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Controlled reduction of 5-alkyl-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridin-4-ylium iodide: enantioselective synthesis of (−)-dihydropinidine and (+)-indolizidine 167B

Luis F. Roa, Dino Gnecco,* Alberto Galindo and Joel L. Terán

Centro de Química del Instituto de Ciencias, BUAP, C.P. 72570, Ciudad Universitaria Puebla, Pue., Mexico

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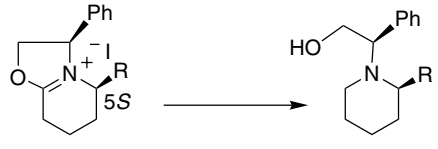
Abstract—A controlled reduction of (+)-(3*R*,5*S*)-5-methyl- and (+)-(3*R*,5*S*)-5-*n*-propyl-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridin-4-ylium iodide **1** and **2** to generate (3*R*,5*S*)-5-methyl- and (3*R*,5*S*)-5-*n*-propyl-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridine **3** and **4**, respectively, is reported. In addition, an enantioselective synthesis of (−)-(2*R*,6*S*)-dihydropinidine and (+)-(2*S*,6*S*)-indolizidine 167B starting from **3** and **4**, respectively, was achieved.

1. Introduction

In a previous publication[1] we described the synthesis of **1** and **2**. In addition, we reported that the iminium function of these compounds in the presence of $NaBH_4$ or $LiAlH_4$ gave the opening structure (2*R*,2′*S*)-2-(2′-methyl-piperidin-1′-yl)-2-phenyl-ethanol **I** and (2*R*,2′*S*)-2-(2′-*n*-propyl-piperidin-1′-yl)-2-phenyl-ethanol **II**, respectively (Scheme 1).

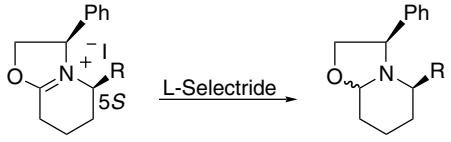


1, R = Me — **I**
2, R = *n*-propyl — **II**

Scheme 1.

2. Results and discussion

Enantiopure compounds **1** and **2** are synthetically useful after a controlled reduction of the iminium function. Herein, we report an efficient reduction of this function with L-Selectride[2] to generate the epimeric mixture of oxazilidines **3**[3] and **4**[4] in excellent yield and high diastereoselectivity[5] (Scheme 2).



1, R = Me — **3**
2, R = *n*-propyl — **4**

Scheme 2.

Reduction of **1** and **2** with L-Selectride in anhydrous THF at −10 °C furnished in 10 min the epimeric mixture **3** and **4** with overall yields of 95% and 93% and with an 8:2 ratio, respectively. This ratio was determined by ^1H NMR from the crude reactions. Each epimeric mixture was readily resolved by preparative flash chromatography. However, the major epimer in the ^1H NMR showed diastereoisomeric contributions with a similar ratio measured from the crude reactions. This situation can be explained as suggested by Amat et al.[5a] and Husson et al.;[6] ''the solution of this bicyclic system is in equilibrium with its iminium tautomeric form''.

* Corresponding author. E-mail: dgnecco@siu.buap.mx

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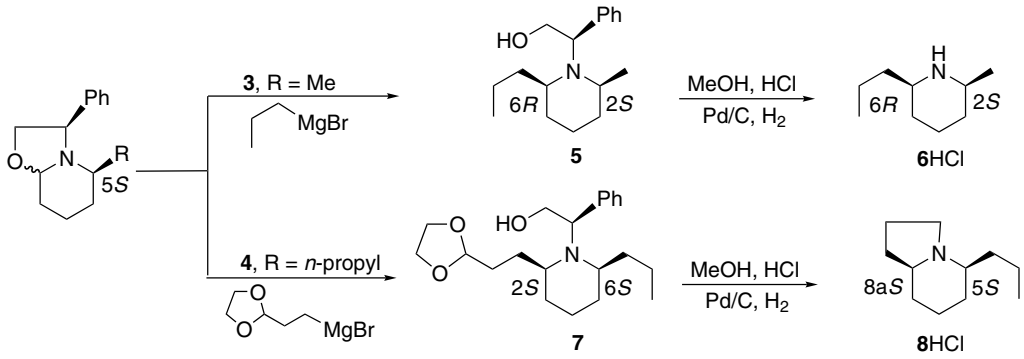

Scheme 3.

To synthesize the dihydropinidine and the indolizidine 167B, we decided to carry out the alkylation at the C-2a position of **3** and **4** with Grignard reagents.[5,7] Firstly, epimeric mixture **3** reacted with *n*-propyl magnesium bromide to give **5** in 90% yield as a single stereoisomer after flash chromatography; $[\alpha]_D = -17.8$ (*c* 1.5, EtOH), {lit.[7a] enantiomer $[\alpha]_D = +18.3$ (*c* 1.16, EtOH)}.

Catalytic hydrogenation of **5** gave the hydrochloride (2*S*,6*R*)-dihydropinidine **6**·HCl[8] in quantitative yield, $[\alpha]_D = -12.9$ (*c* 1.0, EtOH). Enantiomer: {lit.[7a] $[\alpha]_D = +11.9$ (*c* 0.69, EtOH); lit.[5b] $[\alpha]_D = +12.5$ (*c* 1.0, EtOH)}. This result was enough to assign the configuration at C-6 of **5** as (*R*).

Finally, following the same procedure as described above, epimeric mixture **4** was treated with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane to give **7** in 88% yield as a single stereoisomer after flash chromatography. Catalytic hydrogenation of **7** furnished, the hydrochloride (+)-(5*S*,8a*S*)-indolizidine 167B **8**·HCl in quantitative yield, $[\alpha]_D = +107.4$ (*c* 1.0, CH_2Cl_2); lit.[9] $[\alpha]_D = +86.6$ (*c* 1.3, CH_2Cl_2, 78% ee); enantiomer lit.[5a] $[\alpha]_D = -109$ (*c* 1.32, CH_2Cl_2). This result was enough to assign the configuration at C-2 of **7** as (*S*) (Scheme 3).

3. Conclusion

In conclusion, the transformations of **1** and **2** described above provide a convenient and efficient method to synthesize non-racemic chiral *cis*-2,6-disubstituted piperidines with a high diastereoselectivity, which are important for the synthesis of alkaloids.

Further applications of these versatile synthons to the asymmetric synthesis of more complex alkaloid systems are currently in progress.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra at 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. Mass spectra were recorded with a JEOL JEM-AX505HA instrument at a voltage of 70 eV.

4.2. Reduction reaction of pyridin-4-ylium iodide 1 and 2 with L-Selectride

4.2.1. General procedure. A solution of **1** or **2** (1.46 mmol) in anhydrous THF (20 mL) was cooled at −10 °C and then a solution of L-Selectride in THF (1.5 mL,1.0 equiv) slowly added. The resulting mixture was stirred for 10 min and a brine solution (1.0 mL) was added. The reaction was then warmed to 0 °C and an aqueous solution of H_2O_2 (1.0 mL, 30%) was added, followed by 3 M NaOH (1.0 mL). Finally, to this mixture was added AcOEt (20 mL), dried, filtered, and the solvent eliminated in vacuo. The epimeric mixture **3** or **4** was obtained in an overall yield 95% or 93% with an approximate diastereoisomeric ratio of 8:2, respectively.

4.2.2. (3*R*,5*S*)-5-Methyl-3-phenyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridine. Major epimer **3**. Colorless oil. IR (KBr, cm^{-1}): 3443, 2931, 908, 735. Determined from the crude reactions: ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm, *J* Hz): 7.15–7.45 (m, 5H), 4.34 (dd, 7.5, 1H-3), 4.16 (AB, 7.2, 7.8, 1H-2), 3.74 (m, 2.4, 9.6, 1H-2a), 3.62 (AB, 6.9, 7.8 1H-2), 2.40 (m, 1H-5), 2.00 (m, 1H-8), 1.82 (m, 1H-8), 1.60 (m, 2H-6), 1.55 (m, 2H-7), 0.66 (d, 6.3, 3H-9). ^{13}C NMR ($CDCl_3$): 144.4 (1C), 126.4–128.4 (5C), 95.8 (C-2a), 74.5 (C-2), 66.1 (C-3), 57.5 (C-5), 34.7 (C-6), 30.1 (C-8), 22.3 (C-9), 18.4 (C-7).

4.2.3. (3*R*,5*S*)-3-Phenyl-5-*n*-propyl-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridine. Major epimer **4**. Colorless oil. IR (KBr, cm^{-1}): 3440, 2926, 900, 735. Determined from the crude reactions: ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm, *J* Hz): 7.18–7.42 (m, 5H), 4.40 (dd, 3.2, 3.6, 1H-3), 4.33 (AB, 7.6, 1H-2), 3.71 (m, 2.4, 12.0, 1H-2-a), 3.64 (AB, 7.6, 13.6 1H-2), 2.31 (m, 1H-5), 1.22–1.85 (m, 2H-6, 2H-7, 2H-8, 2H-9, 2H-10), 0.52 (t, 7.2, 3H-11). ^{13}C NMR ($CDCl_3$): 139.6 (1C), 126.6–128.3 (5C), 96.1 (C-2-a), 74.7 (C-2), 65.7 (C-3), 57.3 (C-5), 36.9, 31.0, 29.8, 22.6, 18.9, 14.5.

4.3. Reaction of epimeric mixture 3 and 4 with Grignard reagents

4.3.1. General procedure. To a solution of **3** (250 mg, 1.15 mmol) in anhydrous THF (15 mL) at −40 °C was slowly added a solution of *n*-propyl magnesium bromide in THF (2.0 equiv) under nitrogen. The mixture was kept at this temperature for 15 h and then quenched by adding water. The mixture was extracted with AcOEt (3 × 20 mL) and the combined organic layers dried, filtered, and concentrated in vacuo to give oil in yield 97%. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2–MeOH 95:5) to give **5** in 90% yield. Following the same procedure described, epimeric mixture **4** (282 mg, 1.15 mmol) was treated with the Grignard reagent derived from 2-(2-bromoethy)-1,3-dioxolane to give **7** in 88% yield after flash chromatography (SiO_2, CH_2Cl_2–MeOH = 95:5).

4.3.2. (2*S*,6*R*)-1-[(1′*R*)-2′-Hydroxy-1′-phenylethyl]-2-methyl-6-propylpiperidine 5. Yellow oil. IR (KBr, cm^{-1}): 3420, 2928. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm, *J* Hz): 7.25–7.35 (m, 5H), 4.19 (dd, 5.2, 10.4, 1H-2′), 3.85 (t, 10.8, 1H-1′), 3.45 (dd, 5.2, 10.4, 1H-2′), 3.32 (m, 6.4, 1H-2), 3.09 (m, 1H-6), 1.30–1.55 (m, 2H-3, 2H-5, 2H-8, 2H-9), 1.25 (d, 6.4, 3H-7), 1.07 (d, 2H-4), 0.96 (t, 6.8, 3H-10). ^{13}C NMR ($CDCl_3$): 140.1 (1C), 127.3–129.1 (5C), 60.3 (C-1′), 58.9 (C-2′), 52.3 (C-2), 48.5 (C-6), 35.4 (C-3), 29.9 (C-5), 29.8 (C-8), 26.6 (C-9), 20.8 (C-4), 20.7 (C-7), 14.5 (C-10). HRMS (FAB): calcd for $C_{17}H_{27}NO$: 261.4024; found: 261.4011.

4.3.3. (2*S*,6*S*)-2′-[2-(2-[1,3]Dioxolan-2-yl-ethyl)-6-propyl-piperidin-1-yl]-1′(*R*)-phenyl-ethanol 7. Yellow oil. IR (KBr, cm^{-1}): 3422, 2930, 1100, 739. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm, *J* Hz): 7.18–7.40 (m, 5H), 4.88 (t, 4.5, 1H-2-dioxolane), 3.96 (m, 1H-1′), 3.88 (m, 4H-dioxolane), 3.77 (m, 2H-2′), 2.80 (m, 10.0, 1H-2), 2.56 (m, 1H-6), 1.74 (m, 1H-3, 1H-8), 1.70 (m, 1H-5), 1.61 (m, 1H-7), 1.58 (m, 2H-10), 1.54 (m, 1H-8), 1.48 (m, 1H-7), 1.40 (m, 1H-3), 1.29 (m, 2H-9), 1.24 (m, 1H, H-5), 1.10 (m, 1H, H-4), 0.68 (t, 6.0, 3H-11), 0.63 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$): 141.9 (1C), 127.5–128.6 (5C), 104.0 (C-2, dioxolane), 64.5 (2C-dioxolane, C-1′), 63.2 (C-2′), 56.7 (C-2), 54.0 (C-6), 37.4 (C-3), 33.2 (C-7), 32.6 (C-9), 26.7 (C-8), 26.2 (C-10), 23.8 (C-4), 19.9 (C-5), 14.6 (C-11). HRMS (FAB+): calcd for $C_{21}H_{33}NO_3$: 347.4917; found: 347.4910.

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