ARTICLE

OBC
www.rsc.org/obc

Manganese(III) acetate-mediated alkylation of β-keto esters and β-keto amides: an enantio- and diastereo-selective approach to substituted pyrrolidinones

Gregory Bar, Andrew F. Parsons* and C. Barry Thomas
Department of Chemistry, University of York, Heslington, York, UK YO10 5DD.
E-mail: afp2@york.ac.uk; Fax: +44(01904)432516

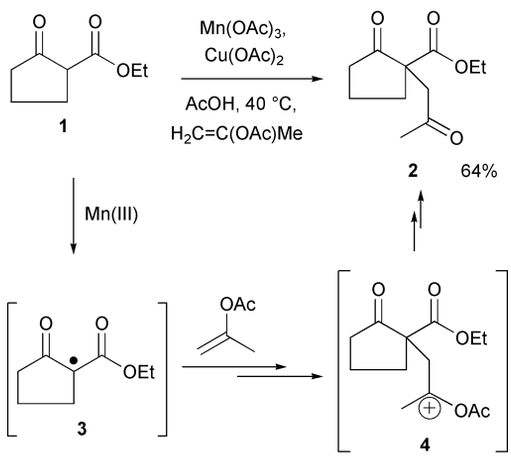
Received 18th September 2002, Accepted 7th October 2002
First published as an Advance Article on the web 13th December 2002

β-Keto esters and β-keto amides can be efficiently alkylated on reaction with enol ethers and manganese(III) acetate in the presence of copper(II) acetate. These intermolecular radical addition reactions can be used to construct quaternary carbon centres in excellent yield and this method has been utilised in a diastereoselective approach to substituted pyrrolidinones.

Introduction

A variety of organic carbonyl compounds can be oxidised by manganese(III) acetate to form carbon-centred radicals.[1–4] This includes 1,3-dicarbonyl compounds such as β-keto amides and particularly, β-keto esters. Reaction with manganese(III) acetate produces (electrophilic) α-carbonyl radicals, which can add to a number of electron-rich double bonds to form new carbon–carbon bonds. In contrast to related tributyltin hydride-mediated reactions, the resulting radical adducts are usually oxidised by a second equivalent of manganese(III) acetate or an alternative co-oxidant, principally copper(II) acetate. This can lead to the formation of alkylcopper(III) intermediates, which can produce alkenes by oxidative elimination, or alternatively, carbocation intermediates can be formed and these can undergo a number of ionic reactions including deprotonation and hydrolysis. Thus, one particularly attractive feature of this oxidative method of radical generation is that versatile functional groups (*e.g.* alkenes or alcohols) can be introduced into the product after carbon–carbon bond formation.

Manganese(III) acetate has been widely exploited in cyclisation reactions[1,5] and a good number of intermolecular carbon–carbon bond forming reactions have been reported. Hence, a range of 1,3-dicarbonyls have been shown to add to electron-rich alkenes,[6–13] alkynes[14] and also enol ethers and esters.[15–17] These types of reactions have employed 1,3-dicarbonyls without substitution at the α-position except for an isolated report by Corey and Ghosh.[18] This work showed that ethyl 2-oxocyclopentanecarboxylate **1** (and also ethyl 2-oxocyclohexanecarboxylate) can be alkylated at the α-position on heating with isopropenyl acetate and manganese(III) acetate in acetic acid (Scheme 1). This gave diketone **2** in 64% yield, presumably *via* regioselective addition of radical **3** to the enol ester, followed by oxidation and hydrolysis of the intermediate oxonium ion **4**. With a view to developing a general approach to sterically congested tricarbonyls we now report our studies on the development of this methodology using a range of β-keto esters and β-keto amides, including chiral pyrrolidinones.[19]



Scheme 1

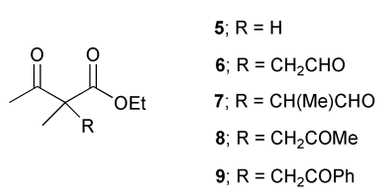


Fig. 1

Results and discussion

Our studies began by exploring the reaction of ethyl 2-methylacetoacetate **5** (1 equiv.) with butyl vinyl ether (6 equiv.) in the presence of manganese(III) acetate (2.3 equiv.) and copper(II) acetate (0.3 equiv.). On heating overnight at 40 °C in CH_2Cl_2, this produced the expected aldehyde **6** in an excellent 92% yield after (silica) column chromatography (Fig. 1). When the same reaction was carried out in glacial acetic acid (at 60 °C for 2–4 h) the yield was only 70–76% and so all subsequent reactions were carried out in CH_2Cl_2. Keto-ester **5** was also reacted with allyl vinyl ether or vinyl acetate in place of butyl vinyl ether. In both cases, these reactions also produced aldehyde **6** in good yield (83–86%). Different enol ethers can be employed and reaction of **5** with ethyl (*E*,*Z*)-prop-1-enyl ether, 2-methoxypropene or trimethyl(1-phenylvinyloxy)silane gave aldehyde **7** and ketones **8** and **9**, in 86%, 81% and 97% yields, respectively. Aldehyde **7** was formed as a 1.3 : 1 mixture of diastereoisomers as indicated by the ^{1}H NMR spectrum.

Our investigations then turned to the use of alternative β-keto esters (Fig. 2). Treatment of the cyclopentanone **1**, the cyclooctanone **10** and the cyclopentenone **11** with butyl vinyl ether or ethyl (*E*,*Z*)-propen-1-yl ether in the presence of manganese(III) acetate and copper(II) acetate gave the expected aldehydes **12**, **13** and **14** in 90%, 95% and 85% yield, respectively. In some cases, acetal rather than aldehyde products were isolated after column chromatography as illustrated by the formation of acetals **17** (93%) and **18** (88%) from esters **15** and **16**, respectively. These acetals can subsequently be hydrolysed to the corresponding aldehydes on stirring overnight with silica in dichloromethane containing a small amount of water.

DOI: 10.1039/b209123b

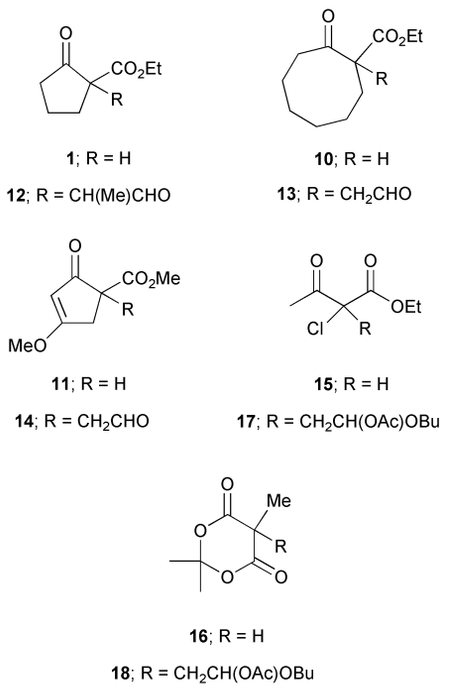
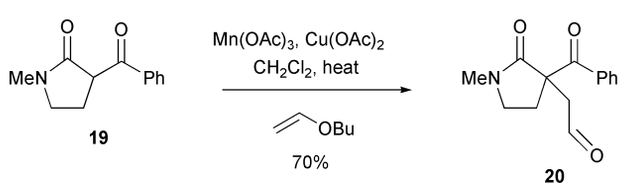


Fig. 2

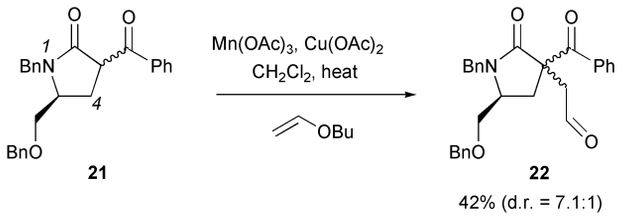
Following on from the alkylation of achiral β-keto esters, we then directed our attention to applying this methodology to the enantio- and diastereoselective formation of quaternary carbon centres.[20] Of particular interest was the formation of substituted pyrrolidinones and pyrrolidines. These compounds have attracted considerable interest because of their use as synthetic intermediates, chiral auxiliaries and ligands as well as the fact that a large number of these compounds exhibit a variety of biological activities.[21] For example, Moloney and co-workers have prepared a range of functionalised pyrrolidinones, from pyroglutamic acid, using ionic alkylation reactions.[22] These type of reactions can however, lead to poly-alkylation, *O*- rather than *C*-alkylation and, in some cases, racemisation of base-sensitive chiral centres. The formation of hindered quaternary centres can also be problematic because of steric effects. In contrast, manganese(III) acetate-mediated radical alkylations offer the potential for regioselective alkylation of pyrrolidinones, leading to the introduction of functionalised side chains at quaternary centres, under non-basic conditions.

Our initial studies involved the alkylation of 3-benzoyl-1-methylpyrrolidin-2-one **19** (Scheme 2), which was prepared in



Scheme 2

50% yield by deprotonation (using LiHMDS at −78 °C) and acylation of 1-methylpyrrolidin-2-one using benzoyl chloride. On reaction of **19** with butyl vinyl ether (5 equiv.) in the presence of manganese(III) acetate (2.3 equiv.) and copper(II) acetate (0.3 equiv.) in boiling dichloromethane, the desired alkylated pyrrolidinone **20** was isolated in 70% yield after column chromatography. *N*-Alkyl-β-keto amides, as well as β-keto esters can therefore be alkylated to form sterically congested quaternary centres.[23] This encouraging result then led us to explore the alkylation of related pyrrolidinones bearing a chiral centre at the C-5 position. Hence, *N*- and *O*-benzylation of commercially available (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (NaH then BnBr) followed by benzoylation at C-3 produced the chiral pyrrolidinone **21** in 57% yield as a 1.8 : 1 mixture of inseparable diastereoisomers (Scheme 3). Mangan-



Scheme 3

ese(III)-mediated alkylation of **21** using butyl vinyl ether in the presence of copper(II) acetate (under the same conditions as for **19**) gave the expected aldehyde **22** in 42% yield as a 7.1 : 1 mixture of inseparable diastereoisomers (as indicated by the ^{1}H NMR spectrum[24]). The introduction of a benzyloxymethyl substituent had therefore resulted in a diastereoselective addition and the product was formed in a good de of 74%, especially considering the alkylation is carried out at 40 °C. Unfortunately, however, the yields were not entirely reproducible and it was believed that the benzyl protecting groups were undergoing side reactions under the oxidising conditions.

As the benzyl protecting groups were believed to be incompatible with the reaction conditions, the corresponding dimethylated derivative **23** was prepared (Fig. 3). In this case,

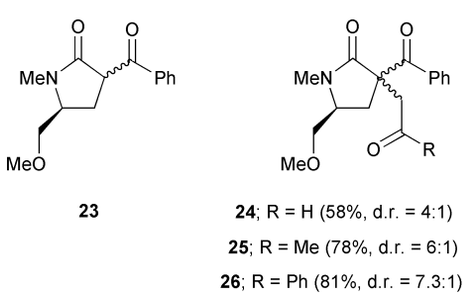
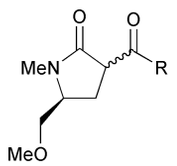


Fig. 3

reaction with butyl vinyl ether in the presence of manganese(III) acetate and copper(II) acetate in boiling dichloromethane, produced aldehyde **24** in 58% yield as a 4 : 1 mixture of inseparable isomers (as indicated by the ^{1}H NMR spectrum). So even though a relatively small methoxymethyl substituent was present at C-5, the de of aldehyde **24** was still around 60%. In contrast to the alkylation of **21**, this reaction did give reproducible results and so the alkylation of **23** was investigated using other enol ethers. Hence, reaction with 2-methoxypropene gave methyl ketone **25** in 78% yield while alkylation using trimethyl(1-phenylvinyloxy)silane afforded phenyl ketone **26** in 81% yield. In these cases, the alkylations gave 6 : 1 and 7.3 : 1 mixtures of inseparable diastereoisomers, after column chromatography.

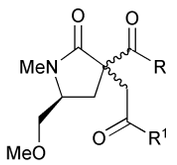
This method of alkylation is also applicable to pyrrolidinone precursors bearing different carbonyl groups at the C-3 position (Fig. 4). Reaction of the dimethylpropionyl precursor **27** with 2-methoxypropene and trimethyl(1-phenylvinyloxy)silane gave the expected tricarbonyls **28** and **29** in 71% and 90% yields, respectively. A similar reaction of methyl ester **30** with trimethyl(1-phenylvinyloxy)silane gave the phenyl ketone **31** in an excellent 91% yield. The diastereoselectivities of these alkylations were similar to those observed for related reactions using the benzoyl derivative **23** (*i.e.* 4–8 : 1).

We also investigated the manganese(III)-mediated reaction of benzoylpyrrolidinone **23** with alkenes rather than enol ethers. On reaction of **23** with styrene (5 equiv.) in the presence of manganese(III) acetate (2.3 equiv.) and copper(II) acetate (0.3 equiv.) in boiling dichloromethane, this unexpectedly gave



27; R = ^{t}Bu

30; R = OMe



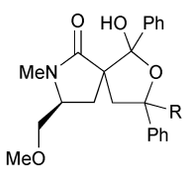
28; R = ^{t}Bu, R^1 = Me (71%, d.r. = 4:1)

29; R = ^{t}Bu; R^1 = Ph (90%, d.r. = 8:1)

31; R = Ph; R^1 = OMe (91%, d.r. = 5.6:1)

Fig. 4

hemiacetal **32** in a good yield of 81% (as a mixture of 2 main diastereoisomers as indicated by the ^{1}H NMR spectrum) (Fig. 5). This presumably arises from reaction of an intermediate benzylic cation with water followed by cyclisation of the resultant benzyl alcohol onto the aromatic ketone. A similar reaction was observed using α-methylstyrene although this gave hemiacetal **33** in a much lower yield of 14%.

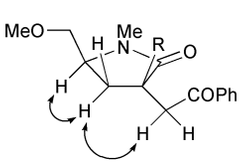


32; R = H

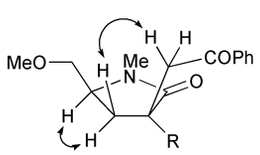
33; R = Me

Fig. 5

The efficiency and diastereoselectivities of these manganese(III)-mediated reactions compares favourably with the reported ionic alkylations, which are carried out at low-temperature. As for related ionic reactions, it was expected that the major diastereoisomer from each of these reactions involved addition of the enol ether (or alkene) to the opposite side of the pyrrolidinone ring to the bulky methoxymethyl substituent (on steric grounds). The ^{1}H NMR spectra and NOESY experiments for **31**, which gave the correlations shown in Fig. 6, for the major and minor diastereoisomers, supported this assignment.



Major isomer



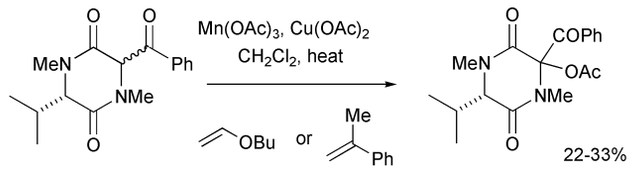
Minor isomer

31; R = CO_2Me

Fig. 6

Conclusions

Manganese(III) acetate can be used to promote the efficient introduction of functionalised (aldehyde or ketone) side-chains at the α-position of α-substituted β-keto esters and amides, including pyrrolidinones. The approach compares favourably with alternative metal-mediated methods of alkylation of 1,3-dicarbonyls[25] and this "one-pot" synthesis also offers an attractive alternative to the classical base-mediated alkylation of β-keto esters and amides (which can be low yielding because of competitive *O*-alkylation[26,27]). Good diastereoselectivities are obtained on alkylation of pyrrolidinones at 40 °C and the ability to prepare tricarbonyl derivatives by alkylation under non-basic conditions is of particular note; this approach could find application in the alkylation of base-sensitive pyrrolidinone substrates. There are limitations to the procedure, for instance, we have found that similar alkylations are not possible for piperazine-2,5-dione derivatives such as **34** (Scheme 4). On



34 **35**

Scheme 4

reaction of **34** with butyl vinyl ether in the presence of manganese(III) acetate and copper(II) acetate in boiling dichloromethane, the acetate derivative **35** was produced in 22% yield (as a single diastereoisomer) together with a mixture of unidentifiable products in low yield. A similar result was obtained when using α-methylstyrene (rather than butyl vinyl ether) and acetate **35** was isolated in 33% yield. For efficient alkylation of α-substituted β-keto amides it therefore appears that a carbon- rather than a nitrogen-based substituent should be present at the α-position. Further applications of this methodology together with mechanistic studies will be the subject of future investigations.

Experimental

General

IR spectra were recorded on an ATI Mattson Genesis FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker AMX 300 spectrometer. The carbon spectra were assigned using DEPT experiments. Coupling constants (*J*) were recorded in Hertz to the nearest 0.5 Hz. Mass spectra were recorded on a Fisons Instruments VG Analytical Autospec Mass Spectrometer. The optical rotation was recorded on a Jasco DIP-370 polarimeter (sodium D-line; 589 nm). Thin layer chromatography (TLC) was performed on Merck aluminium-backed silica gel plates. Compounds were visualised under a UV lamp, using alkaline potassium permanganate solution and/or iodine. Column chromatography was performed using silica gel (Matrix Silica 60, 70–200 micron Fisons or ICN flash silica 60, 32–63 microns). Optical rotations are given in 10^{-1} deg cm^2 g^{-1}.

General procedure for acylation of pyrrolidinones

To a solution of 1-methylpyrrolidin-2-one, (5*S*)-5-(benzyloxymethyl)-1-benzylpyrrolidin-2-one[28] or (5*S*)-5-(methoxymethyl)-1-methylpyrrolidin-2-one[29] (0.30–1.0 g, 3.5–7.0 mmol, 1 equiv.) in dry THF (10–80 cm^3) at −78 °C is added benzoyl chloride or pivaloyl chloride (0.15–1.03 g, 1.06–7.34 mmol, 1.05 equiv.) followed by LiHMDS (1 M solution in dry THF; 2.2–14.3 cm^3, 2.2–14.34 mmol, 2.05 equiv.) dropwise in <5 minutes giving a yellow solution, which is stirred at the same temperature for a further 1 h. For the formation of **30**, LiHMDS (1 M solution in dry THF; 3.5 cm^3, 3.5 mmol, 1 equiv.) is added to a solution of the pyrrolidinone (0.5 g, 3.5 mmol) in THF (40 cm^3) at −78 °C and after 1 h at the same temperature, methyl chloroformate (0.33 g, 3.5 mmol, 1 equiv.) is added and the solution stirred for 0.25 h. The reaction is then quenched by the addition of aqueous HCl or saturated aqueous $NaHCO_3$ (10 cm^3) at −78 °C and the resulting mixture is extracted with ethyl acetate (60 cm^3). Brine (10 cm^3) is added to the aqueous phase, which is extracted with ethyl acetate (3 × 30 cm^3). The organic extracts are collected and washed with saturated aqueous $NaHCO_3$ (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). Solvent evaporation followed by column chromatography (silica) afforded the acylated products **20**, **21**, **23**, **27** and **30** (0.09–0.99 g, 13–68%) as oils.

3-Benzoyl-1-methylpyrrolidin-2-one (19). 49%; oil, R_f 0.3 (6 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3014 (m),

1674 (s), 1448 (w), 1265 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.14–8.10 (2H, m, C*H* aromatics), 7.65–7.42 (3H, m, C*H* aromatics), 4.47 (1H, dd, J = 5 and 9 Hz, O=C–C*H*–COPh), 3.65–3.57 (1H, m, CH_2–CH–COPh), 3.44–3.36 (1H, m, CH_2–CH–COPh), 2.87 (3H, s, N–CH_3), 2.68–2.58 (1H, m, N–CH_2), 2.32–2.19 (1H, m, N–CH_2); δ_C (75 MHz, $CDCl_3$) 196.8 (O=*C*–Ph), 170.5 (O=*C*–N–CH_3), 136.6 (O=C–C_{phenyl}), 133.9 (2 × *C*H aromatics), 130.0 (*C*H aromatic), 128.9 (2 × *C*H aromatics), 50.9 (O=C–*C*H–COPh), 48.6 (CH–CH_2–CH_2–N), 30.4 (N–CH_3), 22.3 (CH–CH_2–CH_2–N); *m/z* (EI) 203 (M^+, 28%), 105 (100), 98 (48); Found: M^+, 203.0945. $C_{12}H_{13}NO_2$ requires for M^+, 203.0946.

(5*S*)-3-Benzoyl-1-benzyl-5-[(benzyloxy)methyl]pyrrolidin-2-one (21). 68%; isolated as an inseparable 2.0 : 1 mixture of diastereoisomers as indicated by the NMR spectra; colourless oil; R_f 0.6 (9 : 1, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3065 (m), 3011 (s, br), 2863 (w, br), 1673 (s, br), 1449 (s), 1230 (s), 1114 (s) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 8.16–8.09 (2H, m, C*H* aromatics), 7.61–7.16 (13H, m, C*H* aromatics), 4.90 (1H, d, J = 15 Hz, C_{Phenyl}–CH_2–N), 4.69 (1H, dd, J = 9 and 6.5 Hz, O=C–C*H*–C=O), 4.45 (1H, d, J = 12 Hz, C_{Phenyl}–CH_2–O), 4.39 (1H, d, J = 12 Hz, C_{Phenyl}–CH_2–O), 4.05 (1H, d, J = 15 Hz, C_{Phenyl}–CH_2–N), 3.85–3.70 (1H, m, Ph–CH_2–O–CH_2–C*H*), 3.53 (1H, dd, J = 10 and 3.5 Hz, CH_3–O–CH_2–CH), 3.40 (1H, dd, J = 10 and 3.5 Hz, CH_3–O–CH_2–CH), 2.74–2.65 (1H, m, N–CH–CH_2–CH_2–C=O), 2.17–2.08 (1H, m, N–CH–CH_2–CH–C=O); δ_C (75 MHz, $CDCl_3$) 197.1 (O=*C*–Ph), 171.6 (O=*C*–N–CH_3), 138.2 (CH_2–C_{Phenyl}), 136.9 (CH_2–C_{Phenyl}), 136.7 (O=C–C_{phenyl}), 133.9 (2 × *C*H aromatics), 130.0 (*C*H aromatic), 129.0 (2 × *C*H aromatics), 128.9 (4 × *C*H aromatics), 128.3 (3 × *C*H aromatics), 128.2 (3 × *C*H aromatics), 73.6 (Ph–CH_2–O–CH_2–CH), 70.2 (Ph–CH_2–O–CH_2–CH), 56.2 (Ph–CH_2–O–CH_2–*C*H), 50.6 (O=C–*C*H–C=O), 45.4 (Ph–CH_2–N), 26.1 (N–CH–CH_2–CH–C=O). *Minor diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 8.16–8.09 (2H, m, C*H* aromatics), 7.61–7.16 (13H, m, C*H* aromatic), 4.86 (1H, d, J = 15 Hz, C_{Phenyl}–CH_2–N), 4.52 (1H, dd, J = 9.0 and 6.5 Hz, O=C–C*H*–C=O), 4.45 (1H, d, J = 12 Hz, C_{Phenyl}–CH_2–O), 4.39 (1H, d, J = 12 Hz, C_{Phenyl}–CH_2–O), 4.28 (1H, d, J = 15 Hz, C_{Phenyl}–CH_2–N), 3.85–3.70 (1H, m, Ph–CH_2–O–CH_2–C*H*), 3.68 (1H, dd, J = 10 and 5.5 Hz, CH_3–O–CH_2–CH), 3.61 (1H, dd, J = 10 and 5.5 Hz, CH_3–O–CH_2–CH), 2.46–2.25 (2H, m, N–CH–CH_2–CH–C=O); δ_C (75 MHz, $CDCl_3$) 196.3 (O=*C*–Ph), 170.9 (O=*C*–N–CH_3), 138.2 (CH_2–C_{Phenyl}), 137.2 (CH_2–C_{Phenyl}), 136.6 (O=C–C_{phenyl}), 133.9 (2 × *C*H aromatics), 130.0 (*C*H aromatic), 129.0 (2 × *C*H aromatics), 128.7 (4 × *C*H aromatics), 128.2 (3 × *C*H aromatics), 127.9 (3 × *C*H aromatics), 73.8 (Ph–CH_2–O–CH_2–CH), 60.8 (Ph–CH_2–O–CH_2–CH), 56.0 (Ph–CH_2–O–CH_2–*C*H), 50.5 (O=C–*C*H–C=O), 46.2 (Ph–CH_2–N), 25.2 (N–CH–CH_2–CH–C=O); *m/z* (CI, NH_3) 400 (M + H^+, 100%); Found: M + H^+, 400.1911. $C_{26}H_{26}NO_3$ requires for M + H^+, 400.1913.

(5*S*)-3-Benzoyl-5-(methoxymethyl)-1-methylpyrrolidin-2-one (23). 57%; isolated as an inseparable 1.75 : 1 mixture of diastereoisomers as indicated by the NMR spectra; R_f 0.4 (6 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3691 (w, br), 3026 (m), 2928 (m), 1674 (s, br), 1448 (m), 1402 (m), 1231 (s) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 8.12–8.10 (2H, m, C*H* aromatics), 7.60–7.35 (3H, m, C*H* aromatics), 4.56 [1H, dd, J = 9 and 6 Hz, O=C–C*H*–C(=O)Ph], 3.83–3.79 (1H, m, CH_3–O–CH_2–C*H*), 3.57–3.44 (1H, m, CH_3–O–CH_2–CH), 3.40–3.25 (1H, m, CH_3–O–CH_2–CH), 3.38 (3H, s, CH_3–O–CH_2–CH), 2.86 (3H, s, N–CH_3), 2.79–2.69 (1H, m, CH_2–CH–COPh), 2.09–2.00 (1H, m, CH_2–CH–COPh); δ_C (75 MHz, $CDCl_3$) 196.9 (O=*C*–Ph), 170.9 (O=*C*–N–CH_3), 136.8 (O=C–C_{phenyl}), 133.8 (2 × *C*H aromatics), 130.0 (*C*H aromatic), 128.9 (2 × *C*H aromatics), 73.5 (CH_3–O–CH_2–CH), 59.6 (CH_3–O–CH_2–CH), 58.6 (CH_3–O–CH_2–*C*H), 50.4 [O=C–*C*H–C(=O)Ph], 28.8 (N–CH_3), 25.9 (CH–CH_2–CH–N). *Minor diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 8.12–8.10 (2H, m, C*H* aromatics), 7.60–7.35 (3H, m, C*H* aromatics), 4.47 [1H, t, J = 7.5 Hz, O=C–C*H*–C(=O)Ph], 3.76–3.69 (1H, m, CH_3–O–CH_2–C*H*), 3.57–3.44 (1H, m, CH_3–O–CH_2–CH), 3.40–3.25 (1H, m, CH_3–O–CH_2–CH), 3.39 (3H, s, CH_3–O–CH_2–CH), 2.91 (3H, s, N–CH_3), 2.39–2.33 (2H, m, CH_2–CH–COPh); δ_C (75 MHz, $CDCl_3$) 196.4 (O=*C*–Ph), 170.6 (O=*C*–N–CH_3), 136.6 (O=C–C_{phenyl}), 133.9 (2 × *C*H aromatics), 130.0 (*C*H aromatic), 128.9 (2 × *C*H aromatics), 76.1 (CH_3–O–CH_2–CH), 59.5 (CH_3–O–CH_2–CH), 58.5 (CH_3–O–CH_2–*C*H), 50.4 [O=C–*C*H–C(=O)Ph], 29.8 (N–CH_3), 25.1 (CH–CH_2–CH–N); *m/z* (CI, NH_3) 265 (M + NH_4^+, 5%), 248 (M + H^+, 100), 105 (7); Found: M + H^+, 248.1284. $C_{14}H_{18}NO_3$ requires for M + H^+, 248.1287.

(5*S*)-3-(2,2-Dimethylpropanoyl)-5-(methoxymethyl)-1-methylpyrrolidin-2-one (27). 30%; isolated as a 1.6 : 1 mixture of inseparable diastereoisomers as indicated by the NMR spectra; colourless oil; R_f 0.3 (6 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3038 (w), 3012 (m), 2971 (m), 2931 (m), 1711 (s), 1679 (s), 1228 (s) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 4.16–4.00 (1H, m, O=C–C*H*–CO^{t}Bu), 3.80–3.71 (1H, m, CH_3–O–CH_2–C*H*), 3.65–3.57 (1H, m, CH_3–O–CH_2–CH), 3.56–3.46 (1H, m, CH_3–O–CH_2–CH), 3.36 (3H, s, CH_3–O–CH_2–CH), 2.85 (3H, s, N–CH_3), 2.35–2.21 (1H, m, CH_2–CH–CO^{t}Bu), 2.06–1.95 (1H, m, CH_2–CH–CO^{t}Bu), 1.21 [9H, s, C(CH_3)$_3$]; δ_C (75 MHz, $CDCl_3$) 214.1 (O=*C*–^{t}Bu), 172.2 (O=*C*–N–CH_3), 73.3 (CH_3–O–CH_2–CH), 59.6 (CH_3–O–CH_2–CH), 58.8 (CH_3–O–CH_2–*C*H), 48.5 (O=C–*C*H–CO^{t}Bu), 45.2 [*C*(CH_3)$_3$], 28.7 (N–CH_3), 28.1 (CH–CH_2–CH–N), 26.0 (3 × CH_3). *Minor diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 4.16–4.00 (1H, m, O=C–C*H*–CO^{t}Bu), 3.72–3.65 (1H, m, CH_3–O–CH_2–C*H*), 3.56–3.46 (1H, m, CH_3–O–CH_2–CH), 3.45–3.36 (1H, m, CH_3–O–CH_2–CH), 3.37 (3H, s, CH_3–O–CH_2–CH), 2.88 (3H, s, N–CH_3), 2.35–2.21 (1H, m, CH_2–CH–CO^{t}Bu), 1.93–1.79 (1H, m, CH_2–CH–CO^{t}Bu), 1.21 [9H, s, C(CH_3)$_3$]; δ_C (75 MHz, $CDCl_3$) 213.5 (O=*C*–^{t}Bu), 171.8 (O=*C*–N–CH_3), 75.9 (CH_3–O–CH_2–CH), 59.4 (CH_3–O–CH_2–CH), 58.4 (CH_3–O–CH_2–*C*H), 48.6 (O=C–*C*H–CO^{t}Bu), 45.2 [*C*(CH_3)$_3$], 29.4 (N–CH_3), 27.4 (CH–CH_2–CH–N), 26.0 (3 × CH_3); *m/z* (CI, NH_3) 228 (M + H^+, 100%); Found: M + H^+, 228.1598. $C_{12}H_{22}NO_3$ requires for M + H^+, 228.1599.

Methyl (5*S*)-5-(methoxymethyl)-1-methyl-2-oxo-3-pyrrolidinecarboxylate (30). 13%; isolated as an inseparable 1.6 : 1 mixture of diastereoisomers as indicated by the NMR spectra; colourless oil; R_f 0.2 (1 : 1, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3009 (m, br), 2955 (w, br), 2929 (w, br), 1737 (s), 1688 (s), 1435 (m), 1403 (m), 1250 (m), 1109 (m) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 3.75–3.55 (4H, m, O=C–CH–CO_2CH$_3$ and CH_3–O–CH_2–C*H*), 3.51–3.26 (6H, m, O=C–C*H*–COOCH_3, CH_3–O–CH_2–CH and CH_3–O–CH_2–CH), 2.80 (3H, s, N–CH_3), 2.51–2.33 (1H, m, CH_2–CH–COOCH_3), 2.15–1.92 (1H, m, CH_2–CH–COOCH_3); δ_C (75 MHz, $CDCl_3$) 170.0 (O=*C*–N–CH_3), 169.1 (O=*C*–OCH_3), 71.8 (CH_3–O–CH_2–CH), 58.3 (CH_3–O–CH_2–CH), 57.2 (CH_3–O–CH_2–*C*H), 51.6 (O=C–O*C*H$_3$), 46.8 (O=C–*C*H–CO_2CH_3), 27.5 (N–CH_3), 25.1 (CH–CH_2–CH–N). *Minor diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 3.75–3.55 (4H, m, O=C–CH–COOCH_3 and CH_3–O–CH_2–C*H*), 3.51–3.26 (6H, m, O=C–C*H*–COOCH_3, CH_3–O–CH_2–CH and CH_3–O–CH_2–CH), 2.80 (3H, s, N–CH_3), 2.33–2.23 (1H, m, CH_2–CH–COOCH_3), 2.15–1.92 (1H, m, CH_2–CH–COOCH_3); δ_C (75 MHz, $CDCl_3$) 169.7 (O=*C*–N–CH_3), 168.8 (O=*C*–OCH_3), 73.8 (CH_3–O–CH_2–CH), 58.1 (CH_3–O–CH_2–CH), 57.0 (CH_3–O–CH_2–*C*H), 51.7 (O=C–O*C*H$_3$), 46.6 (O=C–*C*H–CO_2CH_3), 28.2 (N–CH_3), 24.3 (CH–CH_2–CH–N); *m/z* (CI, NH_3) 202 (M + H^+, 100%); Found: M + H^+, 202.1075. $C_9H_{16}NO_4$ requires for M + H^+, 202.1079.

General procedure for the manganese(III) acetate-mediated alkylations

To a solution of the β-keto ester or β-keto amide (0.05–0.30 g, 0.20–1.50 mmol, 1 equiv.) in degassed dichloromethane (5–10 cm^3) was added the enol ether, enol ester or styrene (0.10–1.35 g, 1.01–8.32 mmol, 5–6 equiv.) followed by manganese(III) acetate dihydrate (0.12–0.93 g, 0.43–3.45 mmol, 2.1–2.3 equiv.) and copper(II) acetate monohydrate (0.01–0.09 g, 0.06–0.41 mmol, 0.3 equiv.). The solution was heated to reflux overnight (typically 18 h). Dichloromethane (40 cm^3) was then added and the resulting suspension removed by filtration. The solution was washed with water (10 cm^3), dried ($MgSO_4$) and following evaporation the crude product was purified using column chromatography (silica) to give the alkylated products (0.03–0.36 g, 42–97%) as oils.

Ethyl 2-methyl-3-oxo-2-(2-oxoethyl)butanoate (6). 92%; colourless oil; R_f 0.45 (7 : 3, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3060 (w, br), 2985 (w, br), 1786 (m), 1716 (s, br), 1461 (m), 1277 (s, br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.63 (1H, s, *H*C=O), 4.14 (2H, q, J = 7 Hz, O–CH_2–CH_3), 2.93 and 2.83 (2H, 2 × d, J = 19 Hz, O=CH–CH_2–C), 2.18 (3H, s, CH_3–C=O), 1.44 (3H, s, CH_3–C–C=O), 1.19 (3H, t, J = 7.0 Hz, O–CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 203.7 (CH_3–*C*=O), 198.2 (H–*C*=O), 170.6 (O=*C*–O), 60.9 (O–*C*H_2–CH_3), 56.0 [O=C–(CH_3)*C*–C(=O)O], 47.6 (O=CH–*C*H_2–C), 25.0 (*C*H_3–C=O), 19.4 (*C*H_3–C–C=O), 12.9 (O–CH_2–*C*H_3); *m/z* (CI, NH_3) 203 (M + NH_4^+, 100%), 187 (M + H^+, 85), 169 (43); Found: M + H^+, 187.0967. $C_9H_{15}O_4$ requires for M + H^+, 187.0970.

Ethyl 2-acetyl-2,3-dimethyl-4-oxobutanoate (7). 86%; isolated as a 1.3–1 : 1 mixture of diastereoisomers as indicated by the ^1H NMR spectra; pale yellow oil; R_f 0.5 (7 : 3, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3574 (w, br), 2993 (w, br), 2943 (w, br), 1785 (s), 1723 (s), 1387 (m), 1303 (m), 1217 (m), 1116 (m), 1040 (m), 928 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.61, 9.60 (1H, 2 × s, 2 × *H*C=O), 4.15 (2H, q, J = 7 Hz, O–CH_2–CH_3), 3.13, 3.05 (1H, 2 × q, J = 7.5 Hz, O=CH–C*H*–CH_3), 2.16 (3H, s, CH_3–C=O), 1.41, 1.36 (3H, 2 × s, CH_3–C–C=O), 1.20, 1.19 (3H, 2 × t, J = 7.0 Hz, 2 × O–CH_2–CH_3), 1.03, 1.01 (3H, 2 × d, J = 7.5 Hz, O=CH–CH–CH_3); δ_C (75 MHz, $CDCl_3$) 203.8, 203.3 (2 × CH_3–*C*=O), 200.8, 200.7 (2 × H–*C*=O), 170.3, 170.1 (2 × O=*C*–O), 61.0, 60.7 (2 × O–*C*H_2–CH_3), 60.6 [O=C–(CH_3)*C*–C(=O)O], 48.3, 48.1 (2 × O=CH–*C*H–CH_3), 25.7, 25.3 (2 × *C*H_3–C=O), 16.5, 15.5 (2 × *C*H_3–C–C=O), 13.0 (O–CH_2–*C*H_3), 8.7, 8.4 (2 × O=CH–CH–*C*H_3); *m/z* (CI, NH_3) 201 (M + H^+, 100%); Found: M + H^+, 201.1124. $C_{10}H_{17}O_4$ requires for M + H^+, 201.1127.

Ethyl 2-acetyl-2-methyl-4-oxopentanoate (8). 81%; colourless oil; R_f 0.7 (7 : 3, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 2986 (m), 1715 (s, br), 1449 (w), 1360 (m), 1278 (m), 1202 (m), 1111 (m), 1022 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.11 (2H, q, J = 7 Hz, O–CH_2–CH_3), 3.03 and 2.95 (2H, 2 × d, J = 18.5 Hz, CH_3CO–CH_2–C), 2.18 (3H, s, CH_3–C=O), 2.07 [3H, s, CH_3–C(=O)CH_2], 1.39 (3H, s, CH_3–C–C=O), 1.17 (3H, t, J = 7.0 Hz, O–CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 206.0, 205.3 [CH_3–*C*=O and CH_3–*C*(=O)CH_2], 172.4 (O=*C*–O), 61.9 (O–*C*H_2–CH_3), 57.1 [O=C–(CH_3)*C*–CO_2], 49.3 (O=C–*C*H_2–C), 30.5 (*C*H_3–CO–CH_2), 26.8 (*C*H_3–CO–C–CH_3), 20.3 (*C*H_3–C–C=O), 14.3 (O–CH_2–*C*H_3); *m/z* (CI, NH_3) 201 (M + H^+, 100%); Found: M + H^+, 201.1126. $C_{10}H_{17}O_4$ requires for M + H^+, 201.1127.

Ethyl 2-acetyl-2-methyl-4-oxo-4-phenylbutanoate (9). 97%; yellow oil; R_f 0.4 (96 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3028 (w), 1712 (s), 1687 (s), 1230 (m), 908 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.97–7.94 (2H, m, aromatics), 7.59–7.54 (1H, m, aromatic), 7.47–7.42 (2H, m, aromatics), 4.21 (2H, q, J = 7 Hz, O–CH_2–CH_3), 3.69 and 3.62 (1H, 2 × d, J = 18.5 Hz, O=C–CH_2–C), 2.34 (3H, s, CH_3–$COCH_2$), 1.57 (3H, s, CH_3–C–C=O), 1.23 (3H, t, J = 7 Hz, O–CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 206.1 [CH_3–*C*OCH_2], 197.5 (Ph–*C*=O), 172.7 (O=*C*–O), 136.9 [C_{phenyl}–$COCH_2$], 133.8, 129.0, 128.4 (*C*H aromatics), 62.0 (O–*C*H_2–CH_3), 57.6 [O=C–(CH_3)*C*–CO_2], 45.0 [CO*C*H_2], 26.8 (*C*H_3–CO–C), 21.1 (*C*H_3–C–CO), 14.3 (O–CH_2–*C*H_3); *m/z* (CI, NH_3) 280 (M + NH_4^+, 57%), 263 (M + H^+, 100); Found: M + H^+, 263.1286. $C_{15}H_{19}O_4$ requires for M + H^+, 263.1283.

Ethyl 1-(1-methyl-2-oxoethyl)-2-oxocyclopentanecarboxylate (12). 90%; isolated as a 1 : 1.7 mixture of diastereoisomers as indicated by the NMR spectra; oil; R_f 0.5 (dichloromethane); ν_{max} ($CHCl_3$) 3490 (w, br), 3028 (s), 2983 (s), 2729 (w, br), 1754 (s), 1465 (s), 1403 (s), 1369 (s), 1231 (s), 1129 (s), 1025 (s) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 9.70 (1H, s, *H*C=O), 4.17 (2H, q, J = 7 Hz, O–CH_2–CH_3), 3.31 (1H, q, J = 7.5 Hz, O=CH–C*H*–CH_3), 2.65–2.35 (2H, m, CH_2–CH_2–CH_2–C=O), 2.35–1.90 (4H, m, CH_2–CH_2–CH_2–C=O), 1.25 (3H, t, J = 7.0 Hz, O–CH_2–CH_3), 1.10 (3H, d, J = 7.5 Hz, O=CH–CH–CH_3); δ_C (75 MHz, $CDCl_3$) 214.3 (*C*=O), 202.2 (H–*C*=O), 170.3 (O=*C*–OC_2H_5), 62.2 (O–*C*H_2–CH_3), 61.6 (O=C–*C*–CO_2), 49.7 (O=CH–*C*H–CH_3), 38.7 (CH_2–CH_2–*C*H_2–C=O), 30.3, 20.3 (CH_2–*C*H_2–CH_2–C=O and *C*H_2–CH_2–CH_2–C=O), 14.3 (O–CH_2–*C*H_3), 9.9 (O=CH–CH–*C*H_3). *Minor diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 9.49 (1H, s, *H*C=O), 4.18 (2H, q, J = 7.0 Hz, O–CH_2–CH_3), 3.32 (1H, q, J = 7.5 Hz, O=CH–C*H*–CH_3), 2.65–2.35 (2H, m, CH_2–CH_2–CH_2–C=O), 2.35–1.90 (4H, m, CH_2–CH_2–CH_2–C=O), 1.27 (3H, t, J = 7.0 Hz, O–CH_2–CH_3), 1.23 (3H, d, J = 7.5 Hz, O=CH–CH–CH_3); δ_C (75 MHz, $CDCl_3$) 214.3 (*C*=O), 201.9 (H–*C*=O), 169.9 (O=*C*–OC_2H_5), 62.0 (O–*C*H_2–CH_3), 61.4 (O=C–*C*–CO_2), 51.1 (O=CH–*C*H–CH_3), 38.4 (CH_2–CH_2–*C*H_2–C=O), 30.1, 20.2 (CH_2–*C*H_2–CH_2–C=O and *C*H_2–CH_2–CH_2–C=O), 14.3 (O–CH_2–*C*H_3), 9.9 (O=CH–CH–*C*H_3); *m/z* (CI, NH_3) 230 (M + NH_4^+, 100%), 213 (M + H^+, 73), 195 (25); Found: M + H^+, 213.1122. $C_{11}H_{17}O_4$ requires for M + H^+, 213.1127.

Ethyl 2-oxo-1-(2-oxoethyl)cyclooctanecarboxylate (13). 95%; oil; R_f 0.7 (7 : 3, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3028 (m), 2936 (m, br), 2861 (w), 1752 (s, br), 1727 (s, br), 1466 (m), 1228 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.70 (1H, t, J = 1.5 Hz, *H*C=O), 4.13 (2H, q, J = 7 Hz, O–CH_2–CH_3), 3.05 and 2.50 (2H, 2 × dd, J = 17 and 1.5 Hz, C–CH_2–CHO), 2.65–2.58 (1H, m, –C*H*CO), 2.30–2.20 (1H, m, –C*H*CO), 2.10–1.10 (13H, m, 5 × –CH_2– inclusive of t, J = 7.0 Hz, O–CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 212.6 (*C*=O), 200.0 (H–*C*=O), 171.7 (O=*C*–OC_2H_5), 62.3 (O–*C*H_2–CH_3), 60.8 (O=C–*C*–CO_2), 44.5 (O=CH–*C*H_2), 37.3, 30.6, 30.4, 30.2, 26.0, 22.6 (6 × –*C*H_2–), 14.3 (2 × O–CH_2–*C*H_3); *m/z* (EI) 240 (M^+, 3%), 212 (11), 194 (21), 151 (24), 143 (13), 137 (22), 130 (17), 109 (54), 97 (64), 81 (33), 55 (100), 41 (96); Found: M^+, 240.1356. $C_{13}H_{20}O_4$ requires for M^+, 240.1361.

Methyl 4-methoxy-2-oxo-1-(2-oxoethyl)cyclopent-3-enecarboxylate (14). 85%; colourless oil; R_f 0.3 (96 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3027 (w, br), 2955 (w, br), 1739 (s), 1699 (s), 1596 (s), 1360 (s), 1228 (s), 1169 (m), 993 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.79 (1H, s, *H*C=O), 5.29 (1H, t, J = 1 Hz, *H*C=C–OCH_3), 3.91 (3H, s, O=C–O*C*H_3), 3.71 (3H, s, HC=C–O*C*H_3), 3.48 [1H, d, J = 19 Hz, C–CH_2–C(OCH_3)=C], 3.48 [1H, dd, J = 19 and 1 Hz, C–CH_2–C(OCH_3)=C], 2.68 (1H, d, J = 18.5 Hz, O=CH–CH_2), 2.50 (1H, dd, J = 18.5 and 1 Hz, O=CH–CH_2); δ_C (75 MHz, $CDCl_3$) 200.0 (C=C–*C*=O), 199.6 (H–*C*=O), 191.3 (C=*C*–O–CH_3), 170.3 (O=*C*–O), 101.8 (H*C*=C–OCH_3), 59.7 (C=C–O–*C*H_3), 56.1 [CH_2–*C*(CO_2CH_3)CH_2], 53.5 (O=C–O–*C*H_3), 48.5 (O=CH–*C*H_2), 39.5 [C–*C*H_2–C(OCH_3)=C]; *m/z* (CI, NH_3) 230 (M + NH_4^+, 47%), 213 (M + H^+, 100); Found: M + H^+, 213.0760. $C_{10}H_{13}O_5$ requires for M + H^+, 213.0763.

Ethyl 2-acetyl-4-(acetyloxy)-2-chloro-4-butoxybutanoate (17). 93%; isolated as a 1 : 1 mixture of inseparable diastereoisomers as indicated by the NMR spectra; colourless oil; R_f 0.8 (99 : 1, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 2961 (w, br), 2938 (w, br), 2874 (w, br), 1734 (s), 1239 (m), 1239 (m), 1087 (m), 1012 (m), 801 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) (1 : 1 mixture of diastereoisomers) 6.04–5.98 (1H, m, AcO–C*H*–COBu), 4.25–4.11 (2H, m, O–CH_2–CH_3), 3.60–3.50 and 3.47–3.37 [2H, 2 × m, CH–O–CH_2–$(CH_2)_2$–CH_3], 2.70–2.39 (2H, m, C–CH_2–CH–), 2.26 and 2.21 (3H, s, CH_3–C=O), 2.00 and 1.99 (3H, s, CH_3–CO_2), 1.55–1.35 (2H, m, CH_2–CH_2–CH_2), 1.33–1.15 (5H, m, CH_2–CH_2–CH_2 and OCH_2CH_3), 0.82 (3H, br t, J = 7.5 Hz, O–CH_2–CH_2–CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) (1 : 1 mixture of diastereoisomers) 197.2, 196.0 (2 × CH_3–*C*=O), 170.6 [2 × CH_3–*C*(=O)O–], 167.1, 166.7 (2 × O=*C*–OC_2H_5), 95.9, 95.3 (BuO–*C*H–OAc), 73.0, 72.8 [O–*C*H_2–$(CH_2)_2$–CH_3], 70.5, 70.2 (2 × O=C–*C*–Cl), 63.5, 63.4 (2 × O–*C*H_2–CH_3), 41.0, 41.7 (2 × C–*C*H_2–CH–), 31.6, 31.5 (2 × –*C*H_2–), 26.2, 26.1 (2 × *C*H_3–C=O–C–Cl), 24.7, 24.6 [2 × *C*H_3–C(=O)O–], 21.4 (O–CH_2–*C*H_3), 19.5, 19.3 (2 × –*C*H_2–), 14.1, 14.0 [2 × O–CH_2–$(CH_2)_2$–*C*H_3]; *m*/*z* (CI, NH_3) 340 ($^{35}M + NH_4^+$, 1%), 263 (100), 229 (20).

1-Butoxy-2-(2,2,5-trimethyl-4,6-dioxo-1,3-dioxan-5-yl)ethyl acetate (18). 88%; colourless oil; R_f 0.3 (96 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3027 (s), 2961 (s, br), 2875 (s, br), 1752 (s, br), 1382 (s, br), 1323 (s, br), 1202 (s, br), 1154 (s, br), 1010 (s, br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.75 (1H, t, J = 5 Hz, AcO–C*H*–COBu), 3.51 and 3.35 [2H, 2 × dt, J = 9.5 and 7.5 Hz, CH–O–CH_2–$(CH_2)_2$–CH_3], 2.50 and 2.43 (2H, 2 × dd, J = 14 and 5 Hz, C–CH_2–CH–), 1.98 (3H, s, CH_3–CO_2), 1.71 (3H, s, CH_3–C–CH_3), 1.69 (3H, s, CH_3–C–CH_3), 1.56 (3H, s, CH_3–C–C=O), 1.52–1.40 and 1.31–1.16 (2 × 2H, m, –CH_2–CH_2–CH_2–CH_3), 0.82 (3H, t, J = 7.5 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 170.7 [CH_3–*C*(=O)–O], 169.8 and 169.5 (2 × *C*O_2), 105.6 (CH_3–*C*–CH_3), 95.2 (AcO–*C*H–COBu), 69.9 (O–*C*H_2–CH_2–CH_2–CH_3), 45.3 (CH_3–*C*–C=O), 43.8 (C–*C*H_2–CH), 31.6 (O–CH_2–*C*H_2–CH_2–CH_3), 30.1 and 28.6 (CH_3–C–*C*H_3), 26.3 (*C*H_3–C–C=O), 21.3 (*C*H_3–CO_2), 19.3 (O–CH_2–CH_2–*C*H_2–CH_3), 14.1 (O–CH_2–CH_2–CH_2–*C*H_3); *m*/*z* (CI, NH_3) 334 (M + NH_4^+, 7%), 216 (100); Found: M + NH_4^+, 334.1866. $C_{15}H_{28}NO_7$ requires for M + NH_4^+, 334.1865.

2-(3-Benzoyl-1-methyl-2-oxopyrrolidin-3-yl)acetaldehyde (20). 70%; oil, R_f 0.05 (9 : 1, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3583 (w, br), 3027 (m, br), 2957 (m, br), 2877 (w, br), 1723 (m), 1673 (s), 1272 (m, br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.66 (1H, s, O=C*H*), 7.78–7.75 (2H, m, C*H* aromatics), 7.49–7.09 (3H, m, C*H* aromatics), 3.51–3.32 (3H, m, N–CH_2–CH_2–C and C–C*H*–CHO), 2.99–2.72 (5H, m, N–CH_3, C–C*H*–CHO and N–CH_2–C*H*–C), 2.09–1.99 (1H, m, N–CH_2–C*H*–C); δ_C (75 MHz, $CDCl_3$) 198.2 (O=*C*–H), 197.7 (O=*C*–Ph), 170.9 (O=*C*–N–CH_3), 135.6 (O=C–C_{phenyl}), 131.2 (*C*H aromatic), 127.4 (2 × *C*H aromatics), 127.3 (2 × *C*H aromatics), 57.8 (O=C–*C*–COPh), 47.7 (C–*C*H_2–C=O), 46.2 (C–CH_2–*C*H_2–N), 29.4 (N–*C*H_3), 28.5 (CH–*C*H_2–CH_2–N); *m*/*z* (EI) 246 (M + H^+, 100%), 204 (32); Found: M + H^+, 246.1133. $C_{14}H_{16}NO_3$ requires for M + H^+, 246.1131.

2-[(5S)-3-Benzoyl-5-(benzyloxymethyl)-1-benzyl-2-oxopyrrolidin-3-yl]acetaldehyde (22). 42%; 7.1 : 1 mixture of inseparable diastereoisomers as indicated by the ^{1}H NMR spectrum; colourless oil; R_f 0.4 (9 : 1, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3026 (s), 2866 (w, br), 1692 (s, br), 1447 (w), 1258 (w, br), 1103 (w, br) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 9.78 (1H, br s, O=C*H*), 7.91–7.88 (2H, m, C*H* aromatics), 7.60–6.90 (13H, m, C*H* aromatic), 4.95 (1H, d, J = 15 Hz, C_{Phenyl}–CH_2–N), 4.36 (1H, d, J = 12 Hz, C_{Phenyl}–CH_2–O), 4.32 (1H, d, J = 12 Hz, C_{Phenyl}–CH_2–O), 4.06 (1H, d, J = 15 Hz, C_{Phenyl}–CH_2–N), 3.70–3.55 (1H, m, Ph–CH_2–O–CH_2–C*H*), 3.45–3.30 (2H, m, Ph–CH_2–O–CH_2–CH), 3.07 [1H, d, J = 16.5 Hz, C–CH_2–C–C(=O)Ph], 2.72 (1H, dd, J = 13 and 7.5 Hz, N–CH–CH_2–CH–C=O), 2.60 [1H, d, J = 16.5 Hz, C–CH_2–C–C(=O)Ph], 2.17 (1H, dd, J = 13 and 7.5 Hz, N–CH–CH_2–CH–C=O); δ_C (75 MHz, $CDCl_3$) 198.7 (O=*C*H), 197.3 (O=*C*–Ph), 172.7 (O=*C*–N–CH_3), 136.3 (CH_2–C_{Phenyl}), 135.0 (CH_2–C_{Phenyl}), 133.5 (O=C–C_{Phenyl}), 131.8, 128.4, 127.8, 127.5, 127.3, 127.2, 127.1, 126.8 (*C*H aromatics), 72.4 (Ph–*C*H_2–O–CH_2–CH), 67.6 (Ph–CH_2–O–*C*H_2–CH), 58.0 (O=C–*C*–C=O), 54.0 (Ph–CH_2–O–CH_2–*C*H), 45.5 (*C*H_2CHO), 44.3 (Ph–*C*H_2–N), 30.6 (N–CH–*C*H_2–C–C=O); *m*/*z* (CI, NH_3) 442 (M + H^+, 100%); Found: M + H^+, 442.2026. $C_{28}H_{28}NO_4$ requires for M + H^+, 442.2018.

The presence of the minor isomer was indicated from the ^{1}H and ^{13}C NMR spectra: δ_H (300 MHz, $CDCl_3$) 9.65 (1H, s, O=C*H*); δ_C (75 MHz, $CDCl_3$) 198.8 (O=*C*H), 196.8 (O=*C*–Ph), 171.6 (O=*C*–N–CH_3), 72.2 (Ph–*C*H_2–O–CH_2–CH), 57.7 (O=C–*C*–C=O), 54.9 (Ph–CH_2–O–CH_2–*C*H), 30.9 (N–CH–*C*H_2–C–C=O).

2-[(5S)-3-Benzoyl-5-(methoxymethyl)-1-methyl-2-oxopyrrolidin-3-yl]acetaldehyde (24). 58%; 4 : 1 mixture of inseparable diastereoisomers as indicated by the ^{13}C NMR spectrum; oil; R_f 0.2 (6 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3008 (w, br), 2929 (w, br), 2880 (w, br), 1692 (s), 1401 (w), 1262 (w), 1129 (w) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 9.74 (1H, br s, O=C–*H*), 7.89–7.85 (2H, m, C*H* aromatics), 7.44–7.30 (3H, m, C*H* aromatics), 3.79–3.65 (1H, m, CH_3–O–CH_2–C*H*), 3.57 (1H, dd, J = 10.5 and 3.5 Hz, CH_3–O–CH_2–CH), 3.37 (1H, dd, J = 10.5 and 4.5 Hz, CH_3–O–CH_2–CH), 3.30 (3H, s, CH_3–O–CH_2–CH), 3.14 (1H, dd, J = 17 and 1 Hz, O=CH–CH_2–C), 2.91 (3H, s, CH_3–N), 2.71 (1H, dd, J = 17 and 1 Hz, O=CH–CH_2–C), 2.61 (1H, dd, J = 13.5 and 7 Hz, N–CH–CH_2–C–C=O), 2.21 (1H, dd, J = 13.5 and 7 Hz, N–CH–CH_2–C–C=O); δ_C (75 MHz, $CDCl_3$) 198.7 (O=*C*–H), 197.2 (O=*C*–Ph), 172.1 (O=*C*–N–CH_3), 134.1 (O=C–C_{Phenyl}), 131.6 (*C*H aromatic), 128.2 (2 × *C*H aromatics), 127.3 (2 × *C*H aromatics), 71.5 (CH_3–O–*C*H_2–CH), 58.2 (CH_3–O–CH_2–*C*H), 57.7 (O=C–*C*–C=O), 56.5 (*C*H_3O–CH_2), 46.4 (*C*H_2–CHO), 30.9 (N–CH–*C*H_2–C–C=O), 27.9 (N–*C*H_3); *m*/*z* (CI, NH_3) 290 (M + H^+, 100%); Found: M + H^+, 290.1392. $C_{16}H_{20}NO_4$ requires for M + H^+, 290.1392.

The presence of the minor isomer was indicated from the ^{1}H and ^{13}C NMR spectra: δ_H (300 MHz, $CDCl_3$) 9.63 (1H, br s, O=C*H*), 7.75–7.72 (2H, m, C*H* aromatics), 1.84 (1H, dd, J = 13 and 6.5 Hz, N–CH–CH_2–C–C=O); δ_C (75 MHz, $CDCl_3$) 198.7 (O=*C*–H), 197.8 (O=*C*–Ph), 171.0 (O=*C*–N–CH_3), 135.9 (O=C–C_{Phenyl}), 131.0 (*C*H aromatic), 127.4 (2 × *C*H aromatics), 127.1 (2 × *C*H aromatics), 71.2 (CH_3–O–*C*H_2–CH), 57.8 (CH_3–O–CH_2–*C*H), 57.7 (O=C–*C*–C=O), 56.6 (*C*H_3O–CH_2), 48.7 (*C*H_2–CHO), 31.8 (N–CH–*C*H_2–C–C=O), 27.6 (N–*C*H_3).

(5*S*)-3-Benzoyl-5-(methoxymethyl)-1-methyl-3-(2-oxopropyl)-pyrrolidin-2-one (25). 78%; isolated as a 6 : 1 mixture of inseparable diastereoisomers as indicated by the ^{13}C NMR spectrum; oil, R_f 0.3 (6 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3055 (w), 3012 (s, br), 2929 (m), 1691 (s), 1674 (s), 1402 (m), 1229 (s) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 7.90–7.72 (1H, m, C*H* aromatic), 7.49–7.21 (4H, C*H* aromatics), 3.74–3.63 (1H, m, CH_3–O–CH_2–C*H*), 3.52–3.46 (3H, m, CH_3–O–CH_2–CH and CH_3–CO–CH_2–C), 3.27 (3H, s, CH_3–O–CH_2–CH), 2.89 (3H, s, CH_3–N), 2.73 (1H, d, J = 18 Hz, CH_3–CO–CH_2–C), 2.59 (1H, dd, J = 14 and 6 Hz, N–CH–CH_2–C–C=O), 2.32 (1H, dd, J = 14 and 8.5 Hz, N–CH–CH_2–C–C=O), 2.04 (3H, s, CH_3–CO–CH_2–C); δ_C (75 MHz, $CDCl_3$) 205.0 (CH_3–*C*O–CH_2–C), 198.1 (O=*C*–Ph), 172.1 (O=*C*–N–CH_3), 135.5 (O=C–C_{Phenyl}), 130.9 (*C*H aromatic), 127.8 (2 × *C*H aromatics), 127.1 (2 × *C*H aromatics), 72.8 (CH_3–O–*C*H_2–CH), 59.4 (O=C–*C*–C=O), 58.3 (CH_2–CO–*C*H_3), 58.1 (CH_3–O–CH_2–*C*H), 56.6 (*C*H_3–O–CH_2–CH), 46.7 (*C*H_2–CO–CH_3), 30.9 (N–CH–*C*H_2–C–C=O), 28.4 (N–*C*H_3); *m*/*z* (CI, NH_3) 304

(M + H^+, 100%); Found: M + H^+, 304.1553. $C_{17}H_{22}NO_4$ requires for M + H^+, 304.1549.

The presence of the minor isomer was indicated from the ^{1}H and ^{13}C NMR spectra: δ_H (300 MHz, $CDCl_3$) 7.75–7.72 (1H, m, C*H* aromatic), 2.17 (1H, dd J = 14 and 6 Hz, N–CH–CH_2–C–C=O); δ_C (75 MHz, $CDCl_3$) 205.0 (CH_3–*C*O–CH_2–C), 198.6 (O=*C*–Ph), 170.2 (O=*C*–N–CH_3), 136.9 (O=C–C_{Phenyl}), 131.9 (*C*H aromatic), 127.8 (2 × *C*H aromatics), 127.1 (2 × *C*H aromatics), 71.5 (CH_3–O–*C*H_2–CH), 59.4 (O=C–*C*–C=O), 58.5 (CH_2–CO–*C*H_3), 58.1 (CH_3–O–CH_2–*C*H), 56.7 (*C*H_3–O–CH_2–CH), 46.7 (*C*H_2–CO–CH_3), 32.3 (N–CH–*C*H_2–C–C=O), 27.6 (N–*C*H_3).

(5*S*)-3-Benzoyl-5-(methoxymethyl)-1-methyl-3-(2-oxo-2-phenylethyl)pyrrolidin-2-one (26). 81%; isolated as a 7.3 : 1 mixture of inseparable isomers as indicated by the NMR spectra; oil; R_f 0.5 (7 : 3, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3059 (w, br), 3026 (m), 2927 (w, br), 1685 (s), 1597 (w), 1448 (m), 1402 (w), 1263 (m), 1231 (m) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 8.10–7.82 (2H, m, C*H* aromatics), 7.61–7.32 (8H, m, C*H* aromatics), 4.15 (1H, d, J = 20 Hz, Ph–CO–CH_2–C), 3.80–3.71 (1H, m, CH_3–O–CH_2–C*H*), 3.59 (1H, dd, J = 11 and 4.5 Hz, CH_3–O–CH_2–CH), 3.49 (1H, dd, J = 11 and 6.5 Hz, CH_3–O–CH_2–CH), 3.39 (1H, d, J = 20 Hz, Ph–CO–CH_2–C), 3.35 (3H, s, CH_3–O–CH_2–CH), 2.97 (3H, s, CH_3–N), 2.80 (1H, dd, J = 15 and 6 Hz, N–CH–CH_2–C–C=O), 2.36 (1H, dd, J = 15 and 9 Hz, N–CH–CH_2–C–C=O); δ_C (75 MHz, $CDCl_3$) 199.9 (CH_2–*C*OPh), 197.8 (O=*C*–Ph), 173.7 (O=*C*–N–CH_3), 137.6 (CH_2–COC_{Phenyl}), 137.2 (O=C–C_{Phenyl}), 134.0 (*C*H aromatic), 132.3 (*C*H aromatic), 129.4 (2 × *C*H aromatics), 129.2 (2 × *C*H aromatics), 128.7 (4 × *C*H aromatics), 75.0 (CH_3–O–*C*H_2–CH), 59.9 (*C*H_3–O–CH_2–CH), 59.4 (O=C–*C*–C=O), 58.5 (CH_3–O–CH_2–*C*H), 44.9 (*C*H_2–CO–Ph), 33.0 (N–CH–*C*H_2–C–CO), 30.2 (N–*C*H_3). *Minor diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 8.10–7.82 (2H, m, C*H* aromatics), 7.61–7.32 (8H, m, C*H* aromatics), 4.42 (1H, d, J = 20 Hz, Ph–CO–CH_2–C), 3.92–3.84 (1H, m, CH_3–O–CH_2–C*H*), 3.59 (1H, dd, J = 11 and 4.5 Hz, CH_3–O–CH_2–CH), 3.49 (1H, dd, J = 11 and 6.5 Hz, CH_3–O–CH_2–CH), 3.43 (1H, d, J = 20 Hz, Ph–CO–CH_2–C), 3.32 (3H, s, CH_3–O–CH_2–CH), 3.17 (1H, dd, J = 15 and 9 Hz, N–CH–CH_2–C–C=O), 2.94 (3H, s, CH_3–N), 1.84 (1H, dd, J = 15 and 8 Hz, N–CH–CH_2–C–C=O); δ_C (75 MHz, $CDCl_3$) 199.9 (CH_2–*C*OPh), 197.8 (O=*C*–Ph), 173.7 (O=*C*–N–CH_3), 137.6 (CH_2–COC_{Phenyl}), 137.2 (O=C–C_{Phenyl}), 134.0 (*C*H aromatic), 131.8 (*C*H aromatic), 129.4 (2 × *C*H aromatics), 129.2 (2 × *C*H aromatics), 128.7 (4 × *C*H aromatics), 73.2 (CH_3–O–*C*H_2–CH), 59.7 (*C*H_3–O–CH_2–CH), 59.4 (O=C–*C*–C=O), 58.3 (CH_3–O–CH_2–*C*H), 46.7 (*C*H_2–CO–Ph), 34.4 (N–CH–*C*H_2–C–C=O), 29.3 (N–*C*H_3); *m*/*z* (CI, NH_3) 366 (M + H^+, 100%); Found: M + H^+, 366.1706. $C_{22}H_{24}NO_4$ requires for M + H^+, 366.1705.

(5*S*)-3-(2,2-Dimethylpropanoyl)-5-(methoxymethyl)-1-methyl-3-(2-oxopropyl)pyrrolidin-2-one (28). 71%; isolated as a 4 : 1 mixture of inseparable isomers as indicated by the NMR spectra; pale yellow oil; R_f 0.3 (7 : 3 dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 2970 (m, br), 2930 (w, br), 2253 (m), 1699 (s), 1682 (s), 1475 (m, br), 1397 (m, br) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 3.54 (2H, m, CH_3–CO–CH_2–C and CH_3–O–CH_2–C*H*), 3.45–3.37 (1H, m, CH_3–O–CH_2–CH), 3.33–3.25 (4H, m, CH_3–O–CH_2–CH and CH_3–O–CH_2–CH), 3.11 (1H, d, J = 17 Hz, CH_3–CO–CH_2–C), 2.80 (3H, s, CH_3–N), 2.59–2.37 (2H, br m, N–CH–CH_2–C–CO), 2.13 (3H, s, CH_3–CO–CH_2–C), 1.15 [9H, s, C(CH_3)$_3$]; δ_C (75 MHz, $CDCl_3$) 209.9 [O*C*–C(CH_3)$_3$], 205.4 (CH_2–*C*OCH_3), 172.8 (O=*C*–N–CH_3), 71.8 (CH_3–O–*C*H_2–CH), 59.1 (*C*H_3–C=O), 58.1 (O=C–*C*–C=O), 56.8 (CH_3–O–CH_2–*C*H), 56.4 (*C*H_3–O–CH_2–CH), 45.2 [*C*(CH_3)$_3$], 44.5 (*C*H_2–CO), 29.5 (N–CH–*C*H_2–C–C=O), 27.4 (N–*C*H_3), 26.7 [C(*C*H_3)$_3$]; *m*/*z* (CI, NH_3) 284 (M + H^+, 100%), 228 (M + H^+ − CH_2COMe, 40); Found: M + H^+, 284.1861. $C_{15}H_{26}NO_4$ requires for M + H^+, 284.1862.

The presence of the minor diastereoisomer was indicated by the ^{1}H and ^{13}C NMR spectra: δ_H (300 MHz, $CDCl_3$) 2.59–2.37 (2H, br m, N–CH–CH_2–C), 1.13 [9H, s C(CH_3)$_3$]; δ_C (75 MHz, $CDCl_3$) 209.0 [*C*OC(CH_3)$_3$], 205.8 (CH_2*C*OCH_3), 171.9 (O=*C*–N), 72.9 (CH_3–O–*C*H_2–CH), 44.1 (*C*H_2CO), 29.9 (N–CH–*C*H_2–C–C=O), 27.5 (N–*C*H_3), 27.0 [C(*C*H_3)$_3$].

(5*S*)-3-(2,2-Dimethylpropanoyl)-5-(methoxymethyl)-1-methyl-3-(2-oxo-2-phenylethyl)pyrrolidin-2-one (29). 90%; isolated as an 8 : 1 mixture of inseparable isomers as indicated by the ^{1}H NMR spectrum; oil; R_f 0.4 (9 : 1, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3013 (w, br), 1695 (s), 1449 (m), 1401 (m), 1228 (s) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 7.86–7.84 (2H, m, C*H* aromatics), 7.49–7.43 (1H, m, C*H* aromatic), 7.37–7.32 (2H, m, C*H* aromatics), 3.82 (1H, d, J = 17.5 Hz, Ph–CO–CH_2–C), 3.61–3.51 (2H, m, CH_3–O–C*H*–CH and CH_3–O–CH_2–C*H*), 3.40 (1H, dd, J = 10 and 4.5 Hz, CH_3–O–C*H*–CH), 3.30 (3H, s, CH_3–O–CH_2–CH), 2.95 (1H, d, J = 17.5 Hz, Ph–CO–CH_2–C), 2.80 (3H, s, CH_3–N), 2.66 (1H, dd, J = 14 and 8 Hz, N–CH–CH_2–C–C=O), 2.42 (1H, dd, J = 14 and 8 Hz, N–CH–CH_2–C–C=O), 1.19 [9H, s, C(CH_3)$_3$]; δ_C (75 MHz, $CDCl_3$) 210.9 [O=*C*–C(CH_3)$_3$], 198.0 (CH_2–*C*OPh), 174.4 (O=*C*–N–CH_3), 137.3 (CH_2–COC_{Phenyl}), 133.6 (*C*H aromatic), 128.9 (2 × *C*H aromatics), 128.8 (2 × *C*H aromatics), 73.4 (CH_3–O–*C*H_2–CH), 60.3 (O=C–*C*–C=O), 59.5 (CH_3–O–CH_2–*C*H), 57.8 (*C*H_3–O–CH_2–CH), 46.1 [*C*(CH_3)$_3$], 43.0 (*C*H_2–CO–Ph), 31.5 (N–CH–*C*H_2–C–C=O), 29.1 (N–*C*H_3), 28.2 [C(*C*H_3)$_3$]; *m*/*z* (CI, NH_3) 346 (M + H^+, 25%), 228 (M + H^+–CH_2COPh, 100); Found: M + H^+, 346.2017. $C_{20}H_{28}NO_4$ requires for M + H^+, 346.2018.

The presence of the minor diastereoisomer was indicated by the ^{1}H and ^{13}C NMR spectra: δ_H (300 MHz, $CDCl_3$) 8.00–7.98 (2H, m, C*H* aromatics), 7.49–7.43 (1H, m, C*H* aromatic), 7.37–7.32 (2H, m, C*H* aromatics), 4.06 (1H, d, J = 17.5 Hz, Ph–CO–C*H*–C), 3.61–3.51 (2H, m, CH_3–O–C*H*–CH and CH_3–O–CH_2–C*H*), 3.40 (1H, dd, J = 10 and 4.5 Hz, CH_3–O–C*H*–CH), 3.30 (3H, s, CH_3–O–CH_2–CH), 3.03 (1H, d, J = 17.5 Hz, Ph–CO–C*H*–C), 3.02 (1H, dd, J = 15 and 5 Hz, N–CH–C*H*–C–C=O), 2.82 (3H, s, CH_3–N), 2.08 (1H, dd, J = 15 and 5 Hz, N–CH–C*H*–C–C=O), 1.16 [9H, s, C(CH_3)$_3$]; δ_C (75 MHz, $CDCl_3$) 210.0 [O=*C*–C(CH_3)$_3$], 198.1 (CH_2–*C*OPh), 57.9 (*C*H_3–O–CH_2–CH), 46.0 [*C*(CH_3)$_3$], 43.0 (*C*H_2–CO–Ph), 28.5 [C(*C*H_3)$_3$].

Methyl (5*S*)-5-(methoxymethyl)-1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)pyrrolidine-3-carboxylate (31). 91%; isolated as a 5.6 : 1 mixture of inseparable isomers as indicated by the NMR spectra; colourless oil; R_f 0.45 (1 : 1, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3693 (w, br), 3008 (m, br), 1736 (s), 1686 (s), 1231 (w) cm^{-1}. *Major diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C*H* aromatics), 7.52 (1H, m, C*H* aromatic), 7.40–7.35 (2H, m, C*H* aromatics), 4.01 (1H, d, J = 18.5 Hz, Ph–CO–CH_2–C), 3.70–3.55 (5H, m, O=C–OCH_3, CH_3–O–CH_2–C*H* and CH_3–O–C*H*–CH), 3.48 (1H, m, CH_3–O–C*H*–CH), 3.31 (3H, s, CH_3–O–CH_2–CH), 3.16 (1H, d, J = 18.5 Hz, Ph–CO–CH_2–C), 2.90 (3H, s, CH_3–N), 2.62 (1H, dd, J = 14 and 4 Hz, N–CH–CH_2–C–C=O), 2.62 (1H, dd, J = 14 and 9 Hz, N–CH–CH_2–C–C=O); δ_C (75 MHz, $CDCl_3$) 196.0 (CH_2–*C*OPh), 170.7 (O=*C*–N–CH_3), 170.5 (O=*C*–OCH$_3$), 135.3 (CH_2–COC_{Phenyl}), 132.5 (*C*H aromatic), 127.7 (2 × *C*H aromatics), 127.3 (2 × *C*H aromatics), 74.8 (CH_3–O–*C*H_2–CH), 58.1 (O=C–*C*–C=O), 56.5 (CH_3–O–CH_2–*C*H), 52.0 (O=C–O*C*H_3), 51.9 (*C*H_3–O–CH_2–CH), 43.4 (*C*H_2–CO–Ph), 30.9 (N–CH–*C*H_2–C–C=O), 29.0 (N–*C*H_3). *Minor diastereoisomer*: δ_H (300 MHz, $CDCl_3$) 7.99–7.98 (2H, m, C*H* aromatics), 7.52 (1H, br s, C*H* aromatic), 7.40–7.35 (2H, m, C*H* aromatics), 4.15 (1H, d, J = 18.5 Hz, Ph–CO–CH_2–C), 3.89–3.79 (1H, m, CH_3–O–CH_2–C*H*), 3.70–3.55 (4H, m, O=C–OCH_3 and CH_3–O–C*H*–CH), 3.48 (1H, m, CH_3–O–C*H*–CH), 3.28 (3H, s, CH_3–O–CH_2–CH), 3.15 (1H, d, J = 18.5 Hz, Ph–CO–CH_2–C), 3.04 (1H, dd, J = 14 and 8 Hz, N–CH–C*H*–C–C=O), 2.84 (3H, s, CH_3–N),

1.68 (1H, dd, J = 14 and 8 Hz, N–CH–C*H*–C–C=O); δ_C (75 MHz, $CDCl_3$) 196.3 (CH_2–*C*OPh), 170.6 (O=*C*–N–CH_3), 170.4 (O=*C*–OCH_3), 135.2 (CH_2–CO*C*$_{Phenyl}$), 132.4 (*C*H aromatic), 127.7 (2 × *C*H aromatics), 127.0 (2 × *C*H aromatics), 71.4 (CH_3–O–*C*H_2–CH), 58.1 (O=C–*C*–C=O), 56.6 (CH_3–O–CH_2–*C*H), 52.4 (O=C–O*C*H_3), 51.9 (*C*H_3–O–CH_2–CH), 43.7 (*C*H_2–CO–Ph), 30.9 (N–CH–*C*H_2–C–C=O), 27.6 (N–*C*H_3); *m/z* (CI, NH_3) 320 (M + H^+, 100%); Found: M + H^+, 320.1496. $C_{17}H_{22}NO_5$ requires for M + H^+, 320.1498.

(8*R*)-1-Hydroxy-8-(methoxymethyl)-7-methyl-1,3-diphenyl-2-oxa-7-azaspiro[4.4]nonan-6-one (32). 81%; isolated as a 6 : 1 mixture of diastereoisomers as indicated by the NMR spectra. *Major diastereoisomer*; colourless oil; R_f 0.4 (9 : 1, dichloromethane–ethyl acetate); $[\alpha]_D^{20}$ = 26.8 (0.175 g/10 cm^3 in $CHCl_3$); ν_{max} ($CHCl_3$) 3304 (m, br), 3015 (s), 2893 (s, br), 1667 (s), 1448 (m), 1392 (m), 1046 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.65–7.68 (2H, m, C*H* aromatics), 7.52–7.44 (3H, m, C*H* aromatics), 7.39–7.23 (5H, m, C*H* aromatics), 5.59–3.49 (1H, m, CH_3–O–CH_2–C*H*), 5.33 (1H, dd, J = 10.5 and 6.5 Hz, O–C*H*PhCH_2), 3.09 (3H, s, C*H*$_3$–O–CH_2–CH), 2.88 (3H, s, C*H*$_3$–N), 2.79–2.70 (3H, m, Ph–CH–C*H*$_2$–C and CH_3–O–C*H*–CH), 2.36 (1H, dd, J = 12 and 6.5 Hz, CH_3–O–C*H*–CH), 1.97 (1H, dd, J = 13.5 and 8 Hz, N–CH–C*H*–C–C=O), 1.50 (1H, dd, J = 13.5 and 7 Hz, N–CH–C*H*–C–C=O); δ_C (75 MHz, $CDCl_3$) 176.2 (N*C*O), 142.5, 141.1, 128.8, 128.7, 128.4, 128.1, 127.3, 127.1 (C and *C*H aromatics), 107.5 [O–*C*(OH)–Ph], 81.0 [O–*C*H(Ph)CH_2], 74.6 (CH_3–O–*C*H_2–CH), 59.3 (*C*H_3–O–CH_2–CH), 57.1 (O=C–*C*–C–OH), 56.7 (CH_3–O–CH_2–*C*H), 46.1 (C–*C*H_2–CH–Ph), 31.3 (N–CH–*C*H_2–C–C=O), 29.6 (N–*C*H_3); *m/z* (CI, NH_3) 368 (M + H^+, 8%), 350 (M + H^+ − H_2O, 100); Found: M + H^+, 368.1861. $C_{22}H_{26}NO_4$ requires for M + H^+, 368.1862.

The presence of the minor diastereoisomer [R_f 0.3 (9 : 1, dichloromethane–ethyl acetate)] was indicated by the NMR spectra: δ_H (300 MHz, $CDCl_3$) 5.61 (1H, dd, J = 9.5 and 5 Hz, O–C*H*PhCH_2), 3.08 (3H, s, C*H*$_3$–O–CH_2–CH), 2.87 (3H, s, C*H*$_3$–N), 2.16–2.05 (1H, m, N–CH–C*H*–C–C=O), 1.72–1.61 (1H, m, N–CH–C*H*–C–C=O); δ_C (75 MHz, $CDCl_3$) 176.4 (N*C*O), 107.5 [O–*C*(OH)–Ph], 81.3 [O–*C*H(Ph)CH_2], 74.3 (CH_3–O–*C*H_2–CH), 59.3 (*C*H_3–O–CH_2–CH), 57.8 (O=C–*C*–C–OH), 55.9 (CH_3–O–CH_2–*C*H), 47.0 (C–*C*H_2–CH–Ph), 29.6 (N–CH–*C*H_2–C–C=O), 29.0 (N–*C*H_3).

(5*R*)-2-Benzoyl-5-isopropyl-1,4-dimethyl-3,6-dioxopiperazin-2-yl acetate (35). 22–33%; single diastereoisomer; solid; mp 153–155 °C; R_f 0.7 (6 : 4, dichloromethane–ethyl acetate); ν_{max} ($CHCl_3$) 3054 (w, br), 2968 (w, br), 1758 (w), 1675 (s), 1394 (m), 1228 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.34–8.25 (2H, m, aromatics), 7.65–7.55 (1H, m, aromatics), 7.51–7.45 (2H, m, aromatics), 3.92 [1H, d, J = 3.5 Hz, N–C*H*(iPr)–C=O], 3.02 (3H, s, N–C*H*$_3$), 2.73 (3H, s, CH–N–C*H*$_3$), 2.44–2.33 (1H, m, CH_3–C*H*–CH_3), 2.18 (3H, s, C*H*$_3$–CO_2), 1.22 (3H, d, J = 7 Hz, C*H*$_3$–CH–CH_3), 1.10 (3H, d, J = 7 Hz, CH_3–CH–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 192.5 (Ph*C*=O), 168.6 (CH_3CO_2), 166.3 (^iPrC–*C*=O), 160.2 (C–*C*=O), 134.6 (O=C–*C*$_{Phenyl}$), 133.5 (2 × *C*H aromatics), 131.3 (*C*H aromatic), 128.1 (2 × *C*H aromatics), 91.3 (AcO–*C*–COPh), 67.4 [$(CH_3)_2$CH–*C*H], 34.0 (N–*C*H_3), 32.2 [$(CH_3)_2$-*C*H–CH], 29.3 (N–*C*H_3), 21.0 (*C*H_3–CO_2), 19.9 (*C*H_3–CH–CH_3), 17.8 (*C*H_3–CH–CH_3); *m/z* (CI, NH_3) 364 (M + NH_4^+, 2%), 347 (M + H^+, 3), 304 (M + H^+–CH_3C=O, 9), 287 (M + H^+ − CH_3CO_2H, 100%); Found: M + H^+, 347.1594. $C_{18}H_{23}N_2O_5$ requires for M + H^+, 347.1607.

Acknowledgements

This work was supported by BP Amoco Chemicals, the European Union (under the ERASMUS scheme) and The University of York.

References

1 B. B. Snider, *Chem. Rev.*, 1996, **96**, 339.
2 T. Linker, *J. Prakt. Chem.*, 1997, **339**, 488.
3 (*a*) G. G. Melikyan, *Aldrichimica Acta*, 1998, **31**, 50; (*b*) G. G. Melikyan, *Organic Reactions*, ed., L. A. Paquette, John Wiley, New York, 1997, 49, 427.
4 A. F. Parsons, *An Introduction to Free Radical Chemistry*, Blackwell Science, Oxford, 2000.
5 For a recent example see: B. B. Snider and R. B. Smith, *Tetrahedron*, 2002, **58**, 25.
6 J. Y. Nédélec and K. Nohair, *Synlett*, 1991, 659.
7 H. Nishino, S-I. Tategami, T. Yamada, J. D. Korp and K. Kurosawa, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 1800.
8 E. I. Heiba and R. M. Dessau, *J. Org. Chem.*, 1974, **39**, 3456.
9 R. Lavilla, A. Spada, I. Carranco and J. Bosch, *J. Org. Chem.*, 2001, **66**, 1487.
10 R. Kumabe, H. Nishino, M. Yasutake, V.-H. Nguyen and K. Kurosawa, *Tetrahedron Lett.*, 2001, **42**, 69.
11 M. Allegretti, A. D'Annibale and C. Trogolo, *Tetrahedron*, 1993, **49**, 10705.
12 G. Midgley and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1103.
13 G. Bar, A. F. Parsons and C. B. Thomas, *Tetrahedron*, 2001, **57**, 4719.
14 P. C. Montevecchi and M. L. Navacchia, *Tetrahedron*, 2000, **56**, 9339.
15 E. J. Corey and A. K. Ghosh, *Chem. Lett.*, 1987, 223.
16 J. M. Mellor and S. Mohammed, *Tetrahedron*, 1993, **49**, 7547.
17 J. M. Mellor and S. Mohammed, *Tetrahedron*, 1993, **49**, 7557.
18 E. J. Corey and A. K. Ghosh, *Tetrahedron Lett.*, 1987, **28**, 175.
19 Part of this work has been reported as a preliminary communication: G. Bar, A. F. Parsons and C. B. Thomas, *Synlett*, 2002, 1069.
20 For related asymmetric manganese(III)-based approaches using chiral auxiliaries see: (*a*) F. Garzino, A. Méou and P. Brun, *Tetrahedron Lett.*, 2000, **41**, 9803; (*b*) B. B. Snider and Q. Zhang, *Tetrahedron Lett.*, 1992, **33**, 5921; (*c*) Q. Zhang, R. M. Mohan, L. Cook, S. Kazanis, D. Peisach, B. M. Foxman and B. B. Snider, *J. Org. Chem.*, 1993, **58**, 7640; (*d*) P. A. Zoretic, X. Weng, M. S. Biggers, M. L. Caspar and D. G. Davis, *Tetrahedron Lett.*, 1992, **33**, 2637; (*e*) R. Galeazzi, G. Mobbili and M. Orena, *Tetrahedron*, 1996, **52**, 1069; (*f*) B. Cardillo, R. Galeazzi, G. Mobbili and M. Orena, *Synlett*, 1995, 1159; (*g*) R. Galeazzi, S. Geremia, G. Mobbili and M. Orena, *Tetrahedron: Asymmetry*, 1996, **7**, 3573.
21 For recent references see for example: (*a*) M. G. Moloney, *Nat. Prod. Rep.*, 1999, **16**, 485; (*b*) P. W. H. Chan, I. F. Cottrell and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2997; (*c*) P. W. H. Chan, I. F. Cottrell and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3007; (*d*) J. E. Baldwin, A. M. Fryer and G. J. Pritchard, *J. Org. Chem.*, 2001, **66**, 2588; (*e*) A. Ali, V. U. Ahmad, B. Ziemer and J. Liebscher, *Tetrahedron: Asymmetry*, 2000, **11**, 4365; (*f*) Y. Aoyagi and R. M. Williams, *Tetrahedron*, 1998, **54**, 13045.
22 M. J. Beard, J. H. Bailey, D. T. Cherry, M. G. Moloney, S. B. Shim, K. A. Statham, M. J. Bamford and R. B. Lamont, *Tetrahedron*, 1996, **52**, 3719.
23 It is interesting to note that a related intramolecular cyclisation of an α-methyl β-amido ester was unsuccessful: D. T. Davies, N. Kapur and A. F. Parsons, *Tetrahedron Lett.*, 1998, **39**, 4397.
24 In these types of compounds, the peaks for the two hydrogen atoms at C-4 are often well separated for each of the two diastereoisomers: J. Ezquerra, C. Pedregal, A. Rubio, B. Yruretagoyena, A. Escribano and F. Sánchez-Ferrando, *Tetrahedron*, 1993, **49**, 8665.
25 (*a*) J. Iqbal, R. R. Srivastava and M. A. Khan, *Tetrahedron Lett.*, 1990, **31**, 1485; (*b*) V. Nair, J. Mathew and J. Prabhakaran, *Chem. Soc. Rev.*, 1997, 127; (*c*) X.-P. Gu, N. Nishida, I. Ikeda and M. Okahara, *J. Org. Chem.*, 1987, **52**, 3192; (*d*) X.-P. Gu, T. Okuhara, I. Ikeda and M. Okahara, *Synthesis*, 1988, 535; (*e*) I. Ikeda, X.-P. Gu, T. Okuhara and M. Okahara, *Synthesis*, 1990, 32; (*f*) Y. Hori, T.-A. Mitsudo and Y. Watanabe, *Tetrahedron Lett.*, 1986, **27**, 5389.
26 P.-K. Chiu and M. P. Sammes, *Tetrahedron*, 1990, **46**, 3439.
27 For an alternative approach to 1,4-dicarbonyl compounds from β-keto esters see: J. B. Brogan and C. K. Zercher, *J. Org. Chem.*, 1997, **62**, 6444.
28 L. J. Breña-Valle, R. C. Sánchez and R. Cruz-Almanza, *Tetrahedron: Asymmetry*, 1996, **7**, 1019.
29 P. D. Williams, D. S. Perlow, L. S. Payne, M. K. Holloway, P. K. S. Siegl, T. W. Schorn, R. J. Lynch, J. J. Doyle, J. F. Strouse, G. P. Vlasuk, K. Hoogsteen, J. P. Springer, B. L. Bush, T. A. Halgren, A. D. Richards, J. Kay and D. F. Veber, *J. Med. Chem.*, 1991, **34**, 887.