Reactivity of the carbonyl group in water. Generation of azomethine ylides from aqueous formaldehyde: Michael addition *versus* dipolar trapping

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The ability of aqueous formaldehyde to generate azomethine ylides has been studied. Treatment of methyl *N*-methylglycinate with dipolarophiles in commercial aqueous formaldehyde gives pyrrolidines by azomethine ylide cycloaddition which competes with a Michael addition.

Introduction

Following our studies on the use of water as a solvent for organic reactions,[1] we recently described results for the reactivity, in water, of the carbonyl group.[2] It has been shown that the carbonyl double bond could serve as a heterodienophile despite its quasi total hydration in water, thus allowing the use of α-activated aldehydes that are commercially available in aqueous solution. In keeping with this idea, we report herein the results of our study of the ability of aqueous formaldehyde to generate azomethine ylides by reaction with amino acid derivatives.

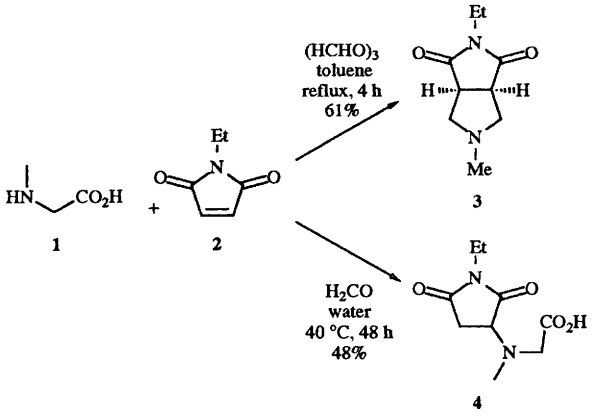
Iminium salts produced from amines or amino acids in aqueous formaldehyde are able to react as heterodienophiles when treated with cyclopentadiene or other dienes.[3] On the other hand, the generation and the trapping of azomethine ylides from amino acids derivatives is well precedented.[4] Examples can be divided into two groups: the ylide can be generated *via* a decarboxylation process (as in the case of amino acids)[5] or *via* a deprotonation step (as in the case of amino esters).[6] Very often, the cycloadditions are conducted in refluxing toluene in order to remove the water produced during the iminium formation azeotropically, although it has been noted that this removal of water is not essential.[7] Solvent polarity was suspected to promote rate enhancements[8] in such cycloadditions that were shown to proceed readily in dimethylformamide, dimethyl sulfoxide, acetonitrile or methanol,[9] and even in acetic acid.[6b,10] In a few cases, aqueous media were used,[11] but never in the case of formaldehyde. All these facts led us to investigate whether a commercial aqueous formaldehyde could be used directly as a source of ylides.

Results and discussion

We started with the reaction of sarcosine **1** (*N*-methylglycine) with an efficient dipolarophile, *N*-ethylmaleimide **2** (NEM), either with paraformaldehyde in refluxing toluene with azeotropic removal of water, or with aqueous formaldehyde. In toluene, the pyrrolidine **3** was produced (61%) resulting from the trapping of the unstabilized ylide obtained after decarboxylation of the iminium salt, while in water, only the succinimide **4** was observed (48%) as a result of the Michael addition of the amino acid onto the electronically deficient double bond of the maleimide (Scheme 1). This (1,4) addition process[12] is especially favourable in water or in methanol as depicted in Table 1. It is even faster in these solvents than in dimethylformamide, which is known to improve the possibility of nucleophilic attack. We have already demonstrated that water (or methanol) may be used as a solvent for Michael additions by the addition of nitroalkanes to α,β-unsaturated carbonyl compounds.[13] Nevertheless, this easy reaction is here an undesired pathway competing with the dipolar process. Furthermore, it is likely that the unstabilized ylide produced after decarboxylation of the iminium salt would be easily protonated in water, thus also preventing the cycloaddition.

Table 1 Formation of the succinimide **4** (1 d, 40 °C) from sarcosine **1** and NEM **2**

Solvent	Yield of **4** (%)
Water	62
MeOH	64
DMF	21
THF	traces
Toluene	0 (6% at 110 °C)



Scheme 1

For these reasons, another carbonyl compound, phenylglyoxal **5** was used, in order to generate stabilized ylides due to the presence of the phenylcarbonyl group. In Table 2 the outcome of this reaction in various solvents is reported. Again in pure water (entry 3), the reaction of sarcosine with phenylglyoxal and *N*-ethylmaleimide resulted in the unique formation of succinimide **4**. But in a 1:1 (v/v) mixture of water and THF at 40 °C (entry 4), adducts **6** and **7** (*endo* and *exo*) were obtained in acceptable yields. This confirms that the presence of water does

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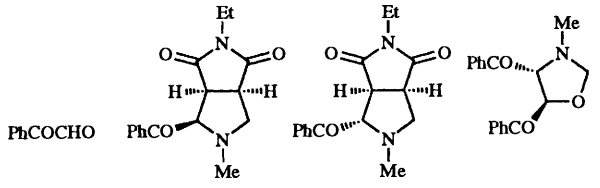
Table 2 Yields (%) for the reaction of phenylglyoxal with sarcosine and NEM **2**

Entry	Solvent	Conditions	*endo* **6**	*exo* **7**	Michael **4**	oxazoline **8**
1	Toluene	Dean-Stark, 6 h	51	19	—	—
2	Toluene	40 °C, 24 h	37	30	—	17
3	Water	40 °C, 10 h	—	—	73	—
4	1:1 Water–THF	40 °C, 10 h	21	43	—	—
5	MeOH	40 °C, 10 h	34	38	—	—

Table 3 Yields (%) for the reaction of formaldehyde with methyl sarcosinate and NEM

Entry	Conditions[a]	**10**	**11**	**12**	**13**
1	A, toluene, 2 h, 110 °C	48	51	—	—
2	A, water, 2 h, 40 °C	18	15	32	3
3	A, 1:3 water–THF, 24 h, 40 °C	31	53	—	6
4	A, 1:3 water–MeOH, 21 h, 40 °C	25	32	12	3
5	A, 1:3 water–DMF, 6 h, 40 °C	34	38	—	—
6	B, water, 2 h, 40 °C	14	16	30	2
7	B, 2:1 water–THF, 6 h, 40 °C	27	37	25	—
8	B, 1:3 water–THF, 8 h, 40 °C	36	54	—	3
9	C, 1:3 water–THF, 5 d, 40 °C	26	47	9	4
10	C, 1:3 water–THF, 6 h, 80 °C	36	55	—	—

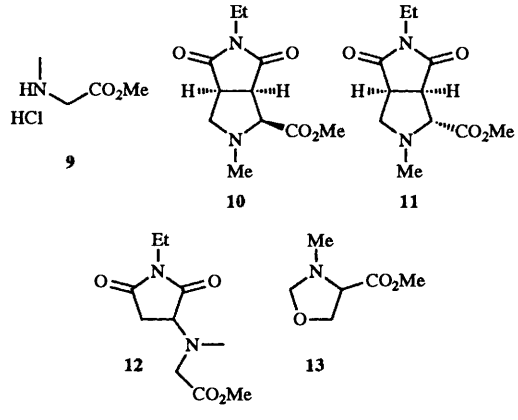
[a] Reactions conducted in closed vessel in solvent (4 cm^3) with equimolar amounts of NEt_3 and **9**. Method A: H_2CO (13.4 mmol), **9** (2 equiv.) NEM, **2** (1 mmol). Method B: as for A with $Yb(OTf)_3$ (0.2 mmol). Method C: H_2CO (4 mmol), **9** (4 mmol) and **2** (1 mmol).



not prevent the dipolar cycloaddition, but still directs the reaction to the favoured Michael pathway. The pyrrolidines **6** and **7** were also obtained in methanol (entry 5).

In refluxing toluene (entry 1), good yields were obtained. However, when the reaction was performed at 40 °C (entry 2), adducts **6** and **7** were obtained together with oxazolidine **8** resulting from the cycloaddition of the decarboxylated ylide with a second molecule of phenylglyoxal.[5b,14] At 40 °C, this oxazolidine cannot undergo a retro (3 + 2) dipolar process and was thus isolated with the two other adducts, while in water–THF or in methanol, the retrocycloaddition occurred readily at 40 °C.[15] This explains why, for reaction conducted at 110 °C, only pyrrolidines **6** and **7** were obtained. Since the stabilized ylides such as those described above tolerate water, we tried the commercial solution of formaldehyde in water again, but this time using an amino acid derivative that would not lead to a decarboxylated ylide. Thus, reaction of the sarcosine methyl ester **9** (as its hydrochloride) with *N*-ethylmaleimide and formaldehyde was studied in various solvents (Table 3). As usual, the cycloaddition occurred in refluxing toluene (entry 1). But in this case, pure water as solvent (entries 2 and 6) could also be used for the dipolar cycloaddition, providing adducts **10** and **11** (*endo* and *exo*) along with the succinimide **12** coming from the Michael addition and the oxazolidine **13**.‡ This reaction proceeded at 40 °C directly using commercial aqueous formaldehyde. The concurrent Michael reaction was inhibited by adding THF to the reaction mixture. Thus, in 1:3 (v/v) water–THF (entries 3, 8, 10), only the desired dipolar cycloaddition was observed. In the same solvent mixture, addition of ytterbium triflate[16] in a catalytic amount (entries 7 and 8) was shown to slightly increase the rate of the reaction, though in pure water, no effect was detected.

Using diethyl fumarate **14** as the dipolarophile led to the same observations regarding the effect of the solvent on the formation of adducts **15** and **16**,§ although smaller amounts of Michael addition product **17** were obtained (Table 4). When diethyl maleate **18** served as the dipolarophile in water (entries 2 and 6), the major adducts were also the 3,4-*trans* pyrrolidines **15** and **16**. The presence of fumarate in the excess of reactants left



after the reaction implied that a Michael–retro–Michael process gave rise to diethyl fumarate which reacted preferentially. Indeed, it was verified that no retro dipolar cycloaddition took place under these conditions. When the rate of the Michael

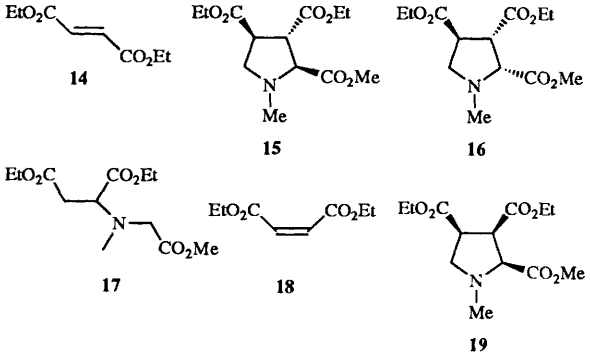
‡ Data for **13**: ν_{max}(neat)/cm^{-1} 3022, 2959, 2886, 2814, 1743, 1457, 1438, 1359, 1285, 1214, 1052 and 1016; δ_H(400 MHz, $CDCl_3$) 2.53 (3 H, s, NCH_3), 3.54 (1 H, dd, *J* 6 and 8, 5-H), 3.76 (3 H, s, CO_2CH_3), 3.87 (1 H, dd, *J* 6 and 8, 4-H), 4.18 (1 H, dd, *J* 8, 4-H), 4.27 (1 H, d, *J* 5, 2-H) and 4.46 (1 H, d, *J* 5, 2-H); δ_C(62 MHz, $CDCl_3$) 41.65 (NMe), 52.32 (CO_2CH_3), 66.48 (C-5), 67.23 (C-4), 88.66 (C-2) and 172.06 (CO, CO_2CH_3).

§ Structural assignments in new compounds throughout the paper were based on comparisons with those reported for very similar molecules.[17]

Table 4 Yields (%) for the reaction of formaldehyde with methyl sarcosinate and diethyl fumarate and maleate

Entry	Conditions[a]	15 + 16	17	19
1	A, **14**, water	50	—	—
2	A, **18**, water	24	5	2
3	A, **14**, 1:3 water–THF	89	—	—
4	A, **18**, 1:3 water–THF[b]	28	—	16
5	B, **14**, water	53	Traces	—
6	B, **18**, water	75	10	—
7	B, **14**, 1:3 water–THF	64	Traces	—
8	B, **18**, 1:3 water–THF	91	3	—

[a] Reactions conducted at 80 °C in closed vessel in solvent (4 cm^3) with NEt_3 (1 equiv.), **9** (1 equiv.) and stopped after 13 h. Method A: H_2CO (4 mmol), **9** (4 mmol) and dipolarophile (1 mmol). Method B: H_2CO (1 mmol), **9** (4 mmol) and dipolarophile (4 mmol). [b] Small amounts of oxazolidine **13** were also obtained.



addition was decreased by adding THF (entry 4), then small amounts of 3,4-*cis* adducts **19** were formed.

In conclusion, although competing with a Michael addition that is accelerated in aqueous media (confirmed here in the case of nitrogen nucleophiles), direct use of a commercially available aqueous formaldehyde as a source of stabilized azomethine ylides, allows the preparation of pyrrolidines in good yield from methyl sarcosinate. Concurrent Michael addition could be prevented by adding THF to the reaction mixture.

Experimental

NMR spectra were recorded on Brüker AM 250, AM 400, AC 200 and AC 250 spectrometers. δ Values are given relative to internal tetramethylsilane; multiplicity is indicated as follows: s for singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet and br for broad; J values are given in Hz. IR spectra were recorded using a Brüker FT instrument. Flash chromatography was performed using 6–35 μm silica gel (60) purchased from the S. D. S. company. TLC was performed using Merck 60 F_{254} plates, and visualized first with UV light and second by heating after alcoholic sulfuric or phosphomolybdic acid treatment. Elementary analyses were performed at the Service Central de Microanalyse du C.N.R.S.

3-Ethyl-7-methyl-*cis*-3,7-diazabicyclo[3.3.0]octane-2,4-dione 3 Sarcosine (534 mg, 6 mmol), *N*-ethylmaleimide (900 mg, 7.2 mmol) and paraformaldehyde (1.35 g, 15 mmol) were heated in refluxing toluene (40 cm^3) with azeotropic removal of water. After 4 h, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2–MeOH, 95:5) to give compound **3** (666 mg, 61%) as a pale yellow powder, mp 56–58 °C (Found: C, 59.1; H, 7.5; N, 15.1. $C_9H_{14}N_2O_2$ requires C, 59.3; H, 7.7; N, 15.4%); ν_{max}(neat)/cm^{-1} 3020, 2793, 1775, 1692, 1477, 1445, 1407, 1380, 1349, 1305, 1216, 1125 and 1048; δ_H(400 MHz, $CDCl_3$) 1.15 (3 H, t, J 7, CH_2CH_3), 2.27 (3 H, s, NCH_3), 2.26–2.34 (2 H, m, 6- and 8-H), 3.13–3.19 (2 H, m, 1- and 5-H), 3.27 (2 H, d, J 10, 6- and 8-H′) and 3.55 (2 H, q, J 7, CH_2CH_3); δ_C(62 MHz, $CDCl_3$) 12.68 (CH_3, Et), 33.65 (CH_2, Et), 40.56 (NCH_3), 44.63 (C-1, C-5), 58.24 (C-6, C-8) and 178.80 (2 CO).

***N*-(1-Ethyl-2,5-dioxopyrrolidin-3-yl)-*N*-methylglycine 4** *N*-Ethylmaleimide (125 mg, 1 mmol) and sarcosine (178 mg, 2 mmol) were heated in water (5 cm^3) at 40 °C for 10 h. Evaporation of the mixture and flash chromatography of the residue (propanol–water, 7:3) gave compound **4** (133 mg, 62%) as a pale yellow oil. Although it was not possible to obtain a satisfactory elemental analysis for this amino acid, proof for its structure was given by unambiguous transformation (diazomethane esterification) to the fully characterized ester **12**. Data for **4**: ν_{max}(neat)/cm^{-1} 2982, 1775, 1700, 1616, 1444, 1403, 1349, 1226, 1131 and 1049; δ_H(250 MHz, D_2O) 1.10 (3 H, t, J 7, CH_2CH_3), 2.36 (3 H, s, NCH_3), 2.85 (1 H, dd, J 5 and 18, 4-H), 2.96 (1 H, dd, J 8 and 18, 4-H′), 3.31 (2 H, s, CH_2CO_2H), 3.54 (2 H, q, J 7, CH_2CH_3) and 4.30 (1 H, dd, J 5 and 8, 3-H); δ_C(62 MHz, D_2O) 12.98 (CH_3, Et), 29.07 (C-4), 33.62 (CH_2, Et), 37.54 (NCH_3), 58.40 (CH_2CO_2H), 61.56 (C-3), 174.92, 175.74 and 177.84 (CO).

Reactions starting from sarcosine, *N*-ethylmaleimide and phenylglyoxal

These reaction mixtures were stirred and heated in a closed vessel (see Table 2). After cooling to room temperature, each mixture was extracted with dichloromethane (4 × 5 cm^3) and the combined extracts were washed with water (5 cm^3) and concentrated under reduced pressure. Flash chromatography of the residue (hexane–ethyl acetate, 8:2 to 100% ethyl acetate) gave the pyrrolidines **6** and **7** and the oxazolidine **8**.

(1*R,5*S**,6*R**)-6-Benzoyl-3-ethyl-7-methyl-3,7-diazabicyclo-[3.3.0]octane-2,4-dione 6.** Pale yellow powder, mp 84–85 °C (from ether–hexane) (Found: C, 67.1; H, 6.6; N, 9.5. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%); ν_{max}(powder with KBr)/cm^{-1} 3000, 2963, 2939, 2872, 1768, 1685, 1596, 1572, 1481, 1451, 1406, 1349, 1314, 1227, 1140, 1061 and 1021; δ_H(400 MHz, $CDCl_3$) 1.20 (3 H, t, J 7, CH_2CH_3), 2.44 (3 H, s, NCH_3), 3.23 (1 H, d, J 10, 5-H), 3.32–3.40 (2 H, m, 8-H), 3.46 (1 H, dd, J 8 and 10, 1-H), 3.61 (2 H, q, J 7, CH_2CH_3), 4.97 (1 H, s, 6-H), 7.50–7.66 and 8.10–8.16 (5 H, 2 m, Ph); δ_C(62 MHz, $CDCl_3$) 12.93 (CH_3, Et), 34.26 (CH_2, Et), 37.28 (NCH_3), 45.01 (C-1), 48.97 (C-5), 55.56 (C-8), 67.44 (C-6), 128.56, 128.95, 133.83, 135.45 (Ph), 178.19, 179.01 (CO) and 198.62 (PhCO).

(1*R,5*S**,6*S**)-6-Benzoyl-3-ethyl-7-methyl-3,7-diazabicyclo-[3.3.0]octane-2,4-dione 7.** Pale yellow powder, mp 112–114 °C (from ether–hexane) (Found: C, 67.1; H, 6.4; N, 9.8. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%); ν_{max}(neat)/cm^{-1} 3021, 1700, 1490, 1445, 1406, 1353 and 1215; δ_H($CDCl_3$, 250 MHz) 1.10 (3 H, t, J 7, CH_2CH_3), 2.33 (3 H, s, NCH_3), 2.62 (1 H, dd, J 8 and 10, 8-H′), 3.28 (1 H, dd, J 1 and 8, 1-H), 3.49 (2 H, q, J 7, CH_2CH_3), 3.58 (1 H, dd, J 1 and 10, 8-H), 3.70 (1 H, t, J 8, 5-H), 4.02 (1 H, d, J 8, 6-H), 7.43–7.68 and 7.99–8.15 (5 H, 2 m, Ph); δ_C(50 MHz, $CDCl_3$) 12.87 (CH_3, Et), 34.26 (CH_2, Et), 40.21 (NCH_3), 43.65 (C-1), 48.96 (C-5), 58.08 (C-8), 72.44 (C-6), 128.00, 128.75, 133.40, 136.97 (Ph), 175.31, 177.67 and 195.15 (3 CO).

(4*R,5*R**)-4,5-Dibenzoyl-3-methyloxazolidine 8.** Pale yellow powder, mp 78–79 °C (ether–hexane) (Found: C, 73.0; H, 6.0; N, 4.8. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%); ν_{max}(powder with KBr)/cm^{-1} 2976, 2956, 2927, 2887, 2871, 1681, 1596, 1581, 1450, 1331, 1292, 1241, 1199, 1139, 1061 and 1000; δ_H(400 MHz, $CDCl_3$) 2.64 (3 H, s, NCH_3), 4.47 (1 H, d, J 6, 5-H), 4.58 (1 H, d, J 6, 4-H), 5.00 (1 H, d, J 4, 2-H), 5.72 (1 H,

d, *J* 4, 2'-H), 7.42–7.55 and 8.03–8.12 (10 H, 2 m, Ph); δ_C(62 MHz, $CDCl_3$) 42.73 (NCH_3), 70.90 (C-5), 77.42 (C-4), 89.40 (C-2), 128.65, 128.71, 128.98, 129.36, 133.66, 133.78, 134.89, 135.35 (2 Ph), 195.43 and 196.93 (2 CO, PhCO).

Reactions starting from methyl sarcosinate hydrochloride and formaldehyde

These reactions, performed in a closed vessel, employed in addition to solvent (4 cm^3) equimolar quantities of triethylamine and hydrochloride. Commercial aqueous formaldehyde was diluted with distilled water to reach the desired concentration. The dipolarophile (*N*-ethylmaleimide or diethyl fumarate or maleate) was added to the mixture which was then heated and stirred (see Tables 3 and 4). After being cooled to room temperature, the mixture was diluted with water (5 cm^3) and extracted with dichloromethane (4 × 5 cm^3). The combined organic layers were washed with water (5 cm^3) and then concentrated under reduced pressure. Flash chromatography of the residue (9:1 hexane–ethyl acetate to 100% ethyl acetate) gave the pyrrolidines **10**, **11**, **15**, **16** and **19**, the Michael adducts **12** and **17** and the oxazolidine **13**. The last three compounds were more successfully prepared using only the two appropriate reactants and omitting the unnecessary third.

Methyl (1*S,5*R**,6*S**)-3-ethyl-7-methyl-2,4-dioxo-3,7-diazabicyclo[3.3.0]octane-6-carboxylate 10.** Syrup (Found: C, 54.8; H, 6.5; N, 11.5. $C_{11}H_{16}N_2O_4$ requires C, 55.0; H, 6.7; N, 11.7%); ν_{max}(neat)/cm^{-1} 3020, 1775, 1708, 1444, 1403, 1352, 1229, 1176 and 1140; δ_H(400 MHz, $CDCl_3$) 1.17 (3 H, t, *J* 7, CH_2CH_3), 2.36 (3 H, s, NCH_3), 3.10–3.18, 3.30–3.38 (4 H, 2 m, 1-, 5- and 8-H), 3.56 (2 H, q, *J* 7 CH_2CH_3), 3.75 (3 H, s, CO_2CH_3) and 3.91 (1 H, s, 6-H); δ_C(62 MHz, $CDCl_3$) 12.14 (CH_3, Et), 33.31 (CH_2, Et), 36.12 (NCH_3), 43.89 (C-1), 48.20 (CO_2CH_3), 50.84 (C-5), 54.53 (C-8), 66.45 (C-6), 169.92 (CO_2CH_3), 176.95 and 178.02 (2 CO).

Methyl (1*S,5*R**,6*R**)-3-ethyl-7-methyl-2,4-dioxo-3,7-diazabicyclo[3.3.0]octane-6-carboxylate 11.** Powder, mp 120 °C (Found: C, 55.2; H, 6.6; N, 11.6. $C_{11}H_{16}N_2O_4$ requires C, 55.0; H, 6.7; N, 11.7%); ν_{max}(powder with KBr)/cm^{-1} 2978, 2952, 2836, 1790, 1761, 1690, 1445, 1405, 1371, 1348, 1226, 1198, 1127 and 1057; δ_H(250 MHz, $CDCl_3$) 1.15 (3 H, t, *J* 7, CH_2CH_3), 2.34 (3 H, s, NCH_3), 2.53 (1 H, dd, *J* 8 and 9.5, 8-H), 3.17 (1 H, d, *J* 8, 6-H), 3.20 (1 H, dt, *J* 1 and 8, 1-H), 3.48 (1 H, dd, *J* 1 and 9.5, 8-H'), 3.50 (1 H, t, *J* 8, 5-H), 3.56 (2 H, q, *J* 7, CH_2CH_3) and 3.82 (3 H, s, CO_2CH_3); δ_C(62 MHz, $CDCl_3$) 12.84 (CH_3, Et), 34.24 (CH_2, Et), 39.93 (NCH_3), 43.34 (C-1), 47.64 (C-5), 52.20 (CO_2CH_3), 57.72 (C-8), 69.72 (C-6), 169.44 (CO_2CH_3), 175.70 and 177.67 (2 CO).

***N*-(*N*-Ethyl-2,5-dioxopyrrolidin-3-yl)-*N*-methylglycine methyl ester 12.** Syrup (Found: C, 52.9; H, 6.9; N, 12.1. $C_{10}H_{16}N_2O_4$ requires C, 52.6; H, 7.1; N, 12.3%); ν_{max}(neat)/cm^{-1} 3020, 1775, 1741, 1703, 1444, 1403, 1379, 1215 and 1129; δ_H(400 MHz, $CDCl_3$) 1.17 (3 H, t, *J* 7, CH_2CH_3), 2.42 (3 H, s, NCH_3), 2.69 (1 H, dd, *J* 5 and 18, 4-H), 2.94 (1 H, dd, *J* 8 and 18, 4-H'), 3.56 and 3.69 (1 H each, 2 d, *J* 17, CH_2CO_2), 3.57 (2 H, q, *J* 7, CH_2CH_3), 3.74 (3 H, s, CO_2CH_3) and 3.98 (1 H, dd, *J* 5 and 8, 3-H); δ_C(50 MHz, $CDCl_3$) 13.05 (CH_3, Et), 32.91 (C-4), 33.52 (CH_2, Et), 37.80 (NCH_3), 51.77 (CO_2CH_3), 56.35 (CH_2CO_2), 61.14 (C-3), 170.94 (CO_2CH_3), 174.61 and 176.21 (2 CO).

3,4-Diethyl 2-Methyl (2*R,3*S**,4*S**) and (2*S**,3*S**,4*S**)-1-methylpyrrolidine-2,3,4-tricarboxylate 15, 16.** Syrup (Found: C, 54.1; H, 7.3; N, 5.0. $C_{13}H_{21}NO_6$ requires C, 54.3; H, 7.4; N, 4.9%); ν_{max}(neat)/cm^{-1} 3020, 1730, 1660, 1630, 1590, 1530, 1490, 1445, 1422, 1370, 1215 and 1020; δ_H(400 MHz, $CDCl_3$) 1.26 and 1.27 (3 H, 2 t, *J* 7, CH_2CH_3), 2.39 and 2.40 (3 H, 2 s, NCH_3), 2.70–2.80 (m, 1 H), 3.30–3.38 (m, 1.6 H), 3.43 (0.7 H, dd, *J* 10 and 3), 3.62 (0.7 H, q, *J* 8), 3.68–3.79 (1 H, m), 3.72 and 3.78 (3 H, 2 s, CO_2CH_3) and 4.10–4.25 (4 H, m, CH_2CH_3); δ_C(62 MHz, $CDCl_3$) 14.07 (CH_3, Et), 39.65 and 40.38 (NCH_3), 44.84 and 45.16 (C-4), 49.25 and 50.08 (C-3), 51.66 and 52.24 (CO_2CH_3), 57.28 and 57.97 (C-5), 60.35, 61.18, 61.36, 61.41 (CH_2, Et), 68.64 and 70.27 (C-2), 170.80, 171.11, 171.61, 172.15, 172.31 and 173.00 (CO).

***N*-(1,2-Diethoxycarbonylethyl)-*N*-methylglycine methyl ester 17.** Syrup (Found: C, 52.4; H, 7.4; N, 5.0. $C_{12}H_{21}NO_6$ requires C, 52.3; H, 7.7; N, 5.1%); ν_{max}(neat)/cm^{-1} 3020, 2980, 1730, 1640, 1490, 1440, 1420, 1290, 1220, 1180 and 1020; δ_H(200 MHz, $CDCl_3$) 1.25 (3 H, t, *J* 7, CH_2CH_3), 130 (3 H, t, *J* 7, CH_2CH_3), 2.43 (3 H, s, NCH_3), 2.65 (1 H, dd, *J* 6 and 16, 2-H), 2.87 (1 H, dd, *J* 9 and 16, 2-H'), 3.45 (2 H, s, CH_2CO_2), 3.72 (3 H, s, CO_2CH_3), 3.86 (1 H, dd, *J* 6 and 9, 1-H) and 4.06–4.31 (4 H, m, CH_2CH_3); δ_C(62 MHz, $CDCl_3$) 13.99 and 14.24 (CH_3, Et), 35.08 (C-2), 38.99 (NCH_3), 51.60 (CO_2CH_3), 55.82 ($CH_2CO_2CH_3$), 60.57 and 60.65 (CH_2, Et), 62.26 (C-1), 170.75, 170.88 and 171.17 (3 CO).

3,4-Diethyl 2-Methyl (2*S,3R*,4S*) 1-methylpyrrolidine-2,3,4-tricarboxylate 19.** Syrup (Found: C, 54.6; H, 7.1; N, 5.1. $C_{13}H_{21}NO_6$ requires C, 54.3; H, 7.4; N, 4.9%); ν_{max}(neat)/cm^{-1} 3022, 2987, 1738, 1439, 1376, 1215, 1023 and 927; δ_H(400 MHz, $CDCl_3$) 1.25 (6 H, t, *J* 7, CH_2CH_3), 2.47 (3 H, s, NCH_3), 2.80–2.88 (1 H, m), 3.35–3.54 (4 H, m), 3.78 (3 H, s, CO_2CH_3) and 4.07–4.20 (4 H, m, CH_2CH_3); δ_C(50 MHz, $CDCl_3$) 14.00 and 14.03 (CH_3, Et), 41.01 (NCH_3), 44.95 (C-4), 49.82 (C-3), 52.35 (CO_2CH_3), 57.95 (C-5), 60.90 and 61.13 (CH_2, Et), 69.64 (C-2), 171.35 (CO_2Me), 171.60 and 172.17 (2 CO).

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