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DIASTEREOSELECTIVE REDUCTION OF CHIRAL ENAMINOLACTONES: A SHORT AND CONVENIENT ROUTE TO ENANTIOPURE (+)-TASHIROMINE

Olivier David, Christian Bellec, Marie-Claude Fargeau-Bellassoued,
and Gérard Lhommet*

Laboratoire de Chimie des Hétérocycles (UMR 7611)
Université Pierre et Marie Curie (Boîte 43), 4 Place Jussieu,
75252 Paris Cedex 05, France. E-mail : lhommet@ccr.jussieu.fr

Abstract - Some chiral β-enamino lactones were reduced catalytically or chemically with good to moderate diastereoselectivity owing to a chiral induction originated from (*S*)-α-methylbenzylamine.
The scope of the present methodology has been extended to the synthesis of an indolizidine alkaloid : (+)-tashiromine. A synthesis of this natural product was achieved in a short and attractive manner (five steps from thiolactam) to enantiopure alkaloid in 25 % overall yield.

INTRODUCTION

We have been interested in the Eschenmoser reaction investigation and in the valorisation of this reaction to have access to various nitrogen-containing fused bicyclic moiety present in the target alkaloids such as pyrrolizidines or indolizidines. In most examples of natural product synthesis using this alkylation-sulfur contraction reaction, the substrate condensed on the thiolactam moiety often involves a primary bromo ester[1-9] whose reduction only permits the creation of a single stereocenter. So we have particularly focused our attention on the condensation of the least currently used substrates such as α- substituted α- bromo esters and bromo lactones whose reduction would generate simultaneously two chiral centers. As for α-substituted bromo esters, we previously reported a direct condensation route without resorting to a triflate intermediate.[10] After a detailed investigation of the double bond reduction[11]- the key step of the process - we extended the scope of this methodology to the synthesis of two alkaloids : (+)-tashiromine and (+)-laburnine in a pure enantiomeric form.[12]

In the case of lactones, we elaborated, a few years ago, a synthesis of N-substituted enamino lactones

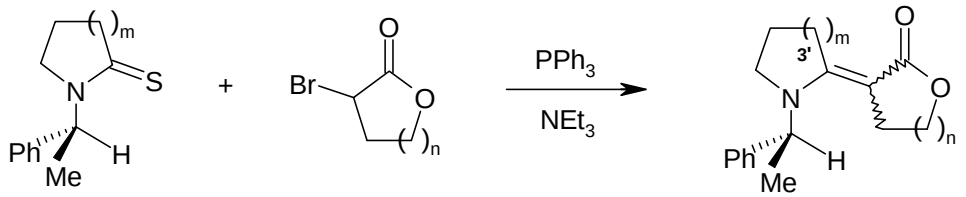
bearing no chiral center. However, our study was then limited to the condensation of bromovalerolactone.[13] In the Eschenmoser reaction, the use of bromo lactones instead of α-substituted bromo esters presents a significant advantage : the condensation with bromo lactones always leads to the expected enamino lactones whatever the size of the thiolactam ring. On the contrary, with α-substituted bromo esters, only pyrrolidine-2-thiones lead to the desired tetrasubstituted enamino esters while the condensation of a six membered ring thiolactam yields the unexpected thienopyridones as the only products. [14] Trisubstituted or tetrasubstituted[15-19] enamino esters have been widely used as synthetic targets in natural product synthesis. However, to our knowledge, only few examples using enamino lactone moieties were reported in literature.[19,20] As far as we are concerned, we wished to generalize the access to these compounds, simultaneously varying the lactone and the thiolactam ring size. In fact, this work was achieved in chiral series in order to create a facial differenciation during the reduction step and to induce a diastereoselectivity in this process. We report herein the synthesis and the diastereoselective reduction of some enamino lactones whose chirality is located on the nitrogen atom, using α-methylbenzylamine as a chiral inductor. An application using the reduction sequence as pivotal step allows us to describe another short and convenient route to (+)-tashiromine in enantiomeric pure form.

RESULTS AND DISCUSSION

The synthesis of chiral β-enamino lactones was carried out transposing the modified Eschenmoser coupling reaction as previously described for N-methyl and N-benzyl substrates.[13] In order to prepare 1-(1*(S)*-phenylethyl)pyrrolidine-2-thione [21] (**1)** or 1-(1*(S)*-phenylethyl)piperidine-2-thione (**2),** 1-(*S*)-phenylethylamine was acylated with 4-chlorobutyryl chloride or 5-chlorovaleryl chloride and the resulting amides were cyclized under phase transfer conditions. The corresponding chiral lactams so obtained were directly transformed into the thiolactams (**1)** and (**2)** by thionation with P_4S_{10}. Thus, compounds **(1)** or **(2)** were heated without solvent at 75°C during half an hour in the presence of α-bromobutyrolactone (**3)** or α-bromovalerolactone (**4)** [23] Triphenylphosphine (or triethylphosphite) and triethylamine were then added and the reaction mixture was treated as reported in the EXPERIMENTAL. Enamino lactones (**5a-c)** were obtained in good yields as a mixture of *E/Z* isomers in which the (*E)*-isomer was the major one, except for **5a** for which the (*Z)*-isomer was not detected (Scheme 1).

E/Z ratios were determined by ^{1}H-NMR spectral measurements. The assignment of (*E*) geometry was effected on the basis of the chemical shift of H-3' (about 2.7 ppm for (*Z*)-isomer and about 3.2 ppm for (*E*)-isomer) for which the methylene protons fall into the deshielding zone of the carbonyl group .[22] Concerning the condensation of thiolactam (**2)** with α-bromovalerolactone (**4)**,[23] the analysis of the crude mixture showed the disappearance of the starting materials and the formation of three major products : Ph_3P=S, undesired Ph_3P=O and the condensation product (**5d)** (m=2;.n=2). Unfortunately many attempts using various eluents did not permit to separate efficiently by chromatography enamino lactone (**5d)** from

Scheme 1



1 m = 1
2 m = 2

3 n = 1
4 n = 2

5a m = 1 , n = 1
5b m = 1 , n = 2
5c m = 2 , n = 1
5d m = 2 , n = 2

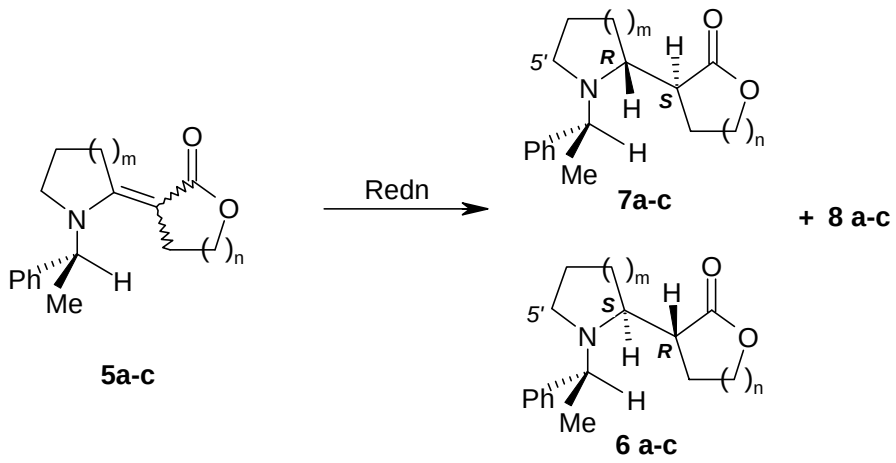
Product	Yield (%)	Ratio *E* / *Z*
5a	85	100/0
5b	70	85/15
5c	65	95/5

triphenylphosphine oxide generated in the reaction. In these conditions, it was not possible to investigate the reduction process with this substrate, since traces of phosphorus compounds strongly inhibit the metal catalyst. Consequently the reaction did not occur.

Due to the decisive nature of this reduction step, a systematic study of ß-enamino lactones reduction was achieved catalytically or chemically in order to investigate the influence of the reducing agent on the observed diastereoselectivity. All the reductions were carried out on the *E*/*Z* mixture of compounds (**5),** which is inseparable by chromatographic methods. In all cases, the expected chiral amino lactones were obtained in good chemical yields as a mixture of two or three diastereoisomers detected in gas chromatography, **6**, **7** and **8**. Diastereoisomer ratios of reduced compounds, determined both by gas chromatography analysis and by ^{13}C NMR spectral measurements, were reported in Scheme 2. In all cases, the main diastereoisomer was **7**, whereas **8** was present in lower proportion or even not detected. For **5b** and **5c** the highest diastereoselectivity was obtained using 5% Pt/C as catalyst whereas no reduction was observed for **5a**. Catalytic hydrogenation in the presence of PtO_2 yielded a moderate diastereoselection and a poor diastereoselectivity was observed in the chemical reduction process with $NaBH(OAc)_3$ /AcOH. With 5% Rh/C as catalyst, we only succeeded in reducing **5c**. Despite a good diastereoselectivity the reduction was too slow (several days) to be efficiently exploited. No reduction occurred with 10% Pd/C (0.1 equiv.) under atmospheric pressure for **5a**, **5b** or **5c** (and under 180 bars for **5a**) and the increase of catalyst amount (0.5 equiv.) only gave rise to debenzylation.

It is interesting to note that all the reductions of **5b** were carried out in AcOEt and not in EtOH orMeOH.

Scheme 2



Reduction of Enamino Lactones (**5a-c)** to Amino Lactones (**6, 7, 8)**.

Redn.	H_2 , PtO_2 [a]			H_2 , 5% Pt/C[a]			$NaBH(OAc)_3$ AcOH			H_2 , 5% Rh/C[a]		
Ratio	**6**	**7**	**8**	**6**	**7**	**8**	**6**	**7**	**8**	**6**	**7**	**8**
5a	12	***69***	19	no reduction			24	***55***	21	no reduction		
5b	30	***70***	-	28	***72***	-	38	***62***	-	no reduction		
5c	27	***68***	5	12	***88***	-	43	***57***	-	10	***90***[b]	-

[a] : in EtOH for **5a** and **5c**, in AcOEt for **5b**.
[b] : very slow

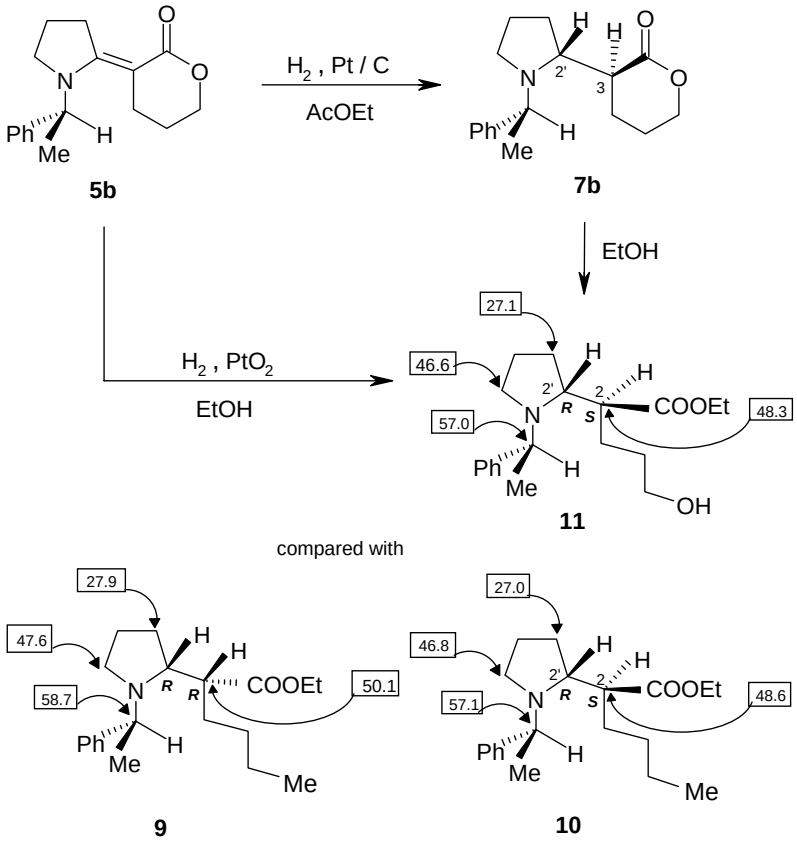
It is interesting to note that all the reductions of **5b** were carried out in AcOEt and not in EtOH or MeOH. Indeed, in these latest solvents, the catalytic hydrogenation of **5b** resulted in concomitant reduction of the exocyclic double bond and the lactone ring opening *via* a transesterification reaction. This second reaction did not occur with five membered ring lactones (**5a)** and (**5c)**.

As we aimed at turning this crucial stereodirecting reduction step to account for a synthetic approach to natural products, it was essential to determine the absolute configuration of the two chiral centers of the major hydrogenated compounds, created in this process. To separate the main diastereoisomer (**7a**, **7b** and **7c)**, each diastereomeric mixture was transformed either to picrate salts (**a** and **b**) or to tetrafluoroborate salt in the case of the reduction mixture of **5c**. Recrystallization in EtOH (**a** and **b**) or AcOEt / EtOH (**c**), then depicratation, afforded diastereoisomers (**7a**, **7b** and **7c)** with d.e. > 99%. To assign its absolute configuration, X-Ray analysis was performed on the picrate salt of **7b** and showed a 2'*R*, 3*S* configuration at

the chiral centers. In the case of the solid (**7c)**, for which a crystal could be obtained, diffraction measurements were directly realized on this chiral aminolactone whose structure was thus also established as the 2'*R*, 3*S* configurations. We have not succeeded in obtaining a crystal of picrate salt of **7a** suitable to X-ray analysis.

It is interesting to note that the 2'*R*, 3*S* configurations could also be indirectly assigned to **7b**. In fact, the comparison of chemical shifts of some significant carbon atoms of both major diastereoisomers (**9)** and (**10)** of 2[1-(1*S*)-phenylethyl-pyrrolidin-2-yl]ethylhexanoate, previously described, whose structures are known (respectively 2*R*, 2'*R* for **9** and 2*S*, 2'*R* for **10**) [11] with those of compound (**11)**, allows us to assign to **11** the structure of **10** (Scheme 3) .The same chiral amino alcohol (**11)** was obtained as a major product either by catalytic hydrogenation of **5b** on PtO_2 in EtOH or by reduction on 5% Pt/C in AcOEt followed by a treatment with EtOH which effects the transesterification reaction. Epimerization at C-3 can be ruled out, as the nucleophilic attack occurs at the carbon of the carbonyl group. Thus, if **11** has the 2'*R*, 2*S* configurations, **7b** normally has the same absolute configurations 2'*R*, 3*S*.

Scheme 3

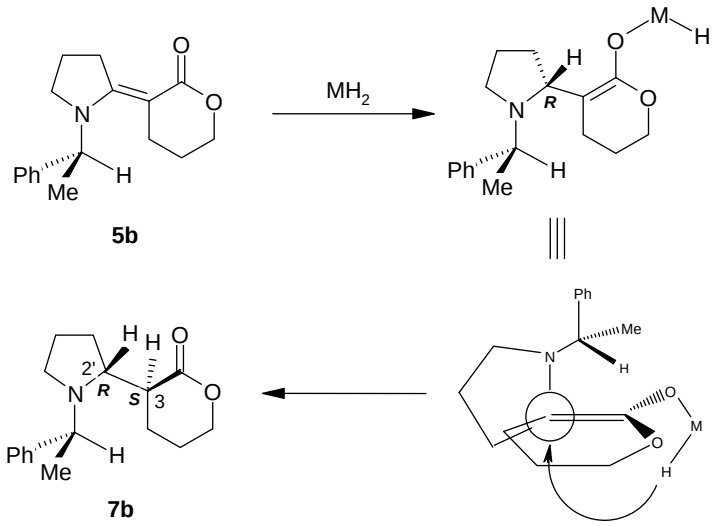


An assignment of the absolute configurations of minor diastereoisomers (**6a)** and (**6b)** can be proposed, based on the C5' chemical shift in ^{13}C NMR. Indeed, this shift is closely related with the diastereoisomer absolute configurations of the β-amino ester series[11,12] and the chiral cyclic amino diesters[12], that we have previously described. Only the chemical shifts of the two major diastereomers (*2S*, *2'R*) and (*2R*, *2'R*) have

been reported for five β-amino esters and diesters : 46.3 ppm < δ C-5'(*2S*, *2'R*) < 46.8 ppm and 47.5 ppm < δ C-5'(*2R*, *2'R*) < 47.8 ppm. However, for the diesters, a correlation leading to a consistent assignment of the two minor diastereomers (*2R*, *2'S*) and (*2S*, *2'S*) has been proposed.[12] For each (*2R*, *2'S*) stereomer, we noted δ C-5' = 48.6 ppm. Besides, for the β-amino ester series, the C-5' chemical shift of the third diastereomer observed is located between 48.5 and 48.7 ppm, which also permits to assign the (*2R*, *2'S*) configurations to this latest series. In the case of the enamino lactone (**5a)** reduction product, we noted δ C-5' = 46.9 ppm for major diastereomer (*3S*, *2'R*) **7a**, in good agreement with the preceding values. On the other hand, concerning **6a**, δ C-5' = 48.4 ppm reasonably allows to assign (*3R*, *2'S*) configurations to this diastereomer; the same result is attributable to **6b** (δ C-5' = 48.8 ppm).

It should be noted that the configurations of the two stereogenic centers created during the reduction of the exocyclic double bond are the same for the enamino lactones (**5a-c)** as for the enamino esters and diesters previously described.[11,12] A similar hypothesis to those suggested for this enamino ester reduction could be advanced for enamino lactones. The most favored transition state structure (Scheme 4) in which the 1,3-allylic strain is minimized, allows the hydrogen approach on the less hindered face and leads to a *S* configuration for the stereocenter at C- 3. The other transition state is strongly disfavored by a significant $A^{(1,3)}$-strain between the oxygen atom and the methylene group of the pyrrolidine ring.

Scheme 4



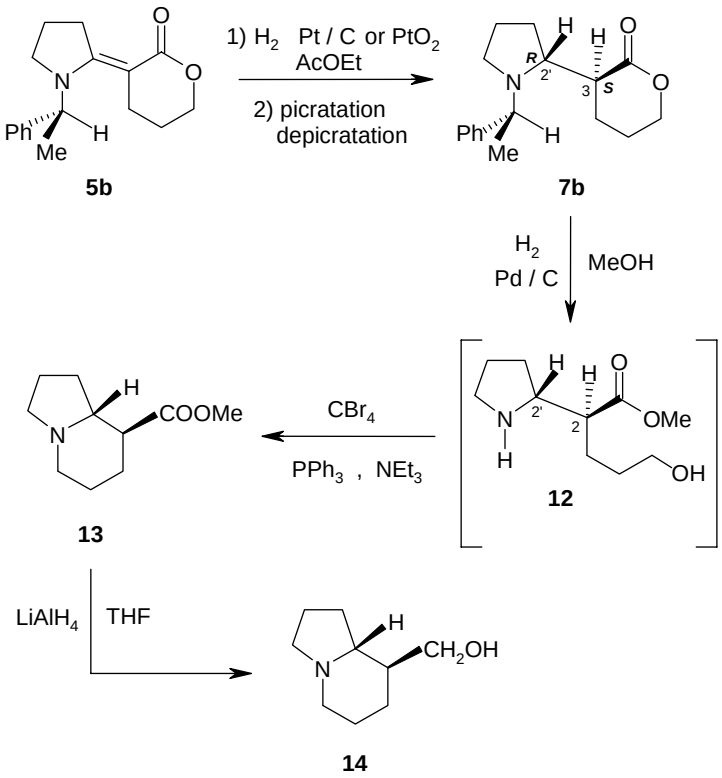
The obtention of a major diastereomer in the reduction step (about 70% in the diastereoisomeric mixture) and the easiness of separation of this hydrogenated compound *via* a picratation-depicratation sequence, encourage us to exploit these results for the synthesis of a natural product. Since piperidine tetrasubstituted enamino esters could not be obtained through the Eschenmoser condensation,[14] it would be interesting to involve the six membered ring compounds (**5c)** and (**5d)** in the synthesis of a indolizidine or quinolizidine alkaloid. However, the ring opening of the five membered lactones (**5c)** and (**5a)** occurred with some difficulties. Hard conditions were necessary and led to epimerisation at C-3, thus reducing the interest for the synthesis. Nevertheless, we successfully developped an enantiomeric approach of (+)-tashiromine **(14)**;

indeed, absolute configurations (*2'R, 3S*) of major diastereoisomer (**7b)** agree with the relative stereochemistry of this alkaloid chiral centers.

In a preceding paper,[12] we described a short and attractive route to this alkaloid which was isolated in 1990 from stems of a deciduous shrub of subtropical Asia: *Maackia tashiroï*. Including our own contribution, only four enantiomeric approachs [24-26] have been previously reported. Among those, the two most recent works [12,26] lead to (+)-tashiromine in a pure enantiomeric form. Indeed $[\alpha]_{20}^{D}$ obtained for this indolizidine by D.C. Ha and his co-workers [26] was in good agreement with the value we reported.[12]

In the present work, the first two steps of our synthetic route (Scheme 5) are the access to chiral β-enamino lactone (**5b)** and its reduction into the diastereoisomeric mixture of **6b**, **7b**, **8b.** The main

Scheme 5



diastereoisomer (**7b)** was isolated by a picratation-depicratation sequence. Once the chiral control achieved, the α-methylbenzyl group was removed by hydrogenolysis in the presence of 10% Pd/C (0.6 equiv) in methanol. Noteworthy was the concomitant lactone ring opening, in these reaction conditions, leading to amino alcohol (**12)**.[27] Under the exposure to Ph_3P/CBr_4, **12** was converted into an alkoxyphosphonium salt;[28] the addition of triethylamine then afforded the cyclization leading to the second ring formation giving rise to the bicyclic ester (**13)**. The synthesis was completed in a last step with the reduction of the ester moiety using $LiAlH_4$ in THF at room temperature; no epimerisation was observed in these conditions for this thermodynamic compound.

Thus (+)-tashiromine (5*R*, 6*S*) (**14)** was isolated in 25 % yield in optically pure form, from chiral thiolactam (**1)**. ^{1}H and ^{13}C NMR spectra were in complete agreement with those previously described.

The measured optical rotation $[\alpha]^{D}_{20} = + 44.8°$ (c 1.58, EtOH) was in total concordance with our value previously assigned[12]: $[\alpha]^{D}_{20} = + 44.7°$ and the one of Ha and co-workers[25] : $[\alpha]^{D}_{20} = + 43.4°$.

CONCLUSION

We have shown that several chiral enamino lactones can be easily obtained by an efficient direct condensation of bromolactones with thiolactams through the Eschenmoser sulfur extrusion reaction. The crucial diastereoselective reduction step which yields to a major diastereomer, was applied to the synthesis of a natural product. Thus, enantiopure (+)-tashiromine was readily prepared in five steps from chiral thiolactam in 25% overall yield.

EXPERIMENTAL SECTION

General :

Melting points (Buchi 535) were uncorrected. Capillary gas chromatography : chromatographs with flame ionization detector using CP-SIL 5 (Chrompack) columns. Column chromatography : silica gel 60 (Merck 230-400 mesh); reactions monitored by TLC on Kieselgel 60 F_{254} (Merck); detection effected by examination under UV light. ^{1}H and ^{13}C NMR spectra : Bruker apparatus at 250 and 62.5 MHz, respectively, in $CDCl_3$ referenced to Me_4Si for the proton spectra and the solvent for the carbon spectra. Elemental analyses : performed by the Service de Microanalyse, Université Pierre et Marie Curie. IR spectra : recorded (Philips PU 9706) as thin films on NaCl plates. Optical rotations : Perkin Elmer 241 digital polarimeter. Dichloromethane was distilled from CaH_2. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Methanol and ethanol were dried by refluxing with magnesium methoxide or ethoxide and distilled. (*S*)-α-Methylbenzylamine was purchased from Aldrich (99% e.e.).

1-(1(*S*)-Phenylethyl)piperidin-2-one :

To a solution of α-methylbenzylamine (20.9 g, 172 mmol) and pyridine (15.3 mL, 189 mmol) in 100 mL of CH_2Cl_2 cooled at 0°C, was added dropwise 29.4 g (189 mmol) of 5-chlorovaleryl chloride. The mixture was stirred at rt for 12 h. The solvent was evaporated, toluene (400 mL), tetrabutylammonium chloride (3.8 g, 17 mmol) and NaOH solution (200 g in 400 mL of water) were then added. The mixture was refluxed for 48 h. The aqueous layer was extracted with CH_2Cl_2 (3x150 mL) then Et_2O (150 mL) and the combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the lactam was obtained (33 g, yield 99 %) and used without further purification in the next step : oil – IR($CHBr_3$) : 1680 cm^{-1} – ^{1}H NMR : (250 MHz, $CDCl_3$): 7.3-7.05 (m,5H), 6.1 (q, 1H, *J* = 7.1 Hz), 3.1-2.95 (m, 1H), 2.8-2.65 (m, 1H), 2.4 (t, 2H, *J* = 6.8 Hz), 1.7-1.5 (m, 4H), 1.45 (d, 3H, *J* = 7.1 Hz); $[\alpha]^{20}_{D} = - 167°$ (c 0.9, CH_2Cl_2); – ^{13}C NMR : 169.3, 140.3, 128.2, 127.1, 127.0, 49.4, 41.2, 33.3, 23.0, 21.0, 15.1.

1-(1(*S*)-Phenylethyl)piperidin-2-thione (2) :

A mixture of 1-(1(*S*)-phenylethyl)piperidin-2-one (15 g, 74 mmol) and P_4S_{10} (6.57 g, 14.8 mmol) was refluxed in 100 mL of benzene during 12 h. The solution was made alkaline (pH ≈ 10) with a saturated K_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2 (4x100 mL). Organic layers were dried over Na_2SO_4 and solvent was evaporated. Crude thiolactam (**2)** was obtained and recrystallized in cyclohexane/ethanol (95/5); 10.68 g (66 %) ; mp 78°C – IR($CHBr_3$) : 1075 cm^{-1} – ^1H NMR : 7.3-7.1 (m, 6H), 3.2-3.0 (m, 3H), 2.95-2.8 (m, 1H), 1.7-1.55 (m, 4H), 1.5 (d, 3H, *J* = 7 Hz) – ^{13}C NMR : 200.3, 138.8, 128.6, 127.7, 127.1, 57.7, 44.1, 41.9, 22.6, 20.2, 14.3; $[\alpha]^{20}_D$ = - 419° (c 1.02, CH_2Cl_2); Anal. Calcd for $C_{13}H_{17}NS$: C, 71.18 ; H, 7.81 ; N, 6.39. Found: C, 71.07 ; H, 7.88 ; N, 6.49.

3-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-ylidene]dihydrofuran-2-one (5a) :

A mixture of 1-[1(*S*)-phenylethyl]pyrrolidine-2-thione (**1)** (10 g, 48.7 mmol) and α-bromobutyrolactone (**3)** (16 g**,** 97.5 mmol) was heated without solvent at 75°C during 30 min. Triethyl phosphite (16 g, 97.4 mmol) and triethylamine (9.8 g, 97.4 mmol) were then added in 50 mL of CH_2Cl_2. After about 2 h. of stirring at rt, the solvent (CH_2Cl_2) was removed. The reaction mixture was heated with ether. The triethylammonium salt which precipitates was filtered. The resulting solution was then cooled at –10°C and leads to the crystallisation of the enamino lactone (**5a)** as a sole (*E*)-diastereoisomer : 10.65 g ; (85%); mp 100°C – IR ($CHBr_3$) :1705, 1590 cm^{-1} – ^1H NMR : 7.4-7.1 (m, 5H), 5.4-5.25 (q, 1H, *J* = 7 Hz), 4.2-4.05 (m, 2H), 3.4-2.8 (m, 6H), 1.9-1.65 (m, 2H), 1.55 (d, 3H, *J* = 7 Hz) – ^{13}C NMR : 174.8, 160.4, 128.8, 127.6, 126.4, 81.3, 64.1, 53.0, 47.3, 33.1, 27.7, 21.2, 17.7 – Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68 ; H, 7.44 ; N, 5.44. Found: C, 74.59 ; H, 7.49 ; N, 5.57.

3-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-ylidene]tetrahydropyran-2-one (5b) :

A mixture of 1-[1(*S*)-phenylethyl]pyrrolidine-2-thione (**1)** (4 g, 19.2 mmol) and α-bromovalerolactone (**4)** (10 g**,** 57.6 mmol) was heated without solvent at 75°C during 0.5 hour. Triphenylphosphine (10 g, 38.4 mmol) and triethylamine (3.9 g, 38.4 mmol) were then added in 20 mL of CH_2Cl_2. The reaction mixture was stirred at rt for 12 h. CH_2Cl_2 was added. The mixture was washed with a saturated NH_4Cl solution (2 x 50 mL), water (50 mL), then dried over Na_2SO_4 and solvent was evaporated. The crude product was chromatographed on a silica gel column (MeCN) to give the enamino lactone (**5b)** as a mixture of *E*/*Z* diastereoisomers, 85/15; 3.7 g ; 3.64 g (70 %); oil – IR ($CHBr_3$) : 1740, 1640 cm^{-1} – ^1H NMR : 7.4-7.15 (m, 5H), 5.7 (q, 0.85H, *J* = 7 Hz), 5.4 (q, 0.15H, *J* = 7 Hz), 4.2 (t, 1.7H, *J* = 5.1 Hz), 4.1 and 3.85 (2m, 0.3H,), 3.45 and 3.25 (2m, 0.3H), 3.25 and 2.9 (2m, 1.7H), 3.15 (t, 1.7H, *J* = 7.8 Hz), 2.6 and 2.5 (2m, 0.3H), 2.6 (m, 1.7H), 2.5 and 2.3 (2m, 0.3H), 1.85 (m, 2H), 1.8 (m, 2H), 1.6 (d, 3H, *J* = 7 Hz) – ^{13}C NMR : **5b(*E*)** 168.3, 166.7, 140.8,128.3, 127.1, 126.4, 87.8, 67.1, 54.6, 47.0, 36.2, 26.0, 23.3, 21.2, 17.3 – **5b(*Z*)** 167.1, 164.1, 141.8, 84.5, 66.5, 55.4, 49.3, 34.7, 25.8, 23.3, 19.7, 16.6 – Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24 ; H, 7.80 ; N, 5.16. Found: C, 74.99 ; H, 7.88 ; N, 5.31.

3-[1-(1(*S*)-Phenylethyl)piperidin-2-ylidene]dihydrofuran-2-one (5c) :

A mixture of 1-[1(*S*)-phenylethyl]piperidine-2-thione (**2)** (3 g, 13.7 mmol) and α-bromobutyrolactone (**3)** (5.64 g**,** 34.2 mmol) was heated without solvent at 75°C during 40 min. Triphenylphosphine (7.17 g, 27.4 mmol) and triethylamine (2.76 g, 27.4 mmol) were then added in 20 mL of CH_2Cl_2. The reaction mixture was stirred at rt for 12 h. The solvent (CH_2Cl_2) was removed and AcOEt was added. A part of phosphines which precipitates were filtered and AcOEt was evaporated. The crude mixture was chromatographed on a silica gel column (CH_2Cl_2 then THF) to give the enamino lactone (**5c)** as a mixture of *E*/*Z* diastereoisomers, 97/3 ; 2.43 g ; (65 %) ; oil – IR ($CHBr_3$) : 1695, 1560 cm^{-1} – ^1H NMR : 7.4-7.1 (m, 5H), 5.6 (q, 0.03H, *J* = 7 Hz), 5.15 (q, 0.97H, *J* = 7 Hz), 4.05 (t, 2H, *J* = 7.2 Hz), 3.25-3.05 (m, 2H), 3.0-2.85 (m, 3H), 2.8-2.7 (m, 1H), 1.7-1.35 (m, 4H), 1.55 (d, 3H, *J* = 7 Hz) – ^{13}C NMR : **5c(*E*)** 173.9, 161.4, 140.6, 128.8, 127.6, 126.9, 86.8, 63.2, 56.1, 40.6, 29.7, 24.3, 21.7, 18.2, 17.2; – **5c(*Z*)** 169.2, 159.4, 141.1, 85.3, 63.2, 60.6, 41.4, 30.0, 26.2, 21.7, 18.6, 15.7 – Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24 ; H, 7.80 ; N, 5.16. Found: C, 75.46 ; H, 7.90 ; N, 5.05.

General procedure for catalytic hydrogenation with platinum oxide.

PtO_2 (114 mg) was added to a degassed solution of β-enamino lactone (**5)** (1.0 mmol) in ethanol (20 mL) (**5a** and **5c**) or AcOEt (20 mL) for **5b**. The resulting suspension was hydrogenated under atmospheric pressure. The reaction was monitored by gas chromatography. At the end of the reaction, after consumption of 1 mol of H_2 per mol of **5**, the solution was filtered. The filter cake was rinsed with EtOH or AcOEt and the solvent removed. The crude mixture of diastereomers (**6**, **7**, **8)** was directly analyzed by gas chromatography and ^{13} C NMR.

General procedure for catalytic hydrogenation with 5% platinum on charcoal.

Platinum on 5% charcoal (55 mg) was added to a degassed solution of β-enamino lactone (**5)** (1.0 mmol) in ethanol (20 mL) (**5a** and **5c**) or AcOEt (20 mL) for(**5b**). The resulting suspension was hydrogenated under atmospheric pressure and treated according to the general procedure used for PtO_2 reduction.

General procedure for catalytic hydrogenation with 5% rhodium on charcoal.

5% Rh/C (55 mg) was added to a degassed solution of β-enamino lactone (**5)** (1.0 mmol) in ethanol (20 mL) or AcOEt (20 mL) for **5b**. The resulting suspension hydrogenated as the same work up as above gave a mixture of diastereoisomers (**6**, **7**, **8)** which was directly analyzed.

General procedure for chemical reduction.

A solution of $NaBH(AcO)_3$ was prepared with $NaBH_4$ (186 mg, 5 mmol) and 2.8 mL of acetic acid cooled at 0°C. After 30 min of stirring at rt, a solution of β-enamino lactone (**5)** (1.0 mmol) in MeCN (5 mL) was added and the mixture stirred for 48 h. The solution was neutralized with a saturated Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2 and extract was washed with water ; organic phase was then dried (Na_2SO_4) and evaporated.

3-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]dihydrofuran-2-one (6a-8a) :

Reduction of **5a**. Yields : 93 % (PtO_2), 87 % ($NaBH(AcO)_3$) ; oil – IR ($CHBr_3$) : 1730 cm^{-1}– ^1H NMR **7a** :7.3-7.05 (m, 5H), 4.2 (m, 2H), 3.85 (q, 1H, *J* = 6.7 Hz), 3.5 (m, 1H), 2.6-2.5 (m, 2H), 2.5-2.3 (m, 2H),

2.2-2.05 (m, 1H), 2.0-1.9 (m, 1H), 1.7-1.5 (m, 3H), 1.25 (d, 3H, J = 6.7 Hz) – ^{13}C NMR **7a** :178.9, 144.5, 127.9, 127.3, 126.3, 66.7, 59.4, 57.8, 46.9, 44.4, 30.9, 24.0, 23.3, 11.9 ; **8a** : 178.4, 145.1, 66.6, 60.7, 60.3, 49.7, 42.3, 27.2, 23.9, 23.5, 17.5 ; **6a** : 179.4, 141.2, 67.2, 58.9, 58.5, 48.4, 44.9, 33.9, 23.7, 23.4, 21.1– **7a** : $[\alpha]^{20}_D$ = – 3.0° (c 1.86, CH_2Cl_2) – Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10 ; H, 8.16 ; N, 5.40. Found: C, 74.32 ; H, 8.01 ; N, 5.45.

3-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]tetrahydropyran-2-one (6b-8b) :

Reduction of **5b**. Yields : 95 % (PtO_2), 91 % (Pt/C), 86 % ($NaBH(AcO)_3$) ; oil – IR ($CHBr_3$) : 1735 cm^{-1} – ^{1}H NMR **7b** : 7.4-7.15 (m, 5H), 4.3-4.1(m, 2H), 3.9 (q, 1H, J = 6.6 Hz), 3.7-3.6 (m, 1H), 2.75-2.55 (m, 2H), 2.5-2.35 (m, 1H), 2.05-1.75 (m, 6H), 1.75-1.6 (m, 2H), 1.35 (d, 3H, J = 6.6 Hz) – ^{13}C NMR **7b** :173.9, 143.4, 128.1, 127.5, 126.5, 68.9, 61.1, 58.2, 47.3, 44.9, 30.4, 24.0, 22.5, 20.5, 12.7 –**7b** : $[\alpha]^{20}_D$ = – 12.4° (c 1.56, CH_2Cl_2) – Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69 ; H, 8.48 ; N, 5.12. Found: C, 74.51 ; H, 8.36 ; N, 5.33.

3-[1-(1(*S*)-Phenylethyl)piperidin-2-yl]dihydrofuran-2-one (6c-8c) :

Reduction of **5c**. Yields : 92 % (PtO_2), 94 % (Pt/C), 84 % ($NaBH(AcO)_3$) , 90 % (Rh/C) ; **7c** : mp 65°C – IR ($CHBr_3$) : 1730 cm^{-1} – ^{1}H NMR **7c** : 7.4-7.1 (m, 5H), 4.05 (m, 2H), 3.9 (q, 1H, J = 6.6 Hz), 2.85-2.75 (m, 1H, $J_{2'-3}$ = 6.3 Hz), 2.7-2.6 (m, 1H), 2.55-2.45 (m, 2H), 2.35-2.1 (m, 2H), 1.70-1.55 (m, 2H), 1.5-1.35 (m, 3H), 1.25 (d, 3H, J = 6.6 Hz), 1.25-1.2 (m, 1H) – ^{13}C NMR **7c** : 178.6, 145.1, 128.0, 127.0, 126.5, 63.4, 56.1, 54.4, 43.3, 41.8, 26.5, 23.8, 22.5, 22.3, 15.4 ; **6c** : 178.5, 143.7, 66.9, 57.5, 53.9, 44.8, 40.8, 25.6, 24.2, 22.4, 22.2, 8.7 ; **8c** : 179.0, 146.0, 66.4, 57.1, 52.6, 42.5, 38.9, 27.0, 22.2, 19.5, 19.2, 11.9 – **7c** : $[\alpha]^{20}_D$ = – 45.6° (c 1.08, CH_2Cl_2) – Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69 ; H, 8.48 ; N, 5.12. Found: C, 74.55 ; H, 8.58 ; N, 5.03.

General procedure for separation of main diastereomers (7a, 7b, 7c) from the mixture (6-7-8) : Picric acid (1.1 eq) was added to a mixture of **6-7-8a** or **6-7-8c** in a few mL of MeOH. Ether was added and picrate which precipitates was filtered, rinsed with Et_2O and then recrystallized in n-BuOH for **a** or ethanol for **b**, up to constant melting point. The depicratation was effected with a saturated K_2CO_3 solution then K_2CO_3 solid. The cake so obtained was triturated with CH_2Cl_2. After three extractions and evaporation of the solvent, pure **7a** (yield 63%) and **7b** (yield 55%) were obtained. Tetrafluoroborate of **6-7-8c** mixture was obtained with 1.2 eq of a HBF_4 solution (48% in water) and the salt was recrystallized in a mixture AcOEt / EtOH 2/1. With the same work up as for depicratation, **7c** was obtained in 65% yield.

4-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]butan-2-ol (11) :

To a degassed solution of β-enamino lactone (**5b)** (540 mg, 2 mmol) in AcOEt (20 mL) was added PtO_2 (270 mg). The resulting suspension was hydrogenated under atmospheric pressure. At the end of the reaction, after consumption of 1 mol of H_2 per mol of **5b**, the solution was filtered. The filter cake was rinsed with AcOEt and the solvent removed. The crude product was chromatographed on a silica gel column (CH_2Cl_2 then MeOH /NH_4OH 9/1) ; 555 mg (87 %); oil – IR ($CHBr_3$) : 3400, 1725 cm^{-1} – ^{1}H NMR : 7.4-7.05 (m, 5H), 4.15-3.95 (m, 3H), 3.5 (t, 2H, J = 6.2 Hz), 3.0-2.95 (m, 1H), 2.6-2.5 (m, 2H), 2.45-2.35 (m, 1H), 1.95-1.8 (m, 2H), 1.75-1.3 (m, 6H), 1.25 (d, 3H, J = 6.6 Hz), 1.2-1.1 (m, 1H), 1.15 (t, 3H, J = 7.1 Hz) – ^{13}C NMR : 175.1,

144.7, 128.2, 127.7, 127.4, 126.7, 62.7, 61.7, 59.8, 57.0, 48.3, 46.7, 30.7, 27.0, 26.1, 23.2, 14.0, 12.4 – Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44 ; H, 9.15 ; N, 4.39. Found: C, 71.57 ; H, 9.08 ; N, 4.32.

Methyl octahydroindolizidine-8-carboxylate (13) :

To a degassed solution of β-amino lactone (**7b)** (600 mg, 2.2 mmol) in MeOH (30 mL) was added 10% Pd/C (300 mg). The resulting suspension was stirred under atmospheric pressure of hydrogen for 24 h. At the end of the reduction, monitored with GC, the solution was filtered, the insoluble material was washed with MeOH and the solvent was removed. The crude pyrrolidine alcohol (**12)** was used without further purification in the next step. To a cooled (0°C) stirred mixture of **12** (422 mg, 2.1 mmol), CBr_4 (836 mg, 2.5 mmol) and CH_2Cl_2 (8 mL) was added Ph_3P (815 mg, 3.1 mmol) in 4 mL of CH_2Cl_2. The mixture was stirred at 0°C for 30 min and Et_3N (2.9 mL) was then added. After 1 h, the residue was extracted with 2M HCl (5x20 mL). The combined aqueous layers were neutralized with solid Na_2CO_3, then extracted with CH_2Cl_2 (3x20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed. The crude product was purified by chromatography on a silica gel column ($CHCl_3$/MeOH, 97/3); oil, 307 mg (80%). $[\alpha]^{20}_D$ = + 69° (c 1.90, MeOH)– IR ($CHBr_3$) 1740 cm^{-1} – ^1H NMR : 3.65 (s, 3H), 3.15-3.0 (m,2H), 2.35-2.2 (m, 1H)), 2.2-2.05 (m, 2H), 2.05-1.85 (m, 3H), 1.8-1.55 (m, 4H), 1.55-1.3 (m, 2H) – ^{13}C NMR : 174.3, 64.7, 53.7, 51.9, 51.0, 47.6, 29.3, 28.9, 27.8, 24.5, 20.2 – Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54 ; H, 9.35 , N, 7.64. Found: C, 65.45 ; H, 9.45 , N, 7.71.

(+)-Tashiromine (14) :

A mixture of ester (**13)** (218 mg, 1.1 mmol) and $LiAlH_4$ (170 mg, 4.4 mmol) was stirred in freshly distilled THF (25 mL) for 24 h at rt. The residue was quenched with 400 µL of water, 400 µL of 15% NaOH solution and then 1 mL of water. After filtration and evaporation of the solvent, the crude product was distilled on a Kugelrohr apparatus (120°C, 0.1 mm Hg) ; white solid, mp 35°C, 146 mg (86%) – IR ($CHBr_3$) 3600-3100 cm^{-1} – ^1H NMR: 3.9-3.8 and 3.7-3.65 (2m, 2H), 3.3-3.2 (m, 2H), 2.3-2.2 (q, 1H, J = 17.8 Hz), 2.2 - 2.0 (m, 3H), 2.0-1.8 (m, 2H), 1.75-1.65 (m, 3H), 1.3 -1.15 (m, 1H) – ^{13}C NMR: 66.5, 65.5, 54.2, 52.7, 44.5, 28.9, 27.6, 25.0, 20.6 ; $[\alpha]^{20}_D$ = + 44.8° (c 1.58, EtOH) – Anal. Calcd for $C_9H_{17}NO$: C, 69.63 ; H, 11.04 ; N, 9.02. Found: C, 69.72 ; H, 11.01 ; N, 9.11.

REFERENCES AND NOTES

1. J.P. Michael and D. Gravestock, *Eur. J. Org. Chem.,* 1998 ,865.
2. J.P. Michael and D. Gravestock, *Synlett*, 1996, 981.
3. M. Ghiaci and M. Adibi, *Org. Prep. Proced. Int.*, 1996, **28**, 474.
4. J. G. Sosnicki and J. Liebscher, *Synlett*, 1996, 1117.
5. M. J. Munchof and A.I. Meyers, *J. Am. Chem. Soc*., 1995, **117**, 5399.
6. J.J. Kiddle, D.L.C. Green, and C.M. Thompson, *Tetrahedron*, 1995, **51**, 2851.
7. G. R. Cook, L. G. Beholz, and J. R. Stille, *Tetrahedron Lett.*, 1994, **35***,* 1669.

8. J. P. Michael, A.S. Howard, R.B. Katz, and M.I. Zwane, *Tetrahedron Lett.*, 1992, **33**, 4751.
9. D. J. Hart, W.-P. Hong, and L.-Y. Hsu *J. Org. Chem.*, 1987, **52**, 4665.
10. P. Marchand, M.-C. Fargeau-Bellassoued, C. Bellec, and G.Lhommet, *Synthesis* , 1994, 1118.
11. J. Blot, A. Bardou, C. Bellec, M.-C.Fargeau-Bellassoued, J.-P. Célérier, G. Lhommet,
12. D. Gardette, and J.-C. Gramain, *Tetrahedron Lett.*, 1997, **38**, 8511.
12. O. David, J. Blot, C. Bellec, M.-C. Fargeau-Bellassoued, G. Haviari, J.-P. Célérier, G. Lhommet, J.-C. Gramain, and D. Gardette, *J. Org. Chem*., 1999, **64**, 3122.
13. P. Marchand, M.-C. Bellassoued, C. Bellec, and G. Lhommet, *Synth. Commun*., 1994, **24**, 2577.
14. P.Marchand, C. Bellec, M.-C. Fargeau-Bellassoued, C. Nezry, and G. Lhommet, *Heterocycles*, 1996, **43**, 63.
15. R. Lin, J. Castells, and H. Rapoport, *J. Org. Chem.*, 1998, **63**, 4069.
16. A. Hernàndez, M. Marcos, and H. Rapoport, *J. Org. Chem.*, 1995, **60**, 2683.
17. M. Hashimoto, K. Yamada, and S. Terashima, *Chem. Lett.*, 1992*,* 975.
18. F. J. Sardina, M. H. Howard, M. Morningstar, and H. Rapoport, *J. Org. Chem.*, 1990, **55**, 5025.
19. A. S. Hernàndez, A. Thaler, J. Castells, and H. Rapoport, *J. Org. Chem.*, 1996, **61**, 314.
20. O. Provot, J.-P. Célérier, H. Petit, and G. Lhommet, *J. Org. Chem*., 1992, **57**, 2163.
21. T. Nikiforov, S. Stanchev, B. Milenkov, and V. Dimitrov, *Heterocycles*, 1986, **24**, 1825.
22. J.P. Michael, G.D. Hosken, and A.S. Howard, *Tetrahedron*, 1988, **44**, 3025.
23. J. J. Wolff, G.Frenking, and K. Harms, *Chem. Ber.*, 1991, **124**, 551.
24. Y. Nagao, W.-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, *J. Org. Chem*., 1990, **55**, 1148.
25. J. L. Gage and B.P. Branchaud, *Tetrahedron Lett.*, 1997, **38**, 7007.
26. D.-C. Ha, S.-H. Park, K.-S. Choi, and C.-S. Yun, *Bull. Korean Chem. Soc*., 1998, **19**, 728.
27. This transesterification reaction of the lactone ring could be effected with ethanol or methanol but this reaction was achieved in MeOH with the aim to simplify NMR spectra of subsequent compounds.
28. Y. Shishido and C. Kibayashi, *J. Org. Chem*., 1992, **57**, 2876.