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Stereocontrolled reduction of chiral pyrrolidine and piperidine β-enamino esters: formal enantioselective synthesis of (+)-calvine

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Abstract—The results of a study dealing with the chemio- and diastereoselective reduction of chiral pyrrolidine and piperidine β-enamino esters **1**, **2** and **3**, **4** into β-amino esters are reported. This approach was successfully applied to a formal synthesis of (+)-calvine.

1. Introduction

Diastereoselective synthesis of chiral α,α′-disubstituted pyrrolidines and piperidines, which are sub-structures present in many naturally occurring and biologically important compounds, is of considerable current interest.[1] In a previous report, we described the diastereoselective preparation of chiral pyrrolidine and piperidine bicyclic β-enamino esters **1**, **2** and **3**, **4** (Fig. 1) by condensation of (*S*)-phenylglycinol on ω-oxo alkynoates or ω-oxo β-keto esters.[2] We now wish to report the results of a study aimed at diastereoselectively reducing the double bond of the β-enamino ester moiety of **1**–**4** in order to obtain the corresponding β-amino esters. Related heterocycles have been indeed already described as useful intermediates in the total synthesis of alkaloids.[1d,3] Finally, as an illustration of the interest of our approach, we will describe a formal synthesis of enantiopure (+)-calvine (**5**).

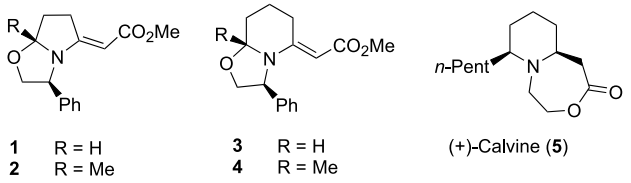
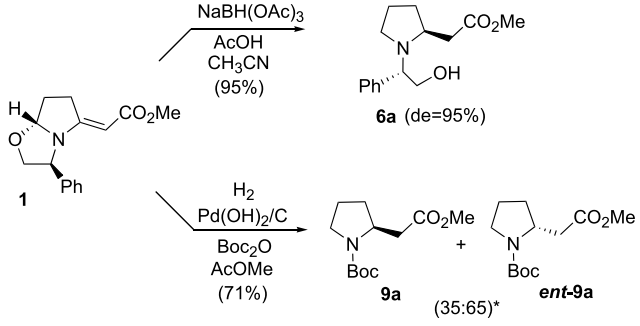


Figure 1.

2. Results and discussion

In order to assess the influence of the reducing agent on the chemio- and diastereoselectivity of the reaction, the reductions of β-enamino esters were carried out either by catalytic hydrogenation or using an hydride. Catalytic hydrogenations were performed under atmospheric pressure using PtO_2 and $Pd(OH)_2$ as catalysts, whereas hydride reductions were carried out with sodium triacetoxyborohydride in acetic acid.[4]

We first investigated the reduction of the pyrrolidine and piperidine bicyclic compounds **1** (Scheme 1) and **3** (Scheme 2), which both contain an angular hydrogen atom. Treatment with sodium triacetoxyborohydride of **1** and **3** led to the reduction of the C–C double bond along with the cleavage of the oxazolidine ring to give compounds **6** and **7**, respectively. Pyrrolidine **6** was obtained in high yield (95%)



*ratio determined by chiral GC analysis

Scheme 1. Reduction of **1**.

Keywords: Reduction; β-Amino esters; Pyrrolidine; Piperidine; Calvine.
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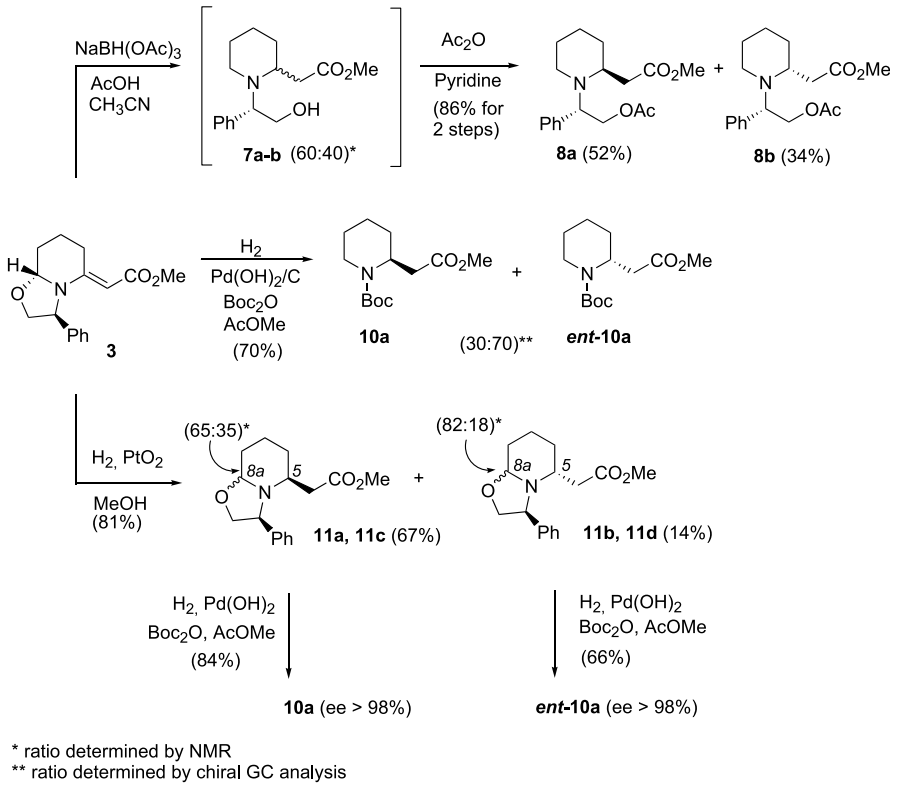
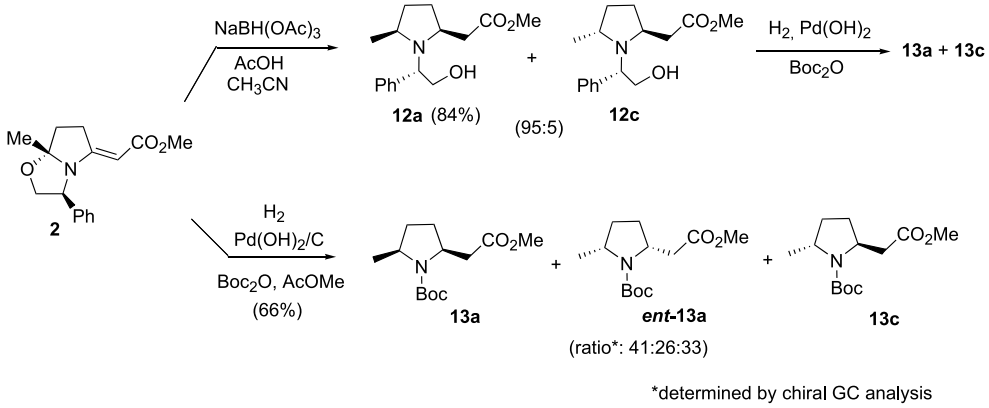


Scheme 2. Reduction of **3**.

and excellent diastereoselectivity (95% de) (Scheme 1). The stereochemistry of the major isomer **6a** was assigned as (2*S*) by comparison of spectroscopic data with that described in the literature.[5] Concerning the piperidine derivative **3** (Scheme 2), the reaction proceeded with poor diastereoselectivity (de=20%) and afforded **7** as an inseparable mixture of diastereomers. The major isomer **7a** was identified as the (2*S*) isomer, since spectroscopic data were found identical to that previously reported for this compound.[5] Acetylation of the crude mixture (Ac_2O, pyridine) resulted in a mixture of two compounds (2*S*)-**8a** and (2*R*)-**8b** that were isolated in 52 and 34% yield, respectively.

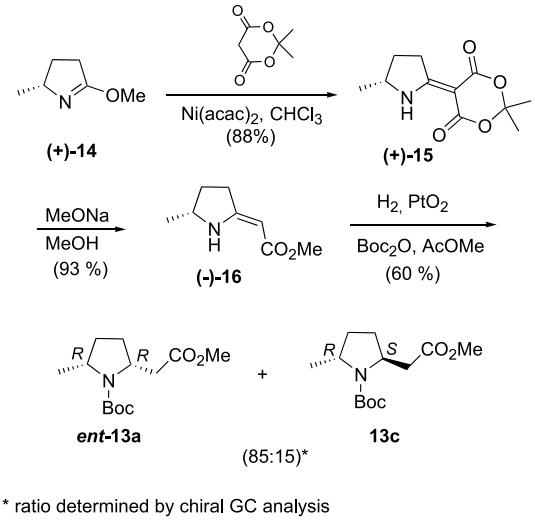
Catalytic hydrogenation in the presence of $Pd(OH)_2$ and Boc_2O of compounds **1** and **3** was then performed (Schemes 1 and 2). In both cases, *N*-debenzylated β-amino esters were obtained transiently and in situ transformed into *tert*-butyl carbamates **9** and **10**, respectively, in 71 and 70% isolated yield. Analysis by chiral GC and optical rotation measurements showed that both compounds were obtained with poor stereoselectivity (ee for **9**: 30% and for **10**: 40%) and that the (2*R*) isomers *ent*-**9a**[6] and *ent*-**10a** [3c] were the major enantiomers.

Hydrogenation of compound **1** in the presence of PtO_2 as the catalyst was surprisingly ineffective.[7] In contrast, under the same reaction conditions, compound **3** was chemioselectively reduced into bicyclic piperidines **11** as a mixture of four isomers (Scheme 2). Column chromatography allowed the isolation of inseparable piperidines **11a**, **11c** (ratio 65:35) on the one hand and of inseparable piperidines **11b**, **11d** (ratio 82:18) on the other hand in, respectively, 67 and 14% yields. In order to secure stereochemistry, each mixture



Scheme 3. Reduction of **2**.

was submitted to hydrogenolysis in the presence of $Pd(OH)_2$ and Boc_2O to yield *N-tert*-butoxycarbonyl derivatives **10** in a one-pot procedure. Analysis of the crude mixtures by chiral GC showed in each case the presence of only one isomer, respectively, piperidines **10a** (ee>98%) and *ent*-**10a** (ee>98%) (Scheme 2). This result demonstrated that the initial mixtures were composed of epimers at C-8a. NOE experiments conducted on each mixture showed a transfer of saturation from one species to the other, which confirmed that both mixtures of oxazolidines consisted of equilibrated C-8a epimers, as previously observed on related compounds by others.[8] The stereochemistry of the C-8a center is of little importance, since alkylation at C-8a of similar oxazolidines by organometallic or silyl enol ether reagents is known to give selectively *cis* disubstituted piperidines, whatever the initial configuration of the angular carbon.[9] Moreover, comparison of the spectroscopic data of *tert*-butyl carbamate **10a** and *ent*-**10a** with that reported in the literature[3c] demonstrated that absolute configuration at C-5 for **11a** and **11c** was (5*S*) and that for **11b** and **11d** was (5*R*).

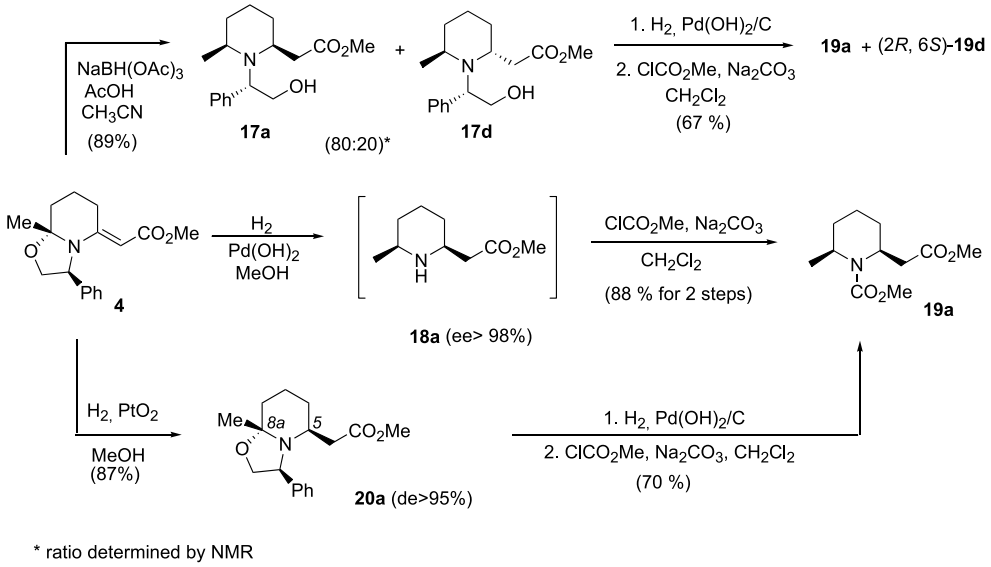


Scheme 4.

Concerning the angularly substituted bicyclic β-enamino ester **2** (Scheme 3), reduction by sodium triacetoxyborohydride diastereoselectively afforded monocyclic disubstituted pyrrolidine **12**, with an excellent diastereomeric excess (de=90%), as previously observed for the pyrrolidine analogue **1**. From the crude mixture, compound **12a** was isolated in 84% yield.

Since we were unable to prepare a crystalline salt from **12a** and hence to determine its absolute configuration, we had to rely upon chemical correlation (Scheme 4). With this aim in mind (*S*)-pyroglutamic acid was transformed into the chiral lactim ether **14** according to a previously described procedure.[10] The latter was condensed with Meldrum's acid in the presence of a catalytic amount of $Ni(acac)_2$ to give in 88% yield β-enamino diester **15**, which in turn underwent successive transesterification and decarboxylation upon heating in a solution of sodium methoxide.[11] Though catalytic hydrogenation of the resulting β-enamino ester **16** had been reported to give stereoselectively the *cis* isomer,[12] in our hands, hydrogenation of **16** in the presence of PtO_2 and Boc_2O gave the *cis* (2*R*, 5*R*) isomer *ent*-**13a** along with the *trans* (2*S*, 5*R*) isomer **13c** as a 85:15 mixture, in 60% overall yield. On the other hand, crude **12** resulting from the reduction of **2** by $NaBH(OAc)_3$ was hydrogenolyzed in the presence of $Pd(OH)_2$ and Boc_2O to yield a mixture of **13a** and **13c** (Scheme 3). Comparison by chiral GC of the two reaction mixtures allowed us to assign the *cis* stereochemistry and a (2*S*, 5*S*) absolute configuration to the major isomer **12a**, whereas a *trans* (2*S*, 5*R*) configuration was assigned to the minor isomer **12c**.

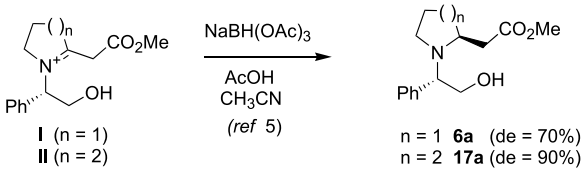
Compound **2** was then hydrogenated in the presence of $Pd(OH)_2$ and Boc_2O. Under these conditions, we obtained, in 66% yield, a disappointing mixture of three isomers, as determined by chiral GC analysis, consisting of a 67:33 mixture of the *cis* isomers ((2*S*,5*S*)-**13a** and (2*R*,5*R*)-*ent*-**13a**; (ratio 61:39)) and of the *trans* isomer (2*S*,5*R*)-**13c** (Scheme 3). Finally, as for compound **1**, hydrogenation of **2** in the presence of PtO_2 left the product unchanged.[7]



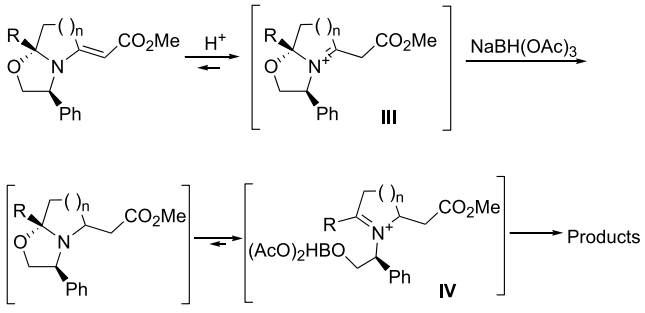
Scheme 5. Reduction of **4**.

Finally, we turned out our attention to the reductions of the angularly substituted piperidine **4** (Scheme 5). Catalytic hydrogenation of this compound in the presence of catalytic $Pd(OH)_2$ (3 atm, 12 h) followed by reaction with methylchloroformate had previously been reported by Meyers[3b] to afford stereoselectively the *cis* (2*S*, 6*S*) isomer **19a**. We repeated this two-step procedure[13] in order to obtain **19a** as a reference compound of established absolute configuration[3b] (Scheme 5).

On the other hand, the chemical reduction of **4** by $NaBH(OAc)_3$ afforded monocyclic β-amino ester **17** as a 80:20 mixture of two isomers in 89% overall yield. In order to assign the stereochemistry of these compounds, the mixture was hydrogenolyzed and then reacted with methylchloroformate. Analysis by chiral and achiral GC led us to attribute to the major isomer **17a** the *cis* (2*S*, 6*S*) configuration and the *trans* (2*R*, 6*S*) configuration to the minor isomer **17d**. Finally, PtO_2 catalyzed hydrogenation gave bicyclic piperidine **20a** as a single isomer, in 87% yield. In contrast to what was observed for the hydrogenation of **3**, no epimerization at the quaternary angular carbon had occurred. Hydrogenolysis of **20a** and subsequent methoxycarbonylation led to compound **19a**, which allowed us to assign the (5*S*, 8a*R*) configuration to the oxazolidine **20a**.



Scheme 6.



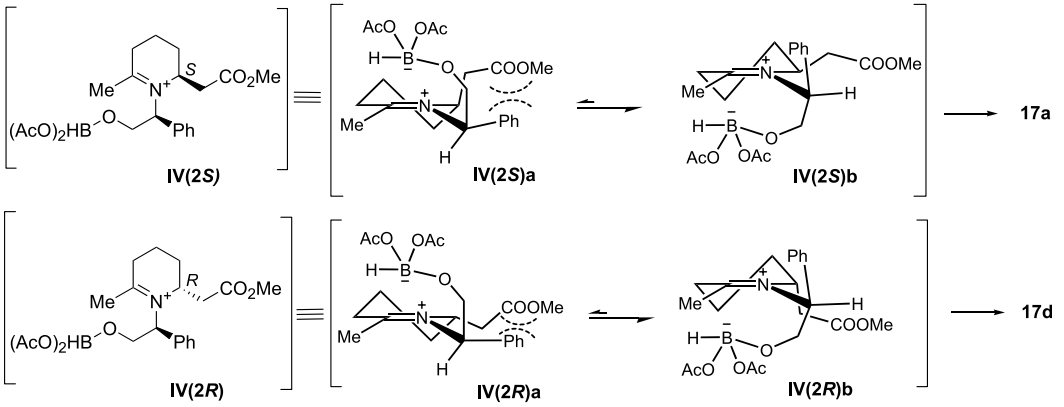
Scheme 7.

Our study clearly showed that bicylic pyrrolidine and piperidine β-enamino esters displayed different behaviours depending on reduction conditions. Considering that these substrates possess three bonds that may be affected under reductive conditions, diastereoselectivity depends on the timing of the different processes. Efficient reduction of pyrrolidines **1** (Scheme 1) and **2** (Scheme 3) in terms of yield and diastereoselectivity required the use of sodium triacetoxyborohydride under acidic conditions. In contrast, reductions of piperidines **3** (Scheme 2) and **4** (Scheme 5) under similar conditions proceeded with lower diastereoselectivities.

In the case of compounds **1** and **3**, we suppose that the double bond was reduced before the cleavage of the oxazolidine ring, which would explain the observed stereoselectivies (respectively, 95 and 20% diastereomeric excess). Indeed, the presence of the oxazolidine moieties is clearly key in these reductions as substantiated by the comparison with the sodium triacetoxyborohydride-mediated reduction of monocyclic iminium ions **I** and **II** that we previously reported[5] to proceed, respectively, in 70 and 90% diastereomeric excess (Scheme 6).

Concerning angularly-substituted compounds **2** and **4**, preliminary reduction of the double bond is also likely to be involved. Moreover, the presence of the methyl substituent instead of an hydrogen atom appeared necessary to induce a better control of the stereochemistry at the C-2 center. In both cases, one can note the major obtention of *cis* α,α'-disubstituted products **12a** and **17a** from compounds **2** and **4**, respectively.[14] Initial reduction of the double bond under acidic conditions would proceed via bicyclic iminium ions **III** (Scheme 7), preferentially from the less hindered *endo* face, to lead mainly to the (*S*) stereochemistry at C-2, with a better control for strained pyrrolidine compounds than for piperidine ones. The resulting bicyclic oxazolidine would be in equilibrium with open borohydride-containing iminium **IV**[12,16] that would evolve toward products through intramolecular hydride delivery to the iminium bonds.

Thus, in the case of piperidine **4**, reduction at C-2 would lead to the formation of two isomeric iminium ions **IV**(2*S*)

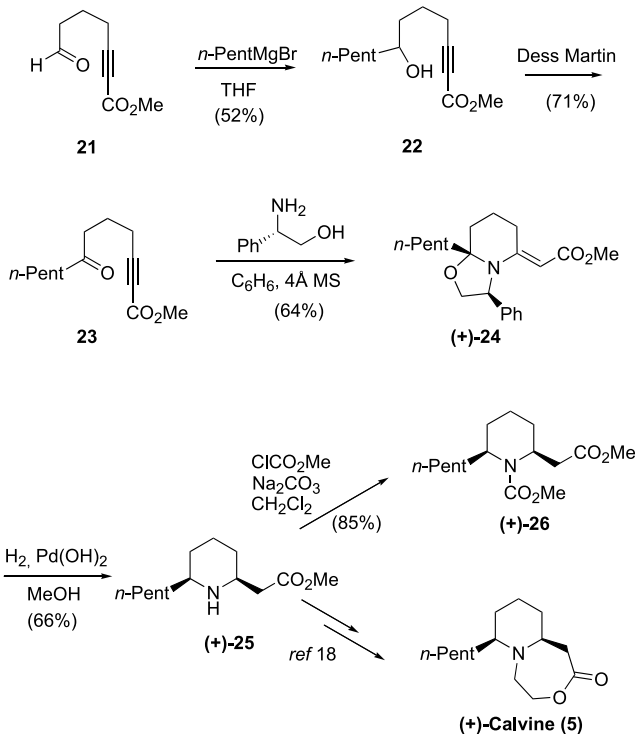


Scheme 8. Proposed mechanism for formation of **17a** and **17d** from piperidine **4**.

and **IV**(2*R*) whose reactive conformations are depicted in Scheme 8. The observed stereochemistry would result from an axial delivery of the hydride from the favoured conformations **IV**(2*S*)**b** and **IV**(2*R*)**b** under stereoelectronic control. In comparison, conformations **IV**(2*S*)**a** and **IV**(2*R*)**a** appear disfavoured due to the strong steric interactions between the phenyl ring of the chiral auxiliary and the C-2 subtituent.[17] In the case of conformation **IV**(2*S*)**a** whose reduction would lead to an unobserved *trans* (2,6) piperidine, the destabilization induced by the above steric constraints would be able to overcome the benefit arising from the minimization of the $A^{1,2}$ allylic strain present in this particular conformation, whereas in conformation **IV**(2*R*)**a**, steric factors and allylic strain are additive to disfavour this conformation. Regarding reduction of pyrrolidine **2**, a similar rationale should be considered to account for the major *cis* stereochemistry of the isolated compounds.

As far as catalytic hydrogenations are concerned, these reduction conditions were efficient and selective only in the case of angular methyl-containing oxazolopiperidine **4** (Scheme 5). PtO_2 catalyzed hydrogenation of **4** afforded bicyclic piperidine **20a** with a complete control of the stereochemistry at C-5 as the result of hydrogen attacking *anti* to the phenyl and methyl substituents. Reduction of **4** in the presence of $Pd(OH)_2$ yielded piperidine **18a** as a single *cis* isomer. This result was assumed to result from the initial reductions of the double and C–O bonds from the *endo* face followed by *N*-debenzylation.[3b] In all other cases (compounds **1**, **2**, and **3**), the poor selectivities observed under these conditions might result from early *N*-debenzylations and/or oxazolidine cleavages, which prevented any stereochemical control during the subsequent reduction of the double bonds. Noteworthy was the (*R*) absolute stereochemistry at C-2 of the major isomers obtained upon hydrogenation of compounds **1** and **3**, a result that contrasts with what was observed in other cases of this study. We have no clear explanation for this result.

In order to illustrate the synthetic potential of our approach, we envisioned to carry out a formal synthesis of (+)-calvine (**5**), a piperidine alkaloid isolated from ladybird beetles of the *Genus Calvia*[18] (Scheme 9). The key step of our strategy relied on the diastereoselective reduction of bicyclic β-enamino ester **24**. The latter was obtained starting from methyl oxo heptynoate **21**[19] in three steps. Addition of *n*-pentylmagnesium bromide to **21** gave alcohol **22**, which was subsequently oxidized to the corresponding ketone **23** according to the Dess–Martin procedure in 71% yield. Condensation of (*S*)-phenylglycinol on compound **23** in refluxing benzene afforded the expected bicyclic oxazolidine **24** in 64% yield, as a single isomer. Catalytic hydrogenation in the presence of $Pd(OH)_2$ yielded the disubstituted piperidine **25** with an excellent diastereomeric excess (de>98%) in the favor of the *cis* disubstituted piperidine. Indeed, this compound exhibited NMR data identical with those reported in the literature for the *cis* (2*S*, 6*S*) isomer.[20] However, the measured absolute optical rotation ($[\alpha]_D^{20}$ +16 (*c* 0.64, $CHCl_3$)) did not agree with that previously reported[20,21] (lit.[20] $[\alpha]_D^{20}$ +23 (*c* 0.52, $CHCl_3$)). In order to secure the enantiomeric excess of (+)-**25**, we synthesized by the same method, the



Scheme 9. Formal synthesis of (+)-calvine.

enantiomer (−)-**25** using (*R*)-phenylglycinol as the chiral inductor ($[\alpha]_D^{20}$ −17 (*c* 1.08, $CHCl_3$)). In order to check the optical purity of these compounds by chiral GC, both enantiomers were transformed into their methoxycarbonyl derivatives **26**.[18,20] This allowed us to confirm that each sample consisted of a single enantiomer. This high diastereoselectivity of the reduction of **24** was consistent with that previously observed for the angularly methylated piperidine **4**. Compound **25**, which is also an alkaloid isolated from *Calvia*, is an intermediate previously described in the total synthesis of (+)-calvine.[20]

3. Conclusion

In conclusion, the reported study enabled us to prepare enantiopure pyrrolidine and piperidine β-amino esters by chemio- and diastereoselective controlled reductions from bicyclic chiral β-enamino esters. In particular, our strategy gives access to *cis* disubstituted heterocycles that are useful intermediates in the synthesis of alkaloids as illustrated by our formal synthesis of (+)-calvine. Further efforts to develop the synthetic applications of these β-amino esters are underway in our laboratory.

4. Experimental

4.1. General

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone ketyl immediately prior to use. CH_2Cl_2 was distilled from calcium hydride. All reactions were carried out under argon. Thin

layer chromatography analyses were performed on Merck precoated silica gel (60 F_{254}) plates and column chromatography on silica gel Gerudan SI 60 (40–60 μm) (Merck). Melting points are uncorrected. IR: Philips PU 9700. Chiral gas chromatographies were performed on a capillary Chrompack CP-Chirasil-DEX CB column and achiral ones on a Chrompack CP-SIL5. Optical rotation: Perkin-Elmer 241 polarimeter. Elemental analysis: Service Régional de Microanalyse de l'Université P. et M. Curie. HMRS were recorded on a JEOL MS 700 mass spectrometer. NMR: Bruker ARX 250 spectrometer (250 and 62.9 MHz for ^1H and ^{13}C, respectively). Spectra were recorded in $CDCl_3$ as solvent. Chemical shifts (δ) were expressed in ppm relative to TMS at $\delta=0$ for ^1H and to $CDCl_3$ at $\delta=77.1$ for ^{13}C and coupling constants (J) in Hertz.

4.2. General procedure for $NaBH(OAc)_3$ mediated reductions

A solution of $NaBH(OAc)_3$ was prepared by portionwise addition of $NaBH_4$ (5 mmol) to glacial acetic acid (25 mol) at 0 °C. After the hydrogen evolution ceased (30 min), a solution of the substrate (1 mmol) in acetonitrile (4 mL) was added. After stirring for 48 h at room temperature, the solvents were evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and the organic layer was neutralized with saturated aqueous Na_2CO_3 solution. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo.

4.2.1. (2*S*)-[1-(2-Hydroxy-1-(*S*)-phenyl-ethyl)-pyrrolidin-2-yl]-acetic acid methyl ester (6a). The above general procedure was followed for the reduction of compound **1** (312 mg, 1.2 mmol). Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 8:2) afforded **6a**[5] (303 mg, 95%) as a solid.

4.2.2. [1-(2-Acetoxy-1-(*S*)-phenyl-ethyl)-piperidin-2-yl]-acetic acid methyl ester (8). The general procedure was followed for the reduction of compound **3** (130 mg, 0.5 mmol) to give a 60:40 mixture of (2*S*)-**7b**[5] and (2*R*)-**7b** isomers (132 mg), which were inseparable by silica gel column chromatography. The crude mixture of isomers **7** (132 mg) was stirred overnight in pyridine (9 mL) and acetic anhydride (3 mL). The solvents were evaporated in vacuo and the residue was dissolved in CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated in vacuo. Silica gel chromatography (cyclohexane/AcOEt 9:1) allowed the separation of the two isomers (2*S*)-**8a** (79 mg, 52%) and (2*R*)-**8b** (53 mg, 34%) as colorless oils.

For (2*S*)-**8a**. $[\alpha]_D^{20}$ +20 (*c* 1.075, $CHCl_3$). IR (neat) ν_{max} 1730 cm^{-1}. ^1H NMR δ 1.38–1.60 (m, 5H), 1.71–1.77 (m, 1H), 1.98 (s, 3H), 2.36–2.40 (m, 2H), 2.65 (m, AB part of ABX spectrum, 2H, $J_{AB}=14.25$ Hz), 3.45–3.52 (m, 1H), 3.66 (s, 3H), 3.96 (t, 1H, $J=6$ Hz), 4.38 (m, AB part of ABX spectrum, 2H, $J_{AB}=11.5$ Hz), 7.20–7.36 (m, 5H). ^{13}C NMR δ 20.7, 20.9, 25.6, 29.9, 32.5, 44.9, 51.5, 53.4, 62.7, 65.1, 127.3, 128.0, 128.3, 141.0, 170.8, 173.2. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.45; H, 7.95; N, 4.11.

For (2*R*)-**8b**. $[\alpha]_D^{20}$ +18 (*c* 0.5, $CHCl_3$). IR (neat) ν_{max} 1740 cm^{-1}. ^1H NMR δ 1.37–1.72 (m, 6H), 1.98 (s, 3H), 2.37–2.52 (m, 2H), 2.62–2.77 (m, 2H), 3.10–3.15 (m, 1H), 3.63 (s, 3H), 4.05 (t, 1H, $J=6.25$ Hz), 4.34 (m, AB part of ABX spectrum, 2H, $J_{AB}=11.5$ Hz), 7.23–7.35 (m, 5H). ^{13}C NMR δ 20.8, 21.0, 25.0, 29.6, 34.2, 44.8, 51.5, 53.3, 62.6, 66.0, 127.5, 128.3 (2C), 139.0, 170.8, 173.1.

4.2.3. (2*S*, 5*S*)-[1-(Hydroxy-1-(*S*)-phenyl-ethyl)-5-methyl-pyrrolidin-2-yl]-acetic acid methyl ester (12a). The general procedure was followed for the reduction of compound **2** (312 mg, 1.14 mmol). Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 8:2) afforded **12a** (266 mg, 84%) as an oil: $[\alpha]_D^{25}$ +23 (*c* 0.98, $CHCl_3$). IR (neat) ν_{max} 3400, 1730 cm^{-1}. ^1H NMR 1.2 (d, 3H, $J=6$ Hz), 1.31–1.48 (m, 3H), 1.70–1.77 (m, 1H), 2.41 (m, AB part of ABX spectrum, 2H, $J_{AB}=14.25$ Hz), 3.07–3.15 (m, 1H), 3.27 (br s, 1H), 3.47–3.54 (m, 1H), 3.66 (s, 3H), 3.59–3.73 (m, 1H), 3.83–3.96 (m, 2H), 7.21–7.38 (m, 5H). ^{13}C NMR δ 21.0, 30.3, 32.0, 43.1, 51.4, 54.3, 58.3, 61.6, 63.4, 127.7, 128.2, 128.7, 136.7, 172.5. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.27; H, 8.23; N, 5.07.

4.2.4. (6*S*)-[1-(2-Hydroxy-1-(*S*)-phenyl-ethyl)-6-methyl-piperidin-2-yl]-acetic acid methyl ester (17). The general procedure was followed for the reduction of compound **4** (161 mg, 0.5 mmol). Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 8:2) afforded **17** (146 mg, 89%) as an inseparable oily 8:2 mixture of isomers. IR (neat) ν_{max} 3440, 1735 cm^{-1}. For major (2*S*,6*S*)-**17a**. ^1H NMR δ 1.02 (d, 3H, $J=6.75$ Hz), 1.28–1.61 (m, 6H), 1.93 (br s, 1H), 2.56 (m, AB part of ABX spectrum, 2H, $J_{AB}=14.5$ Hz), 2.93–3.07 (m, 1H), 3.55–3.68 (m, 1H), 3.70 (s, 3H), 3.69–3.74 (m, 1H), 3.85–3.92 (m, 2H), 7.28–7.35 (m, 5H). ^{13}C NMR δ 14.7, 19.0, 27.7, 30.4, 38.6, 49.8, 49.9, 51.6, 62.5, 66.3, 127.5, 128.4, 129.0, 140.1, 173.4. For minor (2*R*,6*S*)-**17d**. ^1H NMR (only the more significant signals are reported) δ 1.29 (d, 3H, $J=$ 7 Hz), 3.73 (s, 3H). ^{13}C NMR δ 20.3, 20.9, 26.1, 30.6, 37.7, 49.3, 49.6, 51.7, 59.1, 60.7, 127.9, 128.3, 129.1, 140.9, 173.1. HRMS (CI) calcd *m/z* for $C_{17}H_{26}NO_3$ (MH^+): 292.1913. Found: 292.1907.

4.3. General procedure for $Pd(OH)_2$ catalyzed hydrogenation and in situ carbamatation by Boc_2O

A solution of the substrate (1 mmol) in methyl acetate (40 mL) was subjected to hydrogenation (1 atm) in the presence of $Pd(OH)_2/C$ (0.5 equiv in weight) and Boc_2O (2.1 equiv), at room temperature. The progress of the reaction was monitored by GC. The reaction mixture was filtered, the residue thoroughly washed with MeOH and the combined filtrates were concentrated in vacuo.

4.3.1. 2-Methoxycarbonylmethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (9). The general procedure was followed for the reduction of compound **1** (42 mg, 0.16 mmol). Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 8:2) afforded **9**[6] (28 mg, 71%) as an oily mixture of enantiomers.

4.3.2. 2-Methoxycarbonylmethyl-piperidin-1-carboxylic acid *tert*-butyl ester (10). The general procedure was followed for the reduction of compound **3** (94 mg, 0.34 mmol). Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 8:2) afforded **10**[3c] (62 mg, 70%) as an oily mixture of enantiomers.

4.3.3. 2-Methoxycarbonylmethyl-5-methyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (13). *From crude* **12**. The general procedure was followed for the reduction of compound **12** (51 mg, 0.18 mmol). Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 85:15) afforded an inseparable 95:5 mixture **13a** and **13c** (44 mg, 94%) as an oil. For (2*S*,5*S*)-**13a** (from the mixture). IR (neat) ν_{max} 1725, 1690 cm^{-1}. ^1H NMR δ 1.18 (d, 3H, $J=6$ Hz), 1.44 (s, 9H), 1.51–1.55 (m, 1H), 1.67–1.74 (m, 1H), 1.92–2.05 (m, 2H), 2.30 (dd, 1H, $J=9.5$, 15 Hz), 2.75–3.05 (m, 1H), 3.65 (s, 3H), 3.75–3.90 (m, 1H), 4.05–4.15 (m, 1H). ^{13}C NMR δ 21.8, 28.5, 29.7, 31.5, 40.3, 51.5, 54.1, 55.4, 79.3, 154.5, 172.0. HRMS (CI) calcd *m/z* for $C_{13}H_{24}NO_4$ (MH^+): 256.1705. Found: 256.1706.

From compound **2**. The general procedure was followed for the reduction of compound **2** (111 mg, 0.4 mmol). Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 85:15) afforded **13a**, *ent*-**13a** and **13c** (69 mg, 66%) as an inseparable oily mixture of isomers.

From compound **16**. The general procedure was followed for the reduction of compound **16** (233 mg, 1.5 mmol) using PtO_2 (50 mg) in the place of $Pd(OH)_2$. The crude product was chromatographed on silica gel (cyclohexane/AcOEt 85:15) to give an inseparable 85:15 mixture of *ent*-**13a** and **13c** (231 mg, 60%).

4.3.4. 2-Methoxycarbonylmethyl-6-methyl-piperidin-1-carboxylic acid methyl ester (19a). A solution of **4** (107 mg, 0.37 mmol) dissolved in MeOH (10 mL) was subjected to hydrogenation (1 atm) in the presence of $Pd(OH)_2$/C (53 mg) at room temperature for 12 h. The reaction mixture was filtered and the residue washed with MeOH. Concentration in vacuo afforded a crude oil, which was dissolved in CH_2Cl_2 (8 mL). To the ice-cooled solution was added a 0.4 M aqueous solution of Na_2CO_3 (1.85 mL). Methylchloroformate (53 mg, 0.56 mmol) dissolved in CH_2Cl_2 (1 mL) was added dropwise, and the reaction mixture was stirred at room temperature overnight. CH_2Cl_2 was added (15 mL) and the organic layer was successively washed with water (3×10 mL) and brine (10 mL) The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 7:3) afforded compound **19a**[3b] (75 mg, 88%) as an oil: $[\alpha]_D^{20}$ +44 (*c* 0.85, $CHCl_3$) (lit.[3b] $[\alpha]_D^{20}$ +41 (*c* 1.16, $CHCl_3$)).

4.4. General procedure for PtO_2 catalyzed hydrogenation

A solution of the substrate (1 mmol) dissolved in MeOH (30 mL) was subjected to hydrogenation (1 atm) in the presence of PtO_2 (0.25 equiv in weight) at room temperature for 24 h. The reaction mixture was filtered, the residue thoroughly washed with MeOH and the organic layer was concentrated in vacuo.

4.4.1. (3-Phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-5-yl)-acetic acid methyl ester (11). The general procedure was followed for the reduction of compound **3** (158 mg, 0.58 mmol) to give a 85:15 mixture of isomers **11a**, **11c** and **11b**, **11d**. Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 8:2) allowed the isolation of (5*S*)-**11a**,**11c** (107 mg, 67%) as an oily 65:35 mixture of epimers at C-8a and (5*R*)-**11b**,**11d** (23 mg, 14%) as 82:18 mixture of epimers at C-8a. IR (neat) ν_{max} 1735 cm^{-1}.

For major isomer of **11a**, **11c**. ^1H NMR δ 1.26–1.48 (m, 2H), 1.51, 1.67 (m, 2H), 1.78–1.88 (m, 2H), 2.0–2.10 (m, 1H), 2.19–2.28 (m, 1H), 2.84–2.92 (m, 1H), 3.49 (s, 3H), 3.57–3.63 (m, 1H), 3.75–3.84 (m, 2H), 4.13–4.19 (m, 1H), 7.22–7.40 (m, 5H). ^{13}C NMR δ 22.2, 30.0, 32.4, 40.5, 51.4, 57.9, 65.4, 74.6, 95.6, 126.6, 127.3, 128.6, 143.5, 172.4. For minor isomer of **11a**, **11c**. ^1H NMR δ 1.26–1.66 (m, 3H), 1.77–1.85 (m, 2H), 2.0–2.1 (m, 1H), 2.48 (m, AB part of ABX spectrum, 2H, $J_{AB}=15.25$ Hz), 2.98–3.06 (m, 1H), 3.62 (s, 3H), 3.67–3.71 (m, 1H), 4.34–4.44 (m, 2H), 4.49 (t, 1H, $J=3$ Hz), 7.22–7.40 (m, 5H). ^{13}C NMR δ 17.9, 26.9, 30.6, 41.4, 51.4, 55.1, 66.1, 70.0, 89.1, 127.0, 127.5, 128.6, 142.5, 172.5. HRMS (CI) calcd *m/z* for $C_{16}H_{22}NO_3$ (MH^+): 276.1600. Found: 276.1598.

For major isomer of **11b**, **11d**. ^1H NMR δ 1.47–1.78 (m, 5H), 2.0–2.1 (m, 1H), 2.47 (m, AB part of ABX spectrum, 2H, $J_{AB}=14.25$ Hz), 3.44–3.50 (m, 1H), 3.57 (s, 3H), 3.60–3.66 (m, 1H), 3.88–4.00 (m, 1H), 4.10–4.22 (m, 2H), 7.22–7.38 (m, 5H). ^{13}C NMR δ 17.9, 28.8, 29.1, 31.5, 49.7, 51.7, 61.6, 73.4, 87.5, 127.8, 127.9, 128.7, 138.9, 173.1. For minor isomer of **11b**, **11d** (only the more significant signals are reported). ^1H NMR δ 2.70 (m, 1H), 4.38–4.59 (m, 4H).

4.4.2. (5*S*, 8a*R*)-(8a-Methyl-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-5-yl)-acetic acid methyl ester (20a). The general procedure was followed for the reduction of compound **4** (215 mg, 0.75 mmol). Purification of the crude product by silica gel column chromatography (cyclohexane/AcOEt 8:2) afforded **20a** (188 mg, 87%) as an oil: $[\alpha]_D^{20}$ +99 (*c* 1.225, $CHCl_3$). IR (neat) ν_{max} 1730 cm^{-1}. ^1H NMR δ 1.39 (s, 3H), 1.55–1.86 (m, 6H), 2.42 (m, AB part of ABX spectrum, 2H, $J_{AB}=15$ Hz), 3.20–3.30 (m, 1H), 3.52 (s, 3H), 3.66–3.73 (m, 1H), 4.20–4.30 (m, 2H), 7.25–7.38 (m, 5H). ^{13}C NMR δ 17.7, 25.6, 27.9, 32.8, 41.1, 51.4, 53.6, 67.5, 71.1, 94.2, 127.2, 127.4, 128.4, 142.4, 172.4. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.33; H, 7.89; N, 4.79.

4.4.3. (5*R*)-2,2-Dimethyl-5-pyrrolidin-2-ylidene-[1,3]dioxane-4,6-dione (15). To a solution of lactim ether **14** (2.26 g, 20 mmol) in $CHCl_3$ (30 mL) was added Meldrum's acid (2.88 g, 20 mmol) and $Ni(acac)_2$ (10 mg). The reaction mixture was stirred at reflux temperature overnight. The solvent was removed in vacuo and the crude product crystallized in EtOH to afford the expected compound **15**[22] (3.97 g, 88%), as a solid. Mp=150 °C: $[\alpha]_D^{28}$ +26 (*c* 1.08, $CHCl_3$). IR (neat) ν_{max} 3270, 1690, 1640, 1590 cm^{-1}. ^1H NMR δ 1.35 (d, 3H, $J=6.5$ Hz), 1.69 (s, 3H), 1.71 (s, 3H),

2.27–2.41 (m, 1H), 3.20–3.34 (m, 1H), 3.47–3.60 (m, 1H), 4.06–4.20 (m, 1H), 10 (br s, 1H). ^{13}C NMR δ 21.2, 26.6, 26.7, 29.1, 34.8, 56.8, 81.3, 103.1, 163.1, 166.4, 175.9.

4.4.4. (5*R*)-Pyrrolidin-2-ylidene-acetic acid methyl ester (16). A solution of compound **15** (2 g, 8.8 mmol) and sodium methylate (8.8 mmol) in MeOH (50 mL) was refluxed for 12 h. The cooled reaction mixture was concentrated in vacuo and the residue dissolved in water (40 mL). The solution was neutralized to pH=6 by addition of a chilled 1 N HCl aqueous solution. The aqueous layer was extracted with $CHCl_3$ (3×50 mL), the combined organic layer was dried over Na_2SO_4. Concentration in vacuo gave **16** (1.23 g, 93%), which was pure enough to be used in the next step without further purification. Chromatography on silica gel (cyclohexane/AcOEt 80:20) afforded an analytical sample of **16** as an oil: $[\alpha]_D^{29}$ −11 (*c* 1.315, $CHCl_3$). IR (neat) ν_{max} 3350, 1655, 1600 cm^{-1}. ^{1}H NMR δ 1.23 (d, 3H, *J*=6.25 Hz), 1.44–1.58 (m, 1H), 2.06–2.18 (m, 1H), 2.56–2.67 (m, 2H), 3.64 (s, 3H), 3.89 (sext, 1H, *J*=6.5 Hz), 4.48 (s, 1H), 7.9 (br s, 1H). ^{13}C NMR δ 21.2, 29.9, 31.8, 49.5, 54.7, 75.6, 165.5, 170.6. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.60; H, 8.51; N, 9.10.

4.4.5. 7-Hydroxy-dodec-2-ynoic acid methyl ester (22). To a solution of compound **21**[19] (1.75 g, 11.35 mmol) in anhydrous Et_2O (50 mL), cooled at −78 °C, was added dropwise a 2 M solution of *n*-PentMgBr in Et_2O (6.8 mL, 13.6 mmol). The reaction mixture was allowed to warm to −5 °C over 3.5 h and then quenched with aqueous saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (3×40 mL). The organic layers were combined and then washed with brine (30 mL) and dried over Na_2SO_4. Concentration in vacuo gave a crude product, which was purified by silica gel column chromatography (cyclohexane/AcOEt 8:2) to give compound **22** (1.33 g, 52%), as a colorless oil. IR (neat) ν_{max} 1730, 2260, 3430 cm^{-1}. ^{1}H NMR δ 0.90 (t, 3H, *J*=6.5 Hz), 1.31–1.65 (m, 13H), 2.39 (t, 2H, *J*=7 Hz), 3.55–3.70 (m, 1H), 3.77 (s, 3H). ^{13}C NMR δ 14.0, 18.6, 22.6, 23.7, 25.3, 31.3, 36.3, 37.5, 52.6, 71.2, 73.0, 89.6, 154.2. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.81; H, 9.88.

4.4.6. 7-Oxo-dodec-2-ynoic acid methyl ester (23). To a solution of alcohol **22** (1 g, 4.42 mmol) in CH_2Cl_2 (20 mL) was added a Dess–Martin periodinane solution in CH_2Cl_2 (15% in weight, 17 g, 6 mmol). The reaction mixture was stirred at room temperature for 3 h. To the reaction mixture were successively added Et_2O (30 mL), an aqueous saturated $NaHCO_3$ solution (45 mL) and sodium thiosulfate (3 g). The aqueous layer was extracted with Et_2O (3× 30 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (30 mL) and then brine (30 mL) before drying over Na_2SO_4 and concentrating in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 90:10) gave pure **23** (0.7 g, 71%) as a colorless oil. IR (neat) ν_{max} 1720, 1735, 2270 cm^{-1}. ^{1}H NMR δ 0.89 (t, 3H, *J*= 7 Hz), 1.24–1.36 (m, 4H), 1.58 (quint, 2H, *J*=7 Hz), 1.85 (quint, 2H, *J*=7 Hz), 2.37–2.44 (m, 4H), 2.56 (t, 2H, *J*= 7 Hz), 3.74 (s, 3H). ^{13}C NMR δ 13.6, 17.6, 21.1, 22.2, 23.3, 31.1, 40.5, 42.6, 52.2, 73.2, 88.4, 153.7, 209.7. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.93; H, 9.22.

4.4.7. (8a*R*)-(8a-Pentyl-3-phenyl-hexahydro-oxazolo-[3,2-*a*]pyridine-5-ylidene]-acetic acid methyl ester (24). A solution of ketone **23** (400 mg, 1.78 mmol) and (*S*)-phenylglycinol (294 mg, 2.94 mmol) in benzene (20 mL) in the presence of 4 Å molecular sieves (5 g), was refluxed for 24 h. The reaction mixture was cooled to room temperature, filtered and the solvent removed in vacuo. Silica gel column chromatography of the residue (cyclohexane/AcOEt 85:15) afforded pure **24** (390 mg, 64%) as a colorless oil: $[\alpha]_D^{20}$ +161 (*c* 0.375, $CHCl_3$). IR (neat) ν_{max} 1720 cm^{-1}. ^{1}H NMR δ 0.87 (t, 3H, *J*=6.5 Hz), 1.24–1.86 (m, 11H), 2.27–2.34 (m, 1H), 2.68–2.77 (m, 1H), 3.49 (s, 3H), 3.65–3.78 (m, 2H), 4.33 (s, 1H), 4.46 (t, 1H, *J*=8.5 Hz), 4.75 (t, 1H, *J*=8.5 Hz), 7.15–7.39 (m, 5H). ^{13}C NMR δ 13.9, 16.1, 22.6, 24.0, 24.4, 31.1, 31.9, 35.1, 49.9, 62.5, 70.2, 86.0, 96.1, 125.4, 127.5, 128.9, 138.8, 159.4, 169.0. HRMS (CI) calcd *m/z* for $C_{21}H_{30}NO_3$ (MH^+): 344.2226. Found: 344.2225.

4.4.8. (2*S*, 6*S*)-(6-Pentyl-piperidin-2-yl)-acetic acid methyl ester (25). A solution of compound **25** (0.47 g, 1.37 mmol) dissolved in MeOH (25 mL) was subjected to hydrogenation (1 atm) in the presence of $Pd(OH)_2$ (94 mg), at room temperature for 6 h. The reaction mixture was filtered over a Celite® pad, the residue thoroughly washed with MeOH and the solvent removed in vacuo. The residue was dissolved in 1 N NaOH aqueous solution (10 mL) then extracted with CH_2Cl_2. The organic layer was washed with brine and water, dried over Na_2SO_4 and concentrated in vacuo. Silica gel column chromatography of the residue (eluted with AcOEt/MeOH 9:1) afforded pure piperidine **25**[20] (203 mg, 66%): $[\alpha]_D^{20}$ +16 (*c* 0.64, $CHCl_3$).

4.4.9. (2*S*, 6*S*)-2-Methoxycarbonylmethyl-6-pentyl-piperidine-1-carboxylic acid methyl ester (26). To an ice-cooled solution of **25** (57 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added a 0.4 M aqueous solution of Na_2CO_3 (1.25 mL). Methylchloroformate (0.1 mL, 1.3 mmol) was added dropwise, and the reaction mixture was stirred at room temperature overnight. CH_2Cl_2 was added (15 mL) and the organic layer was successively washed with water (3×10 mL) and brine (10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Silica gel column chromatography (cyclohexane/AcOEt 85:15) afforded compound **26**[18,20] (60 mg, 85%) as an oil: $[\alpha]_D^{20}$ +24 (*c* 0.985, $CHCl_3$).

References and notes

1. (a) Daly, J. W.; Garraffo, H. M.; Spande, I. F. Alkaloids from amphibian skins; In *Alkaloids: Chemical and Biochemical Perspectives*; Pelletier, S. W., Ed. Pergamon: Oxford, 1999; Vol. 13, 1, pp 2–161. (b) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633–640. (c) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699–6703. (d) Momose, T.; Toshima, M.; Seki, S.; Koike, Y.; Toyooka, N.; Hirai, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1315–1321. (e) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919–1928.
2. David, O.; Calvet, S.; Chau, F.; Vanucci-Bacqué, C.; Fargeau-

Bellassoued, M.-C.; Lhommet, G. *J. Org. Chem.* **2004**, *69*, 2888–2891.
3. (a) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779–1781. (b) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399–5400. (c) Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2903–2907. (d) Ledoux, S.; Marchalant, E.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **2001**, *42*, 5397–5399. (e) Bardou, A.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1998**, *39*, 5189–5192.
4. Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557–5563.
5. Calvet, S.; David, O.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Tetrahedron* **2003**, *59*, 6333–6339.
6. Harrison, J. R.; O'Brien, P.; Porter, D. W.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623–3631.
7. The use of Pt/C and Pd/C as catalysts equally met with failure.
8. Wong, Y.-S.; Marazano, C.; Gnecco, D.; Génisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729–733.
9. (a) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S.; Takahashi, H. *Tetrahedron* **1998**, *54*, 13955–13970. (b) Berrien, J.-F.; Billion, M.-A.; Husson, H.-P.; Royer, J. *J. Org. Chem.* **1995**, *60*, 2922–2924.
10. Provot, O.; Célérier, J.-P.; Petit, H.; Lhommet, G. *J. Org. Chem.* **1992**, *57*, 2163–2166.
11. Célérier, J.-P.; Deloisy-Marchalant, E.; Lhommet, G.; Maitte, P. *Org. Synth.* **1988**, *67*, 170–175.
12. Vo Thanh, G.; Célérier, J.-P.; Fleurant, A.; Grandjean, C.; Rosset, S.; Lhommet, G. *Heterocycles* **1996**, *43*, 1381–1384.
13. The reaction in the presence of $Pd(OH)_2$ was performed under 1 atm of hydrogen contrary to Ref. 3b. It is of note that the use of Pd/C and Pt/C as catalysts gave rise to the same results with an excellent diastereoselectivity in the favor of the (2*S*, 6*S*) single isomer **18a**.
14. The same result in favor of the *cis* 2,6-disubstituted isomer was previously observed during the reductive cleavage of the oxazolidine ring of bicyclic angularly substituted piperidine with $NaBH_4$, in THF containing TFA.[15]
15. Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475–4477.
16. Palmieri, G. *Eur. J. Org. Chem.* **1999**, 805–811.
17. Fréville, S.; Bonin, M.; Célérier, J.-P.; Husson, H.-P.; Lhommet, G.; Quirion, J.-C.; Thuy, V. M. *Tetrahedron* **1997**, *53*, 8447–8456.
18. Braekman, J.-C.; Charlier, A.; Daloze, D.; Heilporn, S.; Pasteels, J.; Plasman, V.; Wang, S. *Eur. J. Org. Chem.* **1999**, 1749–1755.
19. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491–12509.
20. Laurent, P.; Braekman, J.-C.; Daloze, D. *Eur. J. Org. Chem.* **2000**, 2057–2062.
21. Rougnon-Glasson, S.; Tratrat, C.; Canet, J.-L.; Chalard, P.; Troin, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1561–1567.
22. Bacos, D.; Célérier, J.-P.; Marx, E.; Rosset, S.; Lhommet, G. *J. Heterocycl. Chem.* **1990**, *27*, 1387–1391.