

# New Route to Synthesize Enantiopure 6-Methyl and 6-Ethyl Bicyclic Lactams Derived from (*R*)-(-)-2-Phenylglycinol

Ana M. Lumbreras,<sup>1</sup> Dino Gnecco,\*<sup>1</sup> Joel L. Terán,<sup>1</sup> Jorge Juárez,<sup>1</sup> Ma. Laura Orea,<sup>1</sup> Raúl G. Enríquez<sup>2</sup> and Simón Hernández<sup>2</sup>

<sup>1</sup> Centro de Química, Instituto de Ciencias, Benemérita Universidad Autónoma de Puebla. Lab. Síntesis Orgánica. Edificio 194. Complejo de Ciencias, Ciudad Universitaria. C.P. 72570 Puebla, Pue. México. \*dgnecco@siu.buap.mx.

<sup>2</sup> Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, México, D.F. 04510.

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**Abstract:** The diastereoselective synthesis of bicyclic lactams (-)-(3*R*,6*S*,8*aS*)-6-methyl- and -6-ethyl-3-phenyl-hexahydrooxazol[3,2-*a*]pyridin-5-ones **4(a-b)** and (-)-(3*R*,6*R*,8*aS*)-6-methyl-3-phenyl-hexahydrooxazol[3,2-*a*]pyridin-5-one **4'a** are described.

**Keywords:** Enantiopure bicyclic lactams.

**Resumen:** Se describe la síntesis diastereoselectiva de las biciclo lactamas (-)-(3*R*,6*S*,8*aS*)-6-metil- y -6-etil-3-fenil-hexahidrooxazol[3,2-*a*]piridin-5-onas **4(a-b)**, y la (-)-(3*R*,6*R*,8*aS*)-6-metil-3-fenil-hexahidrooxazol[3,2-*a*]piridin-5-ona **4'a**.

**Palabras clave:** Biciclo lactamas enantiopuras.

## Introduction

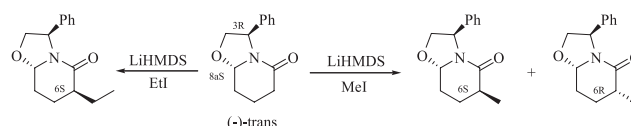
The development of new routes to synthesize chiral 6-alkyl substituted bicyclic lactams derived from 2-phenylglycinol continues to be a topic of significant interest. In this way, Amat and co-workers [1] reported that the treatment of the (-)-*trans* bicyclic lactam with LiHMDS in presence of methyl iodide gave the mixture of diastereomers (-)-(3*R*,6*S*/6*R*,8*aS*)-6-methyl-3-phenyl-hexahydrooxazol[3,2-*a*]pyridin-5-ones in a 85:15 ratio and with 89% yield, while with ethyl iodide afforded exclusively the diastereomer (-)-(3*R*,6*S*,8*aS*)-6-ethyl-3-phenyl-hexahydrooxazol[3,2-*a*]pyridin-5-one in 83% yield. Scheme 1.

Now, we report a new route to synthesize these compounds starting from (-)-(1'*R*)-1-(2'-hydroxy-1'-phenylethyl)-3-methylpyridin-2(1*H*)-one **1a** and (-)-(1'*R*)-1-(2'-hydroxy-1'-phenylethyl)-3-ethylpyridin-2(1*H*)-one **1b** respectively.<sup>2</sup>

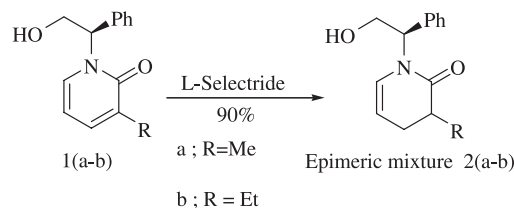
## Results and discussion

Firstly, we carried out the partial reduction of **1(a-b)** to generate the corresponding endocyclic enamides [3]. A solution of **1(a-b)** in THF was treated with L-Selectride® to afford the corresponding epimeric mixture of endocyclic enamides (1'*R*,3*S*/3*R*)-1-(2'-hydroxy-1'-phenylethyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one **2a** and (1'*R*,3*S*/3*R*)-1-(2'-hydroxy-1'-phenylethyl)-3-ethyl-3,4-dihydro-1*H*-pyridin-2-one **2b** approximately in a 60:40 and 90:10 ratio (as determined by <sup>1</sup>H NMR) and with 90% yield respectively [4]. Scheme 2.

Epimeric mixture **2a** was separated by column chromatography (SiO<sub>2</sub>, petroleum ether: AcOEt = 60:40) to give the enamide **3a** in 52% yield [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 149.5 (*c* 3.0 CH<sub>2</sub>Cl<sub>2</sub>), and **3'a** in 34% yield [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 10.9 (*c* 3.0 CH<sub>2</sub>Cl<sub>2</sub>). Attempted separation of **2b** provided exclusively the enamide **3b** in 80% yield [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 154.8 (*c* 1.0 CH<sub>2</sub>Cl<sub>2</sub>). Then, to a solution of **3(a-b)** and **3'a** in anhydrous CHCl<sub>3</sub> was added a catalytic amount of dry



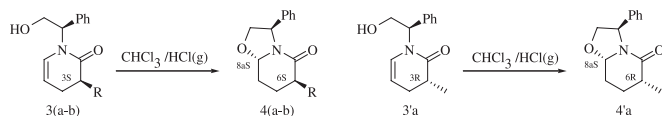
Scheme 1.



Scheme 2.

gaseous hydrochloric acid and stirred at room temperature for 1 hour to afford the bicyclic lactams **4(a-b)** and **4'a** in 90% yield after purification by column [5]. NMR spectral data of **4(a-b)** are in agreement with those reported for *trans* H<sub>3</sub>-H<sub>8a</sub> bicyclic lactams with configuration *S* on C-6 [6]. Optical rotation of **4a** [lit. [6] [ $\alpha$ ]<sub>D</sub><sup>20</sup> -104.7 (*c* 1.0 EtOH); observed [ $\alpha$ ]<sub>D</sub><sup>20</sup> -102.3 (*c* 1.0 EtOH) and **4b** [lit. [6] [ $\alpha$ ]<sub>D</sub><sup>20</sup> -103 (*c* 1.0 EtOH); observed [ $\alpha$ ]<sub>D</sub><sup>20</sup> -100.4 (*c* 1.0 EtOH)]. These results were sufficient to conclude that the configuration on C-3 was *S* for the compounds **3(a-b)**. In addition, NMR spectral data of **4'a** ([ $\alpha$ ]<sub>D</sub><sup>20</sup> -92.5 (*c* 1.02 EtOH)) were enough to deduce that this bicyclic lactam is *trans* H<sub>3</sub>-H<sub>8a</sub>. Compound **4'a** was crystallized from *n*-hexane-dichloromethane and by X-ray crystallographic analysis<sup>7</sup> was confirmed the absolute configuration *R* on C-6. Scheme 3. Figure 1.

To explain the stereochemical implications observed in the reaction of enamides with HCl, we propose that the dry gaseous hydrochloric acid interacts with the  $\pi$ -cloud of the



Scheme 3.

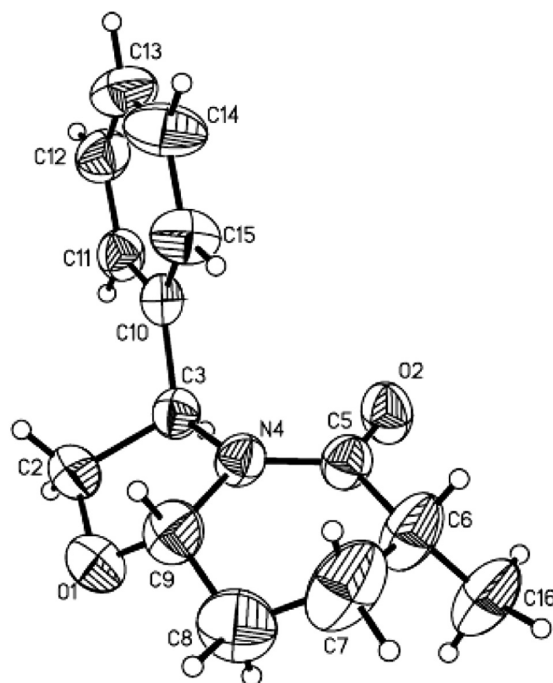


Fig. 1. X-Ray structure 4'a.

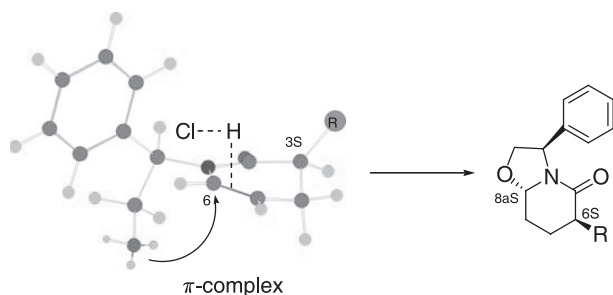


Figure 2.

alkene double bond to generate the  $\pi$ -complex and then, the hydroxyl function of 2-phenylethanol attacks intramolecularly to C-6 for the side less hindered to produce exclusively the bicyclic lactam *trans*. Figure 2.

## Conclusion

In summary, this work contributes with a new and easy methodology to synthesize the enantiopure *trans* bicyclic lactams in

good overall yields. The essential feature of our synthesis compared with the Amat's synthesis is the preparation of enantiopure endocyclic enamides, which could be used as starting material to generate other intermediates.

## Experimental

$^1\text{H}$  NMR spectra were recorded at 300 and 400 MHz, and  $^{13}\text{C}$ -NMR spectra at 75 and 100 MHz (tetramethylsilane as internal reference). IR spectra were obtained with a Nicolet FT-IR Magna 750 spectrometer. Optical rotations were determined at room temperature with a Perkin-Elmer 341 polarimeter, using a 1 dm cell with a total volume of 1 mL and are referenced to the D-line of sodium. X-ray diffractometer Bruker Smart APEX AXS CCD. Mass spectra were recorded with a Jeol JEM-AX505HA instrument at a voltage of 70 eV.

### Preparation of pure diastereomers 3(a-b) and 3'a

**General Procedure.** A solution of 1(a-b) (4.3 mmol) in THF (40 mL) at  $0^\circ\text{C}$  was added slowly a solution of L-Selectride (1 M in THF, 8.6 mmol). The resulting mixture was stirred at room temperature for 12 h and a brine solution (5 mL) was added. After, the reaction was treated with  $\text{H}_2\text{O}_2$  (4.0 mL, 30%) and with a solution of NaOH (5 mL, 1 M) finally, the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL) and the combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography ( $\text{SiO}_2$ , petroleum ether: ethyl acetate = 1:1) to give the diastereomeric mixtures 2a and 2b in a 60:40 and 90:10 ratio and with 90% yield respectively. Finally, separation of the diastereomeric mixture 2a and 2b by column chromatography ( $\text{SiO}_2$ , petroleum ether: ethyl acetate = 60:40) afforded 3a (52%), 3'a (32%) and 3b in 80% yield respectively.

**(-)-(1'R,3S)-1-(2'-Hydroxy-1'-phenylethyl)-3-methyl-3,4-dihydro-1H-pyridin-2-one 3a.** Yellow oil. IR (KBr,  $\text{cm}^{-1}$ ): 3426, 2950, 1647.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm, *J* Hz): 1.22 (d, 3H-7, 6.8), 1.99-2.08 (m, 1H-4), 2.36-2.40 (m, 1H-4), 2.60-2.66 (m, 1H-3), 3.22 (broad, OH), 3.99-4.04 (m 1H-2'), 4.11-4.16 (m 1H-2'), 5.09-5.14 (m 1H-5), 5.83 (dd, 8.4, 5.6, 1H-1'), 6.02 (d, 7.6, 1H-6) 7.22-7.35 (m, 5H-Ph).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ): 15.87 (C-7), 27.69 (C-4), 35.69 (C-3), 56.99 (C-1'), 62.33 (C-2'), 105.94 (C-5), 125.92 (C-6), 127.32-128.61 (5C-Ph), 137.36 ( $\text{C}_{\text{ipso}}$ ), 173.73 (C=O). HRMS (FAB) calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_2$ : 231,2903; found: 231.2898.

**(-)-(1'R,3R)-3-Methyl-1-(2'-hydroxy-1'-phenylethyl)-3,4-dihydro-1H-pyridin-2-one 3'a.** Yellow oil. IR (KBr,  $\text{cm}^{-1}$ ): 3418, 2945, 1646.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm, *J* Hz): 1.25 (d, 3H-7, 6.8), 2.07-2.16 (m, 1H-4), 2.29-2.36 (m, 1H-4), 2.56-2.62 (m, 1H-3), 3.10 (broad, OH), 3.98-4.04 (m 1H-2'), 4.11-4.15 (m 1H-2'), 5.11-5.15 (m 1H-5), 5.85 (dd, 8.4, 5.6, 1H-1'), 5.98 (d, 7.6, 1H-6) 7.25-7.35 (m, 5H-Ph).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ): 15.76 (C-7), 27.91 (C-4), 35.74 (C-3),

57.05 (C-1'), 62.53 (C-2'), 106.40 (C-5), 125.95 (C-6), 127.50-128.62 (5C-Ph), 137.12 (C<sub>ipso</sub>), 173.66 (C=O) HRMS (FAB) calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>: 231,2903; found: 231.2898.

(-)-(1'*R*,3*S*)-3-Ethyl-1-(2'-hydroxy-1' phenylethyl)-3,4-dihydro-1*H*-pyridin-2-one **3b**. IR (KBr, cm<sup>-1</sup>): 3420, 2966, 1645. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN) δ (ppm, *J* Hz): 0.93 (t, 7.2, 3H-8), 1.40-1.48 (m, 2H-7), 2.02-2.08 (m, 1H-4), 2.34-2.42 (m, 1H-3, 1H-4), 3.25 (broad, OH), 3.92-4.00 (m 2H-2'), 5.07-5.10 (m, 1H-5), 5.68 (dd, 6.0, 8.0, 1H-1'), 6.10 (d, 7.6, 1H-6) 7.23-7.33 (m, 5H-Ph). <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>CN): 11.85 (C-8), 23.68 (C-7), 25.33 (C-4), 42.92 (C-3), 57.33 (C-1'), 62.17 (C-2'), 105.61 (C-5), 117.72 (C-6), 126.61-129.0 (5C-Ph), 139.17 (C<sub>ipso</sub>), 172.52 (C=O). HRMS (FAB) calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>2</sub>: 245,3169; found: 245,3155.

### Preparation of *trans* bicyclic lactams **4(a-b)** and **4'a**

**General Procedure.** To a solution either of **3(a-b)** or **3'a** (2.0 mmol) in CHCl<sub>3</sub> (10 mL) at room temperature was added catalytic amounts of dry HCl (g) and the solution was stirred for 1 h. Finally, the solvent was removed to give **4(a-b)** and **4'a** in 90% yield respectively after purification by column (SiO<sub>2</sub>, AcOEt: Petroleum ether = 4:6).

(-)-(3*R*,6*R*,8*aS*)-6-methyl-3-phenyl hexahydrooxazolo[3,2-*a*]pyridin-5-one **4'a**. Colorless crystal mp 112-114°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm, *J* Hz): 1.25 (d 3H-9, 7.2), 1.64-1.80 (m 1H-7, 1H-8), 1.89-1.98 (m, 1H-7), 2.18-2.25 (m, 1H-8), 2.50-2.56 (m, 1H-6), 3.76 (dd, 9.0, 7.5, 1H-2), 4.61 (dd, 9.0, 8.1 1H-2), 5.09 (dd, 7.5, 4.5, 1H-8a), 5.26 (*app* t, 7.8, 7.5 1H-3) 7.25-7.35 (m, 5H-Ph). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 17.36 (C-9), 24.44 (C-7), 25.17 (C-8), 34.75 (C-6), 58.20 (C-3), 72.25 (C-2), 88.45 (C-8a), 126.19-128.68 (5C-Ph), 139.72 (C<sub>ipso</sub>), 172.38 (C=O).

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7. Crystallographic data of **4'a** have been deposited with the Cambridge Crystallographic Data Centre CCDC 618864. Copies of the data can be obtained, free charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK e-mail: deposit@ccdc.cam.ac.uk