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Efficient preparation of (1′*R*)-(−)-1-(2′-hydroxy-1′-phenylethyl)piperidin-2-one: synthesis of (2′*S*,3*R*)-(+)-stenusine

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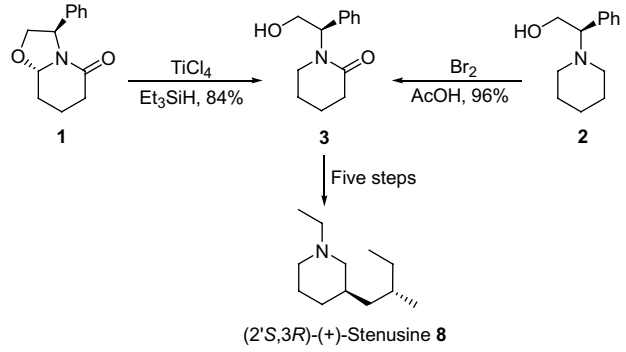
Abstract—An efficient oxidation of (2′*R*)-(−)-2′-phenyl-2′-(piperidin-1-yl)ethanol **2** with bromine to generate the corresponding piperidin-2-one **3** in 96% is described. In addition, starting from **3**, (2′*S*,3*R*)-(+)-stenusine **8** was synthesized in 70% overall yield. The X-ray analysis of piperidine **6**·HCl is also reported.

1. Introduction

Piperidine alkaloids and synthetic analogues are the focus of great interest in the pharmaceutical industry because they exhibit an extensive range of biological activities.[1] As a consequence, the development of new methods for the enantioselective synthesis of piperidine derivatives by stereoselective introduction of substituents at the carbon positions of the heterocycle constitutes an area of current interest.[2] In this context, chiral piperidin-2-ones are versatile synthetic building blocks for the asymmetric synthesis of this class of compounds.[3]

In particular, Micouin et al.[4] reported a preparation of the piperidin-2-one **3** by reduction of oxazololactam **1** following a procedure described by Romo and Meyers[5] for a similar lactam. In addition, starting from **3** an asymmetric synthesis of natural stenusine **8** was carried out.

Herein, we report an efficient oxidation of compound **2**[6] with bromine in the presence of acetic acid[7] to give piperidin-2-one **3** in 96% yield (Scheme 1).



Scheme 1.

2. Results and discussion

Herein we found the conditions for the oxidation at C-2 of **2** with a solution of bromine in acetic acid. The best result was obtained in the conditions described in Table 1 (entry 3).

However, the oxidation of (1′*S*)-(−)-1-(1′-phenylethyl)piperidine under the same conditions afforded the corresponding piperidin-2-one in 50% yield.

The high yield observed for the oxidation of **2** could be explained via a mechanism, which involves the

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Table 1.

Entry	Br_2/AcOH (mmol/mL)	Solution (1 M)	Temperature (°C)	Time (h)	**2** Yield (%)
1	2.0/6	K_2CO_3	90	1	65
2	2.6/8	K_2CO_3	90	1	80
3	3.2/10	NaOH	90	1	96

participation of the hydroxyl function of **2** in the ring close of **I** to give intermediate **II**.

This intermediate in the presence of bromine gives **III**, which generates the hexahydro-oxazolo[3,2-*a*]pyridin-4-ylium **IV**. Finally, compound **IV** under basic conditions provides **V**, which can be rearranged to give lactam **3**[8,9] (Scheme 2).

Finally, alkylation of **3** with (*S*)-(+)-1-bromo-2-methylbutane in the presence of HMPA and *sec*-BuLi gave a diastereoisomeric mixture with a ratio 9:1 (determined by NMR). Purification of this mixture by flash chromatography afforded **4** in 80% yield. The excellent diastereoselectivity is in agreement with that previously reported.[4] Then, reduction of the carbonyl function with Red-Al[10] afforded **5** in quantitative yield. Hydrogenolysis of **5** furnished (2′*S*,3*R*)-(+)-3-(2′-methylbutyl)piperidine hydrochloride **6**·HCl in 95% yield. This compound was crystallized from ethyl acetate and its single-crystal X-ray analysis performed in order to determine the configuration at C-3 (Fig. 1). Finally, starting from **6**·HCl and following the methodology described by Micouin et al.[4] the synthesis of stenusine (2′*S*,3*R*)-(+)-l-ethyl-3-(2-methylbutyl)piperidine **8** was achieved in two steps in 96% yield. Compound **8** is identical to the product described by Enders et al.[11] ($[\alpha]_D$, ^1H, and ^{13}C NMR) (Scheme 3). Some authors[12] have reported the synthesis of the four diastereoisomers of stenusine in different ratios; however, this methodology is only useful for preparing one of them in high yield. Taking into account that (*S*)-phenylglycinol is also commercially available, this procedure can provide access to (2*S*,3*S*)-stenusine.

3. Conclusion

In conclusion, the results reported herein show that oxidation of (2′*R*)-(−)-2′-phenyl-2″-(piperidin-1-yl)ethanol **2** with bromine in the presence of acetic acid is a convenient method to prepare (1′*R*)-(−)-1-(2′-hydroxy-1′-phenylethyl)piperidin-2-one **3** in high yield.

Furthermore to the best of our knowledge, this is the first time intermediates **4**, **5**, **6**·HCl, and **7** have been characterized fully.

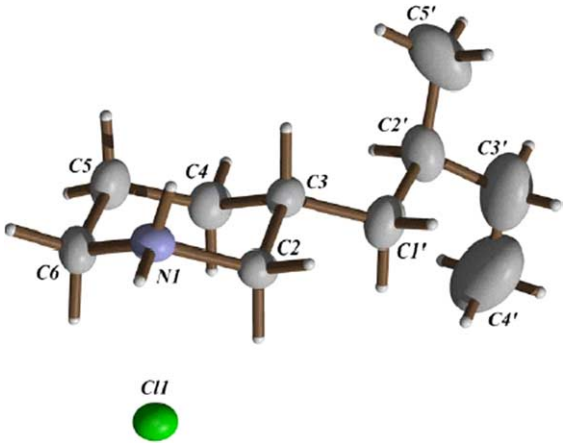
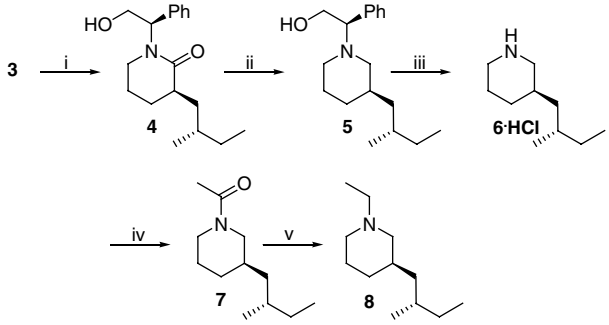
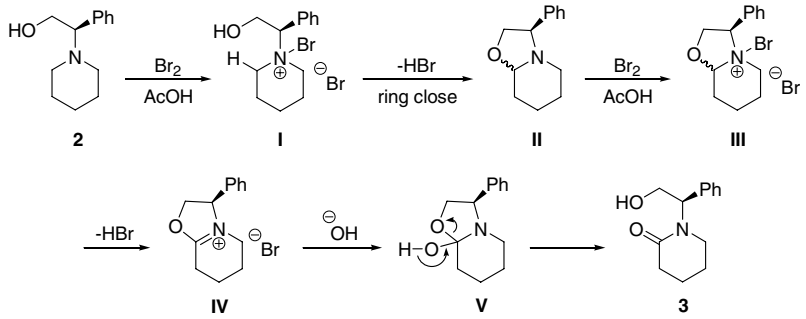


Figure 1. ORTEP view of the crystal structure of compound **6**·HCl. Displacement ellipsoids for non-H atoms are drawn at the 20% probability level.



Scheme 3. Reagents and conditions: (i) *sec*-BuLi, THF, HMPA, −78 °C, then (*S*)-(+)-1-bromo-2-methylbutane, 90%; (ii) Red-Al, THF, 0 °C, 100%; (iii) H_2, Pd–C 10%, MeOH, HCl, 95%; (iv) CH_3COCl, NEt_3, refluxing $CHCl_3$, 96%; (v) Red-Al, THF, 0 °C, 100%.



Scheme 2.

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. Oxidation of compound 2

To a solution of **2** (1.0 g, 4.87 mmol) in acetic acid (5.0 mL, 80%) at 0 °C was added dropwise a solution of bromine (15.60 mmol) in acetic acid (5.0 mL). The mixture was stirred for 20 min and water (30 mL) then added and stirred for 3 h. Afterwards, the reaction was treated with a solution of sodium hydroxide (150 mL, 1.0 M), warmed to 90 °C, and stirred during 1 h. Then, the mixture was cooled at room temperature, saturated with sodium chloride, extracted with dichloromethane (6×80 mL) and the combined organic layer dried over Na_2SO_4 and concentrated under reduced pressure to afford **3** in 96% yield after purification by flash chromatography (SiO_2, AcOEt, AcOEt–MeOH = 95:5).

4.2.1. (1′*R*)-(−)-1-(2′-Hydroxy-1′-phenylethyl)piperidin-2-one 3. White crystals. Mp: 113–115 °C. $[\alpha]_D = -80.0$ (*c* 0.5, CH_2Cl_2). IR (KBr) 1615 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 1.67 (m, 1H), 1.76 (m, 3H), 2.49 (m, 2H), 2.95 (AB, 4.4, 1H), 3.22 (AB, 3.6, 4.4, 1H), 3.79 (br, OH), 4.10 (AB, 5.2, 6.4, 2H), 5.85 (dd, 5.2, 5.6, 1H), 7.21–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): 20.89, 23.11, 32.59, 43.43, 58.29, 61.33, 127.45, 127.58, 128.41, 136.82, 171.34.

4.3. Alkylation of compound 3

To a solution of **3** (0.29 g, 1.32 mmol) in THF (15 mL) under a nitrogen atmosphere at −78 °C was added HMPA (0.6 mL) and *sec*-BuLi (5.3 mmol). The mixture was stirred for 1 h and (*S*)-(+)-1-bromo-2-methylbutane (3.3 mmol) was added and the reaction mixture stirred for 2.5 h. Finally, the mixture was treated with a saturated solution of NH_4Cl (4.0 mL), extracted with ethyl acetate (3×20 mL), dried over Na_2SO_4, and finally, concentrated under reduced pressure. The crude mixture was purified by flash chromatography (SiO_2, AcOEt–petroleum ether 1:1, AcOEt–petroleum ether = 6:4) to give **4** in 90% yield.

4.3.1. (1′*R*,2″*S*,3*R*)-(−)-1-(2-Hydroxy-1′-phenylethyl)-3-(2″-methylbutyl)piperidin-2-one 4. Colorless oil. $[\alpha]_D = -17.3$ (*c* 2.25, CH_2Cl_2). IR (KBr) 1612 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 0.86–0.91 (m, 6H), 1.18–1.48 (m, 5H), 1.64–1.81 (m, 3H), 1.83–1.95 (m, 1H), 2.47 (m, 1H), 2.87 (AB, 5.1, 1H), 3.19 (AB, 5.4, 1H), 3.67 (br, OH), 4.05–4.17 (m, 2H), 5.80 (dd, 5.4, 5.7, 1H), 7.22–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.64, 18.14, 21.25, 25.63, 30.47, 31.58, 39.06, 39.53, 43.63, 58.60, 61.59, 127.41, 127.62, 128.38, 136.93, 175.12. HRMS (FAB): Calcd for $C_{18}H_{27}NO_2$: 289.2042. Found: 289.2010.

4.4. Reduction of compound 4

4.4.1. General procedure. To a solution of **4** (0.25 g, 0.85 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere was added Red-Al (4.22 mmol, solution 65% in toluene) and stirred for 24 h at room temperature. Then, the mixture was cooled at 0 °C and quenched with saturated solution of NH_4Cl (2.0 mL). Then the reaction was filtered and the solution treated with Na_2SO_4. Finally, the solvent was removed in vacuo to give **5** in quantitative yield.

4.4.2. (2′*R*,2″*S*,3*R*)-(−)-2′-[3-(2′-Methylbutyl)piperidin-1-yl]-2′-phenylethanol 5. Colorless oil. $[\alpha]_D = -17.8$ (*c* 1.1, MeOH). IR (KBr) 1456, 704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 0.66–0.73 (m, 1H), 0.83–0.88 (m, 6H), 0.94 (m, 1H), 1.08–1.15 (m, 2H), 1.29 (m, 1H), 1.34–1.48 (m, 2H), 1.60–1.69 (m, 4H), 1.95 (dd, 10, 1H), 2.72 (dd, 9.6, 1H), 2.80 (m, 1H), 3.60 (AB, 5.2, 1H), 4.49 (AB, 5.2, 1H), 4.65 (AB, 9.6, 1H), 7.15–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.45, 19.40, 25.76, 29.97, 30.85, 31.18, 34.28, 41.47, 46.85, 59.78, 59.83, 70.13, 127.62, 127.90, 128.81, 135.21. HRMS (FAB): Calcd for $C_{18}H_{29}NO$: 275.2249. Found: 275.2220.

4.5. Catalytic hydrogenation of compound 5

To a solution of **5**·HCl (0.31 g, 0.994 mmol) in methanol (5 mL) under a hydrogen atmosphere was added Pd/C 10% (0.045 g) and the mixture stirred for 96 h at room temperature. After, the reaction was filtered and the methanolic solution was evaporated under reduced pressure. The solid residue was crystallized in ethyl acetate to afford **6**·HCl in 95 % yield.

4.5.1. (2′*S*,3*R*)-(+)-3-(2′-Methylbutyl)piperidine 6·HCl. White crystals. Mp: 171–173 °C. $[\alpha]_D = +12.7$ (*c* 0.92, MeOH). IR (KBr) 1585, 1449 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 0.84–0.86 (m, 6H), 1.03–1.05 (m, 2H), 1.12–1.22 (m, 2H), 1.33 (m, 1H), 1.42 (m, 1H), 1.88–1.95 (m, 3H), 2.04 (m, 1H), 2.49 (m, 1H), 2.79 (m, 1H), 3.36 (m, 1H), 3.47 (m, 1H). ^{13}C NMR ($CDCl_3$): 11.22, 19.01, 22.12, 28.84, 29.65, 30.70, 30.79, 40.65, 44.36, 49.56.

4.5.2. Crystal structure of 6·HCl. Colorless plate, $0.65 \times 0.60 \times 0.10$ mm^3, $C_{10}H_{22}ClN$. Monoclinic, *C*2, $a = 10.295(2)$, $b = 7.334(2)$, $c = 17.395(4)$ Å, $Z = 4$, $\rho_{calcd} = 0.987$ g cm^{-3}. A set of 3339 reflections was collected at $T = 296(1)$ K using Mo-K_α radiation ($\lambda = 0.71073$ Å, Bruker P4 diffractometer), corresponding to $2\theta_{max} = 55°$. Raw data were corrected for absorption (Ψ-scans, transmission factors in the range 0.777–0.974) and 2971 independent reflections ($R_{int} = 0.0269$) were used for the refinement of 109 parameters, without restraints or constraints (SHELXTL 5.10 package). H atoms bonded to N1 were found on difference maps,

while the remaining H atoms were placed on idealized positions. All H atoms were refined using a riding model. Final R indices: $R_1 = 0.0677$ for 1924 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1883$ for all data. The correctness of the absolute configuration was checked on the basis of a refined Flack parameter: $x = 0.18(12)$ for 1369 measured Friedel pairs. CCDC deposition number: 257396. Structure factors and raw files are available on request to authors.

4.6. Synthesis of (2′*S*,3*R*)-(+)-stenusine 8

To a solution of **6**·HCl (0.127 g, 0.663 mmol) in $CHCl_3$ (10 mL) at 0 °C was added triethylamine (0.5 mL) and the reaction mixture stirred for 30 min. Afterwards, acetyl chloride (0.2 mL) was added and the reaction mixture refluxed and stirred for 90 min. Then, this mixture was treated with a solution of NH_4Cl and extracted with ethyl ether (3×15 mL). The organic layer was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum ether–AcOEt = 40:60) to give **7** in 96 % yield. Reduction of **7** was carried out under the same conditions described in Section 4.4.1 to furnish stenusine **8** in quantitative yield.

4.6.1. (2′*S*,3*R*)-(+)-1-[3-(2′-Methylbutyl)piperidin-1-yl]-ethanone 7. Colorless oil. $[\alpha]_D = +42.2$ (*c* 1.16, MeOH). IR (KBr) 1646, 1440 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 0.81–0.89 (m, 6H), 0.96–1.08 (m, 2H), 1.09–1.23 (m, 2H), 1.33 (m, 1H), 1.40–1.47 (m, 2H), 1.52 (m, 1H), 1.69 (m, 1H), 1.86 (m, 1H), 2.08 (s, 3H), 2.23 (m, 1H), 2.63 (m, 1H), 2.71 (m, 1H), 2.98 (m, 1H). ^{13}C NMR ($CDCl_3$): 11.24, 19.08, 21.44, 24.59, 29.74, 30.67, 30.89, 33.20, 40.37, 42.28, 48.00, 168.26. HRMS (FAB): Calcd for $C_{12}H_{23}NO$: 197.1780. Found: 197.1750.

4.6.2. (2′*S*,3*R*)-(+)-1-Ethyl-3-(2′-methylbutyl)piperidine 8. Colorless oil. $[\alpha]_D = +67.4$ (*c* 0.76, EtOH). IR (KBr) 1585, 1449 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm, *J* Hz): 0.75 (m, 1 H), 0.83 (d, 6.2, 3H), 0.85 (t, 7.2, 7.6, 3H), 0.96 (m, 1H), 1.08 (t, 6.8, 7.6, 3H), 1.11–1.16 (m, 2H), 1.28–1.35 (m, 2H), 1.50 (m, 1H), 1.58 (m, 1H), 1.65 (m, 1H), 1.74–1.80 (m, 2H), 2.32–2.43 (m, 2H), 2.83 (m, 1H), 2.91 (m, 1H). ^{13}C NMR ($CDCl_3$): 11.42, 12.10, 19.34, 25.63, 30.02, 31.11, 31.20, 33.63, 41.92, 52.81, 53.86, 61.00.

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