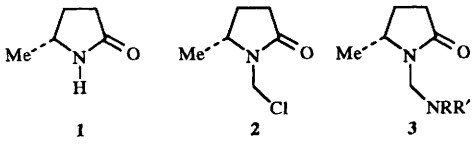
Synthesis of *N*-aminomethylpyrrolidin-2-ones [1,2]

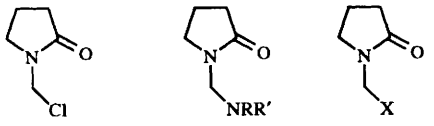
Ping Chen, Dong-Jin Suh and Michael B. Smith *
Rm 151, 215 Glenbrook Road, Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060, USA

Pyrrolidin-2-ones react with formaldehyde and chlorotrimethylsilane to give 1-chloromethylpyrrolidin-2-ones which upon subsequent reaction with primary and secondary amines give 1-aminomethylpyrrolidin-2-ones in good yield.

We have recently shown that (5*R*)-5-methylpyrrolidin-2-one **1** [3] can be converted into (5*R*)-1-chloromethyl-5-methylpyrrolidin-2-one **2** by treatment with chlorotrimethylsilane and paraformaldehyde.[4] This reagent reacted with alcohols bearing an



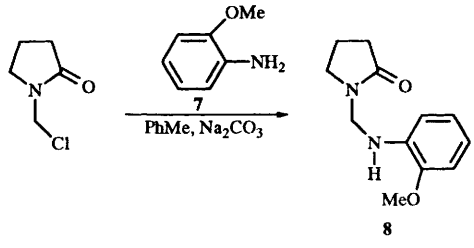
1 **2** **3**



4 **5** **6**

asymmetric centre to produce alkoxymethylpyrrolidin-2-ones with high diastereoselectivity.[4] The NCH_2O signals in the ^1H NMR of these products (*N*-alkoxymethyl lactams) can then be integrated to give the diastereoisomeric ratios.[4] This reagent **2** was offered as an alternative reagent to Mosher's acid,[5] when that reagent cannot give the diastereoisomeric ratio. In this initial study, lactam **2** failed to react with amines and this method could not be extended to include the determination of enantiomeric composition of chiral, non-racemic amines. We have now developed methodology that converts **2** into the corresponding aminomethyl analogue **3** in a reliable and general manner. The conversion of both **2** and the well-known 1-chloromethylpyrrolidin-2-one **4** into **3** and **5**, respectively are reported in this work.

It was not obvious why **2** failed to react with amines since the reaction of amines with **4** was known, but long experience with pyroglutamate derivatives, and C-5 substituted lactams in general, often showed unusual steric effects in various reactions. For this reason, lactam **4** was chosen as a model for these studies. Lactam **4** has been prepared by several procedures [6] and has been shown to react with alcohols (and alkoxides),[6a,7] enolate anions,[8] cyanide,[9] silyl enol ethers [10] and allyl silanes [11] to form the corresponding derivative **6**. In addition, **4** reacts with phosphanes to form the corresponding phosphonium salt [12] and with triethyl phosphite to form the phosphonate ester.[13] Given such a range of reactivity, it is not surprising that **4** has also been shown to react with amines, as mentioned above. The results observed with **2** were therefore surprising and it was believed the problem was simply one of determining proper reaction conditions. In several reports, **4** reacted with tertiary amines to form 1-ammoniomethylpyrrolidin-2-ones such as **6** ($X = NR_3^+$).[14] More pertinent was the reaction of **4** with 2-alkoxyaniline derivatives (such as 2-methoxyaniline **7**) to form **8** in good to moderate yields.[15] When conditions reported



7

8

for the preparation of **8** (refluxing toluene in the presence of sodium carbonate) were applied to the reaction of **2** or **4** with diethylamine, however, little or no **3** or **5** was produced and a mixture of products resulted containing several unidentified decomposition products.

It is noted that the reaction of **4** with *N*-trimethylsilyl-*N*,*N*-diethylamine gave 1-(*N*,*N*-diethylamino)methylpyrrolidin-2-one **5** (R = R′ = Et).[16] Since our ultimate objective was to develop a reagent for determining the enantiomeric purity of amines, direct coupling of the amine with **2** or **4** was desirable. For this reason, this route was not explored. It has been reported that pyrrolidin-2-one itself could be converted into **5** *via* reaction with amines and formaldehyde,[17] but this approach was not examined in detail since it was not clear that this approach would preserve the chiral centre in a chiral, non-racemic amine precursor. The reaction of amines with *N*-hydroxymethylpyrrolidin-2-one **6** (X = OH) is reported to give **5**,[18] but this reagent did not suit our needs. Chlorides **4** and particularly **2** were easier to prepare and thus we did not explore the use of the hydroxymethyl derivative.

Various procedures for the preparation of **3** or **5** were examined, based on the above precedents and also on our experience with **2** and **4** in reactions with alcohols. The known *N*-chloromethylpyrrolidin-2-one **4** was used as a model since it was easy to prepare and would be less sterically hindered than **2**. Hopefully, the procedures developed for **4** could be applied directly to **2**. The best results were obtained when **4** was treated with the amine of interest, with triethylamine used as a base, and then refluxed in dichloromethane. The primary and secondary amines shown in Table 1 (both aliphatic and aromatic) reacted with **4** to generate a variety of *N*-aminomethyl derivatives **5** in good yield. The yields of adducts **5** from primary amines **5a**–**5f** were similar to those obtained from reactions with secondary amines **5g**–**5k**. Chloride **4** reacted with (*R*)-phenethylamine, as well as the ethyl esters of (*S*)-valine and (*S*)-proline under these conditions to provide good yields of **5e**, **5f** and **5g**, respectively. In all three cases, the chiral centre inherent to the amine survived the coupling reaction without racemization, as determined by HPLC and GC–MS analyses. The reaction of **4** with dicyclohexylamine was problematic. This amine required a reaction time of 3 days and gave only 32% of *N*,*N*-dicyclohexyl-

Table 1 Reaction of 1-chloromethylpyrrolidin-2-one **4** with amines[a]

Compound no.	R	R′	Yield (%)	$[\alpha]_D^{20}$
5a	Bu^t	H	78	—
5b	c-C_6H_{11}	H	75	—
5c	Ph	H	78	—
5d	$PhCH_2$	H	75	—
5e	(*S*)-Pr^{i}CHCO$_2$Et	H	71	−49.9 (*c* 4.0)
5f	(*S*)-CHPhMe	H	75	−81.25 (*c* 4.0)
5g	(*S*)-$(CH_2)_3$CH(CO$_2$Et)-		75	−67.75 (*c* 4.14)
5h	Et	Et	70	—
5i	Pr^i	Pr^i	68	—
5j	c-C_6H_{11}	c-C_6H_{11}	32[b]	—
5k	Ph	Me	75	—

[a] *Reagents and conditions:* RR′NH, NEt_3, CH_2Cl_2, reflux, 24 h. [b] Reaction time 3 days.

Table 2 Reaction of (5*R*)-1-chloromethyl-5-methylpyrrolidin-2-one with amines[a]

Compound no.	R	R′	Yield (%)	$[\alpha]_D^{20}$
3a	Et	Et	75	−38.8 (*c* 3.5)
3b	Bu^t	H	68	+12.04 (*c* 3.1)
3c	(*S*)-$(CH_2)_3$CH(CO$_2$Et)-		75	−64.02 (*c* 2.5)
3d	(*S*)-Pr^{i}CHCO$_2$Et	H	79	−30.78 (*c* 4.04)
3e	(*S*)-CHPhMe	H	75	−60.04 (*c* 2.4)

[a] *Reagents and conditions:* RR′NH, NEt_3, CH_2Cl_2, reflux, 24 h.

aminopyrrolidin-2-one **5j**. Since cyclohexylamine gave a 75% yield of **5b**, the second cyclohexyl ring must increase the steric hindrance to a point where reaction with **4** is difficult. Clearly, reaction with the more sterically hindered **2** can be expected to give even poorer results. It therefore seems clear that sterically hindered amines will not give satisfactory results in this reaction. In general, adducts **5** were stable to distillation, chromatography, work-up and reasonable manipulation. It is noted, however, that some adducts, **5**, required repeated column chromatography to provide analytically pure samples, and partial decomposition was observed that lowered the isolated yields.

When lactam **4** reacted with the amines without a chiral centre, the ^{1}H NMR *N*-CH_2NR_2 signals appeared as a single peak in **5** at about δ 4.2–4.3. Chiral amines such as (−)-phenethylamine and the ethyl ester of L-valine resulted in a product where the protons of NCH_2NHR were diastereotopic and appeared as an AB quartet centred at about δ 4.1.

Next, we turned our attention to the reaction of chiral non-racemic lactam **2**[4] with both achiral amines and chiral, non-racemic amines. L-Glutamic acid was cyclized with thionyl chloride in ethanol to give ethyl pyroglutamate.[19] Reduction of the ester with sodium boranuide[19] and conversion into the toluene-*p*-sulfonate[20] allowed reduction to the 5-methyl derivative **1**.[3] In previous work,[4] the toluene-*p*-sulfonate group was changed to an iodo moiety with sodium iodide and then reduced with tributyltin hydride and azoisobutyronitrile (AIBN) to give a 53% yield of (5*R*)-5-methylpyrrolidin-2-one **1**. In this work, we modified a procedure reported by Provot *et al.*[21] and used catalytic hydrogenation of the crude iodide just described (palladium/carbon catalyst in ethanol) and found an improved yield (83%) of **1**. Orlova and Shipov's procedure for the preparation of **4** (formaldehyde and chlorotrimethylsilane)[22] was used to give an 82% yield of **2**.

When **2** was treated with diethylamine or with *tert*-butylamine, a good yield (75 and 68%, respectively) of the adduct (**3a** and **3b**) was obtained (Table 2). The NCH_2NR_2 signal in the ^{1}H NMR appeared as an AB quartet, with satellite signals centred at about δ 4.43/3.63 and 4.66/3.75, respectively. Since the yields of **3a** and **3b** are comparable with the yields of **5h** and **5a**, it appears that **2** reacts as well as **4** under these conditions. The reaction of **2** was also examined with more sterically hindered amines, and with those possessing a chiral centre. The reaction of **2** with (*S*)-phenethylamine, for example, gave a 75% yield of **3c**. Similarly, (*S*)-valine ethyl ester reacted with **2** to give a 75% yield of **3d**, and (*S*)-proline ethyl ester gave a 79% yield of **3e**. In the last three cases, the chiral centres in the amines were not racemized by the reaction conditions. The NCH_2NR_2 signals appeared as an AB quartet with the satellite signals at approximately δ 4.4 and 3.8 in the ^{1}H NMR. It is clear that amines with several structural features can react easily and in good yield with **2** under these conditions.

This constitutes an improved and general method for the preparation of *N*-aminomethylpyrrolidin-2-one derivatives such as **5** from a variety of primary and secondary amines. Even C-5 substituted pyrrolidin-2-ones such as **2**, which are known to be less reactive at nitrogen due to increased steric hindrance, give good yields of adducts such as **3**. This is a useful addition to the chemistry of *N*-chloropyrrolidin-2-one **4** and expands the utility of the aminomethylation reactions reported previously in the patent literature. The next step in this work will use **2** as an NMR probe for the enantiomeric purity of amines (*via* formation of **3** by reaction with chiral non-racemic amines). This will complement previously published and similar work with alcohols.

Experimental

Both ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-270 FT-NMR instrument at 270.13 and 67.3 MHz, respectively, and are reported in ppm downfield from tetramethylsilane (TMS) used as an internal standard. *J* values are given in Hz. Mass spectra were recorded using a Hewlett-Packard 5890 A gas chromatograph equipped with a 25 m × 0.20 mm cross-linked methyl silicone fused-silica capillary column and 5870 series mass selective detector. High resolution mass spectra were obtained by electron impact at 70 eV with a Kratos-MS-50 instrument. Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR. Melting points were determined using an Electron-Thermal 9100 apparatus and are uncorrected. The

specific rotations ($[\alpha]_0$) were measured on a Perkin-Elmer 240 instrument and are given in units of 10^{-1} deg cm^2 g^{-1}. Thin-layer chromatography was performed on silica gel IB-F pre-coated sheets purchased from J. T. Baker. Visualization was accomplished by exposure to iodine vapour. Preparative chromatography was performed with silica gel 60 (63–200 mm), purchased from EM Science and neutral activated aluminium oxide [50–200 micron (70–290 mesh ASTM)], purchased from Janssen Chemical Co. Sonication was accomplished by immersion of the reaction flask in the centre of a Bransonic model 2200 ultrasonic cleaning bath containing a dilute aqueous solution of Alconox detergent.

Dichloromethane was distilled from calcium hydride and 1,2-dimethoxyethane was distilled from lithium aluminium hydride or sodium under argon just prior to use. Anhydrous, reagent grade ethanol and sodium iodide were used directly. The L-glutamic acid and enantiopure α-phenylethylamine were purchased from Janssen Chemical Co. All other reagents were purchased from the Aldrich Chemical Co. and used as received. Glassware for anhydrous reactions was dried in an oven at 120 °C overnight and cooled under a stream of dry argon.

(*S*)-5-Ethoxycarbonylpyrrolidin-2-one was prepared by the procedure we reported earlier.[4] The methods used here for the preparation of (5*S*)-5-(tosyloxymethyl)pyrrolidin-2-one and for the conversion of this toluene-*p*-sulfonate to (5*R*)-5-methylpyrrolidin-2-one were similar to those we reported earlier, but procedural changes that led to improved yields and ease of isolation are presented in this section. The hydrogenation procedure reported here is similar to that described by Provot *et al.*[21] 1-Chloromethyl-5-methylpyrrolidin-2-one, **2**, was prepared using our earlier procedure.[4]

(5*S*)-5-(Tosyloxymethyl)pyrrolidin-2-one

A solution of 5-ethoxycarbonylpyrrolidin-2-one (15.7 g, 100 mmol) in water (50 cm^3) was slowly added to a solution of sodium boranuide ($NaBH_4$; 2.20 g, 58 mmol) in water (50 cm^3) at 0 °C. The mixture was allowed to warm to room temperature and stirring was continued for a further 2 h. The water was evaporated to give a dry residue which was redissolved in water (100 cm^3). The solution was then concentrated to a volume of 40 cm^3 and then treated with sodium hydroxide (5.0 g, 120 mmol), toluene-*p*-sulfonyl chloride (18.10 g, 90 mmol) in dichloromethane (100 cm^3) and tetrabutylammonium hydrogen sulfate (1.03 g, 3.00 mmol) were added. The reaction flask was immersed in an ultrasonic bath maintained at 20 °C and stirred vigorously for 6 h. The organic layer was separated and extracted with dichloromethane (50 cm^3). The organic layers were combined and dried with anhydrous sodium sulfate. The solvent was evaporated to give a residue which was recrystallized from hexane–dichloromethane to give the title compound (14.7 g, 62.1 mmol, 62%) as a white solid, mp 129–130 °C (lit.,[20] 128.5–130 °C); $\delta_H(CDCl_3)$ 7.79 (2 H, d, *J* 8.4), 7.30 (2 H, d, *J* 8.4), 6.20 (1 H, br), 4.00 (3 H, m), 2.46 (3 H, s), 2.32 (3 H, m) and 1.80 (1 H, m); $\delta_C(CDCl_3)$ 178.0, 145.2, 132.3, 129.9, 127.8, 71.8, 52.5, 29.2, 22.7 and 21.5; ν_{max}(neat)/cm^{-1} 1705; $[\alpha]_D^{20}$ −7.1 (*c* 0.10, EtOH) {lit.,[20] $[\alpha]_D^{20}$ −7.1 (*c* 1.0, EtOH)}.

(*R*)-5-Methylpyrrolidin-2-one 1

A modification of Ringdahl and co-workers' procedure was used.[3b,4] A mixture of dry 1,2-dimethoxyethane (800 cm^3), (5*S*)-5-(tosyloxymethyl)pyrrolidin-2-one (53.55 g, 202 mmol) and sodium iodide (91.93 g, 612 mmol) was refluxed for 24 h. The solid was removed by vacuum filtration and the solvent removed at reduced pressure. A stainless steel reaction bomb was charged with dry ethanol (200 cm^3), anhydrous sodium acetate (10.7 g, 130 mmol), dry 5% palladium-on-carbon catalyst (5 g) and crude (5*R*)-5-iodomethylpyrrolidin-2-one (the oil prepared above) in that order. The vessel was flushed with hydrogen, sealed, evacuated briefly, and then pressured to 50 psi (1 psi ≈ 6.89 × 10^3 Pa) of hydrogen. The reaction vessel was maintained at ambient temperature for several hours until hydrogen was no longer absorbed. After the pressure had been released and the reaction bomb opened, the mixture was filtered and the insoluble material washed with ethanol (25 cm^3). The filtrates were combined, concentrated and the residue redissolved in chloroform (300 cm^3). This solution was washed successively with saturated aqueous $Na_2S_2O_3$ (2 × 25 cm^3) and saturated aqueous NaCl (25 cm^3). The organic solution was dried ($MgSO_4$) and filtered, the solvent removed, and the crude product distilled to give the pure title compound (10.35 g, 104 mmol, 82%) as a colourless oil, bp 66 °C/3 mmHg;[3b,4] R_f 0.19 (diethyl ether, silica gel); $\delta_H(CDCl_3)$ 7.66 (1 H, br), 3.77 (1 H, m), 2.26 (3 H, m), 1.66 (1 H, m) and 1.23 (3 H, d, *J* 5.7); $\delta_C(CDCl_3)$ 178.8, 50.3, 30.8, 29.1 and 22.2; ν_{max}(neat)/cm^{-1} 3417, 2972, 1667, 1423, 1381, 1340, 1282 and 1139; *m*/*z* (rel. intensity) 100 (2%), 99 (4), 98 (5), 82 (1), 70 (2), 66 (1), 57 (2), 56 (28), 55 (17) and 54 (5); $[\alpha]_D^{20}$ +16.0 (*c* 1.0, EtOH).

Preparation of 1-chloromethylpyrrolidin-2-one 4

A mixture of pyrrolidin-2-one (74.3 g, 873 mmol) and paraformaldehyde (26.2 g) was heated to reflux in an oil bath for 3 h. The slurry was cooled in an ice bath and then thionyl chloride (103.9 g, 873 mmol) was added, dropwise, over a period of 30 min. The resultant solution was stirred at ambient temperature for 1 h. Distillation *in vacuo* first gave a forerun of unchanged thionyl chloride and this was followed by the title compound **4** (60.64 g, 52%), bp 102–103 °C/2 mm Hg (lit.,[6a] 97–97.5 °C/4 mmHg).

General procedure for the preparation of 1-(*N*-alkylaminomethyl)pyrrolidin-2-ones and 1-(*N*,*N*-dialkylaminomethyl)pyrrolidin-2-ones

A mixture of amine (7.5 mmol) and triethylamine (7.5 mmol) in dry methylene chloride (freshly distilled from CaH_2); 50 cm^3 was treated with a solution of 1-chloromethylpyrrolidin-2-one **4** (7.5 mmol) dropwise, over 1 h at ambient temperature. The reaction mixture was then refluxed for 24 h, cooled and washed with saturated aqueous $NaHCO_3$ (2 × 15 cm^3). The organic layer was dried ($MgSO_4$) and concentrated. The oily residue was purified by chromatography on activated neutral aluminium oxide, eluting with diethyl ether–light petroleum.

1-(*N*-*tert*-butylaminomethyl)pyrrolidin-2-one 5a. 1-Chloromethylpyrrolidin-2-one **4** (1.00 g, 7.5 mmol), *tert*-butylamine (0.55 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound **5a** (0.90 g, 5.65 mmol, 78%) as a colourless oil, R_f 0.16 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 4.24 (2 H, s), 3.53–3.37 (3 H, m), 2.37 (2 H, t, *J* 11.7), 2.01 (2 H, m) and 1.14 (9 H, s); $\delta_C(CDCl_3)$ 175.2, 52.5, 46.1, 31.7, 29.3, 28.8 and 18.0; *m*/*z* (rel. intensity) 113 (36%), 98 (63), 85 (37), 86 (18), 70 (84), 57 (48), 41 (100) and 39 (39); ν_{max}(neat)/cm^{-1} 3446, 2968, 1680 and 1287 (Found: M$^+$, 170.1868. Calc. for $C_9H_{18}N_2O$: *M*, 170.1866).

1-(*N*-Cyclohexylaminomethyl)pyrrolidin-2-one 5b. 1-Chloromethylpyrrolidin-2-one **4** (1.00 g, 7.5 mmol), cyclohexylamine (0.74 g, 7.5 mmol) and triethylamine (0.76 mg, 7.5 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound **5b** (1.10 g, 5.63 mmol, 75%) as a light yellow oil; R_f 0.10 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 4.26 (2 H, s) 3.46–3.39 (3 H, m), 2.44–2.41 (3 H, m), 2.07–1.96 (2 H, m), 1.88–1.84 (2 H, m), 1.74–1.70 (2 H, m) and 1.27–1.05 (6 H, m); $\delta_C(CDCl_3)$ 175.2, 54.8, 53.2, 46.5, 33.4, 32.3, 26.5, 24.9 and 16.1; *m*/*z* (rel. intensity) 196 (10%), 195 (92), 113 (19), 98 (100), 86 (21), 70 (35) and 55 (22); ν_{max}(neat)/cm^{-1} 3450,

2927, 2854, 1686, 1547 and 1493 (Found: M^+, 196.1533. Calc. for $C_{11}H_{20}N_2O$: *M*, 196.1535).

1-(*N*-Phenylaminomethyl)pyrrolidin-2-one 5c. 1-Chloromethylpyrrolidin-2-one **4** (1.00 g, 7.5 mmol), aniline (0.70 g, 7.5 mmol) and triethylamine (0.76, 7.5 mmol) were treated as described above for 24 h. Chromatography of the crude product gave the title compound **5c** (1.117 g, 5.88 mmol, 78%) as a white solid, mp 136.2–137.7 °C; R_f 0.25 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 7.22–7.16 (2 H, m), 6.77–6.73 (3 H, m), 4.76 (2 H, s), 4.40 (1 H, br), 3.40 (2 H, t, *J* 7.0), 2.38 (2 H, t, *J* 7.9) and 1.96 (2 H, m); $\delta_C(CDCl_3)$ 175.6, 145.8, 129.6, 118.8, 113.4, 145.8, 52.0, 46.1, 31.3 and 17.9; *m/z* (rel. intensity) 190 (20%), 105 (100), 104 (78), 98 (81), 84 (2), 85 (41), 77 (100), 70 (35) and 51 (60); ν_{max}(neat)/cm^{-1} 3305, 3120, 3039, 2930, 1660, 1606, 1259, 755 and 697 (Found: M^+, 190.1102. Calc. for $C_{11}H_{14}N_2O$: *M*, 190.1106).

1-(*N*-Benzylaminomethyl)pyrrolidin-2-one 5d. 1-Chloromethylpyrrolidin-2-one **4** (1.00 g, 7.5 mmol), benzylamine (0.80 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound **5d** (1.14 g, 5.63 mmol, 75%) as a colourless oil, R_f 0.27 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 7.32–7.23 (5 H, m), 4.26 (2 H, s), 3.75 (2 H, s), 3.37 (2 H, m), 2.34–2.29 (3 H, m) and 1.93 (2 H, t, *J* 7.0); $\delta_C(CDCl_3)$ 175.9, 140.1 (ipso), 128.6–127.1, 72.5, 46.0, 31.2, 18.0 and 15.1; *m/z* (rel. intensity) 203 (72%), 160 (1), 125 (7), 118 (7), 98 (100), 91 (36) and 70 (30); ν_{max}(neat)/cm^{-1} 3445, 3011, 3000, 2929, 2876, 1682, 1286, 1129, 742 and 700; (Found: M^+, 204.1185. Calc. for $C_{12}H_{16}N_2O$: *M*, 204.1184).

1-{*N*-[(1*S*)-1-Ethoxycarbonyl-2-methylpropyl]aminomethyl}pyrrolidin-2-one 5e. 1-Chloromethylpyrrolidin-2-one **4** (1.00 g, 7.5 mmol), L-valine ethyl ester {0.907 g, 7.5 mmol; $[\alpha]_D^{20}$ +23.0 (*c* 2.0, MeOH)} and triethylamine (0.76, 7.5 mmol) were treated as described above for 24 h. Chromatography of the crude product gave the title compound **5e** (1.28 g, 5.29 mmol, 71%) as a colourless oil, R_f 0.45 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ AB (2 H): 4.30 (1 H, d, *J* 12.5) and 3.95 (1 H, d, *J* 12.5), 4.07 (2 H, m), 3.40 (1 H, m), 3.30 (1 H, m), 3.02 (1 H, d, *J* 5.6), 2.26 (3 H, m), 1.86 (3 H, m), 1.20 (3 H, t, *J* 7.1), 0.86 (6 H, d, *J* 5.6) and 0.78 (3 H, d, *J* 5.6); $\delta_C(CDCl_3)$ 175.5, 175.3, 64.7, 60.7, 57.2, 46.1, 31.9, 31.3, 19.3, 18.0 (2 C) and 14.3; *m/z* (rel. intensity) 242 (9%), 241 (60), 213 (2), 181 (20), 167 (30), 126 (2), 98 (100), 70 (16) and 41 (27); ν_{max}(neat)/cm^{-1} 3449, 2963, 2874, 1725, 1686, 1465 and 1368; $[\alpha]_D^{20}$ −49.90 (*c* 4.0, diethyl ether) (Found: M^+, 242.1603. Calc. for $C_{12}H_{22}N_2O_3$: *M*, 242.1630).

1-{*N*-(1-Phenylethyl)aminomethyl}pyrrolidin-2-one 5f. 1-Chloromethylpyrrolidin-2-one **4** (100 g, 7.5 mmol), (−)-phenylethylamine {0.907 g, 7.5 mmol; $[\alpha]_D^{22}$ −39.0 (*c* = neat)} and triethylamine (0.760 g, 7.5 mmol) were treated as described above for 48 h. Chromatography of the crude product gave the title compound **5f** (1.23 g, 5.63 mmol, 75%) as white crystals, mp 59.7–60.9 °C; R_f 0.34 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 7.33–7.25 (5 H, m), AB (2 H): 4.25 (1 H, d, *J* 12.5) and 3.80 (1 H, q, *J* 6.6), 4.03 (1 H, d, *J* 12.5), 3.33 (2 H, t, *J* 7.4), 2.31–2.23 (2 H, m), 2.15 (1 H, s), 1.89–1.83 (2 H, m) and 1.34 (3 H, d, *J* 6.6); $\delta_C(CDCl_3)$ 175.7, 145.4 (ipso), 128.5, 129.2, 126.6, 56.1, 55.9, 46.9, 31.3, 24.5 and 16.0; *m/z* rel. intensity) 133 (9%), 105 (100), 91 (16), 85 (20), 79 (20), 77 (25), 65 (8), 51 (20) and 41 (18); ν_{max}(neat)/cm^{-1} 3319, 2928, 1670, 1496, 1379, 1266, 1148, 1013, 761 and 702; $[\alpha]_D^{20}$ −81.25 (*c* 4.0, diethyl ether) (Found: M^+, 218.1415. Calc. for $C_{13}H_{18}N_2O$: *M* 218.1419).

1-{[(2*S*)-2-Ethoxycarbonylpyrrolidin-1-yl]methyl}pyrrolidin-2-one 5g. 1-Chloromethylpyrrolidin-2-one **4** (0.930 g, 6.99 mmol), (2*S*)-proline ethyl ester (1.00 g, 6.99 mmol) and triethylamine (0.705 g, 6.99 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound **5g** (1.528 g, 6.368 mmol, 85%) as a light yellow oil, R_f 0.39 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 4.20–4.13 (4 H, m), 3.56–3.50 (2 H, m), 3.38–3.35 (1 H, m), 3.15 (1 H, m), 2.59 (1 H, q, *J* 8.4), 2.35 (2 H, t, *J* 8.7), 2.06–1.82 (6 H, m) and 1.25 (3 H, t, *J* 7.1); $\delta_C(CDCl_3)$ 175.8, 174.1, 63.2, 61.1, 60.7, 52.1, 47.5, 31.2, 29.8, 23.6, 18.1 and 14.3; *m/z* (rel. intensity) 194 (1%), 167 (16), 142 (10), 126 (2), 98 (100), 82 (11), 70 (43), 55 (10) and 41 (22); ν_{max}(neat)/cm^{-1} 2977, 1694, 1494, 1444, 1394, 1374, 1280, 1188 and 1093; $[\alpha]_D^{20}$ −67.75 (*c* 4.14, diethyl ether) (Found: M^+, 240.1476. Calc. for $C_{12}H_{20}N_2O_3$: *M*, 240.1474).

1-(*N*,*N*-Diethylaminomethyl)pyrrolidin-2-one 5h. 1-Chloromethylpyrrolidin-2-one **4** (2.00 g, 15.03 mmol), diethylamine (1.08 g, 15.03 mmol) and triethylamine (1.52 g, 15.03 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound[16,17] **5h** (1.79 g, 10.52 mmol, 70%) as a colourless oil, R_f 0.46 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 4.07 (2 H, s), 3.46 (2 H, t, *J* 7.0), 2.56 (4 H, q, *J* 7.1), 2.37 (2 H, t, *J* 8.1), 2.01 (2 H, br d s) and 1.04 (6 H, t, *J* 7.1); $\delta_C(CDCl_3)$ 175.8, 60.9, 47.4, 45.4, 31.4, 18.2 and 12.4; *m/z* rel. intensity) 170 (2%), 155 (1), 141 (18), 98 (69), 99 (7), 86 (100), 85 (22), 72 (100), 70 (31), 58 (21), 57 (25) and 58 (24); ν_{max}(neat)/cm^{-1} 2969, 1682, 1464 and 1269 (Found: M^+, 170.1413. Calc. for $C_9H_{18}N_2O$: *M*, 170.1419).

1-(*N*,*N*-Diisopropylaminomethyl)pyrrolidin-2-one 5i. 1-Chloromethylpyrrolidin-2-one **4** (1.00 g, 7.5 mmol), diisopropylamine (0.75 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound **5i** (0.94 g, 5.100 mmol, 68%) as a colourless oil, R_f 0.58 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 4.13 (2 H, s), 3.418 (2 H, t, *J* 7.0), 2.97 (2 H, m), 2.43–2.35 (2 H, m), 2.06–1.93 (2 H, m) and 1.07 (12 H, d, *J* 5.6); $\delta_C(CDCl_3)$ 175.2, 54.3, 47.8, 46.6, 32.2, 21.2 and 18.0; *m/z* (rel. intensity) 183 (2%), 155 (17), 127 (0.6), 114 (12), 113 (6), 100 (35), 98 (100), 84 (28), 70 (34) and 56 (38); ν_{max}(neat)/cm^{-1} 2965, 2873, 1686, 1464, 1394, 1282 and 1204 (Found: M^+, 198.1740. Calc. for $C_{11}H_{22}N_2O$: *M*, 198.1732).

1-(*N*,*N*-Dicyclohexylaminomethyl)pyrrolidin-2-one 5j. 1-Chloromethylpyrrolidin-2-one **4** (1.00 g, 7.5 mmol), dicyclohexylamine (1.37 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) were refluxed together for 3 days. Chromatography of the crude material gave an oil that was recrystallized from hexane to give the title compound **5j** (0.67 g, 2.40 mmol, 32%) as white crystals, mp 71.1–72.2 °C; R_f 0.60 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 4.21 (2 H, s), 3.40 (2 H, t, *J* 7.0), 2.48 (2 H, m), 2.41–2.35 (2 H, m), 1.97–1.91 (2 H, m), 1.75–1.68 (8 H, m), 1.23–1.22 (8 H, m) and 1.14 (4 H, m); $\delta_C(CDCl_3)$ 175.1, 57.8, 55.4, 53.4, 45.4, 32.4, 26.6, 26.1 and 18.1; *m/z* (rel. intensity) 278 (1%), 235 (9), 195 (51), 180 (84), 152 (8), 110 (13), 98 (100), 70 (30) and 50 (33); ν_{max}(neat)/cm^{-1} 2924, 2851 and 1448 (Found: M^+, 278.2359. Calc. for $C_{17}H_{30}N_2O$: *M*, 278.2358).

1-[(*N*-Methyl-*N*-phenylamino)methyl]pyrrolidin-2-one 5k. 1-Chloromethylpyrrolidin-2-one **4** (1.00 g, 7.5 mmol), *N*-methylaniline (0.80 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound **5k** (1.07 g, 5.25 mmol, 75%) as a pale yellow oil, R_f 0.48 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 7.25–6.80 (5 H, m), 4.89 (2 H, s), 3.28 (2 H, t, *J* 7.0), 2.99 (3 H, s), 2.38 (2 H, t, *J* 7.9) and 1.97–1.92 (2 H, m); $\delta_C(CDCl_3)$ 175.6, 148.1, 129.4, 116.0, 113.0, 60.2, 46.4, 38.1, 31.0 and 17.9; *m/z* (rel. intensity) 204 (27%), 175 (1), 161 (1), 121 (30), 98 (100), 77 (26), 70 (53) and 41 (30); ν_{max}(neat)/cm^{-1} 3059, 2889, 1678, 1600, 1461, 1360, 1197, 1123, 1035, 968, 875 and 661 (Found: M^+, 204.1266. Calc. for $C_{12}H_{16}N_2O$: *M*, 204.1263).

(5*R*)-1-(*N*,*N*-Diethylaminomethyl)-5-methylpyrrolidin-2-one 3a. (5*R*)-1-Chloromethyl-5-methylpyrrolidin-2-one **2** (0.50 g, 3.19 mmol), diethylamine (0.23 g, 3.19 mmol) and triethylamine (0.33 g, 3.18 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound

3a (0.44 g, 2.39 mmol, 75%) as a colourless oil, R_f 0.46 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ AB (2 H): 4.43 (1 H, d, *J* 12.6) and 3.62 (1 H, d, *J* 12.6), 3.85 (1 H, m), 2.58–2.43 (4 H, m), 2.41–2.36 (3 H, m), 2.21–2.17 (1 H, m), 1.28 (3 H, d, *J* 5.6) and 1.10 (6 H, t, *J* 7.1); $\delta_C(CDCl_3)$ 175.5, 58.1, 52.5, 45.0, 30.7, 26.7, 19.5 and 12.0; *m/z* (rel. intensity) 128 (22%), 112 (100), 98 (45), 84 (45), 71 (13), 59 (44), 44 (11) and 41 (45); ν_{max}(neat)/cm^{-1} 2968, 2874, 1457 and 1380; $[\alpha]_D^{20}$ +38.80 (*c* 3.5, diethyl ether) (Found: M^+, 184.1572. Calc. for $C_{10}H_{20}N_2O$: *M*, 184.1576).

(5*R*)-1-(*N*-*tert*-Butylaminomethyl)-5-methylpyrrolidin-2-one 3b. (5*R*)-1-Chloromethyl-5-methylpyrrolidin-2-one **2** (0.50 g, 3.18 mmol), *tert*-butylamine (0.23 g, 3.18 mmol) and triethylamine (0.32 g, 3.18 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound **3b** (0 396 g, 2.15 mmol, 68%) as colourless oil, R_f 0.23 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ AB (2 H): 4.66 (1 H, d, *J* 12.6) and 3.75 (1 H, d, *J* 12.6), 3.95–3.90 (1 H, m), 2.41–2.49 (2 H, m), 2.23–2.16 (1 H, m), 1.80 (1 H, br d s), 1.61–1.56 (1 H, m), 1.23 (3 H, d, *J* 5.6) and 1.13 (9 H, s); $\delta_C(CDCl_3)$ 175.2, 52.4, 50.2, 44.0, 30.8, 29.5, 26.8 and 19.8; *m/z* (rel. intensity) 128 (22%), 112 (100), 98 (96), 83 (40), 71 (13), 55 (64), 41 (36) and 28 (71); ν_{max}(neat)/cm^{-1} 3446, 2966, 1679, 1458 and 1379; $[\alpha]_D^{20}$ +12.04 (*c* 3.1, diethyl ether) [Found: M^+, 183.1493. Calc. (M^+ − 1 peak) for $C_{10}H_{19}N_2O$: *M*, 183.1497].

(5*R*)-1-{[(2*S*)-2-Ethoxycarbonylpyrrolidin-1-yl]methyl}-5-methylpyrrolidin-2-one 3c. (5*R*)-1-Chloromethyl-5-methylpyrrolidin-2-one **2** (0.15 g, 1.02 mmol), (2*S*)-proline ethyl ester (0.46 g, 1.02 mmol) and triethylamine (0.103 g, 1.02 mmol) were treated as described above for 24 h. Chromatography of the crude material gave the title compound **3c** (0.19 g, 0.77 mmol, 75%) as a light yellow oil, R_f 0.44 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 4.50–4.46 (1 H, d, *J* 13.6), 4.23–4.16 (2 H, m), 3.94–3.89 (1 H, m), 3.86 (1 H, d, *J* 13.6), 3.49–3.47 (1 H, m), 3.30–3.27 (1 H, m), 2.51–2.48 (1 H, m), 2.43–2.36 (2 H, m), 2.19–2.11 (2 H, m), 1.87–1.81 (3 H, m), 1.66–1.63 (1 H, m) and 1.32–1.18 (6 H, m); $\delta_C(CDCl_3)$ 175.5, 173.8, 63.0, 60.8, 58.2, 52.6, 52.3, 30.6, 29.4, 26.8, 23.3, 19.6 and 14.3; *m/z* (rel. intensity) 254 (1%), 181 (16), 155 (13), 142 (13), 112 (100), 83 (18) and 55 (20); ν_{max}(neat)/cm^{-1} 2970, 1738, 1691, 1454 and 1394; $[\alpha]_D^{20}$ −64.02 (*c* 2.5, diethyl ether) (Found: M^+, 254.1625. Calc. for $C_{13}H_{22}N_2O_3$: *M*, 254.1630).

(5*R*)-1-{*N*-[(1*S*)-1-Ethoxycarbonyl-2-methylpropyl]aminomethyl}-5-methylpyrrolidin-2-one 3d. (5*R*)-1-Chloromethyl-5-methylpyrrolidin-2-one **2** (0.50 g, 3.19 mmol), L-valine ethyl ester {0.46 g, 3.19 mmol; $[\alpha]_D^{22}$ +23.0 (*c* 2.0, MeOH)} and triethylamine (0.32 g, 3.19 mmol) were treated as described above for 24 h. Chromatography of the crude product gave the title compound **3d** (0.64 g, 2.51 mmol, 79%) as a colourless oil, R_f 0.21 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ AB (2 H): 4.41 (1 H, d, *J* 15.88) and 3.92 (1 H, *J* 15.9), 4.23–4.15 (2 H, m), 3.84 (1 H, q), 3.07 (1 H, d, *J* 5.7), 2.41–2.31 (3 H, m), 2.15–2.12 (2 H, m), 1.63–1.50 (1 H, m), 1.31 (3 H, t, *J* 7.1), 1.25 (3 H, d, *J* 5.7) and 0.89 (6 H, d, *J* 7.9); $\delta_C(CDCl_3)$ 175.7, 175.0, 64.8, 60.7, 54.3, 52.8, 31.7, 30.3, 26.7, 19.7, 19.5, 18.0 and 14.4; *m/z* (rel. intensity) 128 (5%), 115 (2), 99 (8), 84 (100), 72 (23), 56 (34), 44 (11) and 41 (61); ν_{max}(neat)/cm^{-1} 3357, 2965, 1726, 1685, 1458 and 1379; $[\alpha]_D^{20}$ −30.78 (*c* 4.0, diethyl ether) (Found: M^+, 256.1781. Calc. for $C_{13}H_{24}N_2O_3$: *M*, 256.1787).

(5*R*)-5-Methyl-1-[*N*(-1-phenylethyl)aminomethyl]pyrrolidin-2-one 3e. (5*R*)-1-Chloromethyl-5-methylpyrrolidin-2-one **2** (0.30 g, 1.91 mmol), (−)-phenylethylamine {0.23 g, 1.91 mmol; $[\alpha]_D^{20}$ −39.0 (*c* neat)} and triethylamine (0.19 g, 1.91 mmol) were treated as described above for 24 h. Chromatography of the crude product gave the title compound **3e** (0.34 g, 1.45 mmol, 75%) as a pale yellow oil, R_f 0.42 (diethyl ether on silica gel); $\delta_H(CDCl_3)$ 7.36–7.20 (5 H, m), 4.42 (1 H, d, *J* 12.5), 3.83–3.71 (1 H, m), 3.68–3.66 (2 H, m), 2.38–2.30 (2 H, m), 2.15–2.05 (2 H, m), 1.52–1.46 (1 H, m), 1.33 (3 H, d, *J* 6.8) and 1.03 (3 H, d, *J* 6.8); $\delta_C(CDCl_3)$ 175.9, 145.5 (ipso), 128.5, 127.1, 126.7, 55.4, 53.7, 30.5, 26.9, 24.7, 19.9 and 15.3; *m/z* (rel intensity) 133 (9%), 105 (100), 99 (9), 91 (11), 84 (40), 79 (37), 77 (39), 55 (14), 41 (35) and 28 (88); ν_{max}(neat)/cm^{-1} 3334, 2966, 1666, 1451, 1376, 766 and 706; $[\alpha]_D^{20}$ −60.04 (*c* 2.4 in diethyl ether) (Found: M^+, 232.1565. Calc. for $C_{14}H_{20}N_2O$: *M*, 232.1576).

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Paper 4/05510A
Received 12*th September* 1994
Accepted 13*th February* 1995