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Synthesis of Enantiopure Cis- and Trans-2,3-Disubstituted Piperidines

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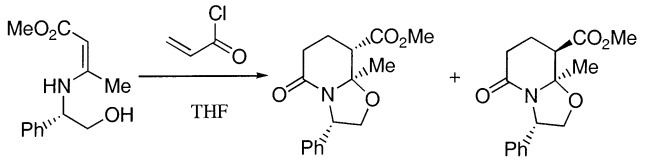
Abstract: The synthesis of enantiopure cis- and trans-2,3-disubstituted piperidines **4** is described. The key step of the synthesis involves the stereoselective reduction of chiral nonracemic lactams **2** by using BH_3·Me_2S. A rationalization of the stereoselectivity is presented.

We recently published the preliminary results of a study concerning the reactivity of chiral nonracemic β-enamino esters with acryloyl chloride.[1] During this study, we found an efficient route to the bicyclic lactams **2** by aza-annulation of the enamino esters **1** (Scheme 1). To our knowledge, this was the first reported aza-annulation of β-enaminocarbonyl compounds bearing an internal nucleophile such as a hydroxyl function. Until our publication, the aza-annulation was limited to the efficient transformation of enamines[2] or β-enaminocarbonyl into δ-lactams. Several research groups have successfully used this aza-annulation procedure in the synthesis of various nitrogen heterocycles.[3]

SCHEME 1



1 **2a** **2b**

In the context of our studies on the synthesis of enantiopure piperidine derivatives from chiral nonracemic bicyclic lactams **2**, we present herein the preparation of 2,3-disubstituted *cis*- and *trans*-piperidines **4**. Chiral nonracemic bicyclic lactams are known to be versatile building blocks for the enantioselective synthesis of pyrrolidines and piperidines derivatives.[4] The introduction of a carbonyl function on the bicyclic δ-lactam should allow an efficient access to enantiopure piperidines substituted on this position.

Only the two diastereoisomers **2a** and **2b** were formed during the aza-annulation of β-enamino ester **1** (Scheme 1). The stereochemical assignment of the two oxazololactams **2a** and **2b** was inferred by NMR spectroscopy (NOE experiments). The configuration of compound **2a** was confirmed by X-ray analysis.

In THF, these two diastereoisomers **2a** and **2b** were obtained in nearly equal amounts. Diastereoisomers **2a** and **2b** were separated by silica gel chromatography and subjected in stereochemical pure form to reduction. Results are presented in Table 1. BH_3·Me_2S reacted chemo- and stereoselectively with either substrate **2a** (entry 1) or substrate **2b** (entry 2) to furnish, respectively, the two diastereomeric piperidines **3a** and **3b**. When a large excess of this reducing agent was used, alcohol **5a** was obtained (entry 3). Bicyclic lactam **2c** bearing an acetal function did not react with BH_3·Me_2S but with the more reactive BH_3·THF to furnish the expected *cis*-piperidine **3c** with an excellent diastereoselectivity (entry 4). Interestingly, K-Selectride and $LiAlH_4$ furnished alcohol **6** arising from the chemoselective reduction of the ester moiety (entries 5 and 6).

The reduction of oxazololactams **2a** and **2b** using 4 equiv of BH_3·Me_2S furnished, respectively, the cis diastereoisomer **3a** and the trans diastereoisomer **3b** with high facial selectivity (entries 1 and 2). These results suggest that the stereoselectivity is not governed by the stereogenic center bearing the ester moiety but by the phenyl-bearing more remote stereocenter present α to nitrogen. Meyers[5] reduced similar bicyclic lactams with BH_3·THF and noted that the reduction occurred with retention of configuration. He rationalized this seemingly anomalous result by the abundance of steric bulk on the exo face of his bicyclic system, forcing the delivery of the

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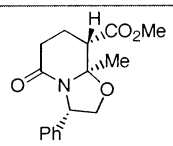
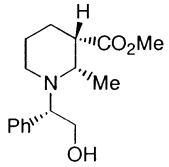
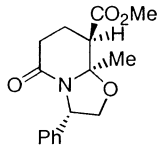
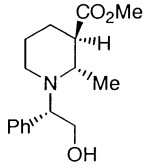
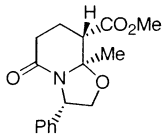
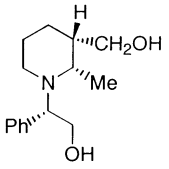
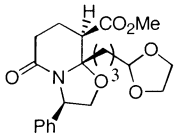
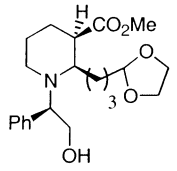
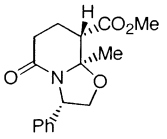
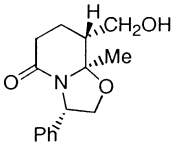
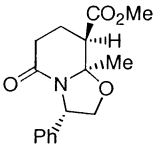
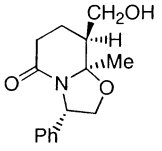
TABLE 1. Stereoselective Reductions of Oxazololactams 2

Entry	Substrate	Reducing conditions	Product	d.e.[b]	Yield [a](%)
1	 **2a**	$BH_3.Me_2S$ (4eq.)/THF	 **3a**	88	61[a]
2	 **2b**	$BH_3.Me_2S$ (4eq.)/THF	 **3b**	90	52[a]
3	 **2a**	$BH_3.Me_2S$ (8eq.)/THF	 **5a**	ND	50
4	 **2c**	BH_3.THF (4eq.)/THF	 **3c**	>90	44
5	 **2a**	K-Selectride (5eq.)/THF	 **6a**	/	53
6	 **2b**	$LiAlH_4$ (1.5eq.)/THF	 **6b**	/	61

[a] Isolated yields of the major diastereoisomers **3**. [b] de determined by ^1H NMR analysis of the crude mixture. ND: not determined.

hydride to occur from the endo face. Rationalization for the stereochemical outcome in hydride reduction with BH_3•Me_2S of the bicyclic lactam **2a** and **2b** is presented in Figures 1 and 2, respectively. Following the reduction of the carbonyl group, the complexation of the borane reagent to the oxygen of the oxazolidine ring in **2a** and **2b** promotes, respectively, the formation of the iminium ion species **2′a** and **2′b**. Both these iminium intermediates can adopt two half-chair-like conformations. Thus, the stereochemical outcome of the reduction can be accounted for by considering the relative stabilities of the two conformers **A** and **B** of each intermediate **2′**. Axial intramolecular hydride delivery on the β-face should be disfavored on both conformations **A** because there is a steric hindrance between the phenyl group and a pseudoequatorial hydrogen present on C6 of the six-membered ring (Figures 1 and 2). In contrast, axial hydride attack on the α-face is favored because, in the required conformations **B**, there is much less steric hindrance (Figures 1 and 2).[6]

It is noteworthy that the oxazolidine cleavage proceeds with retention of configuration in both processes furnishing the same absolute configuration for the new stereogenic center allowing the formation of *cis*-piperidine **3a**

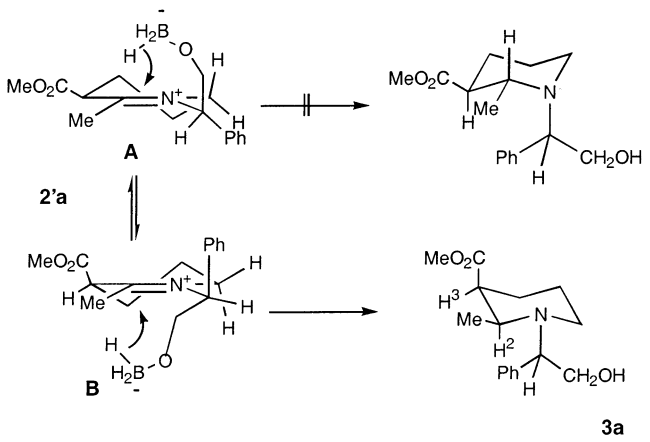


FIGURE 1.

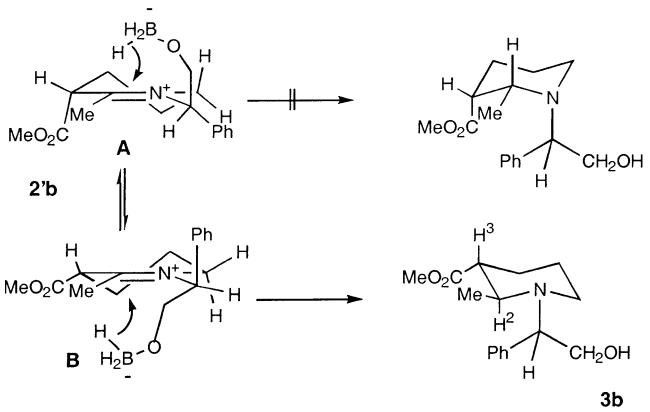
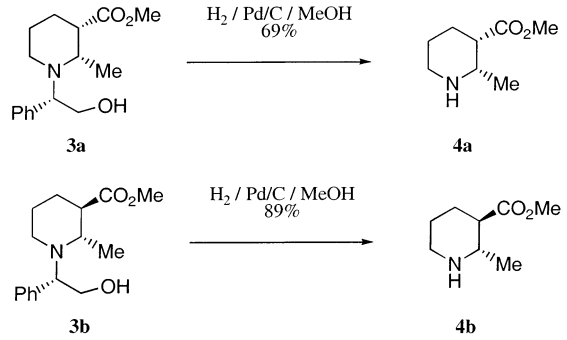


FIGURE 2.

SCHEME 2



from bicyclic lactam **2a** (Figure 1) and *trans*-piperidine **3b** from bicyclic lactam **2b** (Figure 2).

Hydrogenolysis of piperidines **3a** and **3b** with Pd/C in methanol led to the expected *cis*- and *trans*-2-methylnipecotinate esters **4a** and **4b** (Scheme 2). Similar disubstituted piperidines (CO_2Et instead of CO_2Me) were already described in racemic form.[7] The relative cis and trans configurations were determined by ^1H NMR analysis. The coupling constants between H^2 and H^3 on the cis and trans isomers were, respectively, equal to 3.5 and 11.5 Hz.

In summary, oxazolactams **2** formed in two steps from (*S*)-phenylglycinol allow an efficient access to enantiopure cis- and trans-disubstituted piperidines **4** derived from nipecotinic acid. In the same manner, the respective cis and trans enantiomers could be obtained starting with (*R*)-phenylglycinol. Asymmetric syntheses that make further use of chiral scaffolds such as bicyclic lactams **2** are currently in progress for the synthesis of natural products.

Experimental Section

General Comments. ^1H and ^{13}C spectra were, respectively, recorded at 250 and 63 MHz; chemical shifts are reported in ppm from TMS. Melting points were uncorrected. Elemental analyses were carried out at the Service des microanalyses de l'Université Pierre et Marie Curie (Paris VI) in Paris. HRMS were carried out at l'Ecole Normale Supérieure de Paris. Column chromatography was performed on silica gel, 230−400. THF was distilled from sodium/benzophenone ketyl.

***β*-Enaminoester 1.** To a solution of (*S*)-phenylglycinol (3 g, 21.8 mmol) in MeOH (110 mL) was added methyl acetoacetate (2.79 g, 24.1 mmol). The reaction medium was stirred at reflux for 24 h. The organic phase was concentrated at reduced pressure, and *β*-enamino ester **1** crystallized to furnish 5.18 g of a yellow crystal (yield, 100%). ^1H NMR (250 MHz, $CDCl_3$): 1.75 (s, 3H), 3.60−3.85 (m, 2H), 3.61 (s, 3H), 4.50 (s, 1H), 4.55−4.65 (m, 1H), 7.22−7.33 (m, 5H), 9.15 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): 19.8, 50.1, 59.2, 67.2, 84.0, 126.4, 127.8, 128.9, 139.7, 161.9, 171.1. Mp: 61°C. $[\alpha]^{20}_D$: −359 (*c* 0.82, $CHCl_3$). IR ($CHCl_3$): 3398, 1663, 1600 cm^{-1}.

Oxazololactam 2. To a solution of *β*-enamino ester **1** (983 mg, 4.2 mmol) in THF (42 mL) was added at 0 °C acryloyl chloride (0.342 mL, 4.2 mmol). After 3 h at 0 °C, the mixture was quenched with an aqueous solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was concentrated at reduced pressure, and the residue was chromatographed on silica gel (EtOAc/hexane 10/90) to furnish 840 mg of compounds **2a** and **2b** (yield, 70%).

Oxazololactam 2a. ^1H NMR (250 MHz, $CDCl_3$): 1.47 (s, 3H), 2.12−2.24 (m, 2H), 2.49 (m, 1H), 2.65 (m, 1H), 2.76 (dd, *J* = 8.5, 9 Hz, 1H), 3.78 (s, 3H), 3.99 (dd, *J* = 7.8, 9.2 Hz, 1H), 4.55 (dd, *J* = 8.2, 9 Hz, 1H), 5.33 (t, *J* = 8 Hz, 1H), 7.19−7.36 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 20.3, 20.5, 29.8, 50.1, 52.4, 58.7, 70.2, 93.9, 125.5, 127.4, 128.7, 139.2, 168.4, 171.4. Mp: 115 °C. $[\alpha]^{20}_D$: +137 (*c* 0.68, $CHCl_3$). IR ($CHCl_3$): 1734, 1655, 1395 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_4$; C, 66.42; H, 6.62; N, 4.84. Found: C, 66.37; H, 6.78; N, 4.77.

Oxazololactam 2b. ^1H NMR (250 MHz, $CDCl_3$): 1.48 (s, 3H), 2.04−2.12 (m, 2H), 2.39−2.68 (m, 2H), 3.10 (t, *J* = 4 Hz, 1H) 3.65 (s, 3H), 3.87 (dd, *J* = 7.8, 9 Hz, 1H), 4.33 (dd, *J* = 8.2, 8.7 Hz, 1H), 5.24 (t, *J* = 7.7 Hz, 1H), 7.11−7.30 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 19.9, 25.9, 27.5, 47.0, 51.9, 59.4, 70.1, 93.8, 125.7, 127.3, 128.6, 139.6, 169.2, 171.5. Mp: 57 °C. $[\alpha]^{20}_D$: +106 (*c* 0.87, $CHCl_3$). IR ($CHCl_3$): 1736, 1655, 1399 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_4$; C, 66.42; H, 6.62; N, 4.84. Found: C, 66.25; H, 6.78; N, 4.66.

Oxazololactam 2c. Oil. Yield: 31%. ^1H NMR (250 MHz, $CDCl_3$): 1.12−2.74 (m, 11H), 3.68 (m, 2H), 3.72 (s, 3H), 3.77 (m, 2H), 4.01 (dd, *J* = 6.75, 9.0 Hz, 1H), 4.47 (dd, *J* = 8.25, 9.0 Hz, 1H), 4.63 (t, *J* = 4.25 Hz, 1H), 5.36 (t, *J* = 7.0 Hz, 1H), 7.17−7.28 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 17.9, 19.7, 29.5, 33.5, 33.8, 49.1, 52.4, 58.5, 64.8, 69.4, 95.8, 103.9, 125.8, 127.3, 128.5, 139.2, 169.4, 171.5. Anal. Calcd for $C_{21}H_{27}NO_6$; C, 64.77; H, 6.99; N, 3.60. Found: C, 64.06; H, 7.28; N, 3.25.

Piperidine 3a. To a solution of oxazololactam **2a** (230 mg, 0.79 mmol) in THF (8 mL) was added at room temperature a solution of $BH_3{\cdot}Me_2S$ in THF (1.58 mL, 3.17 mmol). The mixture

(6) Replacing methyl ester on **2a** by the more crowed ethyl ester affects the stereochemical outcome of the reduction (de = 66%). This result could be explained by considering that for the intermediate **2a′** (Figure 1) the conformer **A** should be relatively more stable then in the case where a methyl ester is present such as in compound **2a**. This effect should affect the diasteroselectivity of the reduction.

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was stirred for 24 h at room temperature and quenched with 10 mL of H_2O. The aqueous phases was extracted with CH_2Cl_2. The organic phase was evaporated under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/cyclohexane 30/70) to furnish 134 mg of piperidine **3a** (oil, yield 61%). ^{1}H NMR (250 MHz, $CDCl_3$): 0.90 (d, J = 6.5 Hz, 3H), 1.30−1.69 (m, 4H), 2.25−2.40 (m, 1H), 2.56−2.64 (m, 2H), 3.04−3.08 (m, 1H), 3.48 (s, 3H), 3.62−3.82 (m, 3H), 7.12−7.25 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 11.9, 23.5, 23.8, 43.7, 46.3, 51.4, 52.7, 61.8, 64.1, 127.6, 128.2, 128.5, 138.7, 174.0. HRMS: calcd for $C_{16}H_{24}NO_3$ 278.1756, found 278.1761. IR ($CHCl_3$): 3440, 1731 cm^{-1}.

Piperidine 3b. To a solution of oxazololactam **2b** (163 mg, 0.56 mmol) in THF (6 mL) was added at room temperature a solution of BH_3·Me_2S in THF (1.12 mL, 2.25 mmol). The mixture was stirred for 24 h and quenched with 10 mL of H_2O. The aqueous phase was extracted with CH_2Cl_2. The organic phase was evaporated under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/cyclohexane 30/70) to furnish 82 mg of piperidine **3b** (oil, yield, 52%). ^{1}H NMR (250 MHz, $CDCl_3$): 1.13 (d, J = 6.6 Hz, 3H), 1.30 (m, 2H), 1.57 (m, 1H), 1.74 (m, 1H), 2.19 (m, 1H), 2.63−2.70 (m, 2H), 2.78 (m, 1H), 3.46 (dd, J = 5.7, 11 Hz, 1H), 3.54 (s, 3H), 3.85 (t, J = 10.2 Hz, 1H), 4.16 (dd, J = 5.2, 10.5 Hz, 1H), 7.03−7.25 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 18.2, 24.9, 27.7, 44.9, 50.8, 51.5, 54.4, 59.4, 60.8, 127.7, 128.2, 128.6, 135.6, 175.2. HRMS: calcd for $C_{16}H_{24}NO_3$ 278.1756, found 278.1750. IR ($CHCl_3$): 3442, 1732 cm^{-1}.

Piperidine 3c. To a solution of oxazololactam **2c** (14.7 mg, 0.037 mmol) in THF (0.4 mL) was added at room temperature a solution of BH_3·THF in THF (0.15 mL, 0.15 mmol). The mixture was stirred for 24 h and quenched with 2 mL of H_2O. The aqueous phase was extracted with CH_2Cl_2. The organic phase was evaporated under reduced pressure, and the residue was chromatographed on silica gel (AcOEt/cyclohexane 50/50) to furnish 6.3 mg of piperidine **3c** (oil, yield, 44%). ^{1}H NMR (250 MHz, $CDCl_3$): 1.22−1.95 (m, 10H), 2.35 (m, 1H), 2.60−2.76 (m, 2H), 3.15 (m, 1H), 3.59 (s, 3H), 3.71−3.90 (m, 6H), 3.99 (t, J = 5.75 Hz, 1H), 4.77 (t, J = 4.5 Hz, 1H), 7.24−7.30 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 21.3, 21.4, 26.9, 27.3, 33.8, 41.7, 41.9, 51.5, 57.9, 62.7, 64.8, 104.4, 127.6, 128.3, 128.5, 140.1, 174.5. HRMS: calcd for $C_{21}H_{32}NO_5$ 378.2280, found 378.2287. IR ($CHCl_3$): 3448, 1728 cm^{-1}.

Piperidine 4a. To a solution of compound **3a** (110 mg, 0.4 mmol) in MeOH (10 mL) and under an atmosphere of hydrogen was added Pd/C 10% (211 mg, 0.20 mmol). The reaction mixture was stirred for 24 h at room temperature and then filtered over Celite, and after evaporation the crude product was chromatographed on silica gel (MeOH/dichloromethane 15/85) to furnish 43 mg of piperidine **4a** (oil, yield, 69%). ^{1}H NMR (250 MHz, $CDCl_3$): 1.04 (d, J = 6.7 Hz, 3H), 1.27−1.35 (m, 1H), 1.53−1.75 (m, 3H), 1.88−1.93 (m, 1H), 2.47 (q, J = 4.2 Hz, 1H), 2.59 (td, J = 3.5, 10.2 Hz, 1H), 2.89 (dd, J = 3.5, 6.7 Hz, 1H), 2.99 (dt, J = 13.2, 4.2 Hz, 1H), 3.60 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$): 19.0, 22.6, 26.2, 44.0, 45.1, 51.1, 52.2, 174.6. $[\alpha]^{20}_D$: +11 (*c* 0.36, $CHCl_3$). HRMS: calcd for $C_8H_{16}NO_2$ 158.1181, found 158.1185. IR ($CHCl_3$): 3400, 1735 cm^{-1}.

Piperidine 4b. To a solution of compound **3b** (73 mg, 0.26 mmol) in MeOH (6.6 mL) and under an atmosphere of hydrogen was added Pd/C 10% (140 mg, 0.13 mmol). The reaction mixture was stirred for 24 h at room temperature and then filtered over Celite, and after evaporation, the crude product was chromatographed on silica gel (MeOH/dichloromethane 15/85) to furnish 37 mg of piperidine **4b** (oil, yield, 89%). ^{1}H NMR (250 MHz, $CDCl_3$): 1.16 (d, J = 6.2 Hz, 3H), 1.43−1.72 (m, 3H), 1.94−1.98 (m, 1H), 2.30 (td, J = 3.7, 11.5 Hz, 1H), 2.68 (td, J = 3.6, 12 Hz, 1H), 2.93 (qd, J = 4, 8.5 Hz, 1H), 3.11−3.16 (m, 1H), 3.61 (s, 3H), 4.49 (bs, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): 19.4, 23.5, 27.6, 45.4, 48.6, 51.7, 53.5, 174.1. $[\alpha]^{20}_D$: −25 (*c* 1.08, $CHCl_3$). HRMS: calcd for $C_8H_{16}NO_2$ 158.1181, found 158.1184. IR ($CHCl_3$): 3400, 1735 cm^{-1}.

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Supporting Information Available: X-ray analysis of compound **2a** and copies of ^{1}H and ^{13}C NMR spectra for compounds **2a**,**b**, **3a**,**b**, and **4a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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