

## Syntheses of pyridin-4-ylum chions: applications in a synthesis of (+)-coniine

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**Abstract**—The compounds (3*R*,5*S*)-(+)-5-methyl-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridin-4-ylum iodide **4** and (3*R*,5*S*)-(+)-5-*n*-propyl-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridin-4-ylum iodide **5** were synthesized in two steps starting from the bicyclic thiolactam *trans*-(3*R*,2*aS*)-(-)-5-thio-3-phenyl-2,3,6,7,8,2*a*-hexahydro-oxazolo[3,2-*a*]pyridine **1**. In addition, starting from **5** an enantiospecific synthesis of (+)-coniine **7** was achieved.

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### 1. Introduction

Bicyclic lactams such as **A** and **B** permit the stereocontrolled introduction of a substituent at the  $\alpha$  position and have been used as effective starting material in the asymmetric synthesis of alkaloids (Scheme 1).<sup>1–3</sup>

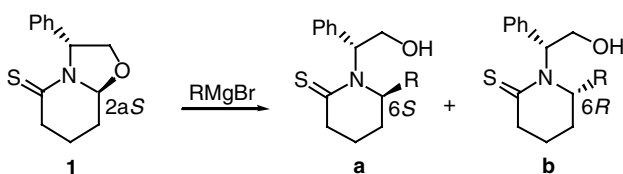
Previously, we described a preparation of the thiolactam *trans*-(3*R*,2*aS*)-(-)-5-thio-3-phenyl-2,3,6,7,8,2*a*-hexahydro-oxazolo[3,2-*a*]pyridine **1**.<sup>4</sup> Herein we report the reactions of this thiolactam with Grignard reagents to generate 6-alkylpiperidin-2-thiones and the reactivity of the reaction products with methyl iodide.

### 2. Results and discussion

Firstly, we investigated the reaction of the thiolactam *trans*-(3*R*,2*aS*)-(-)-5-thio-3-phenyl-2,3,6,7,8,2*a*-hexahydro-oxazolo[3,2-*a*]pyridine **1** with MeMgCl and *n*-propylMgCl in anhydrous THF at  $-20^\circ\text{C}$ , which required

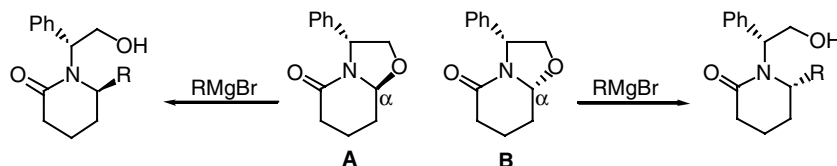
only 2 h to give the corresponding diastereoisomeric mixture 6-methyl-piperidin-2-thiones **2a** and **2b** and 6-*n*-propyl-piperidin-2-thiones **3a** and **3b**, in 95% and 90% yield, respectively. The diastereoisomeric mixtures were subjected to column chromatography furnishing the diastereoisomers **2a** and **3a** in 80% yield, respectively (Table 1).

Table 1



Entry	RMgBr	Products	R	Yield (%)	a:b ratio <sup>a</sup>
1	CH <sub>3</sub> MgCl	<b>2a+2b</b>	CH <sub>3</sub>	95	97:3
2	<i>n</i> -PrMgCl	<b>3a+3b</b>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	90	95:5

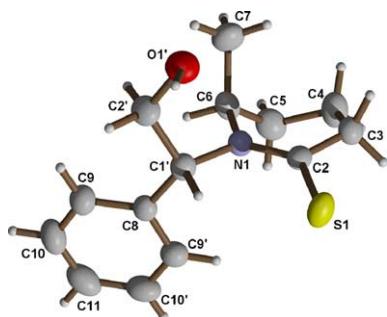
<sup>a</sup> Determined by <sup>1</sup>H NMR.



Scheme 1.

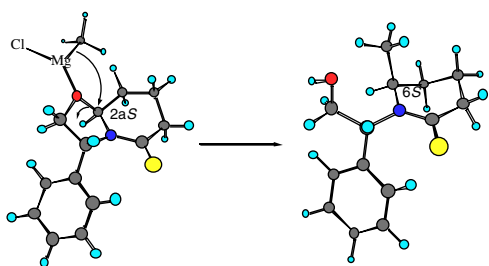
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Fortunately, **2a** can be crystallized from chloroform and its X-ray diffraction analysis was performed. The absolute configuration of the new stereogenic center C-6 of the major diastereoisomer **2a** was determined as (*S*), based on the auxiliary stereocenter, which is C-(1'*R*); [source of chirality: (*R*)-(-)-2-phenylglycinol]. Therefore, we concluded that the absolute configuration of C-6 of the main product **3a** was (*S*) (Fig. 1).

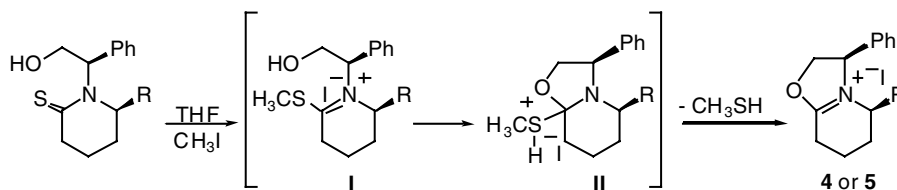


**Figure 1.** Crystal structure of **2a** with thermal ellipsoids at 30% probability level (non-H atoms). Minor disordered positions for the hydroxyl group has been omitted for clarity.

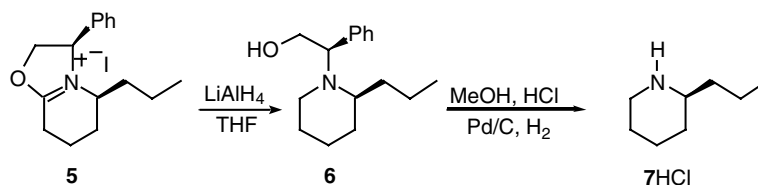
The high stereoselectivity observed in this process can be explained if the magnesium coordinate with the oxygen of the oxazolidine causing the alkyl group to attack from the same face the C–O bond.<sup>5</sup> (Fig. 2).



**Figure 2.**

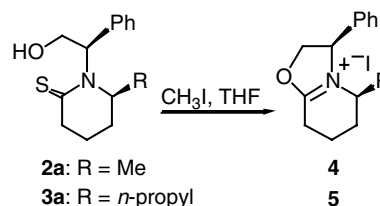


**Scheme 3.**



**Scheme 4.**

In the second part of this work, we studied the reaction of the thione function of **2a** and **3a** with iodomethane, without a previous protection of the hydroxyl group.<sup>6</sup> For this purpose, a solution of these compounds in THF were treated with a large excess of iodomethane at room temperature.<sup>7</sup> After 4 h of stirring, the solvent and unreacted iodomethane were removed in vacuo, giving **4** and **5** in quantitative yield, respectively. The structures of these compounds were determined by <sup>1</sup>H and <sup>13</sup>C NMR (Scheme 2).



**Scheme 2.**

This result could be explained by the nucleophilic attack of the hydroxyl group on the C-2 of the methylsulfanyl intermediate I to give the sulfonium II, which by elimination of the methanethiol group furnishes the 5-alkylhexahydro-oxazolo[3,2-*a*]pyridin-4-ylum iodide **4** or **5** (Scheme 3).

Finally, to corroborate the absolute configuration assigned as (C-6*S*) for compound **3a**, we synthesized the coniine, using as starting material the enantiopure compound **5**. For this purpose, this compound was refluxed in THF in presence of LiAlH<sub>4</sub> to produce **6**<sup>8</sup> as a single isomer in quantitative yield. Finally, the 2-phenylethanol auxiliary of **6** was removed by catalytic hydrogenation, furnishing (*S*)-(+)-coniine **7 HCl**<sup>9</sup> in quantitative yield (Scheme 4).

In conclusion, starting from **1** we have described an easy access to compounds **2a** and **3a** in high yields and with a remarkable diastereoselectivity. In addition, we have found that these compounds can be easily converted into the corresponding pyridin-4-ylum iodide.

We are currently continuing our exploration of the synthetic potential of these useful building blocks towards asymmetric synthesis.

### 3. Experimental

#### 3.1. General

$^1\text{H}$  NMR spectra of  $\text{CDCl}_3$  solutions were recorded with a Varian Unity instrument at 400 MHz (internal tetramethylsilane as reference). IR spectra were obtained with a Nicolet FT-IR Magna 750 spectrometer. Chromatography was carried out using  $\text{SiO}_2$ . 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. Mass spectra were recorded with a JEOL JEM-AX505HA instrument at a voltage of 70 eV. Melting points were determined using a Fisher–Johns apparatus and are uncorrected.

#### 3.2. Reaction of thiolactam *trans*-1 with $\text{MeMgCl}$ and $n\text{-PrMgCl}$

**3.2.1. General procedure.** A solution of **1** (1 equiv) in anhydrous THF (5 mL) was added to a solution of the corresponding Grignard reagent (3 equiv) in THF at  $-20^\circ\text{C}$ . The reaction mixtures were stirred at this temperature during 2 h. The reaction was quenched by addition of saturated aqueous ammonium chloride, and the mixture was extracted with  $\text{AcOEt}$  ( $3 \times 20$  mL). The combined organic extracts were dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo to give the corresponding mayor products **2a** and **3a** in 80%, respectively, after purification by column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH} = 95:5$ ).

**3.2.2. (1*R*,6*S*)-(–)-1-(2'-Hydroxy-1'-phenyl-ethyl)-6-methyl-piperidine-2-thione **2a**.** White solid. Mp  $107\text{--}110^\circ\text{C}$   $[\alpha]_{\text{D}}^{20} = -172.2$  ( $c$  1.1,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr,  $\text{cm}^{-1}$ ) 3387, 2945, 1480.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm,  $J$  Hz): 7.28–7.42 (m, 5H, 1H-1'), 4.38 (dd, 6.0, 1H-2'), 4.26 (m, 1H-2'), 3.57 (m, 1H-6), 3.31 (m, 1H-3), 3.11 (m, 1H-3), 1.98 (m, 1H-5, 1H-4), 1.70 (m, 1H-5), 1.53 (m, 1H-4), 1.30 (t, 6.8, 3H-7).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 203.04 (C-2), 135.44 (1C), 128.62–127.38 (5C), 64.35 (C-1'), 61.91 (C-2'), 50.29 (C-6), 40.02 (C-3), 28.81 (C-5), 19.11 (C-4), 16.24 (C-7). HRMS (FAB+): Calcd for  $\text{C}_{14}\text{H}_{19}\text{NOS}$ : 249.1187; found: 249.1176.

**3.2.2.1. Crystal structure of **2a**.** Colorless, irregular crystal,  $0.5 \times 0.3 \times 0.2$  mm<sup>3</sup>,  $\text{C}_{19}\text{H}_{14}\text{NOS}$ . Orthorhombic,  $\text{P}2_12_12_1$ ,  $a = 9.8878(12)$ ,  $b = 10.5398(10)$ ,  $c = 13.0296(13)$  Å,  $Z = 4$ ,  $\rho_{\text{calc}} = 1.220$  g cm<sup>-3</sup>. A set 3318 reflections was collected at  $T = 296(1)$  K using Mo- $K_\alpha$  radiation ( $\lambda = 0.71073$  Å, Bruker P4 diffractometer), corresponding to  $2\theta_{\text{max}} = 50^\circ$ . Raw data were corrected

for absorption and 2062 independent reflections ( $R_{\text{int}} = 2.71\%$ ) were used for the refinement of 165 parameters, without neither restraints nor constraints (SHELXTL 5.10 package). The hydroxyl group is disordered over two positions, O1 and O1', with site occupation factors 0.331(6) and 0.669(6), respectively. Disordered H atoms for this hydroxyl group were found on difference maps, while remaining H atoms were placed on idealized positions. All H atoms were refined using a riding model. Final  $R$  indices:  $R_1 = 4.10\%$  for 1522 reflections with  $I > 2\sigma(I)$  and  $wR_2 = 10.34\%$  for all data. The correctness of the absolute configuration was checked on the basis of a refined Flack parameter:  $x = -0.11(13)$ . A CIF file has been deposited with the CCDC (Deposition number 223087) and structure factors are available on request.

**3.2.3. (1*R*,6*S*)-(–)-1-(2'-Hydroxy-1'-phenyl-ethyl)-6-*n*-propyl-piperidine-2-thione **3a**.** Yellow oil.  $[\alpha]_{\text{D}}^{20} = -107.2$  ( $c$  3.9,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr,  $\text{cm}^{-1}$ ) 3419, 2956, 1475.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm,  $J$  Hz): 7.27–7.43 (m, 5H, 1H-1'), 4.38 (dd, 6.0, 1H-2'), 4.22 (dd, 10.4, 6.0, 1H-2'), 3.33 (m, 1H-3, 1H-6), 3.05 (m, 1H-3), 2.83 (OH), 1.83 (m, 1H-4), 1.72 (m, 1H-4, 2H-7, 1H-5), 1.26 (m, 2H-8, 1H-5), 0.90 (t, 7.2, 3H-9).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 203.30 (C-2), 135.42 (1C), 128.65–127.45 (5C), 64.46 (C-1'), 62.12 (C-2'), 54.73 (C-6), 40.06 (C-3), 34.41 (C-4), 24.71 (C-7), 19.98 (C-5), 16.24 (C-8), 13.91 (C-9). HRMS (FAB+): Calcd for  $\text{C}_{16}\text{H}_{23}\text{NOS}$ : 277.1500; found: 277.1488.

**3.2.4. Synthesis of (3*R*,5*S*)-(–)-5-alkyl-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridin-4-ylum iodide. General procedure.** To a solution of **2a** or **3a** in anhydrous THF at  $5^\circ\text{C}$  was added dropwise an excess of  $\text{CH}_3\text{I}$  in THF. The resulting mixture was stirred for 4 h at room temperature, then the solvent was removed in vacuo and the corresponding pyridin-4-ylum iodide **4** and **5** were obtained in quantitative yield, respectively.

**3.2.5. (3*R*,5*S*)-(–)-5-methyl-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo [3,2-*a*]pyridin-4-ylum iodide **4**.** Yellow oil.  $[\alpha]_{\text{D}}^{20} = +11.8$  ( $c$  1.0, MeOH); IR (KBr;  $\text{cm}^{-1}$ ) 3445, 1645, 1480.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm,  $J$  Hz): 7.46–7.53 (m, 5H), 5.87 (dd, 7.2, 6.8, 1H-3), 5.65 (dd, 9.2, 8.8, 1H-2), 4.65 (dd, 7.2, 1H-2), 4.37 (m, 5.6, 1H-5), 3.13 (m, 2H-8), 2.45 (m, 1H-7), 2.27 (m, 1H-7), 2.06 (m, 1H-6), 1.78 (m, 1H-6), 0.85 (t, 6.4, 3H-9).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 177.08 (C-2a), 135.95 (1C), 130.13–127.79 (5C), 78.77 (C-2), 66.99 (C-3), 55.00 (C-5), 29.36 (C-8), 25.37 (C-7), 19.74 (C-9), 15.30 (C-6). HRMS (FAB+): Calcd for  $\text{C}_{14}\text{H}_{18}\text{NO}^+$ : 216.1388; found: 216.1376.

**3.2.6. (3*R*,5*S*)-(–)-5-*n*-propyl-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridin-4-ylum iodide **5**.** Yellow oil.  $[\alpha]_{\text{D}}^{20} = +9.2$  ( $c$  1.0, MeOH); IR (KBr,  $\text{cm}^{-1}$ ) 3405, 1648, 1460, 702.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm,  $J$  Hz): 7.47–7.61 (m, 5H), 5.90 (dd, 7.2, 1H-3), 5.66 (dd,

10.0, 9.6, 1H-2), 4.80 (dd, 9.6, 7.4, 1H-2), 4.37 (m, 1H-5), 3.15 (m, 2H-8), 2.43 (m, 1H-7), 2.18 (m, 1H-7), 2.06 (m, 1H-6), 1.87 (m, 1H-6), 0.80–1.21 (m, 2H-9, 2H-10), 0.54 (t, 6.4, 3H-11).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 178 (C-2a), 134.97 (1C), 130.10–127.83 (5C), 78.41 (C-2), 67.25 (C-3), 58.82 (C-5), 33.73 (C-8), 29.51 (C-7), 24.82 (C-9), 18.67 (C-10), 15.30 (C-6), 13.28 (C-11). HRMS (FAB+): Calcd for  $\text{C}_{16}\text{H}_{22}\text{NO}^+$ : 244.1701; found: 244.1690.

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