Enamino Ester Reduction: A Short Enantioselective Route to Pyrrolizidine and Indolizidine Alkaloids. Synthesis of (+)-Laburnine, (+)-Tashiromine, and (−)-Isoretronecanol

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Various chiral pyrrolidine tetrasubstituted β-enamino esters were reduced catalytically or chemically with good to moderate diastereoselectivity owing to a chiral induction originated from (*S*)-α-methylbenzylamine. With endocyclic double bond compounds, the best result was obtained using PtO_2 as hydrogenation catalyst and led to a major syn addition product (e.d. 90%). In the case of exocyclic double bond compounds, hydrogenation over Pd/C gave rise to the higher diastereoselectivity and mainly afforded the unexpected anti addition product (e.d. 84%). The scope of these reductions has been extended to the synthesis of three pyrrolizidine or indolizidine alkaloids: (+)-tashiromine, (+)-laburnine, and (−)-isoretronecanol. Syntheses of these natural products, starting from chiral β-enamino diesters, were achieved in a short and convenient manner, leading to enantiopure compounds in good overall yields.

Introduction

Enamino esters are recognized as very useful intermediates for the synthesis of alkaloids.[1] The specific interest of these compounds resides in their polyfunctionality: they carry simultaneously a nitrogen atom, a double bond (the reduction of which can create one or two stereocenters), and an ester moiety which potentially allows extension of the side chain or ring closure.[2] The β-enamino ester moiety is particularly suitable for the synthesis of the nitrogen-containing fused bicyclic system present in indolizidine[3] or pyrrolizidine alkaloids, whose chirality is generally located in the α- and β-position of the nitrogen atom. In this context, the reduction of the double bond which generates the chiral center(s) will be the key step of the sequence in order to obtain the desired stereochemistry of these alkaloids.

Several synthetic approaches to natural products have been reported, using trisubstituted enamino esters intermediates.[1a−c,4] However, with these substrates, a single stereocenter is generated during the reduction. Aiming to create simultaneously two stereogenic centers in this reduction step, we have been interested for some time in the β-enamino ester synthesis with a tetrasubstituted endocyclic or exocyclic double bond; in particular, we developed a simple route using secondary α-halogeno esters directly instead of triflates in the Eschenmoser coupling reaction.[5] The presence of a chiral center on the β-enamino ester is required to create a facial differenciation during the reduction process, to induce a diastereoselectivity in this pivotal step. This chirality can be localized either on the ester moiety or at the α-position of the nitrogen atom. For our part, we retained this last solution in which the initial source of chirality was supplied by α-methylbenzylamine (ee 99%) which is commercially available under both enantiomeric forms.

In short preceding papers, we described the synthesis with a good diastereoisomeric excess of chiral cyclic amino esters from tetrasubstituted β-enamino esters with an endocyclic[6] or exocyclic[7] double bond. These amino esters, with an appropriate functionalized carbon chain (such as a second ester moiety), are potential precursors of pyrrolizidine and indolizidine alkaloids. Thus, we described in a preliminary paper an asymmetrical synthesis of (−)-isoretronecanol **1** by diastereoselective reduction of enamino diester with an endocyclic double bond.[8] We wish to report in this full account a short and convenient enantioselective synthesis of two other alkaloids: (+)-tashiromine **2** and (+)-laburnine **3** in which the key step is the diastereoselective reduction of a β-enamino diester with an exocyclic ethylenic moiety.

Results and Discussion

Synthesis of Chiral β-Enamino Esters. The synthesis of chiral β-enamino esters **6a**−**e** with an exocyclic

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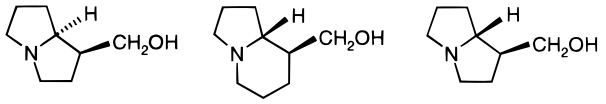


1 2 3

double bond was carried out, transposing the modified Eschenmoser coupling reaction previously described for *N*-benzyl substrates.[5] Thus a mixture of triethylamine and triphenylphosphine was slowly added to a solution of 1-(1(*S*)-phenylethyl)pyrrolidine-2-thione[9] **4** and commercially available secondary α-bromo esters **5a**−**e** in refluxing acetonitrile. Compounds **6a**−**e** were obtained in good yields as a mixture of *E*/*Z* isomers (Scheme 1) in which the *E*-isomer was the major one. *E*/*Z* ratios were determined by ^{1}H NMR measurements. For **6e**, only the *E* isomer was detected.

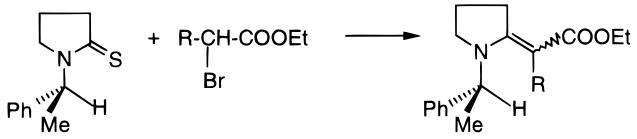
Enamino ester **7**, with an endocyclic double bond, was obtained in 74% yield by condensation of (*S*)-α-methylbenzylamine with methyl 2-acetylcyclopropanecarboxylate in refluxing toluene, following a procedure previously described with various achiral amines (Scheme 2).[10]

Reduction of Chiral β-Enamino Esters. Due to the decisive nature of this step, a systematic study of endo and exocyclic β-enamino esters reduction was carried out catalytically or chemically in order to investigate the influence of the reducing agent on the diastereoselectivity of this step. Catalytic reductions were performed under atmospheric pressure in ethanol or methanol, using PtO_2, 10% Pt/C, and 10% Pd/C as catalysts, whereas chemical reductions were realized with triacetoxyborohydride in acetic acid.[10]

For the enamino ester **7** with an endocyclic double bond, chemical reduction was previously reported by Palmieri et al.;[11] therefore only catalytic hydrogenation was considered with this compound. With 0.04 equiv of Pd/C, the hydrogenation proceeded very slowly and the debenzylation rate was faster than the reduction rate, making this catalyst inappropriate. Reduction in the presence of Pt/C yielded mainly two diastereoisomers **8** and **9** in 5.8/1 ratio. X-ray analysis performed on the major diastereomer permitted the assignment of 2*S*,3*S* absolute configurations to the stereocenters created, corresponding to a cis stereochemistry for compound **8**. A debenzylation reaction on the diastereomeric mixture effected with 0.6 equiv of Pd/C allowed us to assign the same cis geometry to the second major diastereomer **9** whose configurations are 2*R*,3*R* (Scheme 3). A very small percentage of one of the trans isomers (<5%) was detected by gas chromatography. With PtO_2 as catalyst, the percentages of **8** and **9** were respectively 89% and 8% while about 3% of the trans isomer was detected. These results show that a high selectivity is observed in catalytic reduction of **7**; the major diastereomer obtained is that corresponding to the expected syn addition on the less overcrowded face (*Re* face at C_2 and C_3) on the enamino ester moiety and is consistent with theoretical calculations.[6]

For compounds with an exocyclic double bond, **6a**−**e**, all reductions were achieved on the *E*/*Z* isomer mixture,

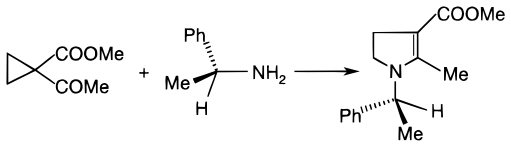
Scheme 1



4 5a-e 6a-e

Product	R	Yield %	Ratio *E*/*Z*
6a	Me	70	90/10
6b	Et	63	75/25
6c	n-Pr	60	75/25
6d	n-Bu	61	75/25
6e	Ph	66	100/0

Scheme 2



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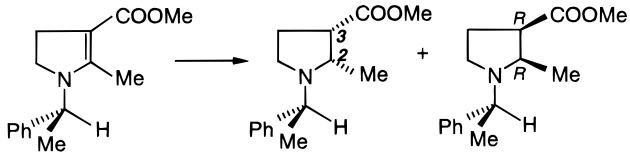
Scheme 3



7 8 9

inseparable by chromatographic methods. In the case of Pd/C, the catalyst with which the parasite debenzylation reaction can be envisaged, we adapted a catalyst amount to 0.04 equiv to avoid this competitive route. However, in these conditions, **6e** was not reduced and the increase of catalyst amount only gave rise to debenzylation.

In all cases, amino esters were obtained in good chemical yields (80−98%) as a mixture of two, three, or four diastereoisomers noted **10**, **11**, **12**, and **13**, according to their elution order in gas chromatography. Diastereoisomer ratios of hydrogenated compounds according to the reducing agents were determined both by CPV analysis and by ^{13}C NMR measurements and were reported in Table 1.

In most cases, the main diastereoisomer formed was **12** whereas **11** was always present in a very small proportion or not detected. However for Pt/C reduction of **6e** and for PtO_2 reduction of **6a**, **6c**, and **6e**, the major diastereomer was **13**. With the exception of the hydrogenation with this last catalyst whose results did not show any regularity depending on the side chain size, the best diastereoselectivity was observed for **6a** reduction independent of the nature of the reducing agent. Besides, the diastereoselectivity decreases when ethyl replaces the methyl group and then does not significantly vary with more chain extension. For all compounds with an alkyl substituent, the highest diastereoselectivity was obtained with 10% Pd/C (e.d. 68−84%); with 10% Pt/C as catalyst, the diastereomeric excess varies between 40 and 60% and with $NaBH(OAc)_3$/AcOH from 22 to 50%.

It was essential to determine absolute configuration of the two chiral centers created for hydrogenated

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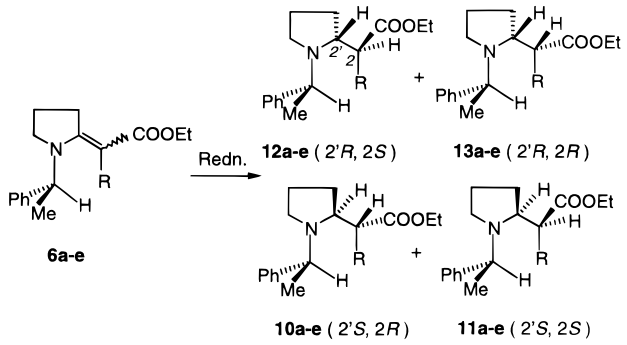
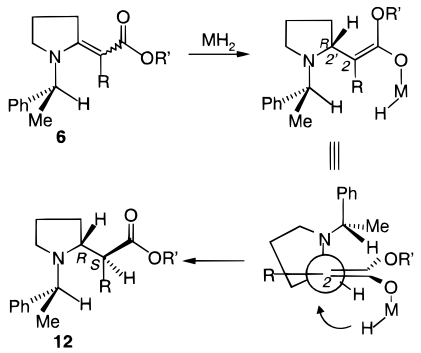
Table 1. Reduction of Enamino Esters 6a-e to Amino Esters 10-13

	H_2 PtO_2				H_2 Pt/C				H_2 Pd/C				$NaBH(OAc)_3$/AcOH			
redn	**10**	**11**	**12**	**13**	**10**	**11**	**12**	**13**	**10**	**11**	**12**	**13**	**10**	**11**	**12**	**13**
6a, R = Me	19		37	44	10	1	80	9	5	3	92		7	3	73	17
6b, R = Et	6		85	9	12		77	11	10		84	6	14		64	22
6c, R= Pr	9		35	56	10	5	71	14	4		89	7	13		61	26
6d, R = Bu	13		49	38	11	5	70	14	4		90	6	9		67	24
6e, R = Ph			3	97			40	60					5		63	31

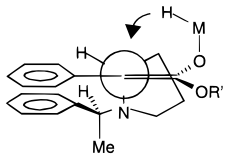
Scheme 4



Scheme 5



Scheme 6



compounds in the diastereoisomeric mixture. The stereochemical assignments for compounds **12a** and **13a** (R = Me) were proven from X-ray analysis.[7,12] Diffraction measurements carried out on **12a** as its picrate salt showed the 2*S*,2′*R* configuration while **13a** had a 2*R*,2′*R* configuration. By comparing ^{13}C NMR chemical shifts of some significant carbon atoms of both major diastereoisomers **12a** and **13a** with those of the series **b**−**d** (R = Et, n-Pr, n-Bu), the same absolute configurations can be respectively assigned[7] to all compounds **12b**−**d** and **13b**−**d** (Scheme 4). For diastereomers resulting from the reduction of **6e** the correlation was more critical due to the perturbation induced by the phenyl ring. The attribution proposed in Table 1 was confirmed by X-ray measurements on the picrate salt of the major diastereomer **13e**, obtained in the PtO_2 reduction, whose configurations were assigned to be 2*R*,2′*R*.

In such catalytic reductions, a stereoselective syn hydrogenation process is generally expected. However, for **6a**−**d**, only the minor **6***Z* stereoisomer would lead to **12a**−**d** which is the major reduced product in the mixture. Hence, it is surprising that starting from an enamino esters *E*/*Z* mixture, both present in notable proportion, a main diastereoisomer is yet obtained up to 92%. Such a result (presence of both syn and anti addition products) is often explained by a double bond migration during the reducing course.[13] But in our case, the too important conformational liberty in the endo- or exocyclic intermediate resulting from a hydrogen addition−elimination sequence cannot simply explain the good diastereoselectivity observed. A more attractive hypothesis has sometimes been advanced to explain such results with diesters substrates.[14] It involved the formation of an enolate intermediate by addition of a MH_2 equivalent on the enamino ester double bond. The chiral amino group would favor the addition on the front face[7] (*Si* face at $C_{2'}$) leading to an *R* configuration for this center. The more favored transition state structure represented in Scheme 5 was based on the conformation in which 1,3-allylic strain was minimized and the C−N bond became oriented perpendicular to the π system. Stereoselective protonation on the rear face (*Re* face at C_2) would lead to the *S* configuration for this carbon. It should be remarked that the hydrogen atom used for C_2 protonation may arise either from the catalyst surface or protic solvent.

Such a model could satisfactorily explain the good diastereoselectivity observed for compounds **12a**−**d** when hydrogenation is carried out in the presence of palladium or platinum. This model could also explain the production of both syn and anti addition compounds in the reduction of only the *E* stereomer of **6e.** Contrary to compounds **6a**−**d**, it should be remarked that the expected syn addition product was the main stereomer obtained with catalytic reductions of this compound. In the case of R = Ph, an important steric strain between aromatic and pyrrolidine rings disfavors the conformation shown in Scheme 5 whereas a π−π interaction between the two phenyl groups promotes the conformation represented in Scheme 6, in which however remains a 1,3-allylic strain. Favored protonation on the upper face (*Si* face at C_2) principally leads to the *R* configuration at this center and yields the main 2*R*,2′*R* diastereoisomer **13e**.

Molecular Modeling Study. The catalytic hydrogenation of the double bond of the studied amino esters must arise from the less crowded face of the double bond. Therefore we undertook a molecular modeling study to determine the most stable conformers of compounds **6a** (*E*) and **7** (absolute configuration *S*) and their geometrical conformations in order to evalue the relative steric

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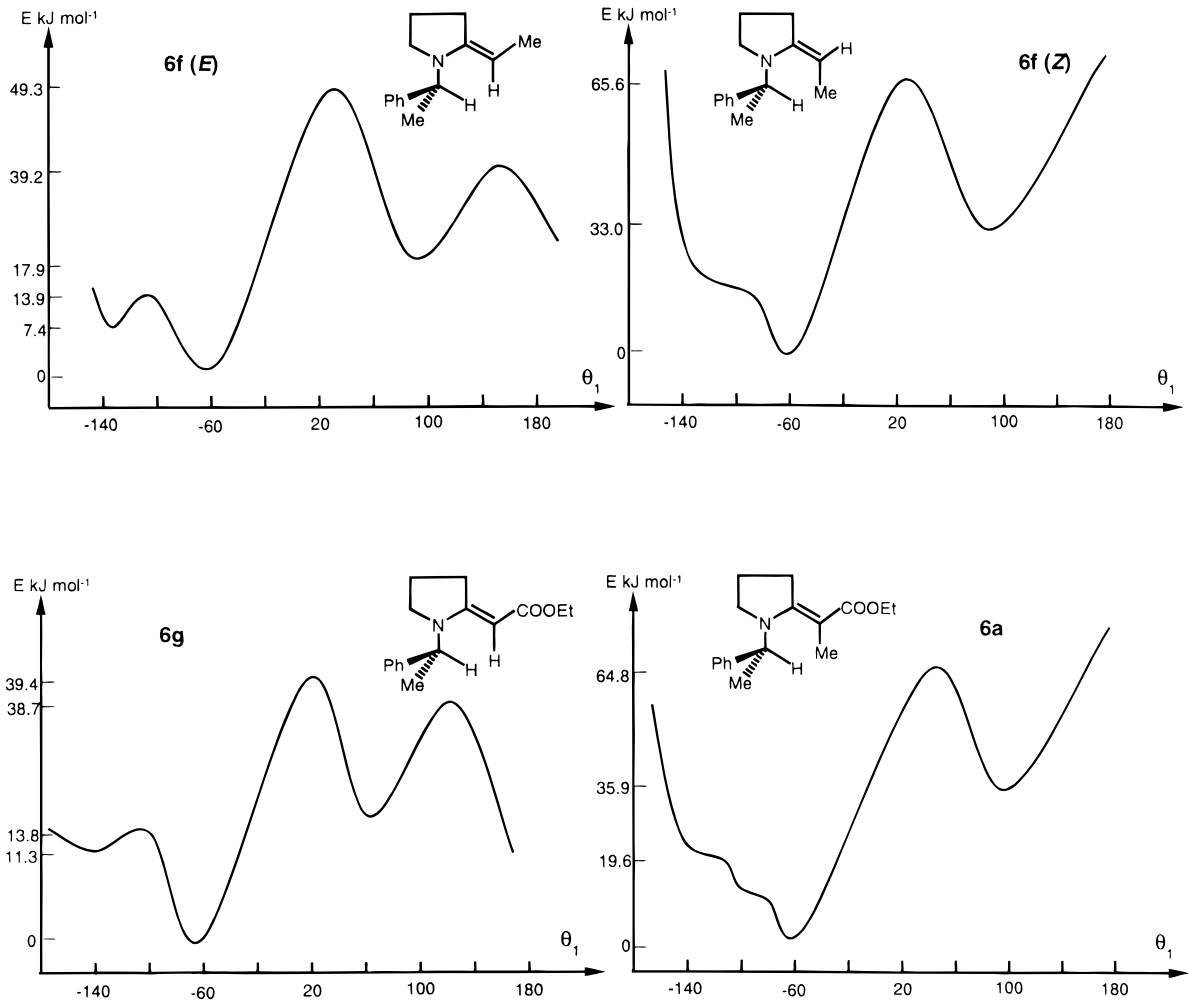
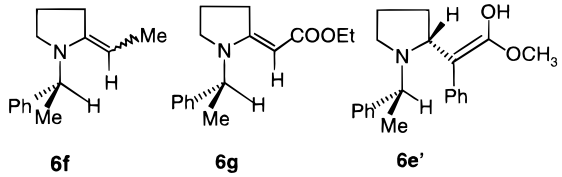


Figure 1. Curves $E = f(\Theta)_1$) for compounds **6a, 6g,** and **6f (*E*) and (*Z*)**.

crowding for each face of the double bond. These calculations were performed using the SYBYL 6.3 software package[15] as described in the Experimental Section. All the generated geometries were minimized using the Tripos force field and optimized using AM1[16] calculations. The conformational spaces of **6a** and **7** were explored using the SYBYL search facility.

In the case of compound **7** with an endocyclic double bond, rotation around the N−C* (θ_1) and the C*−Ph (θ_2) bonds gave a three-dimensional (E, θ_1, θ_2) graph. Its two-dimensional projection on the E, θ_1 plane gave a curve with a single wide minimum with a width of 120° between −50° and −170°. The bottom of the curve was rather flat with a minimum between −80° and −120° (depth of 8.4 kJ mol^{-1}) indicating the presence of only one conformer[17] in which the rear face of the unsaturated ring is severly crowded by the phenyl ring. This explains the very high stereospecificity of the hydrogenation reaction (de > 90%) which proceeds by the less crowded face of the molecule, leading to the 2*R*,3*R* stereochemistry (see scheme in ref 6). The presence of only one conformer is clearly due to the steric interaction between the C_2-CH_3 and the C* substituents. This interaction is minimized when the smaller group (C*-*H*) is in front of the bulky C_2-CH_3 group ("gear effect").

For compounds with an exocyclic double bond, we studied first the simplified (and no synthesized) models **6f(*E*)** and **6f(*Z*)** in order to show the influence of the $C_{2'}$-CH_3 group. The conformational spaces of each compound were explored using SYBYL 6.3 as described above. The two bonds C*−N (θ_1) and C*−Ph (θ_2) were allowed to rotate respectively from 0 to 360° and 0 to 180° by 15° increments. The obtained results were analyzed by graphical representation in three dimensions (E, θ_1, θ_2). Their two-dimensional projections (E, θ_1) were then examined.



6f **6g** **6e'**

For compound **6f(*E*)** the curve $E = f(\theta_1)$ has three marked minima (Figure 1) at nearly 120° from each other as in CRAM models. On the other hand, in the case of compound **6f(*Z*)** the curve $E = f(\theta_1)$ shows a single deep minimum corresponding to a unique conformer in which the rear face of the molecule is overcrowded by the phenyl group. This calculation demonstrates the importance of

(15) Tripos Associates, Inc., 1699 S. Harley Rd., Suite 303, St. Louis, MO 63144.

(16) Merz, K. M.; Besler, B. H. MOPAC version 5.0 ESC, QCPE 589, 1990, with AM1 force field parameters.

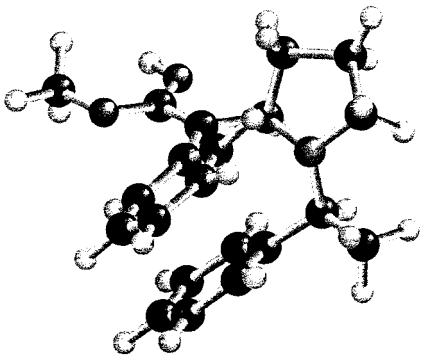


Figure 2.

the "gear effect" between the $C_{2'}$-CH_3 and the substituents of the C* and allows the prediction of a high diastereoselectivity at the $C_{2'}$ for the hydrogenation of the double bond and a *R* configuration of the $C_{2'}$ stereogenic center of the reaction product.

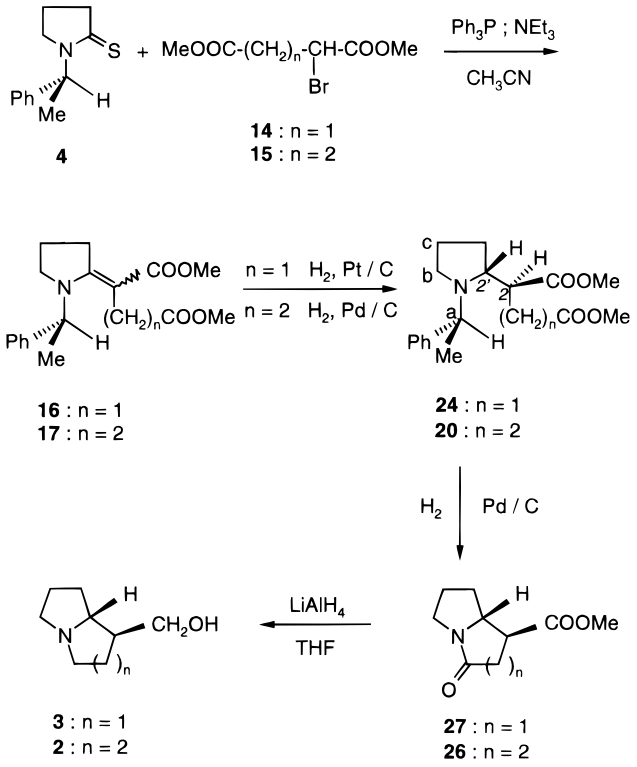
The curves corresponding to functionalized compounds **6g** and **6a** are rather similar to those of **6f(*E*)** and **6f(*Z*)** showing also the importance of the C_2-CH_3 group and allowing the prediction of a higher stereoselectivity of a catalytic hydrogenation reaction for **6a** than for **6g**. In fact catalytic hydrogenation of **6g** was already reported[9] and gave a mixture of two diastereoisomers at $C_{2'}$ in a 87/13 ratio (de = 74%). As expected, the stereoselectivity of the catalytic hydrogenation of **6a** is higher: the ratio of diastereoisomers at $C_{2'}$ is 98/2 and the de 84% and can reach 92% (ratio 96/4) (Table 1) with propyl (**6c**) or butyl groups (**6d**) instead of methyl.

This study shows the interest in molecular modeling as a predicting tool for the stereochemistry of the catalytic hydrogenation reaction. A conformational analysis of the enol **6e′**, obtained after the first step of the hydrogenation process, was performed using SYBYL 6.3 in order to predict the stereochemistry of the hydrogenation product of **6e** (R = Ph). The optimized structure obtained as previously described was subjected to a restrained molecular dynamic simulation lasting 10 ps at a temperature of 1000 K. Structures were selected after analysis of dynamic trajectory and the lowest energy conformers minimized in vacuo by Maximin 2 Tripos force field. Only one conformer was obtained (Figure 2) showing a $\pi-\pi$ interaction between the two phenyl groups which promotes the conformation represented in Scheme 6 and thus explaining the stereochemistry at the C_2 stereogenic center of the reaction product.

Application to the Synthesis of (+)-Tashiromine 2 and (+)-Laburnine 3. This efficient exocyclic enamino ester reduction was applied to alkaloid synthesis. We exploit the main point of the hydrogenation course which is the high level of diastereoselectivity observed despite starting from an unfavorable *E*/*Z* mixture of **6**. The scope of this key step can be extended to the synthesis of two natural products, (+)-tashiromine and (+)-laburnine, as it will lead to the correct relative stereochemistry at the two stereogenic centers in a very simple manner. To form the second ring present in these indolizidine and pyrrolizidine skeletons, we chose to start directly from β-enamino esters with appropriate carbon chains.

(17) The curve shows another minimum at $\theta = 140°$ for an energy of nearly 28 kJ mol^{-1}. The population of the corresponding conformer can be neglected due to its high energy.

Scheme 7



Tashiromine was isolated in 1990 from the stems of a leguminous plant *Maackia tashiroi*, a deciduous shrub of subtropical Asia.[18] Only three syntheses have been reported todate, a racemic one[19] and two enantioselective approaches: a short route described by Nagao and coworkers[20] and a recent synthesis in 13 steps from L-glutamic acid by B. P. Branchaud et al.[21] Absolute configurations of both chiral centers are unknown; only a trans relationship between H_8 and H_9 was ascribed.[18] Consequently tashiromine was determined to be (5*S*,6*R*)-5-hydroxymethylindolizidine or its enantiomer. As for laburnine, this pyrrolizidine alkaloid was first isolated[22] from *Cytisus laburnum* in 1949 by F. Galinovsky and then, among others, from the leaves of *Planchonella anteridifera*, a tree found in the rain forest area of New Guinea.[23] Only two enantioselective syntheses are reported at this time.[24]

The first step of our synthetic route (Scheme 7) is the access to chiral β-enamino diesters readily obtained through modified Eschenmoser sulfide reaction. Therefore we have transposed to α-bromo diesters with desired side chain size, the conditions described above for secondary α-bromo esters. Thus 1-(1(*S*)-phenylethyl)pyrrolidine-2-thione[9] **4** was condensed with dimethyl bromobutanedioate[25] **14** and dimethyl bromopentanedioate[26] **15** to give respectively chiral β-enamino diesters **16** and **17** in 84% and 85% yields. Enamino diesters **16** and **17** were

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Table 2. Reduction of Enamino Diester 17 to Amino Diesters 18−21

	H_2 Pd/C	H_2 PtO_2	H_2 Pt/C	$NaBH(OAc)_3$ AcOH
18	2	8	6	8
19	2	2	1	3
20	*96*	***54***	***82***	***68***
21		36	11	21

obtained as an inseparable diastereomeric mixture of *E*/*Z* isomers in respective 75/25 and 65/35 ratios, determined by ^{1}H NMR measurements.

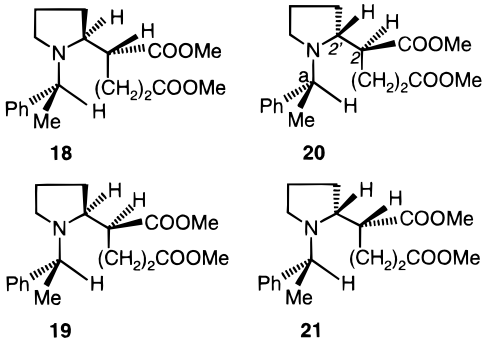
For our studies with model enamino esters **6** showing that catalytic hydrogenation with 10% Pd/C gave rise to the best diastereoselectivity, we first naturally used this catalyst in the case of enamino diesters **16** and **17**. However, that reductions performed on **17** with PtO_2, Pt/C, or $NaBH(OAc)_3$ /AcOH were less selective than with Pd/C was tested. For **17** every reduction produces a diastereomeric mixture of three or four hydrogenated compounds **18**, **19**, **20**, and **21**, the percentages of which are reported in Table 2.

Since Pd/C can induce an undesirable debenzylation reaction, we modified the catalyst amounts in order to obtain a significant reaction rate without appreciable debenzylation. When 10% Pd/C amounts decreased from 0.2 to 0.04 equiv, no debenzylation reaction was observed and simultaneously the fraction of the major diastereoisomer **20** in the mixture surprisingly increased from 58% to 96%. For enamino ester **16**, reduction and debenzylation rates are very close and it is impossible to avoid a debenzylation reaction even with Pd/C amounts lower than 0.04 equiv. So we used in this case 10% Pt/C as catalyst. Unfortunately the percentage of major diastereomer **24** in the mixture **22**−**25** was only 77% but no debenzylation was observed. Stereomers **22**, **23**, and **25** were present as 8%, 2%, and 13% in the mixture, respectively. To separate main diastereoisomers **20** and **24**, each diastereomeric mixture was transformed to picrate salts, and after several recrystallizations, diastereomers **20** and **24** were respectively obtained in 98% and 96% de.

2*S*,2′*R* configurations can be assigned to stereoisomers **20** and **24** while **21** and **25** have 2*R*,2′*R* configurations at both created centers. Once again, these assignments were based on comparison of their chemical shifts in ^{13}C NMR with those of compounds of the series **12a**−**d** and **13a**−**d**.[7] Thus, chemical shifts of C_a, C_b, and C_c were respectively 57.0, 46.6, and 23.2 ppm for **20**, 59.2, 48.1, and 24.1 for **21**, 56.8, 46.3, and 23.1 for **24**, and 58.7, 48.3, and 23.7 for **25**. X-ray analysis performed on the picrate salt of **20** confirms the absolute configurations proposed by NMR assignments. In the case of **24**, the stereochemical assignments will be further proved by the conversion of this stereomer into laburnine whose specific rotation is known. An attribution of absolute configurations of both minor stereomers **18** and **19** will be proposed below using results of the amino diester cyclization step (see Table 3).

The stereocenters are now well established with the desired configuration. Having performed its function of chiral control, the α-methylbenzyl group would be removed, enabling the formation of the second ring present in the target alkaloids. For this purpose, in a third step, the hydrogenolysis of the benzylic amine was performed in the presence of Pd/C and the subsequent ring closure gave rise to the bicyclic lactam esters. The debenzylation

Table 3. Assignment of minor diastereomers 18 and 19



	amino diesters				lactam esters	
	%	C_a	$C_{2'}$	C_2	confign	%
18	8	*S*	*S*	*R*		
					SR + *RS*	98
20	90	*S*	*R*	*S*		
19	2	*S*	*S*	*S*		
					SS + *RR*	2
21	0	*S*	*R*	*R*		

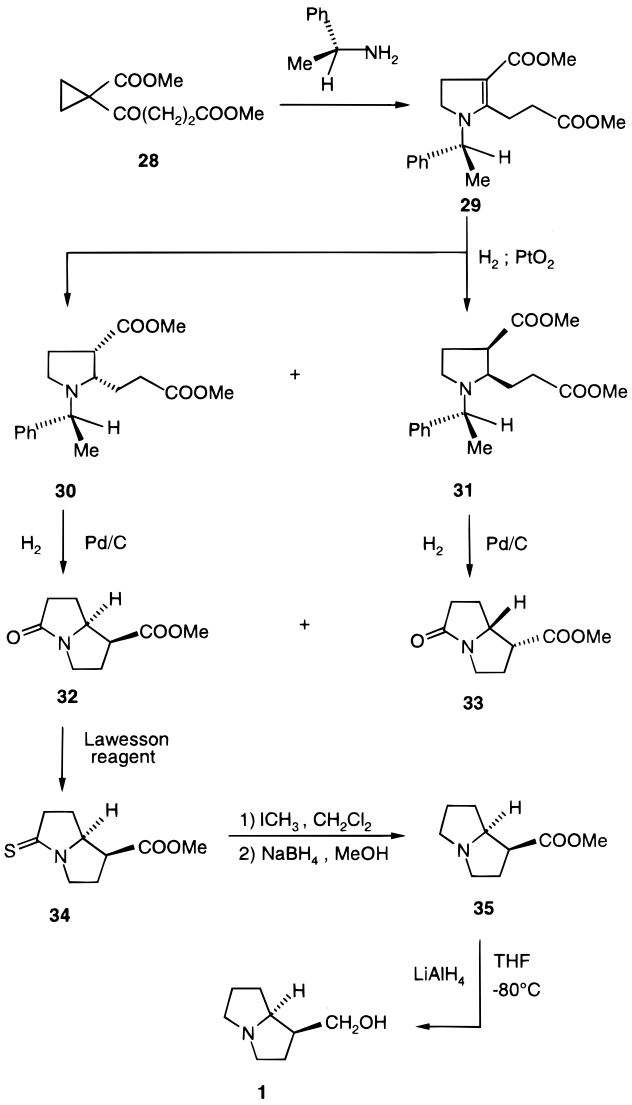
of **20** and **24** was achieved in MeOH under atmospheric pressure of H_2 with a higher amount of catalyst (0.6 equiv) than those used in the reduction step. Thus, chiral lactams **26** and **27** were respectively obtained in quantitative yields as a mixture of two diastereoisomers in the same ratios (99/1 and 98/2) as those of the β-amino diesters they are produced from. The minor diastereomer was separated by chromatography, and compounds **26** and **27** were then obtained in a pure enantiomeric form respectively in 78% and 75% yields.

The investigation of the debenzylation step allows us to suggest absolute stereochemistry for minor amino diester diastereomers **18** and **19** issued from the reduction of **17**, and **22** and **23** resulting from those of **16**. The stereochemistry assignments were proved by comparison of chromatograms, for example of the amino diester mixture **18**, **19**, **20**, and **21** with those of debenzylated diastereomers in the next step. Thus, debenzylation of a mixture, **18** (8%), **19** (2%), **20** (90%), **21** (0%), yields two diastereomeric lactam esters in a 98/2 ratio (Table 3). Since **20** has the 2′*R*,2*S* configuration, **21** is 2′*R*,2*R*, and **18** and **20** on the one hand and **19** and **21** on the other hand lead after cleavage of the chiral auxiliary to two pairs of enantiomers, **18** has a 2′*S*,2*R* configuration and **19** is 2′*S*,2*S*.

The synthesis was completed in a final step with the reduction of both the lactam carbonyl group and ester moieties of **26** and **27**. These reductions were simultaneously achevied using $LiAlH_4$ in THF at room temperature as no epimerization was observed in these conditions. Thus, (+)-tashiromine **2** and (+)-laburnine **3** were isolated in 87% and 85% yields, respectively. ^{1}H and ^{13}C NMR spectra were in complete agreement with those previously described.[19,20,24]

The optical rotation measured for (+)-tashiromine was +44.7 (*c* 1.1, EtOH) but no value for the natural product was reported; hence no comparison with our result was possible. It should be remarked that Y. Nagao et al.[20] mentioned $[\alpha]^{20}_D = -25.9$ (*c* 1.16, EtOH) for the (−) enantiomer rotation, while B. P. Branchaud[21] obtained $[\alpha]^{23}_D = -36.3$ (*c* 0.88, $CHCl_3$) for a product with 92% ee. For (+)-laburnine the measured optical rotation $[\alpha]^{20}_D = +15.4$ (*c* 1.20, EtOH) was in total concordance with that of the natural product: $[\alpha]^{20}_D = +15.5$ (EtOH) in *Cytisus*

Scheme 8



laburnum[22] and +15.4 (*c* 1.44, EtOH) in *Planchonella anteridifera*.[23]

Therefore (+)-tashiromine and (+)-laburnine were synthesized in pure enantiomeric form, in four steps from chiral thiolactam **4** in 25% and 27% overall yields, respectively.

Application to the Synthesis of (−)-Isoretronecanol 1. In the same manner, the good diastereoselectivity observed for the cis hydrogenation of endocyclic enamino ester **7** has been exploited for the pyrrolizidine alkaloid synthesis, the (−)-isoretronecanol.

Isoretronecanol **1** was first isolated from a *Planchonella* species[27] and then from *Phalaenopsis equestris*, an orchidaceae from Philippines.[28] Many syntheses, both racemic and enantioselective, were reported in the literature.[29] This alkaloid, with a cis relationship between H_1 and H_8, is a diastereoisomer of laburnine **3** in which these two protons have a trans relative stereochemistry.

The first step of our approach (Scheme 8) is the synthesis of dihydropyrrole **29** adapting the procedure described previously for **7** and starting from a properly functionalized cyclopropane **28**. Thus, compound **28**[8] reacted with (*S*)-α-methylbenzylamine in refluxing toluene to afford *β*-enamino ester **29** with 83% yield. Dihydropyrrole catalytic hydrogenation over PtO_2 gave the cis diastereoisomers **30** and **31** with a diastereoisomeric excess of 90%, measured by chromatography (87% chemical yield). The absolute configurations of the two created stereocenters have been established in the last step by comparison of the specific rotation of our synthetic sample with those of the natural product. Hydrogenolysis of the α-methylbenzyl group allowed the construction of the second ring. The mixture of **30** and **31** hydrogenated over 10% Pd/C afforded, after heating in toluene at 90 °C, bicyclic lactam esters **32** and **33** in 90% yield.

The lactam moiety was transformed into thiolactam with Lawesson reagent, and optically pure compound **34** was obtained, after recrystallization, in 46% yield. Selective reduction of the thiolactam moiety was realized by its conversion with MeI in CH_2Cl_2 into the corresponding thioiminium salt which was reduced with $NaBH_4$ in MeOH.[30] This sequence supplied the intermediate (−)-chysine **35** in 77% yield. The optical rotation measured for this compound [$[\alpha]^{20}_D = -65$ (*c* 2.16, $CHCl_3$)] is in good agreement with that of its enantiomer, the natural (+)-chysine ($[\alpha]^{25}_D = +64$ (*c* 1.1, $CHCl_3$)).[29] Finally, ester functional group of **35** was reduced with $LiAlH_4$ in THF at −80 °C. In fact, the reduction must be carried out very smoothly at low temperature to avoid epimerization at C_8. (−)-Isoretronecanol **1** was then isolated in an enantiomerically pure form in 83% yield after distillation. The optical rotation measured $[\alpha]^{20}_D = -77.0$ (*c* 2.1, EtOH) is in good agreement with those of the natural product $[\alpha]^{20}_D = -77.5$ (*c* 2.5, MeOH).[29] This pyrrolizidine alkaloid **1** was then obtained in seven steps from activated cyclopropane **28** in 20% overall yield.

Conclusion

In conclusion, we have shown that the use of α-methylbenzylamine as a control element provides in both cases (enamino esters with endo- or exocyclic double bonds) a highly diastereoselective catalytic reduction of the ethylenic moiety. The stereochemistry of hydrogenated compounds depends strongly on the position of the double bond with regard to pyrrolidine ring. Endocyclic double bond enamino esters undergo expected syn hydrogenation while, surprisingly, with exocyclic double bond compounds, the main diastereoisomer formed formally results from an anti-addition of hydrogen on the major *E* enamino ester. We applied this stereodirecting reduction step to the enantioselective synthesis of some alkaloids which was performed in a very short and convenient route. This strategy enables access to 1-hydroxymethylpyrrolizidine or indolizidine in good yields in optically active form.

Experimental Section

General Methods. Melting points are uncorrected. Capillary gas chromatography was performed on a chromatograph with a flame ionization detector using CP-SIL 5 (Chromapack) columns. Column chromatography was performed on silica gel

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60 (Merck 230−400 mesh), and reactions were monitored by TLC on Kieselgel 60 F_{254} (Merck); detection was effected by examination under UV light. ^1H and ^{13}C NMR spectra were recorded 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. The microanalyses were performed by the Service de Microanalyse, Université Pierre et Marie Curie. IR spectra were recorded as thin films on NaCl plate. Dichloromethane was distilled from P_2O_5. Diethyl ether was distilled from CaH_2 and redistilled from $LiAlH_4$. 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% ee).

General Procedure for Eschenmoser Coupling Reaction. A mixture of 1-[1(*S*)-phenylethyl]pyrrolidine-2-thione **(4)** (5.06 g, 24 mmol), bromo esters **5a**−**e**, **14**, or **15** (72 mmol), and sodium iodide (1.82 g, 12 mmol) was refluxed in MeCN (20 mL). A solution of PPh_3 (12.63 g, 48 mmol) and triethylamine (6.7 mL, 48 mmol) in MeCN (100 mL) was added dropwise during 1−2 h. After about 6 to 7 h of stirring under reflux, the reaction mixture was concentrated under reduced pressure, and the residue was diluted with CH_2Cl_2 (15 mL) and then extracted with 1 M HCl (8 × 70 mL). The aqueous layers were combined, neutralized with Na_2CO_3, and then extracted with AcOEt (8 × 70 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed. The crude product was purified by chromatography on a silica gel column (AcOEt/cyclohexane 1/3).

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-ylidene]propanoic Acid Ethyl Ester (6a). Condensation of ethyl 2-bromopropanoate **(5a)** with **4** gave **6a** as a mixture of 90/10 *E*/*Z* diastereomers: yield 89%; oil; ^1H NMR 7.35−7.15 (m, 5H), 5.50 (q, 0.1H, J = 6.9 Hz), 5.40 (q, 0.9H, J = 6.9 Hz), 4.10 (q, 2H, J = 6 Hz), 3.25−3.10 (m, 1H), 3.05−2.95 (m, 2H), 2.90−2.80 (m, 1H), 2.00 (s, 2.7H), 1.85 (s, 0.3H), 1.85−1.60 (m, 2H), 1.55 (d, 3H, J = 7 Hz), 1.25 (t, 3H, J = 6 Hz); ^{13}C NMR 170.1, 167.8, 163.8, 161.5, 141.6, 141.3, 128.0, 127.8, 126.7, 126.4, 89.6, 87.0, 58.5, 55.7, 54.5, 47.8, 46.1, 35.2, 34.9, 21.4, 20.0, 16.8, 16.3, 15.6, 14.7, 14.3; IR (neat) 1675, 1575 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.92; H, 8.22; N, 5.37.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-ylidene]butyric Acid Ethyl Ester (6b). Condensation of ethyl 2-bromobutanoate **(5b)** with **4** gave **6b** as a 75/25 *E*/*Z* mixture: yield 63%; oil; ^1H NMR 7.3−7.2 (m, 5H), 5.4 (q, 0.3H, J = 6.9 Hz), 5.2 (q, 0.7H, J = 6.9 Hz), 4.1 (q, 2H, J = 7.0 Hz), 3.15−2.80 (m, 2H), 2.9 (m, 2H), 2.65−2.10 (m, 2H), 1.80−1.55 (m, 2H), 1.5 (d, 3H, J = 6.9 Hz), 1.2 (q, 3H, J = 7.0 Hz), 1.1 (t, 3H, J = 7.3 Hz); ^{13}C NMR 169.8, 167.4, 162.5, 160.9, 141.5, 141.3, 128.0, 127.8, 127.6, 126.6, 126.5, 126.4, 126.1, 126.0, 96.1, 94.6, 58.1, 55.5, 54.9, 47.5, 46.2, 35.3, 33.7, 24.1, 21.5, 20.9, 20.1, 16.8, 15.3, 14.6, 14.5, 14.1; IR (neat) 1730, 1560 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.33; H, 8.72; N, 4.90.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-ylidene]pentanoic Acid Ethyl Ester (6c). Condensation of ethyl 2-bromopentanoate **(5c)** with **4** gave **6c** as a 75/25 *E*/*Z* mixture: yield 60%; oil; ^1H NMR 7.3−7.2 (m, 5H), 5.3 (q, 0.3H, J = 6.9 Hz), 5.1 (q, 0.7H, J = 6.9 Hz), 4.0 (m, 2H), 3.1−2.8 (m, 2H), 2.9 (m, 2H), 2.6−2.1 (m, 2H), 1.7 (m, 2H), 1.55 (d, 3H, J = 6.9 Hz), 1.50−1.25 (m, 2H), 1.2 (t, 3H, J = 7.0 Hz), 0.8 (m, 3H); ^{13}C NMR 171.0, 168.7, 163.1, 161.7, 141.8, 128.5, 128.2, 127.2, 127.1, 126.9, 126.6, 95.4, 93.8, 58.8, 56.1, 55.3, 48.1, 46.8, 35.8, 34.4, 33.6, 30.5, 23.9, 21.9, 20.6, 17.5, 16.0, 14.6, 14.3, 14.2; IR (neat) 1670, 1560 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.59; H, 9.12; N, 4.56.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-ylidene]hexanoic Acid Ethyl Ester (6d). Condensation of ethyl 2-bromohexanoate **(5d)** with **4** gave **6d** as a 75/25 *E*/*Z* mixture: yield 61%; oil; ^1H NMR 7.3−7.2 (m, 5H), 5.35 (q, 0.3H, J = 6.9 Hz), 5.15 (q, 0.7H, J = 6.9 Hz), 4.05 (m, 2H), 3.10−2.75 (m, 2H), 2.95 (m, 2H), 2.60−2.15 (m, 2H), 1.7 (m, 2H), 1.5 (d, 3H, J = 6.9 Hz), 1.45−1.25 (m, 4H), 1.2 (t, 3H, J = 7.0 Hz), 0.85 (t, 3H, J = 7.3 Hz);^{13}C NMR 170.9, 168.5, 163.1, 161.6, 142.0, 141.7, 128.5, 128.2, 127.2, 127.1, 126.9, 126.6, 95.4, 93.9, 58.8, 56.1, 55.2, 48.0, 46.7, 35.8, 34.4, 33.0, 32.8, 31.1, 28.1, 22.9, 22.7, 22.3, 20.5, 17.4, 16.0, 14.6, 14.4, 13.9; IR (neat) 1670, 1570 cm^{-1}. Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.03; H, 9.35; N, 4.40.

2-Phenyl-2-[1-(1(*S*)-phenylethyl)pyrrolidin-2-ylidene]-ethanoic Acid Ethyl Ester (6e). Condensation of ethyl 2-bromo-2-phenylethanoate **(5e)** with **4** gave **6e** (*E* isomer): yield 66%; oil; ^1H NMR 7.2−7.0 (m, 10H), 4.3 (q, 1H, J = 6.9 Hz), 4.0 (m, 2H), 3.2 (m, 2H), 3.1−2.7 (m, 2H), 1.7 (m, 2H), 1.1−1.0 (m, 6H); ^{13}C NMR 169.8, 162.9, 141.0, 139.5, 132.0, 128.5, 128.3, 128.0, 127.1, 126.8, 126.1, 96.4, 59.0, 52.9, 46.9, 35.9, 21.3, 14.9, 14.6; IR (neat) 1670, 1550 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.90; H, 7.45; N, 4.11.

1-(1(*S*)-Phenylethyl)-2-methyl-4,5-dihydropyrrole-3-carboxylic Acid Methyl Ester (7). A mixture of 1-acetylcyclopropanecarboxylic acid methyl ester (1.42 g, 10 mmol) and (*S*)-α-methylbenzylamine (1.21 g, 10 mmol) in 10 mL of toluene was heated during 16 h at 140 °C. After complete elimination of water in a Dean Stark apparatus, the solvent was evaporated under reduced pressure and the residue was diluted with diethyl ether. The solution was cooled at 0 °C, and the hydrochloride of **7** was prepared by bubbling HCl during 15 min. The salt was extracted with water (20 mL), and the aqueous layer was neutralized until pH 6.8−7.0 with a saturated $KHCO_3$ solution. The organic phase was dried (Na_2SO_4), and solvent was evaporated. The crude compound was distillated under vacuo (135 °C, 0.05 mmHg): yield 74%; oil; ^1H NMR 7.4−7.15 (m, 5H), 4.85 (q, 1H, J = 6.8 Hz), 3.15 (s, 3H), 3.4 (q, 1H, J = 10 Hz), 3.25−3.05 (m, 1H), 2.75−2.6 (m, 2H), 2.3 (s, 3H), 1.55 (d, 3H, J = 6.8 Hz); ^{13}C NMR 167.8, 161.0, 141.1, 128.6, 127.3, 126.5, 95.6, 52.5, 50.0, 45.1, 26.5, 17.5, 12.1; IR (neat) 1665, 1590 cm^{-1}. $[\alpha]_D^{20}$ = +39.9 (*c* 1.96, EtOH). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.11; H, 7.89; N, 5.58.

(2*S*,3*S*)-[1-(1(*S*)-Phenylethyl)-2-methylpyrrolidin-3-yl]-carboxylic Acid Methyl Ester (8−9). To a degassed solution of dihydropyrrole **7** (12.35 g, 50 mmol) in MeOH (50 mL) was added PtO_2 (50 mg), and the mixture was hydrogenated under atmospheric pressure for 24 h. The solution was filtered, the insoluble material was rinsed with MeOH, and the combinated filtrates were evaporated to give a mixture of two cis diastereomers **8** and **9** in an 11/1 ratio which was recrystallized from *n*-hexane: yield 90%; mp 62 °C; ^1H NMR 7.4−7.15 (m, 5H), 3.7 (s, 3H), 3.65−3.4 (m, 2H), 3.2−3.0 (m, 1H), 2.8−2.6 (m, 1H), 2.6−2.45 (m, 1H), 2.3−2.1 (m, 1H), 2.0−1.8 (m, 1H), 1.35 (d, 3H, J = 6.8 Hz), 0.80 (d, 3H, J = 6.8 Hz); ^{13}C NMR 173.7, 145.3, 128.2, 127.4, 126.9, 60.8, 57.0, 51.5, 48.8, 47.5, 24.9, 20.9, 12.5; IR ($CHBr_3$) 1725 cm^{-1}. $[\alpha]_D^{20}$ = −27.7 (*c* 2.03, EtOH). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.51; H, 8.61; N, 5.62.

General Procedure for Catalytic Hydrogenation with Platinum Oxide. To a degassed solution of β-enamino ester **6** (0.75 mmol) in EtOH (10 mL) was added PtO_2 (36 mg). 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 mole of **6**, the solution was filtered. The filter cake was rinsed with EtOH and the solvent removed. The crude mixture of diastereomers **10**−**13** was directly analyzed by gas chromatography and ^{13}C NMR.

General Procedure for Catalytic Hydrogenation with Platinum on 10% Charcoal. To a degassed solution of β-enamino ester **6** (or **7)** (0.75 mmol) in EtOH (10 mL) was added 37 mg of platinum on charcoal (10% w/w). The resulting suspension was hydrogenated and worked up according to the general procedure used for PtO_2 reduction.

General Procedure for Catalytic Hydrogenation with Palladium on 10% Charcoal. To a degassed solution of β-enamino ester **6** (or **7)** (0.75 mmol) in EtOH (10 mL) was added 35 mg of palladium on charcoal (10% w/w). The resulting suspension was hydrogenated, and the same workup as above gave a mixture of **10**−**13** which was directly analyzed.

General Procedure for Chemical Reduction. A solution of $NaBH(AcO)_3$ was prepared with 140 mg of $NaBH_4$ (3.75 mmol) and 2.1 mL of acetic acid (37.5 mmol) cooled at 0 °C. After 30 min of stirring at room temperature, a solution of β-enamino ester **6** (0.75 mmol) in MeCN (5 mL) was added and the mixture stirred for 48 h. The solution was neutralized with a satured Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2 and washed with water; organic phase was then dried (Na_2SO_4) and evaporated.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]propanoic Acid Ethyl Ester (10a−13a). Reduction of **6a**. Yields: 95% (PtO_2), 96% (Pt/C), 90% (Pd/C), 85% ($NaBH(AcO)_3$); oil; ^{1}H NMR 7.30−7.05 (m, 5H), 4.2−3.8 (m, 3H), 3.10−2.95 (m, 1H), 2.60−2.35 (m, 3H), 1.90−1.65 (m, 2H), 1.60−1.45 (m, 2H), 1.25 (d, 3H, J = 7 Hz), 1.15 (t, 3H, J = 7 Hz), 1.10 (d, 3H, J = 7 Hz); ^{13}C NMR **12a** 175.9, 144.8, 127.8, 127.9, 127.6, 126.4, 63.4, 60.0, 57.2, 46.7, 43.2, 28.1, 23.6, 14.4, 14.3, 12.2; **13a** 175.8, 145.2, 128.0, 127.5, 126.5, 62.5, 60.0, 58.6, 48.0, 42.9, 27.2, 24.3, 14.4, 14.3, 10.9; IR (neat) 1730 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.88; H, 9.02; N, 5.19.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]butanoic Acid Ethyl Ester (10b−13b). Reduction of **6b**. Yields: 95% (PtO_2), 83% (Pt/C), 92% (Pd/C), 95% ($NaBH(AcO)_3$); oil; ^{1}H NMR 7.3−7.0 (m, 5H), 4.2−3.8 (m, 3H), 3.25−1.8 (m, 4H), 1.75−1.30 (m, 6H), 1.25 (m, 3H), 1.15 (t, 3H, J = 7.0 Hz), 0.75 (t, 3H, J = 7.3 Hz); ^{13}C NMR **12b** 174.9, 144.9, 128.3−126.2, 62.4, 59.6, 56.6, 50.5, 46.8, 27.1, 23.2, 23.1, 14.0, 12.2; **13b** 175.0, 144.5, 128.3−126.2, 62.8, 59.6, 58.7, 52.0, 47.5, 27.8, 24.1, 19.7, 14.0; IR (neat) 1730 cm^{-1}. Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.73; H, 9.52; N, 4.79.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]pentanoic Acid Ethyl Ester (10c−13c). Reduction of **6c**. Yields: 97% (PtO_2), 95% (Pt/C), 90% (Pd/C), 98% ($NaBH(AcO)_3$); oil; ^{1}H NMR 7.4−7.1 (m, 5H), 4.15−3.80 (m, 3H), 3.1−2.9 (m, 1H), 2.7−1.9 (m, 3H), 1.8−1.3 (m, 6H), 1.35−1.25 (m, 3H), 1.20−1.15 (m, 5H), 0.8 (t, 3H, J = 7.3 Hz); ^{13}C NMR **12c** 175.0, 144.8, 128.3−126.2, 62.7, 59.6, 56.8, 48.4, 46.6, 32.3, 26.9, 23.2, 21.0, 14.1, 13.9, 12.1; **13c** 175.2, 144.5, 128.3−126.2, 62.9, 59.6, 58.6, 50.0, 47.5, 28.9, 27.8, 24.1, 21.0, 14.1,13.9, 12.1; IR (neat) 1720 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.36; H, 9.52; N, 4.80.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]hexanoic Acid Ethyl Ester (10d−13d). Reduction of **6d**. Yields: 95% (PtO_2), 80% (Pt/C), 86% (Pd/C), 98% ($NaBH(AcO)_3$); oil; ^{1}H NMR 7.4−7.1 (m, 5H), 4.1−3.8 (m, 3H), 3.1−2.9 (m, 1H), 2.8−1.8 (m, 3H), 1.75−1.30 (m, 6H), 1.30−0.95 (m, 10H), 0.85−0.75 (m, 3H); ^{13}C NMR **12d** 175.0, 145.0, 128.5−126.4, 62.8, 59.7, 57.1, 48.6, 46.8, 29.8, 27.0, 22.7, 14.1, 13.9, 12.3; **13d** 175.2, 144.8, 128.5−126.4, 63.0, 59.7, 58.7, 50.1, 47.6, 26.4, 27.9, 24.1, 14.0, 13.8, 12.3; IR (neat) 1725 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.81; H, 9.69; N, 4.54.

2-Phenyl-2-[1-(1(*S*)-phenylethyl)pyrrolidin-2-yl]ethanoic Acid Ethyl Ester (10e−13e). Reduction of **6e**. Yields: 95% (PtO_2), 80% (Pt/C), 98% ($NaBH(AcO)_3$); oil; ^{1}H NMR 7.3−7.0 (m, 10H), 4.2 (q, 1H, J = 6.9 Hz), 4.0 (q, 2H, J = 7.0 Hz), 3.65 (m, 1H), 3.4 (d, 1H, J = 9.3 Hz), 2.5 (m, 2H), 1.5 (m, 2H), 1.25 (d, 3H, J = 6.9 Hz), 1.0 (t, 3H, J = 7.0 Hz); ^{13}C NMR **12e** 173.8, 144.8, 137.6−126.3, 64.7, 60.5, 58.6, 58.5, 46.5, 29.4, 24.3, 14.1, 12.5; **13e** 173.1, 144.5, 137.6−126.3, 64.7, 60.3, 58.4, 57.1, 47.1, 29.8, 24.0, 14.1, 12.2; IR (neat) 1720 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.23; H, 8.12; N, 4.06.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-ylidene]butanedioic Acid Dimethyl Ester (16). Condensation of methyl 2-bromobutanedioate **(14)** with **4** gave **16** as a mixture of 75/25 *E*/*Z* isomers: yield 84%; oil; ^{1}H NMR 7.6−7.4 (m, 5H), 5.48 (q, 0.3H, J = 6.9 Hz), 5.11 (q, 0.7H, J = 6.9 Hz), 3.94−3.89 (2s, 6H), 3.63 (s, 1.5H), 3.57 (s, 0.5H), 3.57−3.47 (m, 2H), 3.36 (t, 0.5H, J = 7.7 Hz), 3.32−3.16 (m, 1.5H), 2.85 (t, 0.5H), 2.09−1.98 (m, 2H), 1.89 (d, 0.8H, J = 6.8 Hz), 1.84 (d, 2.2H, J = 6.8 Hz); ^{13}C NMR 173.5, 173.3, 169.6, 167.0, 165.2, 164.2, 141.7, 128.9, 128.2, 127.4, 127.0, 126.9, 87.1, 85.0, 56.3, 55.4, 51.2, 50.1, 47.9, 46.8, 36.1, 35.4, 34.8, 33.9, 21.2, 19.8, 17.7, 15.3; IR (neat) 1730, 1670, 1550 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.15; H, 7.39; N, 4.42.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-ylidene]pentanedioic Acid Dimethyl Ester (17). Condensation of methyl 2-bromopentandioate **(15)** with **4** gave **17** as a 65/35 *E*/*Z* mixture: yield 85%; oil; ^{1}H NMR 7.3−7.2 (m, 5H), 5.35 (q, 0.4H, J = 6.9 Hz), 5.15 (q, 0.6H, J = 6.9 Hz), 3.6−3.5 (2s, 6H), 3.35−2.80 (m, 4H), 2.65−2.30 (m, 4H), 1.9−1.7 (m, 2H), 1.6−1.5 (m, 3H); ^{13}C NMR 174.1, 173.2, 170.5, 168.0, 164.5, 163.3, 141.7, 141.2, 128.6, 128.2, 127.4, 127.0, 126.9, 126.6, 92.2, 90.4, 56.5, 55.6, 51.2, 50.4, 48.2, 47.1, 35.9, 34.7, 35.0, 34.8, 27.0, 24.1, 21.6, 20.3, 17.4, 16.1; IR (neat) 1730, 1670, 1550 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.85; H, 7.53; N, 4.21.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]pentanedioic Acid Dimethyl Ester (20). To a degassed solution of β-enamino diester **17** (3.04 g) in MeOH (120 mL) was added 10% Pd/C w/w (121 mg, 0.04 equiv). The resulting suspension was hydrogenated under atmospheric pressure and the reaction monitored by GC. At the end of the reduction, after consumption of 1 mol of H_2 per mole of enamino diester, the solution was filtered. The filter cake was rinsed with MeOH and solvent removed. The crude mixture of amino diester diastereoisomers was directly analyzed by GC and ^{13}C NMR and then chromatographed on a silica gel column (AcOEt/cyclohexane 1/3). Reduction yield was 95%. The mixture of **18**, **19**, **20** was transformed into the picrate salt which was recrystallized three times in *n*-butanol. The amino diester **20**, liberated with K_2CO_3 and extracted from the cake with CH_2Cl_2, was finally obtained with a diastereomeric purity over 99% and 70% yield: oil; ^{1}H NMR 7.45−7.20 (m, 5H), 4.1 (q, 1H, J = 6.9 Hz), 3.7 (s, 6H), 3.1 (m, 1H), 2.65−2.40 et 2.35−2.15 (2 m, 3H), 2.0−1.4 (m, 8H), 1.34 (d, 3H, J = 6.9 Hz); ^{13}C NMR 174.8, 144.5, 128.5−126.5, 62.6, 57.0, 51.5, 51.2, 48.0, 46.6, 32.1, 27.1, 23.2, 21.4, 12.3; IR (neat) 1730 cm^{-1}. $[\alpha]\ ^{20}_D = +26$ (*c* 1.15, EtOH). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.48; H, 8.09; N, 4.10. ^{13}C NMR spectra of minor diastereomer **21** observed with PtO_2, Pt/C, and chemical reduction: 174.9, 142.9, 128.5−126.5, 62.9, 59.2, 51.4, 51.2, 48.7, 48.1, 32.2, 27.7, 24.5, 24.1, 14.9.

2-[1-(1(*S*)-Phenylethyl)pyrrolidin-2-yl]butanedioic Acid Dimethyl Ester (24). With the same workup as used for **17**, the β-enamino diester **16** (4.08 g) was reduced using 10% Pt/C w/w (204 mg, 0.05 equiv) as catalyst to obtain the crude mixture of diastereomers **22**−**25** with 95% yield. Treatment with picric acid and recrystallizations of picrate salt in *n*-butanol finally gave amino diester **24** with a diastereomeric purity over 98% and 72% yield: oil; ^{1}H NMR 7.38−7.26 (m, 5H), 4.03 (q, 1H, J = 6.8 Hz), 3.68−3.66 (2s, 6H), 3.17 (q, 1H, J = 5.8 Hz), 3.04−2.96 (m, 1H), 2.82−2.71 (m, 1H), 2.60−2.51 (m, 3H), 1.84−1.76 (m, 2H), 1.66−1.58 (m, 2H), 1.31 (d, 3H, J = 6.8 Hz); ^{13}C NMR 174.0, 172.3, 144.0, 127.7−126.2, 61.5, 56.6, 51.3, 51.2, 46.2, 44.4, 33.3, 27.8, 23.0, 11.9; IR (neat) 1730 cm^{-1}. $[\alpha]\ ^{20}_D = +37$ (*c* 1.20, EtOH). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.77; H, 7.91; N, 4.35. ^{13}C NMR spectra of minor diastereomer **25**: 173.8, 173.0, 142.1, 127.7−126.2, 60.9, 58.6, 51.4, 51.3, 48.2, 44.0 29.6, 26.7, 23.6, 14.9.

5-Oxooctahydroindolizin-8-carboxylic Acid Methyl Ester (26). To a degassed solution of amino diester **20** (720 mg) in MeOH (30 mL) was added 10% Pd/C w/w (435 mg, 0.6 equiv). The resulting suspension was stirred under an atmospheric pressure of hydrogen for 24 h. At the end of the reduction, controlled by GC, the solution was filtered, the insoluble material was washed with MeOH, and the solvent was removed. The crude mixture of diastereomers (99/1) of the lactam ester was chromatographed on a silica gel column (AcOEt/cyclohexane 1/3) to give optically pure **26**: reduction yield 88%; white solid, mp 74 °C; ^{1}H NMR 3.66 (s, 3H), 3.53−3.49 (m, 1H), 3.45−3.38 (m, 2H), 3.34−2.28 (m, 2H), 2.14 (m, 1H), 2.09 (m, 1H), 1.95−1.60 (m, 4H), 1.42 (m, 1H); ^{13}C NMR 173.0, 167.9, 60.0, 52.0, 45.8, 44.9, 32.4, 30.4, 25.1, 21.9; IR ($CHBr_3$) 1740, 1625 cm^{-1}. $[\alpha]\ ^{20}_D = +68$ (*c* 1.19, EtOH). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.86; H, 7.72; N, 7.12.

3-Oxohexahydropyrrolizin-1-carboxylic Acid Methyl Ester (27). With the same workup as above, used for **20**,

amino diester **24** (2.2 g) and 10% Pd/C (1.3 g, 0.6 equiv) gave a mixture of diastereomers of lactam esters (98/2) which was chromatographed to give optically pure compound **27**: reduction yield 85%; white solid, mp 43 °C; ^{1}H NMR 4.02−3.93 (m, 1H), 3.68 (s, 3H), 3.60−3.39 (m, 1H), 3.06−2.85 (m, 3H), 2.66−2.58 (m, 1H), 2.16−1.94 (m, 3H), 1.47−1.31 (m, 1H); ^{13}C NMR 172.4, 171.9, 63.7, 52.2, 45.7, 41.1, 38.3, 31.5, 26.6; IR ($CHBr_3$) 1740, 1685 cm^{-1}. [α] $^{20}_D$ = +67 (*c* 1.25, EtOH). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.04; H, 7.20; N, 7.80.

(+)-Tashiromine (8-Methanol octahydroindolizine) (2). A mixture of lactam ester **26** (440 mg, 2.23 mmol) and $LiAlH_4$ (340 mg, 9 mmol) was stirred in freshly distilled THF (40 mL) for 24 h at room temperature. The residue was quenched with 440 μL of water, 440 μl of an aqueous NaOH solution (15%), and then 1 mL of water. After filtration and evaporation of the solvent, the crude product was distillated on a Kugelrohr apparatus (125 °C, 0.3 mmHg): yield 87%; white solid, mp 35 °C; ^{1}H NMR 3.88−3.81 and 3.71−3.64 (2m, 2H), 3.31−3.21 (m, 2H), 2.31−2.20 (q, 1H, *J* = 17.8 Hz), 2.18−2.0 (m, 3H), 1.99−1.78 (m, 2H), 1.76−1.63 (m, 3H), 1.32−1.15 (m, 1H); ^{13}C NMR 66.5, 65.5, 54.2, 52.7, 44.6, 29.1, 27.7, 25.2, 20.8; IR ($CHBr_3$) 3600−3100 cm^{-1}. [α] $^{20}_D$ = +44.7 (*c* 1.1, 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.

(+)-Laburnine (1-Methanol hexahydropyrrolizine) (3). A mixture of bicyclic lactam **27** (350 mg, 1.91 mmol) and $LiAlH_4$ (365 mg, 9.56 mmol) in 40 mL of dried THF worked up according to the procedure used for **26** gave (+)-laburnine **3**: yield 85%; oil; ^{1}H NMR 3.63 (d, 2H, *J* = 6.2 Hz), 3.22−3.09 (m, 2H), 2.99−2.90 (m, 1H), 2.64−2.48 (m, 2H), 2.11 (m, 1H), 2.07−1.48 (m, 7H); ^{13}C NMR 67.5, 64.9, 54.7, 52.7, 48.5, 32.0, 30.1, 25.7; IR (neat) 3600−3100 cm^{-1}. [α] $^{20}_D$ = +15.4 (*c* 1.2, EtOH). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.01; H, 10.62; N, 9.97.

3-[1-(1(*S*)-Phenylethyl)-3-methoxycarbonyl-4,5-dihydropyrrol-2-yl]propanoic Acid Methyl Ester (29). With the same procedure used for **7**, reaction between 4-oxo-4-(1-methyloxycarbonylcyclopropyl)butanoic acid methyl ester **(28)** (14.98 g, 70 mmol) and (*S*)-α-methylbenzylamine (8.47 g, 70 mmol) gave compound **29**: yield 83%; oil; ^{1}H NMR 7.4−7.15 (m, 5H), 4.9 (q, 1H, *J* = 6.8 Hz), 3.65 (s, 3H), 3.6 (s, 3H), 3.55 (m, 1H), 3.3 (m, 1H), 3.3−2.9 (m, 3H), 2.75−2.5 (m, 4H), 1.55 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR 172.9, 167.0, 162.9, 141.0, 128.6, 127.3, 126.5, 95.7, 52.4, 51.7, 50.1, 45.2, 32.4, 26.3, 20.9, 17.7; IR (neat) 1730, 1660, 1570 cm^{-1}. [α] $^{20}_D$ = +29.6 (*c* 1.98, EtOH). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 67.97; H, 7.41; N, 4.51.

(2*S*,3*S*)-3-[1-(1(*S*)-Phenylethyl)-3-methoxycarbonyl-4,5-pyrrolidin-2-yl]propanoic Acid Methyl Ester (30). A mixture of dihydropyrrole **29** (16.1 g, 50.8 mmol) and PtO_2 (125 mg) in MeOH (50 mL) worked up according to the procedure used for the reduction of **7** gave reduced compound **30**: yield 87%; ^{1}H NMR 7.4−7.1 (m, 5H), 3.8−3.7 (m, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 3.25−3.15 (m, 1H), 3.05−2.95 (m, 1H), 2.95−2.85 (m, 1H), 2.75−2.65 (m, 1H), 2.35−2.25 (m, 2H), 2.2−2.1 (m, 1H), 1.95−1.85 (m, 1H), 1.7−1.6 (m, 1H), 1.45−1.35 (m, 1H), 1.35 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR 173.9, 173.5, 144.5, 128.2, 127.5, 126.8, 61.9, 60.4, 51.4, 51.3, 47.2, 46.4, 30.8, 26.2, 25.7, 18.1; IR (neat) 1730 cm^{-1}. [α] $^{20}_D$ = +7.5 (*c* 2.08, EtOH). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.61; H, 8.01; N, 4.42.

(1*S*,8*S*)-5-Oxohexahydropyrrolizin-1-carboxylic Acid Methyl Ester (32). To a degassed solution of N-substituted pyrrole **30** (10.3 g, 32 mmol) in MeOH (30 mL) was added 5% Pd/C w/w (1.5 g). The resulting suspension was stirred for 48 h under an atmospheric pressure of hydrogen. The solution was filtered, the filter cake was washed with MeOH, and the combinated filtrates were evaporated. The residue was dissolved in toluene (50 mL), and the solution was heated at 90 °C for 5 h. The crude product was chromatographed on a silica gel column (THF saturated with NH_3): yield 90%; ^{1}H NMR 4.08 (q, 1H, *J* = 10 Hz), 3.8−3.5 (m, 1H), 3.6 (s, 3H), 3.1−2.85 (m, 2H), 2.7−2.45 (m, 1H), 2.4−2.0 (m, 4H), 1.75−1.5 (m, 1H); ^{13}C NMR 175.4, 172.9, 63.1, 51.8, 45.2, 41.0, 33.6, 30.2, 22.3; IR (neat) 1725, 1680 cm^{-1}. [α] $^{20}_D$ = −16.6 (*c* 2.08, EtOH). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.37; H, 7.07; N, 7.67.

(1*S*,8*S*)-5-Thioxohexahydropyrrolizin-1-carboxylic Acid Methyl Ester (34). A mixture of bicyclic lactam **32** (4.9 g, 26.8 mmol) and Lawesson reagent (5.7 g, 14.1 mmol) was refluxed in dry toluene (50 mL) during 1 h. The solvent was then evaporated, and the solid obtained was recrystallized in Et_2O: yield 56%; mp 81 °C; ^{1}H NMR 4.5−4.3 (m, 1H), 4.05−3.7 (m, 1H), 3.65 (s, 3H), 3.4−3.2 (m, 1H), 3.2−2.9 (m, 3H), 2.55−2.1 (m, 3H), 1.8−1.5 (m, 1H); ^{13}C NMR 196.0, 172.1, 70.2, 51.9, 48.3, 44.5, 44.1, 30.6, 25.2; IR (neat) 1725 cm^{-1}. [α] $^{20}_D$ = −118.2 (*c* 0.9, EtOH). Anal. Calcd for $C_9H_{13}NO_3S$: C, 54.27; H, 6.53; N, 7.03. Found: C, 53.91; H, 6.47; N, 7.11.

(1*S*,8*S*)-Hexahydropyrrolizin-1-carboxylic Acid Methyl Ester (35). A mixture of bicyclic thiolactam **34** (2.2 g, 11 mmol) and methyl iodide (5.46 g, 38.5 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 24 h. The solvent was removed, and the residue was dissolved in MeOH (30 mL). $NaBH_4$ (0.84 g, 22 mmol) was then added. After 12 h of stirring at room temperature, the solution was neutralized with of 1 M HCl (10 mL). After 2 h, K_2CO_3 was added. The gel formed was extracted with $CHCl_3$ (3 × 60 mL). Solvent was evaporated, and the crude product was distillated on a Kugelrohr apparatus (ot 105 °C, 0.05 mmHg): yield 77%; ^{1}H NMR 3.80−3.6 (m, 1H), 3.65 (s, 3H), 3.85−2.7 (m, 1H), 3.2−2.85 (m, 3H), 2.65−2.45 (m, 1H), 2.2−1.95 (m, 1H), 1.95−1.55 (m, 4H), 1.4−1.35 (m, 1H); ^{13}C NMR 174.1, 65.9, 55.7, 53.7, 51.6, 47.4, 28.6, 26.8, 26.4; IR (neat) 1725 cm^{-1}. [α]$^{20}_D$ = −65.1 (*c* 2.16, $CHCl_3$). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.37; H, 8.73; N, 8.19.

(−)-Isoretronecanol (1-Methanol hexahydropyrrolizine) (1). To 10 mL of a 1 M solution of $LiAlH_4$ in THF cooled at −80 °C was added dropwise a solution of **35** (1.1 g, 6 mmol) in 14 mL of freshly distilled THF. The mixture was stirred 24 h at −80 °C and then quenched with 1 mL of water in 10 mL of THF. After filtration and evaporation of the solvent, the crude product was distillated on a Kugelrohr apparatus (ot 180 °C, 0.05 mmHg): yield 87%; ^{1}H NMR 4.33 (br s, 1H), 3.85−3.27 (d, 3H), 3.6 (s, 3H), 3.27−2.77 (m, 2H), 2.77−1.03 (m, 2H); ^{13}C NMR 66.32, 62.97, 55.65, 54.05, 44.33, 27.20, 26.48, 25.95; IR (neat) 3600−2500 cm^{-1}. [α] $^{20}_D$ = −76.8 (*c* 2.1, EtOH). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.91. Found: C, 67.88; H, 10.62; N, 9.75.

Molecular Modeling Study. A molecular modeling study of described molecules was performed using the SYBYL 6.3 package on a Silicon Graphics R 8000 workstation. Structures were built within SYBYL and minimized by the Tripos force field Maximin 2 in vacuo conditions to provide reasonable standard geometries. The conjugate gradient method was used for minimization, and molecules were considered to be minimized when a minimum energy charge of less than 0.021 kJ mol^{-1} for one iteration was reached. Semiempirical AM1 calculations were performed using the MOPAC package implemented in SYBYL and involved the singlet state. The conformational spaces of compounds **6a** and **7** were explored using the SYBYL search facility. Torsion angles were defined, and a qrid search was performed allowing chosen bonds to rotate within a 360° or 180° revolution by 15° increments. The lowest energy conformers thus obtained were submitted to AM1 calculations (MOPAC version 5.0) to optimize their geometry.

The optimized structure of **6e** was subjected to a restrained molecular dynamic simulation lasting 10 ps with a retention time step of 1 fs. The temperature was raised to 1000 K, and molecules were captured every 5 fs. Structures were selected after analysis of dynamic trajectory, and the lowest energy conformers were minimized by Maximin 2.

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