



A Diastereoselective Approach to Enantiopure 3-Substituted Pyrrolidines from Masked Lithium Homo-enolates Derived from Norephedrine

María García-Valverde, Rafael Pedrosa,* and Martina Vicente

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid
Dr. Mergelina s/n, 47011-Valladolid, Spain

S. García-Granda and A. Gutiérrez-Rodríguez

Departamento de Química Física y Analítica, Facultad de Química, Universidad de Oviedo
Julián Claverías 8, 33006-Oviedo, Spain

Abstract N-Alkoxycarbonyl-2-(2'-bromoethyl)oxazolidines derived from norephedrine are transformed into lithium derivatives by reaction with 1 or 2 equiv of *tert*-butyllithium in Et₂O. The lithium intermediates readily cyclize to bicyclic lactams that react with acetaldehyde and benzaldehyde leading to the addition products in excellent chemical yields and moderate diastereoselectivities. Removal of the chiral appendage provides enantiopure 3-substituted pyrrolidines. Copyright © 1996 Elsevier Science Ltd

1,3-Oxazolidines prepared from norephedrine represent a class of chiral masked aldehydes widely used in asymmetric synthesis.¹ These chirons have been exploited in diastereoselective additions to exocyclic carbon-carbon² or carbon-oxygen³ double bonds and cycloadditions⁴ or in nucleophilic ring opening reactions as a source of enantiopure amino⁵ and hydroxy derivatives.⁶ They have also been used as templates in diastereoselective electrophilic additions,⁷ and as chiral lithium enolates for diastereoselective α -alkylation of esters.⁸

As part of our work directed to the formation and use of chiral propanal homo-enolate synthons,⁹ we report herein on the reactivity of lithium derivatives prepared from oxazolidines **5a-e**.

Oxazolidines **5a-d** were prepared in excellent chemical yields and high diastereomeric excess by condensation (benzene, BF₃.Et₂O, r. t., 30 min) of (1R, 2S)-N-ethoxycarbonyl norephedrine (**1**) or (1R, 2S)-N-benzyloxycarbonyl norephedrine (**2**) with 3-chloro-1,1-diethoxypropane (**3**) and 2-(2'-bromoethyl)dioxolane (**4**), respectively (Scheme 1). In the same way the enantiomeric oxazolidine *ent*-**5b** was prepared from (1S, 2R)-N-ethoxycarbonyl norephedrine and **4**, whereas 2-(2'-iodoethyl)oxazolidine (**5e**) was obtained from **5c** by reaction with sodium iodide in dry acetone at room temperature for 24 h.¹⁰

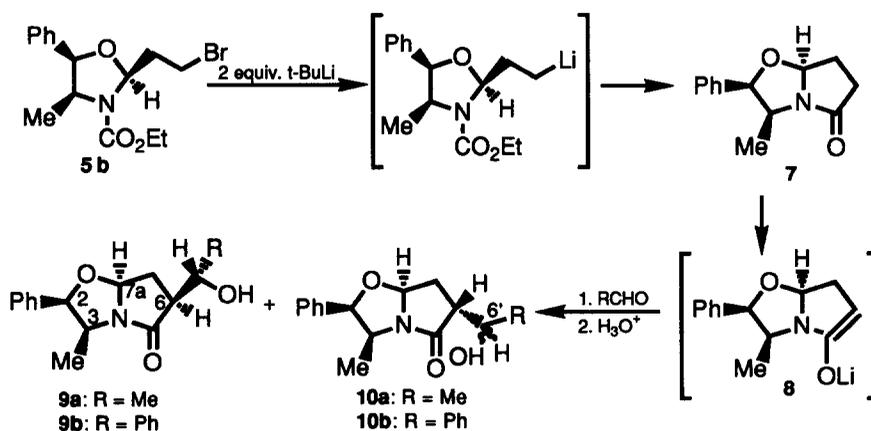
The formation of lithium derivatives was tested by reaction of oxazolidines with alkylolithiums under different reaction conditions (Scheme 2). Thus, treatment of the chloroderivative **5a** with *tert*-butyllithium (1 or 2 equivalents) in Et₂O at -78 °C for 30 min led to the 2-ethyloxazolidine **6** in only 5% yield, after the corresponding hydrolysis, whereas the 2-(2'-bromoethyl) homolog **5b** was transformed into **6** (77%) by

Table 1. Formation of lithiated oxazolidines and hydrolysis to 6-7, following Scheme 2.

Entry	Oxazolidine	R-Li	Solvent	Reaction Time (min)	Product (%)
1	5a	t-BuLi	Et ₂ O	35	6 (5)
2	5b	t-BuLi	Et ₂ O	5	6 (77)
3	5b	t-BuLi	THF	5	6 (65)
4	5b	t-BuLi	Hexane	5	6 (20)
5	5b	t-BuLi	Et ₂ O	30	6 (40) 7 (40)
6	5b	t-BuLi	Et ₂ O	120	7 (80)
7	5e	n-BuLi	Et ₂ O	120	7 (74)

prepared and used by Meyers in asymmetric synthesis.¹¹

On the other hand, when **5b** was treated, successively, with 1 equiv of *tert*-butyllithium at -78 °C in Et₂O for 10 min, and then with 3 equiv of acetaldehyde or benzaldehyde, and the mixture allowed to react for 120 min at the same temperature, only the bicyclic lactam **7** was obtained in 76% yield. These results show that the cyclization of the lithium intermediate is faster than the nucleophilic addition to the carbonyl compounds.

**Scheme 3**

Owing to the easy transformation of oxazolidine **5b** into the bicyclic lactam **7**, we decided to use it as a source of a chiral nonracemic lactam enolate directed to the synthesis of enantiopure 3-substituted pyrrolidines.

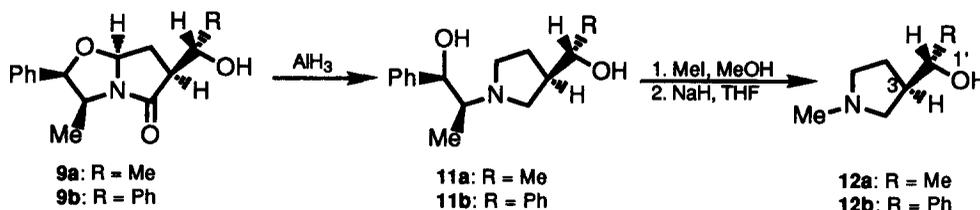
The plan was to start from bromooxazolidine **5b** and react it with two equiv of *tert*-butyllithium affording the enolate **8**, which was then added to acetaldehyde or benzaldehyde to lead to a mixture of diastereoisomers **9** and **10** with two adjacent stereocenters, in good chemical yield and diastereomeric excess (Scheme 3).

Table 2. Reactions of lithium derivative **8** with acetaldehyde and benzaldehyde

Entry	Substrate	R	t ₁ (min)	Temp. (°C)	t ₂ (H)	Yield (%)	9:10 ratio
1	5b	CH ₃	105	-78 to -60	1	86	9a (65) 10a (35)
2	5b	CH ₃	105	-78 to -60	8	88	9a (65) 10a (35)
3	5b	CH ₃	105	-78 to 20	8	84	9a (70) 10a (30)
4	5b	CH ₃	10	-78 to 20	8	71	9a (63) 10a (37)
5	<i>ent-5b</i>	CH ₃	105	-78 to 20	8	83	<i>ent-9a</i> (68) <i>ent-10a</i> (32)
6	5b	C ₆ H ₅	105	-78 to 20	8	74	9b (55) 10b (45)

Table 2 summarizes the data obtained by using different reaction conditions. Both chemical yields and diastereoselectivities were practically unaffected by increasing the reaction time (t₂) with the carbonyl derivative (compare entry 1 versus 2), while the facial discrimination was slightly increased when the reaction mixture was allowed to reach room temperature (entry 3). On the contrary, the chemical yield decreased when the time (t₁) of the first step of the reaction (cyclization-deprotonation) was too short (entry 4). Benzaldehyde reacted with **8** leading to **9b** in lower chemical yield and diastereomeric excess (entry 6) than acetaldehyde. The enantiomer of **9a** was prepared under identical reaction conditions starting from the bicyclic lactam *ent-5b* prepared from (1*S*, 2*R*) norephedrine (entry 5).

The major diastereomers were obtained as pure enantiomers by recrystallization for **9a** and *ent-9a* or by flash chromatography for **9b** from the reaction mixtures. NOESY experiments showed that the angular oxazolidine proton at C-7a was *cis* to the proton at C-6, indicating an *S* configuration at the newly created stereocenter. A detailed ¹H-NMR study of the minor components demonstrated that both **10a** and **10b** were equimolar mixtures of C-6' epimers of the (*6R*)-diastereoisomers.



Scheme 4

The transformation of the lactams **9a**, *ent-9a* and **9b** into pyrrolidines was accomplished by a two-steps procedure. In this way, **9a-b** and *ent-9a* were treated with lithium hydride-aluminium chloride leading to *N*-substituted pyrrolidines **11a-b** and *ent-11a* as pure enantiomers in 89% chemical yield.¹² These compounds were transformed into the final *N*-methylpyrrolidines **12** (72% chemical yield) by quaternization with methyl iodide, and subsequent treatment with sodium hydride in THF¹³ (Scheme 4).

Fortunately, it was possible to grow a single crystal of the compound *ent-11a* for an X-ray study (Figure 1). This determination allowed to confirm the stereochemistry at the pyrrolidine C-3 stereocenter, and to assign the configuration at the C-1' as *R* (*S* for pyrrolidine **11a**).

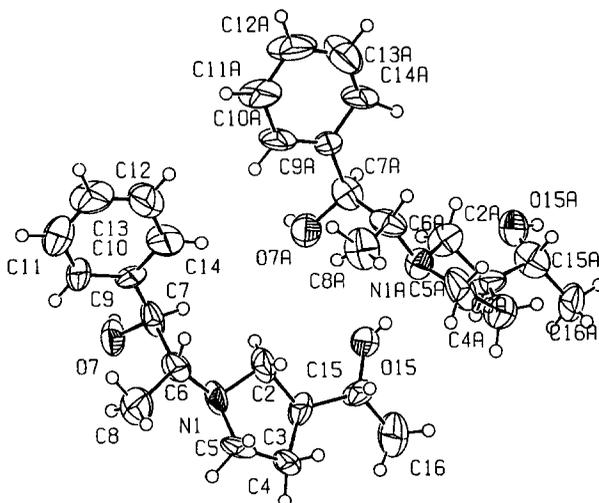


Figure 1. X-ray structure for *ent-11a*

The formation of the major diastereoisomers in these reactions is explained by the addition of the chiral enolate **8** to the *Re* face of the aldehyde. The stereochemistry at the stereocenter in the pyrrolidine ring shows that the enolate preferentially adds by the *endo* face, in agreement with the previously observed stereoselection for these chiral lactams.¹⁴⁻¹⁶ Nevertheless, the presence of a high proportion of the *exo*-isomer in the reaction with benzaldehyde suggests that the relative bulkiness of the electrophile plays an important role in the face-differentiation, directing the incoming reagent to the *exo*-face of the enolate.^{17,18}

Experimental

General. ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) spectra were recorded on a Bruker AC 300 spectrometer with tetramethylsilane as internal standard. IR spectra were recorded on a Philips PU 9706 Spectrometer, as film or KBr dispersion. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter in a 1 dm cell, and concentrations are given in g/100 ml. Mass spectra were recorded on a Hewlett-Packard 5988-A mass spectrometer. Dry tetrahydrofuran (THF) and Et₂O were distilled from sodium metal in the presence of benzophenone ketyl. All reactions were carried out in anhydrous solvents, under an Argon atmosphere and in oven dried glassware. N-Protected norephedrine **1** and **2** were obtained from norephedrine under standard Schotten-Baumann conditions. 3-Chloro-1,1-diethoxypropane and 2-(2'-bromoethyl)-1,3-dioxolane are commercially available, and they were distilled immediately before use.

X-Ray structure determination of 11a: C₁₅H₂₃NO₂, M_r = 249.35, orthorhombic, P 2₁ 2₁ 2₁, a = 12.832 (5), b = 12.881(7), c = 17.660(9) Å, V = 2919 Å³, Z = 8, D_x = 1.13 Mg m⁻³, μ = 0.695 cm⁻¹, F(000) = 1088, T = 293 K. Final conventional R = 0.066 and wR₂ = 0.148 for 858 "observed" reflections (I > 2σ(I)) and 386 variables. There were found two independent molecules in the asymmetric unit. Colorless crystal, size

0.33x0.29x0.26 mm. Throughout the experiment Mo K α radiation was used with a graphite crystal monochromator on an Enraf-Nonius CAD-4 single-crystal diffractometer ($\lambda = 0.71073 \text{ \AA}$). The unit cell dimensions were determined from the angular settings of 25 reflections with Θ between 10 and 15°. The intensity data of 2872 "unique" reflections, in hkl range (-15, -15, -20) to (0, 0, 0) and Θ limits ($0 < \Theta < 22$) were measured, using the ω -2 Θ scan technique and a variable scan rate with a maximum scan time of 60 s per reflection. The intensity of the primary beam was checked throughout the data collection by monitoring three standard reflections every 60 min. The final drift correction factors were between 0.97 and 1.01. On all reflections profile analysis was performed. Lorentz and polarization corrections were applied and the data were reduced to $|F_o|$ values. The structure was solved by direct methods using SHELX86 and expanded by DIRDIF. Isotropic least-squares refinement, using SHELX76 converged to $R = 0.131$. At this stage an empirical absorption correction was applied using DIFABS. The maximum and minimum absorption correction factors were respectively 1.27 and 0.46. Hydrogen atoms were geometrically placed. During the final stages of the refinement on F^2 using SHELXL93 the positional parameters and the anisotropic thermal parameters of the non-H atoms were refined. The function minimized was $Sw(F_o - F_c)^2 + (0.0944 P)^2$ with $s(F_o^2)$ from counting statistics and $P = (\text{Max}(F_o^2, 0) + 2 * F_c^2) / 3$. The maximum shift to e. s. d. ratio in the last full-matrix least-squares cycle was 0.002. The final difference Fourier map showed no peaks higher than 0.23 e \AA^{-3} nor deeper than -0.21 e \AA^{-3} . Absolute configuration was checked from previous knowledge of C(6), C(7), C(6a) and C(7a) chiral centers. Geometrical calculations were made with PARST. All calculations were made on a MicroVAX-3400 at the Scientific Computer Center of the University of Oviedo.

General procedure for the synthesis of 2-(2'-haloethyl)-1,3-oxazolidines. To a solution of N-protected norephedrine **1**, **2** (20 mmol) and 3-chloro-1,1-diethoxypropane or 2-(2'-bromoethyl)-1,3-dioxolane (20 mmol) in 10 ml of benzene was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.94 mL, 10 mmol). The reaction mixture was stirred at room temperature until the reaction was finished (TLC). The mixture was neutralized with a saturated NaHCO_3 solution, extracted with AcOEt, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography.

(2S,4S,5R)-2-(2'-Chloroethyl)-N-ethoxycarbonyl-5-phenyl-4-methyl-1,3-oxazolidine. (5a). Colorless oil. B.p. 165-167°C/0.5 Torr. $[\alpha]_{\text{D}}^{23} = -96.0$ ($c = 1$, EtOH). IR: 1690 cm^{-1} . MS (m/z , %): 297 (M^+ , 0.31), 191 (97), 118 (100). $^1\text{H-NMR}$: 0.79 (d, 3H, $J = 6.7$ Hz), 1.30 (t, 3H, $J = 7.3$ Hz), 1.86 - 2.61 (m, 2H), 3.43 - 3.83 (m, 2H), 4.06 - 4.33 (m, 3H), 5.07 (d, 1H, $J = 5.6$ Hz), 5.31 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 2.7$ Hz), 7.26 - 7.33 (m, 5H). Anal. calcd. for $\text{C}_{15}\text{H}_{20}\text{ClNO}_3$: C, 60.50; H, 6.78; N, 4.71. Found: C, 60.39; H, 6.52; N, 4.84.

(2S,4S,5R)-2-(2'-Bromoethyl)-N-ethoxycarbonyl-5-phenyl-4-methyl-1,3-oxazolidine. (5b). Colorless oil. B.p. 195-197°C/2 Torr. $[\alpha]_{\text{D}}^{23} = -80.2$ ($c = 1$, EtOH). IR: 1690 cm^{-1} . MSCI (m/z , %): 342 ($M^+ + 1$, 25), 344 ($M^+ + 3$, 23), 370 ($M^+ + 29$, 1), 372 ($M^+ + 31$, 25), 206 (100). $^1\text{H-NMR}$: 0.78 (d, 3H, $J = 6.7$ Hz), 1.30 (t, 3H, $J = 7.1$ Hz), 2.25 - 2.43 (m, 1H), 2.55 - 2.77 (m, 1H), 3.51 - 3.62 (m, 2H), 4.16 - 4.41 (m, 3H), 5.07 (d, 1H, $J = 5.6$ Hz), 5.28 (dd, 1H, $J_1 = 6.7$ Hz, $J_2 = 2.5$ Hz), 7.27 - 7.39 (m, 5H). $^{13}\text{C-NMR}$: 14.5, 16.1, 27.3, 38.7, 55.7, 61.3, 80.9, 87.5, 125.8, 127.7, 128.2, 135.7, 153.6. Anal. calcd. for $\text{C}_{15}\text{H}_{20}\text{BrNO}_3$: C, 52.54; H, 5.89; N, 4.10. Found: C, 52.77; H, 5.64; N, 4.22.

(2R,4R,5S)-2-(2'-Bromoethyl)-N-ethoxycarbonyl-5-phenyl-4-methyl-1,3-oxazolidine. (ent-5b). Colorless oil. B.p. 195-197°C/2 Torr. $[\alpha]_{\text{D}}^{23} = -80.5$ ($c = 1$, EtOH). IR: 1690 cm^{-1} . MSCI (m/z , %): 342 ($M^+ + 1$, 25), 344 ($M^+ + 3$, 23), 370 ($M^+ + 29$, 1), 372 ($M^+ + 31$, 25), 206 (100). $^1\text{H-NMR}$: 0.78 (d, 3H, $J = 6.7$ Hz), 1.30 (t, 3H, $J = 7.1$ Hz), 2.25 - 2.43 (m, 1H), 2.55 - 2.77 (m, 1H), 3.51 - 3.62 (m, 2H), 4.16 -

4.41 (m, 3H), 5.07 (d, 1H, $J = 5.6$ Hz), 5.28 (dd, 1H, $J_1 = 6.7$ Hz, $J_2 = 2.5$ Hz), 7.27-7.39 (m, 5H). ^{13}C -NMR: 14.5, 16.1, 27.3, 38.7, 55.7, 61.3, 80.9, 87.5, 125.8, 127.7, 128.2, 135.7, 153.6. Anal. calcd. for $\text{C}_{15}\text{H}_{20}\text{BrNO}_3$: C, 52.54; H, 5.89; N, 4.10. Found: C, 52.54; H, 5.79; N, 4.26.

(2S,4S,5R)-N-Benzoyloxycarbonyl-2-(2'-chloroethyl)-5-phenyl-4-methyl-1,3-oxazolidine (5c). Colorless solid. M.p. 39-40°C (from hexane/EtOAc). $[\alpha]_{\text{D}}^{23} = -59.4$ ($c = 1$, EtOH). IR: 1700 cm^{-1} . MS (m/z , %): 359 (M^+ , 0.05), 91 (100). ^1H -NMR: 0.82 (d, 3H, $J = 6.6$ Hz), 2.01 - 2.90 (m, 2H), 3.67-3.86 (m, 2H), 4.11 - 4.49 (m, 1H), 5.09 (d, 1H, $J = 5.6$ Hz), 5.21 (s, 2H), 5.36 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 2.6$ Hz), 7.23 - 7.48 (m, 10 H). ^{13}C -NMR: 16.2, 37.9, 39.6, 55.8, 66.9, 80.9, 86.5, 125.8, 127.8, 128.1, 128.4, 135.7, 136.2, 153.3. Anal. calcd. for $\text{C}_{20}\text{H}_{22}\text{ClNO}_3$: C, 66.75; H, 6.17; N, 3.89. Found: C, 66.63; H, 6.32; N, 4.02.

(2S,4S,5R)-N-Benzoyloxycarbonyl-2-(2'-bromoethyl)-5-phenyl-4-methyl-1,3-oxazolidine. (5d). Colorless solid. M.p. 48-49°C (from hexane/EtOAc). $[\alpha]_{\text{D}}^{23} = -56.6$ ($c = 1.5$, CHCl_3). IR: 1695 cm^{-1} . ^1H -NMR: 0.78 (d, 3H, $J = 6.6$ Hz), 2.30-2.45 (m, 1H), 2.58-2.83 (m, 1H), 3.55-3.60 (m, 2H), 4.18-4.42 (m, 1H), 5.06 (d, 1H, $J = 5.6$ Hz), 5.18 (s, 2H), 5.31 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 2.2$ Hz), 7.23-7.38 (m, 10 H). ^{13}C -NMR: 16.4, 27.5, 37.2, 56.0, 67.2, 81.3, 88.1, 126.1, 128.0, 128.1, 128.3, 128.4, 128.7, 128.9, 135.8, 153.6. Anal. calcd. for $\text{C}_{20}\text{H}_{22}\text{BrNO}_3$: C, 59.41; H, 5.48; N, 3.47. Found: C, 59.39; H, 5.71; N, 3.22.

Synthesis of (2S,4S,5R)-N-Benzoyloxycarbonyl-2-(2'-iodoethyl)-5-phenyl-4-methyl-1,3-oxazolidine. (5e).¹⁰ To a suspension of NaI (40 mmol) in dry acetone (50 ml) was added dropwise the oxazolidine 5c. The suspension was stirred for 20 h under Argon atmosphere. The solvent was removed and the white precipitate was washed several times with hexane. The solid was filtered, the hexane was evaporated under reduced pressure and the residue was purified by column chromatography. Colorless solid. M.p. 52-53°C (from hexane/EtOAc). $[\alpha]_{\text{D}}^{23} = -78.5$ ($c = 1$, CHCl_3). IR: 1700 cm^{-1} . ^1H -NMR: 0.77 (d, 3H, $J = 6.5$ Hz), 2.11 - 2.42 (m, 1H), 2.53 - 2.83 (m, 1H), 3.27 - 3.32 (m, 2H), 4.19 - 4.43 (m, 1H), 5.03 (d, 1H, $J = 5.6$ Hz), 5.18 (s, 2H), 5.22 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 2.4$ Hz), 7.22 - 7.38 (m, 10 H). ^{13}C -NMR: 16.2, 38.7, 55.7, 66.9, 80.8, 88.7, 125.8, 127.6, 127.8, 128.0, 128.1, 128.4, 135.6, 136.0, 153.2. Anal. calcd. for $\text{C}_{20}\text{H}_{22}\text{INO}_3$: C, 53.22; H, 4.91; N, 3.10. Found: C, 53.14; H, 5.07; N, 3.29.

General procedure for the formation of lithium derivatives and their hydrolysis. To a solution of oxazolidine (5a-e) (10 mmol) in dry THF (50 ml) under Argon atmosphere at -78°C was added 6 ml $^t\text{BuLi}$ (1.6M, 10 mmol). The mixture was stirred at this temperature for the time indicated in Table 1 and was then quenched with water. The mixture was extracted with diethyl ether, the organic layer dried over anhydrous Na_2SO_4 , the solid was filtered, the solvent removed in vacuo, and the residue was purified by flash chromatography.

(2S,4S,5R)-N-Ethoxycarbonyl-2-ethyl-5-phenyl-4-methyl-1,3-oxazolidine.(6). Colorless oil. B.p. 198-200°C/10 Torr. IR: 1690 cm^{-1} . MS (m/z , %): 263 (M^+ , 0.6), 157 (100). ^1H -NMR: 0.79 (d, 3H, $J = 6.6$ Hz), 1.05 (t, 3H, $J = 7.5$ Hz), 1.29 (t, 3H, $J = 7.1$ Hz), 1.72 - 1.91 (m, 1H), 2.00-2.19 (m, 1H), 4.07 - 4.34 (m, 3H), 5.06 (d, 1H, $J = 5.6$ Hz), 5.17-5.29 (m, 1H), 7.26-7.39 (m, 5H). ^{13}C -NMR: 8.1, 14.6, 16.0, 27.1, 55.8, 61.0, 80.6, 89.6, 126.0, 127.6, 128.2, 136.3, 153.8.

(2R,3S,7aS)-2-Phenyl-3-methyl-5-oxo-2,3,5,6,7,7a-hexahydropyrrolo-[2,1-b]-oxazole (7). Colorless oil. B.p. 125-126°C/2 Torr. $[\alpha]_{\text{D}}^{23} = -81.5$ ($c = 0.8$, CHCl_3). IR: 1685 cm^{-1} . ^1H -NMR: 1.00 (d, 3H, $J = 6.8$ Hz), 1.89-2.18 (m, 1H), 2.44-2.53 (m, 1H), 2.60-2.85 (m, 2H), 3.99-4.08 (m, 1H), 5.35 (d, 1H, $J = 6.8$ Hz), 5.41 (t, 1H, $J = 6.0$ Hz), 7.26-7.38 (m, 5H). ^{13}C -NMR: 13.4, 27.1, 35.0, 54.2,

85.9, 92.3, 125.9, 126.1, 128.0, 128.3, 136.1, 173.1. Anal. calcd. for C₁₃H₁₅NO₂: C, 71.86; H, 6.95; N, 6.44. Found: C, 71.70; H, 6.79; N, 6.23.

Synthesis of 6-substituted bicyclic lactams. To a solution of oxazolidine **5b** (4 mmol) in dry THF (30 ml) under Argon atmosphere at -78 °C was added 5 ml ^tBuLi (1.6M in pentane, 8 mmol). The mixture was stirred at this temperature for the time indicated in Table 2 and then, the carbonyl compound (0.44 mmol) was added and the mixture was stirred at the temperature indicated in Table 2. The resulting mixture was quenched with a saturated aqueous solution of NH₄Cl and extracted with diethyl ether. The organic layer was dried over Na₂SO₄ and the solvent evaporated. Diastereomers **9a** and **10a** were separated from the reaction mixture by recrystallization: after elimination of the solvent of the reaction, compound **9a** recrystallizes by simple dilution with Et₂O. From the mother liquor it was possible to isolate the two components of **10a**, that were epimers at C-6', by flash chromatography (silica gel, CH₂Cl₂). Diastereoisomer **9b** was separated from the equimolar mixture of epimers **10b** by flash chromatography (silica gel, CH₂Cl₂).

(1'S,2R,3S,6S,7aS)-2-Phenyl-6-(1'-hydroxyethyl)-3-methyl-5-oxo-2,3,5,6,7,7a-hexahydro-pyrrolo-[2,1-b]-oxazole. (9a). Colorless solid. M.p. 145-146 °C (from Et₂O). [α]_D²³ = -77.0 (c = 1, CHCl₃). IR (neat, cm⁻¹): 3410, 1655. MSCI (m/z, %): 262 (M⁺+ 1, 100), 290 (M⁺+ 29, 9), 302 (M⁺+ 41, 3.6). ¹H-NMR: 0.98 (d, 3H, J = 6.6 Hz), 1.20 (d, 3H, J = 6.4 Hz), 1.70 - 1.80 (m, 1H), 2.49 - 2.58 (m, 1H), 2.69 - 2.78 (m, 1H), 3.95 - 3.99 (m, 2H), 5.01 (s, 1H), 5.32 - 5.39 (m, 2H), 7.26 - 7.41 (m, 5H). ¹³C-NMR: 13.7, 20.5, 31.5, 51.8, 53.9, 69.6, 86.0, 89.9, 126.1, 128.2, 128.4, 135.5, 174.9. Anal. Calcd. for C₁₅H₁₉NO₃: C, 68.94; H, 7.32; N, 5.36. Found: C, 68.70; H, 7.41; N, 5.15.

(2R,3S,6R,7aS)-2-Phenyl-6-(1'-hydroxyethyl)-3-methyl-5-oxo-2,3,5,6,7,7a-hexahydro-pyrrolo-[2,1-b]-oxazole. (10a). First eluted epimer: MSCI (m/z, %): 262 (M⁺+1, 100), 290 (M⁺+ 29, 16), 302 (M⁺+41, 6). ¹H-NMR: 1.03 (d, 3H, J = 6.8 Hz), 1.31 (d, 3H, J = 6.2 Hz), 2.16-2.23 (m, 1H), 2.34-2.44 (m, 1H), 2.77-2.81 (m, 1H), 3.47 (s, 1H), 3.98-4.06 (m, 2H), 5.26 (d, 1H, J = 7.4 Hz), 5.32-5.35 (m, 1H), 7.21-7.39 (m, 5H). ¹³C-NMR: 13.2, 21.1, 28.6, 52.2, 55.8, 69.3, 84.8, 91.3, 128.2, 128.4, 136.4, 136.5, 176.3. Second eluted epimer: ¹H-NMR: 1.02 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.5 Hz), 2.17-2.31 (m, 2H), 2.42-2.50 (m, 1H), 2.85-2.91 (m, 1H), 3.98-4.07 (m, 1H), 4.25-4.35 (m, 1H), 5.28 (d, 1H, J = 7.2 Hz), 5.36-5.40 (m, 1H), 7.22-7.39 (m, 5H). ¹³C-NMR: 13.3, 21.1, 26.5, 52.1, 55.2, 67.1, 85.1, 92.1, 126.3, 128.1, 136.5, 175.2.

(1'R,2S,3R,6R,7aR)-2-Phenyl-6-(1'-hydroxyethyl)-3-methyl-5-oxo-2,3,5,6,7,7a-hexahydro-pyrrolo-[2,1-b]-oxazole. (ent -9a). Colorless solid. M.p. 145-146 °C (from Et₂O). [α]_D²³ = +77.6 (c = 1, CHCl₃). IR: 3410, 1655 cm⁻¹. MSCI (m/z, %): 262 (M⁺+ 1, 100), 290 (M⁺+ 29, 9), 302 (M⁺+ 41, 3.6). ¹H-NMR: 0.98 (d, 3H, J = 6.6 Hz), 1.20 (d, 3H, J = 6.4 Hz), 1.70 - 1.80 (m, 1H), 2.49 - 2.58 (m, 1H), 2.69 - 2.78 (m, 1H), 3.95 - 3.99 (m, 2H), 5.01 (s, 1H), 5.32 - 5.39 (m, 2H), 7.26 - 7.41 (m, 5H). ¹³C-NMR: 13.7, 20.5, 31.5, 51.8, 53.9, 69.6, 86.0, 89.9, 126.1, 128.2, 128.4, 135.5, 174.9. Anal. Calcd. for C₁₅H₁₉NO₃: C, 68.94; H, 7.32; N, 5.36. Found: C, 68.76; H, 7.31; N, 5.22.

(1'R,2R,3S,6S,7aS)-2-Phenyl-6-(1'-hydroxy-1'-phenylmethyl)-3-methyl-5-oxo-2,3,5,6,7,7a-hexahydro-pyrrolo-[2,1-b]-oxazole. (9b). Colorless oil. [α]_D²³ = -138.6 (c = 1, CHCl₃). IR: 3390, 1660 cm⁻¹. MSCI (m/z, %): 324 (M⁺+ 1, 11), 352 (M⁺+ 29, 1.5), 160 (100). ¹H-NMR: 1.02 (d, 3H, J = 6.6 Hz), 1.71-1.84 (m, 1H), 2.04-2.12 (m, 1H), 3.03-3.13 (m, 1H), 3.98-4.07 (m, 1H), 4.84 (d, 1H, J = 9.6 Hz), 5.22 - 5.28 (m, 1H), 5.35 (d, 1H, J = 6.7 Hz), 5.48 (s, 1H), 7.26 - 7.43 (m, 10 H). ¹³C-NMR:

13.5, 31.7, 52.1, 54.2, 76.3, 86.0, 90.5, 126.2, 126.9, 128.3, 128.4, 135.3, 140.8, 174.6. Anal. calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 65.73; H, 6.72; N, 4.51.

(2R,3S,6R,7aS)-2-Phenyl-6-(1'-hydroxy-1'-phenylmethyl)-3-methyl-5-oxo-2,3,5,6, 7,7a-hexahydropyrrolo-[2,1-b]-oxazole. (10b). Equimolar mixture of epimers: 1.00 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.8 Hz), 1.99-2.15 (m, 3H), 2.35-2.43 (m, 1H), 3.16-3.23 (m, 2H), 3.52(s, 2H), 3.94-4.04 (m, 2H), 4.89 (d, 1H, J = 8.1 Hz), 5.18 (d, 1H, J = 7.4 Hz), 5.22-5.29 (m, 4H), 7.18-7.43 (m, 20 H).

Synthesis of pyrrolidines 11. To a suspension of 76 mg $LiAlH_4$ (2.0 mmol) in dry THF was added in small portions 160.2 mg $AlCl_3$ (1.2 mmol). To the mixture, cooled to 0°, was added dropwise a solution of bicyclic lactams (9) (0.4 mmol) in THF. After 15 min at 0°C, the reaction was quenched with water, filtered and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure, and the crude product was recrystallized in hexane/ethyl acetate to yield pyrrolidines 11a and *ent*-11a or purified by flash chromatography to yield 11b.

(1'S,2'R,3R,αS)-N-(2'-Phenyl-2'-hydroxy-1'-methylethyl)-3-(α-hydroxyethyl)-pyrrolidine (11a). Colorless solid. M.p. 99-100°C (from Et_2O). $[\alpha]_D^{23} = +16.3$ (c = 1, $EtOH$). IR: 3350, 1620 cm^{-1} . MSCI (m/z, %): 250 ($M^+ + 1$, 37), 278 ($M^+ + 29$, 3), 142 (100). 1H -NMR: 0.83 (d, 3H, J = 6.6 Hz), 1.22 (d, 3H, J = 6.3 Hz), 1.51-1.62 (m, 1H), 1.92-2.04 (m, 1H), 2.13-2.22 (m, 1H), 2.46-2.53 (m, 1H), 2.60-2.75 (m, 2H), 2.85-2.93 (m, 2H), 3.66-3.75 (m, 1H), 5.03 (d, 1H, J = 3.0 Hz), 7.21-7.35 (m, 5H). ^{13}C -NMR: 11.6, 22.3, 27.5, 44.6, 51.8, 54.1, 65.2, 71.4, 72.8, 125.8, 126.8, 128.0, 141.6.

(1'R,2'S,3S,αR)-N-(2'-Phenyl-2'-hydroxy-1'-methylethyl)-3-(α-hydroxyethyl)-pyrrolidine (*ent*-11a). Colorless solid. M.p. 99-100°C (from Et_2O). $[\alpha]_D^{23} = -16.3$ (c = 1, $EtOH$). IR: 3350, 1620 cm^{-1} . MSCI (m/z, %): 250 ($M^+ + 1$, 37), 278 ($M^+ + 29$, 3), 142 (100). 1H -NMR: 0.83 (d, 3H, J = 6.6 Hz), 1.22 (d, 3H, J = 6.3 Hz), 1.51-1.62 (m, 1H), 1.92-2.04 (m, 1H), 2.13-2.22 (m, 1H), 2.46-2.53 (m, 1H), 2.60-2.75 (m, 2H), 2.85-2.93 (m, 2H), 3.66-3.75 (m, 1H), 5.03 (d, 1H, J = 3.0 Hz), 7.21-7.35 (m, 5H). ^{13}C -NMR: 11.6, 22.3, 27.5, 44.6, 51.8, 54.1, 65.2, 71.4, 72.8, 125.8, 126.8, 128.0, 141.6.

(1'S,2'R,3R,αR)-N-(2'-Phenyl-2'-hydroxy-1'-methylethyl)-3-(α-hydroxy-α-phenylmethyl)-pyrrolidine. (11b). Colorless solid. M.p. 144-145°C (from Et_2O). $[\alpha]_D^{23} = +40.1$ (c = 1, $CHCl_3$). IR: 3400 cm^{-1} . MSCI (m/z, %): 312 ($M^+ + 1$, 10), 340 ($M^+ + 29$, 1), 107(100). 1H -NMR: 0.84 (d, 3H, J = 6.6 Hz), 1.60-1.71 (m, 1H), 1.77-1.89 (m, 1H), 2.48-2.61 (m, 3H), 2.74-3.05 (m, 5H), 4.58 (d, 1H, J = 6.8 Hz), 5.01 (d, 1H, J = 3.1 Hz), 7.21-7.41 (m, 10 H). ^{13}C -NMR: 11.4, 27.4, 44.1, 51.8, 54.0 (CH_2), 65.1, 72.9, 77.8, 125.8, 126.3, 126.9, 127.5, 128.1, 128.4, 141.6, 143.9.

To a solution of pyrrolidines (11) (0.4 mmol) in methanol (6 ml) was added methyl iodide (4 mmol). The mixture was stirred for 48 h at room temperature. The solvent was removed under reduced pressure to yield the corresponding N-methylammonium iodide as a yellow solid. A suspension of this iodide (0.4 mmol) in dry THF was treated with NaH (0.48 mmol). The mixture was stirred at reflux for 4 h. The mixture was cooled to room temperature, quenched with water, and acidified with a diluted HCl solution. The aqueous layer was extracted several times with diethyl ether and then was treated with a diluted NaOH solution. The basic solution was extracted with CH_2Cl_2 , the organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo.

(1'S,3R)-3-(1'-Hydroxyethyl)-1-methylpyrrolidine. (12a). Colorless oil. $[\alpha]_D^{23} = +15.7$ (c = 1.5, CH_2Cl_2). IR: 3300 cm^{-1} . MS (m/z, %): 129(M^+ , 29), 57 (100). 1H -NMR: 1.16 (d, 3H, J = 6.2 Hz), 1.51-1.62 (m, 1H), 1.88-2.00 (m, 1H), 2.07-2.17 (m, 1H), 2.28-2.32 (m, 1H), 2.33 (s, 3H), 2.34-2.49 (m, 1H), 2.61-2.69 (m, 2H), 3.20-3.35 (broad s, 1H), 3.60-3.81 (m, 1H). ^{13}C -NMR: 22.3, 28.6, 41.9,

45.1, 55.9, 58.2, 71.1. Anal. calcd. for C₇H₁₅NO: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.22; H, 11.81; N, 10.63.

(1'R,3S)-3-(1'-Hydroxyethyl)-1-methylpyrrolidine. (ent -12a). Colorless oil. $[\alpha]_{\text{D}}^{23} = -14.9$ (c = 0.45, CH₂Cl₂). IR: 3300 cm⁻¹. MS (m/z, %): 129 (M⁺, 29), 57 (100). ¹H-NMR: 1.16 (d, 3H, J = 6.2 Hz), 1.51-1.62 (m, 1H), 1.88-2.00 (m, 1H), 2.07-2.17 (m, 1H), 2.28-2.32 (m, 1H), 2.33 (s, 3H), 2.34-2.49 (m, 1H), 2.61-2.69 (m, 2H), 3.20-3.35 (broad s, 1H), 3.60-3.81 (m, 1H). ¹³C-NMR: 22.3, 28.6, 41.9, 45.1, 55.9, 58.2, 71.1. Anal. calcd. for C₇H₁₅NO: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.31; H, 11.89; N, 10.68.

(1'R,3R)-3-(1'-Phenyl-1'-hydroxymethyl)-1-methylpyrrolidine.(12b). Colorless solid. M.p. 113-114°C. $[\alpha]_{\text{D}}^{23} = +40.3$ (c = 0.8, CHCl₃). IR: 3380 cm⁻¹. MS (m/z, %): 191 (M⁺, 79), 83 (100). ¹H-NMR : 1.75-2.00 (2H, m), 2.18-2.27 (m, 2H), 2.31 (s, 3H), 2.45-2.54 (m, 1H), 2.78 (dd, 1H, J₁ = 4.8 Hz, J₂ = 2.7 Hz), 2.85-2.92 (m, 1H), 3.70-3.90 (broad s, 1H, OH), 4.6 (d, 1H, J = 5.1 Hz), 7.21-7.42 (m, 5H). ¹³C-NMR: 28.6, 41.6, 44.7, 55.8, 57.9, 77.7, 126.1, 127.0, 128.2, 144.5. Anal. calcd. for C₁₂H₁₇NO: C, 75.35; H, 8.95; N, 7.32. Found: C, 75.12; H, 9.07; N, 7.51.

Acknowledgements. The Authors thank the Spanish DGICYT (Project PB92-0262) for financial support. One of us (M. G.-V.) thanks the Ministerio de Educación y Ciencia for a Predoctoral Fellowship (PFPI).

References and Notes.

- For a review, see: Scolastico, C. *Pure Appl. Chem.* **1988**, *60*, 1689.
- Bernardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J. Org. Chem.* **1988**, *53*, 1600.
- a) Hoppe, I.; Hoppe, D.; Wolff, C.; Egest, E.; Herbst, R. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 67. b) Agami, C.; Couty, F.; Lequesne, C. *Tetrahedron Lett.* **1994**, *35*, 3309.
- Abdallah, H.; Grée, R.; Carrié, R. *Tetrahedron Lett.* **1982**, *23*, 503.
- Andrés, C.; Maestro, A.; Pedrosa, R.; Pérez-Encabo, A.; Vicente, M. *Synlett*, **1992**, 45, and references therein.
- Andrés, C.; Delgado, M.; Pedrosa, R.; Rodríguez, R. *Tetrahedron Lett.* **1993**, *34*, 8325.
- Agami, A.; Couty, F.; Venier, O. *Synlett* **1995**, 1027.
- Falk, J. R.; Manna, S.; Mioskowski, C. *J. Org. Chem.* **1981**, *46*, 3742.
- García-Valverde, M.; Pedrosa, R.; Vicente, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1787.
- D'Aniello, F.; Taddei, M. *J. Org. Chem.* **1992**, *57*, 5247.
- See for instance: Meyers, A. I.; Lefker, B. A.; Sowin, T. J. Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.
- Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36, and references cited therein.
- Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B. *Tetrahedron: Asymmetry* **1993**, *4*, 273.
- Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509.
- Meyers, A. I.; Tschantz, M. A.; Brengel, G. P. *J. Org. Chem.* **1995**, *60*, 4359.
- Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146.
- Ezquerria, J.; Pedregal, C.; Rubio, A.; Vaquero, J. J.; Matía, M. P.; Martín, J.; Dfáz, A.; Navío, J. L. *G. J. Org. Chem.* **1994**, *59*, 4327.
- Bamford, M. J.; Beard, M.; Cherry, D. T.; Moloney, M. G. *Tetrahedron: Asymmetry* **1995**, *6*, 337.

(Received in UK 20 May 1996; revised 24 June 1996; accepted 26 June 1996)