Synthesis of Chiral 3-Substituted-3-aminomethyl-pyrrolidines and Related Compounds

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The preparation of a series of chiral 3-methyl-3-substituted-pyrrolidines/pyrrolidinones starting from (*R*)-4-(methoxycarbonyl)-1-(1*R*-phenethyl)-2-pyrrolidinone (**1**) is described. The chiral α-methylbenzyl functionality serves not only as a nitrogen protecting group for the pyrrolidine nitrogen, but also as a chiral auxillary. The synthesis of the 4-position enantiomers was accomplished by converting the ester of **1** to the ketone, protecting the ketone as the benzyloxime and separation by chromatography. These key intermediates were converted to the (*R*) and (*S*)-3-methyl-3-aminomethylpyrrolidines by removal of the benzyl group followed by oxidation. The 3-methyl-3-(1-aminoethyl)pyrrolidines were obtained *via* a two step reduction of the corresponding oximes. The stereochemical assignments were determined by X-ray crystallography.

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Introduction.

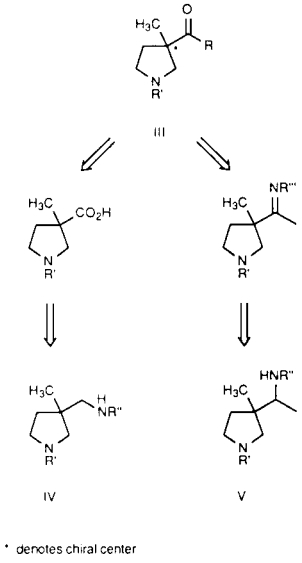
Previously, it was demonstrated that racemic 3-methyl-3-aminomethylpyrrolidines, attached to a quinolone or naphthyridone nucleus provided compounds with potent antibacterial activity [1]. Recent studies in our laboratories [2] as well as those of others [3] have demonstrated that chirality can have a dramatic effect on the biological properties of quinolones. For example, two separated enantiomers can often display differences not only in antibacterial activity and *in vivo* disposition, but in toxicity to mammalian cells as well. These differences can not always be predicted. The enantiomers of *N*-ethylaminomethylpyrrolidines **I** (Figure 1) do not display any differences in antibacterial activity, but the various stereoisomers of the

Figure 1

I II

methylaminomethyl derivative **II** do display differences both *in vitro* and *in vivo* [2]. Therefore, we desired a synthesis of both the *R* and *S* enantiomers of 3-methyl-3-aminomethylpyrrolidines **IV** (Figure 2). In addition, we envisioned that such a synthesis could provide the previously unreported 3-methyl-3-(1-aminoethyl)pyrrolidines **V** (Figure 2), of which four diastereomers are possible. Herein, we describe the synthesis and structure determination of a series of chiral *N*-protected pyrrolidines and pyrrolidinones, which can function as precursors to the desired pyrrolidines depicted in Figure 2.

Figure 2

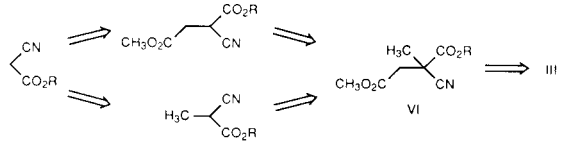


Chemistry.

As shown in Figure 2, compound **III** can serve as an intermediate to both the desired pyrrolidines, **IV** or **V**. Two approaches were simultaneously explored for obtaining compound **III**. The first route consisted of synthesizing an acyclic precursor, which could be converted to the desired pyrrolidine. Lee [4], reported the synthesis of dimethyl (*S*)-2-cyano-2-methylsuccinate (compound **VI**, Figure 3). This compound was ideal in that in addition to having the stereochemistry established at the required center, it also contained a cyano group in the proper position for construction of the pyrrolidine ring. This compound was synthesized from methyl cyanoacetate [4] using (*R*)-menthol as

a chiral auxillary to facilitate the separation of the resulting diastereomers. Cleavage of the menthol ester and reesterification provided the desired chiral dimethyl 2-cyano-2-methylsuccinates. The reported yields were poor and the synthesis required a number of fractional distillations and chromatographic separations. Attempts to reproduce the transesterification with menthol and the alkylations with bromomethylacetate were unsuccessful. As was reported, the synthesis of the menthol cyanoacetate required a large excess of (*R*)-menthol and the alkylation reactions gave many side-products, due to over-alkylation of the resulting products and starting materials. Even proceeding through the methyl 2-cyanopropionate derivative [5] offered little advantage (Figure 3). Thus, the synthesis of the simple dimethyl (±)-2-cyano-2-methylsuccinate in two steps from methyl cyanoacetate could only be achieved in low yields due to the propensity for these compounds to over-alkylate and/or decompose.

Figure 3



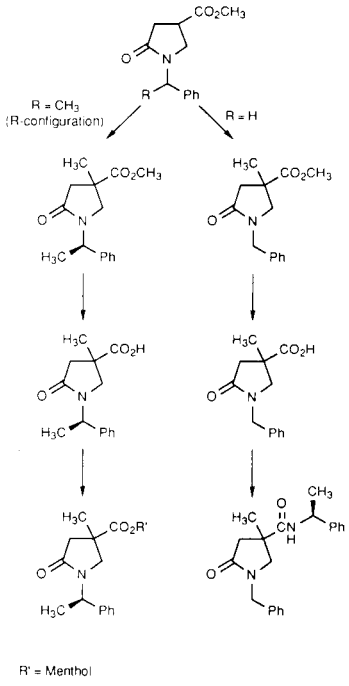
R = (-) Menthol, H, CH_3

The second approach for obtaining compound **III** consisted of starting with a racemic pyrrolidine **1**, making the necessary modifications and separating the stereoisomers at a later stage. Culbertson [6] described the synthesis and separation of the diastereomers of **1**. The use of the chiral α-methylbenzyl function (either *R* or *S*), both as a protecting group and chiral auxillary, allowed for the separation of the resulting 4-position enantiomers. This compound, therefore served as a precursor for the synthesis of the desired chiral pyrrolidine. Thus, the methyl group was introduced into the racemic ester and the resulting stereoisomers were then separated.

Results and Discussion.

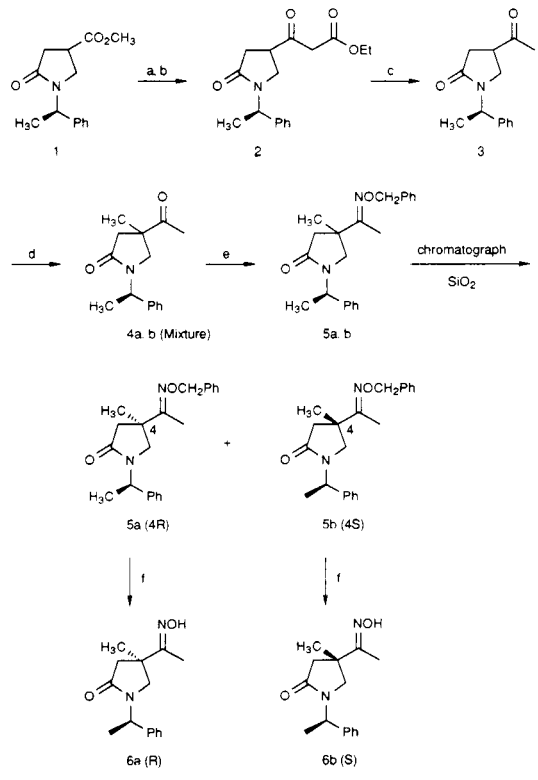
Compound **1a** (R = CH_3) was alkylated, although with some difficulty (Figure 4) using sodium hydride and methyl iodide to provide the 4-methyl-4-ester-2-pyrrolidinone. However, no separation of the diastereomers could be achieved by chromatography or crystallization. The ester was then saponified (sodium hydroxide) and the resulting acid was converted to the (*R*)-menthol ester. These diastereomers also could not be separated by conventional means. The same result was obtained when the acid was converted to the (*R*)-α-methylbenzylamide (Figure 4). Since two chiral auxillaries could hinder the subsequent separation, the sequence just described was repeated on the simple benzylpyrrolidine **1b** (R = H). No separation of the resulting diastereomers was possible.

Figure 4



Since we knew from our work on the synthesis of compound **II** that the diasteromers of the oxime of **3** (Scheme 1) were separable and since we expected the ketone **3** to alkylate better than the ester, we decided to proceed through the ketone **3**. The ketone **3** was obtained by standard techniques as shown in Scheme 1. Decarboxylation of the β-keto ester using lithium chloride/dimethyl sulfoxide/water provided the ketone in higher yields than those obtained using sodium chloride. Alkylation of ketone **3** with sodium hydride/methyl iodide in tetrahydrofuran provided compounds **4a,b** in nearly quantitative yield as a 50:50 mixture of stereoisomers at the 4-position, as indicated by nmr. A similar result to that obtained previously with the ester was also seen in this case. Although separation of the diastereomers of the unalkylated ester or the diastereomers of ketone **3**, could be readily achieved by column chromatography, introduction of a methyl group adjacent to the carbonyl function provided compounds in which the stereoisomers could only be separated with great difficulty. Therefore, the racemic ketone was converted to the simple oximes **6a,b** (mixture). Surprisingly, the distinction on tlc between the 4-position enantiomers became even worse. Various crystallization solvents were investigated with all of the alkylated derivatives just described, but only mixtures of diastereomers were obtained (nmr, hplc). These results indicate that placing a methyl group adjacent to the carbonyl function or oxime causes both groups to look very similar and thus eliminates the ability to separate the enantiomers at that position. There-

Scheme 1



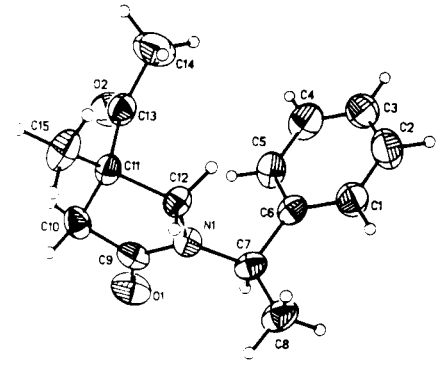
a) NaOH, $MeOH/H_2O$; b) $Mg(OCHCH_2CO_2Et)_2$; c) LiCl/DMSO/H_2O; d) NaH/MeI; e) H_2NOCH_2Ph•HCl/NaOAc/EtOH/H_2O; f) H_2/Pd/C/HCl

fore, we investigated ways to differentiate these groups chemically.

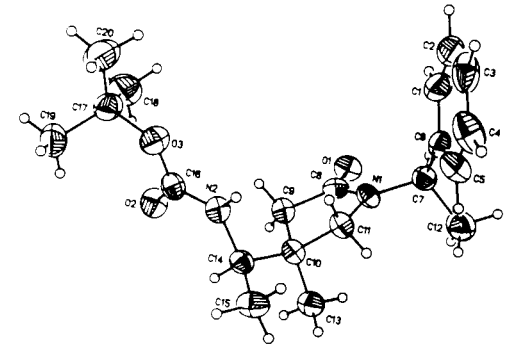
To accomplish this, we investigated the use of oxime ethers. Formation of the methyl oxime ether improved the separation somewhat, so the ethyl and benzyloxy ethers were made. The best separation of diasteromers was achieved with the benzyloxy ether. Treatment of **4a,b** with *O*-benzylhydroxylamine hydrochloride, sodium acetate in ethanol/water and separation of the resulting mixture *via* column chromatography provided compounds **5a** and **5b**, in good yields. The literature indicated that the *O*-benzyloxime could serve as a precursor to the ketone, by hydrolysis, or be reduced to the amine. Accordingly, this compound should have fulfilled our requirements for an intermediate which could provide both pyrrolidines **IV** and **V**. In practice, however, the oximinoether group could not be hydrolyzed to the ketone under a variety of conditions, nor could it be reduced to the amine. Catalytic reduction (Palladium/carbon, ethanol/hydrogen) was very slow and only proceeded when acetic acid was added, but the major product isolated was the *N*-acetyl derivative, and this could not be hydrolyzed to provide the amine. In addition, refluxing a mixture of the *O*-benzyloxime and lithium aluminum hydride in tetrahydrofuran resulted only in recovered starting material. Since the palladium reduction did work except for the *N*-acetyl group being formed, it

Figure 5: Ortep Drawings of Compounds **7b**, **11b**, and **12b**.

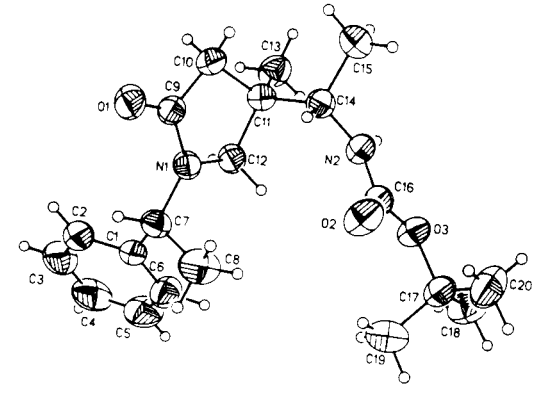
Compound **7b**



Compound **11b**



Compound **12b**

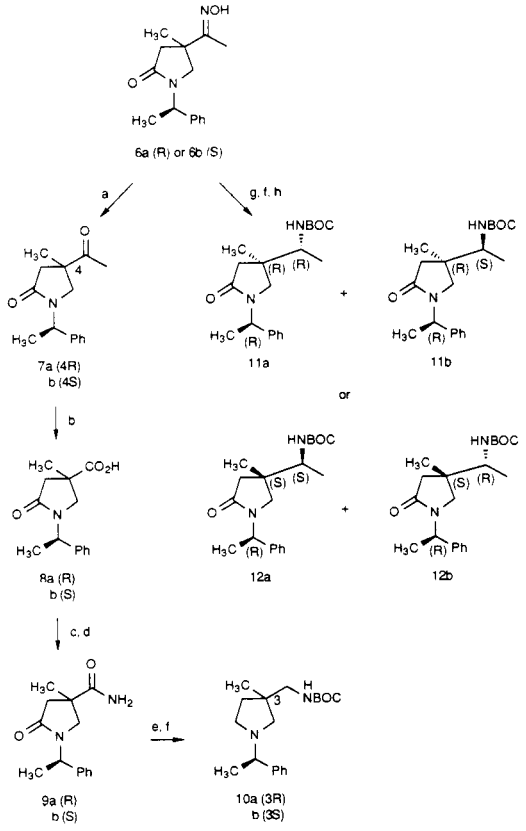


was decided to try the catalytic reduction using hydrochloric acid instead of acetic acid. It was found that treatment of either **5a** or **5b** with palladium/carbon, ethanol/hydrogen and concentrated hydrochloric acid, resulted in *only* the benzyloxy group being removed to provide the oximes **6a** or **6b** in nearly quantitative yield. Therefore, the benzyloxy ether served only as a protecting group of the oxime, allowing for the separation of the 4-position enantiomers.

The oximes **6a** and **6b**, unlike the corresponding *O*-benzyloximes, were then readily hydrolyzed with sodium bisulfite to provide the ketones **7a** and **7b**. Oxidation of each of the ketones with sodium bromite, conversion of the resulting acids to the amides (oxalyl chloride/ammonia) and

reduction with lithium aluminum hydride provided the desired target compounds **10a** and **10b** (Scheme 2).

Scheme 2



a) $NaHSO_3$; b) $NaBrO_2$, NaOH; c) $(COCl)_2$; d) NH_3; e) LAH; f) di-t-butyl-dicarbonate/Et_3N; g) RaNi/MeOH; h) SiO_2 chromatography

The 3-methyl-3-(1-aminoethyl) derivatives (compound **V**, Figure 2) were obtained by Raney nickel reduction of the respective oximes followed by protection of the resulting amines with di-*t*-butyl dicarbonate. Separation by column chromatography provided all four diastereomers **11a, 11b, 12a, 12b** (Scheme 2). The absolute stereochemistry of these compounds **11b** and **12b**, as well as **7b** mentioned above, was determined by X-ray crystallography (Figure 5).

In summary, we have illustrated the synthesis of a series of chiral 3-methyl-3-substituted pyrrolidines. The synthesis of these 6 derivatives was accomplished using a common chiral intermediate with the α-methylbenzyl group acting as a chiral auxillary and a protecting group. The scope of this methodolgy to the synthesis of other chiral 3-alkyl-3-substituted-pyrrolidines is under investigation. Conversion of these compounds to the desired pyrrolidines and their use in the preparation of antibacterial agents will be reported elsewhere.

EXPERIMENTAL

All melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Varian Associates EM-390 or XL-200 using deuteriochloroform or dimethyl sulfoxide-d_6 as the internal reference standard. Purity was determined by microanalysis and by tlc (silica gel 60F 254, Merck). Silica gel chromatography utilized Kieselgel 60 (70-230 mesh or 230-400 mesh for flash chromatography). Mass spectra were determined on a VG analytical 7070E/HF or Finnegan 4500 mass spectrometer.

Table 1

Crystal Data and Experimental Conditions

	7b	**11b**	**12b**
Formula	$C_{15}H_{19}NO_2$	$C_{20}H_{30}N_2O_3$	$C_{20}H_{30}N_2O_3$
Crystallization medium		Ethyl ether-hexanes	
Crystal size	0.50 x 0.18 x 0.18	0.20 x 0.30 x 0.30	0.40 x 0.32 x 0.03
Radiation		MoK $\bar{\sigma}\lambda$ = 0.71073	
Cell dimensions			
a, Å	5.9968 (9)	9.013 (4)	6.646 (2)
b, Å	14.637 (2)	11.437 (6)	12.681 (3)
c, Å	16.252 (3)	10.679 (5)	23.944 (7)
α, deg.	90.000	90.000	90.000
β, deg.	90.000	110.61 (4)	90.000
γ, deg.	90.000	90.000	90.000
Space group	Orthorhombic $P2_12_12_1$	Monoclinic $P2_1$	Orthorhombic $P2_12_12_1$
Z	4	2	4
Calcd. density	1.086	1.117	1.140
μ (cm^{-1})	0.67	0.70	0.71
F(000)	528	376	748
Data range (deg.)	5-50	5-50	5-45
Number reflections measured	3119	4294	3274
Number unique reflections	2527	3641	2634
Number of refined reflections	1903 F_o >45(F)	3394 F_o >0.65(F)	2308 F_o >0.65(F)
Number parameters	164	231	230
Final R factor Rf:	0.0556	0.0578	0.0827
Rw:	0.0792	0.0676	0.0895

Table 2

Atomic Parameters, Bond Angles and Bond Lengths for Compound **7b**

Atomic Parameters

Atom	x	y	z	U(EQ)
O1	0.4808(4)	0.1563(2)	0.5522(2)	0.098(1)
O2	0.5845(5)	-0.0177(2)	0.3708(2)	0.096(1)
N1	0.8202(4)	0.0886(2)	0.5394(1)	0.0567(8)
C1	1.0432(7)	-0.0914(3)	0.6590(3)	0.092(1)
C2	1.0577(9)	-0.1855(3)	0.6576(3)	0.114(2)
C3	0.903(1)	-0.2360(3)	0.6209(3)	0.106(2)
C4	0.7233(9)	-0.1951(3)	0.5856(3)	0.104(2)
C5	0.7042(6)	-0.1003(2)	0.5876(2)	0.083(1)
C6	0.8660(6)	-0.0477(2)	0.6238(2)	0.063(1)
C7	0.8407(6)	0.0556(2)	0.6244(2)	0.064(1)
C8	1.0203(7)	0.1079(2)	0.6694(2)	0.086(1)
C9	0.6426(5)	0.1342(2)	0.5105(2)	0.063(1)
C10	0.6812(5)	0.1547(2)	0.4220(2)	0.069(1)
C11	0.8698(5)	0.0914(2)	0.3964(2)	0.0556(9)
C12	0.9962(4)	0.0786(2)	0.4787(2)	0.0553(8)
C13	-0.7787(6)	-0.0009(3)	0.3707(2)	0.069(1)
C14	0.9393(9)	-0.0729(3)	0.3445(3)	0.121(2)
C15	1.0205(7)	0.1319(3)	0.3293(2)	0.088(1)

Bond Lengths (Å)

O1	-C9	1.227(4)	C5	-C6	1.373(5)
O2	-C13	1.191(5)	C6	-C7	1.520(4)
N1	-C7	1.468(4)	C7	-C8	1.510(5)
N1	-C9	1.342(4)	C9	-C10	1.487(5)
N1	-C12	1.453(3)	C10	-C11	1.520(4)
C1	-C2	1.380(6)	C11	-C12	1.548(4)
C1	-C6	1.366(5)	C11	-C13	1.516(5)
C2	-C3	1.329/(7)	C11	-C15	1.535(5)
C3	-C4	1.358(7)	C13	-C14	1.491(6)
C4	-C5	1.392(5)			

Bond Angles (deg.)

O1	-C9	-N1	124.4(3)	C4	-C5	-C6	120.7(4)
O1	-C9	-C10	127.2(3)	C5	-C6	-C7	119.4(3)
O2	-C13	-C11	122.4(3)	C6	-C7	-C8	115.8(3)
O2	-C13	-C14	119.1(4)	C7	-N1	-C9	124.0(3)
N1	-C7	-C6	109.3(2)	C7	-N1	-C12	123.1(2)
N1	-C7	-C8	110.4(2)	C9	-N1	-C12	112.9(2)
N1	-C9	-C10	108.4(3)	C9	-C10	-C11	105.0(2)
N1	-C12	-C11	102.7(2)	C10	-C11	-C12	101.6(2)
C1	-C2	-C3	121.2(5)	C10	-C11	-C13	110.5(3)
C1	-C6	-C5	117.8(3)	C10	-C11	-C15	113.5(3)
C1	-C6	-C7	122.8(3)	C11	-C13	-C14	118.5(3)
C2	-C1	-C6	120.7(4)	C12	-C11	-C13	107.8(2)
C2	-C3	-C4	119.9(4)	C12	-C11	-C15	111.8(2)
C3	-C4	-C5	119.7(4)	C13	-C11	-C15	111.1(3)

Organic layers were dried with magnesium sulfate. All compounds possesed analytical data consistent with the proposed structure.

(*R*)-4-Acetyl-1-(1-phenylethyl)-2-pyrrolidinone (**3**).

To a solution of 30.25 g (122 mmoles) of 4-carboxymethyl-1-(1*R*-phenylethyl)-2-pyrrolidinone (**1**) in 500 ml of methanol was added 70 ml of 2*N* sodium hydroxide. The mixture was stirred at room temperature for 18 hours and concentrated. The residue was diluted with water and acidified with 2*N* hydrochloric acid. The precipitate which formed was collected and dried to give the

Table 3

Atomic Parameters, Bond Angles and Bond Lengths for Compound **11b**

Atomic Parameters

Atom	x	y	z	U(EQ)
O1	-0.2228(3)	0.3342(2)	-0.7287(2)	0.0679(8)
O2	-0.1469(3)	0.1446(3)	-0.2513(2)	0.079(1)
O3	-0.0749(2)	-0.04080	-0.1787(2)	0.0628(8)
N1	-0.2558(3)	0.1540(3)	-0.6530(2)	0.0525(8)
N2	0.0292(3)	0.0421(3)	-0.3142(2)	0.0555(9)
C1	-0.5133(3)	0.0610(3)	-0.7656(2)	0.0517(9)
C2	-0.5516(4)	0.0628(4)	-0.9026(3)	0.071(1)
C3	-0.6274(4)	-0.0293(5)	-0.9806(4)	0.091(2)
C4	-0.6666(4)	-0.1245(4)	-0.9261(5)	0.097(2)
C5	-0.6287(5)	-0.1304(4)	-0.7906(5)	0.094(2)
C6	-0.5522(4)	-0.0375(3)	-0.7096(3)	0.073(1)
C7	-0.4266(3)	0.1646(3)	-0.6846(3)	0.056(1)
C8	-0.4636(4)	0.1878(4)	-0.5588(4)	0.084(1)
C9	-0.1699(3)	0.2403(3)	-0.6791(2)	0.0509(9)
C10	-0.0002(3)	0.2000(3)	-0.6355(3)	0.060(1)
C11	0.0104(3)	0.0927(3)	-0.5455(3)	0.053(1)
C12	-0.1631(3)	0.0505(3)	-0.5963(3)	0.057(1)
C13	0.1192(4)	-0.0028(4)	-0.5633(3)	0.074(1)
C14	0.0579(3)	0.1335(3)	-0.3987(3)	0.054(1)
C15	-0.2295(4)	0.1757(4)	-0.3372(4)	0.084(1)
C16	-0.0714(3)	0.0573(3)	-0.2477(3)	0.054(1)
C17	-0.1767(4)	-0.0483(3)	-0.0983(3)	0.067(1)
C18	-0.1524(5)	-0.1719(4)	-0.0486(5)	0.100(2)
C19	-0.3498(4)	-0.0291(5)	-0.1896(5)	0.108(2)
C20	-0.1225(6)	0.0383(4)	0.0141(4)	0.100(2)

Bond Angles (deg.)

O1	-C9	-N1	124.4(3)	C3	-C4	-C5	119.6(4)
O1	-C9	-C10	127.2(3)	C4	-C5	-C6	120.4(4)
O2	-C16	-O3	125.9(2)	C6	-C1	-C7	123.4(2)
O2	-C16	-N2	124.8(3)	C7	-N1	-C9	122.0(3)
O3	-C16	-N2	109.3(3)	C7	-N1	-C12	124.6(2)
O3	-C17	-C18	102.7(3)	C9	-N1	-C12	113.4(2)
O3	-C17	-C19	109.0(2)	C9	-C10	-C11	105.6(2)
O3	-C17	-C20	109.7(3)	C10	-C11	-C12	101.4(2)
N1	-C7	-C1	110.9(2)	C10	-C11	-C13	113.2(2)
N1	-C7	-C8	110.6(2)	C10	-C11	-C14	109.2(2)
N1	-C9	-C10	108.0(3)	C11	-C14	-C15	113.6(2)
N1	-C12	-C11	104.8(2)	C12	-C11	-C13	110.4(3)
N2	-C14	-C11	111.3(2)	C12	-C11	-C14	109.5(2)
N2	-C14	-C15	109.8(2)	C13	-C11	-C14	112.5(2)
C1	-C2	-C3	121.2(3)	C14	-N2	-C16	122.0(3)
C1	-C6	-C5	120.1(2)	C16	-O3	-C17	120.6(2)
C1	-C7	-C8	114.4(2)	C18	-C17	-C19	110.3(4)
C2	-C1	-C6	117.8(3)	C18	-C17	-C20	112.0(3)
C2	-C1	-C7	118.7(3)	C19	-C17	-C20	112.7(3)
C2	-C3	-C4	120.9(3)				

Bond Lengths (Å)

O1	-C9	1.218(4)	C3	-C4	1.339(6)
O2	-C16	1.201(4)	C4	-C5	1.366(5)
O3	-C16	1.349(3)	C5	-C6	1.390(5)
O3	-C17	1.463(3)	C7	-C8	1.517(3)
N1	-C7	1.461(3)	C9	-C10	1.505(4)
N1	-C9	1.343(4)	C10	-C11	1.542(4)
N1	-C12	1.453(4)	C11	-C12	1.541(4)
N2	-C14	1.456(4)	C11	-C13	1.524(5)
N2	-C16	1.345(3)	C11	-C14	1.553(3)
C1	-C2	1.379(3)	C14	-C15	1.530(5)
C1	-C6	1.377(5)	C17	-C18	1.499(6)
C1	-C7	1.513(4)	C17	-C19	1.537(5)
C2	-C3	1.368(6)	C17	-C20	1.499(5)

Table 4

Atomic Parameters, Bond Angles and Bond Lengths for Compound **12b**

Atomic Parameters

	x	y	z	U(EQ)
O1	0.2070(5)	0.6824(3)	0.2797(2)	0.056(1)
O2	0.7531(6)	0.7778(3)	0.1131(2)	0.060(1)
O3	0.9844(6)	0.6513(3)	0.1325(1)	0.059(1)
N1	0.5043(6)	0.7257(3)	0.3224(2)	0.044(1)
N2	0.9093(6)	0.7691(3)	0.1969(2)	0.046(2)
C1	0.615(1)	0.5017(5)	0.3886(2)	0.069(2)
C2	0.774(1)	0.4366(5)	0.4042(3)	0.089(3)
C3	0.944(1)	0.4776(8)	0.4274(3)	0.084(3)
C4	0.954(1)	0.5811(7)	0.4365(3)	0.083(3)
C5	0.798(1)	0.6463(5)	0.4215(3)	0.067(2)
C6	0.6257(8)	0.6092(4)	0.3965(2)	0.046(2)
C7	0.4575(8)	0.6805(4)	0.3773(2)	0.050(2)
C8	0.3766(8)	0.7219(4)	0.2788(2)	0.043(2)
C9	0.4785(8)	0.7751(4)	0.2306(2)	0.048(2)
C10	0.6386(7)	0.8459(4)	0.2574(2)	0.042(2)
C11	0.6911(7)	0.7810(4)	0.3087(2)	0.045(2)
C12	0.406(1)	0.7678(5)	0.4182(3)	0.079(3)
C13	0.5430(8)	0.9507(4)	0.2747(2)	0.055(2)
C14	0.8245(7)	0.8662(4)	0.2189(2)	0.043(2)
C15	0.9852(9)	0.9301(4)	0.2474(2)	0.057(2)
C16	0.8700(8)	0.7365(4)	0.1442(2)	0.049(2)
C17	0.965(1)	0.5980(5)	0.0783(2)	0.064(2)
C18	0.752(1)	0.5628(6)	0.0697(3)	0.094(3)
C19	1.036(1)	0.6698(5)	0.0320(2)	0.082(3)
C20	1.103(1)	0.5046(5)	0.0835(3)	0.100(3)

Bond Angles (deg.)

O1	-C8	-N1	125.2(5)	C4	-C5	-C6	122.5(6)
O1	-C8	-C9	127.6(5)	C5	-C6	-C7	123.0(5)
O2	-C16	-O3	126.0(5)	C6	-C7	-C12	114.0(5)
O2	-C16	-N2	124.9(5)	C7	-N1	-C8	123.2(4)
O3	-C16	-N2	109.2(4)	C7	-N1	-C11	124.6(4)
O3	-C17	-C18	109.9(5)	C8	-N1	-C11	112.3(4)
O3	-C17	-C19	110.1(5)	C8	-C9	-C10	104.8(4)
O3	-C17	-C20	103.8(5)	C9	-C10	-C11	100.5(4)
N1	-C7	-C6	110.5(4)	C9	-C10	-C13	109.5(4)
N1	-C7	-C12	110.0(4)	C9	-C10	-C14	113.5(4)
N1	-C8	-C9	107.2(4)	C10	-C14	-C15	112.4(4)
N1	-C11	-C10	104.2(4)	C11	-C10	-C13	110.2(4)
N2	-C14	-C10	112.4(4)	C11	-C10	-C14	112.6(4)
N2	-C14	-C15	110.3(4)	C13	-C10	-C14	110.2(4)
N2	-C14	-C15	110.3(4)	C14	-N2	-C16	121.5(4)
C1	-C6	-C5	116.1(5)	C16	-O3	-C17	120.2(4)
C1	-C6	-C7	120.9(5)	C18	-C17	-C19	111.9(8)
C2	-C1	-C6	120.8(6)	C18	-C17	-C20	110.6(6)
C2	-C3	-C4	119.1(8)	C19	-C17	-C20	110.2(6)
C3	-C4	-C5	120.6(7)				

Bond Lengths (Å)

O1	-C8	1.233(6)	C4	-C5	1.38(1)
O2	-C16	1.196(7)	C5	-C6	1.374(8)
O3	-C16	1.351(7)	C6	-C7	1.509(8)
O3	-C17	1.467(7)	C7	-C12	1.518(8)
N1	-C7	1.468(6)	C8	-C9	1.499(7)
N1	-C8	1.347(6)	C9	-C10	1.533(7)
N1	-C11	1.463(6)	C10	-C11	1.520(7)
N2	-C14	1.453(6)	C10	-C13	1.531(7)
N2	-C16	1.353(7)	C10	-C14	1.563(7)
C1	-C2	1.39(1)	C14	-C15	1.505(7)
C1	-C6	1.378(8)	C17	-C18	1.50(1)
C2	-C3	1.36(1)	C17	-C19	1.511(9)
C3	-C4	1.33(1)	C17	-C20	1.50(1)

acid (25 g), which was used without further purification; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.45 (d, 3H, J = 5 Hz), 2.59 (m, 2H), 3.17 (m, 2H), 3.49 (m, 1H), 5.23 (q, 1H), 7.33 (m, 5H); ms: (DEI) 233 (82), 218 (100).

To a mixture of 25.0 g (107 mmoles) of the acid in 190 ml of tetrahydrofuran was added 20.0 g (123 mmoles) of carbonyldiimidazole and the mixture was stirred at room temperature, under nitrogen for 3 hours. Then 34.5 g (123 mmoles) of magnesium ethyl malonate was added at once, the mixture was refluxed for 1.5 hours and then stirred at room temperature for 18 hours. The reaction was concentrated and the residue was dissolved in 500 ml of methylene chloride and washed with 1*N* hydrochloric acid. The organic layer was dried, filtered and concentrated to give 40 g of the β-keto ester. The residue was dissolved in 110 ml of dimethyl sulfoxide, 5.6 ml of water and 6.5 g (153 mmoles) of lithium chloride was added. The mixture was heated at 130-135 for 1.5 hours. The mixture was allowed to cool to room temperature and partitioned between water and methylene chloride. The organic layer was dried and concentrated to an oil. Bulb-to-bulb distillation provided 19.1 g (83%) of the ketone **3**, bp 160-165° (0.25 mm); ^{1}H nmr (deuteriochloroform): δ 2.10 (s, 3H), 2.19 (s, 3H), 2.68 (m, 2H), 3.05-3.26 (m, 2H), 3.44-3.59 (m, 1H), 5.48 (q, 1H), 7.31 (m, 5H); ms: (DEI) m/e 231 (60), 218 (10), 216 (45), 105 (100); ir (potassium bromide): 1681, 1713 cm^{-1}.

4-Acetyl-4-methyl-1-(1*R*-phenylethyl)-2-pyrrolidinone (**4**).

To a cold suspension (0°) of 3.12 g (78.0 mmoles) of 60% sodium hydride (washed with hexanes and dried) in 150 ml of tetrahydrofuran was added dropwise a solution of 16.45 g (71.2 mmoles) of ketone **3**, in 150 ml of tetrahydrofuran under a nitrogen atmosphere. The mixture was stirred at 0° for 1 hour, and then allowed to warm to room temperature. To this was added 10.8 g (78.0 mmoles) of methyl iodide and stirring was continued for 3 hours. The reaction was partitioned between water and ether, the ether layer was separated, dried and concentrated to give 17 g of **4**, which was pure enough to use in the next step. An analytical sample was obtained by chromatography (silica gel, 20% 2-propanol/hexanes), mp 47-49°; ^{1}H nmr (deuteriochloroform): indicated a mixture of isomers at the 4-position.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.71. Found: C, 73.18; H, 7.82; N, 5.46.

4*R*-Methyl-1-(1*R*-phenylethyl)-4-[1-[(phenylmethoxy)imino]ethyl]-2-pyrrolidinone (**5a**) and 4*S*-Methyl-1-(1*R*-phenylethyl)-4-[1-[(phenylmethoxy)imino]ethyl]-2-pyrrolidinone (**5b**).

A mixture of 7.0 g (28.5 mmoles) of compound **4**, 3.1 g (31.4 mmoles) of potassium acetate and 4.5 g (31.4 mmoles) of benzyloxyhydroxylamine hydrochloride in 100 ml of ethanol and 10 ml of water was stirred at room temperature for 18 hours. The mixture was concentrated and the residue was partitioned between water and chloroform. The organic layer was dried and concentrated to give 10 g of a mixture of **5a** and **5b**. The compounds were separated by chromatography (1:1 ethyl acetate/hexanes) to provide 3.06 g (30%) of **5a**, as an oil; ^{1}H nmr (deuteriochloroform): 1.08 (s, 3H), 1.47 (d, 3H, J = 11 Hz), 1.81 (s, 3H), 2.23 (d, 1H, J = 13 Hz), 2.65 (d, 1H, J = 13 Hz), 2.79 (d, 1H, J = 16 Hz),

3.62 (d, 1H, J = 10 Hz), 5.05 (q, 1H), 7.32 (m, 10H); ms: (DEI, m+1) 351.

Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.03; H, 7.53; N, 8.01.

In addition 5.0 g (50%) of **5b** was obtained as an oil; ^{1}H nmr (deuteriochloroform): δ 1.28 (s, 3H), 1.52 (d, 3H, J = 7 Hz), 1.68 (s, 3H), 2.23 (d, 1H, J = 16 Hz), 2.84 (d, 1H, J = 17 Hz), 3.00 (d, 1H, J = 10 Hz), 3.18 (d, 1H, J = 10 Hz), 4.98 (s, 2H), 5.51 (q, 1H), 7.30 (m, 10H); ms: (DEI, m+1) 351.

Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.96; H, 7.26; N, 7.86.

4*R*-[1-(Hydroxyimino)ethyl]-4-methyl-1-(1*R*-phenylethyl)-2-pyrrolidinone (**6a**).

To a solution of 23.7 g (67.7 mmoles) of **5a** in 600 ml of methanol and 6.5 ml of concentrated hydrochloric acid was added 1 g of 20% palladium on carbon. The reaction was hydrogenated for 20 minutes, filtered through celite and concentrated to provide 20 g of an oil. The oil was dissolved in chloroform and washed with 1*N* sodium hydroxide. The organic layer was dried and concentrated to give 17 g of **6a**, as a white solid, which could be used directly in subsequent steps. An analytical sample was obtained by recrystallization from ethyl acetate/hexanes, mp 115-117°; ^{1}H nmr (deuteriochloroform): δ 1.08 (s, 3H), 1.51 (d, 3H, J = 7 Hz), 1.83 (s, 3H), 2.23 (d, 1H, J = 16 Hz), 2.68 (d, 1H, J = 10 Hz), 2.81 (d, 1H, J = 16 Hz), 3.56 (d, 1H, J = 10 Hz), 5.52 (q, 1H), 7.31 (m, 5H); ms: (EI$^+$, m+1) 261.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.69; N, 10.76. Found: C, 68.98; H, 7.71; N, 10.66.

4*R*-[1-(Hydroxyimino)ethyl]-4-methyl-1-(1*R*-phenylethyl)-2-pyrrolidinone (**6b**).

Compound **6b** was prepared in a yield of 93% starting from 22.0 g (62.8 mmoles) of **5b** as described above for **5a**. An analytical sample was obtained by recrystallization from ethyl acetate/hexanes, mp 101-103°; ^{1}H nmr (deuteriochloroform): δ 1.28 (s, 3H), 1.52 (d, 3H, J = 6 Hz), 1.72 (s, 3H), 2.25 (d, 1H, J = 11 Hz), 2.86 (d, 1H, J = 16 Hz), 3.02 (d, 1H, J = 10 Hz), 3.12 (d, 1H, J = 10 Hz), 5.52 (q, 1H), 7.30 (m, 5H); ms: (EI$^+$, m+1) 261 (7), 243 (45), 112 (44), 105 (100).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.69; N, 10.76. Found: C, 69.18; H, 7.81; N, 10.83.

4*R*-Acetyl-4-methyl-1-(1*R*-phenylethyl)-2-pyrrolidinone (**7a**).

A solution 4.84 g (18.6 mmoles) of **6a** in 50 ml of ethanol/water (1:1) was treated with 8.2 g (78.8 mmoles) of sodium bisulfite. The mixture was heated at 100° for 3 hours, concentrated to one-half its original volume and acidified with 50 ml of 1*N* hydrochloric acid. The mixture was extracted with methylene chloride. The organic layer was separated, dried and concentrated. The residue was crystallized from ethyl acetate/hexanes to provide 3.88 g (85%) of **7a**; mp 86-89°; ^{1}H nmr (deuteriochloroform): δ 1.18 (s, 3H), 1.52 (d, 3H, J = 7 Hz), 2.17 (s, 3H), 2.32 (d, 1H, J = 16 Hz), 2.63 (d, 1H, J = 10 Hz), 2.83 (d, 1H, J = 16 Hz), 3.68 (d, 1H, J = 10 Hz), 5.51 (q, 1H), 7.33 (m, 5H); ms: (EI$^+$) 245 (100), 230 (45).

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.38; H, 8.00; N, 5.74.

4*S*-Acetyl-4-methyl-1-(1*R*-phenylethyl)-2-pyrrolidinone (**7b**).

Compound **7b** was prepared in a yield of 87%, starting from 3.91 g (15.0 mmoles) of **6a** as described above for **7a**, mp 71-72° (ethyl acetate/hexanes); ^{1}H nmr (deuteriochloroform): δ 1.36 (s, 3H), 1.53 (d, 3H, J = 7 Hz), 2.04 (s, 3H), 2.29 (d, 1H, J = 17 Hz), 2.84 (d, 1H, J = 17 Hz), 3.02 (d, 1H, J = 10 Hz), 3.27 (d, 1H, J = 10 Hz), 5.52 (q, 1H), 7.30 (m, 5H); ms: (EI$^+$) 245 (100), 230 (41), 146 (40).

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.25; H, 7.68; N, 5.69.

3*R*-Methyl-5-oxo-1-(1*R*-phenylethyl)-3-pyrrolidinecarboxylic Acid (**8a**).

A mixture of 3.64 g (14.8 mmoles) of **7a**, 9.46 (47.5 mmoles) of sodium hypobromite, 5.28 g (47.5 mmoles) of sodium bromide and 1.9 ml (22.2 mmoles) of 50% sodium hydroxide in 50 ml of water was stirred at room temperature for 4 hours. Then ether was added, the layers were separated and the aqueous layer was acidified with 1*N* hydrochloric acid. This was extracted with ether, the ether was washed with sodium bisulfite, brine and water. The ether was dried, filtered and concentrated. The residue was crystallized from ethyl acetate/hexanes to give 3.6 g (98%) of **7a**, mp 183-185°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.14 (s, 3H), 1.44 (d, 3H, J = 7 Hz), 2.19 (d, 1H, J = 16 Hz), 2.71 (m, 2H), 3.66 (d, 1H, J = 10 Hz), 5.24 (q, 1H), 7.32 (m, 5H), 12.75 (bs, 1H); ms: (EI$^+$) 247.

Anal. Calcd. for $C_{14}H_{17}NO_3 \cdot 0.25H_2O$: C, 66.78; H, 7.01; N, 5.56. Found: C, 66.52; H, 6.72; N, 5.65.

3*S*-Methyl-5-oxo-1-(1*R*-phenylethyl)-3-pyrrolidinecarboxylic Acid (**8b**).

Compound **8b** was prepared in a yield of 91%, starting from 3.08 g (11.8 mmoles) of **7b** as described above for **8a**, mp 70-71° (ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 1.42 (s, 3H), 1.52 (d, 3H, J = 7 Hz), 2.37 (d, 1H, J = 17 Hz), 2.98 (d, 1H, J = 17 Hz), 3.08 (d, 1H, J = 10 Hz), 3.35 (d, 1H, J = 10 Hz), 5.50 (q, 1H), 7.29 (m, 5H), 9.96 (bs, 1H); ms: (EI$^+$) 247 (92), 248 (22), 232 (100).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.08; H, 6.93; N, 5.66. Found: C, 67.79; H, 6.87; N, 5.64.

3*R*-Methyl-5-oxo-1-(1*R*-phenylethyl)-3-pyrrolidinecarboxamide (**9a**).

To a solution of 3.38 g (13.7 mmoles) of **8a** in 50 ml of methylene chloride was added 1.80 g (13.9 mmoles) of oxalyl chloride and 2 drops of dimethylformamide. The reaction was stirred for 2 hours at room temperature, concentrated and the residue was dissolved in 50 ml of tetrahydrofuran. This solution was then added dropwise to a cold solution of 50 ml of ammonium hydroxide in tetrahydrofuran. The mixture was allowed to warm to room temperature, stirred for 18 hours and filtered. The filtrate was concentrated and the residue was crystallized from ethyl acetate/-hexanes to give 1.98 g (58%) of **9a**, mp 154-155°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.09 (s, 3H), 1.43 (d, 3H, J = 7 Hz), 2.10 (d, 1H, J = 17 Hz), 2.67 (d, 1H, J = 10 Hz), 2.76 (d, 1H, J = 16 Hz), 3.59 (d, 1H, J = 10 Hz), 5.24 (q, 1H), 7.06 (bs, 1H), 7.34 (m, 6H); ms: (EI$^+$) 246 (19), 105 (100).

Anal. Calcd. for $C_{14}H_{18}N_2O_2 \cdot 0.1H_2O$: C, 67.77; H, 7.39; N, 11.29. Found: C, 67.56; H, 7.29; N, 11.16.

3*S*-Methyl-5-oxo-1-(1*R*-phenylethyl)-3-pyrrolidinecarboxamide (**9b**).

Compound **9b** was prepared in a yield of 77%, starting from 3.50 g (10.3 mmoles) of **8b** as described above for **9a**. An analytical sample was prepared by preparative tlc (silica gel, ethyl

acetate/methanol 7:1) oil; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.28 (s, 3H), 1.44 (d, 3H, J = 7 Hz), 2.14 (d, 1H, J = 16 Hz), 2.74 (d, 1H, J = 16 Hz), 3.06 (d, 1H, J = 10 Hz), 3.22 (d, 1H, J = 10 Hz), 5.26 (q, 1H), 7.05 (bs, 1H), 7.30 (m, 6H); ms: (EI$^+$) 246 (19), 105 (100).

Anal. Calcd. for $C_{14}H_{18}N_2O_2 \cdot H_2O$: C, 63.62; H, 7.39; N, 10.21. Found: C, 63.65; H, 7.63; N, 10.60.

1,1-Dimethylethyl-[[3*R*-methyl-1-(1*R*-phenylethyl)-3-pyrrolidinyl]-methyl]carbamate (**10a**).

To 0.32 g (8.4 mmoles) of lithium aluminum hydride in 50 ml of tetrahydrofuran was added a solution of 1.0 g (4.1 mmoles) of **9a** in 20 ml of tetrahydrofuran dropwise. The mixture was then refluxed for 8 hours and cooled. The lithium aluminum hydride was decomposed by the addition of 0.4 ml of water, 0.4 ml of 15% sodium hydroxide and 1 ml of water. The mixture was filtered and concentrated to give 0.80 g of an oil. The oil was immediately dissolved in 20 ml of methylene chloride and 0.86 g (8.5 mmoles) of triethylamine and 1.76 g (8.0 mmoles) of di-*t*-butyl dicarbonate was added. The solution was stirred at room temperature for 4 hours, concentrated and the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate, brine, dried and concentrated. The residue was purified by chromatography (silica gel, methylene chloride) to provide 0.70 g (53%) of **10a** (oil); ^{1}H nmr (deuteriochloroform): δ 1.00 (s, 3H), 1.34 (d, 3H, J = 7 Hz), 1.49 (s, 9H), 1.60-1.91 (m, 2H), 2.27 (q, 1H), 2.41 (d, 1H, J = 10 Hz), 2.94 (m, 2H), 3.10 (m, 2H), 6.12 (bs, 1H), 7.26 (m, 5H); ms: (EI$^+$, m + 1) 319 (14), 105 (100).

Anal. Calcd. for $C_{19}H_{30}N_2O_2 \cdot 0.2H_2O$: C, 70.86; H, 9.51; N, 8.71. Found: C, 70.62; H, 9.44; N, 9.18.

1,1-Dimethylethyl-[[3*S*-methyl-1-(1*R*-phenylethyl)-3-pyrrolidinyl]-methyl]carbamate (**10b**).

Compound **10b** was prepared in a yield of 64%, starting from 2.53 g (10.4 mmoles) of **9b** as described above for **10a** above. The compound was purified by chromatography (silica gel, methylene chloride/methanol); ^{1}H nmr (deuteriochloroform): δ 1.07 (s, 3H), 1.34 (d, 3H, J = 7 Hz), 1.48 (s, 9H), 1.61-1.82 (m, 2H), 2.12 (d, 1H, J = 9 Hz), 2.23 (q, 1H), 2.81 (d, 1H, J = 9 Hz), 3.12 (m, 2H), 6.31 (bs, 1H), 7.31 (m, 5H); ms: (EI$^+$, m + 1) 319 (18), 303 (31), 261 (17), 247 (85), 105 (100).

Anal. Calcd. for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 71.30; H, 9.91; N, 8.68.

1,1-Dimethylethyl-[1*R*-[3*R*-methyl-5-oxo-1-(1*R*-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**11a**) and 1,1-Dimethylethyl-[1*S*-[3*R*-methyl-5-oxo-1-(1*R*-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**11b**).

A solution of 2.04 g (7.8 mmoles) of **6a** in 100 ml of methanol saturated with ammonia was treated with 1 g of Raney nickel and stirred under a hydrogen atmosphere for 17 hours. The mixture was filtered through Celite and concentrated to give 1.9 g of an oil. The oil was immediately dissolved in 100 ml of methylene chloride and 0.87 g (8.6 mmoles) of triethylamine and 1.8 g (8.2 mmoles) of di-*t*-butyl dicarbonate was added. The mixture was stirred at room temperature for 18 hours. Water was added and the organic layer was separated, dried and concentrated to give 2.8 g of a mixture of **11a** and **11b**. Chromatography (silica gel, 40% ethyl acetate/hexanes) provided 1.1 g (40%) of **11a**, mp 110-112° (ethyl ether/hexanes); ^{1}H nmr (deuteriochloroform): δ 0.88 (s, 3H), 1.00 (d, 3H, J = 7 Hz), 1.43 (s, 9H), 1.48 (d, 3H, J = 7 Hz), 2.07 (d, 1H, J = 17 Hz), 2.52 (m, 2H), 3.18 (d, 1H, J = 10 Hz), 3.72 (m, 1H), 4.41 (m, 1H), 5.49 (q, 1H), 7.31 (s, 5H); ms: (EI) 346 (2), 289 (14), 202 (100), 105 (76).

Anal. Calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.64; H, 8.95; N, 8.15.

In addition 1.3 g (48%) of **11b**, mp 138-140° (ethyl ether/hexanes); ^{1}H nmr δ (deuteriochloroform): 0.84 (s, 3H), 1.06 (d, 3H, J = 7 Hz), 1.43 (s, 9H), 1.50 (d, 3H, J = 13 Hz), 2.07 (d, 1H, J = 16 Hz), 3.29 (d, 1H, J = 10 Hz), 3.76 (bs, 1H), 4.29 (m, 1H), 5.49 (q, 1H), 7.31 (s, 5H); ms: (EI) 346 (4), 289 (12), 202 (100), 105 (93).

Anal. Calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.53; H, 8.84; N, 8.61.

1,1-Dimethylethyl-[1*S*-[3*S*-methyl-5-oxo-1-(1*R*-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**12a**) and 1,1-Dimethylethyl-[1*R*-[3*S*-methyl-5-oxo-1-(1*R*-phenylethyl)-3-pyrrolidinyl]ethyl]carbamate (**12b**).

Compounds **12a** and **12b** were perpared from compound **6b** as described for **11a** and **11b**. The reaction yielded 4.3 g of a mixture which was chromatographed (silica gel, 40% ethyl acetate/hexanes) to give 1.8 g (38%) of **12a** as an oil; ^{1}H nmr (deuteriochloroform): δ 0.95 (d, 3H, J = 6 Hz), 1.08 (s, 3H), 1.38 (s, 9H), 1.49 (d, 3H, J = 6 Hz), 2.08 (d, 1H, J = 16 Hz), 2.53 (d, 1H, J = 16 Hz), 2.53 (d, 1H, J = 16 Hz), 2.81 (m, 2H), 3.65 (m, 1H), 4.34 (m, 1H), 5.51 (q, 1H), 7.28 (m, 5H); ms: (EI, m + 1) 347 (6), 290 (30), 202 (97), 105 (100).

Anal. Calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.48; H, 9.03; N, 7.94.

In addition 1.28 g (27%) of **12b**, mp 104-107° (ethyl ether/hexanes); ^{1}H nmr (deuteriochloroform): δ 0.95 (d, 3H, J = 7 Hz), 1.08 (s, 3H), 1.40 (s, 9H), 2.11 (d, 3H, J = 17 Hz), 2.42 (d, 1H, J = 16 Hz), 2.89 (s, 2H), 3.65 (m, 1H), 4.17 (m, 2H), 5.51 (q, 1H), 7.31 (m, 5H); ms: (EI, m + 1) 347.

Anal. Calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.59; H, 8.93; N, 8.06.

X-Ray Diffraction Analysis for **7b**, **11a** and **12b**.

All measurements were done at ambient temperature on a Siemens R3m/v diffractometer. The structures were solved by means of direct methods and the refinement was carried out with the Siemens SHELTXL Plus structure determination package. Crystal data and experimental conditions are given in Table 1. Atomic parameters, bond angles and bond lengths are given for each compound in Tables 2, 3, 4, respectively.

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