Cyclocondensation reactions of racemic and prochiral γ-oxo-acid derivatives with (*R*)-phenylglycinol

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This work is dedicated to Prof. Roberto A. Rossi on the occasion of his 60th birthday

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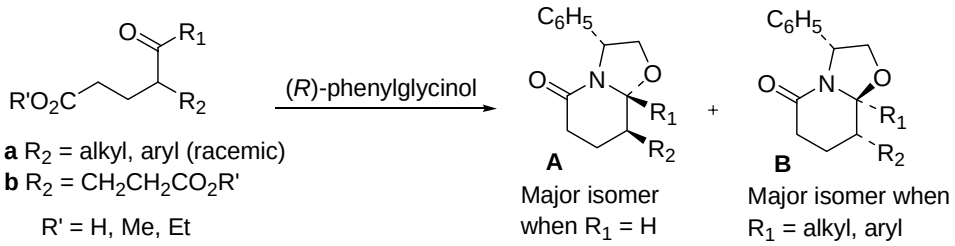
Abstract

The stereochemical outcome of cyclocondensation reactions of racemic and prochiral aldehyde and keto acid derivatives with (*R*)-phenylglycinol, leading to 7-substituted pyrrolidine-derived bicyclic lactams, is described.

Keywords: Chiral bicyclic lactams, (*R*)-phenylglycinol, pyrrolidines, enantioselective synthesis

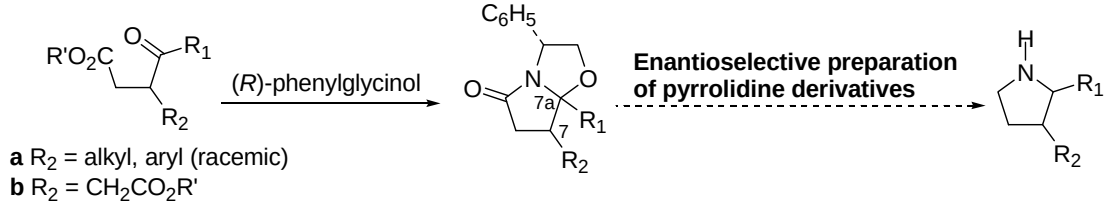
Introduction

In a previous paper[1] we have reported that the cyclocondensation reaction of racemic (**a**) or prochiral (**b**) γ-substituted-δ-oxoacid derivatives with (*R*)-phenylglycinol stereoselectively affords one of the four possible isomers of the corresponding bicyclic lactam in a process that involves a dynamic kinetic resolution of the racemic substrate or the discrimination of the two enantiotopic propionate chains, respectively (Scheme 1). Moreover, a different stereochemical outcome of the reaction was observed when starting from aldehydes (R_1 = H) or ketones (R_1 = alkyl). Thus, aldehydes (R_1 = H) afforded a mixture of isomers **A** and **B** in a ratio of about 4:1, whereas keto-acids (R_1 = alkyl) gave **B** as the major isomers (approximate **A**/**B** ratio 1:4). No isomers with a *trans* R_1/R_2 relationship were isolated.



Scheme 1

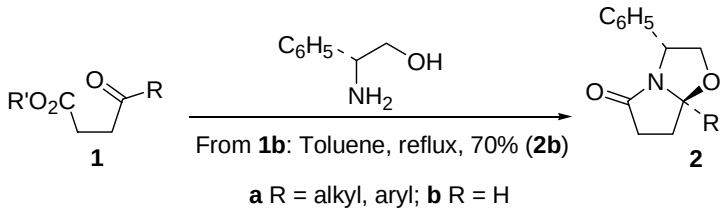
Bicyclic lactams **A** or **B**, which in some cases could be isolated with up to 70% yield as pure isomers, were demonstrated to be versatile chiral synthons for the enantioselective synthesis of piperidine derivatives, including alkaloids and other biologically active piperidines.[2] These excellent results prompted us to investigate the stereoselectivity of cyclocondensation reactions from racemic (**a**) and prochiral (**b**) γ-oxo-acid derivatives (R_1 = H, alkyl or aryl) with (*R*)- or (*S*)-phenylglycinol. The resulting chiral bicyclic lactams would constitute advanced precursors for the enantioselective synthesis of 3- and 2,3-substituted pyrrolidines (Scheme 2).[3] It is worth mentioning that there are many known natural and synthetic biologically active compounds,[4] as well as chiral auxiliaries and ligands[5] containing a pyrrolidine moiety, and consequently new methods providing access to enantiopure derivatives of this heterocycle are of current interest.



Scheme 2

Results and Discussion

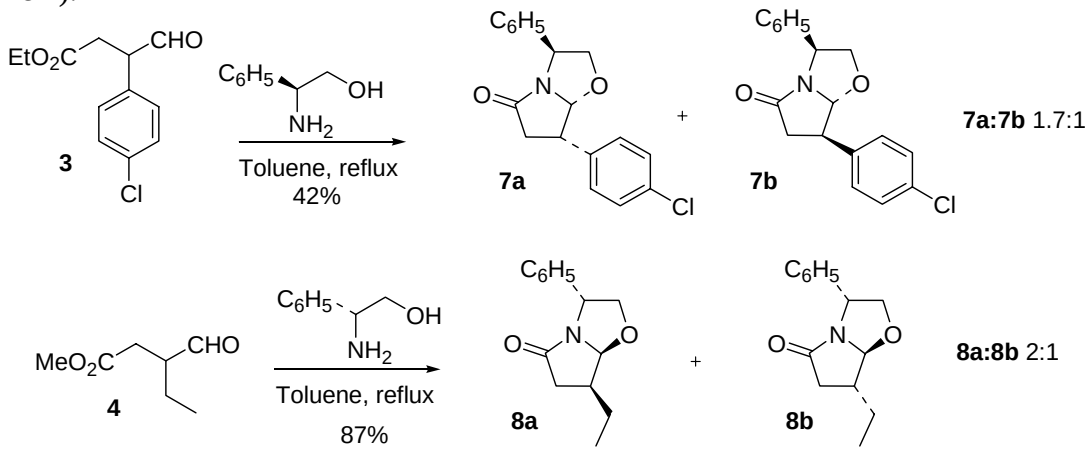
The cyclocondensation of unbranched γ-keto-acids **(1a)** (R' = H) with (*R*)-phenylglycinol has been reported by Meyers[3] to give a single isomer of the corresponding bicyclic lactam **2a**, in which the substituents R and C_6H_5 are *cis* (Scheme 3).[6] However, the preparation of the 7a-unsubstituted lactam **(2b)**[7] by a cyclocondensation process has not previously been reported. Heating a toluene solution of methyl 4-oxobutanoate[8] (**1b**; R' = CH_3) and (*R*)-phenylglycinol with azeotropic removal of water gave lactam **(2b)** as a single isomer in 70% yield. Thus, in contrast with the previously observed different stereochemical outcome of cyclocondensation reactions from aldehydes and ketones derived from δ-oxoacids, aldehydes (**1b**) and ketones (**1a**) derived from γ-oxoacids afford lactams with the same relative configuration at the angular 7a position.



Scheme 3

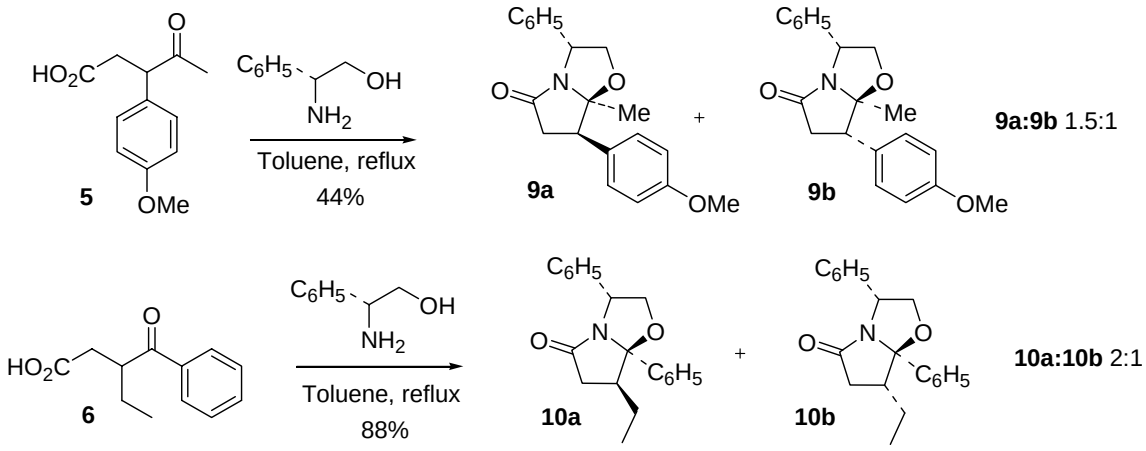
For the cyclocondensation reactions from racemic γ-oxo-acid derivatives we selected the racemic aldehydes **(3)** and **(4)** and ketones **(5)** and **(6)**, bearing an alkyl or aryl substituent at the isomerizable α position of the aldehyde or ketone carbonyl group. Aldehyde **(3)** was prepared as described in the literature,[9] whereas aldehyde **(4)** was obtained by alkylation of the diisopropyl enamine of butyraldehyde with methyl bromoacetate. On the other hand, keto acids **(5)** and **(6)** were obtained by alkylation of the enolate of 4-methoxyphenylacetone and butyrophenone, respectively, with methyl bromoacetate followed by saponification of the methyl ester.

When a solution of an equimolecular mixture of racemic aldehyde-ester **3** and (*S*)-phenylglycinol was heated at reflux overnight with azeotropic removal of water with a Dean-Stark apparatus, a 1.7:1 mixture of the C-7 isomeric lactams **(7a)** and **(7b)**, respectively, was obtained in moderate yield. On the other hand, under the same conditions but using (*R*)-phenylglycinol, the racemic aldehyde-ester **(4)**, bearing an alkyl substituent at the isomerizable 3-position, afforded a 2:1 mixture of lactams **(8a)** and **(8b)**, respectively, in excellent yield (Scheme 4).



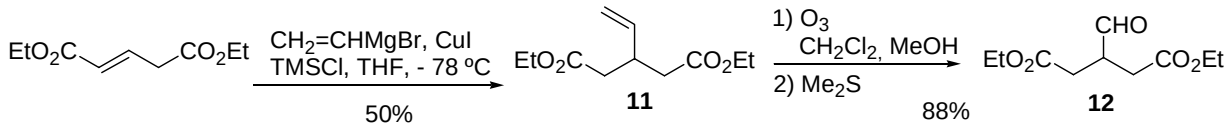
Scheme 4

Similar results were observed in the cyclocondensation reactions of racemic keto-acids **5** and **6** with (*R*)-phenylglycinol. The 3-aryl substituted derivative **5** yielded lactams **9a** and **9b** in a ratio 1.5:1, respectively, in 44% yield, whereas the 3-alkyl keto-acid **6** afforded a 2:1 mixture of lactams **10a** and **10b**, respectively, in 88% yield (Scheme 5).



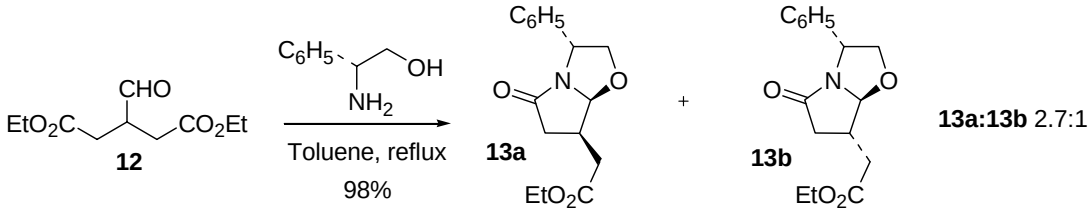
Scheme 5

On the other hand, the required prochiral aldehyde-diester **(12)** was satisfactorily prepared by conjugate addition of vinylmagnesium bromide to diethyl glutaconate by using the procedure reported by Overman,[10] followed by ozonolysis of the resulting 3-vinyl glutarate **(11)** (Scheme 6).



Scheme 6

When a mixture of compound **12** and (*R*)-phenylglycinol was subjected to cyclocondensation under the above described conditions, a 2.7:1 mixture of isomeric lactams **(13a)** and **(13b)** was obtained in nearly quantitative yield (Scheme 7).

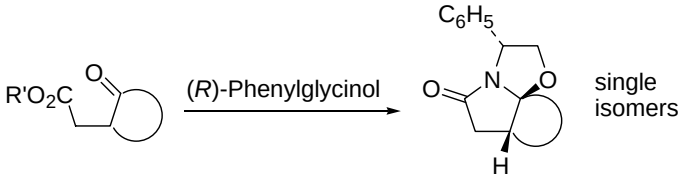


Scheme 7

The relative ratios of isomers **a** and **b** in the above reactions were determined by ^{1}H NMR and HPLC. On the other hand, the absolute configuration of lactams **7b** and **9a** was inferred by comparison of their spectroscopic data with those reported by Meyers for analogous bicyclic lactams bearing a phenyl substituent at the 7 position, which were obtained by an alternative

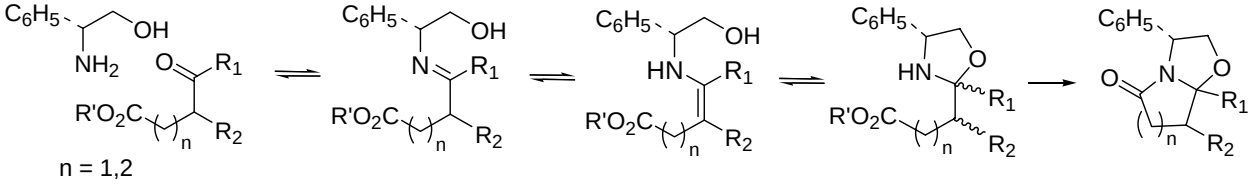
route involving the conjugate addition of organocuprates to α,β-unsaturated derivatives of simple bicyclic lactams.[11] Additionally, the absolute configuration of **9b** was unambiguously determined by X-ray diffraction techniques.

In summary, cyclocondensation of both racemic aldehydes **(3**, **4)** and ketones **(5**, **6)** lead in all cases to bicyclic lactams with the same 3,7a-*cis* relative configuration. However, the stereoselectivity in the dynamic kinetic resolution of the racemic γ-oxoacid derivatives leading to oxazolopyrrolidones is clearly lower than that observed from δ-oxoacid derivatives. Although desymmetrization of the enantiotopic groups of the prochiral γ-oxodiester **(12)** takes place with a slightly better stereoselectivity, it is still lower than when starting from δ-oxodiesters. These stereochemical results are in sharp contrast with those reported in related cyclocondensations from racemic cyclopentanone- and cyclohexanone-2-acetate derivatives, which afford a single isomer of the corresponding tricyclic lactam (Scheme 8).[12]



Scheme 8

The stereochemical outcome of the cyclocondensation reactions of racemic oxoacid derivatives with phenylglycinol can be accounted for by considering that the reaction of the chiral aminoalcohol with the aldehyde or the ketone affords a mixture of four diastereomeric oxazolidines, in equilibrium through the corresponding imines-enamines (Scheme 9), which undergo subsequent irreversible lactamization.



Scheme 9

When racemic γ-oxo-acids **(3-6)** derivatives are used in the cyclocondensation reaction, the difference of energy between the diastereomeric five-membered transition states in the lactamization step is probably lower than when starting from δ-oxoacids, leading to isomers **a** or **b** with scarce stereoselectivity. The stereochemical outcome of cyclocondensations performed from γ-oxo-acids derived from 2-cycloalkanoneacetic acids could be a consequence of the strain imposed by the lower conformational mobility of R_1 and R_2 substituents, which form part of a ring. Similarly, the moderate stereoselectivity observed in the cyclocondensation of the prochiral aldehyde-diester **12** may be a consequence of the low difference of energy between the five-

membered diastereomeric transition states resulting from lactamization of the two diastereotopic acetate chains.

In spite of the above limitations concerning the diastereoselectivity, taking into account the excellent chemical yield of the 7-alkyl substituted bicyclic lactams **8** (87%), **10** (88%), and **13** (98%), the commercial availability of both enantiomers of phenylglycinol, and the fact that the phenylethanol moiety is easily removable,[3] the cyclocondensations reported here can provide a convenient straightforward access to substituted pyrrolidines in both enantiomeric series.

Experimental Section

General Procedures. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini-300 instrument or on a Bruker DMX-500 apparatus. Chemical shifts are reported in δ values downfield from TMS. Coupling constants are accurate to ± 0.2 Hz for ^{1}H and ± 0.6 Hz for ^{13}C. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer and only noteworthy IR absorptions are listed. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 1 dm cell with a total volume of 1 mL. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer or on an Autospec-VG (HRMS) using electron impact mode. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with aqueous potassium permanganate solution. Flash chromatoghraphy was carried out using SiO_2 (silica gel 60, SDS, 35-70 μ). All nonaqueous reactions were performed under an inert atmosphere. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried using standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HMRS were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona and Unidade de Espectrometria de Masas, Santiago de Compostela.

Ethyl 3-(4-chlorophenyl)-4-oxobutanoate (3). Triethyl orthoacetate (11.0 mL, 60.0 mmol) and pivalic acid (0.069 mL, 0.6 mmol) were added to a stirred solution of (*E*)-4-(4-chlorophenyl)-3-buten-2-ol[9a] (1.08 g, 5.9 mmol) in anhydrous DME (85 mL), and the mixture was heated at reflux for 48 h. The solvent was evaporated under reduced pressure, and the residue was taken up with CH_2Cl_2. The organic solution was washed with saturated aqueous $NaHCO_3$, dried, and concentrated to give an oil, which was distilled (120 ºC, 0.01 mm Hg) affording ethyl (*E*)-3-(4-chlorophenyl)-4-hexenoate (1.1 g, 73 %). IR (film) 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, *J* = 7.4 Hz, 3 H), 1.65 (d, *J* = 5.0 Hz, 3 H), 2.65 (m, 2 H), 3.77 (m, 1 H), 4.05 (q, *J* = 7.4 Hz, 2 H), 5.51 (m, 2 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.2 (CH_3), 17.9 (CH_3), 40.8 (CH_2), 44.2 (CH), 60.4 (CH_2), 125.9 (CH), 128.5 (2 CH), 128.7 (2 CH), 132.1 (C), 132.6 (CH), 141.7 (C), 171.6 (C). A stream of ozone gas was

bubbled through a cooled (–78 ºC) solution of ethyl (*E*)-3-(4-chlorophenyl)-4-hexenoate (500 mg, 1.98 mmol) in CH_2Cl_2-MeOH (1:1, 10 mL) for 45 min. The solution was purged with O_2, Me_2S (2 mL) was added, and the stirring was continued for 45 min. The mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2, washed with brine, dried, and concentrated. The residue was chromatographed (AcOEt-hexane) to give pure aldehyde **3**[9] (410 mg, 86%). IR (film) 1735, 1792 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, *J* = 7.0 Hz, 3 H), 2.60 (dd, *J* = 17.0, 6.5 Hz, 1 H), 3.13 (dd, *J* = 17.0, 8.0 Hz, 1 H), 4.11 (m, 3 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 9.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.1 (CH_3), 34.6 (CH_2), 53.9 (CH), 60.8 (CH_2), 129.3 (2 CH), 130.1 (2 CH), 133.2 (C), 134.0 (C), 171.1 (C), 197.9 (C).

Methyl 3-formylpentanoate (4). A solution of butyraldehyde (1.25 mL, 13.8 mmol) and diisopropylamine (1.94 mL, 13.8 mmol) in anhydrous benzene (10 mL) was heated at reflux for 8 h in an apparatus fitted with a Dean-Stark trap. Then, a solution of methyl bromoacetate (1.97 mL, 20.8 mmol) in acetonitrile (5 mL) was added, and the stirring was continued for 20 h. After this time aqueous AcOH (1:3 AcOH-H_2O, 3 mL) was added while heating was maintained for a further 2 h. The resulting mixture was cooled and diluted with H_2O. The organic layer was washed with aqueous $NaHCO_3$, dried, and concentrated to give a residue, which was distilled (93-96 ºC, 0.1 mm Hg) affording pure compound **4**[13] (1.12 g, 56%). IR (film) 1711, 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, *J* = 7.4 Hz, 3 H), 1.59 (m, 1 H), 1.77 (m, 1 H), 2.42 (dd, *J* = 16.0, 4.8 Hz, 1 H), 2.70 (dd, *J* = 16.0, 8.4 Hz, 1 H), 2.76 (m, 1 H), 3.69 (s, 3 H), 9.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.0 (CH_3), 21.5 (CH_2), 32.2 (CH_2), 48.9 (CH), 51.7 (CH_3), 172.2 (C), 202.7 (CH).

3-(4-Methoxyphenyl)-4-oxopentanoic acid (5). A solution of 4-methoxyphenylacetone (2.0 mL, 13.0 mmol) in anhydrous THF (8 mL) was added dropwise to a cooled solution (–78 ºC) of potassium bis(trimethylsilyl)amide (28.6 mL of a 0.5 M solution in toluene, 14.3 mmol) in THF (50 mL), and the mixture was stirred for 30 min. Then methyl bromoacetate (1.35 mL, 14.3 mmol) was added, and the stirring was continued for 3 h at –78 ºC. The solution was diluted with AcOEt (50 mL), washed with brine, dried, and concentrated to give an oil, which, after flash chromatography (AcOEt-hexane), afforded pure methyl 3-(4-methoxyphenyl)-4-oxopentanoate (2.5 g, 81%). IR (film) 1711, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (s, 3 H), 2.50 (dd, *J* = 17.0, 5.2 Hz, 1 H), 3.16 (dd, *J* = 17.0, 9.8 Hz, 1 H), 3.64 (s, 3 H), 3.79 (s, 3 H), 4.13 (dd, *J* = 9.8, 5.2 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 7.13 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.7 (CH_3), 36.7 (CH_2), 51.7 (CH_3), 53.9 (CH_2), 55.2 (CH_3), 114.4 (2 CH), 129.1 (2 CH), 129.2 (C), 159.0 (C), 172.4 (C), 206.9 (C). Exact mass Calcd for $C_{13}H_{16}O_4$: 236.1049. Found: 236.1047. A solution of methyl 3-(4-methoxyphenyl)-4-oxopentanoate (2.0 g, 8.5 mmol) in water (10 mL) and MeOH (50 mL) containing KOH (4.8 g, 86 mmol) was stirred at room temperature for 6 h. The mixture was washed with Et_2O, acidified with 1.0 M HCl, and extracted with AcOEt. The organic solution was dried and concentrated to give acid **5** (1.6 g, 85%) as a white solid, which was crystallized from Et_2O-hexane; mp 124-126ºC. IR (KBr) 1708, 2916 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09 (s, 3 H), 2.55 (dd, *J* = 17.5, 5.0 Hz, 1 H), 3.21 (dd, *J* = 17.5,

10.0 Hz, 1 H), 3.79 (s, 3 H), 4.09 (dd, *J* = 10.0, 5.0 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 10.10-10.80 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.6 (CH_3), 36.7 (CH_2), 53.6 (CH), 55.2 (CH_3), 114.5 (2 CH), 128.9 (C), 129.2 (2 CH), 159.0 (C), 177.8 (C), 206.9 (C). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.52; H, 6.03.

3-Benzoylpentanoic acid (6). A solution of butyrophenone (2.0 g, 13.5 mmol) in anhydrous THF (4 mL) was added to a cooled solution (–78 ºC) of LDA (9.0 mL of a 1.5 M solution in cyclohexane, 13.5 mmol) in THF (8 mL), and the mixture was stirred for 30 min. Then, methyl bromoacetate (1.28 mL, 13.5 mmol) was added and, after 1 h, the cooling bath was removed, and the stirring was continued for 7 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt. The combined organic extracts were dried and concentrated, and the residue was chromatographed (AcOEt-hexane) affording methyl 3-benzoylpentanoate (1.6 g, 54%). IR (film) 1670, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, *J* = 8.0 Hz, 3 H), 1.58 (m, 1 H), 1.78 (m, 1 H), 2.52 (dd, *J* = 17.0, 4.8 Hz, 1 H), 2.96 (dd, *J* = 17.0, 9.5 Hz, 1 H), 3.62 (s, 3 H), 3.85 (m, 1 H), 7.47 (m, 2 H), 7.56 (m, 1 H), 7.98 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.2 (CH_3), 25.3 (CH_2), 34.9 (CH_2), 43.4 (CH), 51.6 (CH_3), 128.2 (2 CH), 128.5 (2 CH), 132.9 (CH), 136.6 (C), 172.9 (C), 202.5 (C). Operating as described for **5**, methyl 3-benzoylpentanoate (1.5 g, 6.8 mmol) was converted to acid **6**[14] (1.1 g, 78%), obtained as a white solid. Mp 74-76 ºC (benzene-hexane), (Lit.[14] mp 68.5-70.0 ºC); IR (KBr) 1681, 1700, 3060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 7.5 Hz, 3 H), 1.57 (m, 1 H), 1.78 (m, 1 H), 2.53 (dd, *J* = 17.4, 4.8 Hz, 1 H), 2.97 (dd, *J* = 17.4, 9.3 Hz, 1 H), 3.82 (m, 1 H), 7.47 (m, 2 H), 7.57 (m, 1 H), 7.96 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.2 (CH_3), 25.3 (CH_2), 34.7 (CH_2), 43.3 (CH), 128.3 (2 CH), 128.6 (2 CH), 133.0 (CH), 136.3 (C), 178.4 (C), 202.3 (C).

Diethyl 3-vinylglutarate (11). A solution of vinylmagnesium bromide (34 mL of a 1.0 M solution in THF, 34 mmol) was added dropwise to a stirring suspension of CuI (647 mg, 3.4 mmol) in anhydrous THF (70 mL), and the resulting mixture was stirred at room temperature for 10 min. Then, the solution was cooled to –78 ºC, and TMSCl (4.3 mL, 34 mmol) and a solution of diethyl glutaconate (2 mL, 11.3 mmol) in THF (5 mL) were introduced sequentially. The resulting mixture was stirred at –78 ºC for 3 h, the cooling bath was removed, and the stirring was continued for 4 h. Saturated aqueous NH_4Cl was added, and the aqueous layer was extracted with AcOEt. The combined organic extracts were dried and concentrated to give a residue, which was chromatographed (1:9 AcOEt-hexane) affording compound **11** (1.2 g, 50%) as a colorless oil. IR (film) 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, *J* = 7.5 Hz, 6 H), 2.35 (dd, *J* = 15.5, 7.5 Hz, 2 H), 2.42 (dd, *J* = 15.5, 6.5 Hz, 2 H), 3.02 (m, 1 H), 4.01 (q, *J* = 7.5 Hz, 4 H), 5.00 (dm, *J* = 10.0 Hz, 1 H), 5.06 (dm, *J* = 17.7 Hz, 1 H), 5.72 (ddd, *J* = 17.7, 10.0, 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.2 (2 CH_3), 36.5 (CH), 38.9 (2 CH), 60.3 (2 CH), 115.5 (CH_2), 139.0 (CH), 171.6 (2 C).

Diethyl 3-formylglutarate (12). Operating as described for **3**, compound **11** (1.1 g, 5.1 mmol) was converted to aldehyde diester **12** (980 mg, 88%), which was obtained as an oil and used without further purification. IR (film) 1713, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, *J*

= 7.5 Hz, 6 H), 2.59 (dd, *J* = 12.6, 6.3 Hz, 2 H), 2.78 (dd, *J* = 12.6, 6.8 Hz, 2 H), 3.18 (m, 1 H), 4.16 (q, *J* = 7.5 Hz, 4 H), 9.77 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.1 (2 CH_3), 33.0 (2 CH_2), 43.7 (CH), 61.0 (2 CH_2), 171.2 (2 C), 200.9 (C). Exact mass Calcd for $C_{10}H_{16}O_5$: 216.0998. Found: 216.0987.

General procedure for the cyclocondensation reactions

The γ-oxoacid derivative (1.01 equiv) was added to a 0.1 M stirred solution of (*R*)- or (*S*)-phenylglycinol in toluene containing 4 Å molecular sieves, and the mixture was heated at reflux overnight with azeotropic elimination of water with a Dean-Stark. The resulting solution was concentrated, and the residue was taken up with CH_2Cl_2. The organic solution was washed with saturated aqueous NH_4Cl, dried, and concentrated. The crude mixture was subjected to flash column chromatography using SiO_2 previously washed with a solution of Et_3N in hexane. In all cases a gradient mixture of hexane and AcOEt was used as the eluent. Yields and ratios of isomeric bicyclic lactams obtained are indicated in the text.

(3*R*,7a*S*)-5-Oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (2b). $[\alpha]^{22}_{D}$ −158 (*c* 1.0, EtOH) [Lit.[7b] $[\alpha]^{20}_{D}$ −161 (*c* 1, EtOH)]; IR (film) 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (m, 1 H), 2.44 (m, 1 H), 2.56 (ddd, *J* = 17.5, 10.5, 4.2 Hz, 1 H), 2.73 (ddd, *J* = 17.5, 10.5, 7.2 Hz, 1 H), 3.80 (dd, *J* = 8.7, 7.5 Hz, 1 H), 4.56 (dd, *J* = 8.7, 7.5 Hz, 1 H), 5.10 (t, *J* = 7.5 Hz, 1 H), 5.27 (dd, *J* = 6.0, 2.4 Hz, 1 H), 7.20-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.4 (CH_2), 31.4 (CH_2), 57.9 (CH), 74.5 (CH_2), 92.7 (CH), 125.6 (2 CH), 127.4 (CH), 128.6 (2 CH), 139.5 (C), 179.3 (C).

(3*S*,7*S*,7a*R*)-7-(4-Chlorophenyl)-5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (7a). White solid, mp 140-142ºC; $[\alpha]^{22}_{D}$ +120 (*c* 0.5, CH_2Cl_2); IR (NaCl) 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (dd, *J* = 18.0, 7.2 Hz, 1 H, H-6), 3.14 (dd, *J* = 18.0, 9.6 Hz, 1 H, H-2), 3.77 (dd, *J* = 8.7, 6.6 Hz, 1 H, H-2), 3.92 (m, 1 H, H-7), 4.40 (dd, *J* = 8.7, 7.8 Hz, 1 H), 5.24 (app t, *J* = 7.2 Hz, 1 H, H-3), 5.37 (d, *J* = 6.0 Hz, 1 H, H-7a), 7.20-7.45 (m, 9 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.8 (C-6), 40.4 (C-7), 58.9 (C-3), 74.0 (C-2), 93.6 (C-7a), 125.7 (2 CH), 127.7 (CH), 128.5 (2 CH), 128.8 (2 CH), 129.7 (2 CH), 133.3 (C), 135.3 (C), 139.4 (C), 179.8 (C-5); *m*/*z* (EI) 313 (12, M^+), 148 (84), 138 (100); Exact mass Calcd for $C_{18}H_{16}NO_2Cl$: 313.0869. Found: 313.0859.

(3*S*,7*R*,7a*R*)-7-(4-Chlorophenyl)-5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (7b). Colorless oil. $[\alpha]^{22}_{D}$ +58 (*c* 0.1, CH_2Cl_2); IR (KBr) 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.92 (dd, *J* = 17.0, 9.3 Hz, 1 H, H-6), 3.03 (dd, *J* = 17.0, 9.3 Hz, 1 H, H-6), 3.57 (td, *J* = 9.3, 3.6 Hz, 1 H, H-7), 3.90 (dd, *J* = 8.7, 6.9 Hz, 1 H, H-2), 4.61 (dd, *J* = 8.7, 7.5 Hz, 1 H, H-2), 5.18 (app t, *J* = 7.2 Hz, 1 H, H-3), 5.26 (d, *J* = 3.6 Hz, 1 H, H-7a), 7.20-7.40 (m, 9 H, Ar); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 40.4 (C-6), 45.2 (C-7), 57.8 (C-3), 75.0 (C-2), 98.5 (C-7a), 125.8 (2 CH), 127.8 (CH), 128.5 (2 CH), 128.8 (2 CH), 129.1 (2 CH), 133.2 (C), 138.5 (C), 139.0 (C), 176.9 (C-5); *m*/*z* (EI) 313 (10, M^+), 148 (80), 138 (100); *m*/*z* (EI) 313 (10, M^+), 148 (80), 138 (100); Exact mass Calcd for $C_{18}H_{16}NO_2Cl$: 313.0869. Found: 313.0862.

(3*R*,7*S*,7a*S*)-7-Ethyl-5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (8a). Colorless oil. $[\alpha]^{22}_{D}$ −125 (*c* 1.0, CH_2Cl_2); IR (film) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz,

assigned by COSY and HSQC experiments) δ 1.02 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.50 (m, 1 H, CH_2), 1.74 (m, 1 H, CH_2), 2.20 (dd, *J* = 17.5, 6.8 Hz, 1 H, H-6), 2.54 (m, 1 H, H-7), 2.81 (dd, *J* = 17.5, 9.3 Hz, 1 H, H-6), 3.79 (dd, *J* = 8.5, 6.5 Hz, 1 H, H-2), 4.50 (app t, *J* = 8.1 Hz, 1 H, H-2), 5.15 (app t, *J* = 7.0 Hz, 1 H, H-3), 5.16 (d, *J* = 5.6 Hz, 1 H, H-7a), 7.26 (m, 3 H, C_6H_5), 7.34 (m, 2 H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz, assigned by COSY and HSQC experiments) δ 12.5 (CH_3), 22.4 (CH_2), 36.6 (C-7), 37.0 (C-6), 58.6 (C-3), 73.7 (C-2), 93.9 (C-7a), 125.7 (C-*m*), 127.4 (C-*p*), 128.7 (C-*o*), 139.8 (C-*i*), 180.8 (C-5); *m*/*z* (EI) 232 (M^++1, 1), 201 (100), 172 (38), 148 (33), 117 (57); Exact mass Calcd for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1257.

(3*R*,7*R*,7a*S*)-7-Ethyl-5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (8b). Colorless oil. $[\alpha]^{22}_D$ –130 (*c* 0.1, CH_2Cl_2); IR (film) 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, assigned by COSY and HSQC experiments) δ 1.03 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.57 (m, 1 H, CH_2), 1.70 (m, 1 H, CH_2), 2.32 (m, 1 H, H-7), 2.47 (dd, *J* = 17.0, 8.8 Hz, 1 H, H-6), 2.73 (dd, *J* = 17.0, 9.3 Hz, 1 H, H-6), 3.86 (dd, *J* = 8.9, 7.3 Hz, 1 H, H-2), 4.57 (dd, *J* = 8.9, 7.6 Hz, 1 H, H-2), 5.00 (d, *J* = 3.2 Hz, 1 H, H-7a), 5.10 (app t, *J* = 7.3 Hz, 1 H, H-3), 7.24 (m, 3 H, C_6H_5), 7.35 (m, 2 H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz, assigned by COSY and HSQC experiments) δ 11.8 (CH_3), 26.3 (CH_2), 38.9 (C-6), 41.5 (C-7), 57.4 (C-3), 74.8 (C-2), 97.7 (C-7a), 125.7 (C-*m*), 127.5 (C-*p*), 128.6 (C-*o*), 139.4 (C-*i*), 177.8 (C-5); *m*/*z* (EI) 232 (M^++1, 1), 201 (100), 172 (38), 117 (56); Exact mass Calcd for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1268.

(3*R*,7*R*,7a*S*)-7-(4-Methoxyphenyl)-7a-methyl-5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole (9a). Colorless oil. $[\alpha]^{22}_D$ –20 (*c* 0.1, CH_2Cl_2); IR (film) 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, assigned by COSY) δ 1.50 (s, 3 H, CH_3), 2.75 (dd, *J* = 17.4, 4.5 Hz, 1 H, H-6), 3.25 (dd, *J* = 17.4, 9.0 Hz, 1 H, H-6), 3.61 (dd, *J* = 9.0, 4.5 Hz, 1 H, H-7), 3.80 (s, 3 H, CH_3O), 4.01 (dd, *J* = 8.7, 6.0 Hz, 1 H, H-2), 4.21 (dd, *J* = 8.7, 8.0 Hz, 1 H, H-2), 5.24 (app t, *J* = 7.2 Hz, 1 H, H-3), 6.89 (d, *J* = 8.7 Hz, 2 H, Ar), 7.17 (d, *J* = 8.7 Hz, 2 H, Ar), 7.24-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.0 (CH_3), 39.8 (C-6), 48.9 (C-7), 55.1 (CH_3O), 58.2 (C-3), 72.6 (C-2), 101.2 (C-7a), 113.7 (2 CH), 125.6 (2 CH), 127.4 (CH), 128.6 (2 CH), 129.3 (2 CH), 129.9 (C), 139.9 (C), 158.9 (C), 179.3 (C-5); *m*/*z* (EI) 307 (16), 222 (100), 139 (29), 105 (87); Exact mass Calcd for $C_{20}H_{21}NO_3$: 323.1521. Found: 323.1517.

(3*R*,7*S*,7a*S*)-7-(4-Methoxyphenyl)-7a-methyl-5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo [2,1-*b*]oxazole (9b). Colorless crystals, mp 110-112ºC; $[\alpha]^{22}_D$ –70 (*c* 0.5, CH_2Cl_2); IR (film) 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, assigned by COSY) δ 1.06 (s, 3 H, CH_3), 2.78 (dd, *J* = 16.0, 7.8 Hz, 1 H, H-7), 3.22 (dd, *J* = 16.0, 13.2 Hz, 1 H, H-6), 3.75 (dd, *J* = 13.2, 7.8 Hz, 1 H, H-7), 3.82 (s, 3 H, CH_3O), 4.22 (dd, *J* = 8.7, 6.6 Hz, 1 H, H-2), 4.67 (dd, *J* = 8.7, 8.0 Hz, 1 H, H-2), 5.24 (app t, *J* = 7.0 Hz, 1 H, H-3), 6.90 (d, *J* = 8.7 Hz, 2 H), 7.18-7.40 (m, 7 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.7 (CH_3), 38.1 (C-6), 52.1 (C-7), 55.2 (CH_3O), 57.4 (C-3), 73.9 (C-2), 102.2 (C-7a), 114.0 (2 CH), 125.7 (2 CH), 127.5 (CH), 128.6 (2 CH), 128.9 (2 CH), 139.4 (C), 158.9 (C), 175.2 (C-5); Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.20; H, 6.64; N, 4.31.

(3*R*,7*S*,7a*R*)-7-Ethyl-5-oxo-3,7a-diphenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole(10a). Colorless oil. $[\alpha]^{22}_D$ –44 (*c* 0.5, CH_2Cl_2); IR (film) 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz,

assigned by COSY) δ 0.94 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.42 (m, 1 H, CH_2), 1.92 (m, 1 H, CH_2), 2.28-2.40 (m, 2 H, H-6 and H-7), 3.04 (dd, *J* = 17.0, 8.5 Hz, 1 H, H-6), 3.90 (t, *J* = 9.0 Hz, 1 H, H-2), 4.60 (dd, *J* = 9.0, 8.0 Hz, 1 H, H-2), 5.15 (app t, *J* = 8.6 Hz, 1 H, H-3), 7.00-7.50 (m, 10 H, Ar); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.3 (CH_3), 22.3 (CH_2), 38.2 (C-6), 47.2 (C-7), 59.3 (C-3), 72.7 (C-2), 104.0 (C-7a), 125.3 (2 CH), 126.7 (2 CH), 127.2 (CH), 127.9 (CH), 128.2 (2 CH), 128.3 (2 CH), 128.4 (2 CH), 138.0 (C), 142.5 (C), 180.8 (C-5); *m*/*z* (EI) 307 (M^+, 19), 222 (100), 193 (29), 105 (75); Exact mass Calcd for $C_{20}H_{21}NO_2$: 307.1572. Found: 307.1555.

(3*R*,7*R*,7a*R*)-7-Ethyl-5-oxo-3,7a-diphenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole(10b). Colorless oil. $[\alpha]^{22}_D$ –36 (*c* 0.5, CH_2Cl_2); IR (film) 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, assigned by COSY) δ 0.70 (m, 1 H, CH_2), 0.79 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.21 (m, 1 H, CH_2), 2.61-2.77 (m, 3 H, H-6 and H-7), 3.87 (t, *J* = 9.0 Hz, 1 H, H-2), 4.70 (dd, *J* = 9.0, 7.8 Hz, 1 H, H-2), 5.11 (app t, *J* = 8.4 Hz, 1 H, H-3), 7.00-7.50 (m, 10 H, Ar); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.2 (CH_3), 24.1 (CH_2), 40.2 (C-6), 49.6 (C-7), 58.6 (C-3), 74.9 (C-2), 104.6 (C-7a), 126.4 (CH), 126.7 (2 CH), 127.4 (CH), 128.2 (4 CH), 128.3 (2 CH), 138.4 (C), 138.5 (C), 177.1 (C-5); *m*/*z* (EI) 307 (M^+, 1), 222 (30), 105 (100); Exact mass Calcd for $C_{20}H_{21}NO_2$: 307.1578. Found: 307.1576.

Ethyl (3*R*,7*R*,7a*S*)-5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole-7-acetate (13a). Colorless oil. $[\alpha]^{22}_D$ –85 (*c* 0.9, $CHCl_3$); IR (film) 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, assigned by COSY and HETCOR experiments) δ 1.26 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.24 (dd, *J* = 17.5, 5.7 Hz, 1 H, H-6), 2.48 (dd, *J* = 17.0, 7.0 Hz, 1 H, CH_2CO), 2.72 (dd, *J* = 17.0, 8.4 Hz, 1 H, CH_2CO), 2.94 (dd, *J* = 17.5, 9.6 Hz, 1 H, H-6), 3.14 (m, 1 H, H-7), 3.81 (dd, *J* = 8.7, 7.0 Hz, 1 H, H-2), 4.16 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.91 (dd, *J* = 8.7, 7.8 Hz, 1 H, H-2), 5.16 (app t, *J* = 7.2 Hz, 1 H, H-3), 5.31 (d, *J* = 6.0 Hz, 1 H, H-7a), 7.20-7.40 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$, 75.5 MHz, assigned by COSY and HETCOR experiments) δ 14.1 (CH_3), 31.1 (C-7), 34.0 (CH_2CO), 37.1 (C-6), 58.6 (C-3), 60.6 (CH_2O), 74.1 (C-2), 93.1 (C-7a), 125.7 (C-*m*), 127.6 (C-*p*), 128.7 (C-*o*), 139.5 (C-*i*), 171.7 (CO_2), 179.3 (C-5); *m*/*z* (EI) 289 (29), 259 (100), 244 (44), 172 (64), 144 (88), 120 (100), 104 (70); Exact mass Calcd for $C_{16}H_{19}NO_4$: 289.1314. Found: 289.1308.

Ethyl (3*R*,7*S*,7a*S*)-5-oxo-3-phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]oxazole-7-acetate (13b). Colorless oil. $[\alpha]^{22}_D$ –85 (*c* 0.8, $CHCl_3$); IR (film) 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 3 H, CH_3), 2.50-2.90 (m, 5 H, C-6, C-7 and CH_2CO), 3.87 (dd, *J* = 8.5, 7.0 Hz, 1 H, H-2), 4.18 (q, *J* = 7.2 Hz, 2 H, CH_2O), 4.57 (dd, *J* = 8.5, 7.8 Hz, 1 H, H-2), 5.10 (d, *J* = 3.3 Hz, 1 H, H-7a), 5.12 (app t, *J* = 7.2 Hz, 1 H, H-3), 7.20-7.40 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.2 (CH_3), 36.0 (C-7), 37.3 (CH_2CO), 38.7 (C-6), 57.7 (C-3), 60.9 (CH_2O), 74.8 (C-2), 125.8 (2 CH), 127.7 (CH), 128.8 (2 CH), 139.3 (C), 171.0 (CO_2), 177.4 (C-5); *m*/*z* (EI) 289 (M^+, 16), 259 (64), 144 (80), 120 (100); Exact mass Calcd for $C_{16}H_{19}NO_4$: 289.1314. Found: 289.1311.

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