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

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Abstract: The diastereoselective synthesis of bicyclic lactams (-)-(3R,6S,8aS)-6-methyl- and -6-ethyl-3-phenyl-hexahydrooxazolo[3,2-a]pyridin-5-ones 4(a-b) and (-)-(3R,6R,8aS)-6-methyl-3-phenyl-hexahydrooxazolo[3,2-a]pyridin-5-one 4′a are reported. A solution of (-)-(1′R)-1-(2′-hydroxy-1′-phenylethyl)-3-methylpyridin-2(1H)-one 1a and (-)-(1′R)-1-(2′-hydroxy-1′-phenylethyl-3-ethylpyridin-2(1H)-one 1b respectively was treated with L-Selectride® to afford the corresponding endocyclic enamides 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(1H)-one 1a and (-)-(1′R)-1-(2′-hydroxy-1′-phenylethyl-3-ethylpyridin-2(1H)-one 1b respectively.2

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,3S/3R)-1-(2′-hydroxy-1′-phenylethyl)-3-methyl-3,4-dihydro-1H-pyridin-2-one 2a and (1′R,3S/3R)-1-(2′-hydroxy-1′-phenylethyl)-3-ethyl-3,4-dihydro-1H-pyridin-2-one 2b approximately in a 60:40 and 90:10 ratio (as determined by 1H NMR) and with 90% yield respectively [4]. Scheme 2.

Epimeric mixture 2a was separated by column chromatography (SiO₂, petroleum ether: AcOEt = 60:40) to give the enamide 3a in 52% yield [α]D 20 = −149.5 (c 3.0 CHCl₃) and 3′a in 34% yield [α]D 20 = −10.9 (c 3.0 CHCl₃). Attempted separation of 2b provided exclusively the enamide 3b in 80% yield [α]D 20 = −154.8 (c 1.0 CHCl₃). Then, to a solution of 3(a-b) and 3′a in anhydrous CHCl₃ was added a catalytic amount of dry 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 H₃-H₃ bicyclic lactams with configuration S on C-6 [6]. Optical rotation of 4a [lit. [6] [α]D 20 = 104.7 (c 1.0 EtOH); observed [α]D 20 = 102.3 (c 1.0 EtOH) and 4b [lit. [6] [α]D 20 = −103 (c 1.0 EtOH); observed [α]D 20 = 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 ([α]D 20 = 92.5 (c 1.02 EtOH)) were enough to deduce that this bicyclic lactam is trans H₃-H₃. Compound 4′a was crystallized from n-hexane-dichloromethane and by X-ray crystallographic analysis 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 π-cloud of the...
alkene double bond to generate the π-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 an easy methodology to synthesize the enantiopure trans bicyclic lactams in good overall yields. The essential feature of our synthesis compare with the Amat’s synthesis is the preparation of enantiopure endocyclic enamides, which could be used as starting material to generate other intermediates.

**Experimental**

\(^1\)H NMR spectra were recorded at 300 and 400 MHz, and \(^1\)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 °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 H₂O₂ (4.0 mL, 30%) and with a solution of NaOH (5 mL, 1 M) finally, the mixture was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated \(\text{in vacuo}\). The residue was purified by flash chromatography (SiO₂, 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 (SiO₂, petroleum ether: ethyl acetate = 60:40) afforded 3a (52%), 3’a (32%) and 3b in 80% yield respectively.

\((-\)-(1’\(R\),3\(S\))-1-(2’-Hydroxy-1’-phenylethyl)-3-methyl-3,4-dihydro-1\(H\)-pyridin-2-one 3a. Yellow oil. IR (KBr, cm⁻¹): 3426, 2950, 1647. \(^1\)H NMR (400 MHz, CDCl₃) δ (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). \(^1\)C NMR (100 MHz, CDCl₃): 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 (C₆), 173.73 (C=O). HRMS (FAB) calcd for C₁₄H₁₇NO₂: 231.2903: found: 231.2898.

\((-\)-(1’\(R\),3\(R\))-3-Methyl-1-(2’-hydroxy-1’-phenylethyl)-3,4-dihydro-1\(H\)-pyridin-2-one 3’a. Yellow oil. IR (KBr, cm⁻¹): 3426, 2950, 1647. \(^1\)H NMR (400 MHz, CDCl₃) δ (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’), 6.02 (d, 7.6, 1H-6) 7.25-7.35 (m, 5H-Ph). \(^1\)C NMR (100 MHz, CDCl₃): 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 (C₆), 173.73 (C=O). HRMS (FAB) calcd for C₁₄H₁₇NO₂: 231,2903: found: 231.2898.
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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_{ipso}), 173.66 (C=O) HRMS (FAB) calcd for C_{14}H_{17}NO_{2}: 231,2903: found: 231.2898.

(−)-(1'R,3S)-3-Ethyl-1-(2'-hydroxy-1' phenylethyl)-3,4-dihydro-1'H-pyridin-2-one 3b.

IR (KBr, cm⁻¹): 3420, 2966, 1645. ¹H NMR (400 MHz, CD₃CN) 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). ¹³C NMR (100 MHz, CD₃CN): 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_{ipso}), 172.52 (C=O). HRMS (FAB) calcd for C_{15}H_{19}NO_{2}: 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 CHCl₃ (10 mL) at room temperature was added cat-alytic 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 (SiO₂, AcOEt: Petroleum ether = 4:6).

(-)-(3'R,6'R,8aS)-6-methyl-3-phenyl hexahydrooxazolo[3,2-a]pyridin-5-one 4'a. Colorless crystal mp 112-114°C. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃): 17.36 (C-9), 24.44 (C-7), 25.17 (C-3), 34.75 (C-6), 58.20 (C-8a), 72.25 (C-2), 88.45 (C-8a), 126.19-128.68 (5C-Ph), 139.72 (C_{ipso}), 172.38 (C=O).

Acknowledgements

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References

3. Mabic, S.; Castagnoli, Jr., N. J. Org. Chem. 1996, 61, 309-313. 4. The so different diastereomeric ratios observed for epimeric mixtures 2a (60:40) and 2b (90:10) could be associated the size of the substituent at C-3.
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.