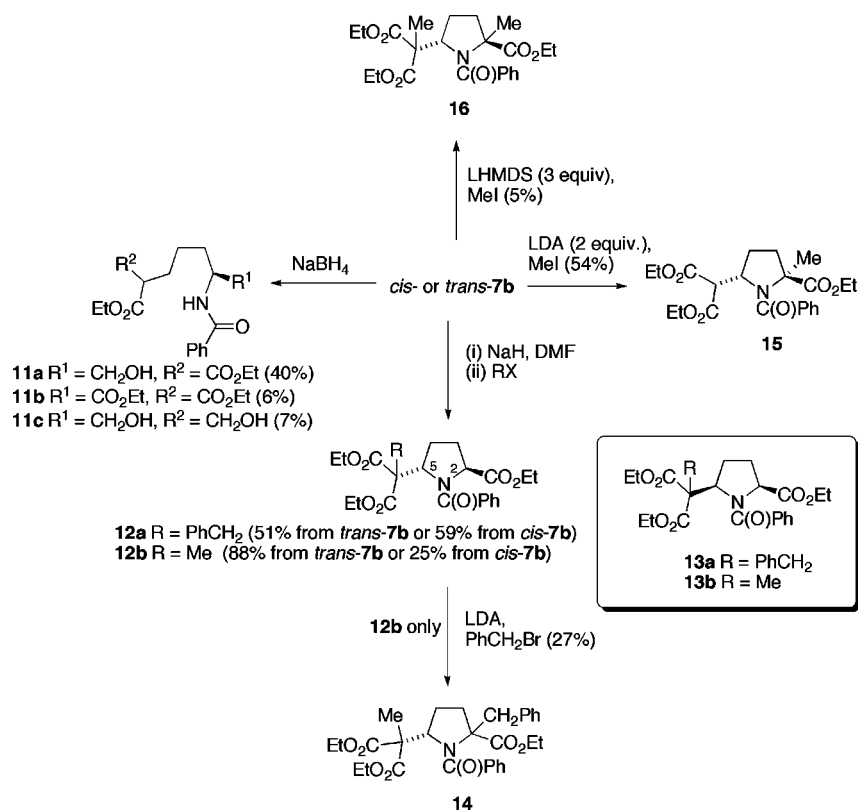
analysis at room temperature (Fig. 1); thus, irradiation of C(5)H gave significant enhancements at C(2)H, NC*H*H, C(3)H, C(4)H, while irradiation of H-2 gave significant enhancements at C(5)H, NCH*H*, C(3)H, C(4)H, consistent with the *cis*-stereochemistry. Simple molecular modelling calculations (Chem3D with MM2 parameters) suggested that the *cis*-2,5-isomer was more stable than the corresponding 2,5-*trans*-isomer by 4.8 kJ mol⁻¹, and that the preferred conformation was one in which the C-2 and C-5 substituents were pseudodiaxial and *trans*- to the bulky *tert*-butoxycarbonylmethyl substituent on a slightly pyramidalised nitrogen atom (Fig. 2).

Alkylation reactions at C-2 and C-5

We anticipated that compound **7b** would prove to be a useful synthetic template enabling direct modification of either the C-2 ethoxycarbonyl or C-5 bis(ethoxycarbonyl)methyl substituents, but observed some unexpected complications in its reactivity (Scheme 5). Attempted reduction of the C-2 ethoxycarbonyl of **7b** (which had been straightforward for enamines **2c**,**3**, giving alcohols **4a**,**b** as noted above in Scheme 1) proved to be problematic, and formation of amide **11a** (40%), along with the inseparable by-products **11b** (6%) and **11c** (7%), was observed. These results are also consistent with a facile β-elimination of starting **7b**, which in this case is followed by α,β-double bond and ester reduction (either once or twice) to give the observed products (Scheme 3).

In an effort to extend the C-6 (bisethoxycarbonyl)methyl substituent using a standard alkylation strategy, deprotonation at the more acidic malonate-type centre followed by electrophilic quench was examined. Treatment of pure *trans*-**7b** with NaH then benzyl bromide in DMF gave a 51% yield of *trans*-**12a**. The stereochemistry of **12a** was unequivocally assigned by VT/NOE analysis in d₆-DMSO at 373 K (Fig. 1). Significantly, irradiation of the benzylic system gave enhancements at C(2)H, C(3)H and C(4)H, suggesting a preferred conformation in which this group is folded under the heterocyclic ring (Fig. 2). By contrast, the *cis*-starting material **7b** gave none of the expected *cis*-product **13a**, but instead a 59% yield of *trans*-**12a** (which was of identical [α]D to the material prepared from *trans*-**7b**). In each of these reactions, starting material (about 10%) was recovered as a mixture of *cis*- and *trans*-isomers but without loss of [α]D, indicating that racemisation was not occurring in the reaction. Since the same *trans*-**12a** was obtained from either *cis* or *trans*-**7b**, optimisation was carried out on a *cis*–*trans*-mixture of **7b** and conditions were established which increased the alkylation yield up to 73%. These results are also consistent with the facile *cis*–*trans*-equilibration of **7b** as described above (Scheme 3, a and b), followed by selective alkylation of the *trans*-isomer in the equilibrium mixture (Scheme 3, c). Moreover, isolation of identical *trans*-**12a** from either *cis* or *trans*-**7b** ruled out the possible formation of ent-*trans*-**12a**
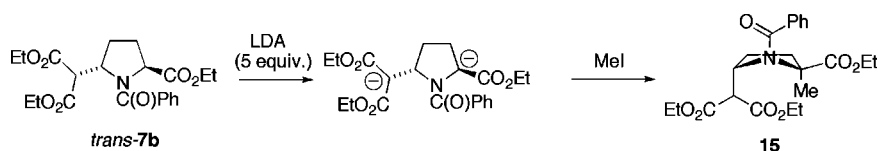
Scheme 5

by initial epimerisation at C-2 of *cis*-**7b** followed by alkylation at C-6 (Scheme 3, *d* and *e*). Alternatively, methylation of pure *trans*-**7b** with KH–methyl triflate gave a 88% yield of *trans*-**12b**. The stereochemistry of **12b** was again assigned by VT/NOE analysis in d₆-DMSO at 373 K (Fig. 2§), and confirmed by single crystal X-ray analysis;²³ this indicated a conformation in which both the C-2 and C-5 substituents were pseudoaxial, that C-3 was out of plane of the remaining ring atoms, the benzoyl carbonyl group was directed towards the C-5 substituent, and C(6)Me was located under the heterocyclic ring. The *cis*-starting material **7b** also gave none of the expected *cis*-product **13b** under these conditions, but instead a 25% yield of *trans*-**12b**. Again, in these reactions, recovered starting material **7b** which was isolated had been equilibrated to a *cis*-, *trans*-mixture. The equilibration sequence shown in Scheme 3 therefore appears to be operating in this case too.

Having compounds **12a,b** in hand gave the opportunity to confirm our earlier hypothesis concerning equilibration by eliminations in derivatives **7b**, since the acidic malonyl H-6 proton was now blocked; when **12b** was treated with base followed by benzyl bromide, alkylation at C-2 occurred to give a 2 : 3 mixture of *cis*- and *trans*-adducts **14**, but only in low yield (27%); presumably this is a result of steric hindrance at the C-2 position due to the proxim-

ity of the distal C-6 methyl group, by analogy with the structure of pyrrolidine **12b** as determined from its NOE analysis (Fig. 2). An attempt to alkylate benzyl derivative **12a** gave none of the expected product, and this is consistent with a highly hindered conformation in which the benzyl group is folded over the C-2 position.

Alternatively, regioselective C-2 modification was also possible: double deprotonation of *trans*-**7b** with excess LDA (5 equivalents) and alkylation (excess MeI) gave monomethyl adduct **15** in good overall yield (54%). In this compound, the room temperature ¹H NMR spectrum exhibited very broad signals, but at 373 K (d₆-DMSO) a highly resolved spectrum was observed; NOE analysis (Fig. 1) indicated the expected enhancements around the ring, but no C-2(Me)/C(5)H enhancements, consistent with the *trans*-relative stereochemistry. This tentative assignment is corroborated by the observation that in the ¹H NMR spectrum, the OCH₂CH₃ signals were not coincident, and that C(6)H did not lie under these signals; this arrangement has also been observed for other *trans*-isomers as described above. We believe that this outcome arises because the intermediate dienolate which is formed alkylates at the more reactive enolate position and in an *anti*-sense to the benzoyl group (which is itself *trans*- to the C-5 malonate residue) with a kinetic pseudoaxial preference (Scheme 6).

Scheme 6
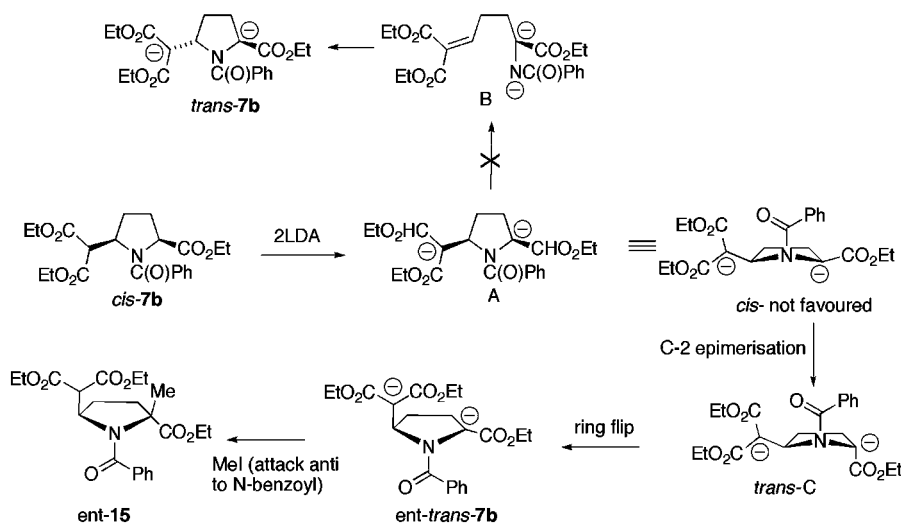
Scheme 7

When this procedure was applied to *cis*-**7b**, a low yield (25%) of *ent*-**15** was obtained, since the material from this reaction exhibited opposite optical rotation to product **15** from the reaction with *trans*-**7b**; this could be improved to a yield of 40% by using lithium tetramethylpiperidide (3 equivalents) as the base. This result is consistent with the fact that the *trans*-C(2)Me–C(5)H stereochemistry is the thermodynamically more stable arrangement in these systems. In this case, in the presence of 5 equivalents of base (LDA), *cis*-**7b** can be expected to form the corresponding *cis*-dienolate A (Scheme 7); however, now the retro-Michael addition which would otherwise equilibrate the less favourable *cis*-isomer to the more favourable *trans*- one (as shown in Scheme 3) is not favoured due to the intermediacy of the adjacent dianion B, so epimerisation to the *trans*-dienolate C can only occur by direct anion inversion at C-2. By a ring flip, this gives the enolate derived from ent-*trans*-**7b**, which of course then alkylates with the same diastereoselectivity as *trans*-**7b**, to give ent-**15**.
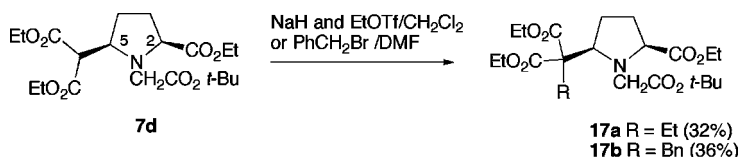
The use of LiHMDS as base also enabled direct formation of the dienolate derived from **7b**, but treatment of this with excess methyl iodide gave a poor yield of pyrrolidine **16** (5%) and as a mixture of diastereomers. This alkylation sequence was not successful using benzyl bromide, or 1,2-dibromoethane.

In the *N*-alkyl *cis*-pyrrolidine series (Scheme 8), compound **7d** proved to be amenable to further manipulation, so that reaction with NaH and ethyl triflate in CH$_2$Cl$_2$, or benzyl bromide in DMF at room temperature, gave products **17a,b** in 32% (along with 29% of recovered starting material) and 36% respectively. The regioselectivity of these alkylations was confirmed by the disappearance of C(6)H–C(5)H COSY correlations, and HMBC and HMQC correlations. Furthermore, coupling constants of >18.5 Hz in-
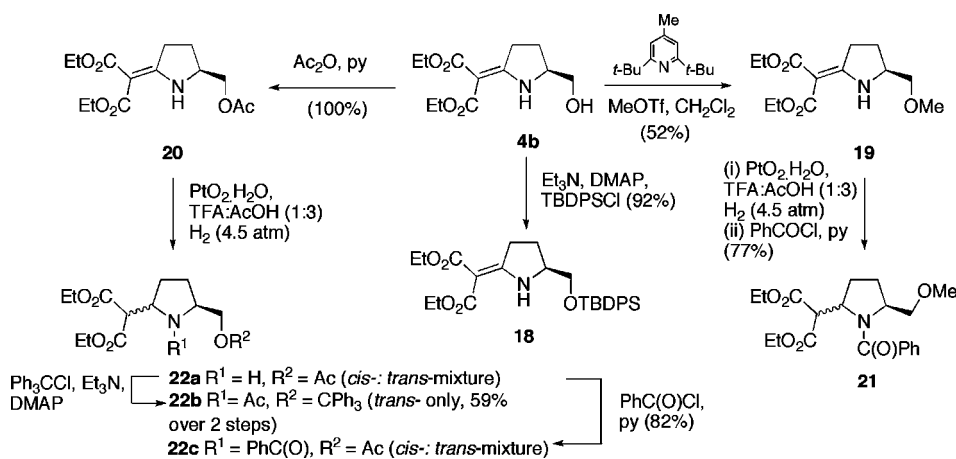
dicated the presence of geminal protons of NC*H*$_2$CO$_2$*t*-Bu thus confirming that alkylations occurred at C-6 and not α- to the *tert*-butyl ester. For the ethyl derivative **17a**, irradiation of C*H*$_2$CO$_2$*t*-Bu gave enhancement to C(5)H, while irradiation of C(2)H resulted in significant enhancement to C(5)H, suggesting *cis*-stereochemistry. For the benzyl derivative **17b**, irradiation of C(5)H gave significant enhancements at C(2)H, C(3)H, C(4)*HH′*, CH$_2$Ph, and C*H*$_2$CO$_2$*t*-Bu, suggesting the *cis*-stereochemistry. For these compounds, molecular modelling calculations (Chem3D with MM2 parameters) suggested that the *cis*-2,5-isomers are more stable than the corresponding *trans*-2,5-isomers by between 2.0–4.5 kJ mol⁻¹. The importance of heterocyclic *N*-alkylcarbonyl derivatives as conformational controlling elements in biologically relevant ligands has recently been reported.[37]

Reductions

A key difficulty in the reduction of these highly functionalised systems is therefore the ease with which equilibration can occur across the 2,5-disubstituted pyrrolidine system (Scheme 3 and Scheme 7); it was of interest to compare the reductive behaviour in systems for which the C-2 ester substituent was not present. Thus, alcohol **4b**, prepared as shown in Scheme 2, was subjected to a range of reductive conditions (including PtO$_2$, H$_2$; NaCNBH$_3$; NaBH$_4$–HOAc), but none gave the desired reduction products. Protection of the alcohol as the TBDPS, methyl ether and acetate derivatives **18**, **19** and **20** could be achieved in good yield (92, 52 and 100% respectively) and for the latter two at least, catalytic reduction was successful, giving pyrrolidine **21** (after *N*-benzylation) and **22a** in good yield (77 and 100% respectively) but as a mixture of inseparable diastereomers. The ¹H NMR spectrum

Scheme 8

This journal is © The Royal Society of Chemistry 2006

Org. Biomol. Chem., 2006, **4**, 2600–2615 | **2605**

Scheme 9

of pyrrolidine **21** (in CDCl$_3$) showed broadening of signals, and variable temperature analysis (373 K in d$_6$-DMSO) also failed to give a resolved spectrum; however, in C$_6$D$_6$ better resolution was achieved. In the case of **22a**, immediate trityl protection gave product **22b**, in which acetyl migration had occurred, whose structure and relative stereochemistry was confirmed by single crystal X-ray analysis,¶ or protection with benzoyl chloride and pyridine gave benzamide **22c** (Scheme 9).

Conclusion

We have identified conditions suitable for the reduction of enamines substituted with ester functions, derived from pyroglutamic acid enabling generation of synthetic intermediates which permit regioselective C-2 or C-6 manipulation, providing access to *trans*- or *cis*-2,5-disubstituted pyrrolidines. Furthermore, an effective spectroscopic protocol involving ^{1}H NOE analysis at high temperature (373 K) has been identified which minimises conformational effects and permits detailed stereochemical assignments to be made in these highly conformationally mobile systems; where possible, these have been confirmed independently by crystallographic analysis.

Experimental

^{1}H NMR spectra were recorded on Varian Gemini 200 (200 MHz) and Bruker AM-500 (500 MHz) spectrometers. ^{13}C NMR spectra were recorded on the same spectrometers at 50.3 MHz and at 125.8 MHz respectively. Low resolution mass spectra were recorded on a VG Masslab 20–250 spectrometer using the CI or on a Hewlet Packard series 1050 spectrometer using APCI in the (APCI$^+$) mode or ES in the (ES+) mode. Sealed mass-to-charge (m/z) peaks are quoted in Daltons as percentage of the base peak. Accurate mass spectra were recorded on a VG Autospec spectrometer operating in positive ion electrospray mode by Dr N. J. Oldham and Mr R. Proctor at the Dyson Perrins Laboratory, Oxford. Gas chromatography mass spectra (GCMS) were recorded on a VG Trio-1 spectrometer. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel 60 F$_{254}$. Plates were

visualised using UV light (254 nm) or a solution of 5% w/v *dodeca*-molybdophosphoric acid in EtOH followed by heat. Flash column chromatography was carried out using Sorbisil(tm) C$_{60}$ H(40–60 mm) silica gel.

(S)-2-Ethyloxycarbonyl-5-thioxo-pyrrolidine 2b[38,39]

To a suspension of Lawesson's reagent (16.00 g, 38.71 mmol) in CH$_2$Cl$_2$ (150 ml) was added ester **2a** (12.15 g, 77.41 mmol) as a solution in CH$_2$Cl$_2$ (150 ml) and the reaction mixture stirred for 1.5 hours. The solvent was removed under reduced pressure and the residue was divided into 2 portions which were purified by flash column chromatography [EtOAc : petrol (40–60) 2 : 3] to give 2b (11 g, 82%) as viscous oil. R_f = 0.22 (3 : 1 petrol (40–60) : EtOAc); v_{max}/cm^{-1} (neat) 3181, 1741, 1503; δ_H (400 MHz, CDCl$_3$) 1.27 (3H, t, J 7.0, OCH$_2$CH_3), 2.27–2.36 (1H, m, C(3)HH), 2.49–2.58 (1H, m, C(3)HH), 2.86–3.02 (2H, m, C(4)H_2), 4.23 (2H, q, J 7.0, OCH_2CH$_3$), 4.51 (1H, dd, J 8.7, 6.2, C(2)H), 8.54 (1H, br, NH); m/z (APCI$^+$) 174 (M + H$^+$, 100%).

(S)-5-(Di(ethoxycarbonyl)methylidene)-pyrrolidine-2-carboxylic acid ethyl ester 2c[26]

Diethyl 2-bromomalonate (18.6 g, 78.0 mmol), NaHCO$_3$ (13.1 g, 156 mmol) and CH$_2$Cl$_2$ (150 ml) were added to thiolactam **2b** (6.75 g, 39.0 mmol). The suspension was heated under reflux for 48 hours, cooled, washed with water, dried with MgSO$_4$, and evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 3 : 2] afforded the enamine **2c** (11.6 g, 100%) as viscous oil. R_f = 0.58 (3 : 2 petrol (40–60) : EtOAc); $[a]_D^{26}$ = −28.9 (c = 1.26, CHCl$_3$); v_{max}/cm^{-1} (neat) 1743, 1691, 1649, 1573; δ_H (400 MHz, CDCl$_3$) 1.15–1.24 (9H, m, 3 × OCH$_2$CH_3), 2.03–2.11 (1H, m, C(3)HH), 2.23–2.33 (1H, m, C(3)HH), 2.99–3.14 (2H, m, C(4)H_2), 4.06–4.17 (6H, m, 3 × OCH_2CH$_3$), 4.37 (1H, dd, J 8.8, 5.6, C(2)H), 9.57 (1H, br, NH); δ_C (50 MHz, CDCl$_3$) 14.1 (OCH$_2$CH_3), 14.3 (2 × OCH$_2$CH_3), 25.9 (C(3)), 33.2 (C(4)), 59.7, 59.8 (2 × OCH_2CH$_3$), 60.8 (C(2)), 61.7 (OCH_2CH$_3$), 88.8 (NCC), 167.5, 169.4, 171.1, 172.1 (C(5), 3 × CO$_2$C$_2$H$_5$); m/z (APCI$^+$) 300 (M + H$^+$, 2%), 254 (100%).

(S)-Methyl 5-(1-ethoxy-1,3-dioxo-3-phenylpropan-2-ylidene)pyrrolidine-2-carboxylate 3

To ethyl 2-bromo-3-oxo-3-phenylpropionate[40] (3.30 g, 12.2 mmol) and NaHCO$_3$ (2.04 g, 24.4 mmol) was added a solution of (S)-methyl 5-thioxopyrrolidine-2-carboxylate.[27,41,42] (0.970 g, 6.10 mmol) in CH$_2$Cl$_2$ (86 ml). The suspension was heated under reflux for 36 hours, cooled, filtered through celite, and the solvent evaporated. Silica gel chromatography [Toluene : EtOAc 4 : 1] afforded the enamine 3 (0.960 g, 50%), as a mixture of diastereomers in a ratio of 1 : 2, as brown oil. $R_f = 0.31$ (3 : 1 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 3038, 1746, 1685, 1600, 1528, 1477; δ_H (200 MHz, CDCl$_3$) 0.63–0.72 (3H, m, OCH$_2$CH$_3$), 2.07–2.41 (2H, m, C(3)H$_2$), 3.05–3.24 (2H, m, C(4)H$_2$), 3.66–3.89 (5H, m, OCH$_2$CH$_3$, OCH$_3$), 4.44–4.56 (1H, m, C(2)H), 7.23–7.59 (5H, m, C$_6$H$_5$), 9.47 (1H, br, NH (minor diastereomer)), 10.94 (1H, br, NH (major diastereomer)); δ_C (50 MHz, CDCl$_3$) (major, minor) 13.3,13.4 (OCH$_2$CH$_3$), 25.3, 26.0 (C(3)), 33.0, 32.4 (C(4)), 52.6 (CO$_2$CH$_3$), 59.4, 59.1 (OCH$_2$CH$_3$), 61.3, 60.7 (C(2)), 98.7, 96.5 (NCC), 125.2, 126.7, 127.6, 127.9, 128.1, 128.9, 129.6, 130.7 (C$_6$H$_5$),142.5, 143.2 (quaternary ArC), 168.8, 169.5, 171.2, 171.5, 173.2,172.0 (C(5), CO$_2$CH$_3$, CO$_2$C$_2$H$_5$), 195.0, 194.8 (C$_6$H$_5$CO); m/z (APCI$^+$) 318 (M + H$^+$, 8%), 272 (100%); HRMS (M + H$^+$) 318.1340, C$_{17}$H$_{20}$NO$_5$ requires 318.1341.

(S)-Ethyl 2-(5-(hydroxymethyl)pyrrolidin-2-ylidene)-3-oxo-3-phenylpropanoate 4a

To a solution of enamine 3 (0.10 g, 0.32 mmol) in absolute ethanol (3 ml) was added sodium borohydride (0.050 g, 1.3 mmol) at 0 °C and stirred for 10 minutes, and then at room temperature for 5 hours. Glacial acetic acid was then carefully added to the mixture with stirring and cooling in an ice bath, until pH 5.0 was reached. The solvent was evaporated in vacuo and silica gel chromatography [EtOAc] afforded the alcohol 4a (0.070 g, 71%), as a mixture of diastereomers in a ratio of 1 : 5, as a viscous oil. $R_f = 0.36$ (EtOAc); ν_{max}/cm^{-1} (neat) 3340, 3044, 1659, 1589, 1476; δ_H (400 MHz, CDCl$_3$) (major) 0.71 (3H, t, J 7.0, OCH$_2$CH$_3$), 1.67–1.75 (1H, m, C(3)HH), 2.03–2.13 (1H, m, C(3)HH), 3.08–3.18 (2H, m, C(4)H$_2$), 3.31 (1H, dd, J 11.4, 6.9, CHHOH), 3.64–3.86 (3H, m, CHHOH, OCH$_2$CH$_3$), 4.04–4.51 (1H, m, C(2)H), 7.25–7.60 (5H, m, C$_6$H$_5$), 11.01 (1H, br, NH); δ_C (100 MHz, CDCl$_3$) 13.5 (OCH$_2$CH$_3$), 22.8 (C(3)), 33.0 (C(4)), 59.5 (OCH$_2$CH$_3$), 62.5 (C(2)), 64.6 (CH$_2$OH), 98.1 (NCC), 125.6, 127.6, 129.4 (ArC), 143.5 (quaternary ArC), 169.13, 173.0 (C(5), COOC$_2$H$_5$), 195.2 (C$_6$H$_5$CO); m/z (APCI$^+$) 290 (M + H$^+$, 4%), 244 (100%). δ_H (400 MHz, CDCl$_3$) (minor) 1.24 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.67–1.75 (1H, m, C(3)HH), 2.03–2.13 (1H, m, C(3)HH), 2.59–2.61 (2H, m, C(4)H$_2$), 3.42–3.58 (2H, m, CH$_2$OH), 3.64–3.86 (1H, m, C(2)H), 4.04–4.51 (2H, m, OCH$_2$CH$_3$), 7.25–7.6 (5H, m, C$_6$H$_5$), 9.47 (1H, br, NH); δ_C (100 MHz, CDCl$_3$) 14.6 (OCH$_2$CH$_3$), 23.8 (C(3)), 31.7 (C(4)), 59.1 (OCH$_2$CH$_3$), 61.6 (C(2)), 65.1 (CH$_2$OH), 95.6 (NCC), 125.6, 128.4, 131.7 (ArC), 142.9 (quaternary ArC), 170.1, 170.8 (C(5), CO$_2$C$_2$H$_5$), 195.4 (C$_6$H$_5$CO).

(S)-Diethyl 2-(2-(hydroxymethyl)pyrrolidin-5-ylidene)malonate 4b

To a solution of enamine 2c (3.0 g, 10 mmol) in absolute ethanol (150 ml) was added sodium borohydride (1.5 g, 40 mmol) at 0 °C and stirring continued for 30 minutes, then at room temperature

for 6 hours. Glacial acetic acid was then carefully added to the mixture with stirring and cooling in an ice bath until pH 5.0 was reached. The mixture was partitioned between CH$_2$Cl$_2$ and water. The organic layer was washed with saturated solution of NaHCO$_3$, water and brine, dried with MgSO$_4$, and the solvent evaporated. Silica gel chromatography [EtOAc : MeOH 95 : 5] gave alcohol 4b (2.1 g, 80%) as viscous oil. $R_f = 0.26$ (3 : 7 petrol (40–60) : EtOAc); $[a]_D^{22} = +19.3$ ($c = 0.14$, CHCl$_3$); ν_{max}/cm^{-1} (neat) 3416, 1644, 1567; δ_H (400 MHz, CDCl$_3$) 1.27 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.28 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.73–1.80 (1H, m, C(3)HH), 2.05–2.15 (1H, m, C(3)HH), 2.78 (1H, s, OH), 3.02–3.20 (2H, m, C(4)H$_2$), 3.52 (1H, dd, J 11, 6.7, CHHOH), 3.71 (1H, dd, J 11, 4.0, CHHOH), 3.98–4.01 (1H, m, C(2)H), 4.14–4.28 (4H, m, 2 × OCH$_2$CH$_3$), 9.59 (1H, br, NH); δ_C (50 MHz, CDCl$_3$) 14.3 (2 × OCH$_2$CH$_3$), 23.8 (C(3)), 33.8 (C(4)), 59.6 (2 × OCH$_2$CH$_3$), 60.4 (C(2)), 66.1 (CH$_2$OH), 87.3 (NCC), 167.8, 169.7, 172.7 (C(5), 2 × CO$_2$C$_2$H$_5$); m/z (APCI$^+$) 258 (M + H$^+$, 8%), 212 (100%); HRMS (M + H$^+$) 258.1340, C$_{12}$H$_{20}$NO$_5$ requires 258.1341.

(S)-N-tert-Butoxycarbonyl-5-(1-ethoxycarbonyl-2-oxo-2-phenyl-ethylidene)-pyrrolidine-2-carboxylic acid methyl ester 5a

To a solution of enamine 3 (1.00 g, 3.15 mmol) in CH$_2$Cl$_2$ (10 ml) at 0 °C was added triethylamine (0.65 ml, 4.7 mmol), di-tert-butyl dicarbonate (0.97 g, 4.7 mmol) as a solution in CH$_2$Cl$_2$ (15 ml), and (dimethylamino)pyridine (0.39 g, 3.2 mmol) as a solution in CH$_2$Cl$_2$ (15 ml). The mixture was refluxed for 48 hours, cooled, washed with water and brine, dried with MgSO$_4$, and evaporated. Silica gel chromatography [toluene : EtOAc 4 : 1] afforded the carbamate 5a (0.96 g, 73%) as a mixture of diastereomers in a ratio of 1 : 2.25, as viscous yellow oil. $R_f = 0.55$ (3 : 2 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 3040, 1744, 1707, 1664, 1602, 1522, 1477; δ_H (400 MHz, CDCl$_3$) (major) 0.86 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.21 (9H, s, C(CH$_3$)$_3$), 2.06–2.10 (1H, m, C(3)HH), 2.30–2.38 (1H, m, C(3)HH), 3.09–3.15 (2H, m, C(4)H$_2$), 3.74 (3H, s, OCH$_3$), 3.91–4.03 (2H, m, OCH$_2$CH$_3$), 4.58 (1H, dd, J 9.4, 3.3, C(2)H), 7.35–7.39 (3H, m, ArH), 7.85–7.88 (2H, m, ArH); δ_C (100 MHz, CDCl$_3$) 13.6 (OCH$_2$CH$_3$), 26.0 (C(3)), 27.7 (C(CH$_3$)$_3$), 31.6 (C(4)), 52.3 (CO$_2$CH$_3$), 60.4 (OCH$_2$CH$_3$), 62.6 (C(2)), 83.2 (C(CH$_3$)$_3$), 112.2 (NCC), 127.8, 128.6, 131.6 (ArC), 138.9 (quaternary ArC), 150.0, 155.2, 167.1, 172.0 (C(5), CO$_2$CH$_3$, CO$_2$C$_2$H$_5$, COC(CH$_3$)$_3$), 192.2 (C$_6$H$_5$CO); m/z (CI$^+$) 418 (M + H$^+$, 12%), 318 (100%), 272 (45%); HRMS (M + H$^+$) 418.1858, C$_{22}$H$_{28}$NO$_7$ requires 418.1866. δ_H (400 MHz, CDCl$_3$) (minor) 0.96 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.43 (9H, s, C(CH$_3$)$_3$), 2.06–2.10 (1H, m, C(3)HH), 2.30–2.38 (1H, m, C(3)HH), 2.67–2.70 (1H, m, C(4)HH), 2.79–2.85 (1H, m, C(4)HH), 3.76 (3H, s, OCH$_3$), 3.91–4.03 (2H, m, OCH$_2$CH$_3$), 4.65 (1H, dd, J 9.3, 3.3, C(2)H), 7.43–7.47 (3H, m, ArH), 7.73–7.75 (2H, m, ArH); δ_C (100 MHz, CDCl$_3$) 14.1 (OCH$_2$CH$_3$), 26.1 (C(3)), 27.8 (C(CH$_3$)$_3$), 31.7 (C(4)), 52.4 (CO$_2$CH$_3$), 60.6 (OCH$_2$CH$_3$), 62.6 (C(2)), 83.3 (C(CH$_3$)$_3$), 115.6 (NCC), 128.2, 128.6, 132.1 (ArC), 139.6 (quaternary ArC), 150.5, 155.5, 166.6, 171.8 (C(5), CO$_2$CH$_3$, CO$_2$C$_2$H$_5$, COC(CH$_3$)$_3$), 193.6 (C$_6$H$_5$CO).

(S)-N-tert-Butoxycarbonyl-5-(ethoxycarbonylethylidene)-2-hydroxymethylpyrrolidine 6

To a solution of carbamate 5a (0.20 g, 0.48 mmol) in absolute ethanol (10 ml) was added sodium borohydride (0.040 g,

0.96 mmol) at 0 °C and the reaction was refluxed for 23 hours. Glacial acetic acid was then carefully added to the mixture with stirring and cooling in an ice bath, until pH 5.0 was reached. The mixture was partitioned between CH_2Cl_2 and water. The organic layer was washed with saturated solution of $NaHCO_3$, water and brine, dried with $MgSO_4$, and the solvent evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 3 : 2] afforded alcohol **6** (0.014 g, 11%). $R_f = 0.60$ (3 : 2 petrol (40–60) : EtOAc); δ_H (400 MHz, $CDCl_3$) 1.41–1.44 (3H, m, OCH_2CH_3), 1.48 (9H, s, $C(CH_3)_3$), 1.93–2.31 (2H, m, C(3)H_2), 2.94–3.07 (1H, m, C(4)HH), 3.38–3.45 (1H, m, C(4)HH), 4.09–4.24 (4H, m, CH_2OH, 2 × OCH_2CH_3), 4.57–4.6 (1H, m, C(2)H), 6.55 (1H, m, CHCO$_2$Et); δ_C (125 MHz, $CDCl_3$) 14.1 (OCH_2CH_3), 25.4 (C(3)), HCH_2CH_2), 28.3 ($C(CH_3)_3$), 29.5 (C(4)), 59.2, 61.3 (CH_2OH, OCH_2CH_3), 62.1 (C(2)), 95.6 ($C(CH_3)_3$), 96.8 (CHCO$_2$Et), 156.5, 168.6, 171.5 (C(5), $COC(CH_3)_3$, $CO_2C_2H_5$); m/z (CI$^+$) 366 (M + H$^+$, 100%), 112 (65%); m/z (EI$^+$) 286 (1%), 224 (100%).

(2*S*,5*S* and 2*S*,5*R*)-5-(Di(ethoxycarbonyl)methyl)-pyrrolidine-2-carboxylic acid ethyl ester 7a

The enamine **2c** (1.00 g, 3.30 mmol) was dissolved in HOAc (7.50 ml) to which was added Adams' catalyst (0.16 g) in TFA (2.5 ml). The hydrogenation apparatus was flushed 3 times with hydrogen, and finally set to a pressure of 4.5 atm and the mixture stirred for 48 hours. Careful filtration through Celite® using EtOAc, followed by solvent removal, gave a residue which was dissolved in CH_2Cl_2 (50 ml) and washed with dilute aqueous ammonia (3.2%) (50 ml), water and brine. The solution was dried over $MgSO_4$ and the solvent removed to give quantitative yield (1.01 g) of amine **7a** as in inseparable mixture of diastereomers in a ratio of 1 : 2. $R_f = 0.37$ (3 : 2 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 3349, 1735; δ_H (400 MHz, $CDCl_3$) (major) 1.26–1.32 (9H, m, 3 × OCH_2CH_3), 1.61–1.65 (1H, m, C(4)HH), 1.85–1.90 (1H, m, C(3)HH), 1.95–2.01 (1H, m, C(4)HH), 2.16–2.23 (1H, m, C(3)HH), 3.30 (1H, d, J 9.3, NCHCH), 3.79–3.82 (1H, m, C(2)H), 3.91 (1H, dd, J 9.3, 7.3, C(5)H), 4.13–4.25 (6H, m, 3 × OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 13.8 (3 × OCH_2CH_3), 29.1 (C(4)), 29.2 (C(3)), 56.9 (C(5)), 58.6 (NCHCH), 59.3 (C(2)), 61.0, 61.4, 61.5 (3 × OCH_2CH_3), 168.0, 168.4, 175.2 (3 × $CO_2C_2H_5$); m/z (APCI$^+$) 302 (M + H$^+$, 18%), 142 (100%).

(2*S*,5*S* and 2*S*,5*R*)-*N*-Benzoyl-5-(di(ethoxycarbonyl)methyl)-pyrrolidine-2-carboxylic acid ethyl ester 7b

(i) Preparation by protection of amine 2c. Dry benzoyl chloride (3.20 ml, 27.4 mmol) was added to a solution of amine **2c** (0.83 g, 2.7 mmol) in dry pyridine (2.50 ml, 30.7 mmol) and the reaction was allowed to stir for 4 hours between 30–40 °C. The reaction was quenched and neutralised at 0 °C with 2 M HCl and stirred for 1 hour. CH_2Cl_2 (50 ml) was added and the organic layer was washed with water and brine. It was dried with $MgSO_4$ and evaporated to give a mixture (1.0 g, 93%) of *cis*- and *trans*-diastereomers, in variable ratios separable by silica gel chromatography [petrol (40–60) : EtOAc 3 : 2]. A small sample of *cis*- was recrystallised from EtOAc, petrol (40–60), to give transparent crystals, for single crystal X-ray analysis (CCDC

reference number 209273[23]). The *trans*-diastereomer, on the other hand, was found to be a transparent oil.

(ii) Preparation by reduction of amide 8. The amide **8** (0.12 g, 0.30 mmol) was dissolved in CH_2Cl_2 (1 ml) to which was added 10% Pd/C (0.07 g) in EtOH (10 ml). The hydrogenation apparatus was flushed 3 times with hydrogen, and finally set to a pressure of 5 atm and the mixture stirred for 23.5 hours. Careful filtration through Celite® using EtOAc, followed by solvent removal gave amine (0.10 g, 80%) as a separable mixture of *cis*- and *trans*-diastereomers **7b**, in a ratio of 9 : 1 using silica gel chromatography [petrol (40–60) : EtOAc 3 : 2].

trans-**7b**. $R_f = 0.50$ (3 : 2 petrol (40–60) : EtOAc); $[a]_D^{25} = -137$ ($c = 0.1$, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3061, 1736, 1648, 1603; δ_H (400 MHz, $CDCl_3$) 1.01 (3H, t, J 7.1, OCH_2CH_3), 1.26 (3H, t, J 7.1, OCH_2CH_3), 1.29 (3H, t, J 7.1, OCH_2CH_3), 1.94–1.98 (1H, m, C(3)H'), 2.21–2.32 (3H, m, C(3)H, C(4)H'H), 3.80–3.91 (2H, m, OCH_2CH_3), 4.10–4.26 (4H, m, 2 × OCH_2CH_3), 4.39 (1H, d, J 5.2, NCHCH), 4.44–4.46 (1H, m, C(2)H), 4.99 (1H, dd, J 5.2, 10.8, C(5)H), 7.32–7.39 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 13.8, 13.9, 14.0 (3 × OCH_2CH_3), 26.1 (C(4)), 29.5 (C(3)), 52.0 (NCHCH), 56.9 (C(5)), 61.3, 61.4, 61.6 (3 × OCH_2CH_3), 62.5 (C(2)), 126.8, 128.2, 129.9 (ArC), 136.6 (quaternary ArC), 167.8, 168.2, 171.4, 171.8 (3 × $CO_2C_2H_5$, C_6H_5CO); m/z (APCI$^+$) 406 (M + H$^+$, 100%), 246 (40%), 105 (5%); HRMS (M + H$^+$) 406.1862, $C_{21}H_{28}NO_7$ requires 406.1866. δ_H (VT) (500 MHz, 373 K in d$_6$-DMSO) 1.02 (3H, t, J 6.5, OCH_2CH_3), 1.21 (3H, t, J 7, OCH_2CH_3), 1.26 (3H, t, J 7, OCH_2CH_3), 1.93–1.94 (1H, m, C(3)H'), 2.12–2.15 (2H, m, C(4)H'H), 2.31–2.39 (1H, m, C(3)H), 3.91 (2H, br, OCH_2CH_3), 4.13–4.15 (3H, m, OCH_2CH_3, NCHCH), 4.20–4.24 (2H, m, OCH_2CH_3), 4.49 (1H, dd, J 2.5, 9.0, C(2)H), 4.80–4.83 (1H, m, C(5)H), 7.37–7.51 (5H, m, C_6H_5).

cis-**7b**. Mp 80–82 °C $R_f = 0.48$ (3 : 2 petrol (40–60) : EtOAc); $[a]_D^{25} = +10$ ($c = 0.1$, $CHCl_3$); ν_{max}/cm^{-1} (neat) 1732, 1650; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, J 6.5, OCH_2CH_3), 1.26 (3H, t, J 7.0, OCH_2CH_3), 1.30 (3H, t, J 7.0, OCH_2CH_3), 2.06 (3H, br, C(3)H_2, C(4)H'), 2.46 (1H, br, C(4)H), 4.11–4.32 (8H, m, C(2)H, NCHCH, 3 × OCH_2CH_3), 4.88–4.94 (1H, m, C(5)H), 7.35–7.45 (5H, m, C_6H_5); δ_C (100 MHz, $CDCl_3$) 13.9, 14.0, 14.1 (3 × OCH_2CH_3), 27.9 (C(4)), 29.7 (C(3)), 54.9 (NCHCH), 57.4 (C(5)), 61.3 (3 × OCH_2CH_3), 61.5 (C(2)), 125.8, 128.4, 130.3 (ArC), 136.6 (quaternary ArC), 167.8, 172.1 (3 × $CO_2C_2H_5$, C_6H_5CO); m/z (ES$^+$) 428 (M + Na, 100%), 406 (M + H$^+$, 90%), 360 (22%), 246 (35%); HRMS (M + H$^+$) 406.1857, $C_{21}H_{28}NO_7$ requires 406.1866. δ_H (VT) (500 MHz, 373 K in d$_6$-DMSO) 1.18 (3H, t, J 7, OCH_2CH_3), 1.21 (3H, t, J 7.5, OCH_2CH_3), 1.25 (3H, t, J 7.5, OCH_2CH_3), 1.97–2.00 (2H, m, C(3)H', C(4)H'), 2.20 (1H, br, C(3)H), 2.30–2.31 (1H, m, C(4)H), 4.01 (1H, d, J 7.5, NCHCH), 4.07–4.12 (4H, m, 2 × OCH_2CH_3), 4.18–4.21 (2H, m, OCH_2CH_3), 4.30–4.31 (1H, m, C(2)H), 4.81 (1H, dd, J 6.0, 7.5 C(5)H), 7.36–7.51 (5H, m, C_6H_5). δ_H (400 MHz, C_6D_6) 0.84 (3H, t, J 7.1, OCH_2CH_3), 0.92 (3H, t, J 7.1, OCH_2CH_3), 1.02 (3H, t, J 7, OCH_2CH_3), 1.32 (1H, br, C(3)H), 1.61 (1H, br, C(3)H'), 2.08–2.18 (1H, m, C(4)H'), 2.32 (1H, br, C(4)H), 3.74–3.95 (2H, m, OCH_2CH_3), 4.00–4.04 (3H, m, C(2)H, OCH_2CH_3), 4.14–4.23 (2H, m, OCH_2CH_3), 4.76 (1H, br, NCHCH), 5.19 (1H, br, C(5)H), 7.00–7.07 (3H, m, ArH), 7.57–7.60 (2H, m, ArH).

(2S,5S and 2S,5R)-N-Acetyl-5-(di(ethoxycarbonyl)methyl)-pyrrolidine-2-carboxylic acid ethyl ester 7c

Acetic anhydride (0.31 ml, 3.3 mmol) was added to a solution of amine **7a** (0.10 g, 0.33 mmol) in pyridine (0.30 ml, 3.7 mmol) and the reaction was allowed to stir for 24 hours at room temperature. The reaction was quenched with water. Dichloromethane was added and the organic layer was washed with 10% HCl, water, saturated solution of NaHCO$_3$, water and brine, dried with MgSO$_4$ and the solvent evaporated. Silica gel chromatography ([petrol (40–60) : EtOAc 1 : 1] afforded the amide **7c** (0.110 g, 100%) as a separable mixture of diastereomers in a 1 : 3.8 ratio.

Minor diastereomer: R_f = 0.46 (2 : 3 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 1740, 1651; δ_H (400 MHz, CDCl$_3$) 1.23–1.28 (9H, m 3 × OCH$_2$CH_3), 1.95 (3H, s, NCOCH_3), 1.98–2.02 (1H, m, C(3)H'), 2.16–2.42 (3H, m, C(3)H, C(4)$H'H$), 4.11–4.25 (6H, m, 3 × OCH_2CH$_3$), 4.33–4.36 (1H, m, C(2)H), 4.40 (1H, d, J 4.7, NCHCH), 4.72–4.76 (1H, m, C(5)H); δ_C (100 MHz, CDCl$_3$) 13.9, 14.0, 14.1 (3 × OCH$_2$$CH_3$), 22.1 (NCO$CH_3$), 26.1 ($C$(4)), 29.4 ($C$(3)), 51.6 (NCH$C$H), 57.2 ($C$(5)), 61.2, 61.9 ($C$(2), 3 × O$CH_2CH_3$), 168.0, 168.4, 170.4, 172.2 (NCOCH$_3$, 3 × CO$_2$C$_2$H$_5$); m/z (APCI$^+$) 344 (M + H$^+$, 20%), 298 (23%), 184 (54%), 142 (100%); HRMS (M + H$^+$) 344.1712, C$_{16}$H$_{26}$NO$_7$ requires 344.1709.

Major diastereomer: R_f = 0.30 (2 : 3 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 1732, 1651; δ_H (400 MHz, CDCl$_3$) 1.20–1.28 (9H, m 3 × OCH$_2$CH_3), 2.01 (3H, s, NCOCH_3), 2.11–2.25 (4H, m, C(3)HH, C(4)HH), 4.05–4.24 (6H, m, 3 × OCH_2CH$_3$), 4.32–4.35 (1H, m, C(2)H), 4.60–4.68 (2H, m, C(5)H, NCHCH); δ_C (100 MHz, CDCl$_3$) 13.9, 14.0, 14.1 (3 × OCH$_2$$CH_3$), 22.6 (NCO$CH_3$), 26.1 ($C$(4)), 28.7 ($C$(3)), 53.3 (NCH$C$H), 57.7 ($C$(5)), 61.1, 61.2, 61.4 ($C$(2), 3 × O$CH_2CH_3$), 167.8, 170.9, 171.3, 172.1 (NCOCH$_3$, 3 × CO$_2$C$_2$H$_5$); m/z (APCI$^+$) 344 (M + H$^+$, 100%), 298 (18%), 184 (23%), 142 (35%); HRMS (M + H$^+$) 344.1699, C$_{16}$H$_{26}$NO$_7$ requires 344.1709.

(2S,5R)-N-tert-Butoxycarbonylmethyl-5-(di(ethoxycarbonyl)-methyl)-pyrrolidine-2-carboxylic acid ethyl ester 7d

A 1 M solution of LiHMDS (0.52 ml) in THF was added to a solution of amine **7a** (0.10 g, 0.34 mmol) in THF (3 ml) at 0 °C and stirred for 15 minutes. *tert*-Butyl bromoacetate (0.12 ml, 0.69 mmol) was added dropwise as a solution in THF (2 ml) and the reaction was allowed to come to room temperature and stir for 7 hours. The reaction was quenched at 0 °C by adding a saturated solution of NH$_4$Cl, followed by addition of water and EtOAc. The organic layer was separated, washed with brine, dried with MgSO$_4$ and the solvent evaporated. Silica gel chromatography ([petrol (40–60) : EtOAc 4 : 1] afforded the amine **7d** (0.072 g, 50%) as a transparent oil. R_f = 0.36 (4 : 1 petrol (40–60) : EtOAc); [α]$_D^{22}$ = −24.6 (c = 0.13, CHCl$_3$); ν_{max}/cm^{-1} (neat) 1735; δ_H (400 MHz, CDCl$_3$) 1.21–1.27 (9H, m, 3 × OCH$_2$CH_3), 1.43 (9H, s, C(CH_3)$_3$), 1.81–1.87 (1H, m, C(4)H'), 1.94–2.02 (1H, m, C(3)H'), 2.14–2.27 (2H, m, C(3)H, C(4)H), 3.45 (1H, d, J 18.3, NCHHCO), 3.48 (1H, d, J 8.1, NCHCH), 3.61 (1H, d, J 18.3, NCHHCO), 3.73 (1H, t, J 7.6, C(2)H), 3.89–3.84 (1H, m, C(5)H), 4.08–4.21 (6H, m, 3 × OCHHCH$_3$); δ_C (100 MHz, CDCl$_3$) 14.0, 14.1, 14.2 (3 × OCH$_2$$CH_3$), 28.2 (C($CH_3$)$_3$), 28.6 ($C$(3)), 29.5 ($C$(4)), 53.0 (N$CH_2$CO), 57.5 (NCH$C$H), 60.4, 61.1 (3 × O$CH_2CH_3$), 62.5 ($C$(5)), 64.9 ($C$(2)), 81.0 ($C$(CH$_3$)$_3$), 168.0, 168.3, 170.9, 174.0

(NCH$_2$CO, 3 × CO$_2$C$_2$H$_5$); m/z (ES$^+$) 438 (M + Na, 100%), 416 (M + H$^+$, 40%); HRMS (M + H$^+$) 416.2283, C$_{20}$H$_{34}$NO$_8$ requires 416.2284.

(S)-N-Benzoyl-5-(di(ethoxycarbonyl)methylidene)-pyrrolidine-2-carboxylic acid ethyl ester 8

To a solution of enamine **2c** (1.88 g, 6.30 mmol) in dry CH$_2$Cl$_2$ (25 ml) were added dry triethylamine (2.60 ml, 18.89 mmol), dry benzoyl chloride (1.50 ml, 12.6 mmol) and (dimethylamino)pyridine (0.77 g, 6.3 mmol) as a solution in CH$_2$Cl$_2$ (5 ml). The mixture was refluxed for 48 hours, cooled, quenched and washed with saturated solution of NH$_4$Cl, water and brine, dried with MgSO$_4$, and the solvent evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 7 : 3] afforded the enamide **8** (1.0 g, 41%) as bright yellow crystals. Mp 85–87 °C, R_f = 0.37 (3 : 2 petrol (40–60) : EtOAc); [α]$_D^{26}$ = −60 (c = 0.08, CHCl$_3$); ν_{max}/cm^{-1} (neat) 1740; δ_H (400 MHz, CDCl$_3$) 1.08 (3H, t, J 7.1, OCH$_2$CH_3), 1.29–1.38 (6H, m, 2 × OCH$_2$CH_3), 2.12–2.31 (1H, m, C(3)HH), 2.34–2.42 (1H, m, C(3)HH), 3.02–3.11 (1H, m, C(4)HH), 3.16–3.23 (1H, m, C(4)HH), 3.76–3.81 (1H, m, OCHHCH$_3$), 3.89–3.92 (1H, m, OCHHCH$_3$), 4.11–4.21 (4H, m, 2 × OCH_2CH$_3$), 4.84 (1H, dd, J 9.8, 2.0, C(2)H), 7.34–7.47 (3H, m, ArH), 7.50–7.60 (2H, m, ArH); δ_C (100 MHz, CDCl$_3$) 14.0, 14.1, 14.4 (3 × OCH$_2$$CH_3$), 25.4 ($C$(3)), 31.6 ($C$(4)), 59.8 (2 × O$CH_2CH_3$), 61.7 (O$CH_2CH_3$), 63.4 ($C$(2)), 109.6 (NC$C$), 128.3, 128.7, 131.9 (ArC), 133.8 (quaternary ArC), 157.0 (C(5)), 165.3, 166.0, 171.1, 171.3 (C(5), 3 × CO$_2$C$_2$H$_5$, C$_6$H$_5$$C$O); m/z (ES$^+$) 404 (M + H$^+$, 60%), 358 (55%), 254 (100%); HRMS (M + H$^+$) 404.1697, C$_{21}$H$_{26}$NO$_7$ requires 404.1709.

(S)-N-Methyl-5-(di(ethoxycarbonyl)methylidene)-pyrrolidine-2-carboxylic acid ethyl ester 9a

To NaH (0.030 g, 0.75 mmol) in dry CH$_2$Cl$_2$ (2 ml) at room temperature under argon was added enamine **2c** (0.11 g, 0.38 mmol) as a solution in dry CH$_2$Cl$_2$ (2 ml) and the solution stirred for 2.75 hours. Methyl triflate (0.11 ml, 0.94 mmol) was added at −30 °C and the reaction allowed to come to room temperature over 3 hours. The reaction was quenched with 2 M HCl at 0 °C, neutralised with saturated solution of NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$ and the solvent evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 1 : 1] afforded the N-methyl enamine **9a** as yellow oil (0.022 g, 19%). R_f = 0.56 (1 : 1 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 1741, 1688, 1578; δ_H (500 MHz, CDCl$_3$) 1.27–1.34 (9H, m, 3 × OCH$_2$CH_3), 2.05–2.10 (1H, m, C(3)H'), 2.25–2.33 (1H, m, C(3)H), 2.87 (NCH_3), 3.07–3.14 (1H, m, C(4)H'), 3.26–3.32 (1H, m, C(4)H), 4.16–4.27 (7H, m, C(2)H, 3 × OCH_2CH$_3$); δ_C (125 MHz, CDCl$_3$) 14.1, 14.2 (3 × OCH$_2$$CH_3$), 25.6 ($C$(3)), 33.1 ($C$(4)), 35.7 (N$CH_3$), 60.0, 61.5 (3 × O$CH_2CH_3$), 68.9 ($C$(2)), 91.5 (NC$C$), 165.0, 167.5, 171.1 ($C$(5), 3 × CO$_2C_2H_5$); m/z (ES$^+$) 336 (M + Na, 84%), 314 (M + H$^+$, 50%), 268 (100%); HRMS (M + H$^+$) 314.1609, C$_{15}$H$_{24}$NO$_6$ requires 314.1604.

(S)-N-Ethyl-5-(di(ethoxycarbonyl)methyl)-pyrrolidine-2-carboxylic acid ethyl ester 9b

To a suspension of NaH (0.18 g, 7.4 mmol) in dry CH$_2$Cl$_2$ (5 ml) was added a solution of enamine **2c** (1.11 g, 3.71 mmol) in CH$_2$Cl$_2$ (5 ml) at 0 °C. The mixture was stirred at this temperature for 15

This journal is © The Royal Society of Chemistry 2006

Org. Biomol. Chem., 2006, **4**, 2600–2615 | 2609

minutes followed by stirring at room temperature for 2.5 hours. Ethyl triflate (1.21 ml, 9.27 mmol) was added to the mixture between −40 and −30 °C and the reaction allowed to come to room temperature and stir for 24 hours. The reaction was quenched with water at 0 °C. Dichloromethane was added and the organic layer was washed with water and brine. It was dried with $MgSO_4$ and evaporated under vacuum, using room temperature water bath. Silica gel chromatography ([petrol (40–60) : EtOAc 3 : 2] afforded the *N*-ethyl enamine **9b** (0.70 g, 58%) as transparent oil. $R_f = 0.39$ (3 : 2 petrol (40–60) : EtOAc); $[a]_D^{24} = +3.5$ ($c = 0.1$, $CHCl_3$); v_{max}/cm^{-1} (neat) 1741, 1689, 1571; δ_H (500 MHz, $CDCl_3$) 1.13 (3H, t, *J* 7.2, NCH$_2$C*H*$_3$), 1.25–1.33 (9H, m 3 × OCH$_2$C*H*$_3$), 2.02–2.08 (1H, m, C(3)H*H*), 2.20–2.28 (1H, m, C(3)H*H*), 3.08–3.16 (1H, m, C(4)H*H*), 3.19–3.26 (1H, m, NC*H*HCH$_3$), 3.31–3.40 (2H, m, C(4)H*H*, NCH*H*CH$_3$), 4.16–4.28 (7H, m, C(2)*H*, 3 × OC*H*$_2$CH$_3$); δ_C (125 MHz, $CDCl_3$) 11.8 (NCH$_2$*C*H$_3$), 14.0, 14.1, 14.2 (3 × OCH$_2$*C*H$_3$), 25.6 (*C*(3)), 33.4 (*C*(4)), 43.2 (N*C*H$_2$CH$_3$), 59.6, 61.0, (3 × O*C*H$_2$CH$_3$), 65.6 (*C*(2)), 91.5 (N*CC*), 163.3 (*C*(5)), 167.9, 171.5 (3 × *C*O$_2$C$_2$H$_5$); *m/z* (ES$^+$) 350 (M + Na, 82%), 328 (M + H$^+$, 30%), 282 (100%); HRMS (M + H$^+$) 328.1763, C$_{16}$H$_{26}$NO$_6$ requires 328.1760.

(*S*)-*N*-*tert*-Butoxycarbonylmethyl-5-(di(ethoxycarbonyl)-methylidene)-pyrrolidine-2-carboxylic acid ethyl ester 9c

A 1 M solution of LiHMDS (0.6 ml) in THF was added to a solution of enamine **2c** (0.12 g, 0.40 mmol) in THF (4 ml) at 0 °C and stirred for 15 minutes. *tert*-Butyl bromoacetate (0.13 ml, 0.78 mmol) was added drop wise as a solution in THF (3 ml) and the reaction was allowed to come to room temperature and stir for 6 hours. The reaction was quenched at 0 °C by adding a saturated solution of NH$_4$Cl, followed by addition of water and EtOAc. EtOAc layer was separated, dried with $MgSO_4$ and evaporated. Silica gel chromatography ([petrol (40–60) : EtOAc 4 : 1] afforded the *N*-alkylated enamine **9c** (0.044 g, 27%) as yellow oil. $R_f = 0.68$ (4 : 1 petrol (40–60) : EtOAc); $[a]_D^{23} = +105.6$ ($c = 0.04$, $CHCl_3$); v_{max}/cm^{-1} (neat) 1750, 1716, 1682, 1578; δ_H (400 MHz, $CDCl_3$) 1.15–1.28 (9H, m, 3 × OCH$_2$C*H*$_3$), 1.42 (9H, s, C(C*H*$_3$)$_3$), 2.01–2.09 (1H, m, C(3)H*H*), 2.25–2.35 (1H, m, C(3)H*H*), 3.00–3.10 (1H, m, C(4)H*H*), 3.16–3.24 (1H, m, C(4)H*H*), 3.71 (1H, d, *J* 18.8, NC*H*HCO), 3.99 (1H, d, *J* 18.8, NCH*H*CO), 4.03–4.22 (6H, m, 3 × OC*H*$_2$CH$_3$), 4.34 (1H, dd, *J* 8.9, 4.0, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 14.3 (3 × OCH$_2$*C*H$_3$), 25.9 (*C*(3)), 27.9 (C(*C*H$_3$)$_3$), 33.0 (*C*(4)), 49.5 (N*C*H$_2$CO), 60.7, 61.2, 61.6 (3 × O*C*H$_2$CH$_3$), 67.0 (*C*(2)), 82.3 (*C*(CH$_3$)$_3$), 93.0 (N*CC*), 163.8, 167.0, 171.1 (*C*(5), N*C*H$_2$*C*O, 3 × *C*O$_2$C$_2$H$_5$); *m/z* (ES$^+$) 436 (M + Na, 58%), 414 (M + H$^+$, 82%), 368 (100%); HRMS (M + H$^+$) 414.2130, C$_{20}$H$_{32}$NO$_8$ requires 414.2128.

(*S*)-Triethyl 5-(2-*tert*-butoxy-2-oxoethylamino)pentane-1,1,5-tricarboxylate 10

The enamine **9c** (0.10 g, 0.24 mmol) was dissolved in HOAc (7.5 ml) to which was added Adams' catalyst (0.05 g) in TFA (2.5 ml). The hydrogenation apparatus was flushed 3 times with hydrogen, and finally set to a pressure of 4.5 atm and the mixture stirred for 48 hours. Careful filtration through Celite® using EtOAc, followed by solvent removal, gave a residue which was dissolved in CH$_2$Cl$_2$ (50 ml) and washed with dilute aq. ammonia (3.2%) (50 ml),

water and brine. The solution was dried over $MgSO_4$ and the solvent removed to give amine **10** (0.074 g, 73%) as transparent oil. $R_f = 0.51$ (3 : 2 petrol (40–60) : EtOAc); v_{max}/cm^{-1} ($CHCl_3$) 3350, 1732, 1682; δ_H (400 MHz, $CDCl_3$) 1.17–1.35 (9H, m, 3 × OCH$_2$C*H*$_3$), 1.37–1.42 (2H, m, C(3)*H*$_2$), 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.57–1.71 (2H, m, C(4)*H*$_2$), 1.84–1.90 (2H, m, C(2)*H*$_2$), 2.15 (1H, br, N*H*), 3.17–3.33 (4H, m, C(5)*H*, C(1)*H*, NHC*H*$_2$), 4.10–4.20 (6H, m, 3 × OC*H*$_2$CH$_3$); δ_C (100 MHz, $CDCl_3$) 14.0, 14.2 (3 × OCH$_2$*C*H$_3$), 23.5 ((*C*(4)), 28.0 (C(*C*H$_3$)$_3$), 28.5 (*C*(2)), 32.8 (*C*(3)), 49.8 (NH*C*H$_2$), 51.8 (*C*(1)), 60.7 (*C*(5)), 61.1, 61.4 (3 × O*C*H$_2$CH$_3$), 81.2 (*C*(CH$_3$)$_3$), 169.3, 170.9, 174.3 (3 × *C*O$_2$C$_2$H$_5$, NHCH$_2$*C*O); *m/z* (ES$^+$) 418 (M + Na, 100%), 418 (M + H$^+$, 89%); HRMS (M + H$^+$) 418.2440, C$_{20}$H$_{36}$NO$_8$ requires 418.2441.

(*S*)-Diethyl 2-(4-benzamido-5-hydroxypentyl)malonate 11a

To a solution of amide **7b** (1.27 g, 3.12 mmol) in absolute ethanol (50 ml) was added sodium borohydride (0.470 g, 12.5 mmol) at 0 °C and stirring continued for 30 minutes, then at room temperature for 15 hours. Glacial acetic acid was then carefully added to the mixture with stirring and cooling in an ice bath, until pH 5.0 was reached. The mixture was partitioned between CH$_2$Cl$_2$ and water. The organic layer was washed with saturated solution of NaHCO$_3$, water and brine, dried with $MgSO_4$, and evaporated. Silica gel chromatography [CH$_2$Cl$_2$: MeOH 9 : 1] afforded the alcohol **11a** (0.46 g, 40%). $R_f = 0.79$ (9 : 1 CH$_2$Cl$_2$: MeOH); δ_H (400 MHz, $CDCl_3$) 1.18–1.27 (6H, m, 2 × OCH$_2$C*H*$_3$), 1.39–1.48 (2H, m, CHCH$_2$C*H*$_2$), 1.59–1.71 (2H, m, CH$_2$CHC*H*$_2$), 1.87–1.97 (2H, m, C*H*$_2$CH(CO$_2$Et)$_2$), 3.33 (1H, t, *J* 7.4, C*H*(CO$_2$Et)$_2$), 3.65–3.69 (2H, m, C*H*$_2$OH), 4.09–4.24 (5H, m, HNC*H*, 2 × OC*H*$_2$CH$_3$), 6.60 (1H, br, N*H*), 7.35–7.58 (3H, m, Ar*H*), 7.76–7.81 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.0, 14.2 (2 × OCH$_2$*C*H$_3$), 23.8 (CH*C*H$_2$CH$_2$), 28.4 (*C*H$_2$CH(CO$_2$Et)$_2$), 30.7 (CH$_2$CH*C*H$_2$), 51.7, 51.8 (*C*H(CO$_2$Et)$_2$, HN*C*H), 61.4 (2 × O*C*H$_2$CH$_3$), 65.0 (*C*H$_2$OH), 128.3, 128.6, 131.6 (Ar*C*), 134.2 (quaternary Ar*C*), 168.2, 169.4 (2 × *C*O$_2$C$_2$H$_5$); *m/z* (CI$^+$) 366 (M + H$^+$, 100%), 112 (65%); *m/z* (EI$^+$) 334 (27%), 320 (6%), 122 (18%), 105 (100%) along with minor amounts of triethyl (*S*)-5-(benzoylamino)-1,1,5-pentanetricarboxylate **11b** (0.08 g, 6%) $R_f = 0.96$ (9 : 1 CH$_2$Cl$_2$: MeOH); $[a]_D^{25} = +19.2$ ($c = 0.19$, $CHCl_3$); v_{max}/cm^{-1} (neat) 3329, 1732, 1645; δ_H (400 MHz, $CDCl_3$) 1.21–1.25 (6H, m, 2 × OCH$_2$C*H*$_3$), 1.28 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.78–1.84 (2H, m, CHCH$_2$C*H*$_2$), 1.90–2.05 (4H, m, HNCHC*H*$_2$, C*H*$_2$CH(CO$_2$Et)$_2$), 3.31 (1H, t, *J* 7.5, C*H*(CO$_2$Et)$_2$), 4.11–4.26 (6H, m, 3 × OC*H*$_2$CH$_3$), 4.80 (1H, dt, *J* 5.3, 7.3, HNC*H*), 6.74 (1H, d, *J* 7.7, N*H*), 7.42–7.54 (3H, m, Ar*H*), 7.79–7.82 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (3 × OCH$_2$*C*H$_3$), 23.0 (CH*C*H$_2$CH$_2$), 28.2 (*C*H$_2$CH(CO$_2$Et)$_2$), 32.2 (HNCH*C*H$_2$), 51.7 (*C*HCO$_2$Et), 52.3 (HN*C*H), 61.4, 61.6 (3 × O*C*H$_2$CH$_3$), 127.0, 128.6, 131.7 (Ar*C*), 133.9 (quaternary Ar*C*), 167.0, 169.2, 172.4 (*C*OPh, 3 × *C*O$_2$C$_2$H$_5$); *m/z* (CI$^+$) 408 (M + H$^+$, 100%), 334 (25%), 122 (15%), 105 (20%); HRMS (M + H$^+$) 408.2023, C$_{21}$H$_{30}$NO$_7$ requires 408.2022 and minor amounts of ethyl (*S*)-6-(benzoylamino)-7-hydroxy-2-(hydroxymethyl)heptanoate **11c** (0.07 g, 7% (1 : 1)) $R_f = 0.52$ (9 : 1 CH$_2$Cl$_2$: MeOH); (Diastereomer 1) δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.36–1.46 (2H, m, CHCH$_2$C*H*$_2$), 1.60–1.69 (2H, m, NHCHC*H*$_2$), 1.73–1.79 (2H, m, HOCH$_2$CHC*H*$_2$), 2.51–2.55 (1H, m, C*H*CO$_2$Et), 3.67–3.75 (2H, m, OHC*H*$_2$CHNH), 4.08–4.14 (2H, m, HOC*H*$_2$CHCO$_2$Et), 4.22

2610 | *Org. Biomol. Chem.*, 2006, **4**, 2600–2615

This journal is © The Royal Society of Chemistry 2006

(2H, q, J 7.1, OCH_2CH$_3$), 4.78 (1H, m, HNCH), 7.00 (1H, d, J 7.9, NH), 7.36–7.53 (3H, m, ArH), 7.75–7.80 (2H, m, ArH); δ_C (100 MHz, CDCl$_3$) 14.1 (OCH$_2$$CH_3$), 22.8 (CHCH$_2$$CH_2$), 26.8 (HNCH$CH_2$), 33.0 (HOCH$_2$$CHCH_2$), 50.6 ($CHCO_2$Et), 52.2 (HN$C$H), 60.6 (HO$CH_2$CHCO$_2$Et), 61.7 (O$CH_2CH_3$), 64.7 (OH$CH_2$CHNH), 127.0, 128.6, 131.9 (ArC), 133.7 (quaternary ArC), 167.6, 172.8 (COPh, CO$_2$C$_2$H$_5$); m/z (CI$^+$) 324 (M + H$^+$, 100%), 122 (65%). (Diastereomer 2) δ_H (400 MHz, CDCl$_3$) 1.29 (3H, t, J 7.1, OCH$_2$CH_3), 1.36–1.46 (2H, m, CHCH$_2$CH_2), 1.60–1.69 (2H, m, NHCHCH_2), 1.73–1.79 (1H, m, HOCH$_2$CHCHH), 1.89–1.93 (1H, m, HOCH$_2$CHCHH), 2.51–2.55 (1H, m, CHCO$_2$Et), 3.63–3.66 (2H, m, OHCH_2CHNH), 4.08–4.14 (3H, m, HOCH_2CHCO$_2$Et, HNCH), 4.22 (2H, q, J 7.1, OCH_2CH$_3$), 6.82 (1H, d, J 8.2, NH), 7.36–7.53 (3H, m, ArH), 7.75–7.80 (2H, m, ArH); δ_C (100 MHz, CDCl$_3$) 14.1 (OCH$_2$$CH_3$), 23.4 (CHCH$_2$$CH_2$), 27.9 (HNCH$CH_2$), 31.0 (HOCH$_2$$CHCH_2$), 50.6 ($CHCO_2$Et), 51.6 (HN$C$H), 60.6 (OH$CH_2$CHCO$_2$Et), 62.8 (O$CH_2CH_3$), 65.4 (OH$CH_2$CHNH), 127.0, 128.6, 131.6 (ArC), 134.2 (quaternary ArC), 168.2, 175.1 (COPh, CO$_2$C$_2$H$_5$).

(2*S*,5*S*)-*N*-Benzoyl-5-(di(ethoxycarbonyl)(benzyl)methyl)-pyrrolidine-2-carboxylic acid ethyl ester 12a

To NaH (0.05 g, 2 mmol) in dry DMF (3 ml) at 0 °C was added amide **7b** (0.800 g, 1.97 mmol) (mixture of both diastereomers) as a solution in dry DMF (9 ml) and the solution stirred for 15 minutes. Dry benzyl bromide (0.24 ml, 2.0 mmol) was added at 0 °C and stirred for 5 minutes followed by room temperature stirring for 17.5 hours. The reaction was quenched with saturated solution of NH$_4$Cl at 0 °C and extracted with CH$_2$Cl$_2$. The organic layer was washed with water, dried over MgSO$_4$ and evaporated. Silica gel chromatography (2 columns [petrol (40–60) : EtOAc 3 : 2] and [CH$_2$Cl$_2$: EtOAc 4 : 1]) afforded the title compound **12a** as colourless oil (0.71 g, 73%). R_f = 0.48 (3 : 2 petrol (40–60) : EtOAc); $[a]_D^{25}$ = −66 (*c* = 0.1, CHCl$_3$); ν_{max}/cm^{-1} (neat) 1736, 1656; δ_H (400 MHz, CDCl$_3$) 0.96 (3H, br, OCH$_2$CH_3), 1.03 (3H, t, J 7.1, OCH$_2$CH_3), 1.23–1.30 (3H, br, m, OCH$_2$CH_3), 1.87 (1H, br, C(3)H'), 2.15 (1H, br, C(4)H), 2.21–2.33 (2H, m, C(3)H, C(4)H'), 3.46 (2H, br, CH_2C$_6$H$_5$), 3.77–3.82 (2H, br, OCH_2CH$_3$), 3.87–3.95 (1H, m, OCHHCH$_3$), 3.99–4.05 (1H, m, OCHHCH$_3$), 4.10–4.18 (1H, m, OCHHCH$_3$), 4.19–4.24 (1H, m, OCHHCH$_3$), 4.51 (1H, dd, J 9.0, 1.7, C(2)H), 5.58 (1H, br, C(5)H), 7.13–7.23 (5H, m, CH$_2$C$_6$$H_5$), 7.34–7.4 (3H, m, COAr$H$), 7.56–7.57 (2H, m, COArH); δ_C (100 MHz, CDCl$_3$) 13.5, 13.6, 13.9 (3 × OCH$_2$$CH_3$), 27.3 ($C$(4)), 30.0 ($C$(3)), 40.1 ($CH_2C_6H_5$), 61.1, 61.2, 61.5 (3 × OCH$_2$CH$_3$), 62.1 (C(5)), 63.8 (C(2)), 65.1 (NCHCBn), 126.5, 128.0, 130.2 (CH$_2$ArC), 136.7 (quaternary CH$_2$ArC),128.3, 128.4, 130.5 (COArC), 137.3 (quaternary COArC), 169.5, 170.1 (2 × CO$_2$C$_2$H$_5$), 172.4 C(2)CO$_2$C$_2$H$_5$), 173.6 (NCO); m/z (ES$^+$) 518 (M + Na, 100%), 496 (M + H$^+$, 22%); HRMS (M + H$^+$) 496.2346, C$_{28}$H$_{34}$NO$_7$ requires 496.2335.

δ_H (VT) (500 MHz, 373 K in d$_6$-DMSO) 0.96 (3H, t, J 7, OCH$_2$CH_3), 1.04–1.07 (3H, m, OCH$_2$CH_3), 1.20 (3H, t, J 7, OCH$_2$CH_3), 1.88–1.90 (1H, m, C(3)H'), 2.14–2.16 (1H, m, C(4)H), 2.19–2.26 (1H, m, C(4)H'), 2.29–2.38 (1H, m, C(3)H), 3.35 (2H, s, OCH$_2$C$_6$H$_5$), 3.83 (2H, q, J 7, OCH$_2$CH$_3$), 3.91–3.95 (1H, m, OCHHCH$_3$), 3.99–4.03 (1H, m, OCHHCH$_3$), 4.15 (2H, q, J 7, OCH$_2$CH$_3$), 4.54 (1H, dd, J 9.5, 2.5, C(2)H), 5.63 (1H, dd, J

9.0, 2.0, C(5)H), 7.19–7.25 (5H, m, CH$_2$C$_6$$H_5$), 7.43–7.47 (3H, m, COArH), 7.50–7.52 (2H, m, COArH).

(2*S*,5*S*)-*N*-Benzoyl-5-(1,1-di(ethoxycarbonyl)ethyl)pyrrolidine-2-carboxylic acid ethyl ester 12b

From MeI. To a suspension of NaH (0.04 g, 1 mmol) in THF (1 ml) was added drop wise a solution of *cis*-**7b** (0.20 g, 0.49 mmol) in THF (2 ml) at 0 °C. After 30 minutes of stirring at 0 °C, MeI (0.11 g, 0.77 mmol) was added as a solution in THF (1 ml) and the mixture was allowed to come to room temperature and stirred for 27 hours. Water was added at 0 °C followed by extraction with Et$_2$O. The Et$_2$O layer was dried with MgSO$_4$ and evaporated. Silica gel chromatography ([petrol (40–60) : EtOAc 3 : 2] afforded the title compound **12b** (0.050 g, 25%) as white crystals. A small sample was recrystallised from EtOAc, petrol (40–60), to give transparent crystals, for single crystal X-ray analysis (CCDC reference number 209274[23]). *trans*-**7b** gave the same yield under similar conditions.

From MeOTf. To a suspension of KH (0.0280 g, 0.676 mmol) in dry Et$_2$O (4.5 ml) was added a solution of *trans*-**7b** (0.23 g, 0.56 mmol) in dry Et$_2$O (2 ml) at 0 °C under argon. The mixture was stirred at this temperature for 15 minutes followed by stirring at room temperature for 2.5 hours. Methyl triflate (0.10 ml, 0.84 mmol) was added to the mixture between −40 and −30 °C and the reaction allowed to come to room temperature over 2.5 hours. The reaction was quenched with 2 M HCl at 0 °C, and neutralised with saturated solution of NaHCO$_3$. EtOAc was added and the organic layer was washed with brine. It was dried with MgSO$_4$ and the solvent evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 3 : 2] afforded the title compound **12b** (0.21 g, 88%). Mp 74–76 °C; R_f = 0.49 (3 : 2 petrol (40–60) : EtOAc); $[a]_D^{25}$ = −94.4 (*c* = 0.3, CHCl$_3$); ν_{max}/cm^{-1} (neat) 1726, 1657; δ_H (400 MHz, CDCl$_3$) 0.99 (3H, t, J 7.0, OCH$_2$CH_3), 1.18–1.30 (6H, m, 2 × OCH$_2$CH_3), 1.51 (3H, s, NCHCCH_3), 1.92–1.93 (1H, m, C(3)H'), 1.98–2.03 (1H, m, C(4)H), 2.27–2.41 (2H, m, C(3)H, C(4)H'), 3.76–3.99 (2H, m, OCH_2CH$_3$), 4.03–4.33 (4H, m, 2 × OCH_2CH$_3$), 4.54 (1H, d, J 7.9, C(2)H), 5.42 (1H, d, J 7.4, C(5)H), 7.30–7.43 (3H, m, ArH), 7.46–7.53 (2H, m, ArH); δ_C (100 MHz, CDCl$_3$) 13.8, 13.9 (3 × OCH$_2$$CH_3$), 17.0 (NCHC$CH_3$), 27.2 ($C$(4)), 30.4 ($C$(3)), 52.1 ((NCH$CCH_3$), 60.1 ($C$(5)), 61.2, 61.3, 61.4 (3 × OCH$_2$CH$_3$), 63.6 (C(2)), 127.7, 128.2, 130.2 (ArC), 136.8 (quaternary ArC), 170.6, 171.1, 172.3, 173.1 (NCO, 3 × CO$_2$C$_2$H$_5$); m/z (ES$^+$) 442 (M + Na, 100%), 420 (M + H$^+$, 12%); HRMS (M + H$^+$) 420.2019, C$_{22}$H$_{30}$NO$_7$ requires 420.2022. δ_H (VT) (500 MHz, 373 K in d$_6$-DMSO) 0.96 (3H, t, J 7, OCH$_2$CH_3), 1.17 (3H, t, J 7, OCH$_2$CH_3), 1.24 (3H, t, J 7, OCH$_2$CH_3), 1.44 (3H, s, NCHCCH_3), 1.88–1.90 (1H, m, C(3)H'), 1.90–1.97 (1H, m, C(4)H), 2.15–2.23 (1H, m, C(4)H'), 2.30–2.41 (1H, m, C(3)H), 3.83 (2H, dq, J 7, 5, OCH_2CH$_3$), 4.04 (2H, dq, J 7, 5, OCH_2CH$_3$), 4.19 (2H, q, J 7, OCH_2CH$_3$), 4.58 (1H, dd, J 8.0, 1.5, C(2)H), 5.21 (1H, dd, J 9.0, 1.5, C(5)H), 7.39–7.44 (5H, m, C$_6$$H_5$).

N-Benzoyl-5-(1,1-di(ethoxycarbonyl)ethyl)-2-benzyl-pyrrolidine-2-carboxylic acid ethyl ester 14

To a 1.6 M solution of ^{n}BuLi in hexanes (0.30 ml, 0.45 mmol) in THF (3 ml) was added diisopropylamine (40 μl, 0.49 mmol), at 0 °C and stirred for 15 minutes. The temperature was lowered to −78 °C and *trans*-amide **12b** (0.16 g, 0.25 mmol) was added

This journal is © The Royal Society of Chemistry 2006

Org. Biomol. Chem., 2006, **4**, 2600–2615 | 2611

as a solution in THF (2 ml) and stirred for 30 minutes. Benzyl bromide (75 µl, 0.49 mmol) was added and the reaction mixture allowed to come to room temperature and stir for 4 hours. The reaction was quenched at 0 °C by adding saturated solution of NH$_4$Cl (1.5 ml) followed by addition of water and EtOAc. The EtOAc layer was separated, dried with MgSO$_4$ and evaporated. Silica gel chromatography ([petrol (40–60) : EtOAc 7 : 3] afforded the title compound **14** (0.050 g, 27%) as an inseparable mixture of *trans*- and *cis*-diastereomers in a ratio of 3 : 2 along with 41% recovery of starting material. R_f = 0.42 (3 : 2 petrol (40–60) : EtOAc); v_{max}/cm^{-1} (neat) 1736, 1669, 1602, 1479; m/z (ES$^+$) 532 (M + Na, 22%), 510 (M + H$^+$, 80%), 420 (100%); HRMS (M + H$^+$) 510.2499, C$_{29}$H$_{35}$NO$_7$ requires 510.2499.

δ_H (400 MHz, CDCl$_3$) (*trans*-diastereomer) 1.13–1.37 (9H, m, 3 × OCH$_2$CH_3), 1.77–1.79 (4H, m, C(4)H, NCHCCH_3), 2.09–2.15 (1H, m, C(4)H'), 2.42–2.44 (1H, m, C(3)H), 2.63–2.73 (C(3)H'), 3.13 (1H, br, CHHC$_6$H$_5$), 3.20 (1H, d, J 7.5, CHHC$_6$H$_5$), 4.08–4.17 (2H, m, OCH_2CH$_3$), 4.24–4.32 (4H, m, 2 × OCH_2CH$_3$), 6.66–6.7 (1H, m, C(5)H), 7.19–7.59 (8H, m, ArH), 7.79–7.86 (2H, m, NCOArH); δ_C (100 MHz, CDCl$_3$) 12.3 (NCHCCH$_3$), 13.7, 13.9, 14.6 (3 × OCH$_2$$CH_3$), 23.2 ($C$(4)), 31.0 ($C$(3)), 36.4 ($CH_2C_6H_5$), 60.7, 62.6, 62.7 (3 × OCH$_2$CH$_3$), 62.9 (C(5)), 66.4 (C(2)), 71.9 (NCHCCH$_3$), 127.1, 128.8, 131.9, 140.9, 139.1, 139.9 (ArC), 132.7, 137.1 (quaternary ArC), 166.1, 168.0, 171.1, 172.1 (NCO, 3 × COOC$_2$H$_5$).

δ_H (400 MHz, CDCl$_3$) (*cis*-diastereomer) 1.13–1.37 (9H, m, 3 × OCH$_2$CH_3), 1.77–1.79 (4H, m, NCHCCH_3), 2.42–2.44 (1H, m, C(4)H'), 2.57–2.61 (1H, m, C(3)H'), 2.63–2.73 (2H, m, C(3)H, CHHC$_6$H$_5$), 3.02 (1H, d, J 7.4, CHHC$_6$H$_5$), 4.08–4.17 (2H, m, OCH_2CH$_3$), 4.24–4.32 (4H, m, 2 × OCH_2CH$_3$), 5.83–5.85 (1H, m, C(5)H), 7.19–7.59 (8H, m, ArH), 7.79–7.86 (2H, m, NCOArH); δ_C (100 MHz, CDCl$_3$) 12.3 (NCHCCH$_3$), 13.8, 14.1, 14.6 (3 × OCH$_2$$CH_3$), 24.0 ($C$(4)), 31.6 ($C$(3)), 45.5 ($CH_2C_6H_5$), 60.4, 62.6, 62.7 (3 × OCH$_2$CH$_3$), 62.9 (C(5)), 66.4 (C(2)), 71.9 (NCHCCH$_3$), 127.1, 128.8, 131.9, 140.9, 139.1, 139.9 (ArC), 132.7, 137.1 (quaternary ArC), 166.0, 168.0, 170.7, 172.3 (NCO, 3 × CO$_2$C$_2$H$_5$).

(2*S*,5*S*)-*N*-Benzoyl-5-(di(ethoxycarbonyl)methyl)-2-methyl-pyrrolidine-2-carboxylic acid ethyl ester 15

Using LDA as a base. Diisopropylamine (0.19 ml, 1.4 mmol) was added as solution in THF (3 ml) to a 1.5 M solution of ^{n}BuLi in hexanes (0.84 ml, 1.3 mmol), at 0 °C and stirred for 15 minutes. Temperature was lowered to −78 °C and *trans*-**7b** (0.10 g, 0.25 mmol) was added as a solution in THF (4 ml) and the reaction was allowed to come to room temperature (2.5 hours). The temperature was again lowered to −78 °C and MeI (0.16 ml, 2.5 mmol) was added as a solution in THF (3 ml) and the reaction was allowed to come to room temperature and stir for 24 hours. At 0 °C, a saturated solution of NH$_4$Cl was added and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried with MgSO$_4$ and evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 3 : 2] afforded amide **15** (0.060 g, 54%) as a yellow oil. *cis*-Amide **7b** using the same procedure gave a lower yield (25%) of the *ent*-**15**. This yield was improved using the following procedure.

Using LTMP as a base. A solution of lithium tetramethylpiperidide (LTMP) was prepared by the addition of a solution

of ^{n}BuLi in hexanes (1.65 ml, 1.65 mmol, 1 M) to a solution of 2,2,6,6-tetramethylpiperidine (0.29 ml, 1.7 mmol) in THF at −78 °C. After 15 minutes, the reaction flask was transferred to an ice bath for 5 minutes, then was cooled to −78 °C. A solution of *cis*-**7b** (0.22 g, 0.55 mmol) in THF (3 ml) at −78 °C was then added to the cold solution of LTMP. After 30 minutes, the mixture was warmed to 0° for 5 minutes, then was cooled to −78 °C and MeI (0.14 ml, 2.2 mmols) was added. After 1 hour, the reaction mixture was warmed to 0 °C for 5 minutes and saturated solution NaHCO$_3$ (2 ml) and brine (2 ml) were added sequentially. The resulting mixture was extracted with EtOAc thoroughly, dried over MgSO$_4$, and evaporated. Silica gel chromatography ([petrol (40–60) : EtOAc 3 : 2] afforded the methylated amide *ent*-**15** (0.10 g, 40%). R_f = 0.43 (3 : 2 petrol (40–60) : EtOAc); product from *trans*-[α]$_D^{23}$ = −23 (c = 0.013, CHCl$_3$); product from *cis*-[α]$_D^{24}$ = +13 (c = 0.04, CHCl$_3$); v_{max}/cm^{-1} (neat) 1726, 1657; δ_H (400 MHz, CDCl$_3$) 1.14 (3H, br, OCH$_2$CH_3), 1.24–1.41 (6H, m, 2 × OCH$_2$CH_3), 1.77 (3H, br, C(2)CH_3), 1.94–2.04 (1H, m, C(3)H), 2.14–2.28 (2H, m, C(3)H', C(4)H'), 2.37 (1H, br, C(4)H), 3.32 (1H, br, NCHCH), 3.91–4.27 (6H, m, 3 × OCH_2CH$_3$), 4.79 (1H, br, C(5)H), 7.27–7.49 (5H, m, C$_6$H$_5$); δ_C (100 MHz, CDCl$_3$) 13.8, 13.9, 14.1 (3 × OCH$_2$$CH_3$), 23.1 (C(2)$CH_3$), 26.2 ($C$(4)), 36.7 ($C$(3)), 54.1 (N$CHC$H), 59.7 ($C$(5)), 61.4, 61.5, 61.6 (3 × OCH$_2$CH$_3$), 67.42 (C(2)), 125.3, 127.2, 129.9 (ArC), 136.9 (quaternary ArC), 166.7, 167.6, 170.2, 173.6 (NCO, 3 × COOC$_2$H$_5$); m/z (ES$^+$) 442 (M + Na, 100%), 420 (M + H$^+$, 45%); HRMS (M + H$^+$) 420.2023, C$_{22}$H$_{30}$NO$_7$ requires 420.2022. δ_H (VT) (500 MHz, 373 K in d^8-toluene) 0.91–0.94 (3H, m, OCH$_2$CH_3), 1.03–1.07 (6H, m 2 × OCH$_2$CH_3), 1.75 (3H, s, C(2)CH_3), 1.92–1.95 (1H, m, C(3)H), 2.03–2.05 (1H, m, C(3)H'), 2.24–2.26 (1H, m, C(4)H), 2.32–2.34 (1H, m, C(4)H'), 3.76 (1H, br, NCHCH), 3.77–3.87 (2H, m, OCH_2CH$_3$), 3.97–4.03 (4H, m, 2 × OCH_2CH$_3$), 4.96–5.0 (1H, m, C(5)H), 7.06–7.10 (3H, m, ArH), 7.43–7.45 (2H, m, ArH).

N-Benzoyl-5-(1,1-di(ethoxycarbonyl)ethyl)-2-methyl-pyrrolidine-2-carboxylic acid ethyl ester 16

A 1 M solution of LiHMDS (1.94 ml) in THF was added to a solution of *trans*-amide **7b** (0.26 g, 0.65 mmol) in THF (5 ml) at 0 °C and stirred for 15 minutes. Methyl iodide (0.16 ml, 2.6 mmol) was added and the reaction was allowed to come to room temperature and stir for 20 hours. The reaction was quenched at 0 °C by adding saturated solution of NH$_4$Cl, followed by addition of water and EtOAc. The organic layer was separated, washed with water and brine, dried with MgSO$_4$ and evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 7 : 3] afforded the doubly methylated amide **16** (0.014 g, 5%) as a mixture of inseparable diastereomers in a ratio of 1 : 3, along with amide **12b** (0.012 g, 4.0%) and recovered starting material **7b** (0.091 g, 35%). The stereochemistry of the two diastereomers of product **16** could not be established. R_f = 0.55 (3 : 2 petrol (40–60) : EtOAc); v_{max}/cm^{-1} (neat) 1725, 1642; δ_H (400 MHz, CDCl$_3$) 0.99–1.14 (9H, m, 3 × OCH$_2$CH_3 (minor diastereomer)), 1.23 (3H, t, J 7.2, OCH$_2$CH_3), 1.29 (3H, t, J 7.0, OCH$_2$CH_3), 1.34 (3H, t, J 7.2, OCH$_2$CH_3), 1.51 (3H, s, NCHCCH_3 or C(2)CH_3), 1.63 (3H, s, NCHCCH_3 or C(2)CH_3), 1.92–2.00 (2H, m, C(3)$H$$H$), 2.27–2.42 (2H, m, C(4)$H$$H$), 3.79–3.91 (6H, m, 3 × OCH_2CH$_3$ (minor diastereomer)), 4.09–4.23 (6H, m, 3 × OCH_2CH$_3$), 5.00 (1H, br, C(5)H (minor diastereomer)), 5.41 (1H, br, C(5)H), 7.35–7.46

(5H, m, C$_6$H$_5$); δ_C (100 MHz, CDCl$_3$ (major diastereomer) 13.8, 13.9, 14.1 (3 × OCH$_2$CH$_3$), 17.1 (NCHCCH$_3$), 25.1, 26.7 (C(4), C(3)), 29.7 (C(2)CH$_3$), 52.1 (NCHCCH$_3$), 57.5 (C(5)), 61.2, 61.3, 61.4 (3 × OCH$_2$CH$_3$), 68.4 (C(2)), 126.9, 127.7, 129.4 (ArC), 137.5 (quaternary ArC), 170.9, 171.1, 172.4, 174.3 (NCO, 3 × CO$_2$C$_2$H$_5$); m/z (ES$^+$) 456 (M + Na, 100%), 434 (M + H$^+$, 20%); HRMS (M + H$^+$) 434.2184, C$_{23}$H$_{32}$NO$_7$ requires 434.2179.

(2S,5R)-N-tert-Butoxycarbonylmethyl-5-(di(ethoxycarbonyl)-(ethyl)methyl)-pyrrolidine-2-carboxylic acid ethyl ester 17a

To NaH (0.016 g, 0.40 mmol) in dry CH$_2$Cl$_2$ (1 ml) at 0 °C was added amine **7d** (0.097 g, 0.23 mmol) as a solution in dry CH$_2$Cl$_2$ (2 ml) and the solution stirred for 15 minutes, followed by 2.5 hours of stirring at room temperature. Ethyl triflate (37 µl, 0.28 mmol) was added at 0 °C and the reaction allowed to come to room temperature and stir for 20 hours. The reaction was quenched with water at 0 °C and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$ and evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 4 : 1] afforded the ethylated amine **17a** as yellow oil (0.033 g, 32%) along with recovered starting material **7a** (0.028 g, 29%). R_f = 0.42 (4 : 1 petrol (40–60) : EtOAc); v_{max}/cm^{-1} (neat) 1733; δ_H (500 MHz, CDCl$_3$) 0.86 (3H, t, J 7.5, CCH$_2$CH$_3$), 1.18–1.27 (9H, m, 3 × OCH$_2$CH$_3$), 1.46 (9H, s, C(CH$_3$)$_3$), 1.92–2.17 (6H, m, C(3)H$_2$, C(4)H$_2$, CH$_2$CH$_3$), 3.50 (1H, d, J 18.6, NCHHCO), 3.62 (1H, d, J 18.6, NCHHCO), 3.74–3.77 (1H, m, C(2)H), 4.06–4.22 (7H, m, C(5)H, 3 × OCH$_2$CH$_3$); δ_C (100 MHz, CDCl$_3$) 9.5 (CCH$_2$CH$_3$), 14.0, 14.2 (3 × OCH$_2$CH$_3$), 26.3 (CCH$_2$CH$_3$), 27.8 ((C(3)), 28.3 (C(CH$_3$)$_3$), 28.6 (C(4)), 53.0 (NCH$_2$CO), 60.3, 60.7, 60.9 (3 × OCH$_2$CH$_3$), 62.4 (NCHCEt), 64.1 (C(2)), 65.6 (C(5)), 80.9 (C(CH$_3$)$_3$), 170.8, 171.1, 171.3, 174.0 (NCH$_2$CO, 3 × CO$_2$C$_2$H$_5$); m/z (ES$^+$) 466 (M + Na, 100%), 444 (M + H$^+$, 27%); **HRMS** (M + H$^+$) 444.2586, C$_{22}$H$_{38}$NO$_8$ requires 444.2597.

(2S,5R)-N-tert-Butoxycarbonylmethyl-5-(di(ethoxycarbonyl)-(benzyl)methyl)-pyrrolidine-2-carboxylic acid ethyl ester 17b

To NaH (0.02 g, 0.48 mmol) in dry DMF (2 ml) at 0 °C was added amine **7d** (0.10 g, 0.25 mmol) as a solution in dry DMF (2 ml) and the solution stirred for 15 minutes. Dry benzyl bromide (58 µl, 0.48 mmol) was added at 0 °C and stirred for 5 minutes followed by room temperature stirring for 24 hours. The reaction was quenched with saturated solution of NH$_4$Cl at 0 °C and extracted with CH$_2$Cl$_2$. The organic layer was washed with water and brine, dried over MgSO$_4$ and evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 4 : 1] afforded the benzylated amine **17b** as transparent oil (0.044 g, 36%). R_f = 0.77 (7 : 3 petrol (40–60) : EtOAc); v_{max}/cm^{-1} (neat) 1732, 1604; δ_H (500 MHz, C$_6$D$_6$) 0.78–0.84 (6H, m, 2 × OCH$_2$CH$_3$), 0.93 (3H, t, J 7.0, OCH$_2$CH$_3$), 1.32 (3H, s, C(CH$_3$)$_3$), 1.38 (6H, s, C(CH$_3$)$_3$), 2.18–2.31 (3H, m, C(3)H$_2$, C(4)H), 2.34–2.39 (1H, m, C(4)H'), 3.21 (1H, d, J 13.7, CHHC$_6$H$_5$), 3.65 (1H, d, J 13.7, CHHC$_6$H$_5$), 3.83 (1H, d, J 18.7, NCHHCO), 3.84–3.93 (4H, m, 2 × OCH$_2$CH$_3$), 4.0–4.03 (3H, m, C(2)H, OCH$_2$CH$_3$), 4.10 (1H, d, J 18.7, NCHHCO), 4.63 (1H, t, J 6.6, C(5)H), 7.0–7.35 (5H, m, C$_6$H$_5$); δ_C (100 MHz, C$_6$D$_6$) 13.9, 14.0, 14.1 (3 × OCH$_2$CH$_3$), 28.2 (C(CH$_3$)$_3$), 28.4, 29.3 (C(3), C(4)), 39.7 (CH$_2$C$_6$H$_5$), 53.5 (NCH$_2$CO), 60.4, 61.1, 61.2 (3 × OCH$_2$CH$_3$), 64.5 (NCHCBn), 66.4 (C(2)), 66.6 (C(5), 80.6

(C(CH$_3$)$_3$), 126.8, 128.5, 130.7 (ArC), 138.4 (quaternary ArC), 168.9, 170.6, 171.1, 173.4 (NCH$_2$CO, 3 × CO$_2$C$_2$H$_5$); m/z (ES$^+$) 528 (M + Na, 100%), 506 (M + H$^+$, 13%); HRMS (M + H$^+$) 528.2562, C$_{27}$H$_{39}$NO$_8$Na requires 528.2573.

(S)-Diethyl 2-(2-((tert-butyldiphenylsilyloxy)methyl)pyrrolidin-5-ylidene)malonate 18

To a solution of alcohol **4b** (0.87 g, 3.4 mmol) in dry CH$_2$Cl$_2$ (6 ml) was added dry triethylamine (0.56 ml, 4.0 mmol), tert-butyldiphenylsilyl chloride (2.03 g, 7.41 mmol) as a solution in dry CH$_2$Cl$_2$ (2 ml), and (dimethylamino)pyridine (0.020 g, 0.15 mmol) as a solution in dry CH$_2$Cl$_2$ (2 ml) and the mixture was stirred for 48 hours. Water and CH$_2$Cl$_2$ were added and CH$_2$Cl$_2$ layer was washed with saturated solution of NH$_4$Cl, water and brine, dried with MgSO$_4$, and the solvent evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 4 : 1] afforded the protected alcohol **18** (1.5 g, 92%) as transparent oil. R_f = 0.76 (3 : 2 petrol (40–60) : EtOAc); $[a]_D^{21}$ = −27.5 (c = 1.24, CHCl$_3$); v_{max}/cm^{-1} (neat) 3357, 3020, 1681, 1643, 1565; δ_H (500 MHz, CDCl$_3$) 1.06 (9H, s, C(CH$_3$)$_3$), 1.28–1.34 (6H, m 2 × OCH$_2$CH$_3$), 1.74–1.79 (1H, m, C(3)HH), 2.05–2.10 (1H, m, C(3)HH), 3.09–3.17 (2H, m, C(4)H$_2$), 3.55 (1H, dd, J 10.4, 6.4, CHHOTBDPS), 3.64 (1H, dd, J 10.4, 4.4, CHHOTBDPS), 4.00–4.04 (1H, m, C(2)H), 4.20 (2H, q, J 7.1, OCH$_2$CH$_3$), 4.23–4.25 (2H, m, OCH$_2$CH$_3$), 7.38–7.45 (6H, m, 2(rings) × 3ArCH), 7.64–7.65 (4H, m, 2(rings) × 2ArCH), 9.73 (1H, s, NH); δ_C (125 MHz, CDCl$_3$) 14.3 (2 × OCH$_2$CH$_3$), 19.0 (C(CH$_3$)$_3$), 23.7 (C(3)), 26.6 (C(CH$_3$)$_3$), 33.8 (C(4)), 59.4, 59.5 (2 × OCH$_2$CH$_3$), 61.2 (C(2)), 66.5 (CHHOTBDPS), 87.2 (NCC), 127.7 (2(rings) × 2ArC), 129.7 (2 (rings) × 1ArC), 132.8 (2 (rings) × 1quaternary ArC), 135.4 (2(rings) × 2ArC), 167.7, 169.6, 172.3 (C(5), 2 × CO$_2$C$_2$H$_5$); m/z (ES$^+$) 518 (M + Na, 35%), 496 (M + H$^+$, 100%), 450 (32%); HRMS (M + H$^+$) 496.2511, C$_{28}$H$_{38}$NO$_5$Si requires 496.2519.

(S)-Diethyl 2-(2-(methoxymethyl)pyrrolidin-5-ylidene)malonate 19

Alcohol **4b** (0.31 g, 1.2 mmol) was dissolved in dry CH$_2$Cl$_2$ (2 ml) and added to a solution of 2,6-di-tert-butyl-4-methylpyridine (0.75 g, 3.7 mmol) in dry CH$_2$Cl$_2$ (3 ml) at room temperature. The solution was cooled to 0 °C and methyl triflate (0.41 ml, 3.7 mmol) was added. After being stirred at room temperature for 20 hours, the mixture was poured into saturated solution of NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$, and evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 3 : 2] gave methyl ether **19** (0.17 g, 52%) as yellow liquid. R_f = 0.51 (2 : 3 petrol (40–60) : EtOAc); v_{max}/cm^{-1} (neat) 3309, 1643, 1247; δ_H (400 MHz, CDCl$_3$) 1.24 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.25 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.61–1.68 (1H, m, C(3)HH), 2.03–2.11 (1H, m, C(3)HH), 2.97–3.06 (1H, m, C(4)HH), 3.10–3.18 (1H, m, C(4)HH), 3.23 (1H, dd, J 9.4, 7.7, CHHOMe), 3.32 (3H, s, OCH$_3$), 3.40 (1H, dd, J 9.4, 4.1, CHHOMe), 3.98–4.01 (1H, m, C(2)H), 4.12 (2H, q, J 7.1, OCH$_2$CH$_3$), 4.16 (2H, q, J 7.1, OCH$_2$CH$_3$), 9.56 (1H, br, NH); δ_C (100 MHz, CDCl$_3$) 14.3 (2 × OCH$_2$CH$_3$), 24.0 (C(3)), 33.6 (C(4)), 59.1 (C(2)), 59.5 (CH$_2$OCH$_3$), 59.5, 59.7 (2 × OCH$_2$CH$_3$), 75.4 (CH$_2$OMe), 87.3 (NCC), 167.7, 169.6, 172.4 (C(5), 2 × COOC$_2$H$_5$); m/z (ES$^+$) 294 (M + Na, 100%), 272 (M + H$^+$, 2%),

226 (96%); HRMS (M + Na) 294.1317, $C_{13}H_{21}NO_5Na$ requires 294.1317.

(S)-Diethyl 2-(2-(acetoxymethyl)pyrrolidin-5-ylidene)malonate 20

Acetic anhydride (4.60 ml, 48.5 mmol) was added to a solution of alcohol **4b** (1.25 g, 4.85 mmol) in dry pyridine (4.50 ml, 54.3 mmol) and the reaction was allowed to stir for 1.5 h at room temperature. Glacial acetic acid was then added to the mixture with cooling in an ice bath until pH 5.0 was reached and stirred for 1 h. The mixture was partitioned between CH_2Cl_2 and water. The organic layer was washed with saturated solution of $NaHCO_3$, water and brine, dried with $MgSO_4$ and evaporated to give the acetate **20** (1.45 g, 100%). $R_f = 0.44$ (1 : 1 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 3306, 1745, 1688, 1646, 1570; δ_H (400 MHz, CDCl$_3$) 1.21 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.27 (3H, t, J 7.1, OCH$_2$CH$_3$), 1.66–1.75 (1H, m, C(3)HH), 2.06 (3H, s, OCOCH$_3$), 2.10–2.19 (1H, m, C(3)HH), 3.01–3.20 (2H, m, C(4)H$_2$), 3.87 (1H, dd, J 11.2, 7.5, CHHOAc), 4.05–4.09 (1H, m, C(2)H), 4.11–4.22 (5H, m, CHHOAc, 2 × OCH$_2$CH$_3$), 9.58 (1H, br, NH); δ_C (100 MHz, CDCl$_3$) 14.3 (2 × OCH$_2$CH$_3$), 20.7 (OCOCH$_3$), 24.2 (C(3)), 33.3 (C(4)), 58.4 (C(2)), 59.7 (2 × OCH$_2$CH$_3$), 66.4 (CH$_2$OAc), 87.9 (NCC), 167.6, 169.6, 170.7, 172.3 (C(5), OCOCH$_3$, 2 × CO$_2$C$_2$H$_5$); m/z (ES$^+$) 300 (M + H$^+$, 25%), 254 (100%); HRMS (M + H$^+$) 300.1439, $C_{14}H_{22}NO_6$ requires 300.1447.

(S)-Diethyl 2-(N-benzoyl-2-(methoxymethyl)pyrrolidin-5-yl)malonate 21

The enamine **19** (0.11 g, 0.39 mmol) was dissolved in HOAc (7.5 ml) to which was added Adams' catalyst (0.050 g) in TFA (2.5 ml). The hydrogenation apparatus was flushed 3 times with hydrogen, and finally set to a pressure of 4.5 atm and the mixture stirred for 48 hours. Careful filtration through Celite® using EtOAc, followed by solvent removal, gave a residue which was dissolved in CH_2Cl_2 (50 ml) and washed with dilute aqueous ammonia (3.2%) (50 ml), water and brine. The solution was dried over $MgSO_4$ and the solvent removed to give crude amine (0.096 g) as an inseparable *cis*- : *trans*-mixture. Dry benzoyl chloride (3.20 ml, 27.4 mmol) was added to a solution of this amine (0.096 g, 0.35 mmol) in dry pyridine (0.32 ml, 3.9 mmol) and the reaction was allowed to stir for 3 hours at room temperature. The reaction was quenched and neutralised at 0 °C with 2 M HCl and stirred for 1 hour. Dichloromethane (50 ml) was added and the organic layer was washed with water and brine. It was dried with $MgSO_4$ and evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 3 : 2] afforded the amide **21** (0.11 g, 77%, over 2 steps) as an inseparable mixture of *cis*- and *trans*-diastereomers, in a ratio of 2 : 1. $R_f = 0.5$ (3 : 2 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 1728, 1632, 1260; m/z (ES$^+$) 400 (M + Na, 100%), 378 (M + H$^+$, 37%), 218 (15%); δ_H (400 MHz, C$_6$D$_6$) *cis*-diastereomer, 0.83–0.97 (6H, m 2 × OCH$_2$CH$_3$), 1.30–1.47 (1H, m, C(3)HH′), 1.68–1.72 (1H, m, C(3)HH′), 2.08–2.14 (1H, m, C(4)H′), 2.16–2.24 (1H, m, C(4)HH′), 2.91 (3H, s, OCH$_3$), 3.23–3.25 (1H, br. m, CH$_2$OMe), 3.85 (1H, br, C(2)H), 3.89–4.09 (4H, m, 2 × OCH$_2$CH$_3$), 4.45 (1H, br, NCHCH), 5.12 (1H, q, J 7.5, C(5)H), 7.01–7.09 (3H, m, ArH), 7.41–7.46 (2H, br. m, ArH); δ_C (100 MHz, C$_6$D$_6$) 14.1, 14.2 (2 × OCH$_2$CH$_3$), 26.2 (C(4)), 27.7 (C(3)), 55.5 (NCHCH), 57.8 (C(5)), 58.7 (C(2), CH$_2$OCH$_3$), 61.3, 61.7 (2 × OCH$_2$CH$_3$),

74.5 (CH$_2$OMe), 127.1, 128.6, 129.6 (ArC), 138.6 (quaternary ArC), 167.9, 168.4, 170.4 (NCOPh, 2 × CO$_2$C$_2$H$_5$). δ_H (400 MHz, C$_6$D$_6$) *trans*-diastereomer, 0.83–0.97 (6H, m 2 × OCH$_2$CH$_3$), 1.68–1.72 (1H, m, C(3)HH′), 1.94–2.06 (1H, m, C(3)HH′), 2.16–2.24 (1H, m, C(4)H′), 2.25–2.39 (1H, m, C(4)HH′), 2.70 (5H, br, OCH$_3$, CH$_2$OMe), 3.89–4.09 (5H, m, C(2)H, 2 × OCH$_2$CH$_3$), 4.87 (1H, br, NCHCH), 5.22 (1H, br, C(5)H), 7.01–7.09 (3H, m, ArH), 7.61–7.62 (2H, br, ArH); δ_C (100 MHz, C$_6$D$_6$) 14.1 (2 × OCH$_2$CH$_3$), 26.2 (C(4)), 27.8 (C(3)), 52.5 (NCHCH), 57.5 (C(5)), 59.7 (C(2), CH$_2$OCH$_3$), 61.4 (2 × OCH$_2$CH$_3$), 73.9 (CH$_2$OMe), 127.8, 128.6, 130.0 (ArC), 138.9 (quaternary ArC), 167.5, 168.6, 170.9 (NCOPh, 2 × CO$_2$C$_2$H$_5$); HRMS (M + H$^+$) 378.1922, $C_{20}H_{28}NO_6$ requires 378.1917.

(2S,5S)-N-Diethyl-2-(N-acetyl-2-(trityloxymethyl)pyrrolidine-5-yl)malonate 22b

The enamine **20** (1.16 g, 3.88 mmol) was dissolved in HOAc (7.5 ml) to which was added Adams' catalyst (0.164 g) in TFA (2.5 ml). The hydrogenation apparatus was flushed 3 times with hydrogen, and finally set to a pressure of 4.5 atm and the mixture stirred for 72 hours. Careful filtration through Celite® using EtOAc, followed by solvent removal, gave a residue which was dissolved in CH_2Cl_2 (50 ml) and washed with dilute aqueous ammonia (3.2%) (50 ml), water and brine. The solution was dried over $MgSO_4$ and the solvent removed to give crude amine **22a** (1.05 g) as an inseparable *cis*- : *trans*-mixture. This mixture of amine **22a** (0.090 g, 0.33 mmol) was dissolved in dry CH_2Cl_2 (2 ml) and added to a solution of triphenylmethyl chloride (0.10 g, 0.36 mmol) in dry CH_2Cl_2 (1 ml), followed by addition of (dimethylamino)pyridine (0.01 g, 0.09 mmol) as a solution in dry CH_2Cl_2 (1 ml) and dry triethyl amine (0.06 ml, 0.6 mmol), and the mixture was stirred for 24 hours. The mixture was poured into ice–water and extracted with CH_2Cl_2. The organic layer was washed with saturated solution of NH_4Cl, water and brine, dried with $MgSO_4$, and evaporated. Silica gel chromatography ([petrol (40–60) : EtOAc 4 : 1 then petrol (40–60) : EtOAc 3 : 2]) afforded the amide **22b** (0.050 g, 59%, over 2 steps) as white crystals. Mp 148–150 °C; $R_f = 0.38$ (3 : 2 petrol (40–60) : EtOAc); $[a]_D^{25} = -12.9$ ($c = 0.03$, CHCl$_3$); ν_{max}/cm^{-1} (neat) 1728, 1642; δ_H (400 MHz, CDCl$_3$) 1.22–1.29 (6H, m 2 × OCH$_2$CH$_3$), 1.88 (3H, s, NCOCH$_3$), 1.92–2.05 (2H, m, C(3)H$_2$), 2.06–2.18 (2H, m, C(4)H$_2$), 3.05 (1H, dd, J 9.4, 8.2, CHHO(Ph)$_3$), 3.13 (1H, dd, J 9.4, 4.0, CHH(Ph)$_3$), 3.90–3.96 (1H, m, C(2)H), 4.11–4.23 (4H, m, 2 × OCH$_2$CH$_3$), 4.49–4.53 (1H, m, C(5)H), 4.56 (1H, d, J 4.2, NCHCH), 7.23–7.33 (9H, m, 3(rings) × 3ArCH), 7.36–7.43 (6H, m, 3(rings) × 2ArCH); δ_C (100 MHz, CDCl$_3$) 14.0, 14.1 (2 × OCH$_2$CH$_3$), 22.7 (NCOCH$_3$), 25.7 (C(4)), 27.2 (C(3)), 50.4 (NCHCH), 56.76 (C(5)), 59.2 (C(2)), 61.2 (2 × OCH$_2$CH$_3$), 64.4 (CH$_2$OC(Ph)$_3$), 87.1 (OC(Ph)$_3$), 127.2 (3(rings) × 1ArC), 127.9 (3(rings) × 2ArC), 128.5 (3(rings) × 2ArC), 143.6 (3(rings) × 1 quaternary ArC), 168.2, 168.6, 170.0 (NCOCH$_3$, 2 × CO$_2$C$_2$H$_5$); m/z (ES$^+$) 566 (M + Na, 72%), 544 (M + H$^+$, 100%); HRMS (M + H$^+$) 544.2700, $C_{33}H_{38}NO_6$ requires 544.2699.

N-Benzoyl-2-(acetoxymethyl)-5-(di(ethoxycarbonyl)methyl)-pyrrolidine-2-methyl acetate 22c

The enamine **20** (1.17 g, 3.89 mmol) was dissolved in HOAc (7.5 ml) to which was added Adams' catalyst (0.164 g) in TFA

(2.5 ml). The hydrogenation apparatus was flushed 3 times with hydrogen, and finally set to a pressure of 3 atm and the mixture stirred for 72 hours. Careful filtration through Celite® using EtOAc, followed by solvent removal, gave a residue which was dissolved in CH_2Cl_2 (50 ml) and washed with dilute aq. ammonia (3.2%) (50 ml), water and brine. The solution was dried over $MgSO_4$ and the solvent removed to give the amine as white liquid. Dry benzoyl chloride (0.50 ml, 4.2 mmol) was added to a solution of amine (0.123 g, 0.42 mmol) in dry pyridine (0.40 ml, 4.7 mmol) and the reaction was allowed to stir for 24 hours at room temperature. Glacial acetic acid was then added to the mixture with cooling in an ice bath until pH 5.0 was reached and stirred for 1 hour. The mixture was partitioned between CH_2Cl_2 and water. CH_2Cl_2 layer was washed with saturated solution of $NaHCO_3$, water and brine, dried with $MgSO_4$, and the solvent evaporated. Silica gel chromatography [petrol (40–60) : EtOAc 1 : 1] resulted in an inseparable mixture of amide diastereomers **22c** (0.12 g, 82% over 2 steps) in a ratio of 5 : 2. R_f = 0.41 (1 : 1 petrol (40–60) : EtOAc); ν_{max}/cm^{-1} (neat) 1745, 1636, 1578; m/z (ES$^+$) 428 (M + Na, 69%), 406 (M + H$^+$, 100%); δ_H (400 MHz, CDCl$_3$) Major-diastereomer, 1.25–1.33 (6H, m 2 × OCH$_2$CH_3), 1.78–1.90 (1H, m, C(3)HH'), 1.99 (3H, s, CO$_2$CH_3), 2.04–2.20 (1H, m, C(4)HH), 2.26–2.30 (1H, m, C(3)HH'), 2.33–2.40 (1H, m, C(4)HH), 3.90–3.95 (1H, m, CHHOAc), 3.99–4.02 (2H, m, CHHOAc, C(2)H), 4.11–4.31 (5H, m, NCHCH, 2 × OCH_2CH$_3$), 4.78–4.85 (1H, m, C(5)H), 7.37–7.62 (5H, m, C$_6$$H_5$); δ_C (100 MHz, CDCl$_3$) 13.9 (2 × OCH$_2$$CH_3$), 20.7 (CO$_2$$CH_3$), 26.7 ($C$(3)), 27.1 ($C$(4)), 54.1 (NCH$C$H), 57.5 ($C$(5)), 58.4 ($C$(2)), 61.4, 61.5 (2 × O$CH_2CH_3$), 64.4 ($CH_2$OAc), 126.2, 128.6, 129.7 (ArC), 138.8 (quaternary ArC), 167.9, 167.8, 170.4, 171.9 (NCOPh, 2 × CO$_2$C$_2$H$_5$, CO$_2$CH$_3$). δ_H (400 MHz, CDCl$_3$) Minor-diastereomer, 1.25–1.33 (6H, m 2 × OCH$_2$CH_3), 1.78–1.90 (1H, m, C(3)HH'), 1.99 (3H, s, CO$_2$CH_3), 2.04–2.20 (2H, m, C(3)HH', C(4)HH), 2.26–2.30 (1H, m, C(4)HH), 3.65–3.72 (1H, m, CH_2OAc), 4.11–4.31 (5H, m, C(2)H, 2 × OCH_2CH$_3$), 4.51 (1H, br, NCHCH), 4.78–4.85 (1H, m, C(5)H), 7.37–7.62 (5H, m, C$_6$$H_5$); δ_C (100 MHz, CDCl$_3$) 14.0 (2 × OCH$_2$$CH_3$), 20.7 (CO$_2$$CH_3$), 25.7 ($C$(4)), 27.5 ($C$(3)), 51.3 (NCH$C$H), 56.8 ($C$(5)), 58.4 ($C$(2)), 61.4, 61.5 (2 × O$CH_2CH_3$), 64.9 ($CH_2$OAc), 126.8, 128.5, 130.0 (ArC), 137.0 (quaternary ArC), 167.9, 167.8, 170.4, 171.9 (NCOPh, 2 × CO$_2$C$_2$H$_5$, CO$_2$CH$_3$).

Acknowledgements

References

1 H. He, B. Shen and G. T. Carter, *Tetrahedron Lett.*, 2000, **41**, 2067–2071.
2 H. Watanabe, M. Okue, H. Kobayashi and T. Kitahara, *Tetrahedron Lett.*, 2002, **43**, 861–864.
3 D. A. DeGoey, H.-J. Chen, W. J. Flosi, D. J. Grampovnik, C. M. Yeung, L. L. Klein and D. L. Kempf, *J. Org. Chem.*, 2002, **67**, 5445–5453.
4 S. Hanessian, M. Bayrakdarian and X. Luo, *J. Am. Chem. Soc.*, 2002, **124**, 4716–4721.
5 G. T. Wang, Y. W. Chen, S. Wang, R. Gentles, T. Sowin, W. Kati, S. Muchmore, V. Giranda, K. Stewart, H. Sham, D. Kempf and W. G. Laver, *J. Med. Chem.*, 2001, **44**, 1192–1201.
6 N. Valls, M. Vallribera, S. Carmelli and J. Bonjoch, *Org. Lett.*, 2003, **5**, 447–450.
7 P. W. H. Chan, I. F. Cottrell and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3007–3012.
8 E. L. Bentz, R. Goswami, M. G. Moloney and S. M. Westaway, *Org. Biomol. Chem.*, 2005, **3**, 2872–2882.
9 C. Najera and M. Yus, *Tetrahedron: Asymmetry*, 1999, **10**, 2245–2303.
10 F. J. Sardina and H. Rapoport, *Chem. Rev.*, 1996, **96**, 1825–1869.
11 M. Pichon and B. Figadere, *Tetrahedron*, 1996, **7**, 927–964.
12 K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer and C. Chen, *J. Am. Chem. Soc.*, 2006, **128**, 3538–3539.
13 J. Eustache, P. V. d. Weghe, D. L. Nouen, H. Uyehara, C. Kabuto and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 4043–4053.
14 M. C. Elliot and S. V. Wordingham, *Synlett*, 2006, 1162–1170.
15 K. Shiosaki, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 2, pp. 865–892.
16 R. Lin, J. Castells and H. Rapoport, *J. Org. Chem.*, 1998, **63**, 4069–4078.
17 D. E. Davies, P. M. Doyle, R. D. Farrant, R. D. Hill, P. B. Hitchcock, P. N. Sanderson and D. W. Young, *Tetrahedron Lett.*, 2003, **44**, 8887–8891.
18 M. C. Elliott and M. S. Long, *Tetrahedron Lett.*, 2002, **43**, 9191–9194.
19 T. Honda and M. Kimura, *Org. Lett.*, 2000, **2**, 3925–3927.
20 G. V. Thanh, J.-P. Celerier, A. Fleurant, C. Grandjean, S. Rosset and G. Lhommet, *Heterocycles*, 1996, **43**, 1381–1384.
21 A.-Z. A. Elassar and A. A. El-Khair, *Tetrahedron*, 2003, **59**, 8463–8480.
22 E. Kleinpeter and A. Schulenburg, *Tetrahedron Lett.*, 2005, **46**, 5995–5997.
23 S. R. Hussaini and M. G. Moloney, *Org. Biomol. Chem.*, 2003, **1**, 1838–1841.
24 S. R. Hussaini and M. G. Moloney, *Tetrahedron Lett.*, 2004, **45**, 1125–1127.
25 M. J. Beard, J. H. Bailey, D. T. Cherry, M. G. Moloney, S. B. Shim, K. Statham, M. Bamford and R. B. Lamont, *Tetrahedron*, 1996, **52**, 3719–3740 and corrigenda 1997, **53**, 1177.
26 M. D. Bachi, R. Breiman and H. Meshulam, *J. Org. Chem.*, 1983, **48**, 1439–1444.
27 J. S. Petersen, G. Fels and H. Rapoport, *J. Am. Chem. Soc.*, 1984, **106**, 4539–4547.
28 A. V. R. Rao, M. K. Gurjar and J. Vasudevan, *J. Chem. Soc., Chem. Commun.*, 1995, 1369.
29 J. H. Bailey, D. Cherry, J. Dyer, M. G. Moloney, M. J. Bamford, S. Keeling and R. B. Lamont, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2783–2792.
30 J. Dyer, S. Keeling, A. King and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2793–2804.
31 E. Vazquez, A. Galindo, D. Gnecco, S. Bernes, J. L. Teran and R. G. Enriquez, *Tetrahedron: Asymmetry*, 2001, **12**, 3209–3211.
32 D. Seebach, J. D. Aebi, M. G. Coquaz and R. Naef, *Helv. Chim. Acta*, 1987, **70**, 1194–1216.
33 D. Seebach and J. D. Aebi, *Tetrahedron Lett.*, 1984, **25**, 2545–2548.
34 D. Seebach and A. Fadel, *Helv. Chim. Acta*, 1985, **68**, 1243.
35 A. Jeanguenat and D. Seebach, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2291–2298 and references therein.
36 S. E. Denmark and H. Matsuhashi, *J. Org. Chem.*, 2002, **67**, 3479–3486.
37 N. K. Minami, J. E. Reiner and J. E. Semple, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2625–2628.
38 M. C. Elliott and M. S. Long, *Org. Biomol. Chem.*, 2004, **2**, 2003–2011.
39 F. Busque, P. de March, M. Figueredo, J. Font, T. Gallagher and S. Milan, *Tetrahedron: Asymmetry*, 2002, **13**, 437–445.
40 K. Steinbeck and B. Osterwinter, *Tetrahedron Lett.*, 1979, **20**, 861–862.
41 B. Rigo, E. G. Samira, P. Gautret and D. Couterier, *Synth. Commun.*, 1994, **24**, 2597–2607.
42 T. P. Andersen, P. B. Rasmussen, I. Thomsen, S.-O. Lawesson, P. Jorgensen and P. Lindhardt, *Liebigs Ann. Chem.*, 1986, 269–279.
43 D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746–749.