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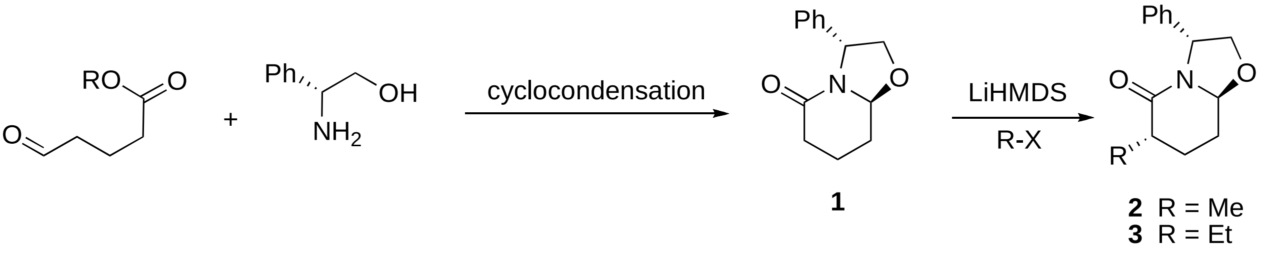
A SHORT SYNTHESIS OF INDOLIZIDINE (+)-209B FROM (3*R*,6*S*,8a*S*)-(-)-6-METHYL-3-PHENYLHEXAHYDROOXAZOLO[3,2-a]-PYRIDIN-5-ONE

Dino Gnecco,[a] Ana M. Lumbreras,[a] Joel L. Terán,*[a] Alberto Galindo,[a] Jorge R. Juárez,[a] María L. Orea,[a] Alejandro Castro,[a] Raúl G. Enríquez,[b] and William F. Reynolds[c]

[a] Organic Synthesis Laboratory, Chemistry Centre, Science Institute, BUAP, Building 194, Science Complex, City University, 72570, Puebla, Pue., México
[b] Chemistry Institute, UNAM, Outside circuit, México, D. F. 04510
[c] Department of Chemistry, University of Toronto, Toronto, Ont., Canada
cs001512@siu.buap.mx

Abstract – The synthetic potential of enantiopure (3*R*,6*S*,8a*S*)-(-)-6-methyl-3-phenylhexahydrooxazolo[3,2-*a*]pyridin-5-one **2** is illustrated by a short synthesis of the 5,8-disubstituted indolizidine alkaloid (+)-**209B**.

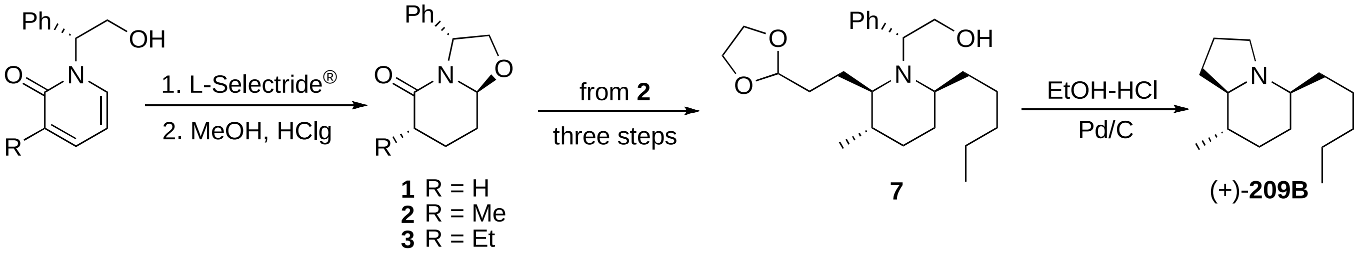
(3*R*,8a*S*)-(-)-3-Phenylhexahydrooxazolo[3,2-*a*]pyridin-5-one **1** has generated considerable interest, because this compound has demonstrated to be useful intermediate in the synthesis of natural products and functionalized piperidines.[1,2] Amat *et al.*[3] reported the synthesis of this compound in 73% yield through a cyclocondensation reaction of (*R*)-(-)-2-amino-2-phenylethanol with ethyl 5-oxopentanoate. After, by alkylation of compound **1** they prepared compounds **2** and **3** (Scheme 1).



Scheme 1

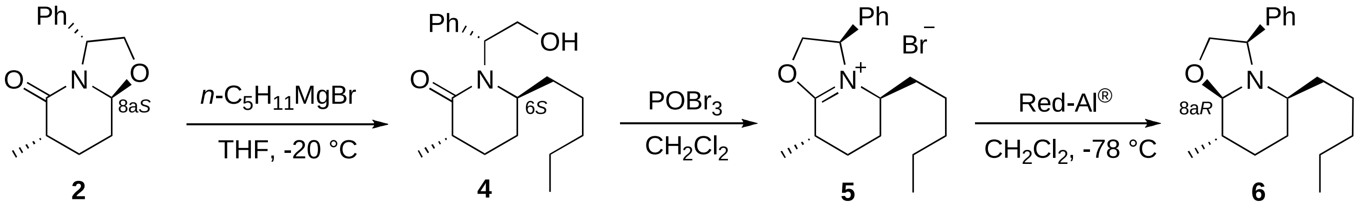
In this sense, we have recently reported a new strategy to prepare the enantiopure compounds **1**, **2** and **3** in good overall yields using as starting material the corresponding (1'*R*)-(-)-1-(2'-hydroxy-1'-

phenylethyl)pyridin-2(1*H*)-ones.[4,5] Now, as part of our ongoing studies toward the synthesis of 5,8-disubstituted indolizidines, we describe a successive stereo- and enantiocontrolled introduction of substituents onto enantiopure compound **2** to prepare the intermediate (*R*)-(-)-2-((2'*R*,3'*S*,6'*S*)-2'-(2-(1,3-dioxolan-2-yl)ethyl)-3'-methyl-6'-pentyl-piperidin-1'-yl)-2-phenylethanol **7**, which is precursor of the 5,8-disubstituted indolizidine (+)-**209B** (Scheme 2).



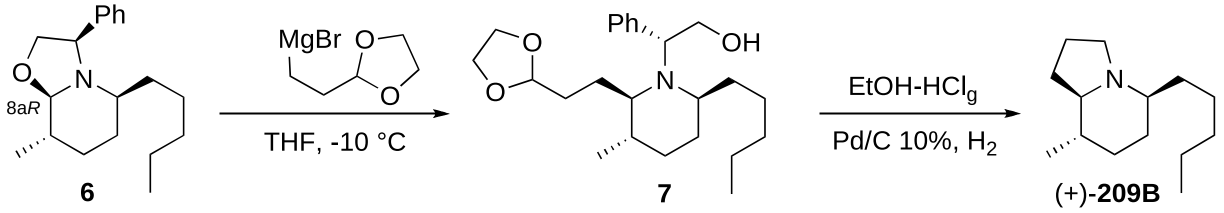
Scheme 2

Treatment of a solution of compound **2** in anhydrous THF at -20 °C with an excess of pentylmagnesium bromide afforded a mixture of two diastereoisomers in 80% yield in a 95:5 ratio (determined by ^{1}H-NMR). This mixture was purified by column chromatography over silica gel to give the (1'*R*,3*S,*6*S*)-(-)-1-(2'-hydroxy-1'-phenylethyl)-3-methyl-6-pentylpiperidin-2-one **4** in 70% isolated yield. The absolute configuration at the new stereocentre C-6 was assigned as (*S*), in agreement with that reported by Terán *et al.*[4] After, a solution of **4** in anhydrous dichloromethane at 10 °C was treated with POBr$_3$ and refluxed for 1h. The crude product was purified by flash chromatography over silica gel affording the unstable oxazoliminium bromide **5** in 90% yield (sensitive to aerial degradation). Immediately, a solution of **5** in dichloromethane at -78 °C was treated with 1.1 equivalent of Red-Al® and stirred for 20 min to give a mixture of two isomers in 85% yield in a 90:10 ratio.[6] ^{1}H-NMR was valuable for the structural analysis of this mixture and the major isomer was characterized by a H-8a proton which, appeared as a doublet at 3.40 ppm, $J_{H\text{-}8a}$-$J_{H\text{-}8}$ = 8.4 Hz.[7] This result was enough to define the *trans* relationship H$_{8a}$-H$_8$ and the configuration of C-8a as (*R*). Flash chromatography over silica gel of this mixture afforded the compound (3*R*,5*S*,8*S*,8a*R*)-(-)-8-methyl-5-pentyl-3-phenylhexahydrooxazolo[3,2-*a*]pyridine **6** in 70% isolated yield (Scheme 3).



Scheme 3

After, a solution of **6** in anhydrous THF at -10 °C was treated with an excess of [2-(1,3-dioxolan-2-yl)-ethyl]magnesium bromide to give a mixture of two isomers in 80% yield in a ratio 90:10. Grignard reagents took place with retention of the configuration at the C-8a stereocentre, generating the corresponding 2,3-*trans* isomer **7**. Consequently, the equatorial methyl substituent at C-8 does not change the stereochemical result previously observed in the α-amidoalkylation reactions reported.[1] This mixture was separated by flash chromatography over silica gel to provide the isomer **7** in 65% isolated yield. Finally, hydrogenolysis of compound **7** furnished the indolizidine (+)-**209B**[8] in 90% yield $[\alpha]_D$ +93 (*c* 1.0, MeOH). NMR spectral data of this alkaloid are in good agreement with those previously reported by Holmes *et al.* for the synthetic indolizidine (-)-**209B**. This Dendrobatid alkaloid has been identified as a trace component and its optical rotation is not available at present due to insufficient material.[9,10] (Scheme 4).



Scheme 4

To our knowledge, this is the first time that the synthesis of the unnatural indolizidine (+)-**209B** is reported using as starting material the (3*R*,6*S*,8a*S*)-(-)-6-methyl-3-phenylhexahydrooxazolo[3,2-*a*]-pyridin-5-one **2**. In addition the present strategy offers a practical stereocontrolled synthesis of 2,3,6-trisubstituted piperidines and *trans*-5,8-disubstituted indolizidines. The synthesis of *trans*-1,4-disubstituted quinolizidines is in progress and the results will be forthcoming.

EXPERIMENTAL

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 1dm 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.

(1'*R*,3*S*,6*S*)-(-)-1-(2'-Hydroxy-1'-phenylethyl)-3-methyl-6-pentylpiperidin-2-one 4.

To a solution of **2** (0.29 g, 1.32 mmol) in anhydrous THF (15 mL) under nitrogen atmosphere and at -20 °C was added pentylmagnesium bromide (3 eq.) and the reaction mixture was stirred at room temperature for 6 h. Finally, this mixture was treated with a saturated aqueous solution of NH_4Cl (4.0 mL), extracted with EtOAc (3x10 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2: MeOH = 95:5) affording **4** in 70% yield.

Compound **4**. Pale yellow oil, $[\alpha]_D$ -8 (*c* 1, CH_2Cl_2). IR (KBr) 3386, 2978, 1615 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, *J* Hz) δ 0.80 (t, 3H, *J* = 7.4), 0.96 (d, 3H, *J* = 7.2), 1.26- 1.80 (m, 12H), 2.40 (m, 1H), 3.20 (m, 1H), 4.18 (AB, 1H, H-2', *J* = 4.0, 11.5), 4.24 (AB, 1H, H-2', *J* = 7.5, 11.5), 4.50 (br, OH), 5.02 (dd, 1H, H-1,' *J* = 4.0, 7.5), 7.20-7.30 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.1, 22.2 (2C), 24.4 (2C), 26.3 (2C), 29.8, 36.5 43.0, 57.9, 66.0, 126-130, 138.0, 174.2. HRMS Calcd for $C_{19}H_{29}NO_2$: 303.2198; found: 303.2178.

(3*R*,5*S*,8*S*,8a*R*)-(-)-8-Methyl-5-pentyl-3-phenyl-hexahydro-2*H*-oxazolo[3,2-*a*]pyridine 6.

To a stirred solution of **4** (0.200 g, 0.661 mmol) in anhydrous CH_2Cl_2 (5 mL) at 10 °C under nitrogen atmosphere was added dropwise a solution of $POBr_3$ (0.234 g, 0.820 mmol) in CH_2Cl_2 (5 mL) and, then the reaction mixture was refluxed for 1 h. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2: MeOH = 95:5) affording the unstable oxazoliminium bromide **5** in 90% yield. Immediately, a solution of this compound in anhydrous CH_2Cl_2 (15 mL) under nitrogen atmosphere was treated with Red-Al® (1.01 mmol, 65% in toluene) at -78 °C and stirred for 20 min. Then, the reaction mixture was quenched with saturated aqueous of NH_4Cl (2 mL), extracted with CH_2Cl_2 (3x10 mL), dried with Na_2SO_4 and concentrated under reduced pressure to give a mixture of two isomers in 85% yield in a 90:10 ratio. Compound **6** was isolated as oil in 70% yield after chromatography over silica gel using a gradient of CH_2Cl_2: petroleum ether = 80:20.

Compound **6**. Pale yellow oil, $[\alpha]_D$ -76 (*c* 1, CH_2Cl_2). IR (KBr), 2978, 1160 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, *J* Hz) δ 0.89 (t, 3H, *J* = 7.2), 1.10 (d, 3H, *J* = 7.5), 1.28-1.60 (m, 12H), 1.89 (m, 1H), 2,28 (m, 1H), 3.40 (d, 1H, *J* = 8.4), 3.60 (t, 1H, *J* = 7.5), 3.70 (t, 1H, *J* = 7.5), 4.20 (t, 1H, *J* = 7.5, 11.5), 7.18-7.30 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.1, 14.2, 22.2, 24.3 (2C), 30.6 (2C), 34.4, 37.0, 62.0, 64.1, 73.8, 100.6, 126-128, 144.1. HRMS (FAB): Calcd for $C_{19}H_{29}NO$: 287.4397; found: 287.4370.

(*R*)-(-)-2-((2'*R*,3'*S*,6'*S*)-2'-(2-(1,3-Dioxolan-2-yl)ethyl)-3'-methyl-6'-pentylpiperidin-1'-yl)-2-phenylethanol 7.

To a stirred solution of **6** (0.150g, 0.523 mmol) in anhydrous THF (10 mL) under nitrogen atmosphere at 0 °C was dropwise added [2-(1,3-dioxolan-2-yl)ethyl]magnesium bromide in THF (1.5 mmol), and then the reaction mixture was stirred at rt for 8 h. After, the reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL), extracted with CH_2Cl_2 (3x10 mL), dried with Na_2SO_4 and concentrated under reduced pressure to give a mixture of two isomers in 80% yield in a ratio 90:10. The major product **7** was

isolated as oil in 65% yield after chromatography over silica gel using a gradient of CH_2Cl_2-MeOH.
Compound **7**. Pale yellow oil, $[\alpha]_D$ -55 (*c* 1, CH_2Cl_2). IR (KBr), 3450, 2967 cm^{-1}. ^1H-NMR (400 MHz, $CDCl_3$, *J* Hz) δ 0.89 (t, 3H, *J* = 7.0), 1.10 (d, 3H, *J* = 7.2), 1.28-1.40 (m, 11H), 1.50-1.75 (m, 5H), 2.22-2.24 (m, 2H), 3.85-4.10 (m, 7H), 4.82 (t, 3H, *J* = 4.0, 11.5), 7.25-7.35 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ 14.13, 19.50, 22.34, 22.83 (2C), 25.68, 29.12, 30.85, 31.37, 32.28 (2C), 53.50, 59.93, 63.43, 64.96, 65.10 (2C), 104.60, 127.63-129.84, 140.90. HRMS (FAB): Calcd for $C_{24}H_{39}NO_3$: 389.2930; found: 389.2910.

(5*S*,8*S*,8a*R*)-(+)-8-Methyl-5-pentyloctahydroindolizine (+)-**209B.**

To a stirred solution of **6** (80 mg, 2.06 mmol) in EtOH-HCl (g) (7 mL) was added 10% Pd/C (20 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere for 18 h. The crude product was purified by flash chromatography on basic alumina (petroleum ether/CH_2Cl_2 90:10) to afford (+)-**209B** in 90% yield.

Indolizidine (+)-**209B**. Colorless oil, $[\alpha]_D$ +93 (*c* 1, MeOH). Indolizidine (-)-209B lit.,[11] $[\alpha]_D$ -91.3 (*c* 0.58, MeOH); lit.,[12] $[\alpha]_D$ -94.3 (*c* 1.85, MeOH). IR (KBr), 2929, 2862 cm^{-1}. ^1H-NMR (400 MHz, $CDCl_3$, *J* Hz) δ 0.76 (3H, t, *J* = 7.2), 0.84 (3H, d, *J* = 7.2), 1.10-1.90 (m, 20H), 3.40 (m, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.2, 18.90, 20.54, 22.74, 25.64, 29.12, 31.30, 32.40, 33.60, 34.66, 36.62, 51.80, 63.70, 70.42. HRMS (FAB): Calcd for $C_{14}H_{27}N$: 209.2143; found: 209.2150.

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