

# Synthesis of the Four Stereoisomers of Several 3-(1-Aminoethyl)pyrrolidines. Important Intermediates in the Preparation of Quinolone Antibacterials

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The use of *S*- $\alpha$ -methylbenzyl as a chiral auxiliary at  $N_1$  allowed separation of diastereomeric 2-pyrrolidinones substituted with an ester, ketoester, ketone and oxime at the  $C_4$  position. Reduction of each diastereomer of 4-[1-(hydroxyimino)ethyl]-1-(1-phenylethyl)-2-pyrrolidinone, **10s** and **10r**, provided a pair of epimeric amines, [**11sr** and **11ss**] and [**11rs** and **11rr**], that were separated by chromatography. The four stereoisomers of 4-(1-aminoethyl)-1-(1-phenylethyl)-2-pyrrolidinone, **11**, were elaborated into several stereochemically pure 3-(1-aminoethyl)pyrrolidines, **1** and **15-23**. These compounds are useful intermediates ( $C_7$  side chains) for quinolone antibacterials.

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## Introduction.

Pyrrolidinyl substituted naphthyridines, such as PD-118896 and PD-127152 (Figure 1), have been shown to possess excellent antibacterial activity and pharmacological profiles [1]. In exploring the structure-activity relationship of the pyrrolidine side chain we have shown that *N*-methylation of the 3-aminomethylpyrrolidinyl substituent increases *in vivo* activity [1]. We decided to explore the effect of moving this methyl group to the carbon adjacent to the terminal amine (Figure 1).

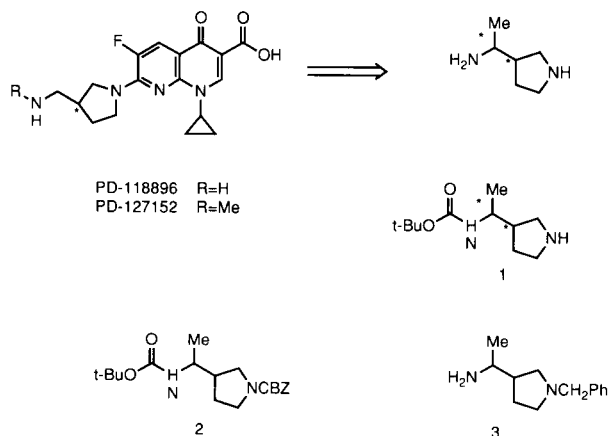
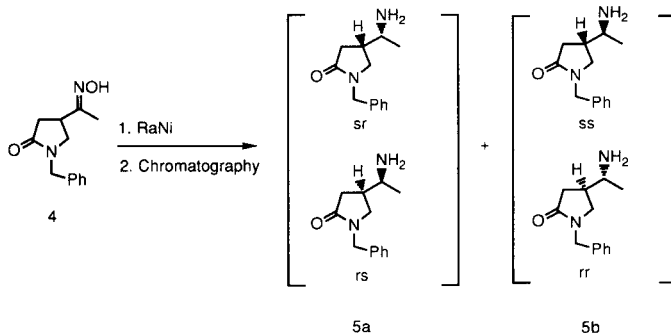


Figure 1

It has been reported that each pair of unresolved diastereomers of pyrrolidine **1** imparted a different spectrum of antibacterial activity when used as a side chain for quinolones. Each of these diastereomeric pairs was obtained when the pyrrolidines **2** were separated into enan-

tiomeric pairs of diastereomers by hplc and converted to **1**. The absolute stereochemistry at  $C_4$  and  $C_{1'}$  was not described [2]. Similarly, while **3** gave no useful separation, we found that 4-(1-aminoethyl)-1-benzyl-2-pyrrolidinones were separable by column chromatography into two pairs of diastereomers, **5a** and **5b** (Scheme 1). We now report the novel synthesis of all four stereoisomers of several 3-(1-aminoethyl)pyrrolidines, including **1**. While this work was in progress, the absolute stereochemistry for one of the compounds in this series was communicated [3].

Scheme 1 [a]



[a] Chiral descriptors specify stereochemistry of the  $C_4$  and  $C_{1'}$  centers.

## Results and Discussion.

The chromatographic separation of pyrrolidinones **5** was useful in that unresolved diastereomeric pairs could be separated. However, the problem of separating enan-

tiomers remained. If we removed the problem of enantiomers by fixing the C<sub>4</sub> center, and applied this chromatographic separation to two mixtures [5sr and 5ss] and [5rs and 5rr] [4], all four diastereomers of **5** could be separated. In our earlier work, the diastereomerically pure esters **6r** and **6s** [4] were obtained from dimethyl itaconate [5]. We felt that the chiral oximes **10s** and **10r** could be prepared from the known esters **6**. This would fix the chirality at C<sub>4</sub> and, assuming no racemization on reduction, would allow chromatographic separation of all four stereoisomers of **11** (Scheme 2).

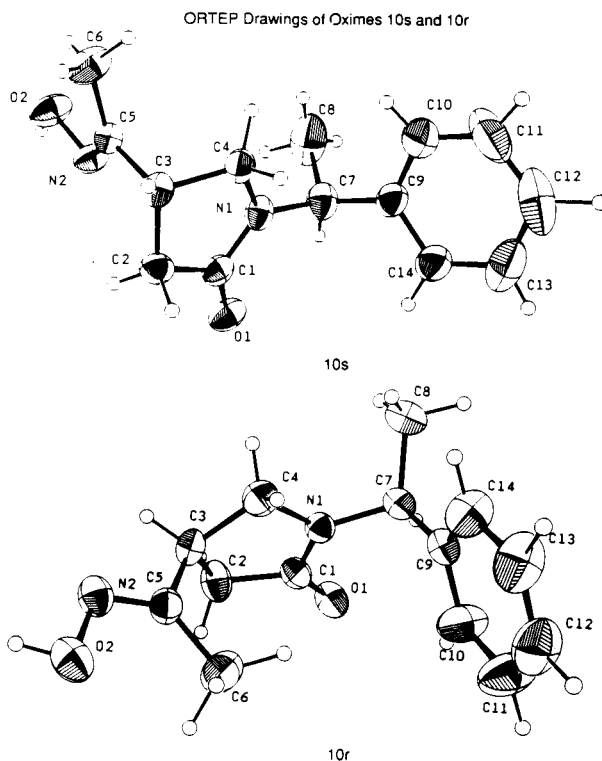
Acid hydrolysis of **6r** gave the corresponding carboxylic acid with no racemization (Scheme 2). Stereospecific conversion **7r** to the corresponding ketone by formation of the acid chloride and subsequent reaction with methyl cuprate failed. Instead, a mixture of **9a** and **9b**, resulting from epimerization at C<sub>4</sub> and the tertiary alcohols arising from dialkylation were obtained.

Treatment of the acid, **7r**, with carbonyldiimidazole, followed by addition of the magnesium salt of the half ester of ethyl malonate [6], gave the ketoesters, **8a** and **8b**, as a mixture of diastereomers. Although racemization had occurred, these diastereomers were easily separated by column chromatography. Decarboxylation of each of these ketoesters gave a 1:1 mixture of diastereomeric ketones **9**. Although the decarboxylation conditions led to epimerization of the C<sub>4</sub> position, the pure diastereomers **9a** and **9b** were once again readily separated by column chromatography. These ketones racemized on standing overnight in deuteriochloroform solution. On the basis of this observation, we expected epimerization in the formation of their corresponding oximes. We found that when a diastereomeric mixture of ketones **9** was converted to oximes **10**, column chromatography gave the pure oxime diastereomers,

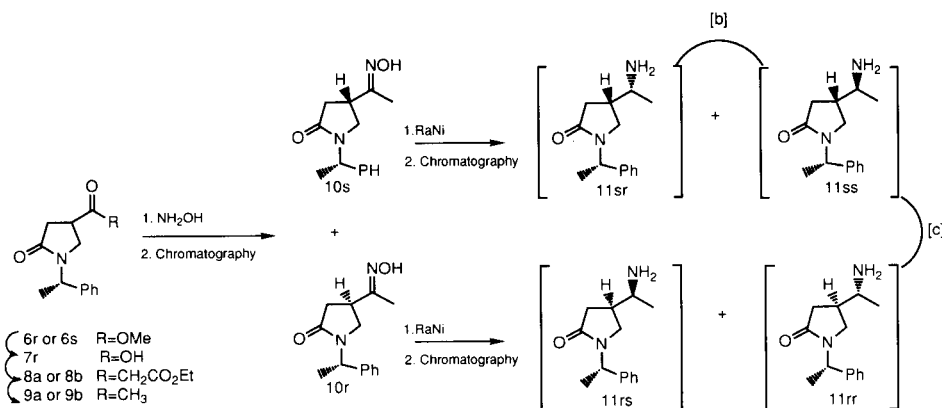
### 10s and 10r.

Recrystallization of **10s** and **10r** gave crystals suitable for X-ray crystallographic analysis. Using the known stereochemistry of the S- $\alpha$ -methylbenzylamine substituent, the stereochemistry at C<sub>4</sub> was unambiguously determined for each diastereomer. The ORTEP structures for oximes **10s** and **10r** are shown in Figure 2. The crystal data and experimental conditions are included in Table 1 and the crystallographic coordinates can be found in Table 2 [7].

Figure 2



Scheme 2 [a]



[a] The chiral decriptors specify stereochemistry at the C<sub>4</sub> and C<sub>1</sub> centers. [b] Separable by chromatography. [c] Separable if C<sub>4</sub> stereochemistry fixed before chromatography.

Table 1  
Crystal Data and Experimental Conditions

	10s	10r	12rr	12sr	14ss
Formula	C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O	C <sub>19</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	C <sub>19</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	C <sub>16</sub> H <sub>24</sub> N <sub>2</sub> O
Crystallization medium	diethyl ether/hexane	diethyl ether/hexane	ethyl acetate	dichloromethane/heptane	diethyl ether
Crystal size, mm	0.15 x 0.20 x 0.25	0.20 x 0.15 x 0.15	0.40 x 0.12 x 0.20	0.32 x 0.22 x 0.12	0.42 x 0.40 x 0.38
Radiation (Å)	CuKα: 1.54056	CuKα: 1.54056	MoKα: 0.71073	MoKα: 0.71073	MoKα: 0.71073
Cell dimension					
a, Å	11.91480(20)	6.8028(3)	10.047(6)	5.893(1)	6.0058(9)
b, Å	8.7203(4)	8.9244(3)	10.530(6)	6.367(2)	10.928(1)
c, Å	13.7431(6)	11.1684(5)	18.341(9)	13.079(6)	23.040(4)
α, deg				96.17(3)	
β, deg				91.87(3)	
γ, deg				96.20(2)	
Space group	Monoclinic P 2 <sub>1</sub>	Monoclinic P 2 <sub>1</sub>	Orthorhombic P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	Tridinic P <sub>1</sub>	Orthorhombic P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Z	4(2 molecules per asymmetric units)	2	4	1	4
Calcd density(g/cm <sup>3</sup> )	1.177	1.208	1.138	1.105	1.144
Scan speed(2θ, deg.min <sup>-1</sup> )	4	4	2.5 (variable)	2.5 (variable)	2.5 (variable)
μ(mm <sup>-1</sup> )	0.61	0.62	0.68	0.67	0.69
F(000)=	527.90	263.95	692	180	568
T. of data collection, °C	21	21	ambient	ambient	ambient
Data range measured, deg.	2<2θ<143.5	2<2θ<3.5	5<2θ<40	5<2θ<55	5<2θ<55
Ranges	-14≤h<14 -10≤k<0 -16≤l<0	-7≤h≤7 0≤k≤10 0≤l≤13	0<h<10 0<k<11 0<l<18	0<h<8 -9<k<9 -17<l<17	0<h<8 0<k<15 0<l<30
No. of reflections measured	3105	4135	2247	5205	4350
No. of unique reflections	2910	1391	1816	4481	3482
No. of reflections with I <sub>net</sub> >2.5 sigma (I <sub>net</sub> )	1792	1295	1789	4070	3301
No. of parameters	427	235	223	219	174
Final R factor. R <sub>f</sub> :	0.046	0.032	0.047	0.0702	0.0496
R <sub>w</sub> :	0.019	0.021	0.063	0.0837	0.0641

Table 2:  
Fractional Coordinates for Oximes 10s and 10r With e. s. d.'s in Parentheses

Atom	10s Molecule 1			10s Molecule 2			10r		
	x	y	z	x	y	z	x	y	z
O1	0.0977 (3)	0.34713	0.10430 (24)	0.7479 (3)	0.8526 (7)	0.3544 (3)	0.70573 (3)	0.84836	0.57736 (16)
O2	-0.1286 (4)	0.0843 (6)	-0.2353 (3)	0.9008 (3)	0.0779 (6)	0.3710 (3)	0.69542 (3)	1.57436 (3)	0.67385 (20)
N1	0.1190 (3)	0.4440 (7)	-0.0451 (3)	0.6864 (3)	0.6293 (6)	0.4087 (3)	0.94384 (25)	0.99765 (3)	0.66923 (16)
N2	-0.0958 (4)	0.2036 (7)	-0.1629 (3)	0.8404 (4)	0.2084 (7)	0.3929 (3)	0.77853 (3)	1.47774 (3)	0.60822 (19)
C1	0.0571 (5)	0.4037 (7)	0.0212 (4)	0.7603 (5)	0.7132 (8)	0.3726 (4)	0.79436 (4)	0.96798 (4)	0.58824 (21)
C2	-0.0671 (5)	0.4373 (8)	-0.0230 (4)	0.8575 (5)	0.6151 (9)	0.3579 (5)	0.75666 (5)	1.10374 (4)	0.51169 (3)
C3	-0.0744 (4)	0.4714 (7)	-0.1336 (4)	0.8507 (5)	0.4743 (8)	0.4239 (4)	0.87615 (4)	1.23065 (4)	0.57341 (23)
C4	0.0509 (5)	0.5199 (8)	-0.1340 (4)	0.7212 (5)	0.4680 (8)	0.4220 (4)	1.02311 (4)	1.14783 (4)	0.66056 (3)
C5	-0.1078 (4)	0.3337 (8)	-0.2026 (3)	0.9012 (4)	0.3277 (8)	0.3979 (4)	0.75190 (4)	1.34079 (4)	0.63650 (23)
C6	-0.1474 (7)	0.3647 (9)	-0.3119 (5)	1.0209 (6)	0.3334 (10)	0.3806 (6)	0.61443 (9)	1.28569 (6)	0.72521 (6)
C7	0.2460 (5)	0.4334 (9)	-0.0245 (4)	0.5754 (5)	0.6861 (8)	0.4248 (4)	1.02524 (3)	0.88791 (3)	0.75666 (21)
C8	0.2789 (6)	0.3185 (12)	-0.0962 (8)	0.4751 (6)	0.6041 (11)	0.3532 (5)	1.2495 (4)	0.88085 (5)	0.75316 (4)
C9	0.3001 (4)	0.5895 (8)	-0.0246 (4)	0.5739 (4)	0.6757 (7)	0.5353 (4)	0.94855 (4)	0.91796 (4)	0.87932 (20)
C10	0.3148 (6)	0.6593 (12)	-0.1095 (5)	0.4838 (5)	0.6153 (8)	0.5692 (5)	0.75892 (4)	0.87755 (5)	0.89960 (25)
C11	0.3597 (8)	0.8031 (14)	-0.1095 (7)	0.4831 (6)	0.6114 (11)	0.6677 (6)	0.67952 (6)	0.90262 (6)	1.00900 (3)
C12	0.3959 (6)	0.8811 (11)	-0.0207 (8)	0.5752 (7)	0.6709 (9)	0.7364 (4)	0.78932 (7)	0.96926 (6)	1.09932 (3)
C13	0.3847 (7)	0.8122 (11)	0.0650 (6)	0.6711 (6)	0.7355 (9)	0.7047 (5)	0.97797 (6)	1.00876 (5)	1.08363 (3)
C14	0.3351 (5)	0.6680 (10)	0.0636 (4)	0.6667 (4)	0.7347 (8)	0.6046 (5)	1.05649 (5)	0.98335 (5)	0.97146 (3)

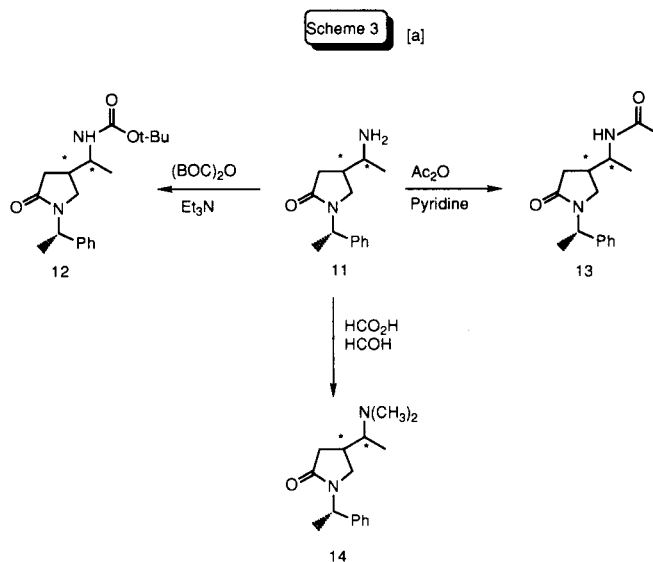
Reduction of each of the oximes, **10s** or **10r**, with Raney Nickel or platinum oxide gave a pair of diastereomers, [**11sr** and **11ss**] or [**11rs** and **11rr**], which were separated by column chromatography (Scheme 2). The optical purity of each diastereomer of **11** was determined by gas chromatography after derivatizing the terminal amine with a *tert*-butyldimethylsilyl group [8]. The results shown in Table 3 indicate that the separation by column chromatography of **11sr** from **11ss** and **11rs** from **11rr** gave each isomer in a  $\geq 97:1$  ratio. However, reduction of each oxime with Raney Nickel resulted in 3-15% racemization at C<sub>4</sub> with the oxime **10r** being slightly more prone to epimerization. Alternatively, platinum oxide gave only 1-3% racemization of the C<sub>4</sub> center. This epimerization resulted in contamination of each fraction with traces of its enantiomer.

Table 3

		Isomer Ratio [a]				
		[b]		[b]		
		11sr	11ss	11rs	11rr	
RaNi Reduction	10s →	11sr	95	1	4	[d]
		11ss	1	96	[d]	3
	10r →	11rs	11 [c]	[d]	89	[d]
		11rr	[d]	18 [c]	[d]	82
PtO <sub>2</sub> Reduction	10s →	11sr	94	3	3	[d]
		11ss	[d]	99	[d]	1
	10r →	11rs	2	[d]	98	[d]
		11rr	[d]	3	2	95

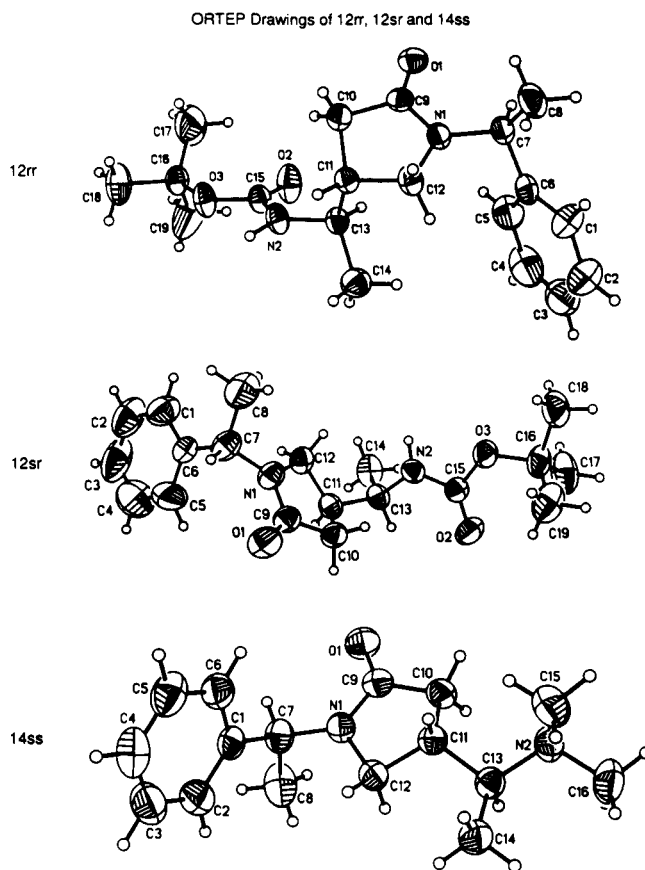
[a] Isomer ratios were determined by GC as described in the experimental section. [b] Separable by chromatography. [c] The starting oxime **10r** contained 3% of **10s**, thus accounting for 3% of **11sr** and 3% of **11ss** present. [d] Not detected.

Each diastereomer **11sr**, **11ss**, **11rs** and **11rr** was subjected to carbamylation, acetylation and dimethylation to give **12**, **13** and **14** respectively (Scheme 3). While the four diastereomers of the acetyl derivative **13** were all viscous oils, **12sr**, **12rr** and **14ss** gave crystals suitable for X-ray analysis. The ORTEP structures for **12sr**, **12rr** and **14ss** (Figure 3) define the absolute stereochemistry at the C<sub>1'</sub> center for all four diastereomeric amines **11**. The crystal data and experimental conditions are included in Table 1 and the crystallographic coordinates can be found in Table 4 [9].



[a] \* represents a pure chiral center.

Figure 3



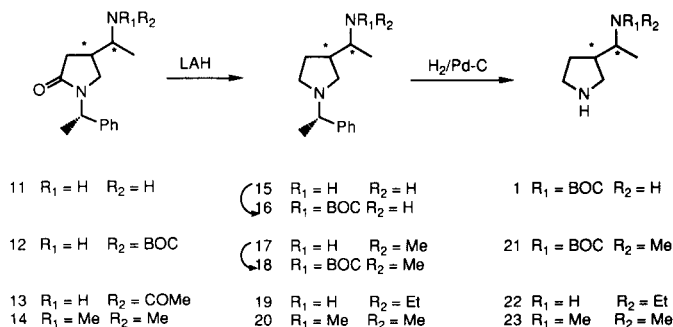
Reduction of each diastereomer of the amides **11-14** with lithium aluminum hydride gave the corresponding pyrrolidines **15**, **17**, **19** and **20** (Scheme 4). Protection of

Table 4  
Fractional Coordinates for 12rr, 12sr and 14ss

Atom	12rr			12sr			14ss		
	x	y	z	x	y	z	x	y	z
C1	1.4804 (5)	0.3221 (5)	0.6185 (3)	-0.7000 (3)	-0.3194 (3)	-0.2007 (2)	-0.2483 (3)	0.6339 (1)	0.56684 (7)
C2	1.5944 (6)	0.3036 (7)	0.6605 (4)	-0.8685 (3)	-0.3723 (3)	-0.1336 (2)	-0.4066 (4)	0.7254 (2)	0.56408 (9)
C3	1.5891 (8)	0.2387 (7)	0.7216 (4)	-1.0193 (3)	-0.5391 (3)	-0.1567 (2)	-0.3912	0.8277 (2)	0.6002 (1)
C4	1.4737 (8)	0.1827 (6)	0.7437 (4)	-1.0071 (3)	-0.6635 (3)	-0.2430 (3)	-0.2228 (4)	0.8404 (2)	0.63846 (9)
C5	1.3563 (6)	0.2010 (4)	0.7015 (3)	-0.8361 (3)	-0.6214 (3)	-0.3117 (2)	-0.0629 (4)	0.7512 (2)	0.64153 (9)
C6	1.3599 (4)	0.2725 (4)	0.6394 (2)	-0.6754 (3)	-0.4432 (3)	-0.2906 (2)	-0.0746 (3)	0.6490 (2)	0.60599 (8)
C7	1.2321 (4)	0.2981 (4)	0.5981 (2)	-0.4932 (3)	-0.3958 (3)	-0.3665 (2)	-0.2560 (3)	0.5197 (2)	0.52966 (7)
C8	1.2488 (4)	0.3658 (5)	0.5258 (2)	-0.3351 (3)	-0.1923 (3)	-0.3360 (2)	-0.4256 (5)	0.5217 (2)	0.48055 (8)
N1	1.1428 (3)	0.3702 (3)	0.6461 (1)	-0.5989 (2)	-0.3927 (2)	-0.4691 (2)	-0.2912 (2)	0.4123 (1)	0.56634 (5)
C9	1.0134 (4)	0.3447 (4)	0.6550 (2)	-0.5774 (3)	-0.5421 (3)	-0.5484 (2)	-0.1635 (3)	0.3107 (2)	0.56315 (7)
O1	0.9542 (3)	0.2528 (3)	0.6275 (1)	-0.47930	-0.70030	-0.54430	0.0086 (2)	0.3007 (1)	0.53524 (6)
C10	0.9539 (4)	0.4454 (4)	0.7039 (2)	-0.6989 (3)	-0.4760 (3)	-0.6415 (2)	-0.2710 (3)	0.2140 (1)	0.60079 (7)
C11	1.0752 (3)	0.5049 (3)	0.7404 (2)	-0.8566 (3)	-0.3187 (2)	-0.5966 (2)	-0.4325 (3)	0.2865 (1)	0.63910 (6)
C12	1.1828 (4)	0.4872 (3)	0.6822 (2)	-0.7320 (3)	-0.2243 (3)	-0.4942 (2)	-0.4942 (3)	0.3950 (2)	0.59983 (7)
C13	1.1044 (3)	0.4401 (3)	0.8156 (2)	-0.9188 (2)	-0.1553 (2)	-0.6674 (2)	-0.6321 (3)	0.2151 (1)	0.66163 (7)
N2	0.9995 (3)	0.4747 (3)	0.8641 (2)	-0.7164 (2)	-0.0350 (2)	-0.7008 (2)	-0.7928 (3)	0.2983 (2)	0.69499 (8)
C14	1.2388 (4)	0.4734 (4)	0.8463 (2)	-1.0786 (3)	-0.0064 (3)	-0.6162 (2)	-0.5576 (3)	0.1057 (1)	0.69364 (6)
C15	0.9129 (4)	0.3937 (4)	0.8931 (2)	-0.6650 (2)	-0.0381 (2)	-0.7995 (2)	-0.4429 (4)	0.1323 (2)	0.74769 (8)
O2	0.9150 (3)	0.2798 (3)	0.8835 (2)	-0.7630 (2)	-0.1532 (2)	-0.8709 (1)	-0.7359 (4)	0.0189 (2)	0.7032 (1)
C16	0.9137 (4)	0.3919 (4)	0.9705 (2)	-0.3991 (3)	0.1596 (3)	-0.9068 (2)			
O3	0.8235 (3)	0.4559 (3)	0.9338 (1)	-0.4857 (2)	0.1109 (2)	-0.8074 (1)			
C17	0.6321 (6)	0.3268 (8)	0.9160 (4)	-0.5809 (3)	0.2407 (3)	-0.9700 (2)			
C18	0.6343 (5)	0.4976 (5)	1.0023 (3)	-0.2065 (3)	0.3357 (3)	-0.8742 (2)			
C19	0.7635 (6)	0.3086 (7)	1.0262 (4)	-0.3067 (3)	-0.0320 (3)	-0.9623 (2)			

each diastereomer of the unsubstituted and monomethylated pyrrolidines **15** and **17** with di-*tert*-butyl dicarbonate gave **16** and **18**, assuring regiospecific coupling of N<sub>1</sub> to the quinolone substrate, **24**. The chiral auxiliary, the *S*- $\alpha$ -methylbenzyl moiety, was then removed by hydrogenolysis to give each diastereomer of the 3-(1-aminoethyl)pyrrolidines **1** and **21-23**.

Scheme 4 [a]



[a] \* represents a pure chiral center.

In summary, *S*- $\alpha$ -methylbenzyl as a chiral auxiliary allowed diastereomeric separation of several 2-pyrrolidinones substituted at the C<sub>4</sub> position, including oximes **10r** and **10s**. Reduction of each oxime without racemization fixed the chirality of C<sub>4</sub>, and allowed chromatographic separation of the resulting diastereomeric pairs [**11rs** and **11rr**] and [**11ss** and **11sr**] (Scheme 2). Each diastereomer of amine **11** was modified to give various 3-(1-aminoethyl)pyrrolidines **15-23** and **1**. These compounds, particularly pyrrolidines **1** and **21-23**, are useful intermediates in the synthesis of quinolone anti-infectives. The biological activity and structure-activity relationships for these compounds is beyond the scope of this paper. Some initial biological results have been communicated [10] and a detailed discussion will be the topic of a future publication.

## EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were taken on a Varian XL-300 spectrometer operating at 299.7 MHz for <sup>1</sup>H and 75 MHz for <sup>13</sup>C, a Varian XL-200 spectrometer operating at 199.8 MHz for <sup>1</sup>H and 50 MHz for <sup>13</sup>C or a Bruker AM250 spectrometer operating at 250 MHz for <sup>1</sup>H and 63 MHz for <sup>13</sup>C. Infrared spectra (ir) were determined on a Mattson Cygnus 100, a Biorad FTS 45 or Nicolet MX1 with 4 cm<sup>-1</sup> resolution. All mass spectra reported are electron impact unless reported otherwise and were obtained on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with an 11/250 Data System. Chemical ionization (CI) mass spectra were obtained on either a Finnigan 4500 GCMS using methane as the

reagent gas or a Fison Trio-2A (VG Biotech) using 1% ammonia in methane as the reagent gas. High resolution mass spectra were obtained on a VG Analytical 7070E/HF spectrometer. Elemental analysis was obtained on either a CEC Model 240 or 440 Elemental Analyzer. Column chromatography was performed with E. Merck silica gel 60, 70-230 or 230-400 mesh. Tetrahydrofuran (THF) was dried over sodium/benzophenone. Solutions were dried over magnesium sulfate.

### Methyl 5-Oxo-1-(1-phenylethyl)-3-pyrrolidinecarboxylates (**6r** and **6s**).

(*S*)-1-Phenylethylamine (77.6 g, 0.640 mole) and dimethyl itaconate (101 g, 0.639 mole) were combined in 1.5 l of toluene. The reaction was warmed to reflux. Toluene (400 ml x 3) was periodically distilled off over the first 8 hours to remove the methanol formed. Additional toluene (800 ml) was added to the reaction. After refluxing for another 15 hours, the reaction was allowed to cool then concentrated *in vacuo*. The residue was dissolved in methylene chloride (500 ml) and this solution was washed with 1*N* hydrochloric acid (3 x 100 ml). The organic phase was dried, filtered and concentrated to an oil (155 g). The crude material, suspended in ether/hexane (approximately 100 ml/1.3 l) was warmed gently. The supernatant was decanted from some insoluble residue, concentrated, then resuspended in ether/hexane (approximately 150 ml/60 ml). The cloudy solution was seeded with a pure crystal of **6r**. After standing for 20 days, the reaction was filtered. The resulting crystals were washed with ether/hexane (1/1) and dried to give pure **6r** as waxy, oily colorless crystals (mp 66.5-69.5°, 29.9 g, 19%). The filtrate was concentrated and chromatographed [silica gel/ethyl acetate:hexane (1:1)] giving **6s** (R<sub>f</sub> = 0.21, 33.8 g, 20%) as a viscous oil, a mixture of **6s** and **6r** (30.3 g, 19%) and **6r** (R<sub>f</sub> = 0.13, 25.7 g, 16%) as a solid. Analytical data for each isomer is listed below.

### Methyl [*S*-(*R*\*,*S*\*)]-5-Oxo-1-(1-phenylethyl)-3-pyrrolidinecarboxylate (**6r**).

Compound **6r** was obtained as a solid; <sup>1</sup>H nmr (deuteriochloroform/200 MHz):  $\delta$  1.54 (d, J = 7.0 Hz, 3H), 2.60-2.87 (m, 2H), 3.10-3.33 (m, 2H), 3.43-3.63 (m, 1H), 3.65 (s, 3H), 5.51 (q, J = 7.0 Hz, 1H), 7.22-7.47 (m, 5H); ir (liquid film): 2953, 1738, 1690, 1426, 1272, 1202, 702 cm<sup>-1</sup>; ms: (m/z) 247 (M<sup>+</sup>, base), 232 (M<sup>+</sup> -CH<sub>3</sub>), 216 (M<sup>+</sup> -OCH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph); Rotation: [ $\alpha$ ]<sub>D</sub> = -117° (c 1.1%, methanol).

Anal. Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.76; H, 7.02; N, 5.59.

### Methyl [*S*-(*R*\*,*R*\*)]-5-Oxo-1-(1-phenylethyl)-3-pyrrolidinecarboxylate (**6s**).

Compound **6s** was obtained as a viscous oil; <sup>1</sup>H nmr (deuteriochloroform/250 MHz):  $\delta$  1.54 (d, J = 7.1 Hz, 3H), 2.59-2.84 (m, 2H), 3.01-3.27 (m, 2H), 3.50-3.62 (m, 1H), 3.72 (s, 3H), 5.50 (q, J = 7.1 Hz, 1H), 7.24-7.37 (m, 5H), traces of ethyl acetate were observed; ir (liquid film): 2980, 1739, 1691, 1427, 1272, 702 cm<sup>-1</sup>; ms: (m/z) 247 (M<sup>+</sup>), 232 (M<sup>+</sup> -CH<sub>3</sub>, base), 216 (M<sup>+</sup> -OCH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph); Rotation: [ $\alpha$ ]<sub>D</sub> = -81.3° (c 0.9%, methanol).

Anal. Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>·0.25ethyl acetate: C, 66.90; H, 7.11; N, 5.20. Found: C, 67.16; H, 7.01; N, 5.32.

### 5-Oxo-1-(1-phenylethyl)-3-pyrrolidinecarboxylic Acid (**7**).

Crude **6** (1.28 moles) was suspended in 6*N* hydrochloric acid (2.8 l) and warmed to reflux over 1 hour. After refluxing 6 hours, the heat was removed and the reaction stirred for approximately

16 hours. The reaction was filtered and the filter pad was washed with 700 ml of ether/hexane (2:5). After drying the product was obtained as a white solid (mp 198-202°, 97.1 g, 32%); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>/250 MHz): δ 1.46 (d, J = 7.1 Hz, 3H), 2.43-2.62 (m, 2H), 3.05-3.27 (m, 2H), 3.45-3.55 (m, 1H), 5.24 (q, J = 7.1, 1H), 7.25-7.39 (m, 5H), 12.7 (br s, 1H); ir (potassium bromide): 2957, 1740, 1655, 1491, 1453, 1217, 1186, 701 cm<sup>-1</sup>; ms: (m/z) 233 (M<sup>+</sup>), 218 (M<sup>+</sup> -CH<sub>3</sub>, base), 105 (CHCH<sub>3</sub>Ph), 91 (CH<sub>2</sub>Ph).

*Anal.* Calcd. for C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub>·0.10H<sub>2</sub>O: C, 66.42; H, 6.52; N, 5.96; H<sub>2</sub>O, 0.77. Found: C, 66.52; H, 6.27; N, 5.70; H<sub>2</sub>O, 0.53.

Additional material was obtained by concentrating the acidic filtrate above. The residue was suspended in methylene chloride/water (1:1) and extracted over 8 hours using a liquid/liquid extractor. The organic layer was concentrated to a viscous oil (137 g), dissolved in 1N sodium hydroxide (950 ml) and extracted with diethyl ether (3 x 200 ml). The basic aqueous layer (pH = 12.3) was acidified with concentrated hydrochloric acid. A solid formed when the pH of the solution was approximately 4.3. At pH = 3.0 the solid disappeared. At pH = 1.8 an oil was present which solidified on further stirring. The reaction was filtered and the filter pad was washed with ether/hexane (2:5) then dried to give a white solid (88.4 g, 30%).

([S(R\*)]) Ethyl β,5-Dioxo-1-(1-phenylethyl)-3-pyrrolidinepropanoates (**8a** and **8b**).

The acid **7** (20.0 g, 85.7 mmoles) was suspended in dry THF (350 ml). The suspension was warmed to 40°. Carbonyldiimidazole (16.0 g, 98.6 mmoles) was added to the reaction in portions over 15 minutes. The reaction was warmed to 45° and stirred for 24 hours. To the reaction was added bis(3-ethoxy-1,3-dioxopropoxy)magnesium [7] (30.7 g, 107 mmoles). The reaction was warmed to reflux over 0.5 hours, refluxed 3.5 hours, then allowed to cool. The reaction was concentrated *in vacuo*. The residue in methylene chloride (600 ml) was washed with water (2 x 150 ml) and dilute sodium bicarbonate (saturated solution diluted 10 fold, 2 x 200 ml). Emulsions were present in all washes. The aqueous phases were washed with methylene chloride (2 x 100 ml). The organic layers were combined and washed with saturated sodium chloride (3 x 150 ml), dried and concentrated to give the desired product as a brown oil (29.8 g). The crude product was chromatographed (silica gel/ethyl acetate) giving, a pure diastereomer **8a** (Rf = 0.45, 10.5 g, 40%), a mixture of isomers **8a** and **8b** (9.68 g, 37%) and a pure diastereomer **8b** (Rf = 0.30, 1.61 g, 6%) as viscous oils. The analytical data for each isomer is given below.

#### Higher Rf Isomer (**8a**).

Compound **8a** was obtained as a viscous oil; <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 1.14-1.32 (m, 3H), 1.54 (d, J = 7.1 Hz, 3H), 2.57-2.78 (m, 2H), 3.05-3.24 (m, 1H), 3.30-3.46 (m, 1H), 3.48 (s, less than 1H), 3.59 (dd, J = 7.2, 6.4 Hz, 1H), 4.11-4.30 (m, 2H), 5.02 (s, less than 1H), 5.49 (q, J = 7.1 Hz, 1H), 7.22-7.43 (m, 5H), 12.19 (s, less than 1H), enol tautomer present; ir (liquid film): 2979, 1746, 1717, 1689, 1427, 1269, 1030, 703 cm<sup>-1</sup>; ms: (m/z) 303 (M<sup>+</sup>), 288 (M<sup>+</sup> -CH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph, base); Rotation: [α]<sub>D</sub> = -53.4° (c 1.0%, methanol).

*Anal.* Calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>·0.25H<sub>2</sub>O: C, 66.32; H, 7.04; N, 4.55. Found: C, 66.37; H, 7.02; N, 4.28.

#### Lower Rf Isomer (**8b**).

Compound **8b** was obtained as a viscous oil; <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 1.16-1.35 (m, 3H), 1.54 (d, J = 7.1 Hz, 3H), 2.58-2.78 (m, 2H), 2.97-3.27 (m) + 3.32-3.64 (m) + 4.94 (s)-5H total, 4.07-4.27 (m, 2H), 5.51 (q, J = 7.1 Hz, 1H), 7.19-7.46 (m, 5H), 12.04 (s, less than 1H), enol tautomer present; ir (liquid film): 2982, 1747, 1714, 1692, 1428, 1266, 703 cm<sup>-1</sup>; ms: (m/z) 304 (M<sup>+</sup> + 1), 288 (M<sup>+</sup> -CH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph, base); Rotation: [α]<sub>D</sub> = -80.1° (c 1.0%, methanol).

*Anal.* Calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>·0.25H<sub>2</sub>O: C, 66.32; H, 7.04; N, 4.55. Found: C, 66.08; H, 6.80; N, 4.20.

The diastereomers **8a** and **8b** were recombined with the purified mixture of isomers and used in the next step.

#### ([S(R\*)]) 4-Acetyl-1-(1-phenylethyl)-2-pyrrolidinones (**9a** and **9b**).

The ketoesters **8** (19.9 g, 65.8 mmoles) were dissolved in DMSO (84.0 ml). To the solution was added sodium chloride (8.30 g, 142 mmoles) and water (4.38 ml, 243 mmoles). The reaction was warmed to 130-135° for 20 hours, cooled to room temperature and partitioned between water (400 ml) and methylene chloride (80 ml). The resulting layers were separated. The aqueous layer was washed with methylene chloride (6 x 75 ml). The organic layers were combined, extracted with water (3 x 80 ml), dried and concentrated to give crude **9** (15.9 g) as a dark oil. The crude product was chromatographed [silica gel/THF:hexane (1:1)] giving, a pure diastereomer **9a** (Rf = 0.22, 5.53 g, 36%), a mixture of isomers **9a** and **9b** (3.14 g, 21%) and a pure diastereomer **9b** (Rf = 0.11, 5.54 g, 33%) as viscous oils. The analytical data for each isomer is given below.

#### Higher Rf Isomer (**9a**).

Compound **9a** was obtained as a viscous oil; <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.51 (d, J = 7.3 Hz, 3H), 2.16 (s, 3H), 2.63 (d, J = 8.4 Hz, 2H), 2.97-3.30 (m, 2H), 3.40-3.63 (m, 1H), 5.46 (q, J = 7.3 Hz, 1H), 7.18-7.43 (m, 5H); ir (liquid film): 2977, 1714, 1689, 1426, 788, 702 cm<sup>-1</sup>; ms: (m/z) 232 (M<sup>+</sup> + 1), 216 (M<sup>+</sup> -CH<sub>3</sub>), 188 (M<sup>+</sup> -COCH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph), 43 (COCH<sub>3</sub>, base); Rotation: [α]<sub>D</sub> = -92.5° (c 1.0%, methanol).

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.67; H, 7.56; N, 5.81.

#### Lower Rf Isomer (**9b**).

Compound **9b** was obtained as a viscous oil; <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.53 (d, J = 7.2 Hz, 3H), 2.09 (s, 3H), 2.65 (d, J = 8.0 Hz, 2H), 3.08-3.38 (m, 2H), 3.47 (t, J = 8.0 Hz, 1H), 5.48 (q, J = 7.2 Hz, 1H), 7.20-7.43 (m, 5H); ir (liquid film): 2988, 1715, 1688, 1427, 702 cm<sup>-1</sup>; ms: (m/z) 232 (M<sup>+</sup> + 1), 216 (M<sup>+</sup> -CH<sub>3</sub>), 188 (M<sup>+</sup> -COCH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph), 43 (COCH<sub>3</sub>, base); Rotation: [α]<sub>D</sub> = -105.4° (c 1.1%, methanol).

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>·0.25hexane: C, 73.63; H, 8.17; N, 5.54. Found: C, 73.34; H, 7.85; N, 5.28.

The diastereomers **9a** and **9b** were recombined with the purified mixture of isomers and used in the next step.

#### 4-[1-(Hydroxyimino)ethyl]-1-(1-phenylethyl)-2-pyrrolidinones (**10r** and **10s**).

To a solution of ketones **9** (12.9 g, 56.0 mmoles) in pyridine (223 ml) was added hydroxylamine hydrochloride (4.27 g, 61.6 mmoles). The reaction was warmed to 45°. After stirring for 24 hours, the pyridine was removed *in vacuo*, and the residue was



dissolved in chloroform (230 ml). The chloroform layer was extracted with 0.5*N* hydrochloric acid (11 x 75 ml), dried and concentrated to a solid (14.2 g). The crude product was chromatographed [silica gel/ethyl acetate] giving **10s** (Rf = 0.40, mp 109-110°, 5.36 g, 39%), a mixture of **10s** and **10r** (3.21 g, 23%) and **10r** (Rf = 0.31, mp 125-127°, 3.15 g, 23%) as solids. The analytical data for each isomer is given below. Portions of both diastereomers were recrystallized from ether/hexane to obtain crystals suitable for X-ray analysis.

[S(*R\**),*R\**]-4-[1-(Hydroxyimino)ethyl]-1-(1-phenylethyl)-2-pyrrolidinone (**10s**).

Compound **10s** was obtained as a crystalline solid; <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 1.50 (d, J = 7.0 Hz, 3H), 1.85 (s, 3H), 2.56-2.68 (m, 2H), 2.93-3.22 (m, 2H), 3.34 (dd, J = 9.6, 7.0 Hz, 1H), 5.51 (q, J = 7.0 Hz, 1H), 7.22-7.43 (m, 5H), 8.65 (s, 1H); ir (potassium bromide): 3209, 2952, 1659, 1450, 1266, 1233, 963, 785, 697 cm<sup>-1</sup>; ms: (m/z) 247 (M<sup>+</sup> + 1), 229 (M<sup>+</sup> -OH), 188 (M<sup>+</sup> -CNOHCH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph, base); Rotation: [α]<sub>D</sub> = -69.3° (c 1.0%, methanol).

Anal. Calcd. for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.11; H, 7.33; N, 11.26.

[S(*R\**),*S\**]-4-[1-(Hydroxyimino)ethyl]-1-(1-phenylethyl)-2-pyrrolidinone (**10r**).

Compound **10r** was obtained as a crystalline solid; <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 1.53 (d, J = 7.2 Hz, 3H), 1.70 (s, 3H), 2.49-2.70 (m, 2H), 2.92 (dd, J = 9.8, 6.4 Hz, 1H), 3.03-3.20 (m, 1H), 3.48 (dd, J = 9.7, 8.3 Hz, 1H), 5.53 (q, J = 7.2 Hz, 1H), 7.19-7.40 (m, 5H), 8.12 (s, 1H); ir (potassium bromide): 3257, 2982, 1649, 1446, 1299, 907, 788, 699 cm<sup>-1</sup>; ms: (m/z) 247 (M<sup>+</sup> + 1), 229 (M<sup>+</sup> -OH), 188 (M<sup>+</sup> -CNOHCH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph, base); Rotation: [α]<sub>D</sub> = -119° (c 1.0%, methanol).

Anal. Calcd. for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.11; H, 7.65; N, 11.19.

X-ray Diffraction Analysis for **10s** and **10r**.

X-ray measurements were performed on a single-crystal diffractometer (Enraf-Nonius CAD4) using the ω-2θ scanning mode (2θ max = 143.5°) and graphite-monochromated CuKα radiation (λ = 1.5418 Å). Crystal data and parameters are summarized in Table 1. The unit cell parameters were determined by a least-squares fit for 2θ angles for 30 reflections (24 for **10r**) in the range of 60° < 2θ < 100°. Two standard reflections were monitored at every 80 reflection intervals throughout the data collection and showed no significant fluctuation (within 2%). The observed intensities were corrected for Lorentz and polarization effects. No correction of the absorption effect was done. The structure was solved by direct methods. The positional parameters were refined by a full-matrix least-squares analysis. The H atoms were located in computed positions. For non-hydrogen atoms anisotropic thermal parameters were refined and an isotropic refinement was applied to hydrogen atoms. No abnormally short contact distances were observed in the crystal packing. The function minimized was Σw(|Fo| - |Fc|)<sup>2</sup>. The weighting scheme used for refinement was based on counting statistics. At convergence, none of the positional and thermal parameters shifted more than 30% of their standard deviations. For all crystallographic computations, the NRCVAX [11] system of programs was used, and atomic scattering factors and the terms of the anomalous dispersion correction were taken from International Tables for X-ray crystallography [12].

4-(1-Aminoethyl)-1-(1-phenylethyl)-2-pyrrolidinones (**11sr** and **11ss**).

The oxime **10s** (12.7 g, 51.7 mmoles) was dissolved in methanol saturated with ammonia (150 ml) and placed in a Parr shaker with Raney nickel (4.00 g). The reaction was placed under 50 psig of hydrogen and shaken for 20 hours. An additional 5.00 g of Raney nickel was added to the reaction. The reaction was recharged with hydrogen to 51 psig, shaken for another 3 hours, then filtered. The filtrate was concentrated to an oil (11.7 g) which was chromatographed [silica gel/chloroform:ethanol:triethylamine (20:1:1)] to give; **11sr** (Rf = 0.33, 3.94 g, 32%), a mixture of **11sr** and **11ss** (3.85 g, 32%) and **11ss** (Rf = 0.24, 3.66 g, 30%) as viscous oils. The analytical data for the pure diastereomers is given below. This method was used for the preparation of **1**.

[4S-[1(*R\**),4*R\**(*S\**)]-4-(1-Aminoethyl)-1-(1-phenylethyl)-2-pyrrolidinone (**11sr**).

Compound **11sr** was obtained as a viscous oil; <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.07 (d, J = 6.3 Hz, 3H), 1.22 (br s, 2H-disappears with deuterium oxide wash), 1.51 (d, J = 7.1 Hz, 3H), 1.93-2.30 (m, 2H), 2.40 (dd, J = 16.2, 8.7 Hz, 1H), 2.73-2.92 (m, 1H), 3.13 (d, J = 7.7 Hz, 2H), 5.49 (q, J = 7.1 Hz, 1H), 7.17-7.47 (m, 5H); ir (liquid film): 3354, 2972, 1676, 1495, 1431, 1377, 1308, 1273, 1225, 787, 701 cm<sup>-1</sup>; ms: (m/z) 233 (M<sup>+</sup> + 1), 105 (CHCH<sub>3</sub>Ph), 44 (CHNH<sub>2</sub>CH<sub>3</sub>, base); Rotation: [α]<sub>D</sub> = -99.1° (c 1.0%, methanol).

Anal. Calcd. for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O·0.25H<sub>2</sub>O: C, 71.00; H, 8.72; N, 11.83. Found: C, 70.80; H, 8.58; N, 11.78.

[4S-[1(*R\**),4*R\**(*R\**)]-4-(1-Aminoethyl)-1-(1-phenylethyl)-2-pyrrolidinone (**11ss**).

Compound **11ss** was obtained as a viscous oil; <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 0.99 (d, J = 6.4 Hz, 3H), 1.31 (br s, 2H-disappears with deuterium oxide wash), 1.50 (d, J = 7.3 Hz, 3H), 1.90-2.37 (m, 2H), 2.53 (dd, J = 16.4, 9.1 Hz, 1H), 2.77-3.13 (m, 3H), 5.47 (q, J = 7.3 Hz, 1H), 7.17-7.43 (m, 5H); ir (liquid film): 3354, 2972, 1676, 1495, 1430, 1376, 1308, 1274, 1225, 787, 701 cm<sup>-1</sup>; ms: (m/z) 233 (M<sup>+</sup> + 1), 105 (CHCH<sub>3</sub>Ph, base), 44 (CHNH<sub>2</sub>CH<sub>3</sub>); Rotation: [α]<sub>D</sub> = -94.0° (c 1.0%, methanol).

Anal. Calcd. for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O·0.25H<sub>2</sub>O: C, 71.00; H, 8.72; N, 11.83. Found: C, 70.90; H, 8.49; N, 11.86.

4-(1-Aminoethyl)-1-(1-phenylethyl)-2-pyrrolidinones (**11rs** and **11rr**).

Using the procedure above, reduction of the oxime **10r** (11.8 g, 47.9 mmoles) with Raney nickel (3.00 g) gave **11rs** (Rf = 0.33, 3.96 g, 34%), a mixture of **11rs** and **11rr** (1.97 g, 17%) and **11rr** (Rf = 0.24, 5.14 g, 43%) as viscous oils. Isomer **11rr** solidifies to a waxy solid on standing. The analytical data for the pure diastereomers is given below.

[4R-[1(*S\**),4*R\**(*S\**)]-4-(1-Aminoethyl)-1-(1-phenylethyl)-2-pyrrolidinone (**11rs**).

Compound **11rs** was obtained as a viscous oil; <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.03 (d, J = 6.1 Hz, 3H), 1.21 (br s, 2H-disappears with deuterium oxide wash), 1.52 (d, J = 7.0 Hz, 3H), 2.00-2.30 (m, 2H), 2.38-2.60 (m, 1H), 2.62-2.90 (m, 2H), 3.44 (dd, J = 9.7, 7.7 Hz, 1H), 5.52 (q, J = 7.0 Hz, 1H), 7.17-7.50 (m, 5H); ir (liquid film): 3356, 2974, 1683, 1495, 1426, 1273, 786, 701 cm<sup>-1</sup>; ms: (m/z) 233 (M<sup>+</sup> + 1), 215 (M<sup>+</sup> -NH<sub>3</sub>), 189 (M<sup>+</sup> -CHNH<sub>2</sub>CH<sub>3</sub>), 105 (CHCH<sub>3</sub>Ph), 44 (CHNH<sub>2</sub>CH<sub>3</sub>, base); Rotation: [α]<sub>D</sub> = -116° (c 1.1%, methanol).

*Anal.* Calcd. for  $C_{14}H_{20}N_2O \cdot 0.75H_2O$ : C, 68.40; H, 8.82; N, 11.39. Found: C, 68.77; H, 8.68; N, 11.30.

[4*R*-[1(*S*\*)],4*R*\*(*R*\*)]-4-(1-Aminoethyl)-1-(1-phenylethyl)-2-pyrrolidinone (**11rr**).

Compound **11rr** was obtained as a waxy solid;  $^1H$  nmr (deuteriochloroform/200 MHz):  $\delta$  0.91 (d,  $J = 6.3$  Hz, 3H), 1.39 (br s, 2H, disappears with deuterium oxide wash), 1.51 (d,  $J = 7.3$  Hz, 3H), 2.02-2.37 (m, 2H), 2.43-2.80 (m, 3H), 3.25-3.43 (m, 1H), 5.51 (q,  $J = 7.3$  Hz, 1H), 7.17-7.43 (m, 5H); ir (liquid film): 3360, 2973, 1678, 1495, 1426, 1274, 786, 701  $cm^{-1}$ ; ms: (m/z) 233 ( $M^+ + 1$ ), 215 ( $M^+ - NH_3$ ), 189 ( $M^+ - CHNH_2CH_3$ ), 105 (CHCH<sub>3</sub>Ph), 44 (CHNH<sub>2</sub>CH<sub>3</sub>, base); Rotation:  $[\alpha]_D^{25} = -128^\circ$  (c 1.2%, methanol).

*Anal.* Calcd. for  $C_{14}H_{20}N_2O \cdot 0.15CHCl_3$ : C, 67.92; H, 8.12; N, 11.19. Found: C, 68.29; H, 8.38; N, 11.23.

#### Platinum Oxide Reduction of Oxime (**10**).

In a typical procedure, the oxime **10r** (50.0 g, 0.20 mole) was dissolved in methanol (1.0  $\theta$ ). After adding platinum oxide (5.00 g), the suspension was placed under hydrogen gas (50 psig) and shaken for 64 hours. The reaction was filtered and the filtrate concentrated *in vacuo*. The crude residue was chromatographed [silica gel/chloroform:ethanol:triethylamine (20:1:1)] to give, **11rs** (16.5 g), a mixture of **11rs** and **11rr** (13.9 g) and **11rr** (14.7 g). This method was used to prepare **21**, **22** and **23**.

#### Gas Chromatographic Analysis of the Purified Diastereomers of (**11**) [8].

The purified diastereomer of **11** (approximately 2 mg) and *N*-methyl-*N*-(*tert*-butyldimethylsilyl)trifluoroacetamide containing 1% *t*-butyldimethylchlorosilane (0.40 ml) were combined in a vial fitted with a teflon lined cap. The reaction was heated for 24 hours at 130°. An aliquot of this mixture (1.0  $\mu$ l) was injected through a split injector (split set at 40 cc/minute) onto a DB-5 capillary column (30 m x 0.25 mm ID, 0.25 micrometer layer) in a Varian 6000 GC with helium as the carrier gas (20 psig). The flow rate was 31.0 cm/sec and = 0.9 cc/minute and detection was by FID. The injector temperature was 260°, the detector temperature was 325° and the oven temperature was programmed as follows: 80° for four minutes, 80-300° at 10°/minute and hold at 300° for 7 minutes. Peaks of interest eluted between 24 and 26 minutes with baseline resolution.

[3*S*-[1(*R*\*)],3*R*\*(*S*\*)]- $\alpha$ -Methyl-1-(1-phenylethyl)-3-pyrrolidinemethanamine (**15sr**).

To dry THF (150 ml) chilled in an ice bath was added 95% lithium aluminum hydride (2.34 g, 58.6 mmoles) portionwise. The ice bath was removed and a solution of **11sr** (6.81 g, 29.3 mmoles) in dry THF (100 ml) was added dropwise. The reaction was warmed to reflux. After 24 hours the reaction was cooled to room temperature and quenched by addition of water (2.3 ml), then 15% sodium hydroxide solution (2.3 ml), followed by more water (7.2 ml). The reaction was filtered and the filter pad was washed with THF. The filtrate was concentrated and the residue partitioned between methylene chloride (50 ml) and water (15 ml). The resulting phases were separated and the aqueous phase was washed with methylene chloride (3 x 10 ml). The organic layers were combined, dried and concentrated to give crude product (6.49 g). This material was distilled through a short path column to give **15sr** as an oil (bp 89-96° at 0.15 mm Hg, 5.56 g, 87%);  $^1H$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.04 (d,  $J = 6.2$  Hz, 3H),

1.31-1.73 (m, 6H, contains 1.38, d,  $J = 6.6$  Hz), 1.77-2.11 (m, 2H), 2.13-2.27 (m, 1H), 2.38-2.57 (m, 2H), 2.65-2.81 (m, 1H), 2.81-2.93 (m, 1H), 3.19 (q,  $J = 6.6$  Hz, 1H), 7.16-7.43 (m, 5H); ir (liquid film): 2961, 2775, 1584, 1492, 1452, 1370, 1150, 763, 702  $cm^{-1}$ ; ms: (CI) (m/z) 259 ( $M^+ + C_3H_5$ ), 247 ( $M^+ + C_2H_5$ ), 219 ( $M^+ + 1$ , base); Rotation:  $[\alpha]_D^{25} = -50.3^\circ$  (c 1.0%, methanol).

*Anal.* Calcd. for  $C_{14}H_{22}N_2$ : C, 77.01; H, 10.16; N, 12.83. Found: C, 76.70; H, 10.21; N, 12.46.

[3*S*-[1(*R*\*)],3*R*\*(*R*\*)]- $\alpha$ -Methyl-1-(1-phenylethyl)-3-pyrrolidinemethanamine (**15ss**).

Using the procedure above, reduction of **11ss** (7.42 g, 31.9 mmoles) with 95% lithium aluminum hydride (2.55 g, 63.9 mmoles) gave **15ss** as an oil (bp 91-100° at 0.25 mm Hg, 5.57 g, 80%);  $^1H$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.00 (d,  $J = 6.3$  Hz, 3H), 1.24-1.47 (m, 5H, contains 1.37, d,  $J = 6.6$  Hz), 1.49-1.67 (m, 1H), 1.80-2.16 (m, 3H), 2.38-2.59 (m, 2H), 2.65-2.86 (m, 2H), 3.16 (q,  $J = 6.6$  Hz, 1H), 7.13-7.38 (m, 5H); ir (liquid film): 2961, 2775, 1952, 1883, 1815, 1753, 1584, 1492, 1452, 1370, 1150, 763, 702  $cm^{-1}$ ; ms: (m/z) 219 ( $M^+ + 1$ ), 174 ( $M^+ - CHNH_2CH_3$ ), 105 (CHCH<sub>3</sub>Ph), 44 (CHNH<sub>2</sub>CH<sub>3</sub>, base); Rotation:  $[\alpha]_D^{25} = -43.4^\circ$  (c 1.2%, methanol).

*Anal.* Calcd. for  $C_{14}H_{22}N_2$ : C, 77.01; H, 10.16; N, 12.83. Found: C, 76.66; H, 10.08; N, 12.50.

[3*R*-[1(*S*\*)],3*R*\*(*S*\*)]- $\alpha$ -Methyl-1-(1-phenylethyl)-3-pyrrolidinemethanamine (**15rs**).

Using the procedure above, reduction of **11rs** (3.44 g, 14.8 mmoles) with 95% lithium aluminum hydride (1.18 g, 29.6 mmoles) gave **15rs** as an oil. The  $^1H$  nmr for the distilled material showed slight impurities present. The product was used in the next step without further purification (bp 92-101° at 0.10 mm Hg, 2.53 g, 78%);  $^1H$  nmr (deuteriochloroform + deuterium oxide/200 MHz):  $\delta$  1.03 (d,  $J = 6.1$  Hz), 1.30-1.63 (m), 1.82-2.58 (m), 2.58-2.95 (m), 3.13-3.33 (m), 7.13-7.75 (m);  $^{13}C$  nmr (deuteriochloroform/63 MHz):  $\delta$  22.6, 23.2, 28.0, 46.4, 51.4, 52.9, 56.9, 66.0, 126.6, 126.8, 127.1, 128.3; ir (liquid film): 2961, 2777, 1452, 1370, 1150, 763, 702  $cm^{-1}$ ; ms: (m/z) 218 ( $M^+$ ), 203 ( $M^+ - CH_3$ ), 174 ( $M^+ - CHNH_2CH_3$ ), 113 ( $M^+ - CHCH_3Ph$ ), 105 (CHCH<sub>3</sub>Ph, base); Rotation:  $[\alpha]_D^{25} = -43^\circ$  (c 1.1%, methanol).

[3*R*-[1(*S*\*)],3*R*\*(*R*\*)]- $\alpha$ -Methyl-1-(1-phenylethyl)-3-pyrrolidinemethanamine (**15rr**).

Using the procedure above, reduction of **11rr** (4.51 g, 19.4 mmoles) with 95% lithium aluminum hydride (1.55 g, 38.8 mmoles) gave **15rr** as an oil. The  $^1H$  nmr for the distilled material showed impurities present. The product was carried on in the next step without further purification (bp 83-94° at 0.05 mm Hg, 2.93 g, 69%);  $^1H$  nmr (deuteriochloroform + deuterium oxide/200 MHz):  $\delta$  0.97 (d,  $J = 6.5$  Hz), 1.23-1.77 (m), 1.80-2.22 (m), 2.27-2.92 (m), 3.10-3.30 (m), 7.13-7.42 (m);  $^{13}C$  nmr (deuteriochloroform/63 MHz):  $\delta$  22.5, 23.2, 27.2, 46.0, 51.0, 52.9, 56.8, 66.0, 126.5, 126.8, 127.1, 128.3; ir (liquid film): 2962, 2780, 1452, 1370, 1151, 764, 702  $cm^{-1}$ ; ms: (m/z) 218 ( $M^+$ ), 203 ( $M^+ - CH_3$ ), 174 ( $M^+ - CHNH_2CH_3$ ), 113 ( $M^+ - CHCH_3Ph$ ), 105 (CHCH<sub>3</sub>Ph, base); Rotation:  $[\alpha]_D^{25} = -42^\circ$  (c 0.9%, methanol).

1,1-Dimethylethyl [3*S*-[1(*R*\*)],3*R*\*(*S*\*)]-[1-[1-(1-Phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**16sr**).

The amine **15sr** (5.16 g, 23.6 mmoles) was added to a cold solution of di-*t*-butyl dicarbonate (5.67 g, 26.0 mmoles), 1*N* sodium

hydroxide (26 ml) and *tert*-butyl alcohol (35 ml). The ice bath was removed and the reaction was stirred at room temperature. After 24 hours the reaction was diluted with water (100 ml) and extracted with ether (5 x 25 ml), which was dried and concentrated to give crude product. Chromatography [silica gel/methylene chloride:ethanol (90:10)] gave pure **16sr** (Rf = 0.24, 4.87 g, 62%); <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.06 (d, J = 6.6 Hz, 3H), 1.30-1.68 (m, 13H—contains 1.38 (d, J = 6.7 Hz) and 1.46 (s)), 1.83-2.23 (m, 2H), 2.25-2.60 (m, 3H), 2.68-2.90 (m, 1H), 3.19 (q, J = 6.5 Hz, 1H), 3.40-3.63 (m, 1H), 5.26-5.47 (m, 1H), 7.17-7.43 (m, 5H), traces of methylene chloride were observed; ir (liquid film): 3341, 2972, 2787, 1718, 1507, 1454, 1365, 1245, 1170, 1089, 1049, 1024, 871, 764, 701 cm<sup>-1</sup>; ms: (m/z) 319 (M<sup>+</sup> + 1, base), 303 (M<sup>+</sup> -OCH<sub>3</sub>), 57 (*t*-Bu); Rotation: [α]<sub>D</sub> = -14.7° (c 1.0%, methanol).

*Anal.* Calcd. for C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>·0.15CH<sub>2</sub>Cl<sub>2</sub>: C, 69.45; H, 9.22; N, 8.46. Found: C, 69.68; H, 9.17; N, 8.50.

1,1-Dimethylethyl [3*S*-[1(*R*\*),3*R*\*(*R*\*)]-[1-[1-(1-Phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**16ss**).

Using the procedure above, **15ss** (5.04 g, 23.1 mmoles), di-*t*-butyl dicarbonate (5.54 g, 25.4 mmoles), and 1*N* sodium hydroxide (25 ml) in *tert*-butyl alcohol (35 ml) gave **16ss** (Rf = 0.33, 5.18 g, 68%); <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.11 (d, J = 6.2 Hz, 3H), 1.30-2.00 (m, 14H—contains 1.37, d, J = 6.3 Hz), 2.03-2.38 (m, 3H), 2.43-2.63 (m, 1H), 2.65-2.85 (m, 1H), 3.14 (q, J = 6.4 Hz, 1H), 3.37-3.63 (m, 1H), 5.20 (br s, 1H), 7.17-7.43 (m, 5H), traces of methylene chloride were observed; ir (liquid film): 3340, 2976, 1718, 1493, 1453, 1391, 1365, 1248, 1178, 764, 702, 668 cm<sup>-1</sup>; ms: (m/z) 319 (M<sup>+</sup> + 1, base), 261 (M<sup>+</sup> -*t*-Bu), 245 (M<sup>+</sup> -O-*t*-Bu), 57 (*t*-Bu); Rotation: [α]<sub>D</sub> = -30.2° (c 1.0%, methanol).

*Anal.* Calcd. for C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>·0.15CH<sub>2</sub>Cl<sub>2</sub>: C, 69.45; H, 9.22; N, 8.46. Found: C, 69.15; H, 8.98; N, 8.22.

1,1-Dimethylethyl [3*S*-[1(*S*\*),3*R*\*(*S*\*)]-[1-[1-(1-Phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**16rs**).

Using the procedure above, the crude amine **15rs** (2.26 g, 10.4 mmoles), di-*t*-butyl dicarbonate (2.71 g, 12.4 mmoles), 1*N* sodium hydroxide (12 ml) and *tert*-butyl alcohol (50 ml) gave **16rs** (Rf = 0.24, 1.64 g, 47% (33% over two steps)); <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.16 (d, J = 7.3 Hz, 3H), 1.32-1.66 (m, 13H), 1.85-2.27 (m, 2H), 2.30-2.87 (m, 4H), 3.10-3.33 (m, 1H), 3.40-3.67 (m, 1H), 5.65 (br s, 1H), 7.17-7.43 (m, 5H), traces of methylene chloride were observed; ir (liquid film): 3310, 2961, 1718, 1507, 1364, 1247, 1157, 964 cm<sup>-1</sup>; ms: (CI) (m/z) 359 (M<sup>+</sup> + C<sub>3</sub>H<sub>5</sub>), 319 (M<sup>+</sup> + 1, base); Rotation: [α]<sub>D</sub> = -51.0° (c 1.0%, methanol).

*Anal.* Calcd. for C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>·0.20CH<sub>2</sub>Cl<sub>2</sub>: C, 68.75; H, 9.13; N, 8.35. Found: C, 68.96; H, 8.86; N, 8.13.

1,1-Dimethylethyl [3*R*-[1(*S*\*),3*R*\*(*R*\*)]-[1-[1-(1-Phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**16rr**).

Using the procedure above, crude **15rr** (2.60 g, 11.9 mmoles), di-*t*-butyl dicarbonate (3.12 g, 14.3 mmoles) and 1*N* sodium hydroxide (14 ml) in *tert*-butyl alcohol (50 ml) gave **16rr** (Rf = 0.33, 1.76 g, 45% (28% over two steps)); <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.07 (d, J = 7.3 Hz, 3H), 1.32-1.55 (m, 12H), 1.55-1.77 (m, 1H), 1.77-2.03 (m, 1H), 2.03-2.87 (m, 5H), 3.07-3.30 (m, 1H), 3.43-3.70 (m, 1H), 5.13 (br s, 1H), 7.17-7.43 (m, 5H), traces of methylene chloride were observed; ir (liquid film): 3380, 2972, 2781, 1684, 1510, 1165 cm<sup>-1</sup>; ms: (CI) (m/z) 359 (M<sup>+</sup> + C<sub>3</sub>H<sub>5</sub>), 319 (M<sup>+</sup> + 1, base); Rotation: [α]<sub>D</sub> = -43.0° (c 1.1%, methanol).

*Anal.* Calcd. for C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>·0.10CH<sub>2</sub>Cl<sub>2</sub>: C, 70.17; H, 9.31; N, 8.57. Found: C, 70.39; H, 9.10; N, 8.70.

1,1-Dimethylethyl [*R*-(*R*\*,*S*\*)]-[1-(3-Pyrrolidinyl)ethyl]carbamate (**1ss**).

The pure diastereomer **16ss** (1.19 g, 3.74 mmoles), 20% palladium on carbon (0.30 g) and acetic acid (100 ml) were placed under hydrogen gas (50 psig) in a Parr shaker. After shaking for 18 hours, additional catalyst (0.30 g) was added. After shaking two more hours the suspension was filtered. The filtrate was concentrated, dissolved in water (75 ml) and extracted with ether. The pH of the aqueous layer was adjusted from 4.5 to 11.5 with 50% sodium hydroxide and extracted with methylene chloride (5 x 20 ml). The combined organic layers were dried and concentrated to give **1ss** as a waxy solid (0.72 g, 90%); <sup>1</sup>H nmr (deuteriochloroform + deuterium oxide/200 MHz): δ 1.11 (d, J = 6.5 Hz, 3H), 1.30-1.63 (m, 10H), 1.73-2.15 (m, 2H), 2.43-2.67 (m, 1H), 2.77-3.12 (m, 3H), 3.45-3.70 (m, 1H); ir (potassium bromide): 3324, 3192, 2965, 1688, 1552, 1365, 1284, 1254, 1178, 1095, 1044, 1031 cm<sup>-1</sup>; ms: (m/z) 215 (M<sup>+</sup> + 1), 157 (M<sup>+</sup> -*t*-Bu), 141 (M<sup>+</sup> -O-*t*-Bu), 113 (M<sup>+</sup> -CO<sub>2</sub>-*t*-Bu), 70 (M<sup>+</sup> -CHNHBocCH<sub>3</sub>, base).

This isomer was purified in the following experiment by coupling to a quinolone substrate.

[*S*-(*R*\*,*R*\*)]-1-Cyclopropyl-7-[3-[1-[(1,1-dimethylethoxy)carbonyl]amino]ethyl]-1-pyrrolidinyl]-6-fluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic Acid (**25ss**).

To the amine **1ss** (0.65 g, 3.03 mmoles) and 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, **24**, (0.73 g, 2.76 mmoles) in acetonitrile (30 ml) was added triethylamine (0.41 g, 4.05 mmoles). The reaction was refluxed for 27 hours, cooled to room temperature overnight and filtered. The filter pad was washed with ether to give **25ss** after air drying (mp 217-219° dec, 1.09 g, 85%); <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.08-1.67 (m, 16H), 1.73-2.05 (m, 1H), 2.07-2.50 (m, 2H), 3.27-3.97 (m, 6H), 4.37-4.60 (m, 1H), 6.86 (d, J = 7.4 Hz, 1H), 7.91 (d, J = 14 Hz, 1H), 8.68 (s, 1H); ir (potassium bromide): 3418, 2975, 1713, 1630, 1512, 1470, 1356, 1249, 1168 cm<sup>-1</sup>; ms: (m/z) 459 (M<sup>+</sup>), 415 (M<sup>+</sup> -CO<sub>2</sub>), 402 (M<sup>+</sup> -*t*-Bu), 359 (base), 57 (*t*-Bu).

*Anal.* Calcd. for C<sub>24</sub>H<sub>30</sub>FN<sub>3</sub>O<sub>5</sub>·0.25H<sub>2</sub>O: C, 62.12; H, 6.63; N, 9.06; F, 4.09. Found: C, 62.06; H, 6.51; N, 8.92; F, 4.19.

1,1-Dimethylethyl [*R*-(*R*\*,*S*\*)]-[1-(3-Pyrrolidinyl)ethyl]carbamate (**1sr**).

Using the procedure for the synthesis of **1ss**, the pure diastereomer **16sr** (1.83 g, 5.75 mmoles), 20% palladium on carbon (1.00 g—no additional catalyst was needed after 18 hours) and acetic acid (75 ml) gave crude product. Trituration with ether gave **1sr** as a waxy solid (mp 75-78.5°, 0.48 g, 39%); <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.15 (d, J = 6.5 Hz, 3H), 1.32-1.57 (m, 10H—contains 1.44, s), 1.80-2.15 (m, 2H), 2.67-3.10 (m, 4H), 3.43-3.70 (m, 1H), 4.57 (br s, 1H—vanishes with deuterium oxide wash); ir (potassium bromide): 3321, 2976, 1687, 1559, 1166 cm<sup>-1</sup>; ms: (m/z) 215 (M<sup>+</sup> + 1), 70 (M<sup>+</sup> -CHNHBocCH<sub>3</sub>), 57 (*t*-Bu, base).

*Anal.* Calcd. for C<sub>11</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 61.65; H, 10.35; N, 13.07. Found: C, 61.35; H, 10.49; N, 12.80.

Additional usable material (0.77 g) could be obtained by concentrating the filtrate.

1,1-Dimethylethyl [*S*-(*R*\*,*R*\*)]-[1-(3-Pyrrolidinyl)ethyl]carbamate (**1rs**).

Using the procedure above, **16rs** (1.11 g, 3.49 mmoles), 20% palladium on carbon (0.30 g + 0.40 g) and acetic acid (100 ml) gave a yellow oil. Trituration with pentane followed by filtration

and air drying gave **Irs** as a tan solid (mp 71.5-74.5°, 0.47 g, 62%); <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.15 (d, J = 6.5 Hz, 3H), 1.30-1.60 (m, 10H-contains 1.44, s), 1.70-2.13 (m, integrates to 2H with deuterium oxide wash), 2.66-3.10 (m, 4H), 3.42-3.70 (m, 1H), 4.62 (br s, 1H-vanishes with deuterium oxide wash); ir (potassium bromide): 3321, 3179, 2974, 1693, 1364, 1294, 1252, 1167 cm<sup>-1</sup>; ms: (m/z) 215 (M<sup>+</sup> + 1), 57 (t-Bu, base).

*Anal.* Calcd. for C<sub>11</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>·0.25H<sub>2</sub>O: C, 60.38; H, 10.36; N, 12.80. Found: C, 60.37; H, 10.09; N, 12.62.

Additional usable material (0.21 g) could be obtained from concentrating the filtrate.

1,1-Dimethylethyl [R(R\*,R\*)]-[1-(3-Pyrrolidinyl)ethyl]carbamate (**Irr**).

Using the procedure above, **16rr** (1.52 g, 4.78 mmoles), 20% palladium on carbon (0.40 g + 0.40 g) and acetic acid (100 ml) gave an oil. Trituration with ether/pentane (1/1), followed by filtration and air drying gave **Irr** as an off white solid (mp 85.5-88.5°, 0.37 g, 35%); <sup>1</sup>H nmr (deuteriochloroform/200 MHz): δ 1.12 (d, J = 6.5 Hz, 3H), 1.21-1.67 (m, 10H-contains 1.44, s), 1.73-2.17 (m, integrates to 2H with deuterium oxide wash), 2.50-2.68 (m, 1H), 2.80-3.17 (m, 3H), 3.43-3.75 (m, 1H), 4.50 (br s, 1H-vanishes with deuterium oxide wash); ir (potassium bromide): 3325, 2966, 1689, 1551, 1365, 1284, 1254, 1180, 1095 cm<sup>-1</sup>; ms: (m/z) 215 (M<sup>+</sup> + 1, base), 57 (t-Bu).

*Anal.* Calcd. for C<sub>11</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>·0.25H<sub>2</sub>O: C, 60.38; H, 10.36; N, 12.80. Found: C, 60.36; H, 10.16; N, 12.63.

Additional usable material (0.64 g) could be obtained by concentrating the filtrate.

[3R-[1(S\*),3R\*(S\*)]-N-[1-[5-Oxo-1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]acetamide (**13rs**).

A solution of the amine **11rs** (10.0 g, 43.0 mmoles) in pyridine (50 ml) and acetic anhydride (250 ml) was stirred for 18 hours, then evaporated to an oil. This oil was purified by column chromatography [silica gel/methylene chloride:ethanol (20:1)] to give **13rs** as a very viscous oil (9.20 g, 72%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 0.97 (d, J = 6.7 Hz, 3H), 1.52 (d, J = 7.2 Hz, 3H), 1.88 (s, 3H), 2.15-2.25 (m, 1H), 2.36-2.60 (m, 2H), 2.78 (dd, J = 5.8, 10.1 Hz, 1H), 3.39 (dd, J = 8.1, 10.0 Hz, 1H), 3.85-4.00 (m, 1H), 5.05-5.10 (br m, 1H), 5.49 (q, J = 9.1 Hz, 1H), 7.20-7.40 (m, 5H), traces of ethanol observed; ir (potassium bromide): 3309, 2973, 1690, 1660, 1450, 1371, 700 cm<sup>-1</sup>; ms: (m/z) 275 (M<sup>+</sup> + 1), 246, 188, 160, 133, 105, 84, 44 (base); Rotation: [α]<sub>D</sub> = -165° (c 0.4%, chloroform).

*Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>·0.50C<sub>2</sub>H<sub>5</sub>OH: C, 68.66; H, 8.47; N, 9.42. Found: C, 68.37; H, 8.09; N, 9.57.

[3R-[1(S\*),3R\*(R\*)]-N-[1-[5-Oxo-1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]acetamide (**13rr**).

Using the procedure above, **11rr** (10.0 g, 43.0 mmoles), pyridine (50 ml) and acetic anhydride (250 ml) gave **13rr** as a colorless solid (8.30 g, 70%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 0.99 (d, J = 6.7 Hz, 3H), 1.52 (d, J = 7.0 Hz, 3H), 1.84 (s, 3H), 2.20-2.55 (m, 3H), 2.70-2.80 (m, 1H), 3.30-3.40 (m, 1H), 3.90-4.05 (m, 1H), 5.47 (q, J = 7.1 Hz, 1H), 5.75-5.85 (br m, 1H), 7.20-7.40 (m, 5H); ir (potassium bromide): 3291, 1667, 1658, 1550, 705 cm<sup>-1</sup>; ms: (m/z) 275 (M<sup>+</sup> + 1, base), 246, 188, 160, 105, 84, 44; Rotation: [α]<sub>D</sub> = -120° (c 1.1%, chloroform).

*Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 70.04; H, 8.08; N, 10.21.

Found: C, 70.08; H, 8.10; N, 10.23.

[3S-[1(R\*),3R\*(R\*)]-N-[1-[5-Oxo-1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]acetamide (**13ss**).

Using the procedure above, **11ss** (9.72 g, 41.8 mmoles), pyridine (50 ml) and acetic anhydride (200 ml) gave **13ss** as a viscous oil (9.50 g, 83%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 1.09 (d, J = 6.7 Hz, 3H), 1.49 (d, J = 7.1 Hz, 3H), 1.98 (s, 3H), 2.20-2.55 (m, 3H), 2.95-3.20 (m, 2H), 4.05-4.15 (m, 1H), 5.46 (q, J = 7.1 Hz, 1H), 6.10-6.25 (br d, 1H), 7.20-7.40 (m, 5H); ir (potassium bromide): 3529, 3455, 2899, 1601, 1489, 1381 cm<sup>-1</sup>; ms: (m/z) 275 (M<sup>+</sup> + 1), 246, 188, 160, 105 (base); Rotation: [α]<sub>D</sub> = 149° (c 1.1%, chloroform).

*Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.09; H, 8.01; N, 9.84.

[3S-[1(R\*),3R\*(S\*)]-N-[1-[5-Oxo-1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]acetamide (**13sr**).

Using the procedure above, **11sr** (6.30 g, 27.1 mmoles), pyridine (50 ml) and acetic anhydride (200 ml) gave **13sr** as a viscous oil after chromatography [silica gel/methylene chloride:methanol (97:3)] (7.40 g, 97%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 1.11 (d, J = 6.6 Hz, 3H), 1.49 (d, J = 7.0 Hz, 3H), 1.93 (s, 3H), 2.15-2.30 (m, 2H), 2.40-2.55 (m, 1H), 2.95-3.10 (m, 1H), 3.15-3.25 (m, 1H), 3.95-4.05 (m, 1H), 5.46 (q, J = 7.1 Hz, 1H), 5.75-5.85 (br d, 1H), 7.20-7.40 (m, 5H), traces of methanol observed; ir (potassium bromide): 3296, 2975, 1658, 1541, 1492, 1373, 1156, 702 cm<sup>-1</sup>; ms: (m/z) 275 (M<sup>+</sup> + 1), 246, 188, 160, 105 (base); Rotation: [α]<sub>D</sub> = -37.4° (c 0.5%, chloroform).

*Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>·0.25CH<sub>3</sub>OH: C, 69.12; H, 8.21; N, 9.92. Found: C, 68.87; H, 8.27; N, 9.65.

[3R-[1(S\*),3R\*(S\*)]-N-Ethyl-α-methyl-1-(phenylethyl)-3-pyrrolidinemethanamine (**19rs**).

To a solution of **13rs** (9.20 g, 33.5 mmoles) in dry THF (150 ml) was added 95% lithium aluminum hydride (2.60 g, 65.1 mmoles). The resulting slurry was heated at reflux for 18 hours then cooled and cautiously quenched with water (2.6 ml), then 15% sodium hydroxide solution (3.0 ml), and finally water (6.0 ml). The resulting suspension was filtered and evaporated to an oil. This oil was distilled to give **19rs** (bp 107-112° at 0.1 mm Hg, 7.10 g, 86%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 1.00-1.08 (m, 6H), 1.36 (d, J = 6.5 Hz, 3H), 1.20-1.50 (m, 1H-overlapping with doublet), 1.85-2.20 (m, 4H), 2.45-2.60 (m, 2H), 2.60-2.85 (m, 3H), 3.17 (q, J = 6.7 Hz, 1H), 7.15-7.39 (m, 5H); <sup>13</sup>C nmr (deuteriochloroform/63 MHz): δ 15.6, 18.4, 23.2, 27.7, 41.5, 44.0, 52.7, 56.7, 57.2, 65.9, 126.8, 127.2, 128.3, 145.7; ir (potassium bromide): 2959, 2790, 1451, 1309, 1156, 701 cm<sup>-1</sup>; ms: (m/z) 274 (M<sup>+</sup> + 1), 201, 186, 105, 72 (base); ms: (high resolution) Calcd. for C<sub>16</sub>H<sub>26</sub>N<sub>2</sub> (M<sup>+</sup> + 1): 247.2174. Found: 247.2174; Rotation: [α]<sub>D</sub> = -27.8° (c 1.0%, 95% ethanol).

*Anal.* Calcd. for C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>·0.20H<sub>2</sub>O: C, 76.87; H, 10.64; N, 11.21. Found: C, 77.16; H, 10.42; N, 9.96.

[3R-[1(S\*),3R\*(R\*)]-N-Ethyl-α-methyl-1-(phenylethyl)-3-pyrrolidinemethanamine (**19rr**).

Using the procedure above, reduction of **13rr** (8.00 g, 29.2 mmoles) with 95% lithium aluminum hydride (2.20 g, 55.1 mmoles) gave **19rr** as an oil (bp 110° at 0.10 mm Hg, 6.10 g, 84%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 0.95 (d, J = 6.3 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H), 1.36 (d, J = 6.6 Hz, 3H),

1.50-1.70 (m, 1H), 1.90-2.20 (m, 4H), 2.30-2.40 (m, 1H), 2.40-2.60 (m, 3H), 2.65-2.80 (m, 2H), 3.15 (q,  $J = 6.6$  Hz, 1H), 7.15-7.35 (m, 5H); ir (liquid film): 2956, 2921, 2796, 2770, 1492, 1452, 1314, 1153, 700  $\text{cm}^{-1}$ ; ms: (m/z) 247 ( $M^+ + 1$ , base), 201, 186, 105; Rotation:  $[\alpha]_D = -64^\circ$  (c 0.9%, 95% ethanol).

*Anal.* Calcd. for  $C_{16}H_{26}N_2 \cdot 0.10H_2O$ : C, 77.43; H, 10.64; N, 11.29. Found: C, 77.50; H, 10.53; N, 11.56.

[3S-[1( $R^*$ ),3R\*( $R^*$ )]-N-Ethyl- $\alpha$ -methyl-1-(phenylethyl)-3-pyrrolidinemethanamine (**19ss**).

Using the procedure above, reduction of **13ss** (9.50 g, 34.6 mmoles) with 95% lithium aluminum hydride (2.65 g, 66.3 mmoles) gave **19ss** (6.88 g, 81%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  0.98 (d,  $J = 6.2$  Hz, 3H), 1.10 (t,  $J = 7.1$  Hz, 3H), 1.37 (d,  $J = 6.6$  Hz, 3H), 1.60-1.70 (m, 1H), 1.80-2.05 (m, 1H), 2.10-2.20 (m, 2H), 2.35-2.60 (m, 4H), 2.65-2.80 (m, 2H), 3.15 (q,  $J = 6.6$  Hz, 1H), 7.15-7.35 (m, 5H); ir (liquid film): 2969, 2926, 2782, 1452, 1143, 700  $\text{cm}^{-1}$ ; ms: (m/z) 245, 201, 186, 155, 121, 105, 84, 72, 49 (base); Rotation:  $[\alpha]_D = -13.1^\circ$  (c 1.3%, 95% ethanol).

*Anal.* Calcd. for  $C_{16}H_{26}N_2$ : C, 77.99; H, 10.64; N, 11.37. Found: C, 77.68; H, 10.58; N, 11.19.

[3S-[1( $R^*$ ),3R\*( $S^*$ )]-N-Ethyl- $\alpha$ -methyl-1-(phenylethyl)-3-pyrrolidinemethanamine (**19sr**).

Using the procedure above, reduction of **13sr** (7.50 g, 27.3 mmoles) with 95% lithium aluminum hydride (2.14 g, 53.6 mmoles) gave **19sr** (5.21 g, 77%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.00-1.15 (m, 6H), 1.37 (d,  $J = 6.5$  Hz, 3H), 1.35-1.55 (m, 1H-overlapped with doublet), 1.74-1.94 (m, 1H), 2.10-2.25 (m, 2H), 2.45-2.60 (m, 4H), 2.65-2.75 (m, 1H), 2.75-2.90 (m, 1H), 3.19 (q,  $J = 6.5$  Hz, 1H), 7.13-7.37 (m, 5H); ir (liquid film): 2968, 2783, 1492, 1313, 701  $\text{cm}^{-1}$ ; ms: (m/z) 245 ( $M^+$ ), 201, 186, 174, 155, 141, 121, 105 (base), 96, 72; Rotation:  $[\alpha]_D = 57.6^\circ$  (c 1.2%, 95% ethanol).

*Anal.* Calcd. for  $C_{16}H_{26}N_2$ : C, 77.99; H, 10.64; N, 11.37. Found: C, 78.22; H, 10.63; N, 11.11.

[R( $R^*$ , $R^*$ )]-N-Ethyl- $\alpha$ -methyl-3-pyrrolidinemethanamine (**22rr**).

The amine **19rr** (5.40 g, 21.9 mmoles) was dissolved in methanol (100 ml) and 20% palladium on carbon (1.00 g) was added. The resulting slurry was shaken under hydrogen gas (50 psig) in a Parr shaker 21 hours. The resulting suspension was filtered and the filtrate distilled to remove the methanol. The remaining oil was distilled to give **22rr** as an oil (bp 85-89° at 10.0-12.0 mm Hg, 2.40 g, 77%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.04 (d,  $J = 6.2$  Hz, 3H), 1.11 (t,  $J = 7.0$  Hz, 3H), 1.35-1.50 (m, 2H), 1.85-2.10 (m, 2H), 2.50-2.65 (m, 2H), 2.70-2.80 (m, 2H), 2.85-3.10 (m, 3H), traces of methanol observed;  $^{13}\text{C}$  nmr (deuteriochloroform/50 MHz):  $\delta$  15.5, 18.7, 28.8, 41.5, 46.1, 47.0, 50.1, 56.9; ir (liquid film): 3279, 2963, 1452, 1373  $\text{cm}^{-1}$ ; ms: (m/z) 143 ( $M^+ + 1$ ), 97, 82, 72 (base); ms: (high resolution) Calcd. for  $C_8H_{18}N_2$  ( $M^+ + 1$ ): 143.1548. Found: 143.1552; Rotation:  $[\alpha]_D = -25.0^\circ$  (c 1.1%, 95% ethanol).

*Anal.* Calcd. for  $C_8H_{18}N_2 \cdot 0.03CH_3OH$ : C, 67.35; H, 12.75; N, 19.56. Found: C, 67.13; H, 13.39; N, 19.39.

[S( $R^*$ , $S^*$ )]-N-Ethyl- $\alpha$ -methyl-3-pyrrolidinemethanamine (**22rs**).

Using the procedure above, **19rs** (6.82 g, 27.7 mmoles) and 20% palladium on carbon (1.00 g) gave **22rs** as an oil (bp 85-92° at 10-12 mm Hg, 3.20 g, 81%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.00-1.15 (m, 6H), 1.30-1.50 (m, 1H), 1.80-2.05 (m, 2H), 2.45-2.80 (m, 4H), 2.85-3.00 (m, 2H), 3.09 (dd,  $J = 10.6$  and 7.7 Hz,

1H); ir (liquid film): 3269, 2965, 1450, 1372  $\text{cm}^{-1}$ ; ms: (m/z) 285 ( $2M^+ + 1$ ), 143 ( $M^+ + 1$ , base); Rotation:  $[\alpha]_D = 42.0^\circ$  (c 0.6%, 95% ethanol).

*Anal.* Calcd. for  $C_8H_{18}N_2$ : C, 67.55; H, 12.75; N, 19.69. Found: C, 67.58; H, 12.98; N, 19.60.

[R( $R^*$ , $S^*$ )]-N-Ethyl- $\alpha$ -methyl-3-pyrrolidinemethanamine (**22sr**).

Using the procedure above, **19sr** (5.11 g, 20.7 mmoles) and 20% palladium on carbon (1.00 g) gave **22sr** as an oil (bp 87-92° at 10-12 mm Hg, 2.38 g, 80%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.00-1.15 (m, 6H), 1.30-1.50 (m, 1H), 1.80-1.90 (m, 1H), 1.90-2.05 (m, 1H), 2.45-2.75 (m, 5H), 2.85-2.95 (m, 2H), 3.08 (dd,  $J = 10.5$ , 7.7 Hz, 1H), traces of methanol observed; ir (liquid film): 3281, 2966, 1452, 1373  $\text{cm}^{-1}$ ; ms: (CI) (m/z) 285 ( $2M^+ + 1$ ), 143 ( $M^+ + 1$ ); Rotation:  $[\alpha]_D = -46^\circ$  (c 1.0%, 95% ethanol).

*Anal.* Calcd. for  $C_8H_{18}N_2 \cdot 0.05CH_3OH$ : C, 67.22; H, 12.75; N, 19.47. Found: C, 67.09; H, 13.16 [15]; N, 19.35.

[S( $R^*$ , $R^*$ )]-N-Ethyl- $\alpha$ -methyl-3-pyrrolidinemethanamine (**22ss**).

Using the procedure above, **19ss** (6.68 g, 27.1 mmoles) and 20% palladium on carbon (1.00 g) gave **22ss** as an oil (bp 88-92° at 10-12 mm Hg, 3.28 g, 85%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.03 (d,  $J = 6.1$  Hz, 3H), 1.10 (t,  $J = 7.3$  Hz, 3H), 1.30-1.50 (m, 1H), 1.80-2.05 (m, 2H), 2.40-2.50 (m, 3H), 2.55-2.80 (m, 1H), 2.85-3.10 (m, 3H); ir (liquid film): 3324, 2957, 2808, 1455, 1373  $\text{cm}^{-1}$ ; ms: (m/z) 142 ( $M^+$ ), 97, 72 (base); Rotation:  $[\alpha]_D = 23.2^\circ$  (c 1.1%, 95% ethanol).

*Anal.* Calcd. for  $C_8H_{18}N_2$ : C, 67.55; H, 12.75; N, 19.69. Found: C, 67.35; H, 13.14; N, 19.57.

1,1-Dimethylethyl [3R-[1( $S^*$ ),3R\*( $R^*$ )]-1-[5-Oxo-1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**12rr**).

A solution of di-*tert*-butyl dicarbonate (7.64 g, 35.0 mmoles) in methylene chloride (50 ml) was added portionwise to a stirred solution of **11rr** (6.68 g, 28.7 mmoles) and triethylamine (3.54 g, 35.0 mmoles) in methylene chloride (250 ml). The resulting solution was stirred at room temperature for 20 hours and then concentrated to give a light yellow oil. This crude product was purified by column chromatography [silica gel/heptane:2-propanol (4:1)] to give **12rr** as a white waxy solid (5.43 g, 57%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  0.96 (d,  $J = 6.7$  Hz, 3H), 1.38 (s, 9H), 1.52 (d,  $J = 7.2$  Hz, 3H), 2.23-2.55 (m, 3H), 2.66 (dd,  $J = 9.8$ , 7.0 Hz, 1H), 3.32 (dd,  $J = 9.8$ , 8.1 Hz, 1H), 3.50-3.70 (m, 1H), 4.35-4.45 (m, 1H), 5.50 (q,  $J = 7.1$  Hz, 1H), 7.23-7.37 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  16.1, 18.6, 28.3, 34.6, 37.6, 44.6, 48.7, 48.9, 79.5, 127.2, 127.6, 128.6, 139.7, 155.2, 173.24; ir (potassium bromide): 3319, 1697, 1666, 1527, 1175, 702  $\text{cm}^{-1}$ ; ms: (m/z) 333 ( $M^+ + 1$ ), 277 ( $M^+ - t\text{-Bu}$ ), 188, 160, 120, 105 ( $\text{CHCH}_2\text{Ph}$ ), 84, 77, 57 (*t*-Bu, base); Rotation:  $[\alpha]_D = -116^\circ$  (c 1.0%, chloroform).

*Anal.* Calcd. for  $C_{19}H_{28}N_2O_3$ : C, 68.65; H, 8.49; N, 8.43. Found: C, 68.55; H, 8.53; N, 8.13.

1,1-Dimethylethyl [3R-[1( $S^*$ ),3R\*( $S^*$ )]-1-[5-Oxo-1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**12rs**).

Using the procedure above, **11rs** (5.95 g, 25.6 mmoles), di-*tert*-butyl dicarbonate (6.77 g, 31.0 mmoles) and triethylamine (3.14 g, 31.0 mmoles) gave **12rs** as a white, wax-like glass (7.46 g, 88%);  $^1\text{H}$  nmr ( $\text{DMSO-}d_6$ /250 MHz): 0.90 (d,  $J = 6.5$  Hz, 3H), 1.34 (s, 9H), 1.44 (d,  $J = 7.1$  Hz, 3H), 2.04-2.20 (m, 1H), 2.21-2.41 (m, 2H), 2.69 (dd,  $J = 9.6$ , 6.5 Hz, 1H), 3.28-3.42 (m, 2H), 5.25 (q,  $J = 7.1$  Hz, 1H), 6.78 and 6.85 (2 x d,  $J = 8.6$  and 7.9 Hz, 1H), 7.24-7.37

(m, 5H);  $^{13}\text{C}$  nmr (DMSO- $d_6$ /63 MHz):  $\delta$  16.7, 18.4, 28.2, 34.5, 36.9, 45.0, 48.5, 48.7, 77.5, 126.8, 127.2, 128.4, 140.4, 155.1, 172.6; ir (potassium bromide): 1701, 1682, 1526, 1182, 1069, 699  $\text{cm}^{-1}$ ; ms: (m/z) 333 ( $\text{M}^+ + 1$ ), 277 ( $\text{M}^+ - t\text{-Bu}$ ), 214, 188, 160, 105 (CHCH $_3$ Ph), 84, 77, 57 ( $t\text{-Bu}$ , base); Rotation:  $[\alpha]_D = -127^\circ$  (c 1.0%, chloroform).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_3$ : C, 68.65; H, 8.49; N, 8.43. Found: C, 68.45; H, 8.59; N, 8.38.

1,1-Dimethylethyl [3S-[1(*R*\*),3R\*(*S*\*)]-1-[5-Oxo-1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**12sr**).

Using the procedure above, **11sr** (10.2 g, 44.0 mmoles), di-*tert*-butyl dicarbonate (11.6 g, 53.0 mmoles) and triethylamine (5.36 g, 53.0 mmoles) gave **12sr** as a white solid (mp 120-121 $^\circ$ , 13.2 g, 90%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.10 (d, J = 6.6 Hz, 3H), 1.41 (s, 9H), 1.50 (d, J = 7.2 Hz, 3H), 2.14-2.29 (m, 2H), 2.45 (dd, J = 19.5, 12.2 Hz, 1H), 2.99-3.06 (m, 1H), 3.12-3.19 (m, 1H), 3.57-3.68 (m, 1H), 4.81 (br d, J = 9.1 Hz, 1H), 5.45 (q, J = 7.1 Hz, 1H), 7.19-7.35 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  16.0 and 16.1, 19.3, 28.3 and 28.4, 35.3, 38.1, 45.3, 48.8 and 48.9, 49.4, 79.3, 126.9, 127.4, 128.5, 140.2, 155.5, 173.2; ir (potassium bromide): 3400-3200, 1718, 1662, 1540, 1437, 1365, 1249, 1159, 697  $\text{cm}^{-1}$ ; ms: (m/z) 332 ( $\text{M}^+$ ), 276 ( $\text{M}^+ - t\text{-Bu}$ ), 259, 217, 188 (base), 155, 133, 105 (CHCH $_3$ Ph), 84, 57 ( $t\text{-Bu}$ ); Rotation:  $[\alpha]_D = -32^\circ$  (c 1.0%, chloroform).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_3$ : C, 68.65; H, 8.49; N, 8.43. Found: C, 68.66; H, 8.64; N, 8.38.

1,1-Dimethylethyl [3S-[1(*R*\*),3R\*(*R*\*)]-1-[5-Oxo-1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**12ss**).

Using the procedure above, **11ss** (10.0 g, 43.0 mmoles), di-*tert*-butyl dicarbonate (11.4 g, 52.0 mmoles) and triethylamine (5.26 g, 52.0 mmoles) gave **12ss** as a white solid (mp 148-149 $^\circ$ , 13.0 g, 91%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.08 (d, J = 6.7 Hz, 3H), 1.43 (s, 9H), 1.50 (d, J = 7.1 Hz, 3H), 2.20-2.56 (m, 3H), 2.97-3.13 (m, 2H), 3.70-3.83 (m, 1H), 4.76 (br d, J = 9.1 Hz, 1H), 5.48 (q, J = 7.1 Hz, 1H), 7.23-7.36 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  16.0, 19.1, 25.4, 28.4, 34.1, 37.4, 45.0, 48.8, 79.4, 127.0, 127.5, 128.5, 140.0, 155.5, 173.2; ir (potassium bromide): 3336, 1712, 1655, 1363, 1257, 1165, 1079, 1021, 701  $\text{cm}^{-1}$ ; ms: (CI) (m/z) 373 ( $\text{M}^+ + \text{C}_3\text{H}_5$ ), 361 ( $\text{M}^+ + \text{C}_2\text{H}_5$ ), 333 ( $\text{M}^+ + 1$ ), 277 (base), 188, 173; Rotation:  $[\alpha]_D = -110^\circ$  (c 1.0%, chloroform).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_3$ : C, 68.65; H, 8.49; N, 8.43. Found: C, 68.50; H, 8.61; N, 8.57.

[3R-[1(*S*\*),3R\*(*R*\*)]-*N*, $\alpha$ -Dimethyl-1-(1-phenylethyl)-3-pyrrolidine-methanamine (**17rr**).

Using the procedure for the synthesis of **15sr**, **12rr** (11.8 g, 35.5 mmoles) in THF (100 ml), and lithium aluminum hydride (2.84 g, 71.0 mmoles) in THF (250 ml) gave crude **17rr** as a yellow oil (7.85 g, 93%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  0.94 (d, J = 6.3 Hz, 3H), 1.12-1.40 (m, 1H), 1.36 (d, J = 6.4 Hz, 3H), 1.50-1.63 (m, 1H), 1.88-2.07 (m, 1H), 2.09-2.20 (m, 2H), 2.25-2.45 (m, 2H), 2.39 (s, 3H), 2.49-2.62 (m, 1H), 2.72-2.81 (m, 1H), 3.15 (q, J = 6.5 Hz, 1H), 7.21-7.33 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.7, 23.2, 27.4, 34.1, 43.5, 52.8, 56.5, 59.3, 65.9, 126.8, 127.1, 128.3, 145.6; ir (liquid film): 3349, 1451, 1155, 764, 702  $\text{cm}^{-1}$ ; ms: (m/z) 234 ( $\text{M}^+ + 2$ ), 233 ( $\text{M}^+ + 1$ ), 232 ( $\text{M}^+$ ), 201, 186, 127, 105 (CHCH $_3$ Ph, base), 82, 58; ms: (high resolution) Calcd. for  $\text{C}_{15}\text{H}_{24}\text{N}_2$  ( $\text{M}^+$ ): 232.1934. Found: 232.1920; Rotation:  $[\alpha]_D =$

$-75^\circ$  (c 1.9%, chloroform).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{24}\text{N}_2 \cdot 0.25\text{H}_2\text{O}$ : C, 76.06; H, 10.43; N, 11.83. Found: C, 76.20; H, 10.16; N, 11.57.

[3R-[1(*S*\*),3R\*(*S*\*)]-*N*, $\alpha$ -Dimethyl-1-(1-phenylethyl)-3-pyrrolidine-methanamine (**17rs**).

Using the procedure above, **12rs** (5.30 g, 16.0 mmoles) and lithium aluminum hydride (1.27 g, 32.0 mmoles) gave **17rs** as a clear liquid (3.54 g, 94%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.01 (d, J = 6.2 Hz, 3H), 1.36 (d, J = 6.5 Hz, 3H), 1.40-1.55 (m, 1H), 1.83-2.02 (m, 1H), 2.04-2.20 (m, 2H), 2.27-2.44 (m, 2H), 2.35 (s, 3H), 2.63-2.69 (m, 1H), 2.74-2.85 (m, 1H), 3.16 (q, J = 6.6 Hz, 1H), 7.20-7.34 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.7, 23.2, 27.7, 34.0, 43.9, 52.8, 56.9, 59.2, 66.0, 126.8, 127.2, 128.3, 145.8; ir (liquid film): 3754, 1452, 1156, 763, 703  $\text{cm}^{-1}$ ; ms: (m/z) 234 ( $\text{M}^+ + 2$ ), 233 ( $\text{M}^+ + 1$ ), 232 ( $\text{M}^+$ ), 201 (base), 186, 174, 105 (CHCH $_3$ Ph).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{24}\text{N}_2 \cdot 0.20\text{H}_2\text{O}$ : C, 76.35; H, 10.42; N, 11.87. Found: C, 76.55; H, 10.69; N, 11.57.

[3S-[1(*R*\*),3R\*(*S*\*)]-*N*, $\alpha$ -Dimethyl-1-(1-phenylethyl)-3-pyrrolidine-methanamine (**17sr**).

Using the procedure above, **12sr** (15.0 g, 45.0 mmoles) and lithium aluminum hydride (3.60 g, 90.0 mmoles) gave **17sr** as a light yellow oil (9.12 g, 86%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.02 (d, J = 6.2 Hz, 3H), 1.38 (d, J = 6.6 Hz, 3H), 1.43-1.54 (m, 1H), 1.78-1.92 (m, 1H), 2.09-2.29 (m, 2H), 2.35-2.40 (m, 1H), 2.38 (s, 3H), 2.46 (t, J = 6.9 Hz, 2H), 2.83-2.93 (m, 1H), 7.20-7.34 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.5, 23.3, 27.6, 33.9, 43.6, 53.0, 56.8, 59.1, 66.1, 126.8, 127.2, 128.3, 145.7; ir (liquid film): 1452, 1370, 763, 701  $\text{cm}^{-1}$ ; ms: (CI) (m/z) 261 ( $\text{M}^+ + \text{C}_2\text{H}_5$ ), 233 ( $\text{M}^+ + 1$ , base), 201, 186; Rotation:  $[\alpha]_D = -49^\circ$  (c 0.9%, chloroform).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{24}\text{N}_2 \cdot 0.25\text{H}_2\text{O}$ : C, 76.06; H, 10.43; N, 11.83. Found: C, 76.10; H, 10.54; N, 12.04.

[3S-[1(*R*\*),3R\*(*R*\*)]-*N*, $\alpha$ -Dimethyl-1-(1-phenylethyl)-3-pyrrolidine-methanamine (**17ss**).

Using the procedure above, **12ss** (12.7 g, 38.0 mmoles) and lithium aluminum hydride (2.80 g, 70.0 mmoles) gave **17ss** as a faint yellow oil (7.30 g, 80%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  0.98 (d, J = 6.2 Hz, 3H), 1.37 (d, J = 6.6 Hz, 3H), 1.47-1.70 (m, 2H), 1.81-1.95 (m, 1H), 2.08-2.23 (m, 2H), 2.30-2.58 (m, 3H), 2.39 (s, 3H), 2.65-2.78 (m, 1H), 3.16 (q, J = 6.6 Hz, 1H), 7.21-7.37 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.7, 23.3, 27.2, 34.1, 43.3, 52.9, 56.5, 59.4, 66.0, 126.8, 127.1, 128.3, 145.8; ir (liquid film): 1452, 1370, 1151, 764, 702  $\text{cm}^{-1}$ ; ms: (m/z) 232 ( $\text{M}^+$ ), 217, 201, 186, 127, 105 (CHCH $_3$ Ph, base), 96, 82, 58; Rotation:  $[\alpha]_D = -38^\circ$  (c 1.0%, chloroform).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{24}\text{N}_2 \cdot 0.50\text{H}_2\text{O}$ : C, 74.64; H, 10.44; N, 11.61. Found: C, 74.82; H, 10.29; N, 11.48.

1,1-Dimethylethyl [3R-[1(*S*\*),3R\*(*R*\*)]-Methyl[1-[1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**18rr**).

Using the procedure for the synthesis of **12rr**, di-*tert*-butyl dicarbonate (3.71 g, 17.0 mmoles) in methylene chloride (50 ml) and a solution of **17rr** (3.33 g, 14.0 mmoles) and triethylamine (1.72 g, 17.0 mmoles) in methylene chloride (100 ml) gave **18rr** as a yellow oil, which solidified on cooling to 0 $^\circ$ , after column chromatography [silica gel/ethyl acetate] (4.17 g, 75%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  0.92 and 0.95 (2 x d superimposed,

3H), 1.36 (d,  $J = 6.5$  Hz, 3H), 1.40-1.60 (m, 1H), 1.46 (s, 9H), 1.75-1.93 (m, 2H), 2.08-2.35 (m, 2H), 2.55-2.71 (m, 4H), 2.90-3.09 (m, 1H), 3.11-3.24 (m, 1H), 3.75-3.90 and 3.98-4.12 (m, 1H), 7.18-7.37 (m, 5H), traces of ethyl acetate observed;  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.0 and 17.3, 23.1, 27.3 and 27.7, 28.5, 41.5, 52.1, 53.8, 55.2, 57.7, 65.8, 79.1 and 79.3, 126.9, 127.1, 128.3, 145.6, 156.0; ir (potassium bromide): 1685, 1488, 1448, 1397, 1367, 1336, 1320, 1190, 1160, 1144, 766, 700  $\text{cm}^{-1}$ ; ms: (m/z) 333 ( $\text{M}^+ + 1$ ), 317, 227, 186, 171, 105 ( $\text{CHCH}_3\text{Ph}$ ), 84, 49 (base); Rotation:  $[\alpha]_{\text{D}} = -25^\circ$  (c 0.3%, chloroform).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 0.75$ ethyl acetate: C, 69.31; H, 9.61; N, 7.03. Found: C, 69.04; H, 9.59; N, 7.05.

1,1-Dimethylethyl [3*R*-[1(*S*),3*R*(*S*)]-Methyl[1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**18rs**).

Using the procedure above, **17rs** (3.45 g, 14.8 mmoles), di-*tert*-butyl dicarbonate (3.93 g, 18.0 mmoles) and triethylamine (1.82 g, 18.0 mmoles) gave **18rs** as a yellow oil (3.92 g, 79%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.05 (d,  $J = 6.7$  Hz, 3H), 1.30-1.45 (m, 12H), 1.85-2.09 (m, 2H), 2.10-2.28 (m, 1H), 2.30-2.50 (m, 2H), 2.54 and 2.64 (2 x s, 3H), 2.65-2.85 and 2.89-3.06 (2 x m, 1H), 3.16 (q,  $J = 6.6$  Hz, 1H), 3.75-3.91 and 3.98-4.13 (2 x m, 1H), 7.15-7.35 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  16.6 and 16.7, 22.9 and 23.0, 27.8, 28.5, 41.5, 52.5 and 52.7, 54.0, 55.5, 56.5 and 56.8, 65.8, 79.0 and 79.3, 126.8, 126.9, 127.1, 128.3, 145.2 and 145.6, 155.7 and 155.8; ir (liquid film): 2978, 1702, 1681, 1453, 1366, 1142, 702  $\text{cm}^{-1}$ ; ms: (CI) (m/z) 361 ( $\text{M}^+ + \text{C}_2\text{H}_5$ ), 335, 334, 333 ( $\text{M}^+ + 1$ , base), 317, 305, 277, 233, 105 ( $\text{CHCH}_3\text{Ph}$ ); Rotation:  $[\alpha]_{\text{D}} = -71^\circ$  (c 0.7%, chloroform).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 0.10\text{H}_2\text{O}$ : C, 71.86; H, 9.71; N, 8.38. Found: C, 72.23; H, 10.11; N, 8.21.

1,1-Dimethylethyl [3*S*-[1(*R*),3*R*(*S*)]-Methyl[1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**18sr**).

Using the procedure above, **17sr** (9.00 g, 38.7 mmoles), di-*tert*-butyl dicarbonate (10.2 g, 46.5 mmoles) and triethylamine (4.71 g, 46.5 mmoles) gave **18sr** as a pale yellow oil (10.9 g, 84%);  $^1\text{H}$  nmr (DMSO- $d_6$ /300 MHz/75 $^\circ$ ):  $\delta$  1.03 (d,  $J = 6.7$  Hz, 3H), 1.28 (d,  $J = 6.7$  Hz, 3H), 1.33-1.42 (m, 10H), 1.78-1.88 (m, 1H), 2.14-2.28 (m, 2H), 2.40 (dd,  $J = 16.2$ , 7.3 Hz, 1H), 2.50 (t,  $J = 7.8$  Hz, 1H), 2.54-2.64 (m, 4H), 3.24 (q,  $J = 6.6$  Hz, 1H), 3.75-3.93 (m, 1H), 7.20-7.31 (m, 5H);  $^{13}\text{C}$  nmr (DMSO- $d_6$ /75 MHz/75 $^\circ$ ):  $\delta$  15.7, 22.4, 27.6, 27.7, 28.0, 40.5, 51.7, 54.2, 55.0, 64.1, 77.8, 126.1, 126.4, 127.6, 145.1, 154.4; ir (liquid film): 1692, 1453, 1366, 1148, 702  $\text{cm}^{-1}$ ; ms: (m/z) 334 ( $\text{M}^+ + 2$ ), 333 ( $\text{M}^+ + 1$ , base), 332 ( $\text{M}^+$ ), 317 ( $\text{M}^+ - \text{CH}_3$ ), 277, 261, 227, 171, 105 ( $\text{CHCH}_3\text{Ph}$ ), 58; Rotation:  $[\alpha]_{\text{D}} = -28^\circ$  (c 1.0%, chloroform).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 0.10\text{H}_2\text{O}$ : C, 71.86; H, 9.71; N, 8.38. Found: C, 71.80; H, 9.89; N, 8.44.

1,1-Dimethylethyl [3*S*-[1(*R*),3*R*(*R*)]-Methyl[1-(1-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**18ss**).

Using the procedure above, **17ss** (7.13 g, 31.0 mmoles), di-*tert*-butyl dicarbonate (8.08 g, 37.0 mmoles) and triethylamine (3.74 g, 37.0 mmoles) gave **18ss** as a yellow liquid (9.15 g, 88%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.03 and 1.20 (2 x d,  $J = 6.7$  and 6.1 Hz, 3H), 1.38 (d,  $J = 6.4$  Hz, 3H), 1.39-1.50 (m, 1H), 1.45 (s, 9H), 1.63-1.80 (m, 1H), 1.90-2.01 (m, 1H), 2.15-2.37 (m, 2H), 2.42-2.55 (m, 1H), 2.65 and 2.70 (2 x s, 3H), 2.84-2.99 (m, 1H), 3.10-3.21 (m, 1H), 3.72-4.11 (m, 1H), 7.16-7.34 (m, 5H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.1 and 17.3, 23.2, 27.3 and

27.7, 28.5 and 28.6, 41.7 and 42.9, 52.5, 53.7 and 54.0, 55.1 and 55.3, 57.1 and 57.2, 65.8, 79.1 and 79.3, 126.9, 127.1, 128.3, 145.4 and 145.5, 155.9 and 156.1; ir (liquid film): 1692, 1453, 1366, 1148, 702  $\text{cm}^{-1}$ ; ms: (m/z) 333 ( $\text{M}^+ + 1$ ), 332 ( $\text{M}^+$ ), 317 ( $\text{M}^+ + 1 - \text{CH}_3$ ), 261, 227, 158, 105 ( $\text{CHCH}_3\text{Ph}$ ), 77, 57 (*t*-Bu, base); Rotation:  $[\alpha]_{\text{D}} = -26^\circ$  (c 1.0%, chloroform).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 0.25\text{H}_2\text{O}$ : C, 71.28; H, 9.72; N, 8.31. Found: C, 71.11; H, 9.88; N, 8.45.

1,1-Dimethylethyl [*S*-(*R*\*,*S*\*)]-Methyl[1-(3-pyrrolidinyl)ethyl]carbamate (**21rs**).

Using the procedure for the synthesis of **22rr**, **18rs** (3.35 g, 10.0 mmoles), 20% palladium on carbon (1.00 g) and methanol (100 ml) gave crude **21rs** as a pale yellow oil (2.20 g, 90%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.13 (d,  $J = 6.7$  Hz, 3H), 1.30-1.48 (m, 1H), 1.46 (s, 9H), 1.83-1.98 (m, 1H), 2.06-2.27 (m, 1H), 2.55-2.80 (m, 4H), 2.83-3.25 (m, 4H), 3.73-3.92 and 3.97-4.12 (2 x m, 1H), traces of methanol observed;  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.1 and 17.5, 28.0 and 28.5, 30.6, 43.6 and 43.9, 46.9, 50.3 and 50.6, 53.4, 55.0, 79.3 and 79.5, 155.6 and 156.0; ir (liquid film): 1706, 1672, 1137, 871, 772  $\text{cm}^{-1}$ ; ms: (m/z) 229 ( $\text{M}^+ + 1$ ), 228 ( $\text{M}^+$ ), 173, 155, 102, 98, 97, 96, 82, 70, 69, 68, 58 (base), 57; Rotation:  $[\alpha]_{\text{D}} = -2^\circ$  (c 1.4%, chloroform).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}_2 \cdot 0.50\text{CH}_3\text{OH}$ : C, 61.44; H, 10.72; N, 11.46. Found: C, 61.27; H, 10.58; N, 11.43.

1,1-Dimethylethyl [*R*-(*R*\*,*R*\*)]-Methyl[1-(3-pyrrolidinyl)ethyl]carbamate (**21rr**).

Using the procedure above, **18rr** (3.19 g, 9.60 mmoles), and 20% palladium on carbon (1.00 g) gave crude **21rr** as a faint yellow waxy solid (2.16 g, 99%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.09 (d,  $J = 6.7$  Hz, 3H), 1.40-1.48 (m, 1H), 1.46 (s, 9H), 1.70-1.84 (m, 1H), 2.12-2.27 (m, 1H), 2.47-2.62 (m, 1H), 2.70 and 2.73 (2 x s, 3H), 2.90-3.03 (m, 2H), 3.10 (dd,  $J = 10.8$ , 7.7 Hz, 1H), 3.78-3.90 and 3.98-4.10 (2 x m, 2H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.2 and 17.5, 27.7 and 27.8, 28.3, 29.5 and 29.8, 43.6, 46.5, 50.8 and 51.0, 53.3 and 54.6, 78.9 and 79.2, 155.5 and 155.8; ir (liquid film): 1677, 1398, 1367, 1332, 1150, 1141, 754, 749  $\text{cm}^{-1}$ ; ms: (m/z) 229 ( $\text{M}^+ + 1$ ), 228 ( $\text{M}^+$ ), 173, 155, 102, 98, 97, 96, 82, 70, 57 (*t*-Bu, base); Rotation:  $[\alpha]_{\text{D}} = +15^\circ$  (c 0.4%, chloroform).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}_2$ : C, 63.12; H, 10.59; N, 12.27. Found: C, 63.06; H, 10.59; N, 12.26.

1,1-Dimethylethyl [*R*-(*R*\*,*S*\*)]-Methyl[1-(3-pyrrolidinyl)ethyl]carbamate (**21sr**).

Using the procedure above, **18sr** (10.1 g, 30.4 mmoles) and 20% palladium on carbon (1.00 g) gave **21sr** as a clear, colorless liquid after vacuum distillation (bp 100-105 $^\circ$  at 1 mm Hg, 4.47 g, 63%);  $^1\text{H}$  nmr (deuteriochloroform/250 MHz):  $\delta$  1.12 (d,  $J = 6.7$  Hz, 3H), 1.28-1.52 (m, 10H), 1.80-1.98 (m, 1H), 2.05-2.23 (m, 1H), 2.51-2.79 (m, 4H), 2.80-3.08 (m, 3H), 3.73-3.87 and 3.96-4.08 (2 x m, 1H);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  17.1 and 17.5, 27.9 and 28.4, 30.7, 43.7 and 43.9, 47.1, 50.5 and 50.8, 53.4, 54.9, 79.1 and 79.4, 155.6 and 155.9; ir (liquid film): 3500-3250, 1683, 1458, 1366, 1150, 872  $\text{cm}^{-1}$ ; ms: (m/z) 229 ( $\text{M}^+ + 1$ ), 228 ( $\text{M}^+$ ), 211, 199, 171, 155, 97, 82, 70, 58 (base); Rotation:  $[\alpha]_{\text{D}} = -1^\circ$  (c 1.0%, chloroform).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}_2 \cdot 0.25\text{H}_2\text{O}$ : C, 61.90; H, 10.61; N, 12.03. Found: C, 61.62; H, 10.56; N, 12.10.

1,1-Dimethylethyl [S-(R\*,R\*)]-Methyl[1-(3-pyrrolidinyl)ethyl]-  
carbamate (**21ss**).

Using the procedure above, **18ss** (8.16 g, 24.5 mmoles) and 20% palladium on carbon (1.00 g) gave **21ss** as a colorless oily liquid after vacuum distillation which crystallized into a white, wax-like solid upon cooling to 0° (bp 100-102° at 1 mm Hg, 4.26 g, 75%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 1.08 (d, J = 6.7 Hz, 3H), 1.40-1.54 (m, 10H), 1.71-1.82 (m, 1H), 2.06-2.20 (m, 1H), 2.47-2.58 (m, 2H), 2.69 and 2.73 (2 x s, 3H), 2.86-3.08 (m, 3H), 3.77-3.86 and 3.98-4.15 (2 x m, 1H); <sup>13</sup>C nmr (deuteriochloroform/63 MHz): δ 17.1 and 17.4, 27.5 and 27.7, 28.2, 29.4 and 29.8, 43.6, 46.5 and 46.6, 50.9 and 51.1, 53.3 and 54.6, 78.9 and 79.1, 155.5 and 155.7; ir (liquid film): 3500-3300, 1696, 1397, 1152, 872 cm<sup>-1</sup>; ms: (m/z) 229 (M<sup>+</sup> + 1), 228 (M<sup>+</sup>), 171 (M<sup>+</sup> - t-Bu), 155, 125, 102, 97, 82, 70, 58, 57 (t-Bu, base); Rotation: [α]<sub>D</sub> = -12° (c 0.5%, chloroform).

Anal. Calcd. for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>·0.25H<sub>2</sub>O: C, 61.90; H, 10.61; N, 12.03. Found: C, 62.30; H, 10.74; N, 11.93.

[4S-[1(R\*),4R\*(S\*)]-4-[1-(Dimethylamino)ethyl]-1-(1-phenylethyl)-  
2-pyrrolidinone (**14sr**).

The chiral amine **11sr** (6.50 g, 28.0 mmoles) was cooled in an ice/water bath. To the cold amine was added 88% formic acid (3.66 g, 69.9 mmoles) and 35% formaldehyde (6.00 g, 69.9 mmoles). The ice bath was removed and the reaction was warmed slowly over 1 hour. Gas evolution occurred. The reaction was then warmed to reflux for 5 hours, cooled to room temperature, and made basic (pH approximately 14) with 1N sodium hydroxide solution. The reaction was extracted five times with diethyl ether. The combined ether layers were washed four times with saturated sodium chloride solution, dried, filtered and concentrated to an oil (7.17 g, 98%). The residue was Kugelrohr distilled to give **14sr** as a clear oil (bp 140-157° at 0.20-0.25 mm Hg, 6.37 g, 87%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 0.88 (d, J = 6.5 Hz, 3H), 1.52 (d, J = 7.1 Hz, 3H), 2.03-2.32 (m, 8H - contains 2.14, s), 2.35-3.55 (m, 2H), 3.01-3.30 (m, 2H), 5.48 (q, J = 7.1 Hz, 1H), 7.19-7.40 (m, 5H); ir (liquid film): 2936, 1695, 1424, 1224, 701 cm<sup>-1</sup>; ms: (m/z) 261 (M<sup>+</sup> + 1), 72 (CHN(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>, base); Rotation: [α]<sub>D</sub> = -70° (c 1.2%, methanol).

Anal. Calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.48; H, 9.47; N, 10.55.

[4S-[1(R\*),4R\*(R\*)]-4-[1-(Dimethylamino)ethyl]-1-(1-phenylethyl)-  
2-pyrrolidinone (**14ss**).

Using the procedure above, **11ss** (3.90 g, 16.8 mmoles), 88% formic acid (2.19 g, 42.0 mmoles) and 35% formaldehyde (3.60 g, 42.0 mmoles) gave a white solid (3.92 g, 90%). This residue was recrystallized from diethyl ether to give **14ss** as white crystals (mp 101.5-103°, 1.31 g, 30%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 0.83 (d, J = 6.4 Hz, 3H), 1.51 (d, J = 7.1 Hz, 3H), 2.08-2.59 (m, 10H - contains 2.18, s), 2.87-3.07 (m, 2H), 5.50 (q, J = 7.1 Hz, 1H), 7.19-7.40 (m, 5H); ir (liquid film): 2969, 1679, 1426, 1269, 1223, 1027, 702 cm<sup>-1</sup>; ms: (CI) (m/z) 301 (M<sup>+</sup> + C<sub>3</sub>H<sub>5</sub>), 289 (M<sup>+</sup> + C<sub>2</sub>H<sub>5</sub>), 261 (M<sup>+</sup> + 1, base); Rotation: [α]<sub>D</sub> = -80° (c 1.0%, methanol).

Anal. Calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.68; H, 9.46; N, 10.71.

The filtrate was concentrated to give additional material which was used without further purification (2.52 g, 58%).

[4R-[1(S\*),4R\*(S\*)]-4-[1-(Dimethylamino)ethyl]-1-(1-phenylethyl)-2-  
pyrrolidinone (**14rs**).

Using the procedure above, **11rs** (12.0 g, 51.7 mmoles), 88% formic acid (6.75 g, 129 mmoles) and 35% formaldehyde (11.1 g, 129 mmoles) gave **14rs** as an oil which was used without further purification (12.5 g, 92%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 0.84 (d, J = 6.0 Hz, 3H), 1.52 (d, J = 7.1 Hz, 3H), 1.97-2.20 (m, 7H - contains 2.11, s), 2.20-2.58 (m, 3H), 2.88 (dd, J = 10.1, 6.8 Hz, 1H), 3.38 (dd, J = 10.1, 7.3 Hz, 1H), 5.51 (q, J = 7.1 Hz, 1H), 7.18-7.43 (m, 5H); ir (liquid film): 2970, 2787, 1452, 1372, 1313, 1213, 1158, 964, 764, 702 cm<sup>-1</sup>; ms: (m/z) 261 (M<sup>+</sup> + 1), 105 (CHCH<sub>3</sub>Ph), 72 (CHN(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>, base); Rotation: [α]<sub>D</sub> = -95° (c 1.0%, methanol).

Anal. Calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O·0.15H<sub>2</sub>O: C, 73.05; H, 9.31; N, 10.65. Found: C, 73.37; H, 9.38; N, 10.25.

[4R-[1(S\*),4R\*(R\*)]-4-[1-(Dimethylamino)ethyl]-1-(1-phenylethyl)-  
2-pyrrolidinone (**14rr**).

Using the procedure above, **11rr** (12.0 g, 51.7 mmoles), 88% formic acid (6.75 g, 129 mmoles) and 35% formaldehyde (11.1 g, 129 mmoles) gave **14rr** as an oil which was used without further purification (11.3 g, 83%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz): δ 0.73 (d, J = 5.9 Hz, 3H), 1.52 (d, J = 7.1 Hz, 3H), 2.15 (s, 6H), 2.22-2.63 (m, 5H), 3.22-3.38 (m, 1H), 5.52 (q, J = 7.1 Hz, 1H), 7.18-7.43 (m, 5H); ir (liquid film): 2974, 2779, 1689, 1424, 1269, 702 cm<sup>-1</sup>; ms: (m/z) 261 (M<sup>+</sup> + 1), 105 (CHCH<sub>3</sub>Ph), 72 (CHN(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>, base); Rotation: [α]<sub>D</sub> = -129° (c 1.1%, methanol).

Anal. Calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O·0.15H<sub>2</sub>O: C, 73.05; H, 9.31; N, 10.65. Found: C, 73.00; H, 9.69; N, 10.39.

X-ray Diffraction Analysis for **12rr**, **12sr** and **14ss**.

X-ray measurements were performed on a single crystal diffractometer (Siemens R3m/v for **12rr** and **14ss** and Syntex P2, for **12sr**) using  $\theta/2\theta$  scanning mode ( $2\theta$  scan range: 5-55 degrees for **12sr** and **14ss** and 5-40 degrees for **12rr**) and graphite-monochromated MoK $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). The crystal data and parameters are summarized in Table 1. The unit cell parameters were determined by a least-squares fit of  $2\theta$  angles for 25 (33 for **14ss**) reflections in the range of  $20^\circ \leq 2\theta \leq (30^\circ \text{ for } \mathbf{12rr}, 29^\circ \text{ for } \mathbf{12sr} \text{ and } 35^\circ \text{ for } \mathbf{14ss})$ . Three standard reflections were monitored at every 100 reflection intervals throughout the data collection and showed no significant fluctuation (less than 3% for **12rr** and **12sr** and a linear decay of approximately 2% for **14ss**). The observed intensities were corrected for Lorentz and polarization effects. No correction of the absorption effect was done. The structure was solved by direct methods. The positional parameters were refined by a full-matrix least-squares analysis. The H atoms were located in computed positions (Riding Method - except for the hydrogen bonded to N2 in **12rr** which was located on a difference map and allowed to refine to a distance of 0.94(5)  $\text{\AA}$ ). For non-hydrogen atoms anisotropic thermal parameters were refined and an isotropic refinement was applied to hydrogen atoms. No abnormally short contact distances were observed in the crystal packing. The function minimized was  $\Sigma w(F_o - F_c)^2$ . The weighting scheme used for refinement was based on counting statistics. At convergence, none of the positional and thermal parameters shifted more than 30% of their standard deviations. For all crystallographic computations, the Siemens SHELXTL PLUS system of programs was used. Atomic scattering factors and the terms for anomalous dispersion correction were taken from the



International Tables for X-ray crystallography [12].

In the case of **12rr** the configuration is based on the known configuration of the starting material. A check of the opposite configuration gave virtually identical R indices so that the absolute configuration could not be based on the application of the Hamilton ratio test [13]. A refinement of Rogers  $\eta$  parameters [14] gave a positive value, 5.5 (3.9) versus -5.2 (4.0) for the opposite configuration but the large esd makes the refinement statistically dubious.

[3S-[1(R\*),3R\*(S\*)]-N,N, $\alpha$ -Trimethyl-1-(1-phenylethyl)-3-pyrrolidinemethanamine (**20sr**).

Using the procedure for the synthesis of **15sr**, lithium aluminum hydride (1.89 g, 47.2 mmoles) in THF (100 ml) and **14sr** (6.15 g, 23.6 mmoles) in THF (65 ml) gave **20sr** as an oil after distillation (bp 95-105° at 0.10-0.15 mm Hg, 4.65 g, 80%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz):  $\delta$  0.86 (d, J = 6.2 Hz, 3H), 1.23-1.46 (m, 4H-contains 1.39, d, J = 6.6 Hz), 1.74-1.95 (m, 1H), 2.08-2.46 (m, 10H), 2.46-2.61 (m, 1H), 3.00-3.24 (m, 2H-contains 3.18, q, J = 6.6 Hz), 7.11-7.38 (m, 5H); ir (liquid film): 2971, 2772, 1452, 1266, 1220, 1095, 1046, 762, 701 cm<sup>-1</sup>; ms: (m/z) 247 (M<sup>+</sup> + 1), 201 (M<sup>+</sup> -HN(CH<sub>3</sub>)<sub>2</sub>), 105 (CHCH<sub>3</sub>Ph), 72 (CHN(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>), 47 (base); Rotation:  $[\alpha]_D = -38^\circ$  (c 1.1%, methanol).

Anal. Calcd. for C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.70; H, 10.98; N, 11.32.

[3S-[1(R\*),3R\*(R\*)]-N,N, $\alpha$ -Trimethyl-1-(1-phenylethyl)-3-pyrrolidinemethanamine (**20ss**).

Using the procedure above, **14ss** (5.24 g, 20.1 mmoles) and lithium aluminum hydride (1.61 g, 40.2 mmoles) gave **20ss** as an oil (bp 96-102° at 0.15 mm Hg, 3.97 g, 80%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz):  $\delta$  0.83 (d, J = 6.4 Hz, 3H), 1.38 (d, J = 6.6 Hz, 3H), 1.54-1.78 (m, 1H), 1.78-2.04 (m, 2H), 2.07-2.41 (m, 9H-contains 2.19, s), 2.41-2.62 (m, 1H), 2.90 (dd, J = 8.5, 7.7 Hz, 1H), 3.17 (q, J = 6.6 Hz, 1H), 7.12-7.36 (m, 5H); ir (liquid film): 2970, 2776, 1598, 1452, 1370, 1314, 1267, 1219, 1159, 1095, 762, 701 cm<sup>-1</sup>; ms: (m/z) 247 (M<sup>+</sup> + 1), 201 (M<sup>+</sup> -NH(CH<sub>3</sub>)<sub>2</sub>), 105 (CHCH<sub>3</sub>-Ph), 72 (CHN(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>, base); Rotation:  $[\alpha]_D = -31^\circ$  (c 1.1%, methanol).

Anal. Calcd. for C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>·0.10H<sub>2</sub>O: C, 77.43; H, 10.64; N, 11.29. Found: C, 77.52; H, 11.02; N, 11.06.

[3R-[1(S\*),3R\*(S\*)]-N,N, $\alpha$ -Trimethyl-1-(1-phenylethyl)-3-pyrrolidinemethanamine (**20rs**).

Using the procedure above, **14rs** (11.6 g, 44.5 mmoles) and lithium aluminum hydride (3.56 g, 89.0 mmoles) gave **20rs** as an oil (bp 98-109° at 0.10 mm Hg, 9.06 g, 83%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz):  $\delta$  0.85 (d, J = 6.4 Hz, 3H), 1.24 (m, 4H-contains 1.36, d, J = 6.6 Hz), 1.77-2.00 (m, 1H), 2.00-2.48 (m, 10H-contains 2.14, s), 2.61-2.83 (m, 2H), 3.19 (q, J = 6.6 Hz, 1H), 7.12-7.37 (m, 5H); ir (liquid film): 2972, 2775, 1452, 1369, 1158, 763, 701 cm<sup>-1</sup>; ms: (m/z) 247 (M<sup>+</sup> + 1), 201 (M<sup>+</sup> -(CH<sub>3</sub>)<sub>2</sub>NH), 141 (M<sup>+</sup> -CHCH<sub>3</sub>Ph), 105 (CHCH<sub>3</sub>Ph), 72 (CHN(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>, base); Rotation:  $[\alpha]_D = -47^\circ$  (c 0.9%, methanol).

Anal. Calcd. for C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.96; H, 10.72; N, 11.36.

[3R-[1(S\*),3R\*(R\*)]-N,N, $\alpha$ -Trimethyl-1-(1-phenylethyl)-3-pyrrolidinemethanamine (**20rr**).

Using the procedure above, **14rr** (10.4 g, 40.1 mmoles) and lithium aluminum hydride (3.20 g, 80.1 mmoles) gave **20rr** as an oil (bp 103-109° at 0.10 mm Hg, 7.99 g, 81%); <sup>1</sup>H nmr (deuterio-

chloroform/250 MHz):  $\delta$  0.75 (d, J = 6.4 Hz, 3H), 1.37 (d, J = 6.6 Hz, 3H), 1.58-1.77 (m, 1H), 1.81-2.46 (m, 11H-contains 2.17, s), 2.51-2.66 (m, 1H), 2.85-3.03 (m, 1H), 3.15 (q, J = 6.6 Hz, 1H), 7.15-7.38 (m, 5H); ir (liquid film): 2969, 2776, 1452, 1370, 1310, 1267, 1158, 1095, 762, 701 cm<sup>-1</sup>; ms: (m/z) 247 (M<sup>+</sup> + 1), 201 (M<sup>+</sup> -(CH<sub>3</sub>)<sub>2</sub>NH), 141 (M<sup>+</sup> -CHCH<sub>3</sub>Ph), 105 (CHCH<sub>3</sub>Ph), 72 (CHN(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>, base); Rotation:  $[\alpha]_D = -50^\circ$  (c 1.0%, methanol).

Anal. Calcd. for C<sub>16</sub>H<sub>26</sub>N<sub>2</sub>: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.95; H, 10.75; N, 11.23.

[R-(R\*,S\*)]-N,N, $\alpha$ -Trimethyl-3-pyrrolidinemethanamine (**23sr**).

Using the procedure for the synthesis of **22rr**, **20sr** (5.42 g, 22.0 mmoles), 20% palladium on carbon (1.50 g) and methanol (100 ml) gave **23sr** as an oil after distillation (bp 89-104° at 10.0 mm Hg, 1.76 g, 56%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz):  $\delta$  0.91 (d, J = 6.4 Hz, 3H), 1.19-1.40 (m, 1H), 1.75-2.12 (m, 3H), 2.20 (s, 6H), 2.25-2.47 (m, 1H), 2.69 (dd, J = 10.9, 8.1 Hz, 1H), 2.82-3.02 (m, 2H), 3.10 (dd, J = 10.9, 7.6 Hz, 1H); <sup>13</sup>C nmr (deuteriochloroform/63 MHz):  $\delta$  9.5, 30.8, 40.2, 44.2, 47.0, 51.7, 63.2; ir (liquid film): 3299, 2966, 1453, 1404, 1369, 1267, 1162, 1095, 1045 cm<sup>-1</sup>; ms: (m/z) 143 (M<sup>+</sup> + 1), 72 (CHN(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>, base); ms: (high resolution) Calcd. for C<sub>9</sub>H<sub>18</sub>N<sub>2</sub> (M<sup>+</sup> + 1): 143.1548. Found: 143.1539; Rotation:  $[\alpha]_D = -22^\circ$  (c 1.0%, methanol).

Anal. Calcd. for C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>·0.10H<sub>2</sub>O: C, 66.71; H, 12.74; N, 19.45. Found: C, 66.95; H, 12.64; N, 19.09.

[S-(R\*,R\*)]-N,N, $\alpha$ -Trimethyl-3-pyrrolidinemethanamine (**23ss**).

Using the procedure above, **20ss** (2.89 g, 11.7 mmoles) and 20% palladium on carbon (1.00 g) gave **23ss** as an oil (bp 83-110° at 10.0 mm Hg, 1.19 g, 72%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz):  $\delta$  0.87 (d, J = 6.4 Hz, 3H), 1.47-1.67 (m, 1H), 1.82-2.13 (m, 2H), 2.22 (s, 7H-integrates to 6H with deuterium oxide exchange), 2.28-2.53 (m, 2H), 2.82-2.98 (m, 2H), 3.04 (dd, J = 10.5, 7.5 Hz, 1H); <sup>13</sup>C nmr (deuteriochloroform/63 MHz):  $\delta$  9.7, 30.7, 40.2, 44.2, 46.8, 51.0, 62.8; ir (liquid film): 3279, 1540, 1458, 1266, 1158, 1096, 1047 cm<sup>-1</sup>; ms: (CI) (m/z) 183 (M<sup>+</sup> + C<sub>3</sub>H<sub>5</sub>), 171 (M<sup>+</sup> + C<sub>2</sub>H<sub>5</sub>), 143 (M<sup>+</sup> + 1, base); ms: (high resolution) Calcd. for C<sub>8</sub>H<sub>18</sub>N<sub>2</sub> (M<sup>+</sup> + 1): 143.1548. Found: 143.1542; Rotation:  $[\alpha]_D = -1.0^\circ$  (c 1.4%, methanol).

Anal. Calcd. for C<sub>8</sub>H<sub>18</sub>N<sub>2</sub>·0.12CO<sub>2</sub>: C, 66.11; H, 12.30; N, 18.99. Found: C, 66.23; H, 12.27; N, 18.61.

[S-(R\*,S\*)]-N,N, $\alpha$ -Trimethyl-3-pyrrolidinemethanamine (**23rs**).

Using the procedure above, **20rs** (8.81 g, 35.8 mmoles) and 20% palladium on carbon (2.00 g) gave **23rs** as an oil after fractional distillation (bp 81-84° at 14 mm Hg, 3.53 g, 68%); <sup>1</sup>H nmr (deuteriochloroform/250 MHz):  $\delta$  0.90 (d, J = 6.1 Hz, 3H), 1.17-1.41 (m, 1H), 1.73-2.13 (m, 2H), 2.20 (s, 6H), 2.25-2.47 (m, 1H), 2.68 (dd, J = 11.0, 7.9 Hz, 1H), 2.81-3.00 (m, 2H), 3.08 (dd, J = 11.0, 7.3 Hz, 1H); <sup>13</sup>C nmr (deuteriochloroform/63 MHz):  $\delta$  9.3, 30.7, 40.1, 44.1, 46.9, 51.6, 63.1; ir (liquid film): 3304, 2972, 1458, 1366, 1265, 1159, 1096, 1043 cm<sup>-1</sup>; ms: (CI) (m/z) 143 (M<sup>+</sup> + 1, base), 97 (M<sup>+</sup> -(CH<sub>3</sub>)<sub>2</sub>NH); Rotation:  $[\alpha]_D = 22^\circ$  (c 1.0%, methanol).

Anal. Calcd. for C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>·0.10H<sub>2</sub>O: C, 66.71; H, 12.74; N, 19.45. Found: C, 66.41; H, 12.79; N, 19.79.

[R-(R\*,R\*)]-N,N, $\alpha$ -Trimethyl-3-pyrrolidinemethanamine (**23rr**).

Using the procedure above, **20rr** (7.65 g, 31.0 mmoles) and 20% palladium on carbon (2.00 g) gave **23rr** as an oil after fractional distillation (bp 83-86° at 15-17 mm Hg, 3.04 g, 68%); <sup>1</sup>H nmr (deuteriochloroform + deuterium oxide/250 MHz):  $\delta$  0.87 (d,

$J = 6.3$  Hz, 3H), 1.44-1.68 (m, 1H), 1.97-2.52 (m, 10H-contains 2.22, s), 2.78-3.11 (m, 3H-contains 3.01, dd,  $J = 10.5, 7.5$  Hz);  $^{13}\text{C}$  nmr (deuteriochloroform/63 MHz):  $\delta$  9.6, 30.7, 40.2, 44.2, 46.9, 51.3, 62.8; ir (liquid film): 3300, 2963, 1458, 1374, 1266, 1096, 1047  $\text{cm}^{-1}$ ; ms: (CI) ( $m/z$ ) 142 ( $\text{M}^+$ ), 112 ( $\text{M}^+ - 2\text{CH}_3$ ), 97 ( $\text{M}^+ - (\text{CH}_3)_2\text{NH}$ , base); Rotation:  $[\alpha]_{\text{D}} = 0^\circ$  (c 1.0%, methanol).

*Anal.* Calcd. for  $\text{C}_8\text{H}_{18}\text{N}_2 \cdot 0.10\text{H}_2\text{O}$ : C, 66.71; H, 12.74; N, 19.45. Found: C, 66.78; H, 13.00; N, 19.74.

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