Dynamic Kinetic Resolution and Desymmetrization Processes: A Straightforward Methodology for the Enantioselective Synthesis of Piperidines

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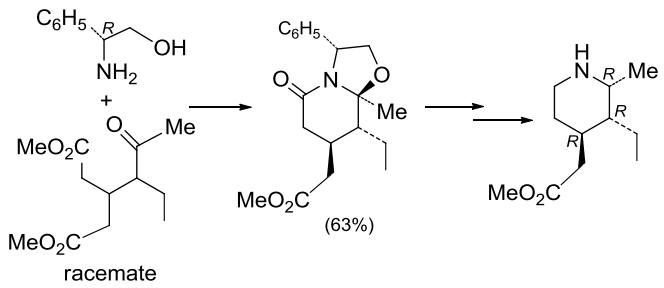
Abstract: A straightforward procedure for the synthesis of enantiopure polysubstituted piperidines is reported. It consists of the direct generation of chiral non-racemic oxazolo[3,2-*a*]piperidone lactams that already incorporate carbon substituents on the heterocyclic ring, and the subsequent removal of the chiral auxiliary. The key step is a cyclocondensation reaction of (*R*)-phenylglycinol, or other aminoalcohols, with racemic or prochiral δ-oxo(di)acid derivatives, in highly stereoselective processes involving dynamic kinetic resolution and / or desymmetrization of diastereotopic or enantiotopic ester groups.

Abstract in Spanish: Se describe un procedimiento directo para la síntesis enantioselectiva de piperidinas polisustituidas. Consiste en la generación directa de oxazolo[3,2-*a*]piperidonas quirales no racémicas que ya incorporan sustituyentes carbonados en las diferentes posiciones del heterociclo, y en la posterior eliminación del auxiliar quiral. La etapa clave es una reacción de ciclocondensación entre el (*R*)-fenilglicinol, u otros aminoalcoholes quirales, con derivados de δ-oxoácidos racémicos o proquirales, en procesos altamente estereoselectivos que implican una resolución cinética dinámica y/o la desimetrización de grupos diastereotópicos o enantiotópicos.

Graphical Abstract



Introduction

The development of new and efficient methodologies for the generation or two or more stereogenic centers with high diastereo- and enantioselectivity in a single synthetic step is one of the most challenging subjects in organic synthesis, particularly in the field of bioactive natural or synthetic products. The preparation of a single enantiomer from a racemate may be achieved via a conventional resolution or by exploiting the differences in reactivity (kinetic resolution). Although enzyme-catalyzed kinetic resolution of racemates has become a classical approach for the synthesis of enantiopure compounds,[1] it suffers, like conventional resolution processes, from the drawback that the maximum yield of one enantiomer is always limited to 50%. This situation dramatically changes when the racemic substrate or the two diastereomers resulting from the initial reaction with a chiral reagent have a chirally labile stereogenic center capable of undergoing in situ racemization[2] or epimerization during the reaction to form a chirally stable

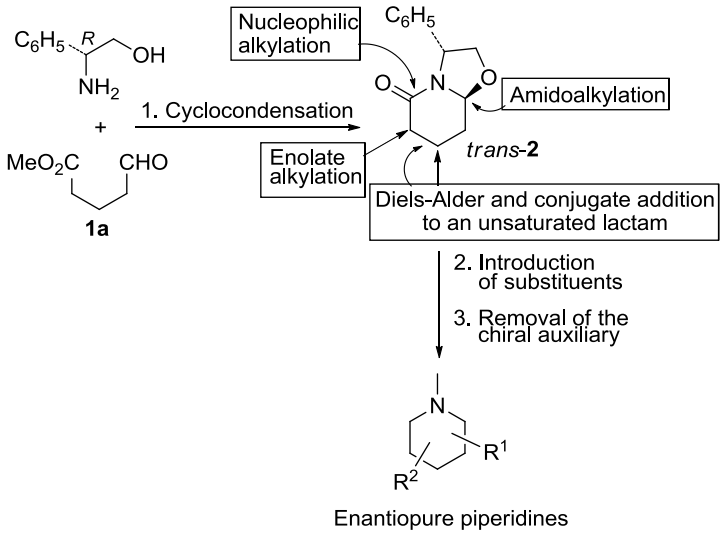
enantiopure product in up to 100% chemical yield (dynamic kinetic resolution).[3] Although these processes represent a viable and useful tool for preparing enantiopure chiral compounds, they have been scarcely used in synthetic sequences due to the structural restrictions imposed by the substrate. When the reaction involves the generation of additional stereogenic centers, this methodology can convert a racemic compound into one of several possible enantiopure stereoisomers.

On the other hand, although enzyme-mediated desymmetrizations of prochiral or meso substrates, generally diesters, also constitute classical approaches for the synthesis of enantiopure compounds and have become powerful synthetic tools,[4] the chemical, non-enzymatic, differentiation of two enantiotopic functional groups is still little developed in spite of the impressive advances in this field over the last years.

Since the piperidine ring is the central structure of many biologically active alkaloid natural products[5] and therapeutic agents, much effort has been devoted to the development of general methods and strategies for the enantioselective synthesis of piperidine derivatives.[6] In this context, cyclocondensation reactions of δ-oxoacid derivatives with chiral nonracemic aminoalcohols have received considerable attention,[7] since the resulting oxazolopiperidone lactams have proven to be versatile

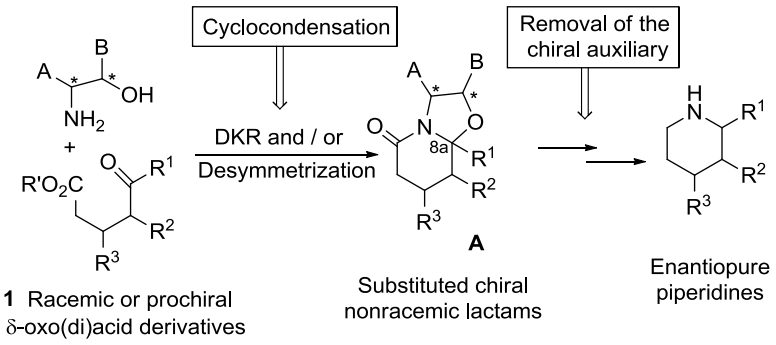
building blocks for the enantioselective synthesis of piperidine-containing derivatives.[8] In particular, in previous work we have demonstrated that simple phenylglycinol-derived bicyclic lactams *trans*-**2**, *cis*-**2**, and their enantiomers allow the stereocontrolled formation of C-C bonds at the different positions of the nitrogen heterocycle.[7d,f-h,j] Our approach consists of three phases: (i) a cyclocondensation reaction of (*R*)- or (*S*)-phenylglycinol with methyl 5-oxopentanoate (**1a**) to generate the required bicyclic lactam, (ii) successive stereoselective introduction of the ring substituents taking advantage of the functionalization and conformational rigidity of the bicyclic lactam system, and (iii) reductive removal of the chiral auxiliary (Scheme 1). Although this approach gives excellent results from the stereoselective and diversity points of view, leading to enantiopure piperidines with a variety of substitution patterns, it has the inconvenience that the substituents have to be introduced step by step.

Scheme 1



In this paper we report a more straightforward procedure for the synthesis of enantiopure polysubstituted piperidines. It consists of the direct generation of chiral nonracemic oxazolopiperidone lactams **A** that already incorporate the carbon substituents on the heterocyclic ring, and the subsequent reductive removal of the chiral auxiliary (Scheme 2). The key step is a cyclocondensation reaction of (*R*)-phenylglycinol, or other aminoalcohols, with racemic or prochiral δ-oxo(di)acid derivatives, in processes involving dynamic kinetic resolution (DKR) and/or desymmetrization of enantiotopic or diastereotopic ester groups.

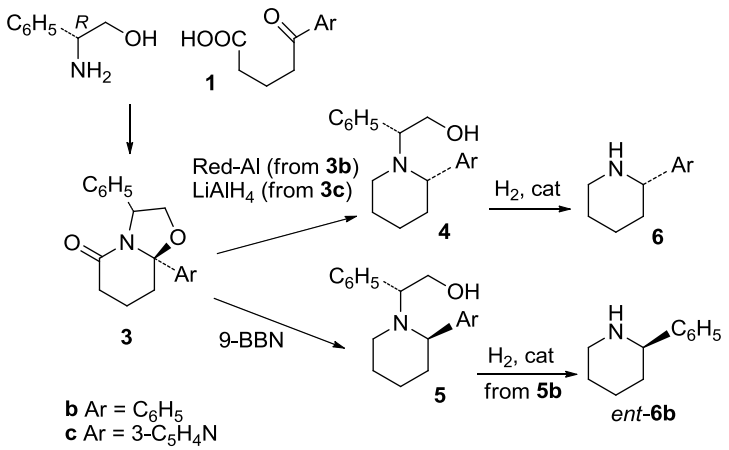
Scheme 2



Results and Discussion

Phenylglycinol-Derived Lactams. The efficiency of the approach depicted in Scheme 2 for the generation of 2-substituted piperidines from lactams bearing a substituent at the angular 8a-position relies on the stereocontrol in the reductive opening of the oxazolidine ring.[9] To study the stereoselectivity of this process from an 8a-aryl substituted lactam we prepared lactam **3b,** which was readily obtained in 90% yield as a single stereoisomer by cyclocondensation of (*R*)-phenylglycinol with 5-phenyl-5-oxopentanoic acid (**1b,** Scheme 3).

Scheme 3

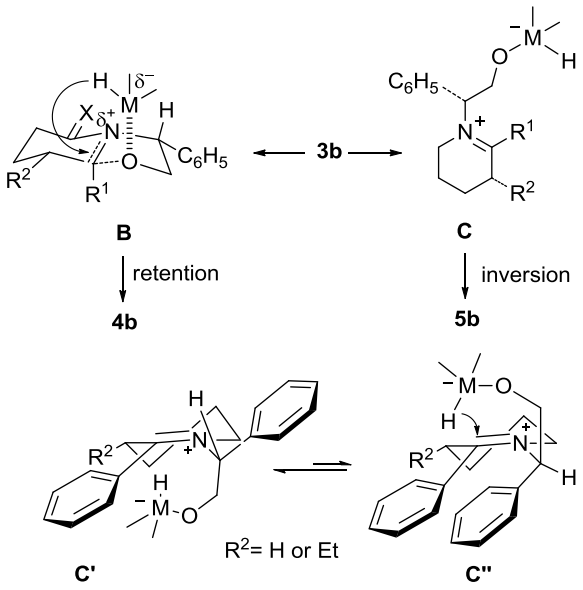


Interestingly, treatment of lactam **3b** with Red-Al gave 2-phenylpiperidine **4b** (54%) as the only stereoisomer detectable by spectroscopic methods. In contrast, 9-BBN reduction of **3b** stereoselectively provided 2-phenylpiperidine **5b** (75%), resulting from an inversion of the configuration at C-8a (**5b**:**4b** ratio 97:3). However, reduction of **3b** with AlH_3 or BH_3 showed poor stereoselectivity, affording mixtures of **4b** and **5b** in which the former was the major stereoisomer (~7:3 ratio). Removal of the chiral inductor of **4b** and **5b** by hydrogenolysis using Pd/C as the catalyst gave (*S*)-2-phenylpiperidine (**6b**) and (*R*)-2-phenylpiperidine (*ent*-**6b**), respectively. The above three-step sequence opens a short enantiodivergent route to 2-arylpiperidines from easily available achiral δ-oxoacids.

The remarkable difference in the stereoselectivity of the above reductions can be explained in terms of the reactive

intermediates **B** and **C** ($R^1 = C_6H_5$, $R^2 = H$) as depicted in Scheme 4. Thus, the stereoselectivity in the Red-Al reduction of **3b**, leading to 2-substituted piperidine **4b** with retention of configuration, also observed in the reduction of related 8a-alkyl substituted lactams,[8g,10] can be rationalized by considering that, after the reduction of the carbonyl lactam, the reductive cleavage of the oxazolidine ring takes place through complexation of the oxygen with the reductant, followed by delivery of the hydride from the same face of the C-O bond (**B**). The opposite stereochemical result observed in the reduction with 9-BBN suggests that, in this case, the reaction takes place via the ion paired intermediate **C**. The intramolecular delivery of the hydride under stereoelectronic control from the preferred conformation **C'** accounts for the stereoselective formation of isomer **5b**. Due to steric interactions, the 9-BBN reduction of intermediate **B** is slower than the formation of the iminium salt **C**. Moreover, the presence of the 8a-phenyl group ($R^1 = C_6H_5$) contributes to the stabilization of this intermediate **C**, making the C-O bond more prone to undergo cleavage than in related 8a-alkyl lactams.

Scheme 4



To further illustrate the potential of the cyclodehydration-stereocontrolled reduction sequence here developed, we undertook the synthesis of the tobacco alkaloid (–)-anabasine.[11] The required bicyclic lactam **3c** was obtained as a single stereoisomer by cyclocondensation of keto-acid **1c** with (*R*)-phenylglycinol in refluxing toluene. Although treatment of **3c** with Red-Al or BH_3 afforded complex mixtures resulting from partial reduction of the heteroaromatic ring, more satisfactorily, reduction with 9-BBN in refluxing THF provided (73%) a 37:63 mixture of isomers **4c** and **5c**, respectively. The lower stereoselectivity of this reduction as compared with the 9-BBN reduction of the related phenyl substituted lactam **3b** probably reflects the lesser ability of pyridine, a π-deficient heterocycle, to

stabilize the intermediate iminium ion **C** in comparison with a phenyl group. In this series, the best result regarding stereoselectivity was obtained when **3c** was treated with an excess of $LiAlH_4$. The desired piperidine **4c** was obtained in 78% yield along with only minor amounts (6%) of its epimer **5c**. Hydrogenolysis of pure isomer **4c** over Pearlman's catalyst afforded (–)-anabasine (**6c**).

We then examined the stereochemical outcome of cyclocondensations of (*R*)-phenylglycinol with racemic γ-alkyl δ-oxoacid derivatives, both aldehydes and ketones, which incorporate a chirally labile stereogenic center capable of undergoing in situ racemization or epimerization during reaction.[12] Cyclocondensation reactions from aldehyde esters **1d–1f**, bearing an alkyl substituent at the α-position of the aldehyde carbonyl group, took place in good chemical yield and stereoselectivity, leading to the enantiopure oxazolopiperidone 3-H/8a-H *cis* lactams **7d–7f**, respectively, as the major products[13] (Table 1), thus indicating that a dynamic kinetic resolution had occurred.[14] Minor amounts of the corresponding diastereoisomeric 3-H/8a-H *trans* lactams **8** were also formed (approximate **7**/**8** ratio, 4–5:1). Similar stereoselective cyclodehydrations occurred from α-alkyl substituted ketones **1g–i**, including both dialkyl (non-cyclic and cyclic) and alkyl aryl ketones, although in all these

cases the respective 3-H/8a-R^1 *trans* lactams **8g-i** were the major products (approximate **7**/**8** ratio, 1:4).[15]

Figure of Table 1

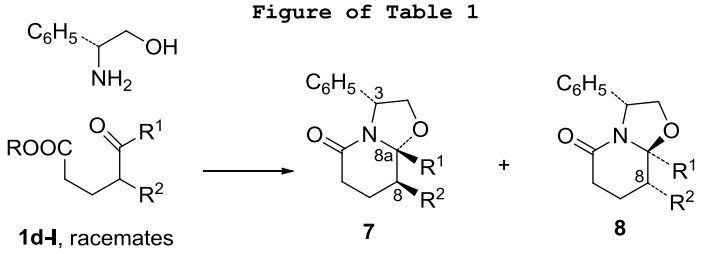
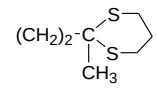


Table 1. Cyclocondensation reactions from racemic γ-substituted δ-oxoacid derivatives.

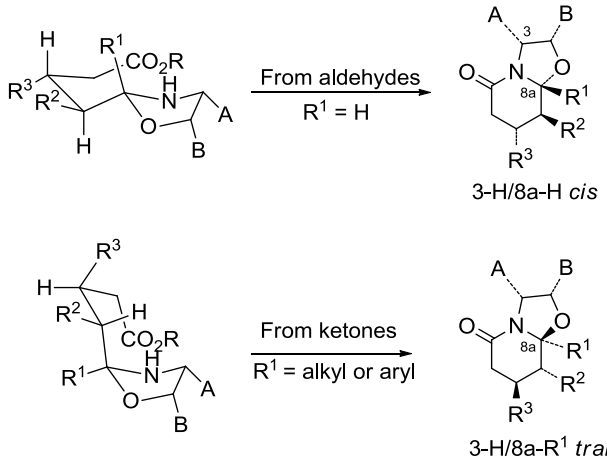
	R	R_1	R_2	yield (%)	**7**/**8** ratio
d	Me	H	Et	79	4:1
e	Me	H		71	6:1
f	Me	H	$CH_2CH{=}CH_2$	71	7:1
g	H	C_6H_5	Et	50	1[a]:4
h	H	Me	Et	60	1:4
i	H	$-(CH_2)_4-$		70	1:5[b]
j	Me	H	OTBDMS	50	[c]
k	Me	H	OAc	45	[d]
l	H	CH_2OBn	OMEM	74	[e]

[a] The minor stereoisomer was the C_{8a}-epimer of **7g**. [b] The relative stereochemistry of **8i** was confirmed by

X-ray crystallography. [c] Lactam **7j**, its C_8-epimer (3:2 ratio), and minor amounts of **8j** (undetermined stereochemistry at C_8). [d] Lactams **7k**, 8a-*epi*-**7k**, and 8a-*epi*-**8k** in a 5:2:2 ratio. [e] **8l** and its C_8-epimer in a 3:2 ratio, and minor amounts of **7l**.

These results can be accounted for by considering that the two diastereoisomeric imines initially formed in the reaction of (*R*)-phenylglycinol with racemic oxoesters **1d-i** are in equilibrium via an enamine and, consequently, that a mixture of four equilibrating oxazolidines is formed.[16,17] Subsequent irreversible lactamization takes place faster from the diastereoisomer that allows a less hindered approach of the ester group to the nitrogen atom, via a transition state in which the alkyl substituent in the incipient chair-like six-membered lactam is equatorial (Scheme 5; A = C_6H_5, B = R^3 = H, R^1 = H, alkyl or aryl, R^2 = alkyl).

Scheme 5



In contrast, cyclocondensation of δ-oxoacid derivatives (**1j-l**) bearing a protected hydroxyl group at the α-position of

the aldehyde or ketone carbonyl group took place with low stereoselectivity, thus indicating that the presence of an oxygenated substituent on the epimerizable stereocenter inhibits DKR.[18]

To study enantioselective desymmetrizations of prochiral δ-oxodiesters with (*R*)-phenylglycinol, we selected the glutaric and pimelic acid derivatives **1m,n** and **1r**, respectively. Interestingly, cyclocondensation of aldehyde diester **1m** and ketodiester **1n** with (*R*)-phenylglycinol stereoselectively afforded the respective lactams **9m** (3-H/8a-H *cis*) and **10n** (3-H/8a-R^1 *trans*), as the major products, together with minor amounts (approximate 4:1 ratio) of a second diastereoisomer, **10m** and **9n**, respectively (Table 2). Similarly, cyclocondensation of the prochiral aldehyde diester **1r** gave lactam **9r** (3-H/8a-H *cis*) in very high stereoselectivity (ratio **9r**/**10r**, 9:1). It is worth mentioning that again cyclocondensations involving aldehydes lead to lactams with a *cis* 3-H/8a-H relationship whereas in the case of ketones the preferential formation of the 3-H/8a-R^1 *trans* isomeric lactams is observed.

Figure of Table 2

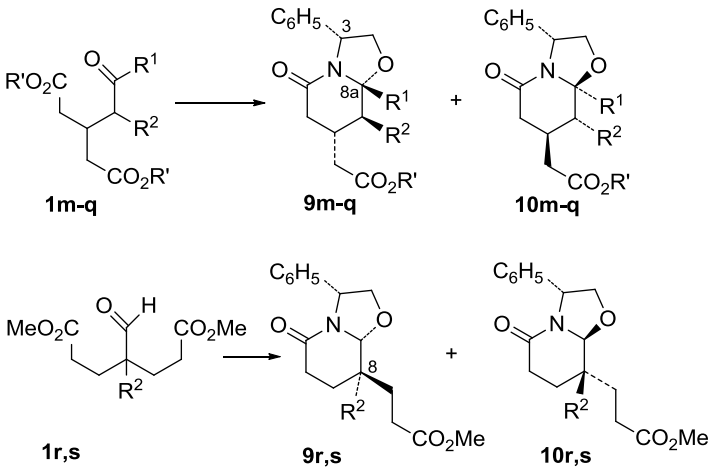


Table 2. Cyclocondensation reactions of (*R*)-phenylglycinol with prochiral or racemic δ-oxodiesters.

	R′	R_1	R_2	yield (%)	**9**/**10** ratio
m	Me	H	H	95	4:1
n	Et	Me	H	77[a]	1:4[b]
o	Et	H	Et	77	4:1
p	Et	Me	*n*-Pr	55[c]	1:9
q	Me	Me	Et	81[c]	1:5
r	-	-	H	67	9:1
s	-	-	Et	50	9:1[d]

[a]Using *p*-TsOH as a catalyst. [b]The relative stereochemistry of **10n** was confirmed by X-ray crystallography. [c]Using glacial AcOH as a

catalyst. [d]Isomers **9s** and **10s** were isolated accompanied by their respective C_8 epimers (**9s'** and **10s'**; 1:1 mixtures).

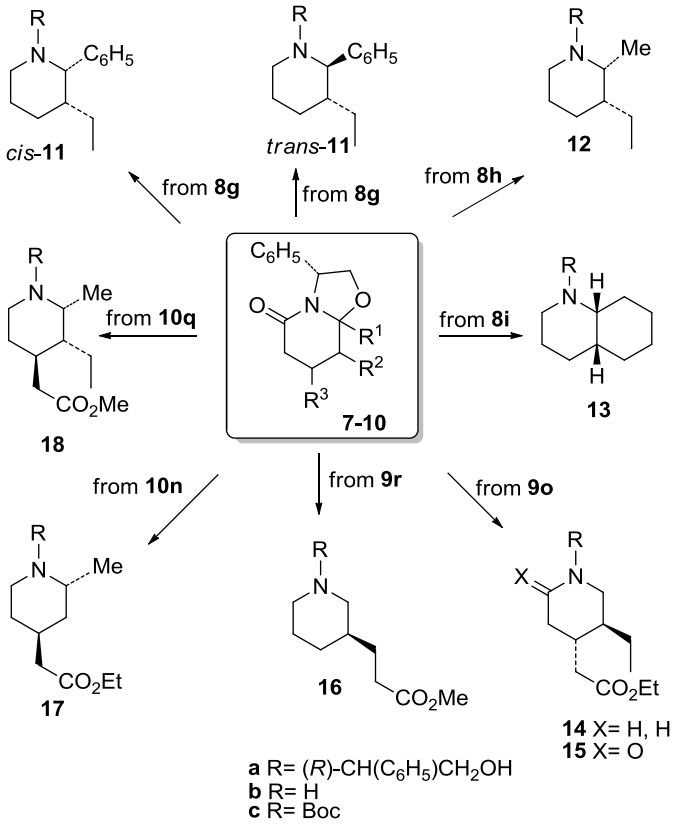
The above results can be rationalized by taking into account that, after the formation of the corresponding oxazolidines, lactamization occurs faster through a chairlike transition state in which the diastereotopic acetate (R^3 in Scheme 5) or propionate chain (R^2 in Scheme 5) that does not undergo cyclization is equatorial. In accordance with this interpretation, the presence of an ethyl substituent at the prochiral carbon atom in **1s** (R^2 = Et) suppresses the discrimination between the two propionate chains, and lactams **9s** and **10s** (9:1 ratio) were formed among with equimolecular amounts of their respective C-8 epimers **9s'** and **10s'**[19] In this case, either the ethyl substituent or one of the propionate chains is axially oriented.

As could be expected from the above results, treatment of racemic δ-oxodiesters **1o-q** with (*R*)-phenylglycinol under the usual conditions predominantly afforded one of the eight possible stereoisomeric lactams, **9o** (3-H/8a-H *cis* in the aldehyde series), **10p**, and **10q** (3-H/8a-R^1 *trans* in the ketone series), respectively. Three stereogenic centers with a well-defined absolute configuration have been generated in a single synthetic step. These reactions involve DKR, with epimerization of the configurationally labile stereocenter in

the substrate, and differentiation of the two diastereotopic acetate chains via a transition state in which the substituents R^2 and R^3 of the incipient chairlike six-membered lactam are equatorial (Scheme 5).

The substituted chiral lactams **7–10** are immediate precursors of a variety of diversely substituted enantiopure piperidine derivatives, including 4-piperidineacetates. Starting from the 8a-phenyl substituted bicyclic lactam **8g**, the best stereoselectivities in the reductive opening of the oxazolidine ring were obtained, as in the reduction of the deethyl analog **3b**, with Red-Al (retention of the configuration at C-8a) and 9-BBN (inversion), to give piperidines *cis*-**11a** (56%) and *trans*-**11a** (86%), respectively, as single stereoisomers detectable by spectroscopic methods (Scheme 6). Reduction of **8g** with AlH_3 and BH_3 showed the same level of stereoselectivity we had observed in the reduction of **3b**, thus revealing that the C-8 substituent has no influence on the stereoselectivity of the reduction (see Scheme 4; R^1 = C_6H_5, R^2 = Et). Removal of the benzylic *N*-substituent of the epimeric piperidines **11a** by hydrogenolysis over palladium afforded piperidines *cis*-**11b** (70%) and *trans*-**11b** (60%), respectively. In this way, starting from easily available racemic γ-substituted δ-oxoacids, the above three-step sequence provides a stereodivergent entry to enantiopure *cis*- and *trans*-3-alkyl-2-arylpiperidines.

Scheme 6



The phenyl substituent at the angular 8a-position has a dramatic influence on the stereoselectivity of the above reductions with 9-BBN because 9-BBN reduction of lactam **8h,** bearing a 8a-methyl substituent, led to a 9:1 mixture (55%) of *cis*-piperidine **12a** (retention of the configuration at C-8a) and its C-2 epimer. As expected, reduction of **8h** with Red-Al or AlH_3 afforded *cis*-piperidine **12a** as a single stereoisomer (60% and 84% yield, respectively), thus providing an efficient entry to enantiopure *cis*-2,3-dialkylpiperidines. Hydrogenolysis of **12a** over Pearlman's catalyst in the presence of $(Boc)_2O$ afforded *cis*-2-methyl-3-

ethylpiperidine **12c** (82%). Similarly, tricyclic lactam **8i** was stereoselectively reduced (70%) with AlH_3 and then debenzylated in good yields to the enantiopure *cis*-perhydroquinoline **13b**, either directly or via the *N*-Boc derivative **13c**.

The reductive opening of the oxazolidine ring from lactams bearing an ester function was chemoselectively accomplished with borane. Thus, lactams **9o** and **9r** were efficiently converted to *trans*-3-ethyl-4-piperidineacetate **14b** (70%) and 3-piperidinepropionate **16b** (91%), respectively, by treatment with BH_3-THF followed by debenzylation of the resulting piperidines **14a** and **16a**. Alternatively, hydrogenolysis of the C-N bond of **9o** with Ca in liquid NH_3, followed by treatment of the resulting oxylactams with Et_3SiH in TFA, afforded the 6-oxo derivative **15b** (48%), the enantiomer of a crucial intermediate in the synthesis of benzo[*a*]- and indolo[2,3-*a*]quinolizidine alkaloids.[20] Reductions using borane were also highly stereoselective (retention of configuration) for 8a-methyl substituted lactams **10n** and **10q**, leading to the respective piperidineacetate derivatives **17a** (55%; the C-2 epimer was isolated in 19% yield) and **18a** (66%), which were debenzylated to give **17b** (or **17c**) and **18b** in excellent yield. A similar two-step sequence from the minor lactam **9n** led to *ent*-**17b** and *ent*-**17c**.

The above results make evident that substituted phenylglycinol-derived lactams **7–10**, easily accessible by cyclocondensation reaction of (*R*)-phenylglycinol with racemic or prochiral δ-oxoacid derivatives, are useful chiral synthons that allow the straightforward preparation of a variety of diversely substituted enantiopure piperidines.

Other Aminoalcohol-Derived Lactams. With the aim of improving the diastereoselectivity of the above phenylglycinol-induced cyclocondensations, we undertook a study of the behavior of other aminoalcohols in similar cyclocondensation reactions involving DKR and/or differentiation of enantiotopic or diastereotopic ester groups. For this purpose we selected several 1,3- and 1,2-aminoalcohols[21] (**19-23**) and a variety of δ-oxoacid derivatives including unbranched aldehydes (**1a**) and ketones (**1t**), simple racemic aldehydes (**1d**) and ketones (**1h** and **1u**), prochiral aldehydo- (**1m** and **1r**) and ketone- (**1n**) diesters bearing enantiotopic ester groups, and racemic aldehydo- (**1v**) and ketone- (**1q**) diesters bearing diastereotopic ester groups. The results are summarized in Table 3.[22]

We initially explored the use of 1,3-aminoalcohols **19** and **20**.[23] Although aminoalcohol *rac*-**19**, the higher homolog of phenylglycinol, underwent cyclodehydration with aldehyde esters **1a** and **1d** to give the corresponding bicyclic lactams

rac-**24a,b** and *rac*-**25a,b**, no reaction was observed with ketones **1t** and **1u**. Taking into account furthermore that the stereoselectivity of the above reactions with aldehydes was low, no additional studies were performed with **19**.

Figure of Table 3

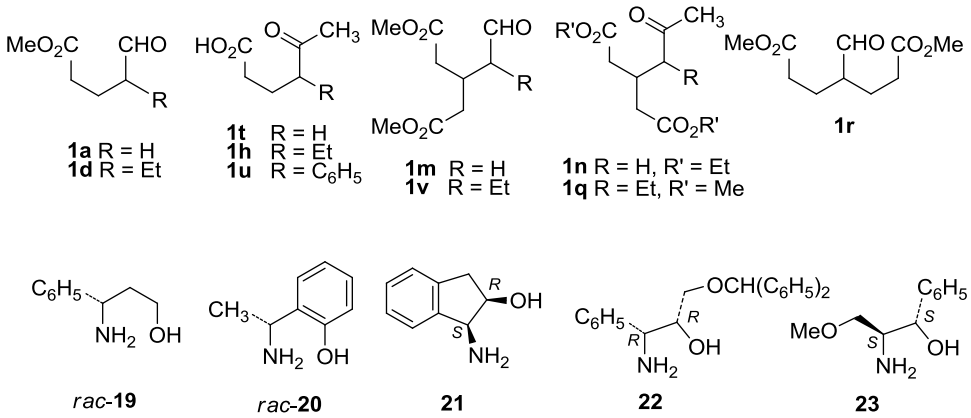
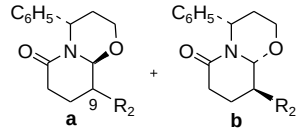
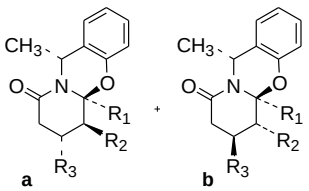
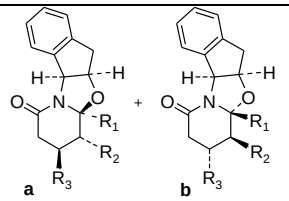
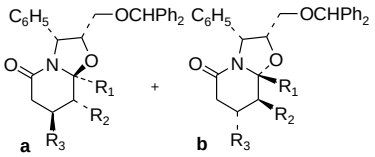
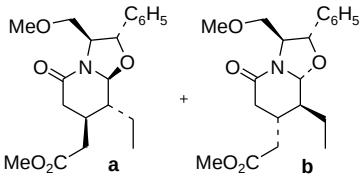


Table 3. Cyclocondensation reactions of aminoalcohols with racemic or prochiral δ-oxoacid derivatives.

starting materials	products		R_1	R_2	R_3	yield	**a:b** ratio
1a + *rac*-**19**		*rac*-**24**	—	H	—	68%[a]	7:3
1d + *rac*-**19**		*rac*-**25**	—	Et	—	70%[a]	4[b]:3
1a + *rac*-**20**		*rac*-**26**[c]	H	H	H	90%	—[d]
1d + *rac*-**20**		*rac*-**27**	H	Et	H	80%	1:1[d]
1t + *rac*-**20**		*rac*-**28**[c]	CH_3	H	H	80%	—[d]
1h + *rac*-**20**		*rac*-**29**	CH_3	Et	H	45%	9:1[d]
1u + *rac*-**20**[e]		*rac*-**30**	CH_3	C_6H_5	H	42%	9:1[d]
1n + *rac*-**20**[e]		*rac*-**31**	CH_3	H	CH_2CO_2Et	38%	3:2[d]
1a + **21**		**32**	H	H	H	70%	4:1
1d + **21**		**33**	H	Et	H	87%	7:5:3[f]
1m + **21**		**34**	H	H	CH_2CO_2Me	78%	4:1
1t + **21**		**35**	CH_3	H	H	99%	1:10
			CH_3	Et	H	74%	1:8[g]

1h + **21** **1u** + **21** **1n** + **21**[h] **1q** + **21**		**36** **37**[c] **38** **39**	CH_3 CH_3 CH_3	C_6H_5 H Et	H CH_2CO_2Et CH_2CO_2Me	86% 64% 68%	1:13[g] 5:9 2:3
1d + **22** **1m** + **22** **1r** + **22** **1v** + **22** **1h** + **22** **1q** + **22**[h]		**40** **41** **42** **43** **44** **45**	H H H H CH_3 CH_3	Et H $(CH_2)_2CO_2$ Et Et Et	H CH_2CO_2Me H CH_2CO_2Me H CH_2CO_2Me	78% 86% 80% 77% 81% 58%[j]	1:9 1:14 1:20 1:15[i] 3:2 5:2[k]
1v + **23**		**46**	—	—	—	70%	2:1[l]

[a]The initially formed *cis*-oxazine, which has not undergone lactamization, was isolated in ~10% yield. [b]1:1 mixture of C-9 epimers. [c]The relative stereochemistry of *rac*-**26**, *rac*-**28**, and **37b** was confirmed by X-ray crystallography. [d]Trace amounts of the epimer at the piperidine α-position were also detected. [e]In the presence of a catalytic amount of *p*-TsOH. [f]**a**:**b**:**c** ratio (**c** is the epimer of **b** at the piperidine α-position). [g]Trace amounts of the epimer at the piperidine β-position were also detected. [h]In the presence of a catalytic amount of glacial AcOH. [i]Minor amounts of the epimer at the piperidine γ-position were also isolated. [j] Based on consumed **1q**. [k] Minor amounts of a third diastereomer were formed. [l] Other stereoisomers (about 15%) were also formed.

In contrast, aminophenol *rac*-**20** reacted with both aldehydes (**1a** and **1d**) and ketones (**1h,1n,1t,1u**). Although no stereoselectivity was observed from racemic aldehyde **1d** or from prochiral ketone **1n**, reaction with racemic ketones **1h** and **1u** gave the respective tricyclic lactams *rac*-**29** and *rac*-**30** in good stereoselectivity (**a**/**b** diastereomeric ratios 9:1)

but only moderate chemical yield.[24] The isolation of considerable amounts of 2-vinylphenol can account for the low yield of the above reactions.

More successful results were obtained when using *cis*-1-amino-2-indanol **21**,[25] a conformationally rigid analog of phenylglycinol.[24] Thus, although no DKR was observed from racemic aldehyde **1d**, enantioselective desymmetrization of two enantiotopic ester groups was produced in the cyclocondensation of **21** with aldehyde **1m**, which took place in good chemical yield with a stereoselectivity similar to that previously observed when using phenylglycinol. Lactam **34a** was isolated in about 60% yield as the major product (**a**/**b** diastereomeric ratio 4:1). Similarly, cyclocondensation of **21** with racemic ketones (**1h** and **1u**) took place in excellent chemical yield and even better stereoselectivity than when using phenylglycinol. Enantiopure tetracyclic lactams **36b** and **37b** were isolated in 61% and 77% yield, respectively, after column chromatography, thus making evident that dynamic kinetic resolution, with epimerization of the stereocenter α to the ketone carbonyl, had occurred to a considerable extent. However, only moderate stereoselectivities were observed in cyclocondensations involving desymmetrization of acetate chains from ketodiesters **1n** and **1q**. The higher stereoselectivities observed from racemic ketones **1h** and **1u** as compared with racemic aldehyde **1d** in the above

cyclocondensations with aminoalcohols *rac*-**20** and **21** could be explained by considering that lactamization of the intermediate oxazine or oxazolidine, both of them bearing an additional fused ring, occurs more slowly in the case of the ketones due to steric effects. Consequently, the oxazolidine-enamine equilibrium induces DKR.

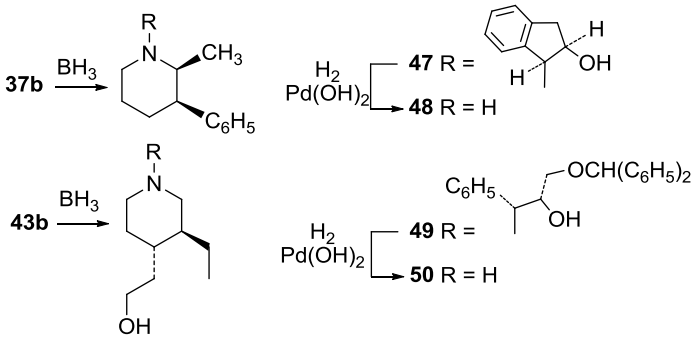
The best results in terms of chemical yield and stereoselectivity in cyclocondensation reactions with aldehydes were obtained when using aminoalcohol **22**.[26] Thus, **22** reacted with racemic aldehyde **1d** to give a 9:1 stereoisomeric mixture of lactams **40** in 78% yield, which clearly indicated that a DKR had again occurred. Similarly, prochiral aldehydo-diesters **1m** and **1r** underwent highly enantioselective desymmetrizations during cyclocondensation with **22** to give 14:1 and 20:1 stereoisomeric mixtures of the respective lactam esters **41** and **42** in excellent yield. The major isomers **b** were isolated in 80% and 76% yield, respectively. Finally, racemic oxodiester **1v** on reaction with aminoalcohol **22** stereoselectively provided enantiopure lactam **43b**, which was isolated in 66% yield, in a highly stereoselective process that involves a tandem DKR-desymmetrization of two diastereotopic acetate chains, with generation of three stereogenic centers in a single synthetic step. In contrast with the above satisfactory results,

similar cyclocondensations from racemic ketones **1h** and **1q** occurred with low stereoselectivity.

The higher stereoselectivities observed in cyclocondensations promoted by aminoalcohols **21** (from ketones) and **22** (from aldehydes) as compared with phenylglycinol can be rationalized taking into account that the substituents at the 4 and 5 ring positions in the intermediate oxazolidine (A and B in Scheme 5) are on the same face of the ring, thus making the opposite face more easily accessible. In agreement with this interpretation, and in sharp contrast with the above result from *erythro* aminoalcohol **22**, cyclocondensation of *threo* aminoalcohol **23**[27] with racemic diester **1v** took place with low stereoselectivity to give a 2:1 diastereomeric mixture of lactams **46a** and **46b**, among with other stereoisomers.

Finally, to fully illustrate the synthetic usefulness of aminoalcohols **21** and **22** as chiral auxiliaries in the above cyclocondensation reactions, lactams **37b** and **43b** were converted into the corresponding enantiopure piperidines **48** and **50** by a two-step sequence involving borane reduction, followed by removal of the auxiliary by catalytic hydrogenation from the resulting *N*-substituted piperidines **47** and **49**, respectively (Scheme 7).

Scheme 7



Conclusion

Cyclocondensation reactions of phenylglycinol with racemic or prochiral δ-oxo(di)acid derivatives in processes involving dynamic kinetic resolution and/or desymmetrization of diastereotopic or enantiotopic ester groups take place with consistently good to excellent stereoselectivity (diastereoisomeric ratios 4-9:1). As both enantiomers of phenylglycinol are commercially available, this aminoalcohol provides easy access to enantiopure piperidines in both enantiomeric series. On the other hand, although aminoindanol **21** and protected aminopropanodiol **22** also promote highly stereoselective cyclocondensation reactions, their usefulness as chiral inductors is less general. Thus, whereas aminoindanol, whose two enantiomers are also commercially available, gives excellent stereoselectivities (diastereoisomeric ratios 8-13:1) in cyclocondensations from racemic ketones involving DKR, the less accessible alcohol **22** works with exceptionally high stereoselectivities (diastereoisomeric ratios 9-20:1) in cyclocondensations from

aldehydes involving either DKR or desymmetrization of ester chains.

The highly enantioselective processes reported herein, leading to a variety of (poly)substituted lactams in a single synthetic step, represent a conceptual extension of the potential of oxazolopiperidone lactams as chiral synthons for the enantioselective synthesis of diversely substituted piperidine derivatives.

Experimental Section

General Procedure for Cyclocondensation Reactions. A solution of aminoalcohol (1.2 equiv) and 1,5-dicarbonyl compound (1 equiv) in anhydrous toluene containing molecular sieves (4Å) was heated at reflux for 12–66 h, with azeotropic removal of water produced by a Dean-Stark apparatus. The resulting suspension was filtered through Celite, the filtrate was concentrated, and the residue was taken up with EtOAc, dried, and concentrated. The resulting residue was chromatographed to afford the desired lactams. The epimeric ratios were determined by using HPLC and/or ^{1}H NMR.

(3*R*,8a*R*)-5-Oxo-3,8a-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (3b). Operating as in the above general procedure, from (*R*)-phenylglycinol (1.7 g, 12.4 mmol) and 5-phenyl-5-oxopentanoic acid (**1b**; 2 g, 10.4 mmol) in

anhydrous toluene (21 mL) for 25 h, lactam **3b** (2.7 g, 90%) was obtained as a white solid after flash chromatography (SiO_2 previously washed with hexane-Et_3N; gradient 7:3 hexane–EtOAc to EtOAc): m.p. 119–122 °C (THF–hexane); $[\alpha]^{22}_D$ +9.2 (*c* 1.0, MeOH), $[\alpha]^{22}_D$ +20.4 (*c* 0.63, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.60 (m, 1H, H-7), 1.74 (m, 1H, H-7), 1.95 (ddd, *J* = 14.0, 12.6, 3.9 Hz, 1H, H-8), 2.23 (ddd, *J* = 12.6, 3.9, 0.9 Hz, 1H, H-8), 2.45 (ddd, *J* =18.6, 10.5, 7.8 Hz, 1H, H-6), 2.63 (ddd, *J* = 18.6, 7.8, 0.9 Hz, 1H, H-6), 3.62 (t, *J* = 9.0 Hz, 1H, H-2), 4.39 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 5.28 (t, *J* = 9.0 Hz, 1H, H-3), 7.08–7.20 (m, 5H, ArH), 7.31–7.39 (m, 3H, ArH), 7.46–7.49 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 15.3 (CH_2), 30.7 (CH_2), 36.8 (CH_2), 60.4 (CH), 69.2 (CH_2), 97.1 (C), 126.6 (CH), 127.6 (CH), 127.2 (CH), 128.3 (CH), 127.9 (CH), 137.8 (C), 141.2 (C), 170.8 (C); IR (film): ν = 1650 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77; found: C, 77.83; H, 6.51; N, 4.76.

(3*R*,8a*R*)-5-Oxo-3-phenyl-8a-(3-pyridyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (3c). Operating as in the above general procedure, from (*R*)-phenylglycinol (1.26 g, 9.12 mmol) and 5-oxo-5-(3-pyridyl)pentanoic acid[28] (**1c**; 1.48 g, 7.6 mmol) in toluene (15 mL) for 24 h lactam **3c** (1.2 g, 58%) was obtained after flash chromatography (95:5

Et_2O–Et_2NH): m.p. 103–106 °C (Et_2O); $[\alpha]^{22}_D$ + 4.3 (*c* 1.0, EtOH); ^1H NMR ($CDCl_3$, 300 MHz, HETCOR): δ = 1.58 (m, 1H, H-7), 1.83 (m, 1H, H-7), 1.98 (td, *J* = 12.9, 3.9 Hz, 1H, H-8), 2.23 (dt, *J* = 12.9, 3.9 Hz, 1H, H-8), 2.51 (ddd, *J* = 18.6, 10.5, 6.4 Hz, 1H, H-6), 2.68 (dd, *J* = 18.6, 8.1 Hz, 1H, H-6), 3.65 (t, *J* = 9.3 Hz, 1H, H-2), 4.46 (dd, *J* = 9.3, 8.1 Hz, 1H, H-2), 5.35 (t, *J* = 8.1 Hz, 1H, H-3), 7.06–7.21 (m, 5H, ArH), 7.30 (ddd, *J* = 8.1, 4.8, 1.8 Hz, 1H, H-5pyr), 7.77 (dt, *J* = 8.1, 2.4 Hz, 1H, H-4pyr), 8.60 (dd, *J* = 4.8, 1.8 Hz, 1H, H-6pyr), 8.76 (dd, *J* = 2.4, 0.9 Hz, 1H, H-2pyr); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 15.2 (CH_2), 30.7 (CH_2), 36.7 (CH_2), 60.2 (CH), 69.3 (CH_2), 95.9 (C), 122.9 (CH), 127.2 (CH), 127.5 (CH), 128.3 (CH), 134.5 (CH), 136.9 (C), 137.6 (C), 148.4 (CH), 149.8 (CH), 170.8 (C); IR (KBr): ν = 1653 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52; found: C, 73.51; H, 6.25; N, 9.64.

General Procedure for Reduction Reactions. *Method A.* A mixture of 9-BBN (0.5M in THF, 1–10 equiv) and lactam (1 equiv) was heated at reflux for 5–8 h. Then, the crude mixture was cooled at 0 °C, a 1:1 solution of aqueous 2N NaOH and 30% H_2O_2 was slowly added, and the stirring was continued at 0 °C for 30 min. Brine was added at 0 °C, the aqueous phase was extracted with EtOAc, the combined organic extracts were dried and concentrated, and the residue was chromatographed.

Method B. Red-Al (0.1M in THF, 2.5–5 equiv) was added to a solution of lactam (1 equiv) in anhydrous THF, and the mixture was heated at reflux for 8 h. The crude mixture was diluted with EtOAc and ice–H_2O, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried and concentrated, and the residue was chromatographed.

Method C. $LiAlH_4$ (3.2–6.6 equiv) was slowly added to a cooled (0 °C) suspension of $AlCl_3$ (1.4–4.4 equiv) in anhydrous THF, and the mixture was stirred at room temperature for 30 min. The temperature was lowered to –78 °C, the corresponding lactam (1 equiv) was added, and the resulting suspension was stirred at –78 °C for 90 min and at room temperature for 2 h. The mixture was cooled to 0 °C, and the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried and concentrated, and the residue was chromatographed.

Method D. BH_3 (1M THF, 3 equiv) was added to a solution of lactam (1 equiv) in anhydrous THF at –78 °C. The mixture was stirred at 0 °C for 2 h and at room temperature for 3 h, poured into saturated aqueous 0.2N NaOH and extracted with EtOAc. The combined organic extracts were dried and concentrated, and the residue was chromatographed.

(2*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-phenylpiperidine (4b). Operating as described in the above Method B, from lactam **3b** (100 mg, 0.34 mmol) and Red-Al (0.1M in THF, 17 mL,

1.7 mmol) in anhydrous THF (2 mL) for 8 h, piperidine **4b** (51.5 mg, 54%) was obtained after flash chromatography (hexane): m.p. 61–62 °C (hexane) (lit[29] 60.9 °C); $[\alpha]^{22}_{D}$ –165.1 (*c* 0.95, $CHCl_3$) (lit[29] $[\alpha]^{20}_{D}$ –165.9 (*c* 1.0, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.12–1.26 (m, 1H, H-4), 1.53–1.76 (m, 5H, 2H-3, H-4, 2H-5), 1.91 (td, *J* = 12.0, 2.1 Hz, 1H, H-6), 3.12 (dm, *J* = 12.0 Hz, 1H, H-6), 3.29 (dd, *J* = 10.8, 3.0 Hz, 1H, H-2), 3.38 (dd, *J* = 9.0, 3.9 Hz, 1H, H-1′), 3.54 (bs, 1H, OH), 4.00 (dd, *J* = 11.3, 3.9 Hz, 1H, H-2′), 4.03 (dd, *J* = 11.3, 9.0 Hz, 1H, H-2′), 6.99–7.06 (m, 2H, ArH), 7.25–7.44 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 24.9 (CH_2), 26.3 (CH_2), 37.8 (CH_2), 45.7 (CH_2), 59.3 (CH_2), 61.8 (CH), 65.4 (CH), 127.1 (CH), 127.6 (CH), 127.8 (CH), 127.9 (CH), 128.7 (CH), 129.3 (CH), 134.4 (CH), 144.0 (C); IR (film): ν = 3441 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98; found: C, 80.86; H, 8.33; N, 4.91.

(2*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-phenylpiperidine (5b). Operating as in the above Method A, from lactam **3b** (1 g, 3.4 mmol) and 9-BBN (0.5M in THF, 68.2 mL, 34 mmol) in THF (40 mL) for 8 h, piperidine **5b** (720 mg, 75%) was obtained after flash chromatography (hexane, 7:3 hexane–EtOAc): m.p. 77–78 °C (Et_2O–hexane), (lit[27] 78 °C); $[\alpha]^{22}_{D}$ –30.2 (*c* 1.1, $CHCl_3$), (lit[29] $[\alpha]^{20}_{D}$ –30.3 (*c* 1.08, $CHCl_3$)); ^{1}H NMR ($CDCl_3$,

300 MHz, COSY, HETCOR): δ = 1.25–1.80 (m, 7H, 2H-3, 2H-4, 2H-5, OH), 2.51 (td, *J* = 11.3, 2.7 Hz, 1H, H-6), 2.95 (dm, *J* = 11.3 Hz, 1H, H-6), 3.76 (dd, *J* = 9.9, 2.7 Hz, 1H, H-2), 3.83 (t, *J* = 6.6 Hz, 1H, H-1′), 4.04 (m, 2H, 2H-2′), 7.20–7.42 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 25.1 (CH_2), 26.4 (CH_2), 37.0 (CH_2), 47.6 (CH_2), 59.7 (CH_2), 62.7 (CH), 65.8 (CH), 126.6 (CH), 127.0 (CH), 128.0 (CH), 127.6 (CH), 128.5 (CH), 140.1 (C), 144.8 (C); IR (film): ν = 3405 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98; found: C, 80.90; H, 8.37; N, 4.95.

(2*S*)- and (2*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-pyridylpiperidine (4c and 5c). Lactam **3c** (100 mg, 0.34 mmol) was slowly added to a suspension of $LiAlH_4$ (129 mg, 3.4 mmol) in anhydrous THF (6 mL) at room temperature. The resulting mixture was stirred for 15 h and cooled to 0 °C. The reaction was quenched with H_2O. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. Flash chromatography (EtOAc) afforded piperidines **4c** (70 mg, 78%) and **5c** (5 mg, 6%). **4c**: $[\alpha]^{22}_D$ –120.0 (*c* 1.3, $CHCl_3$), (lit[30]: $[\alpha]^{22}_D$ –123.1 (*c* 1.3, $CHCl_3$));.^{1}H NMR ($CDCl_3$, 300MHz): δ = 1.18–1.25 (m, 1H), 1.55–1.77 (m, 5H), 1.96 (td, *J* = 12.0, 2.4 Hz, 1H), 3.13 (dm, *J* = 12.0 Hz, 1H), 3.34 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.41 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.87 (dd, *J* = 11.0, 5.4 Hz, 1H), 4.05 (t,

J = 11.0 Hz, 1H), 6.97–7.00 (m, 2H), 7.31–7.34 (m, 3H), 7.37 (dd, *J* = 8.1, 4.8 Hz, 1H), 7.78 (dt, *J* = 8.1, 2.1 Hz, 1H), 8.56–8.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 24.7 (CH_2), 26.2 (CH_2), 37.8 (CH_2), 45.7 (CH_2), 59.5 (CH_2), 62.4 (CH), 62.6 (CH), 123.9 (CH), 127.9 (CH), 128.0 (CH), 129.2 (CH), 133.9 (C), 135.2 (CH), 139.4 (C), 148.8 (CH), 149.7 (CH); IR (film): ν = 3408 cm^{-1}; **5c**: $[\alpha]^{22}_D$ –22.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ = 1.41–1.88 (m, 6H), 2.55 (td, *J* = 11.4, 2.7 Hz, 1H), 2.92 (dm, *J* = 11.4 Hz, 1H), 3.78 (t, *J* = 6.6 Hz, 1H), 3.93 (dd, *J* = 11.1, 2.7 Hz, 1H), 4.03 (dd, *J* = 11.1, 6.6 Hz, 1H), 4.12 (dd, *J* = 11.1, 6.6 Hz, 1H), 7.16–7.38 (m, 6H), 7.79 (dt, *J* = 7.8, 1.8 Hz, 1H), 8.28 (dd, *J* = 4.5, 1.8 Hz, 1H), 8.52 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 24.9 (CH_2), 26.2 (CH_2), 37.0 (CH_2), 46.9 (CH_2), 59.8 (CH_2), 62.6 (CH), 63.0 (CH), 123.6 (CH), 126.6 (CH), 127.8 (CH), 128.0 (CH), 135.2 (CH), 140.1 (C), 140.4 (C), 147.9 (CH), 149.1 (CH); IR (film): ν = 3355 cm^{-1}.

(2*R*,3*R*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-methylpiperidine (12a). Operating as in the above Method C, from lactam **8h** (200 mg, 0.77 mmol), $AlCl_3$ (154 mg, 1.1 mmol), and $LiAlH_4$ (191 mg, 5.1 mmol) in anhydrous THF (15 mL), piperidine **12a** (160 mg, 84%) was obtained after flash chromatography (1:1 hexane–EtOAc): $[\alpha]^{22}_D$ –15.2 (*c* 1.36, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): δ = 0.79 (t, *J* = 7.5 Hz,

3H, CH_3), 0.85 (d, *J* = 7.0 Hz, 3H, CH_3), 1.19 (q, *J* = 7.0 Hz, 2H, CH_2), 1.29–1.54 (m, 4H, H-3, 2H-4, H-5), 1.61 (m, 1H, H-5), 2.45 (m, 1H, H-6), 2.66 (dd, *J* = 9.0, 3.6 Hz, 1H, H-6), 2.78 (ddd, *J* = 13.5, 6.6, 3.6 Hz, 1H, H-2), 3.78 (m, 3H, H-1', H-2'), 7.24–7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 9.9 (CH_3), 11.8 (CH_3), 23.5 (CH_2), 24.5 (CH_2), 25.4 (CH_2), 42.4 (CH), 44.0 (CH_2), 53.7 (CH), 62.0 (CH_2), 64.7 (CH), 127.4 (CH), 128.2 (CH), 128.3 (CH), 139.2 (C); IR (film): ν = 3414 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{25}NO$: C, 76.68; H, 10.19; N, 5.66; found: C, 76.39; H, 10.12; N, 5.51.

Ethyl (3*S*,4*S*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine-4-acetate (14a). Operating as in the above Method D, from lactam **9o** (175 mg, 0.52 mmol) and BH_3 (1M in THF, 1.58 mL, 1.58 mmol) in THF (8 mL), piperidine **14a** was obtained (103 mg, 61%) after flash chromatography (8:2 EtOAc–hexane to EtOAc): $[\alpha]^{22}_D$ –53.0 (*c* 0.5, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ =□0.88 (t, *J* = 7.2 Hz, 3H, CH_3), 1.13 (m, 1H, CH_2), 1.22 (t, *J* = 7.2 Hz, 3H, CH_3), 1.23–1.43 (m, 3H, H-3, H-4, H-5), 1.49 (m, 1H, CH_2), 1.74 (m, 2H, H-5, H-6ax), 2.01 (dd, *J* = 14.7, 8.7 Hz, 1H, CH_2), 2.02 (t, *J* = 10.5 Hz, 1H, H-2ax), 2.49 (dd, *J* = 14.7, 4.0 Hz, 1H, CH_2), 2.85 (m, 2H, H-2eq, H-6eq), 3.62 (dd, *J* = 10.0, 5.2 Hz, 1H, H-2'), 3.72 (dd, *J* = 10.0, 5.2 Hz, 1H, H-1'), 3.97 (t, *J* = 10.0 Hz, 1H, H-2'), 4.08 (q, *J* = 7.2 Hz, 2H, CH_2), 7.15–7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 11.1

(CH_3), 14.2 (CH_3), 23.6 (CH_2), 31.7 (CH_2), 37.1 (CH), 38.4 (CH_2), 42.6 (CH), 46.0 (CH_2), 56.9 (CH_2), 60.0 (CH_2), 60.2 (CH_2), 70.0 (CH), 127.8 (CH), 128.1 (CH), 1.28.8 (CH), 135.2 (C), 173.0 (C); IR (film): ν = 3440, 1732 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.16; N, 4.38; found: C, 71.38; H, 9.32; N, 4.36.

General Procedure for Hydrogenolysis Reactions. A solution of the piperidine (1 equiv) in MeOH or EtOAc containing Pd-C or $Pd(OH)_2$-C was hydrogenated at 25 °C until disappearance of starting material was observed by TLC. The catalyst was removed by filtration and washed with hot MeOH, and the solution was concentrated to give the substituted piperidines after flash chromatography.

(*S*)-2-Phenylpiperidine (6b). Following the above general procedure, from piperidine **4b** (150 mg, 0.53 mmol) and Pd-C (10 %, 37.5 mg) in MeOH (25 mL) was obtained piperidine **6b** (50 mg, 58 %) as a transparent oil after flash chromatography (CH_2Cl_2): $[\alpha]^{22}_D$ −26.9 (*c* 1.0, MeOH), $[\alpha]^{22}_D$ −63.8 (*c* 0.5, $CHCl_3$), (lit[29] $[\alpha]^{20}_D$ −27.0 (*c* 0.43, MeOH)); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.43–1.93 (m, 6H), 2.78 (td, *J* = 11.6, 3.1 Hz, 1H), 3.19 (dm, *J* = 11.6 Hz 1H), 3.58 (dd, *J* = 10.4, 2.4 Hz, 1H), 7.19–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ = 25.4 (CH_2), 25.9 (CH_2), 34.9 (CH_2), 47.8 (CH_2), 62.3 (CH), 126.5 (CH),

126.9 (CH), 128.2 (CH), 145.4 (C); IR (film): ν = 3420 cm^{-1}; HMRS calcd for $C_{11}H_{15}N$ 161.1199; found 161.1204.

(*S*)-3-(2-Piperidyl)pyridine [(−)-*S*-Anabasine] **(6c).** Following the above general procedure, from piperidine **4c** (150 mg, 0.53 mmol) and 10% $Pd(OH)_2$-C (40 mg) in MeOH (12 mL) was obtained pure anabasine (**6c**, 70 mg, 81%) as a transparent oil after flash chromatography (95:5 EtOAc–EtOH): $[\alpha]^{22}_D$ −74.7 (*c* 0.1, $CHCl_3$), (lit[30]: $[\alpha]^{23}_D$ −75.5 (*c* 0.1, $CHCl_3$)); $[\alpha]^{22}_D$ −77.04 (*c* 0.5, MeOH); (lit[31]: $[\alpha]^{24}_D$ −79.2 (*c* 0.5, MeOH)); ^{1}H NMR ($CDCl_3$, 300MHz): δ = 1.50–2.0 (m, 6H), 2.80 (td, *J* = 11.4, 3.0 Hz, 1H), 3.20 (dm, *J* = 11.4 Hz, 1H), 3.64 (dd, *J* = 10.2, 2.7 Hz, 1H), 7.24 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.72 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.48 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.58 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 25.2 (CH_2), 25.6 (CH_2), 34.7 (CH_2), 47.6 (CH_2), 59.8 (CH), 123.4 (CH), 134.1 (CH), 140.4 (C), 148.5 (CH), 148.6 (CH).

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Legends

Scheme 1. Synthetic Strategy. First Generation Oxazolopiperidone Lactams.

Scheme 2. Synthetic Strategy. Second Generation Oxazolopiperidone Lactams.

Scheme 3. Enantiodivergent Synthesis of 2-Arylpiperidines. Enantioselective Synthesis of (−)-Anabasine.

Scheme 4. Stereoselective Reduction of 8a-Substituted Lactams.

Scheme 5. Lactamization Step during Cyclocondensation of δ-Oxoacid Derivatives with 1,2-Aminoalcohols.

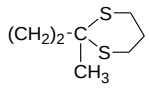
Scheme 6. Synthesis of Diversely Substituted Enantiopure Piperidines.

Scheme 7. Removal of the Chiral Auxiliary.

Tables

Table 1. Cyclocondensation reactions from racemic γ-substituted δ-oxoacid derivatives.

Insert here **Figure of Table 1**

	R	R^1	R^2	yield (%)	**7**/**8** ratio
d	Me	H	Et	79	4:1
e	Me	H		71	6:1
f	Me	H	$CH_2CH=CH_2$	71	7:1
g	H	C_6H_5	Et	50	1[a]:4
h	H	Me	Et	60	1:4
i	H	$-(CH_2)_4-$		70	1:5[b]
j	Me	H	OTBDMS	50	[c]
k	Me	H	OAc	45	[d]
l	H	CH_2OBn	OMEM	74	[e]

[a]The minor stereoisomer was the C_{8a}-epimer of **7g**. [b]The relative stereochemistry of **8i** was confirmed by X-ray crystallography. [c]Lactam **7j**, its C_8-epimer (3:2 ratio), and minor amounts of **8j** (undetermined stereochemistry at C_8). [d]Lactams **7k**, 8a-*epi*-**7k**, and 8a-*epi*-**8k** in a 5:2:2 ratio. [e]**8l** and its C_8-epimer in a 3:2 ratio, and minor amounts of **7l**.

Table 2. Cyclocondensation reactions of (*R*)-phenylglycinol with prochiral or racemic δ-oxodiesters.

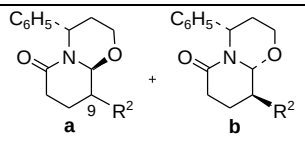
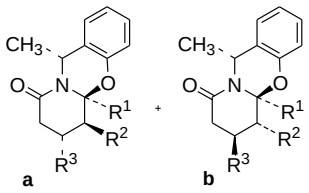
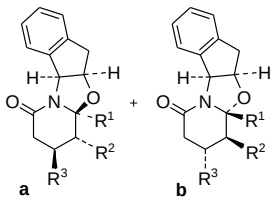
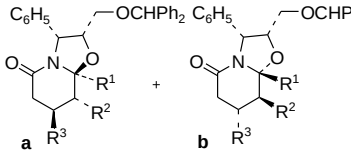
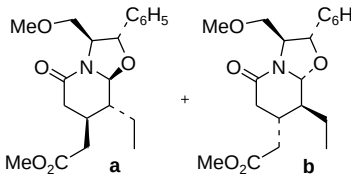
Insert here **Figure of Table 2**

	R′	R^1	R^2	yield (%)	**9**/**10** ratio
m	Me	H	H	95	4:1
n	Et	Me	H	77[a]	1:4[b]
o	Et	H	Et	77	4:1
p	Et	Me	*n*Pr	55[c]	1:9
q	Me	Me	Et	81[c]	1:5
r	-	-	H	67	9:1
s	-	-	Et	50	9:1[d]

[a]Using *p*-TsOH as a catalyst. [b]The relative stereochemistry of **10n** was confirmed by X-ray crystallography. [c]Using glacial AcOH as a catalyst. [d]Isomers **9s** and **10s** were isolated accompanied by their respective C_8 epimers (**9s′** and **10s′**; 1:1 mixtures).

Table 3. Cyclocondensation reactions of aminoalcohols with racemic or prochiral δ-oxoacid derivatives.

Insert here **Figure of Table 3**

starting materials	products		R^1	R^2	R^3	yield	**a:b** ratio
1a + *rac*-**19**		*rac*-**24**	—	H	—	68%[a]	7:3
1d + *rac*-**19**		*rac*-**25**	—	Et	—	70%[a]	4[b]:3
1a + *rac*-**20**		*rac*-**26**[c]	H	H	H	90%	—[d]
1d + *rac*-**20**		*rac*-**27**	H	Et	H	80%	1:1[d]
1t + *rac*-**20**		*rac*-**28**[c]	CH_3	H	H	80%	—[d]
1h + *rac*-**20**		*rac*-**29**	CH_3	Et	H	45%	9:1[d]
1u + *rac*-**20**[e]		*rac*-**30**	CH_3	C_6H_5	H	42%	9:1[d]
1n + *rac*-**20**[e]		*rac*-**31**	CH_3	H	CH_2CO_2Et	38%	3:2[d]
1a + **21**		**32**	H	H	H	70%	4:1
1d + **21**		**33**	H	Et	H	87%	7:5:3[f]
1m + **21**		**34**	H	H	CH_2CO_2Me	78%	4:1
1t + **21**		**35**	CH_3	H	H	99%	1:10
1h + **21**		**36**	CH_3	Et	H	74%	1:8[g]
1u + **21**		**37**[c]	CH_3	C_6H_5	H	86%	1:13[g]
1n + **21**[h]		**38**	CH_3	H	CH_2CO_2Et	64%	5:9
1q + **21**		**39**	CH_3	Et	CH_2CO_2Me	68%	2:3
1d + **22**		**40**	H	Et	H	78%	1:9
1m + **22**		**41**	H	H	CH_2CO_2Me	86%	1:14
1r + **22**		**42**	H	$(CH_2)_2CO_2$	H	80%	1:20
1v + **22**		**43**	H	Et	CH_2CO_2Me	77%	1:15[i]
1h + **22**		**44**	CH_3	Et	H	81%	3:2
1q + **22**[h]		**45**	CH_3	Et	CH_2CO_2Me	58%[j]	5:2[k]
1v + **23**		**46**	—	—	—	70%	2:1[l]

[a]The initially formed *cis*-oxazine, which has not undergone lactamization, was isolated in ~10% yield. [b]1:1 mixture of C-9 epimers. [c]The relative stereochemistry of *rac*-**26**, *rac*-**28**, and **37b** was confirmed by X-ray crystallography. [d]Trace amounts of the epimer at the piperidine α-position were also detected. [e]In the presence of a catalytic amount of *p*-TsOH. [f]**a**:**b**:**c** ratio (**c** is the epimer of **b** at the piperidine α-position). [g]Trace amounts of the epimer at the piperidine β-position were also detected. [h]In the presence of a catalytic amount of glacial AcOH. [i]Minor amounts of the epimer at the piperidine γ-position were also isolated. [j] Based on consumed **1q**. [k] Minor amounts of a third diastereomer were formed. [l] Other stereoisomers (about 15%) were also formed.

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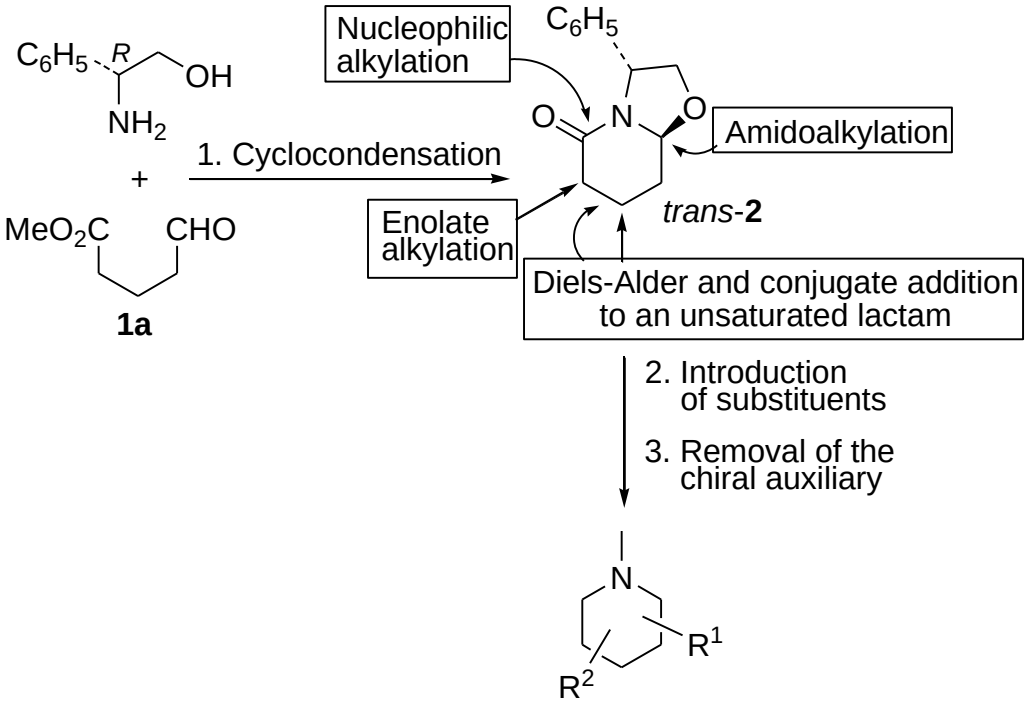
As many as three stereogenic centers can be generated in high chemical yield and excellent stereoselectivity in a single synthetic step by a cyclocondensation reaction between a chiral non-racemic aminoalcohol and a racemic δ-oxodiester in a process involving a tanden dynamic kinetic resolution-diastereoselective differentiation of two acetate chains. This is the key step of a straightforward procedure for the enantioselective synthesis of diversely substituted piperidines.

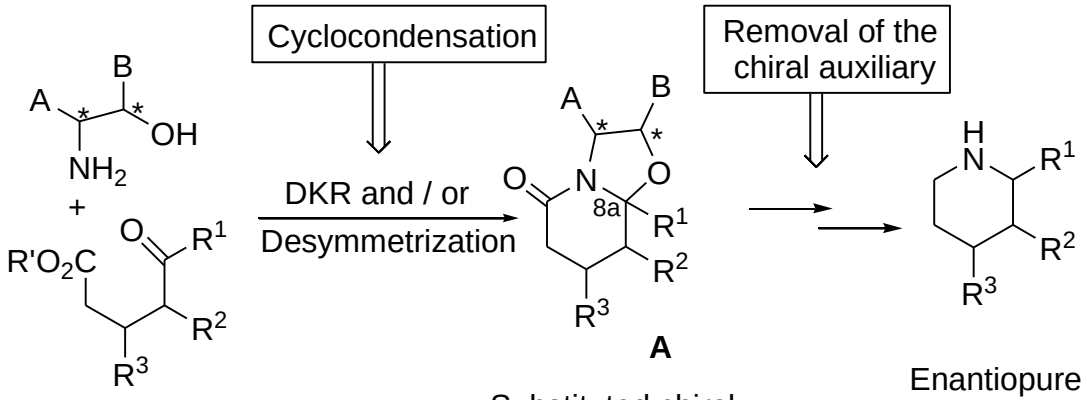
Keywords: Asymmetric synthesis, Cyclocondensation, Chiral auxiliaries, Dynamic Kinetic Resolution, Enantiopure piperidines.

Scheme 1

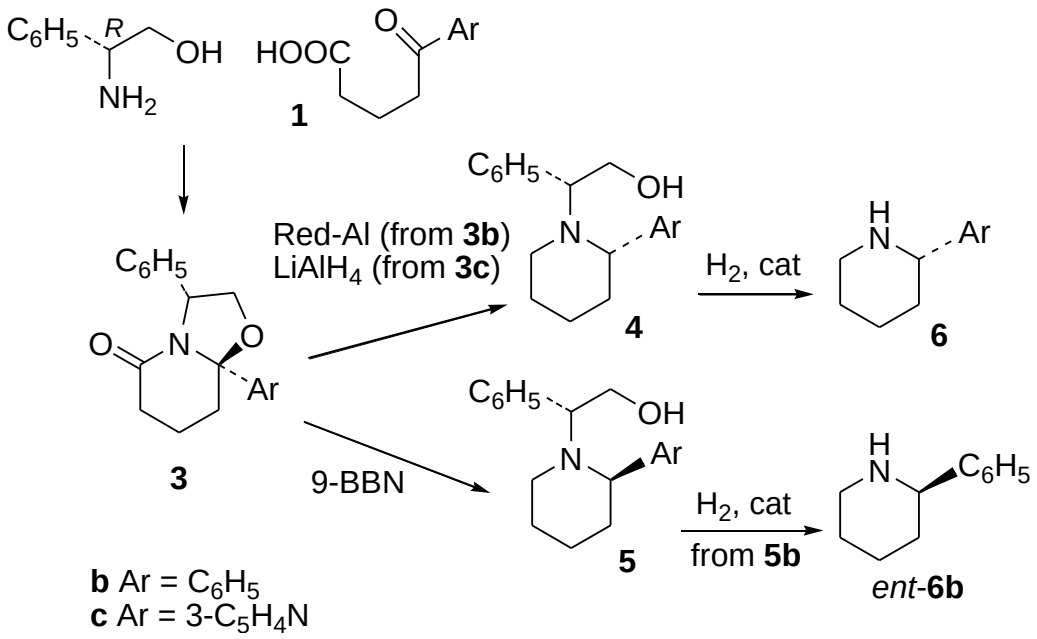


Enantiopure piperidines

Scheme 2


Cyclocondensation
Removal of the chiral auxiliary
DKR and / or
Desymmetrization
A
B
OH
NH2
+
R'O2C
O
R1
R2
R3
N
8a
H
1 Racemic or prochiral δ-oxo(di)acid derivatives
Substituted chiral nonracemic lactams
Enantiopure piperidines

Scheme 3


C6H5
R
OH
NH2
HOOC
O
Ar
1
Red-Al (from 3b)
LiAlH4 (from 3c)
C6H5
O
N
O
Ar
3
4
H2, cat
6
9-BBN
5
from 5b
ent-6b
b Ar = C6H5
c Ar = 3-C5H4N

Scheme 4

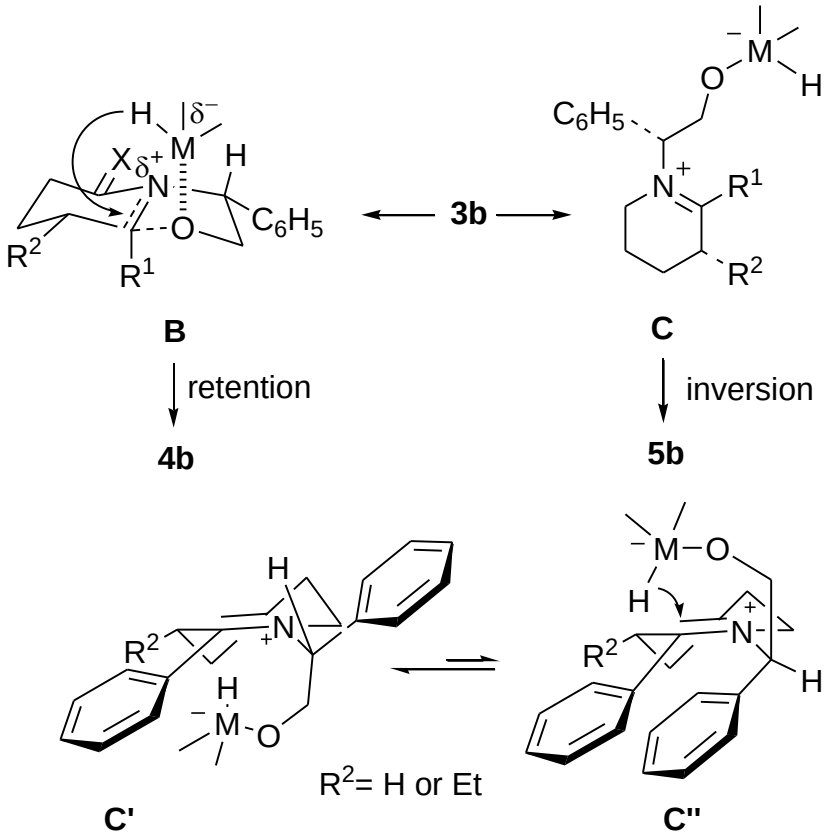
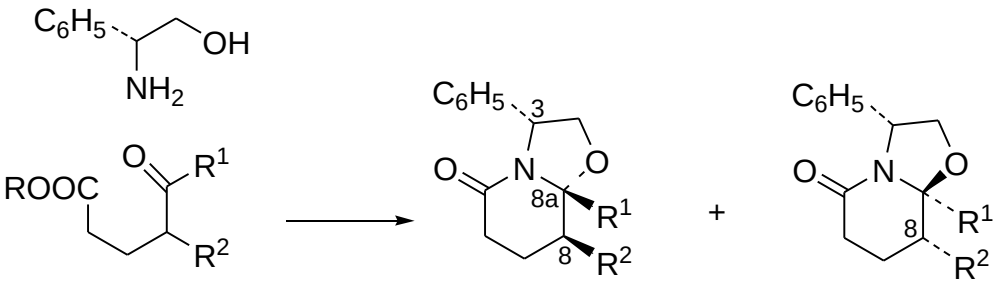
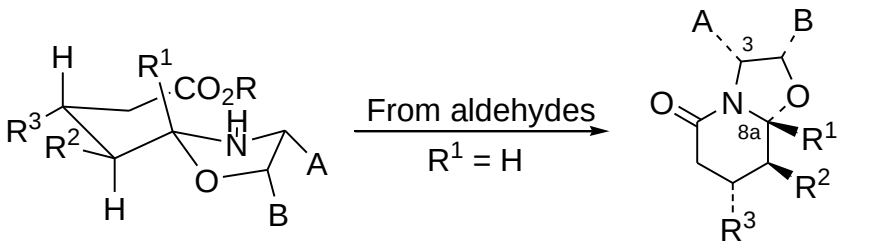


Figure of Table 1



1d-l, racemates **7** **8**

Scheme 5


From aldehydes
R1 = H
3-H/8a-H cis

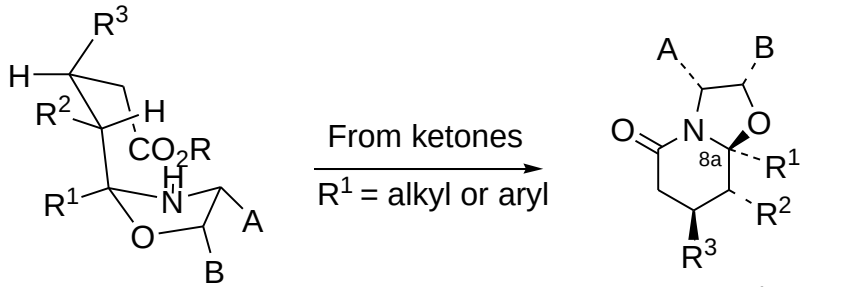
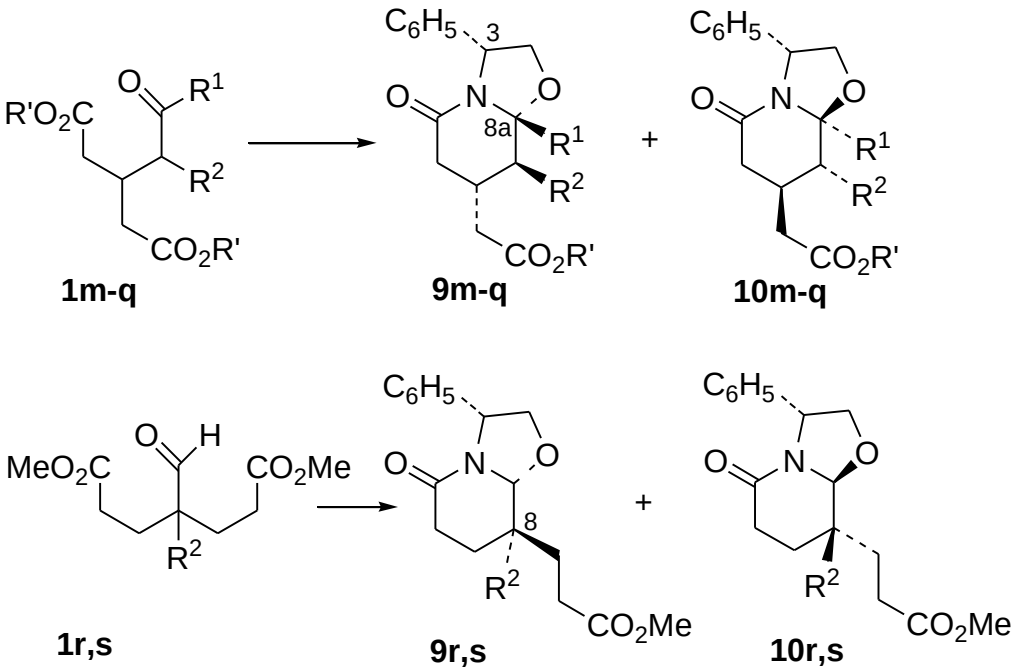

From ketones
R1 = alkyl or aryl
3-H/8a-R1 trans

Figure of Table 2



Scheme 6

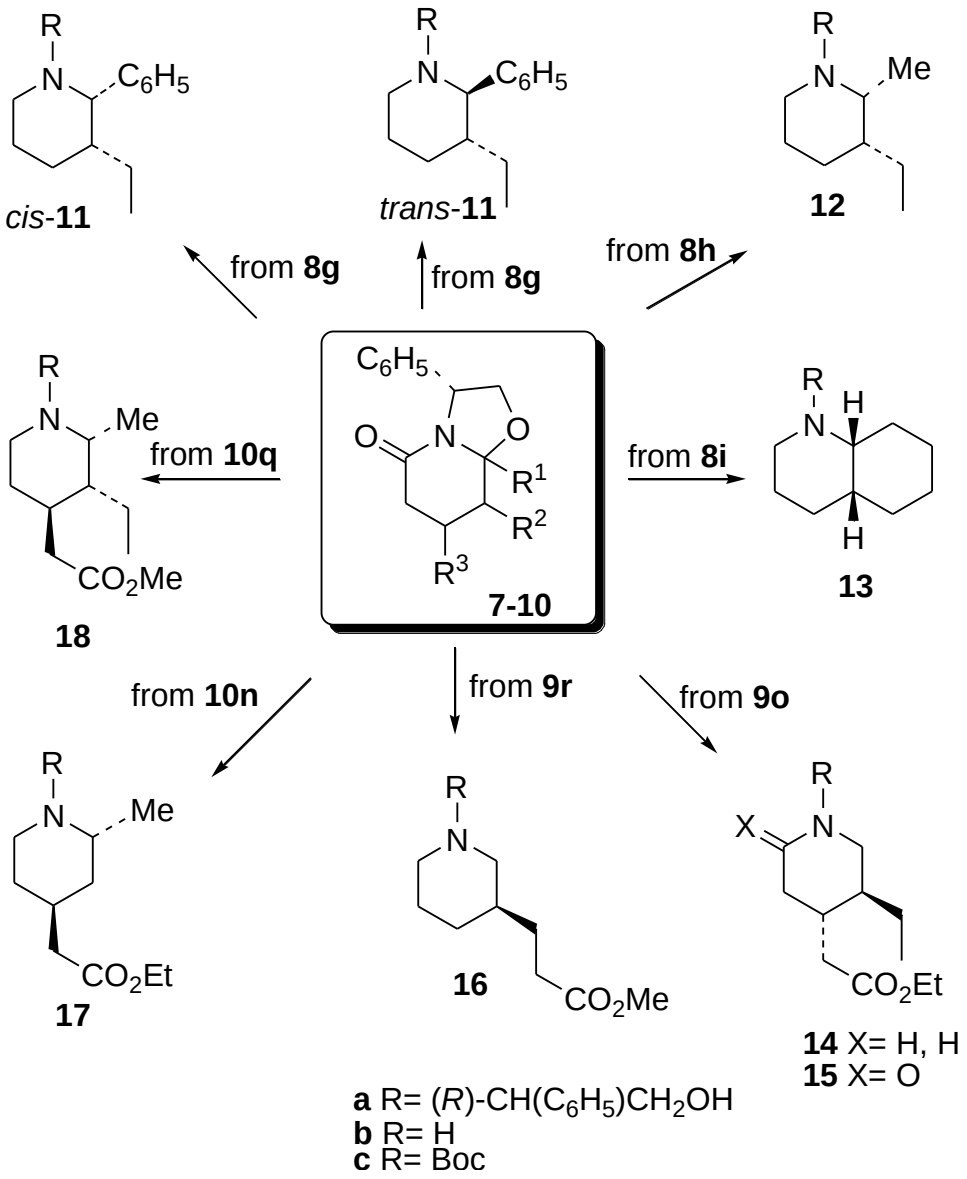
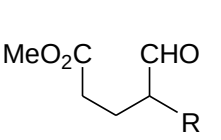
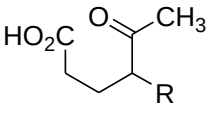

R
N
C6H5
cis-11
trans-11
Me
12
from 8g
from 8g
from 8h
from 10q
from 8i
CO2Me
18
7-10
13
from 10n
from 9r
from 9o
CO2Et
17
16
CO2Me
X
14 X= H, H
15 X= O
a R= (R)-CH(C6H5)CH2OH
b R= H
c R= Boc

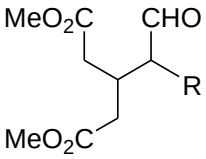
Figure of Table 3



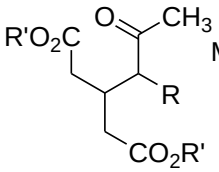
1a R = H
1d R = Et



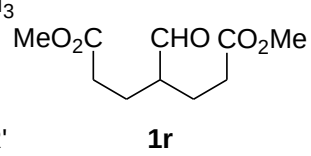
1t R = H
1h R = Et
1u R = C_6H_5



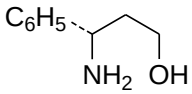
1m R = H
1v R = Et



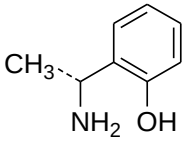
1n R = H, R' = Et
1q R = Et, R' = Me



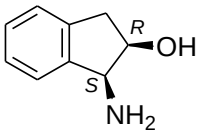
1r



rac-**19**



rac-**20**



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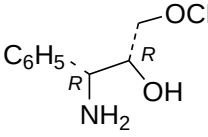
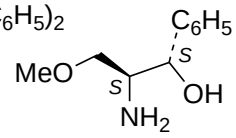


22



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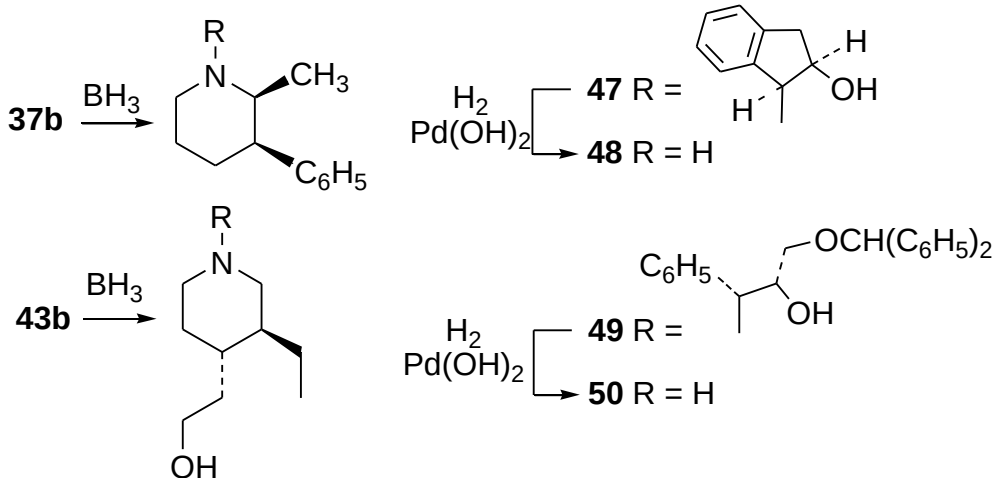
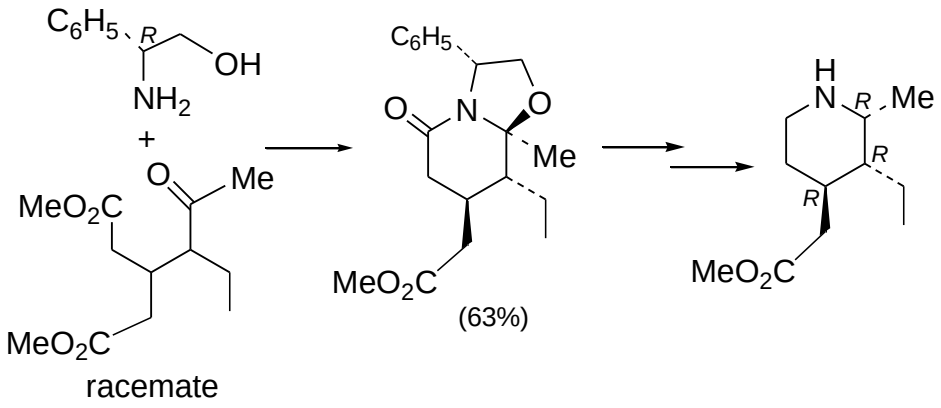
Scheme 7


37b
BH3
R
N
CH3
C6H5
H2
Pd(OH)2
47 R =
H
OH
H
48 R = H
43b
BH3
R
N
OH
C6H5
OCH(C6H5)2
OH
H2
Pd(OH)2
49 R =
50 R = H

Graphical Abstract



Supporting Information

Dynamic Kinetic Resolution and Desymmetrization Processes: A Straightforward Methodology for the Enantioselective Synthesis of Piperidines

Mercedes Amat,*[a] Oriol Bassas,[a] Núria Llor,[a] Margalida Cantó,[a] Maria Pérez,[a] Elies Molins,[b] and Joan Bosch,*[a]

Cyclocondensation Reactions

(3*R*,8*S*,8a*R*)- and **(3*R*,8*R*,8a*S*)-8-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-a]pyridine (7d** and **8d).** *Method A*. Operating as in the general procedure, from methyl 4-formylhexanoate[1] (**1d**; 1.2 g, 7.6 mmol) and (*R*)-phenylglycinol (1.2 g, 9.1 mmol) in toluene (25 mL) for 18 h, compounds **7d** (1.23 g, 64%) and **8d** (310 mg, 16%) were obtained after flash chromatography (EtOAc). **7d** (higher R_f): m.p. 97–100 °C (Et_2O–hexane); $[\alpha]^{22}_D$ –23.5 (*c* 1.0, EtOH); ^1H NMR ($CDCl_3$, 300 MHz, HETCOR): δ = 1.05 (t, *J* = 7.4 Hz, 3H, CH_3), 1.34–1.50 (m, 2H, H-7, CH_2), 1.70–1.91 (m, 2H, H-8, CH_2), 2.05 (m, 1H, H-7), 2.35 (ddd, *J* = 18.0, 11.2, 7.0 Hz, 1H, H-6), 2.42 (ddd, *J* = 18.0, 7.2, 2.5 Hz, 1H, H-6), 4.00 (d, *J* = 9.0 Hz, 1H, H-2), 4.13 (dd, *J* = 9.0, 6.7 Hz, 1H, H-2), 4.52 (d, *J* = 8.8 Hz,

1H, H-8a), 4.92 (d, *J* = 6.7 Hz, 1H, H-3), 7.21–7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 10.8 (CH_3), 23.6 (CH_2), 24.0 (CH_2), 31.2 (CH_2), 40.7 (CH), 58.7 (CH), 73.6 (CH_2), 92.4 (CH), 126.1 (CH), 128.3 (CH), 127.2 (CH), 141.4 (C), 167.1 (C); IR (KBr): ν = 1655 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70; found: C, 73.59; H, 7.89; N, 5.81. **8d** (lower R_f): m.p. 77–80 °C (Et_2O); $[\alpha]^{22}_D$ – 103.5 (*c* 1.1, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz, HETCOR): δ = 1.03 (t, *J* = 7.4 Hz, 3H, CH_3), 1.37 (m, 1H CH_2), 1.51 (m, 2H, H-7, H-8), 1.80 (m, 1H, CH_2), 1.96 (m, 1H, H-7), 2.36 (ddd, *J* = 18.5, 11.3, 6.5 Hz, 1H, H-6), 2.57 (dd, *J* = 18.0, 5.0 Hz 1H, H-6), 3.74 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.47 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.67 (d, *J* = 7.8 Hz, 1H, H-8a), 5.24 (t, *J* = 7.8 Hz, 1H, H-3), 7.25–7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 10.9 (CH_3), 22.7 (CH_2), 24.5 (CH_2), 31.3 (CH_2), 41.1 (CH), 58.1 (CH), 72.3 (CH_2), 92.6 (CH), 125.9 (CH), 128.6 (CH), 127.3 (CH), 139.4 (C), 168.7 (C); IR (KBr): ν = 1660 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70; found: C, 73.04; H, 7.71; N, 5.51.

Method B. A mixture of racemic methyl 4-formylhexanoate[1] (**1d**; 3.8 g, 24.4 mmol), (*R*)-phenylglycinol (3.3 g, 24.4 mmol), and anhydrous Na_2SO_4 (13.5 g, 95 mmol) in Et_2O (80 mL) was stirred at 0 °C for 1 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced

pressure. The residue was heated at 70 °C for 2 h under vacuum (10-15 mm Hg). Column chromatography (SiO_2 previously washed with 8:2 hexane–Et_3N; 1:1 hexane–EtOAc as eluent) of the residue successively afforded lactams **7d** (4.3 g, 71%) and **8d** (444 mg, 8%).

(3*R*,8*R*,8a*R*)- and **(3*R*,8*S*,8a*S*)-8-[2-(2-Methyl-1,3-dithian-2-yl)ethyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (7e** and **8e).** *Method A*. Operating as in the general procedure, from methyl 4-formyl-6-(2-methyl-1,3-dithian-2-yl)hexanoate[2] (**1e**; 200 mg, 0.7 mmol) and (*R*)-phenylglycinol (115 mg, 0.84 mmol) in toluene (2 mL) for 14 h, lactams **8e** (21.3 mg, 10%) and **7e** (124.8 mg, 61%) were obtained after flash chromatography (1:1 hexane–EtOAc). **7e** (lower R_f): $[\alpha]^{22}_D$ +10.4 (*c* 0.65, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.47–1.60 (m, 2H), 1.64 (s, 3H), 1.80–2.25 (m, 7H), 2.28–2.45 (m, 2H), 2.83–2.88 (m, 4H), 4.01 (dd, *J* = 9.0, 1.5 Hz, 1H), 4.12 (dd, *J* = 9.0, 5.7, 1H), 4.55 (d, *J* = 9.0 Hz, 1H), 4.92 (d, *J* = 5.7 Hz, 1H), 7.21–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 24.5 (CH_2), 25.0 (CH_2), 26.3 (2 CH_2), 26.6 (CH_2), 27.6 (CH_3), 31.2 (CH_2), 38.3 (CH_2), 39.2 (CH), 48.8 (C), 58.6 (CH), 73.6 (CH_2), 92.5 (CH), 126.0 (CH), 127.2 (CH), 128.2 (CH), 141.2 (C), 166.8 (C); IR (film): ν = 1651 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{27}NO_2S_2$: C, 63.62; H, 7.21; N, 3.71; found: C, 63.73; H, 7.32; N, 3.67. **8e** (higher

R_f): m.p. 170–172 °C (THF–Et_2O); $[\alpha]^{22}_D$ –73.8 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.58–1.60 (m, 3H), 1.62 (s, 3H), 1.93–2.07 (m, 6H), 2.40 (m, 1H), 2.59 (dd, *J* = 19.5, 4.8 Hz, 1H), 2.83–2.87 (m, 4H), 3.74 (dd, *J* = 8.7, 7.8 Hz, 1H), 4.48 (dd, *J* = 8.7, 7.8 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 5.24 (t, *J* = 7.8 Hz, 1H), 7.25–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 23.8 (CH_2), 25.3 (CH_2), 26.5 (2 CH_2), 27.3 (CH_2), 27.8 (CH_3), 31.5 (CH_2), 38.6 (CH_2), 39.9 (CH), 49.0 (C), 58.2 (CH), 72.5 (CH_2), 92.9 (CH), 126.0 (CH), 127.5 (CH), 128.7 (CH), 139.4 (C), 168.5 (C); IR (film): ν = 1657 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{27}NO_2S_2$: C, 63.62, H, 7.21; N, 3.71; found: C, 63.67; H, 7.42; N, 3.77.

Method B. Operating as in the above Method B, from methyl 4-formyl-6-(2-methyl-1,3-dithian-2-yl)hexanoate[2] (**1e**; 200 mg, 0.7 mmol), (*R*)-phenylglycinol (3.3 g, 24.4 mmol), and anhydrous Na_2SO_4 (13.5 g, 95 mmol) in Et_2O (80 mL), lactams **8e** (16.7 mg, 8%) and **7e** (99.3 mg, 45%) were obtained after column chromatography (SiO_2 previously washed with 8:2 hexane–Et_3N; 1:1 hexane–EtOAc as eluent).

(3*R*,8*R*,8a*R*)- and **(3*R*,8*S*,8a*S*)-8-Allyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-a]pyridine (7f** and **8f).** Operating as in the above Method B, from methyl 4-formyl-6-heptenoate[3] (**1f**; 4.6 g, 29 mmol), (*R*)-phenylglycinol (3.97

g, 29 mmol), and anhydrous Na_2SO_4 (17 g) in Et_2O (115 mL), lactams **7f** (5.3 g, 71%) and **8f** (753 mg, 10%) were obtained after column chromatography (3:1 hexane–EtOAc to EtOAc). **7f**: $[\alpha]^{22}_D$ –32,8 (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.45 (dddd, *J* = 13.8, 13.8, 12.0, 7.2 Hz, 1H, H-7), 2.02 (m, 3H, H-7, H-8, CH_2), 2.30 (ddd, *J* = 18.0, 12.0, 6.6 Hz, 1H, H-6), 2.42 (ddd, *J* = 18.0, 7.2, 1.8 Hz, 1H, H-6), 2.62 (m, 1H, CH_2), 4.02 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.10 (dd, *J* = 9.0, 6.9 Hz, 1H, H-2), 4.54 (d, *J* = 8.7 Hz, 1H, H-8a), 4.92 (d, *J* = 6.6 Hz, 1H, H-3), 5.12 (m, 2H, CH_2), 5.86 (dddd, *J* = 16.5, 10.2, 7.8, 6.0 Hz, 1H, CH), 7.20–7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ 23.5 (CH), 31.1 (CH□=$_2$), 35.3 (CH_2), 38.9 (CH), 58.8 (CH), 73.5 (CH_2), 91.7 (CH), 117.2 (CH_2), 126.0 (CH), 128.2 (CH), 127.1 (CH), 134.4 (CH), 141.2 (C), 166.9 (C); IR (film): ν = 1655 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{19}NO_2 \cdot 1/4\ H_2O$: C, 73.40, H, 7.51, N, 5.35; found: C, 73.71, H, 7.25, N, 5.41. **8f**: $[\alpha]^{22}_D$ –59.9 (*c* 1.06, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.53 (m, 1H, H-7), 1.66 (m, 1H, H-8), 1.96 (m, 1H, H-7), 2.07 (dt, *J* = 16.5, 8.4 Hz, 1H, CH_2), 2.35 (ddd, *J* = 18.6, 12.0, 6.6 Hz, 1H, H-6), 2.56 (m, 2H, H-6, CH_2), 3.76 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.48 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.71 (d, *J* = 8.4 Hz, 1H, H-8a), 5.13 (m, 2H, CH_2), 5.25 (t, *J* = 7.8 Hz, 1H, H-3), 5.83 (dddd, *J* = 16.5, 10.2,

8.1, 6.0 Hz, 1H, CH), 7.25–7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 22.8 (CH_2), 31.4 (CH_2), 35.9 (CH_2), 39.6 (CH), 58.3 (CH), 72.4 (CH_2), 92.0 (CH), 117.4 (CH_2), 126.0 (CH), 128.6 (CH), 127.5 (CH), 134.6 (CH), 139.4 (C), 168.6 (C); IR (film): ν = 1658 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{19}NO_2 \cdot 1/4\ H_2O$: C, 73.40, H, 7.51, N, 5.35; found: C, 73.27; H, 7.25; N, 5.51.

(3*R*,8*S*,8a*R*)- and **(3*R*,8*R*,8a*R*)-8-Ethyl-5-oxo-3,8a-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (**8a-*epi*-**7g** and **8g**). Operating as in the general procedure, from 4-benzoylhexanoic acid (**1g**; 1 g, 4.5 mmol) and (*R*)-phenylglycinol (623 mg, 4.5 mmol) in toluene (9 mL) for 72 h, lactams **8g** (580 mg, 41%) and 8a-*epi*-**7g** (125 mg, 9%) were obtained after flash chromatography (gradient 4:6 Et_2O–hexane to Et_2O). 8a-*epi*-**7g**: m.p. 115–117°C (THF–hexane); $[\alpha]^{22}_D$ +22.9 (*c* 0.63, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.95 (t, *J* = 8.1 Hz, 3H, CH_3), 1.11 (m, 1H, CH_2), 1.67 (m, 2H, H-7), 1.96–2.05 (m, 2H, H-8, CH_2), 2.39 (ddd, *J* = 11.4, 6.3, 4.5 Hz, 1H, H-6), 2.48 (ddd, *J* = 11.4, 4.5, 1.2 Hz, 1H, H-6), 3.54 (t, *J* = 5.4 Hz, H-2), 4.34 (dd, *J* = 5.4, 4.8 Hz, 1H, H-2), 5.13 (dd, *J* = 5.4, 4.8 Hz, 1H, H-3), 7.12–7.18 (m, 4H, ArH), 7.32–7.37 (m, 4H, ArH), 7.46–7.48 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.7 (CH_3), 17.9 (CH_2), 18.4 (CH_2),

27.2 (CH_2), 44.7 (CH), 61.2 (CH), 69.6 (CH_2), 99.2 (C), 126.9 (CH), 127.7 (CH), 127.3 (CH), 128.2 (CH), 127.9 (CH), 128.0 (CH), 138.0 (C), 143.0 (C), 170.9 (C); IR (film): ν = 1659 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{23}NO \cdot 1/4H_2O$: C, 77.39; H, 7.27; N, 4.30; found: C, 77.55; H, 7.18; N, 4.16. HMRS calcd for $C_{21}H_{23}NO$ 321.1716, found: 321.1728. **8g**: $[\alpha]^{22}_D$ +30.0 (*c* 0.47, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.58 (m, 1H, CH_2), 0.90 (t, *J* = 4.5 Hz, 3H, CH_3), 1.40 (m, 1H, H-7), 1.73–1.87 (m, 3H, H-7, H-8, CH_2), 2.53 (ddd, *J* = 11.4, 6.0, 5.1 Hz, 1H, H-6), 2.74 (dd, *J* = 11.4, 5.1 Hz, 1H, H-6), 3.63 (t, *J* = 5.4 Hz, H-2), 4.40 (dd, *J* = 5.4, 4.8 Hz, 1H, H-2), 5.22 (t, *J* = 5.4 Hz, 1H, H-3), 6.91 (m, 2H, ArH), 7.10 (m, 2H, ArH), 7.33–7.40 (m, 6H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.5 (CH_3), 20.4 (CH_2), 22.9 (CH_2), 31.1 (CH_2), 46.8 (CH), 61.0 (CH), 70.0 (CH_2), 98.8 (C), 127.4 (CH), 127.7 (CH), 127.2 (CH), 128.3 (CH), 127.9 (CH), 128.0 (CH), 137.9 (C), 138.1 (C), 170.2 (C); IR (film): ν = 1658 cm^{-1}; HMRS calcd for $C_{21}H_{23}NO_2$ 321.1717, found 321.1728.

(3*R*,8*S*,8a*R*)- and **(3*R*,8*R*,8a*S*)-8-Ethyl-8a-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (7h** and **8h)**. Operating as in the general procedure, from 4-ethyl-5-oxohexanoic acid[4] (**1h**, 2.9 g, 18.5 mmol) and (*R*)-phenylglycinol (2.5 g, 18.5 mmol) in toluene (37 mL) for 24 h, lactams **7h** (622 mg, 13%) and **8h** (2.2 g, 47%) were obtained

after flash chromatography (SiO_2 previously washed with hexane–Et_3N; gradient 9:1 hexane–EtOAc to EtOAc). **7h**: m.p. 90–92 °C (THF–hexane); $[\alpha]^{22}_D$ –1.82 (*c* 0.86, MeOH); ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (t, *J* = 7.0 Hz, 3H), 1.25 (m, 1H), 1.31 (s, 3H), 1.46 (m, 1H), 1.83 (m, 2H), 2.06 (m, 1H), 2.33 (ddd, *J* = 18.0, 9.0, 9.0 Hz, 1H), 2.40 (ddd, *J* = 18.5, 9.0, 3.0 Hz, 1H), 3.88 (dd, *J* = 9.0, 1.8 Hz, 1H), 4.42 (dd, *J* = 9.0, 7.2 Hz, 1H), 4.92 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 11.8 (CH□=$_3$), 17.9 (CH_3), 22.7 (CH_2), 23.4 (CH_2), 30.0 (CH_2), 45.6 (CH), 58.9 (CH), 71.1 (CH_2), 95.2 (C), 126.0 (CH), 127.0 (CH), 128.2 (CH), 141.5 (C), 166.9 (C); IR (KBr): ν = 1650 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{21}NO_2$: C, 74.10, H, 8.16; N, 5.40; found: C, 74.24; H, 8.24; N, 5.41. **8h**: $[\alpha]^{22}_D$ –160.5 (*c* 0.89, MeOH); ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.01 (t, *J* = 7.2 Hz, 3H), 1.24 (m, 1H), 1.30 (s, 3H), 1.51 (m, 2H), 1.75 (m, 1H), 2.02 (m, 1H), 2.44 (dd, *J* = 18.0, 9.3 Hz, 1H), 2.61 (ddd, *J* = 18.0, 9.3, 2.1 Hz, 1H), 3.92 (dd, *J* = 9.0, 8.1 Hz, 1H), 4.46 (dd, *J* = 9.0, 8.1 Hz, 1H), 5.33 (t, *J* = 8.1 Hz, 1H), 7.19–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.7 (CH_3), 18.5 (CH_3), 21.8 (CH_2), 23.0 (CH_2), 30.5 (CH_2), 46.2 (CH), 58.6 (CH), 69.3 (CH_2), 95.8 (C), 125.1 (CH), 126.7 (CH), 128.2 (CH), 139.6 (C), 168.9 (C); IR (film): ν = 1653 cm^{-1}; elemental analysis

calcd (%) for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.41; found: C, 74.39; H, 8.23; N, 5.57.

(3*R*,7a*S*,11a*R*)- and **(3*R*,7a*R*,11a*S*)-5-Oxo-3-phenyl-2,3,5,6,7,7a,8,9,10,11-decahydrooxazolo[3,2-*j*]quinoline (7i** and **8i).** Operating as in the general procedure, from 3-(2-oxocyclohexyl)propanoic acid[4] (**1i**; 326 mg, 1.9 mmol) and (*R*)-phenylglycinol (526 mg, 3.8 mmol) in toluene (4 mL) for 36 h, lactams **7i** (61 mg, 12%) and **8i** (300 mg, 58%) were obtained after flash chromatography (SiO_2 previously washed with hexane–Et_3N; gradient 4:6 hexane–Et_2O to Et_2O). **7i** (lower R_f): $[\alpha]^{22}_D$ −21.9 (*c* 1.12, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41□=–1.79 (m, 7H), 1.95–2.22 (m, 4H), 2.32 (dd, *J* = 18.0, 8.5 Hz, 1H), 2.42 (ddd, *J* = 18.0, 8.5, 3.0 Hz, 1H), 3.91 (dd, *J* = 9.2, 1.7 Hz, 1H), 4.39 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.94 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.26–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 19.2 (CH_2), 22.2 (CH_2), 22.6 (CH_2), 27.5 (CH_2), 29.5 (CH_2), 30.5 (CH_2), 38.6 (CH), 59.4 (CH), 71.0 (CH_2), 94.2 (C), 126.3 (CH), 127.3 (CH), 128.5 (CH), 142.0 (C), 167.4 (C); IR (film): ν = 1655 cm^{-1}; HMRS calcd for $C_{17}H_{21}NO_2$ 271.1578, found: 271.1572. **8i** (higher R_f): m.p. 90–92 °C (Et_2O–hexane); $[\alpha]^{22}_D$ −129.0 (*c* 1.5, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.40–1.74 (m, 8H), 1.85 (dm, *J* = 14.0 Hz, 1H), 1.93 (m, 1H), 2.14 (m, 1H), 2.48 (ddd, *J* = 18.5, 10.4, 8.0 Hz, 1H), 2.65 (dd, *J* = 18.5, 7.6 Hz, 1H), 3.87 (dd, *J* = 8.8, 8.0

Hz, 1H), 4.50 (t, *J* = 8.8 Hz, 1H), 5.34 (t, *J* = 8.0 Hz, 1H), 7.16–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 19.5 (CH_2), 22.3 (CH_2), 22.4 (CH_2), 27.8 (CH_2), 30.1 (CH_2), 31.0 (CH_2), 39.5 (CH), 58.6 (CH), 69.5 (CH_2), 94.6 (C), 125.2 (CH), 127.0 (CH), 128.4 (CH), 140.0 (C), 169.3 (C); IR (film): ν = 1655 cm^{-1}; X-ray crystal structure: see reference 5; elemental analysis calcd (%) for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80, N, 5.16; found: C, 75.11; H, 7.91; N, 5.19.

(3*R*,8*S*,8a*R*)- and **(3*R*,8*R*,8a*R*)-8-(*tert*-Butylsilyloxy)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (7j** and 8-*epi*-**7j).** Operating as in the general procedure, from methyl 4-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate[6] (**1j**; 1.08 g, 4.15 mmol) and (*R*)-phenylglycinol (0.64 g, 4.57 mmol) in toluene (15 mL) at reflux for 16 h, lactam **7j** (420 mg, 30%), its C_8-epimer (285 mg, 20%), and minor amounts of **8j** (undetermined stereochemistry at C_8) were obtained after flash chromatography (SiO_2 previously washed with hexane–Et_3N; gradient 1:1 hexane–EtOAc to EtOAc as eluent). **7j**: $[\alpha]^{22}_D$ +43.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.17 (s, 3H, CH_3), 0.18 (s, 3H, CH_3), 0.93 (s, 9H, CH_3), 1.82 (dddd, *J* = 13.8, 10.2, 10.2, 7.2 Hz, 1H, H-7), 2.03 (m, 1H, H-7), 2.34 (ddd, *J* = 17.5, 10.2, 6.6 Hz, 1H, H-6), 2.45 (ddd, *J* = 17.5, 7.2, 4.0 Hz, 1H, H-6), 3.96 (ddd, *J* = 10.2, 7.2, 5.4 Hz, 1H, H-8), 4.04 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2),

4.14 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.64 (d, *J* = 7.2 Hz, 1H, H-8a), 4.04 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.14 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.64 (d, *J* = 7.2 Hz, 1H, H-8a), 4.90 (dd, *J* = 6.6, 1.2 Hz, 1H, H-3), 7.27 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = −4.8 (CH_3), −4.5 (CH_3), 18.1 (CH_3), 25.7 (CH_3), 28.3 (CH_2), 30.2 (CH_2), 58.8 (CH), 70.3 (CH), 73.7 (CH_2), 92.1 (CH), 126.3 (CH), 127,4 (CH), 128.4 (CH), 141.1 (CH), 168.8 (C); IR (film): ν = 1665 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{19}NO_3Si$: C, 65.67, H, 8.41, N, 4.03; found: C, 65.67; H, 8.56; N, 4.02. 8-*epi*-**7j**: $[\alpha]^{22}_D$ −6.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.7 (s, 3H, CH_3), 0.17 (s, 3H, CH_3), 0.97 (s, 9H, CH_3), 1.88 (m, 1H, H-7), 2.00 (m, 1H, H-7), 2.28 (ddd, *J* = 18.0, 6.3, 1.2 Hz, 1H, H-6), 2.58 (ddd, *J* = 18.0, 12.6, 7.0 Hz, 1H, H-6), 3.98 (dd, *J* = 8.5, 1.2 Hz, 1H, H-2), 4.15 (dd, *J* = 8.5, 7.2 Hz, 1H, H-2), 4.42 (m, 1H, H-8), 4.78 (d, *J* = 1.8 Hz, 1H, H-8a), 4.89 (dd, *J* = 7.2, 1.2 Hz, 1H, H-3), 7.19–7.45 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = −5,2 (CH_3), −4,4 (CH_3), 18.4 (CH_3), 25.8 (CH_3), 26.4 (CH_2), 26.9 (CH_2), 58.2 (CH), 64.5 (CH), 73,8 (CH_2), 89.7 (CH), 126.3 (CH), 127.1 (CH), 128.1 (CH), 141.5 (C), 167.1 (C); IR (film): ν = 1661 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{19}NO_3Si$: C, 65.67, H, 8.41, N, 4.03; found: C, 65.39; H, 8.45; N, 4.15.

(3*R*,8*S*,8*aR*)- and **(3*R*,8*S*,8*aS*)-8-Acetoxy-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (7k** and 8a-*epi*-**8k).** Operating as in the general procedure, from (*R*)-phenylglycinol (344 mg, 2.42 mmol) and methyl 4-acetoxy-5-oxopentanoate[6] (**1k**, 380 mg, 2.02 mmol) in toluene (6 mL) for 24 h, a mixture of lactams **7k**, 8a-*epi*-**7k** and 8a-*epi*-**8k** in 5:2:2 ratio (248 mg, 45%) was obtained. Flash chromatography (SiO_2 previously washed with hexane–Et_3N; gradient 1:1 hexane–EtOAc to EtOAc as eluent) afforded pure **7k** and 8a-*epi*-**8k**. **7k**: ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 2.15 (s, 3H, CH_3), 3.85 (dd, *J* = 8.1, 2.7 Hz, 1H, H-3), 4.08 (dd, *J* = 9.0, 1.5 Hz, 1H, H-2), 4.19 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 4.92 (d, *J* = 7.5 Hz, 1H, H-8a), 5.15 (ddd, *J* = 9.6, 7.5, 5.1 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 20.9 (CH_3), 24.4 (CH_2), 29.8 (CH_2), 58.6 (CH), 70.8 (CH), 74.0 (CH_2), 89.0 (CH), 170.0 (C), 174.5 (C); IR (film): ν = 1655, 1738 cm^{-1}. 8a-*epi*-**8k**: ^1H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 1.82 (s, 3H, CH_3), 3.86 (dd, *J* = 7.8, 1.8 Hz, 1H, H-2), 4.52 (dd, *J* = 8.4, 6.6 Hz, 1H, H-2), 4.91 (dd, *J* = 6.6, 1.8 Hz, 1H, H-3), 5.31 (dd, *J* = 8.4, 5.4 Hz, 1H, H-8), 5.58 (bs, 1H, H-8a), 7.17–7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 23.0 (CH_2), 23.6 (CH_3), 27.8 (CH_2), 61.0 (CH), 76.3 (CH_2), 78.0 (CH), 91.2 (CH), 169.6 (C), 177.3 (C); IR (film): ν = 1655, 1774 cm^{-1}.

(3*R*,8*R*,8a*S*)- and **(3*R*,8*S*,8a*S*)-8a-(Benzyloxymethyl)-8-[(2-methoxyethoxy)methoxy]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-a]pyridine (8l** and 8-*epi*-**8l).** Operating as in the general procedure, from 6-(benzyloxy)-4-[(2-methoxyethoxy)methoxy]-5-oxohexanoic acid[6] (**1l**; 6 g, 17.6 mmol) and (*R*)-phenylglycinol (2.9 g, 21.2 mmol) in toluene (180 mL) for 12 h, a mixture of lactams **8l** and its C_8 epimer (5.6 g, 72%, 3:2 ratio), and lactam **7l** (191 mg, 2%) were obtained after flash chromatography (6:4 hexane–EtOAc to EtOAc). **8l**: ^{1}H NMR ($CDCl_3$, 200 MHz, selected resonances) δ = 3.38 (s, 3H), 3.57 (m, 2H), 3.73 (m, 2H), 3.96 (dd, *J* = 8.8, 6.8 Hz, 1H), 4.50 (d, *J* = 9.5 Hz, 1H); 4.53 (dd, *J* = 8.8, 6.8 Hz, 1H), 4.56 (s, 2H), 4.83 (d, *J* = 6.6 Hz, 1H), 4.97 (dd, *J* = 8.0, 3.5 Hz, 1H), 5.03 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): □ = 22.5 (CH_2), 29.2 (CH_2), 58.9 (CH_3), 59.1 (CH), 67.0 (CH_2), 68.1 (CH_2), 70.9 (CH_2), 71.5 (CH_2), 73.3 (CH_2), 76.0 (CH), 93.7 (C), 94.5 (CH_2), 125.8 (CH), 127.1 (CH), 127.6 (CH), 128.2 (CH), 125.3 (CH), 127.7 (CH), 137.1 (C), 139.6 (C), 169.2 (C). 8-*epi*-**8l**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.20 (m, 2H), 2.47 (m, 2H), 3.38 (d, *J* =10.4 Hz, 1H), 3.40 (s, 3H), 3.48 (d, *J* =10.4 Hz, 1H), 3.58 (m, 2H), 3.73 (m, 2H), 4.09 (dd, *J* = 8.8, 5.8 Hz, 1H), 4.38 (d, *J* = 12.2 Hz, 1H), 4.40 (dd, *J* = 8.8, 7.4 Hz, 1H), 4.45 (masked, 1H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.92 (d, *J* = 7.0 Hz, 1H), 5.43 (dd, *J* = 7.4, 5.8 Hz, 1H), 7.30 (m, 10H);

^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 21.8 (CH_2), 26.4 (CH_2), 58.8 (CH), 58.9 (CH_3), 66.9 (CH_2), 70.3 (CH_2), 70.7 (CH), 71.5 (CH_2), 71.6 (CH_2), 73.3 (CH_2), 95.0 (C), 95.6 (CH_2), 127.1 (CH), 127.6 (CH), 128.3 (CH), 128.5 (CH), 127.3 (CH), 127.8 (CH), 137.5 (C), 139.7 (C), 170.2 (C). **71**: $[\alpha]^{22}_D$ –32.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.96 (m, 1H, H-7), 2.11 (m, 1H, H-7), 2.36 (m, 2H, H-6), 3.39 (s, 3H, CH_3), 3.59 (m, 2H, CH_2), 3.62 (d, *J* = 10.0 Hz, 1H, CH_2), 3.73 (m, 2H, CH_2), 3.89 (dd, *J* = 8.7, 2.5 Hz, 1H, H-2), 3.91 (d, *J* = 10.0 Hz, 1H, CH_2), 4.15 (dd, *J* = 11.1, 6.7 Hz, 1H, H-8), 4.50 (dd, *J* = 8.7, 7.8 Hz, H-2), 4.54 (s, 2H, CH_2), 4.81 (d, *J* = 6.9 Hz, 1H, CH_2), 4.97 (dd, *J* = 7.8, 2.5 Hz, 1H, H-3), 5.02 (d, *J* = 6.9 Hz, 1H, CH_2), 7.29 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 23.9 (CH_2), 29.7 (CH_2), 58.8 (CH_3), 59.8 (CH), 66.9 (CH_2), 69.2 (CH_2), 71.5 (CH_2), 73.4 (CH_2), 73.5 (CH_2), 76.2 (CH), 93.8 (C), 94.7 (CH_2), 126.1 (CH), 127.2 (CH), 128.2 (CH), 128.3 (CH), 127.3 (CH), 127.5 (CH), 137.3 (C), 141.1 (C), 167.3 (C).

Methyl (3*R*,7*S*,8a*R*)- and **(3*R*,7*R*,8a*S*)-5-Oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (9m** and **10m).** Operating as in the general procedure, from (*R*)-phenylglycinol (39.6 mg, 0.29 mmol) and dimethyl 3-(2-oxoethyl)glutarate[7] (**1m**, 70 mg, 0.35 mmol) in toluene (15 mL) for 8 h, lactams **9m** (19.6 mg, 20%) and **10m** (60.2 mg, 75%)

were obtained after flash chromatography (Et_2O). **10m** (higher R_f): $[\alpha]^{22}_D$ −77.2 (*c*, 0.55, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.36 (td, *J* = 12.5, 9.5 Hz, 1H), 2.04 (dd, *J* = 17.5, 7.5 Hz, 1H), 2.35–2.46 (m, 4H), 2.66 (ddd, *J* = 17.5, 5.0, 1.5 Hz, 1H), 3.67 (s, 3H), 3.75 (dd, *J* = 9.0, 8.0 Hz, 1H), 4.48 (dd, *J* = 9.0, 8.0 Hz, 1H), 5.00 (dd, *J* = 9.5, 6.0 Hz, 1H), 5.20 (t, *J* = 8.0 Hz, 1H), 7.23–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 26.6 (CH), 34.4 (CH_2), 37.6 (CH_2), 39.6 (CH_2), 51,7 (CH_3), 57.9 (CH), 72.6 (CH_2), 87.9 (CH), 126.0 (CH), 127.6 (CH), 128.7 (CH), 139.2 (C), 167.6 (C), 171.7 (C); IR (film): ν = 1732, 1677 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{19}NO_4$: C, 65.60; H, 6.83; N, 4.43; found: C, 65.42; H, 6.62; N, 4.84. **9m** (lower R_f): $[\alpha]^{22}_D$ −56.0 (*c*, 0.74, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.55 (td,□= *J* = 12.0, 9.0 Hz, 1H), 1.96 (dd, *J* = 17.5, 10.5 Hz, 1H), 2.38–2.45 (m, 3H), 2.46 (dm, *J* = 12.0 Hz, 1H), 2.51 (ddd, *J* = 17.5, 5.0, 1.0 Hz, 1H), 3.67 (s, 3H), 3.99 (dd, *J* = 9.0, 1.0 Hz, 1H), 4.14 (dd, *J* = 9.0, 7.0 Hz, 1H), 4.86 (m, 2H), 7.24–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 27.4 (CH), 34.2 (CH_2), 37.5 (CH_2), 39.9 (CH_2), 51.7 (CH_3), 58.6 (CH), 73.9 (CH_2), 88.1 (CH), 126.3 (CH), 127.5 (CH), 128.5 (CH), 141,2 (C), 165.8 (C), 171.7 (C); IR (film): ν = 1732, 1677 cm^{-1}; HMRS calcd for $C_{16}H_{19}NO_4$ 289.1319, found 289,1314.

Ethyl (3*R*,7*S*,8a*R*)- and **(3*R*,7*R*,8a*S*)-8a-Methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (9n** and **10n)**. Operating as in the general procedure, a mixture of (*R*)-phenylglycinol (2.7 g, 19.6 mmol), diethyl 3-acetonylglutarate[8] (**1n**; 4 g, 16.4 mmol), and a few drops of *p*-TsOH in toluene (33 mL) was stirred at reflux for 18 h. The solvent was eliminated under reduced pressure, and the residue was dissolved in EtOAc and washed with 5% aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried, and evaporated. Flash chromatography (1:9 hexane–EtOAc) of the residue afforded lactams **9n** (912 mg, 16%) and **10n** (3.4 g, 61%). **9n**: $[\alpha]^{22}_D$ –19.6 (*c* 0.35, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.26 (t, *J* = 7.2 Hz, 3H), 1.51 (s, 3H), 1.73 (t, *J* = 12.3 Hz, 1H), 1.95 (dd, *J* = 20.0, 12.0 Hz, 1H), 2.36 (dd, *J* = 12.3, 4.8 Hz, 1H), 2.39 (d, *J* = 6.3 Hz, 2H), 2.50–2.68 (m, 2H), 3.96 (dd, *J* = 9.5, 2.0 Hz, 1H), 4.14 (m, 2H), 4.49 (dd, *J* = 9.5, 7.2 Hz, 1H), 4.92 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.20–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.1 (CH_3), 23.5 (CH_3), 27.2 (CH), 36.9 (CH_2), 40.6 (CH_2), 40.9 (CH_2), 58.8 (CH), 60.6 (CH_2), 71.4 (CH_2), 93.0 (C), 126.2 (CH), 127.4 (CH), 128.5 (CH), 141.4 (C), 165.9 (C), 171.4 (C); IR (film): ν = 1666, 1739 cm^{-1}; HMRS calcd for $C_{18}H_{23}NO_4$ 317.1627, found 317.1627. **10n**: m.p. 49–51 °C (THF–hexane); $[\alpha]^{22}_D$ –188.0 (*c*

1.05, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.27 (t, *J* = 7.2 Hz, 3H), 1.47 (s, 3H), 1.53 (t, *J* = 12.6 Hz, 1H), 2.10 (dd, *J* = 18.0, 10.2 Hz, 1H), 2.26 (ddd, *J* = 12.6, 2.7, 1.8 Hz, 1H), 2.40 (d, *J* = 7.2 Hz, 2H), 2.60 (m, 1H), 2.83 (dd, *J* = 18.0, 6.3 Hz, 1H), 3.96 (dd, *J* = 10.8, 8.1 Hz, 1H), 4.15 (m, 2H), 4.52 (t, *J* = 9.0, 1H), 5.35 (t, *J* = 8.4 Hz, 1H), 7.17–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.1 (CH_3), 24.0 (CH_3), 26.7 (CH), 37.3 (CH_2), 40.4 (CH_2), 41.3 (CH_2), 58.4 (CH), 60.6 (CH_2), 69.7 (CH_2), 93.5 (C), 125.4 (CH), 127.2 (CH), 128.6 (CH), 139.7 (C), 168.6 (C), 171.3 (C); IR (film): ν = 1665, 1739 cm^{-1}; X-ray crystal structure: see reference 5; elemental analysis calcd (%) for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41; found: C, 68.07; H, 7.35; N, 4.36.

Ethyl (3*R*,7*S*,8*S*,8a*R*)- and **(3*R*,7*R*,8*R*,8a*S*)-8-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (9o** and **10o)**. Operating as in the general procedure, from (*R*)-phenylglycinol (21 mg, 0.15 mmol) and diethyl 3-(1-formylpropyl)glutarate[7] (**1o**; 40 mg, 0.15 mmol) in toluene (1 mL) for 14 h, lactams **9o** (30 mg, 61%) and **10o** (9 mg, 16%) were obtained after flash chromatography (hexane). **9o**: $[\alpha]^{22}_{D}$ –25.3 (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz, COSY): δ = 1.01 (t, *J* = 7.2 Hz, 3H, CH_3), 1.22 (t, *J* = 7.0 Hz, 3H, CH_3), 1.65–1.77 (m, 3H, CH_2, H-8), 2.12 (dd, *J* = 10.2, 5.2 Hz, 1H, H-6), 2.18 (dd, *J* = 9.3, 5.2 Hz, 1H, CH_2), 2.27 (m, 1H, H-7), 2.51

(dd, J = 9.3, 2.7 Hz, 1H, CH_2), 2.53 (dd, J = 10.2, 3.6 Hz, H-6), 4.01 (dd, J = 8.5, 1.5 Hz, 1H, H-2), 4.10 (q, J = 7.0 Hz, 2H, CH_3), 4.15 (dd, J = 8.5, 7.0 Hz, 1H, H-2), 4.65 (d, J = 8.5 Hz, H-8a), 4.91 (dd, J = 6.5, 1.5 Hz, 1H, H-3), 7.21–7.33 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 9.8 (CH_3), 14.2 (CH_3), 21.6 (CH_2), 31.2 (CH), 37.4 (CH_2), 38.2 (CH_2), 44.1 (CH), 58.7 (CH), 60.7 (CH_2), 70.4 (CH_2), 90.7 (CH), 126.3 (CH), 127.5 (CH), 128.5 (CH), 141.1 (C), 166.2 (C), 171.6 (C); IR (film): ν = 1731, 1665 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{27}NO_4 \cdot 1/4\ H_2O$: C, 67.67; H, 7.94; N, 4.22; found: C, 67.94; H, 7.65; N, 4.17. **10o**: $[\alpha]^{22}_D$ –46.1 (*c* 3.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.02 (t, J = 7.5 Hz, 3H), 1.27 (t, J = 7.8 Hz), 1.51–1.85 (m, 3H), 2.10–2.25 (m, 2H), 2.33 (m, 1H), 2.60 (dd, J = 14.7, 3.6 Hz, 1H), 2.73 (dd, J = 17.0, 4.8 Hz, 1H), 3.76 (dd, J = 8.7, 8.0 Hz, 1H), 4.11–4.19 (m, 2H), 4.48 (dd, J = 8.0, 8.7 Hz, 1H), 4.81 (d, J = 8.7 Hz, 1H), 5.26 (t, J = 8.0 Hz, 1H), 7.24–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 9.8 (CH_3), 14.1 (CH_3), 20.9 (CH_2), 29.9 (CH), 37.1 (CH_2), 37.6 (CH_2), 43.7 (CH), 58.2 (CH), 60.8 (CH_2), 72.5 (CH_2), 90.8 (CH), 126.0 (CH), 127.6 (CH), 128.8 (CH), 139.3 (C), 167.7 (C), 171.7 (C); IR (film): ν = 1731, 1665 cm^{-1}.

Ethyl (3*R*,7*S*,8*S*,8a*R*)- and **(3*R*,7*R*,8*R*,8a*S*)-8a-Methyl-5-oxo-3-phenyl-8-propyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2*a*] pyridine-7-acetate (9p** and **10p).** Operating as in the general procedure, from (*R*)-phenylglycinol (384 mg, 2.8 mmol), ethyl 3-(ethoxycarbonylmethyl)-4-propyl-5-oxohexanoate[4] (**1p**; 670 mg, 2.34 mmol), and AcOH (0.63 mL, 1.17 mmol) in toluene (5 mL) for 24 h, lactams **9p** (50 mg, 5%) and **10p** (410 mg, 49%) were obtained after flash chromatography (hexane). **9p**: $[\alpha]^{22}_{D}$ −17.5 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.97 (t, *J* = 6.9 Hz, 3H, CH_3), 1.23 (t, *J* = 7.2 Hz, 3H), 1.40 (s, 3H), 1.43–1.79 (m, 5H), 2.13 (dd, *J* = 17.7, 5.4 Hz, 1H), 2.18–2.28 (m, 2H), 2.57 (m, 1H), 2.64 (dd, *J* = 17.7, 7.2 Hz, 1H), 3.97 (dd, *J* = 9.3, 2.1 Hz, 1H), 4.09 (qd, *J* = 7.2, 2.4 Hz, 2H), 4.44 (dd, *J* = 9.3, 6.9 Hz, 1H), 4.95 (d, *J* = 6.9 Hz, 1H), 7.26–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.2 (CH_3), 14.5 (CH_3), 18.8 (CH_3), 22.2 (CH_2), 32.9 (CH_2), 33.1 (CH), 36.7 (CH_2), 40.0 (CH_2), 48.8 (CH), 58.9 (CH), 60.7 (CH_2), 71.3 (CH_2), 95.7 (C), 126.3 (CH), 127.3 (CH), 128.4 (CH), 141.3 (C), 166.2 (C), 171.9 (C); IR (film): ν = 1663, 1732 cm^{-1}; HMRS calcd for $C_{21}H_{29}NO_4$ 359.2093, found 359.2096. **10p**: $[\alpha]^{22}_{D}$ −57.7 (*c* 0.88, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.92 (t, *J* = 7.2 Hz, 3H, CH_3), 1.28 (t, *J* = 6.9 Hz, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.40–1.58 (m, 5H, CH_2CH_2, H-8), 2.18 (dd, *J* = 17.5, 7.0 Hz, 1H, H-6), 2.22 (dd, *J* = 14.7, 9.6 Hz,

1H, CH_2), 2.50 (m, 1H, H-7), 2.64 (dd, *J* = 14.7, 2.7 Hz, 1H, CH_2), 2.82 (dd, *J* = 17.5, 6.6 Hz, 1H, H-6), 3.96 (dd, *J* = 9.3, 7.2 Hz, 1H, H-2), 4.17 (q, *J* = 6.9 Hz, 2H, CH_2), 4.41 (dd, *J* = 9.3, 8.4 Hz, 1H, H-2), 5.31 (t, *J* = 7.2 Hz, 1H, H-3), 7.21–7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.2 (CH_3), 14.5 (CH_3), 19.6 (CH_3), 22.3 (CH_2), 31.8 (CH_2), 31.9 (CH), 37.4 (CH_2), 39.0 (CH_2), 48.4 (CH), 58.7 (CH), 60.7 (CH_2), 69.6 (CH_2), 96.4 (C), 125.6 (CH), 127.2 (CH), 128.5 (CH), 139.5 (C), 168.1 (C), 171.9 (C); IR (film): ν = 1738 cm^{-1}; HMRS calcd for $C_{21}H_{29}NO_4$ 359.2093, found 359.2096; elemental analysis calcd (%) for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90; found: C, 70.56; H, 8.06; N, 4.25.

Methyl (3*R*,7*S*,8*S*,8a*R*)- and **(3*R*,7*R*,8*R*,8a*S*)-8-Ethyl-8a-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (9q** and **10q).** Operating as in the general procedure, a mixture of (*R*)-phenylglycinol (1.45 g, 10 mmol), dimethyl 3-(1-ethyl-2-oxopropyl)pentadionate[7] (**1q**; 2.16 g, 8.85 mmol), and AcOH (0.25 mL, 4.4 mmol) in toluene (25 mL) was stirred at reflux for 66 h. The solvent was eliminated under reduced pressure, and the residue was dissolved in EtOAc and washed with 5% aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried, and evaporated. Flash chromatography (gradient 5:1 to 1:1 hexane–

EtOAc) afforded lactams **9q** (530 mg, 18%) and **10q** (1.83 g, 63%). **10q** : $[\alpha]^{22}_{D}$ +71.5 (*c* 0.63, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.06 (t, *J* = 7.2 Hz, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.42–1.55 (m, 2H, H-8, CH_2), 1.59–1.67 (m, 1H, CH_2), 2.20 (dd, *J* = 17.2, 7.2 Hz, 1H, H-6), 2.22–2.35 (m, 2H, H-7, CH_2), 2.65 (dd, *J* = 14.8, 2.8 Hz, 1H, CH_2), 2.80 (dd, *J* = 17.2, 6.8 Hz, H-6), 3.71 (s, 3H, CH_3O), 3.98 (dd, *J* = 8.8, 6.8 Hz, 1H, H-2), 4.42 (dd, *J* = 8.8, 8.0 Hz, 1H, H-2), 5.32 (dd, *J* = 8.0, 6.8 Hz, 1H, H-3), 7.23–7.27 (m, 3H, ArH), 7.31–7.35 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 13.6 (CH_3), 19.4 (CH_3), 22.2 (CH_2), 31.6 (CH), 37.2 (CH_2), 38.5 (CH_2), 50.0 (CH), 51.6 (CH_3), 58.4 (CH), 69.4 (CH_2), 96.3 (C), 125.4 (CH), 127.0 (CH), 128.3 (CH), 139.4 (C), 167.8 (C), 172.1 (C); IR (film): ν = 1658, 1735 cm^{-1}; HMRS calcd for $C_{19}H_{25}NO_4$ 331.1784, found 331.1773; elemental analysis calcd (%) for $C_{19}H_{25}NO_4$: C, 68.80; H, 7.60; N, 4.23; found: C, 68.04; H, 8.06; N, 4.15.

Methyl (3*R*,8*R*,8a*R*)- and **(3*R*,8*S*,8a*S*)-5-Oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-8-propionate (9r** and **10r)**. Operating as in the general procedure, from dimethyl 4-formylpimelate[4] (**1r**; 500 mg, 2.3 mmol) and (*R*)-phenylglycinol (317 mg, 2.3 mmol) in toluene (4.6 mL) for 20 h, a mixture of lactams **9r** (434.8 mg, 65%), and **10r** (12 mg, 2%, 9:1 ratio) were obtained after flash chromatography (SiO_2

previously washed with 7:3 hexane–Et_3N; 9:1 hexane–EtOAc as eluent). **9r**: $[\alpha]^{22}_D$ –60.9 (*c* 0.8, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, COSY): δ = 1.52 (dddd, *J* = 13.5, 11.5, 11.5, 6.5 Hz, 1H, H-7), 1.77 (m, 1H, H-1′), 1.91 (m, 1H, H-8), 1.99 (m, 1H, H-7), 2.05 (m, 1H, H-1′), 2.32 (ddd, *J* = 18.0, 11.5, 6.5 Hz, 1H, H-6), 2.42 (ddd, *J* = 18.0, 6.5, 2.5 Hz, 1H, H-6), 2.57 (td, *J* = 9.0, 6.5 Hz, 2H, 2H-2′), 3.70 (s, 3H, CH_3), 4.02 (dd, *J* = 5.7, 2.0 Hz, 1H, H-2), 4.11 (dd, *J* = 9.5, 5.7 Hz, 1H, H-2), 4.54 (d, *J* = 9.0 Hz, 1H, H-8a), 4.91 (d, *J* = 5.7 Hz, 1H, H-3), 7.23–7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 24.4 (CH_2), 26.8 (CH_2), 30.9 (CH_2), 31.2 (CH_2), 38.6 (CH), 51.4 (CH_3), 58.5 (CH), 73.5 (CH_2), 92.4 (CH), 126.0 (CH), 127.2 (CH), 128.2 (CH), 141.1 (C), 166.8 (C), 173.4 (C); IR (film) ν = 1663, 1735 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{21}NO_4$: C, 65.61; H, 6.98; N, 4.62; found: C, 65.66; H, 7.01; N, 4.64. **10r**: $[\alpha]^{22}_D$ –64.5 (*c* 0.4, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, COSY): δ = 1.50–1.82 (m, 3H, H-7, H-8, CH_2), 1.84–2.08 (m, 2H, H-7, CH_2), 2.30–2.62 (m, 4H, H-6, CH_2), 3.69 (s, 3H, CH_3), 3.73 (t, *J* = 8.1 Hz, 1H, H-2), 4.47 (t, *J* = 8.1 Hz, 1H, H-2), 4.70 (d, *J* = 7.8 Hz, 1H, H-8a), 5.22 (t, *J* = 8.1 Hz, 1H, H-3), 7.24–7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 23.8 (CH_2), 27.5 (CH_2), 31.2 (CH_2), 31.4 (CH_2), 39.1 (CH), 51.6 (CH_3), 58.0 (CH), 72.4 (CH), 92.8 (CH), 125.9 (CH), 127.5 (CH), 128.6 (CH), 139.3 (C), 168.3 (C), 173.5

(C); IR (film): ν = 1651, 1735 cm^{-1}; HMRS calcd for $C_{17}H_{21}NO_4$ 303.1468, found: 303.1470.

Method B. A mixture of dimethyl 4-formylpimelate[4] (**1r**; 640 mg, 2.9 mmol), (*R*)-phenylglycinol (398 mg, 2.9 mmol), and anhydrous Na_2SO_4 (800 mg) in Et_2O (10 mL) was stirred at 0 °C for 2 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was heated at 100 °C for 4 h under vacuum (10–15 mm Hg). Column chromatography (SiO_2 previously washed with 7:3 hexane–Et_3N; 9:1 hexane–EtOAc as eluent) of the residue afforded lactams **9r** (497 mg, 58%) and **10r** (50 mg, 6%).

Methyl (3*R*,8*R*,8a*R*)- and **(3*R*,8*S*,8a*S*)-8-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-8-propionate (9s and 10s).** Operating as in the general procedure, from dimethyl 4-ethyl-4-formylpimelate[9] (**1s**; 450 mg, 2.3 mmol) and (*R*)-phenylglycinol (272 mg, 1.9 mmol) in toluene (4 mL) for 24 h, a 1:1 mixture of lactam **10s** and its C_8-epimer **10s'** (higher R_f, 25 mg, 4%) and a 1:1 mixture of lactam **9s** and its C_8-epimer **9s'** (lower R_f, 225 mg, 37%) were obtained after flash chromatography (SiO_2 previously washed with 7:3 hexane–Et_3N; gradient 7:3 hexane–EtOAc to EtOAc as eluent). **9s**: ^1H NMR ($CDCl_3$, 300 MHz, from a mixture of **9s** and **9s'**) δ = 0.89 (t, *J* = 7.5 Hz, 3H), 1.48 (ddd, *J* = 14.4, 8.1, 3.0 Hz, 1H),

1.56–1.64 (m, 3H), 1.73 (m, 1H), 1.81 (ddd, *J* = 14.4, 5.7, 3.0 Hz, 1H), 2.15 (dd, *J* = 4.5, 2.1 Hz, 1H), 2.22–2.31 (m, 2H), 2.57 (dd, *J* = 4.5, 3.0 Hz, 1H), 3.69 (s, 3H), 4.11 (masked, 2H), 4.63 (s, 1H), 4.82 (t, *J* = 4.8 Hz, 1H), 7.21–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, from a mixture of **9s** and **9s'**) δ = 6.7 (CH_3), 17.5 (CH_2), 28.0 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 28.9 (CH_2), 37.9 (C), 51.5 (CH_3), 57.7 (CH), 73.6 (CH_2), 94.9 (CH), 127.2 (CH), 127.3 (CH), 128.1 (CH), 140.8 (C), 166.9 (C), 173.9 (C). **9s'**: ^{1}H NMR ($CDCl_3$, 300 MHz, from a mixture of **9s** and **9s'**) δ = 1.00 (t, *J*= 7.8 Hz, 3H), 1.51 (masked, 1H), 1.56–1.64 (m, 3H), 1.73 (m, 1H), 1.92 (td, *J*= 11.1, 5.4 Hz, 1H), 2.22–2.31 (m, 2H), 2.42 (ddd, *J*= 16.5, 11.1, 5.4 Hz, 1H), 2.68 (ddd, *J*= 16.5, 11.1, 5.4 Hz, 1H), 3.69 (s, 3H, CH_3), 4.11 (dd, *J*= 6.9, 5.4 Hz, 2H), 4.63 (s, 1H), 4.88 (dd, *J*= 5.4, 3.6 Hz, 1H), 7.21–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, from a mixture of **9s** and **9s'**) δ = 7.8 (CH_3), 22.5 (CH_2), 28.4 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 31.2 (CH_2), 37.6 (C), 51.6 (CH_3), 57.9 (CH), 73.6 (CH_2), 94.8 (CH), 127.2 (CH), 127.4 (CH), 128.2 (CH), 140.7 (C), 166.9 (C), 173.7 (C); HMRS calcd for $C_{19}H_{25}NO_4$ (a mixture of **9s** and **9s'**) 331.1783, found 331,1774. **10s**: ^{1}H NMR ($CDCl_3$, 300 MHz, from a mixture of **10s** and **10s'**) δ = 0.66 (t, *J* = 7.8 Hz, 3H), 1.29–1.60 (m, 4H), 1.68 (td, *J* = 11.1, 5.7 Hz, 1H), 1.74 (td, *J* =

5.4, 1.5 Hz, 1H), 1.98–2.27 (m, 3H), 2.42 (td, *J* = 11.1, 5.7 Hz, 1H), 3.46 (masked, 1H), 3.49 (s, 3H), 4.22 (dd, *J* = 14.4, 7.5 Hz, 1H), 4.67 (s, 1H), 4.97 (dd, *J* = 14.4, 7.5 Hz, 1H), 7.04–7.17 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, from a mixture of **10s** and **10s'**) δ = 6.5 (CH_3), 16.9 (CH_2), 26.8 (CH_2), 27.9 (CH_2), 28.9 (CH_2), 31.4 (CH_2), 38.0 (C), 51.6 (CH_3), 58.0 (CH), 72.3 (CH_2), 94.6 (CH), 126.0 (CH), 127.5 (CH), 128.6 (CH), 139.2 (C), 168.1 (C), 174.0 (C). **10s'**: ^{1}H NMR ($CDCl_3$, 300 MHz, from a mixture of **10s** and **10s'**) δ = 0.79 (t, *J*= 7.8 Hz, 3H), 1.29–1.60 (m, 4H), 1.77–1.86 (m, 2H), 1.98–2.27 (m, 3H), 2.41 (masked, 1H), 3.49 (s, 3H), 3.55 (td, *J*= 7.5, 2.4 Hz, 1H), 4.26 (dd, *J*= 9.3, 7.5 Hz, 1H), 4.65 (s, 1H), 5.05 (dd, *J*= 17.0, 9.3 Hz, 1H), 7.04–7.17 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, from a mixture of **10s** and **10s'**) δ = 8.0 (CH_3), 21.7 (CH_2), 26.9 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 29.2 (CH_2), 37.7 (C), 51.6 (CH_3), 58.1 (CH), 72.2 (CH_2), 94.1 (CH), 125.9 (CH), 127.5 (CH), 128.6 (CH), 139.3 (C), 168.0 (C), 173.9 (C).

(4*RS*,9a*SR*)- and **(4*RS*,9a*RS*)-6-Oxo-4-phenylperhydropyrido [2,1-*b*][1,3]oxazine (*rac*-24a** and ***rac*-24b**). Operating as in the general procedure, from methyl 5-oxopentanoate (**1a**; 1.02 g, 7.57 mmol) and 3-amino-3-phenyl-1-propanol[10] (***rac*-19**; 1.29 g, 8.3 mmol) in toluene (20 mL) for 36 h, lactams ***rac*-24a** (831 mg, 47%) and ***rac*-24b** (363 mg, 21%, 2.3:1 ratio) were obtained after flash chromatography (SiO_2 previously washed

with 1:1 hexane–Et_2NH; gradient 2:1 to 1:1 hexane–EtOAc as eluent). *rac*-**24a**: ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.68 (m, 1H, H-8), 1.82 (m, 1H, H-9), 1.90 (m, 1H, H-9), 1.95 (m, 1H, H-8), 2.24–2.25 (m, 2H, H-3), 2.49 (m, 2H, H-7), 3.82 (td, *J* = 11.4, 4.2 Hz, 1H, H-2), 3.93 (ddd, *J* = 11.4, 4.8, 2.4 Hz, 1H, H-2), 4.76 (t, *J* = 4.2 Hz, 1H, H-9a), 6.11 (bs, 1H, H-4), 7.20–7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 16.7 (CH_2), 27.0 (CH_2), 28.8 (CH_2), 32.7 (CH_2), 48.7 (CH), 63.5 (CH_2), 81.4 (CH), 126.3 (CH), 128.4 (CH), 126.5 (CH), 138.1 (C), 169.5 (C); IR (film): ν = 1650 cm^{-1}; HMRS calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1259. *rac*-**24b**: m.p. 80–82 °C (hexane); ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.70–1.83 (m, 2H, H-8, H-9), 1.95 (m, 1H, H-8), 1.98 (dddd, *J* = 14.4, 6.4, 2.7, 1.2 Hz, 1H, H-3), 2.20 (m, 1H, H-9), 2.41 (m, 2H, H-7), 2.58 (dddd, *J* = 14.4, 12.0, 7.5, 4.8 Hz, 1H, H-3), 3.67 (ddd, *J* = 12.0, 10.2, 6.3 Hz, 1H, H-2), 3.95 (m, 1H, H-2), 5.15 (dd, *J* = 9.0, 4.3 Hz, 1H, H-9a), 5.38 (dd, *J* = 4.8, 2.7 Hz, 1H, H-4), 7.18–7.38 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 17.4 (CH_2), 27.8 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 53.2 (CH), 60.7 (CH_2), 81.0 (CH), 125.9 (CH), 128.0 (CH), 126.5 (CH), 141.5 (C), 168.6 (C); IR (KBr): ν = 1642 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; found: C, 72.58; H, 7.29; N, 6.19.

9-Ethyl-6-oxo-4-phenylperhydropyrido[2,1-*b*][1,3]oxazine (*rac*-25). Operating as in the general procedure, from methyl 4-formylhexanoate[1] (**1d**; 725 mg, 4.59 mmol) and aminoalcohol *rac*-**19**[10] (769 mg, 5.05 mmol) in toluene (20 mL) for 36 h, lactams *rac*-**25a** (1:1 mixture of C_9 epimers; 466 mg, 39%) and *rac*-**25b** (368 mg, 31%) were obtained after flash chromatography (3:1 to 1:2 hexane–EtOAc). *rac*-**25a** (9-H / 9a-H *trans*): m.p. 49–50 °C (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.91 (t, J = 7.5 Hz, 3H, CH_3), 1.27 (m, 1H, CH_2), 1.48 (m, 1H, H-9), 1.55 (m, 1H, H-8), 1.65 (m, 1H, CH_2), 1.99 (dddd, J = 14.4, 5.7, 5.7, 3.6 Hz, 1H, H-8), 2.23–2.37 (m, 2H, H-3), 2.45 (ddd, J = 17.4, 9.5, 5.4 Hz, 1H, H-7), 2.61 (ddd, J = 17.4, 5.4, 4.8 Hz, 1H, H-7), 3.77 (td, J = 11.4, 4.2 Hz, 1H, H-2), 3.94 (dm, J = 11.4 Hz, 1H, H-2), 4.41 (d, J = 5.7 Hz, 1H, H-9a), 6.11 (bs, 1H, H-4), 7.18–7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 11.2 (CH_3), 21.5 (CH_2), 24.0 (CH_2), 27.3 (CH_2), 31.0 (CH_2), 40.7 (CH), 48.5 (CH), 63.5 (CH_2), 86.6 (CH), 126.4 (CH), 128.7 (CH), 126.7 (CH), 138.2 (C), 170.0 (C); IR (KBr): ν = 1654 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{21}NO_2 \cdot 1/4\ Et_2O$: C, 73.48; H, 8.52; N, 5.04; found: C, 73.45; H, 8.26; N, 5.24. *rac*-**25a** (9-H / 9a-H *cis*): ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.86 (t, J =7.5 Hz, 3H, CH_3), 1.32 (m, 1H, CH_2), 1.42 (m, 1H, CH_2), 1.61 (m, 1H, H-9), 1.68 (m, 1H, H-8), 1.81 (qd, J = 13.0, 5.1

Hz, 1H, H-8), 2.22 (m, 1H, H-3), 2.32 (m, 1H, H-3), 2.45 (ddd, *J* = 17.7, 12.3, 6.3 Hz, 1H, H-7), 2.63 (ddd, *J* = 17.7, 4.8, 2.1 Hz, 1H, H-7), 3.87 (td, *J* = 11.5, 3.6 Hz, 1H, H-2), 4.01 (ddd, *J* = 11.5, 4.2, 2.4 Hz, 1H, H-2), 4.56 (d, *J* = 3.3 Hz, 1H, H-9a), 6.12 (d, *J* =4.2 Hz, 1H, H-4), 7.24–7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 11.4 (CH_3), 22.0 (CH_2), 23.4 (CH_2), 27.3 (CH_2), 32.7 (CH_2), 39.8 (CH), 50.1 (CH), 64.5 (CH_2), 83.2 (CH), 126.6 (CH), 128.6 (CH), 126.7 (CH), 138.6 (C), 170.3 (C); IR (film): ν = 1654 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40; found: C, 73.70; H, 8.29; N, 5.27. *rac*-**25b**: ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.99 (t, *J* =7.5 Hz, 3H, CH_3), 1.22 (m, 1H, CH_2), 1.43 (m, 1H, H-8), 1.68 (m, 1H, H-9), 1.86 (m, 1H, CH_2), 1.97 (m, 2H, H-3, H-8), 2.44 (m, 2H, H-7), 2.56 (m, 1H, H-3), 3.64 (ddd, *J* = 12.3, 10.2, 6.6 Hz, 1H, H-2), 3.92 (dd, *J* = 10.2, 8.1 Hz, 1H, H-2), 4.75 (d, *J* = 8.7 Hz, 1H, H-9a), 5.40 (dd, *J* = 4.8, 2.4 Hz, 1H, H-4), 7.18–7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 10.8 (CH_3), 22.6 (CH_2), 23.6 (CH_2), 27.6 (CH_2), 31.6 (CH_2), 41.0 (CH), 53.1 (CH), 60.8 (CH_2), 84.8 (CH), 125.9 (CH), 128.0 (CH), 126.4 (CH), 141.6 (C), 168.5 (C); IR (film): ν = 1650 cm^{-1}; HMRS calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1572.

(6*RS*,11a*SR*)-6-Methyl-4-oxo-1,2,3,4,6,11a-hexahydropyrido [2,1-*b*]-1,3-benzoxazine (*rac*-26). Operating as in the general procedure, from methyl 5-oxopentanoate (**1a**; 500 mg, 3.85 mmol) and 2-(1-aminoethyl)phenol[11] (*rac*-**20**; 594 mg, 4.33 mmol) in toluene (15 mL) for 24 h, lactam *rac*-**26** (725 mg, 88%) was obtained after flash chromatography (SiO_2 previously washed with 1:1 hexane-Et_3N; 10:1 hexane–EtOAc as eluent): m.p. 99–101 °C (hexane); ^1H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 1.52 (d, J = 6.6 Hz, 3H, CH_3), 1.79 (m, 1H, H-2), 2.04 (m, 2H, H-1, H-2), 2.27 (m, 1H, H-1), 2.39 (ddd, J =18.0, 10.8, 5.4 Hz, 1H, H-3), 2.52 (dddd, J = 18.0, 4.8, 4.2, 1.8 Hz, 1H, H-3), 5.23 (t, J = 3.6 Hz, 1H, H-9a), 5.65 (q, J = 6.6 Hz, 1H, H-10), 6.84 (dd, J = 7.8, 1.2 Hz, 1H, H-8), 6.95 (td, J = 7.8, 1.2 Hz, 1H, H-6), 7.10 (dt, J = 7.8, 0.6 Hz, 1H, H-5), 7.13 (tdd, J = 7.8, 1.2, 0.6 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 16.3 (CH_2), 21.7 (CH_3), 28.0 (CH_2), 32.7 (CH_2), 46.5 (CH), 78.3 (CH), 116.9 (CH), 121.5 (CH), 125.1 (C), 127.5 (CH), 127.8 (CH), 153.2 (C), 168.7 (C); IR (KBr): ν = 1638 cm^{-1}; X-ray crystal structure: see reference 5; elemental analysis calcd (%) for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45; found: C, 71.95; H, 6.91; N, 6.47.

(1*RS*,6*SR*,11a*RS*)- and **(1*RS*,6*RS*,11a*SR*)-1-Ethyl-6-methyl-4-oxo-1,2,3,4,6,11a-hexahydropyrido[2,1-*b*]-1,3-benzoxazine** (*rac*-**27a** and *rac*-**27b**). Operating as in the general procedure, from methyl 4-ethyl-5-oxopentanoate[1] (**1d**; 250 mg, 1.58 mmol) and aminophenol *rac*-**20**[11] (286 mg, 1.74 mmol) in toluene (6 mL) for 20 h, a 1:1 mixture of lactams *rac*-**27a** and *rac*-**27b** (313 mg, 76%) was obtained after flash chromatography (SiO_2 previously washed with 1:1 hexane–Et_3N; 95:5 hexane–EtOAc as eluent). *rac*-**27a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.05 (t, *J* = 7.5 Hz, 3H), 1.50 (d, *J* = 6.9 Hz, 3H), 1.52 (m, 2H), 1.74 (m, 1H), 2.08 (m, 2H), 2.39 (ddd, *J* = 17.7, 7.2, 5.1 Hz, 1H), 2.50 (ddd, *J* = 17.7, 8.1, 5.4 Hz, 1H), 4.92 (d, *J* = 4.2 Hz, 1H), 5.64 (q, *J* = 6.9 Hz, 1H), 6.85 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.96 (td, *J* = 7.8, 1.2 Hz, 1H), 7.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.5 (CH_3), 21.0 (CH_2), 21.6 (CH_3), 23.5 (CH_2), 30.0 (CH_2), 39.0 (CH), 46.3 (CH), 83.2 (CH), 116.8 (CH), 121.5 (CH), 125.1 (C), 127.4 (CH), 127.6 (CH), 152.9 (C), 168.8 (C); IR (film): ν = 1661 cm^{-1}; HMRS calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1415. *rac*-**27b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.03 (t, *J* = 7.5 Hz, 3H), 1.53 (d, *J* = 6.9 Hz, 3H), 1.50–2.00 (m, 5H), 2.43 (ddd, *J* = 18.0, 12.3, 6.3 Hz, 1H), 2.56 (ddd, *J* = 18.0, 5.4, 1.8 Hz, 1H), 5.08 (bs, 1H), 5.69 (q, *J* = 6.9 Hz, 1H), 6.85 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.95 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.09-7–16 (m, 2H); ^{13}C NMR

($CDCl_3$, 75.4 MHz): δ = 11.6 (CH_3), 21.7 (CH_2), 21.8 (CH_3), 23.7 (CH_2), 32.6 (CH_2), 39.5 (CH), 47.1 (CH), 79.9 (CH), 117.1 (CH), 121.4 (CH), 125.5 (C), 127.5 (CH), 127.6 (CH), 153.6 (C), 169.0 (C); IR (film): ν = 1661 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71; found: C, 73.31; H, 7.92; N, 5.59.

(6*RS*,11a*SR*)-6,11a-Dimethyl-4-oxo-1,2,3,4,6,11a-hexahydro-pyrido[2,1-*b*]-1,3-benzoxazine (*rac*-28). Operating as in the general procedure, from 5-oxohexanoic acid (**1t**; 500 mg, 3.84 mmol) and aminophenol *rac*-**20**[11] (562 mg, 4.11 mmol) in toluene (15 mL) for 24 h, lactam *rac*-**28** (690 mg, 77%) was obtained after flash chromatography (SiO_2 previously washed with 1:1 hexane–Et_3N; 1:1 hexane–EtOAc as eluent): m.p. 83–85 °C (hexane); ^1H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 1.61 (s, 3H, CH_3), 1.64 (d, *J* = 7.2 Hz, 3H, CH_3), 1.75 (m, 1H, H-2), 1.95 (m, 1H, H-2), 2.11 (dddd, *J* = 13.2, 8.4, 4.2, 0.6 Hz, 1H, H-1), 2.21 (ddd, *J* = 13.2, 8.4, 3.6 Hz, 1H, H-1), 2.45 (ddd, *J* = 18.0, 7.2, 5.4 Hz, 1H, H-3), 2.50 (dddd, *J* = 18.0, 7.2, 5.4, 0.6 Hz, 1H, H-3), 5.56 (q, *J* = 7.2 Hz, 1H, H-10), 6.81 (dd, *J* = 7.8, 1.2 Hz, 1H, H-8), 6.98 (td, *J* = 7.8, 1.8 Hz, 1H, H-6), 7.14 (tm, *J* = 7.8 Hz, 1H, H-7), 7.17 (dm, *J* = 7.8 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.6 (CH_2), 21.3 (CH_3), 26.1 (CH_3), 33.2 (CH_2), 37.3 (CH_2), 46.1 (CH), 86.5 (C), 117.3 (CH), 121.6 (CH), 124.7 (CH), 126.6 (CH),

127.7 (CH), 150.3 (C), 169.2 (C); IR (KBr): ν = 1645 cm^{-1}; HMRS calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1259; X-ray crystal structure: see reference 5; elemental analysis calcd (%) for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; found: C, 72.76; H, 7.68; N, 6.04.

(1*RS*,6*SR*,11a*RS*)- and **(1*RS*,6*RS*,11a*SR*)-1-Ethyl-6,11a-dimethyl-4-oxo-1,2,3,4,6,11a-hexahydropyrido[2,1-*b*]-1,3-benzoxazine (*rac*-29a** and ***rac*-29b).** Operating as in the general procedure, from 4-ethyl-5-oxohexanoic acid [4] (**1h**; 209 mg, 1.32 mmol) and aminophenol *rac*-**20**[11] (200 mg, 1.46 mmol) in toluene (8 mL) for 20 h, a 9:1 mixture of lactams *rac*-**29a** and *rac*-**29b** (155.4 mg, 45%) was obtained after flash chromatography (SiO_2 previously washed with 1:1 hexane–Et_3N; gradient hexane to 19:1 hexane–EtOAc as eluent). *rac*-**29a**: ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.04 (t, *J* = 7.2 Hz, CH_3), 1.48 (m, 2H, H-1, CH_2), 1.61 (s, 3H, CH_3), 1.68 (d, *J* = 6.9 Hz, 3H, CH_3), 1.69 (m, 1H, H-2), 1.74 (m, 1H, H-2), 1.91 (m, 1H, CH_2), 2.37 (ddd, *J* = 17.7, 9.8, 6.0 Hz, 1H, H-3), 2.55 (td, *J* = 17.7, 5.0 Hz, 1H, H-3), 5.54 (q, *J* = 6.9 Hz, 1H, H-10), 6.80 (dd, *J* = 8.1, 1.2 Hz, 1H, ArH), 6.97 (td, *J* = 7.5, 1.2 Hz, 1H, ArH), 7.10–7.18 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 12.4 (CH_3), 20.1 (CH_2), 21.0 (CH_2), 21.5 (CH_3), 24.9 (CH_3), 31.8 (CH_2), 46.3 (CH), 46.8 (CH), 88.1 (C), 117.3 (CH), 121.4 (CH), 124.8 (C), 126.4 (CH), 127.5

(CH), 150.4 (C), 169.4 (C); IR (KBr): ν = 1647 film; HMRS calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1571.

(1*RS*,6*RS*,11a*SR*)- and **(1*RS*,6*SR*,11a*RS*)-6,11a-Dimethyl-4-oxo-1-phenyl-1,2,3,4,6,11a-hexahydropyrido[2,1-*b*]-1,3-benzoxazine (*rac*-30a** and ***rac*-30b).** Operating as in the general procedure, from 5-oxo-4-phenylhexanoic acid[12] (**1u**; 260 mg, 1.26 mmol) and aminophenol *rac*-**20**[11] (137 mg, 1.39 mmol) in toluene (2 mL) for 26 h, a 9:1 mixture of lactams *rac*-**30a** and *rac*-**30b** (163 mg, 42%) was obtained after flash chromatography (Et_2O). *rac*-**30a** (selected resonances): ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.53 (s, 3H, CH_3), 1.72 (d, *J* = 7.2 Hz, 3H, CH_3), 1.84 (m, 1H, H-2), 2.42–2.60 (m, 2H, H-2, H-3), 2.65 (dm, *J* = 17.8 Hz, 1H, H-3), 3.09 (dd, *J* = 12.0, 2.4 Hz, 1H, H-1), 5.71 (q, *J* = 7.2 Hz, 1H, H-10), 6.70 (dd, *J* = 8.0, 0.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 21.3 (CH_3), 23.5 (CH_2), 24.7 (CH_3), 33.7 (CH_2), 47.6 (CH), 51.6 (CH), 86.9 (C), 169.7 (C); IR (KBr): ν = 1647 cm^{-1}; HMRS calcd for $C_{20}H_{21}NO_2$ 307.1572, found 307.1572. *rac*-**30b** (selected resonances): ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.27 (s, 3H, CH_3), 1.65 (d, *J* = 6.8 Hz, 3H, CH_3), 2.06 (m, 1H, H-2), 2.76 (ddd, *J* = 17.6, 5.2, 2.0 Hz, 1H, H-3), 3.37 (dd, *J* = 13.2, 2.4 Hz, 1H, H-1), 5.57 (q, *J* = 6.8 Hz, 1H, H-10), 6.77 (dd, *J* = 8.0, 0.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 20.4

(CH_3), 21.5 (CH_3), 22.2 (CH_2), 33.0 (CH_2), 46.0 (CH), 50.1 (CH), 89.2 (C), 168.1 (C); IR (KBr): ν = 1647 cm^{-1}.

Ethyl (2*RS*,6*SR*,11a*RS*)- and **(2*RS*,6*RS*,11a*SR*)-6,11a-Dimethyl-4-oxo-1,2,3,4,6,11a-hexahydropyrido[2,1-*b*]-1,3-benzoxazine-2-acetate** (*rac*-**31a** and *rac*-**31b**). Operating as in the general procedure, aminophenol *rac*-**20**[11] (305 mg, 2.23 mmol) and a few drops of *p*-TsOH were added to a solution of diethyl 3-acetonylglutarate[8] (**1n**; 501 mg, 2.03 mmol) in toluene (5 mL), and the mixture was stirred at reflux for 24 h. The solvent was eliminated under reduced pressure, and the residue was dissolved in EtOAc and washed with 5% aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried, and evaporated. Flash chromatography (hexane to 10:1 hexane–EtOAc) of the residue afforded a 3:2 mixture of lactams *rac*-**31a** and *rac*-**31b** (243 mg, 37%). *rac*-**31** (selected resonances from the mixture of epimers): ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.27 and 1.28 (2t, J = 7.2 Hz, 3H), 1.61 and 1.64 (2s, 3H), 1.62 and 1.67 (2d, J = 6.8 Hz, 3H), 5.48 and 5.62 (q, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1 (CH_3), 21.1 (CH_3), 21.2 (CH_3), 26.9 (CH_3), 38.7 (CH_2), 38,9 (CH_2), 39.4 (CH_2), 39.5 (CH_2), 45,5 (CH), 46,9 (CH), 60.5 (CH_2), 60.6 (CH_2); 85,6 86,5 (C), 167.3 (CH), 168.8 (CH), 171.1 (C), 171.3 (C); IR

(KBr): ν = 1647 cm-1; HMRS calcd for $C_{18}H_{23}NO_4$ (mixture of epimers) 317.1627, found 317.1627.

(5a*S*,10a*R*,11a*S*)- and **(5a*S*,10a*R*,11a*R*)-4-Oxo-1,2,3,4,5a, 10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo[3,2-*a*]pyridine (32a** and **32b).** Operating as in the general procedure, from methyl 5-oxopentanoate (**1a**; 159 mg, 1.22 mmol) and (1*S*,2*R*)-*cis*-1-amino-2-indanol (**21**; 201 mg, 1.35 mmol) in toluene (5 mL) for 18 h, lactams **32a** (148 mg, 54%) and **32b** (45.5 mg, 16%), were obtained after flash chromatography (SiO_2 previously washed with 1:1 hexane–Et_3N; gradient 4:1 to 2:1 hexane–EtOAc as eluent). **32a**: $[\alpha]^{22}_D$ +265.6 (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.44 (m, 1H, H-1), 1.71 (m, 1H, H-2), 1.94 (m, 1H, H-2), 2.17 (m, 1H, H-1), 2.34 (ddd, *J* = 18.0, 11.0, 6.8 Hz, 1H, H-3), 2.43 (ddd, *J* = 18.0, 6.8, 2.4 Hz, 1H, H-3), 3.20 (bs, 2H, H-9), 4.81 (ddd, *J* = 5.6, 4.4, 2.4 Hz, 1H, H-9a), 4.85 (dd, *J* = 10.0, 3.2 Hz, 1H, H-10a), 5.50 (d, *J* = 5.6 Hz, 1H, H-4b), 7.18–7.27 (m, 3H, H-6, H-7, H-8), 8.00 (d, *J* = 7.6 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 17.7 (CH_2), 28.0 (CH_2), 31.0 (CH_2), 36.4 (CH_2), 64.3 (CH), 81.1 (CH), 88.5 (CH), 124.8 (CH), 127.3 (CH), 128.5 (CH), 128.6 (CH), 140.1 (C), 141.4 (C), 168.3 (C); IR (film): ν = 1650 cm^{-1}; HMRS calcd for $C_{14}H_{15}NO_2$ 229.1103, found 229.1104. **32b**: m.p. 97–99 °C (hexane); $[\alpha]^{22}_D$ +275.7 (*c* 0.26, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR):

δ = 1.52 (m, 1H, H-1), 1.61 (dddd, *J* = 16.0, 11.0, 6.0, 2.6 Hz, 1H, H-2), 1.88 (m, 1H, H-2), 2.22 (m, 1H, H-1), 2.34 (ddd, *J* = 17.4, 11.0, 6.0 Hz, 1H, H-3), 2.47 (dm, *J* = 17.6 Hz, 1H, H-3), 3.14 (dd, *J* = 18.0, 2.4 Hz, 1H, H-9), 3.34 (dd, *J* = 18.0, 7.4 Hz, 1H, H-9), 4.70 (dd, *J* = 8.2, 4.2 Hz, 1H, H-10a), 5.05 (ddd, *J* = 7.4, 6.8, 2.4 Hz, 1H, H-9a), 5.92 (d, *J* = 6.8 Hz, 1H, H-4b), 7.19–7.30 (m, 3H, H-6, H-7, H-8), 7.60 (d, *J* = 6.8 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 17.2 (CH_2), 28.2 (CH_2), 31.2 (CH_2), 38.7 (CH_2), 62.4 (CH), 79.2 (CH), 84.9 (CH), 124.5 (CH), 126.6 (CH), 127.6 (CH), 128.8 (CH), 139.6 (C), 141.5 (C), 167.6 (C); IR (KBr): ν = 1651 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11; found: C, 73.66; H, 6.74; N, 5.78.

(1*R*,5a*S*,10a*R*,11a*S*)- and **(1*S*,5a*S*,10a*R*,11a*R*)-1-Ethyl-4-oxo-1,2,3,4,5a,10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo[3,2-*a*]pyridine (33a** and **33b).** Operating as in the general procedure, from methyl 4-formylhexanoate[1] (**1d**; 191 mg, 1.21 mmol) and aminoindanol **21** (200 mg, 1.33 mmol) in toluene (4 mL) for 10 h, lactams **33a** (132 mg, 42%), 11a-*epi*-**33b** (53.5, 17%) and **33b** (86 mg, 28%) were obtained after flash chromatography (Et_2O). **33a**: m.p. 65–66 °C (hexane); $[\alpha]^{22}_D$ +196.2 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 0.90 (t, *J* = 7.8 Hz, 3H, CH_3), 1.21 (m, 1H, CH_2), 1.35 (m, 1H, H-2), 1.44 (m, 1H, H-1), 1.71 (m, 1H, CH_2), 1.94 (dddd, *J*

= 13.6, 7.2. 3.6, 2.4 Hz, 1H, H-2), 2.37 (ddd, *J* = 18.0, 11.4, 7.2 Hz, 1H, H-3), 2.45 (ddd, *J* = 18.0, 6.6, 2.4 Hz, 1H, H-3), 3.18 (d, *J* = 3.5 Hz, 2H, H-9), 4.50 (d, *J* = 9.0 Hz, 1H, H-10a), 4.76 (ddd, *J* = 6.0, 3.5, 3.5 Hz, 1H, H-9a), 5.48 (d, *J* = 6.0 Hz, 1H, H-4b), 7.16–7.24 (m, 3H, H-6, H-7, H-8), 7.97 (d, *J* = 5.2 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 10.7 (CH_3), 23.7 (CH_2), 23.8 (CH_2), 31.4 (CH_2), 36.4 (CH_2), 40.4 (CH), 64.5 (CH), 81.0 (CH), 92.2 (CH), 124.8 (CH), 127.3 (CH), 128.5 (CH), 128.7 (CH), 140.2 (C), 141.5 (C), 168.3 (C); IR (KBr): ν = 1647 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; found: C, 74.73; H, 7.48; N, 5.41. 11a-*epi*-**33b**: $[\alpha]^{22}_D$ +260.3 (*c* 0.69, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.75 (m, 4H, CH_3, CH_2), 1.18 (m, 1H, CH_2), 1.74 (m, 1H, H-2), 1.89 (m, 1H, H-2), 2.01 (m, 1H, H-1), 2.33 (m, 2H, H-3), 3.18 (bs, 2H, H-9), 4.80 (ddd, *J* = 5.6, 3.6, 2.0 Hz, 1H, H-9a), 5.02 (d, *J* = 3.6 Hz, 1H, H-10a), 5.52 (d, *J* = 5.6 Hz, 1H, H-4b), 7.17–7.27 (m, 3H, H-6, H-7, H-8), 7.92 (d, *J* = 7.2 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 11.2 (CH_3), 15.6 (CH_2), 21.1 (CH_2), 27.4 (CH_2), 36.4 (CH_2), 36.4 (CH), 64.2 (CH), 81.0 (CH), 90.4 (CH), 124.6 (CH), 127.3 (CH), 128.2 (CH), 128.3 (CH), 140.1 (C), 141.2 (C), 168.3 (C); IR (film) 1651 cm^{-1}; HMRS calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1416. **33b**: m.p. 80–81 °C (hexane); $[\alpha]^{22}_D$ +242.8 (*c* 0.51, $CHCl_3$); ^{1}H NMR

($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 0.95 (t, *J* = 7.5 Hz, 3H, CH_3), 1.26 (m, 2H, H-2, CH_2), 1.44 (m, 1H, H-1), 1.69 (m, 1H, CH_2), 1.85 (dddd, *J* = 13.8, 6.6, 3.0, 1.8 Hz, 1H, H-2), 2.35 (ddd, *J* = 18.0, 12.0, 6.0 Hz, 1H, H-3), 2.50 (ddd, *J* = 18.0, 5.4, 1.8 Hz, 1H, H-3), 3.12 (dd, *J* = 18.0, 2.4 Hz, 1H, H-9), 3.31 (dd, *J* = 18.0, 7.5 Hz, 1H, H-9), 4.32 (d, *J* = 7.8 Hz, 1H, H-10a), 5.02 (ddd, *J* = 7.5, 6.6, 2.4 Hz, 1H, H-9a), 5.87 (d, *J* = 6.6 Hz, 1H, H-4b), 7.17 (d, *J* = 7.2 Hz, 1H, H-8), 7.21–7.27 (m, 2H, H-6, H-7), 7.58 (dt, *J* = 7.2, 0.6 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 11.0 (CH_3), 22.9 (CH_2), 24,7 (CH_2), 31,4 (CH_2), 38.8 (CH_2), 41.2 (CH), 62.5 (CH), 79.1 (CH), 89.0 (CH), 124.5 (CH), 126.7 (CH), 127.6 (CH), 128.8 (CH), 139.7 (C), 141.5 (C), 167.5 (C); IR (KBr): ν = 1645 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; found: C, 74.46; H, 7.42; N, 5.42.

Methyl (2*R*,5a*S*,10a*R*,11a*S*)- and **(2*S*,5a*S*,10a*R*,11a*R*)-4-Oxo-1,2,3,4,5a,10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo[3,2-*a*]pyridine-2-acetate (34a and 34b).** Operating as in the general procedure, from dimethyl 3-(2-oxoethyl)pentadionate[7] (**1m**, 256 mg, 1.27 mmol) and aminoindanol **21** (208 mg, 1.39 mmol) in toluene (5 mL) for 6 h, lactams **34a** (256 mg, 61%), and **34b** (71 mg, 17%) were obtained after flash chromatography (Et_2O). **34a**: $[\alpha]^{22}_D$ +149.9 (*c* 0.71, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.28 (td, *J* = 12.0, 10.0 Hz, 1H, H-

1), 2.07 (dd, J = 17.2, 10.4 Hz, 1H, H-3), 2.25 (dm, J = 12.0 Hz, 1H, H-1), 2.34 (m, 2H, CH_2), 2.40 (m, 1H, H-2), 2.60 (ddd, J = 17.2, 6.0, 1.2 Hz, 1H, H-3), 3.20 (bs, 2H, H-9), 3.68 (s, 3H, CH_3), 4.84 (ddd, J = 6.0, 4.0, 2.0 Hz, 1H, H-9a), 4.91 (dd, J = 10.0, 3.2 Hz, 1H, H-10a), 5.49 (d, J = 6.0 Hz, 1H, H-4b), 7.18–7.28 (m, 3H, H-6, H-7, H-8), 8.00 (d, J = 7.2 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 27.4 (CH), 34.1 (CH_2), 36.5 (CH_2), 37.5 (CH_2), 40.0 (CH_2), 51.7 (CH_3), 64.3 (CH), 81.5 (CH), 87.8 (CH), 124.8 (CH), 127.4 (CH), 128.6 (CH), 128.7 (CH), 140.2 (C), 141.1 (C), 166.8 (C), 171.8 (C); IR (film): ν = 1650, 1731 cm^{-1}; HMRS calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1314. **34b:** ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.32 (td, J = 12.4, 9.2 Hz, 1H, H-1), 2.07 (dd, J = 17.6, 11.6 Hz, 1H, H-3), 2.28 (m, 2H, H-1, H-2), 2.35 (m, 2H, CH_2), 2.62 (ddd, J = 17.6, 4.8, 2.0 Hz, 1H, H-3), 3.16 (dd, J = 18.0, 2.0 Hz, 1H, H-9), 3.33 (dd, J = 18.0, 7.2 Hz, 1H, H-9), 3.67 (s, 3H, CH_3), 4.75 (dd, J = 9.2, 4.4 Hz, 1H, H-10a), 5.07 (ddd, J = 7.2, 7.2, 2.0 Hz, 1H, H-9a), 5.89 (d, J = 7.2 Hz, 1H, H-4b), 7.19–7.29 (m, 3H, H-6, H-7, H-8), 7.58 (d, J = 6.8 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 26.6 (CH), 34.2 (CH_2), 37.4 (CH_2), 38.7 (CH_2), 39.6 (CH_2), 51.7 (CH_3), 62.3 (CH), 79.5 (CH), 84.3 (C), 124.5 (CH), 126.6 (CH), 127.7 (CH), 128.9 (CH), 139.4 (C),

141.4 (C), 166.3 (C), 171.7 (C); IR (film): ν = 1650, 1735 cm^{-1}; HMRS calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1314.

(5a*S*,10a*R*,11a*S*)- and **(5a*S*,10a*R*,11a*R*)-11a-Methyl-4-oxo-1,2,3,4,5a,10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo[3,2-*a*]pyridine (35a** and **35b).** Operating as in the general procedure, from 5-oxohexanoic acid (**1t**; 162 mg, 1.20 mmol) and aminoindanol **21** (200 mg, 1.33 mmol) in toluene (4 mL) for 15 h, lactams **35a** (29 mg, 9%) and **35b** (white solid, 288 mg, 90%) were obtained after flash chromatography (SiO_2 previously washed with 1:1 hexane–Et_3N; EtOAc as eluent). **35a:** ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.46 (s, 3H), 5.06 (td, *J* = 5.4, 0.6 Hz, 1H), 5.58 (d, *J* = 5.4 Hz, 1H), 7.19–7.28 (m, 3H), 8.03 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): = 16.8 (CH□$_2$), 23.5 (CH_3), 29.6 (CH_2), 34.2 (CH_2), 36.8 (CH_2), 64.3 (CH), 78.3 (CH), 93.3 (C), 124.7 (CH), 125.8 (CH), 127.1 (CH), 128.8 (CH), 140.3(C), 141.2 (C), 168.3 (C); IR (film): ν = 1650 cm^{-1}. **35b**: m.p. 67–68 °C (hexane); $[\alpha]^{22}_D$ +283.1 (*c* 0.51, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.98 (s, 3H), 1.62 (m, 1H), 1.75 (m, 1H), 1.92 (m, 1H), 2.04 (m, 1H), 2.41 (ddd, *J* = 18.0, 9.6, 7.8 Hz, 1H), 2.54 (ddd, *J* = 18.0, 7.8, 3.0 Hz, 1H), 3.19 (dd, *J* = 17.7, 1.8 Hz, 1H), 3.32 (dd, *J* = 17.7, 6.6 Hz, 1H), 4.93 (td, *J* = 6.6, 1.8 Hz, 1H), 6.02 (d, *J* = 6.6 Hz, 1H), 7.20–7.30 (m, 3H), 7.53 (dm, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 17.1 (CH_2), 26.9 (CH_3), 30.0 (CH_2),

35.7 (CH_2), 40.0 (CH_2), 63.8 (C), 79.1 (CH), 94.0 (C), 124.9 (CH), 125.9 (CH), 127.4 (CH), 128.5 (CH), 140.7(C), 141.8 (C), 167.8 (C); IR (film) 1648 cm^{-1}; HMRS calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1259.

(1*S*,5a*S*,10a*R*,11a*R*)-1-Ethyl-11a-methyl-4-oxo-1,2,3,4,5a, 10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo[3,2-*a*]pyridine (36b). Operating as in the general procedure, from 4-ethyl-5-oxohexanoic acid[4] (**1h**; 139 mg, 0.88 mmol) and aminoindanol **21** (144 mg, 0.97 mmol) in toluene (4 mL) for 8 h, lactams **36a** (19 mg, 8%) and **36b** (145 mg, 61%) were obtained after flash chromatography (SiO_2 previously washed with 1:1 hexane–Et_3N; 5:4 hexane–EtOAc as eluent). **36b:** m.p. 114–115 °C (hexane); $[\alpha]^{22}_D$ +259.9 (*c* 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 0.84 (s, 3H, CH_3), 0.98 (t, *J* = 7.5 Hz, 3H, CH_3), 1.11 (m,1H, CH_2), 1.31 (dddd, *J* = 14.0, 13.0, 9.6, 8.4 Hz, 1H, H-2), 1.48 (m, 1H, H-1), 1.73 (m, 1H, CH_2), 1.97 (dddd, *J* = 14.0, 8.1, 4.2, 2.4. 1H, H-2), 2.46 (ddd, *J* = 18.6, 9.6, 8.4 Hz, 1H, H-3), 2.57 (ddd, *J* = 18.6, 8.4, 2.4 Hz, 1H, H-3), 3.17 (dm, *J* = 17.0 Hz, 1H, H-9), 3.29 (dd, *J* = 17.7, 6.3 Hz, 1H, H-9), 4.88 (td, *J* = 6.3, 1.5 Hz, 1H, H-9a), 5.98 (d, *J* = 6.3 Hz, 1H, H-4b), 7.19–7.30 (m, 3H, H-6, H-7, H-8), 7.55 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 11.9 (CH_3), 21.9 (CH_2), 22.0 (CH_3), 23.1 (CH_2), 30.2 (CH_2), 39.8 (CH_2), 46.6 (CH), 64.1 (CH), 78.9 (CH), 96.1 (C), 124.9 (CH), 125.9

(CH), 127.4 (CH), 128.4 (CH), 140.6 (C), 142.0 (C), 167.8 (C); IR (film): ν = 1647 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16; found: C, 75.12; H, 7.70; N, 5.13

(1*S*,5a*S*,10a*R*,11a*S*)- and **(1*R*,5a*S*,10a*R*,11a*R*)-11a-Methyl-1-phenyl-4-oxo-1,2,3,4,5a,10,10a,11a–octahydroindeno[1′,2′:4,5] oxazolo[3,2-*a*]pyridine (37a** and **37b).** Operating as in the general procedure, from 4-phenyl-5-oxohexanoic acid[12] (**1u**; 255 mg, 1.24 mmol) and aminoindanol **21** (203 mg, 1.36 mmol) in toluene (4 mL) for 24 h, lactams **37a** (25 mg, 6%) and **37b** (308 mg, 77%) were obtained after flash chromatography (EtOAc). **37a:** m.p. 177–179 °C (hexane–acetone); $[\alpha]^{22}_D$ +8.5 (*c* 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.29 (s, 3H, CH_3), 2.00–2.07 (m, 1H, H-2), 2.24–2.36 (m, 1H, H-2), 2.58 (ddd, *J* = 18.0, 8.8, 8.8 Hz, 1H, H-3), 2.66 (ddd, *J* = 18.0, 8.8, 2.4 Hz, 1H, H-3), 2.95 (dd, *J* = 13.2, 4.4 Hz, 1H, H-1), 3.21–3.22 (m, 2H, H-9), 4.98–5.00 (m, 1H, H-9a), 5.63 (d, *J* = 6.0 Hz, 1H, H-4b), 7.21–7.33 (m, 8H, ArH), 8.09 (d, *J* = 7.6 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 19.1 (CH_3), 22.5 (CH_2), 30.6 (CH_2), 37.1 (CH_2), 49.4 (CH), 64.8 (CH), 75.5 (CH), 95.1 (C), 124.9 (CH), 127.3 (CH), 127.4 (CH), 128.1 (CH), 128.7 (CH), 128.9 (CH), 129.1 (CH), 138.5 (C), 140.8 (C), 141.3 (C), 168.0 (C); IR (KBr): ν = 1640 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63;

N, 4.39; found: C, 78.98; H, 6.54; N, 4.25. **37b**: m.p. 113–114 °C (hexane); $[\alpha]^{22}_{D}$ +65.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.76 (s, 3H, CH_3), 2.04 (dddd, *J* = 13.5, 8.1, 3.6, 1.8 Hz, 1H, H-2), 2.20 (dddd, *J* = 13.5, 13.5, 10.2, 7.8 Hz, 1H, H-2), 2.61 (ddd, *J* = 18.6, 10.2, 8.1 Hz, 1H, H-3), 2.76 (ddd, *J* = 18.6, 7.8, 1.8 Hz, 1H, H-3), 2.99 (dd, *J* = 13.5, 3.6 Hz, 1H, H-1), 3.11 (d, *J* = 17.7 Hz, 1H, H-9), 3.28 (dd, *J* = 17.7, 6.6 Hz, 1H, H-9), 5.04 (td, *J* = 6.6, 1.5 Hz, 1H, H-9a), 6.07 (d, *J* = 6.6 Hz, 1H, H-4b), 7.14–7.35 (m, 8H, ArH), 7.58 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 22.4 (CH_2), 22.5 (CH_3), 30.7 (CH_2), 39.9 (CH_2), 50.1 (CH), 64.3 (CH), 79.1 (CH), 95.6 (C), 124.8 (CH), 125.9 (CH), 127.1 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 128.8 (CH), 138.8 (C), 140.7 (C), 141.8 (C), 167.4 (C); IR (KBr): ν = 1650 cm^{-1}; X-ray crystal structure: see reference 5; elemental analysis calcd (%) for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39; found: C, 78.82; H, 6.65; N, 4.39.

Ethyl (2*R*,5a*S*,10a*R*,11a*S*)- and (2*S*,5a*S*,10a*R*,11a*R*)-11a-Methyl-4-oxo-1,2,3,4,5a,10,10a,11a-octahydroindeno[1′,2′:4,5]oxazolo[3,2-*a*]pyridine-2-acetate (38a and **38b)**. Operating as in the general procedure, from diethyl 3-acetonylglutarate[8] (**1n**; 200 mg, 0.82 mmol) and aminoindanol **21** (134 mg, 0.90 mmol) in toluene (4 mL) for 24 h, lactams **38a** (63 mg, 23%) and **38b** (112 mg, 41%) were obtained after flash

chromatography (5:1 hexane–EtOAc to EtOAc). **38a**: $[\alpha]^{22}_{D}$ +9.7 (*c* 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.23 (t, *J* = 7.2 Hz, 3H, CH_3), 1.32 (t, *J* = 12.0 Hz, 1H, H-1), 1.50 (s, 3H, CH_3), 2.06 (dd, *J* = 18.0, 9.0 Hz, 1H), 2.14 (dd, *J* = 12.0, 4.4 Hz, 1H, H-1), 2.28 (m, 2H, H-9), 2.51–2.55 (m, 1H, H-2), 2.66 (dd, *J* = 18.0, 7.4 Hz, 1H, CH_2), 3.13 (d, *J* = 17.6 Hz, 1H, CH_2), 3.23 (dd, *J* = 17.6, 6.6 Hz, 1H, CH_2), 4.12 (q, *J* = 7.2 Hz, 2H, CH_2), 5.08 (t, *J* = 5.6 Hz, 1H, H-9a), 5.56 (d, *J* = 5.6 Hz, 1H, H-4b), 7.17–7.28 (m, 3H, ArH), 8.03 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 14.1 (CH_3), 24.0 (CH_3), 26.9 (CH), 36.7 (CH_2), 36.9 (CH_2), 40.6 (CH_2), 41.0 (CH_2), 60.6 (CH_2), 64.3 (CH), 78.6 (CH), 93.1 (C), 124.8 (CH), 127.2 (CH), 128.6 (CH), 129.0 (CH), 140.6 (C), 140.9 (C), 167.0 (C), 171.5 (C); IR (film): ν = 1650, 1731 cm^{-1}; HMRS calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1629. **38b**: $[\alpha]^{22}_{D}$ +158.7 (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.01 (s, 3H, CH_3), 1.26 (t, *J* = 6.8 Hz, 3H, CH_3), 1.44 (t, *J* = 12.4 Hz, 1H, H-1), 2.06–2.13 (m, 2H, CH_2), 2.33–2.35 (m, 2H, H-9), 2.34–2.40 (m, 1H, H-2), 2.75 (dd, *J* = 18.0, 5.6 Hz, 1H, CH_2), 3.19 (d, *J* = 17.6 Hz, 1H, CH_2), 3.32 (dd, *J* = 17.6, 6.6 Hz, 1H, CH_2), 4.15 (q, *J* = 6.8 Hz, 2H, CH_2), 4.94 (t, *J* = 6.8 Hz, 1H, H-9a), 6.01 (d, *J* = 6.8 Hz, 1H, H-4b), 7.21–7.30 (m, 3H, ArH), 7.52 (d, *J* = 6.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ

= 14.2 (CH_3), 26.7 (CH), 27.4 (CH_3), 36,8 (CH_2), 40.0 (CH_2), 40.6 (CH_2), 42.0 (CH_2), 60.6 (CH_2), 63.8 (CH), 79.5 (CH), 93.7 (C), 125.0 (CH), 125.9 (CH), 127.6 (CH), 128.7 (CH), 140.8 (C), 141.7 (C), 167.1 (C), 171.4 (C); IR (film): ν = 1650, 1731 cm^{-1}; HMRS calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1620.

Methyl (1*R*,2*R*,5a*S*,10a*R*,11a*S*)- and **(1*S*,2*S*,5a*S*,10a*R*,11a*R*)-1-Ethyl-11a-methyl-4-oxo-1,2,3,4,5a,10,10a,11a-octahydroindeno [1′,2′:4,5]oxazolo[3,2-*a*]pyridine-2-acetate (39a** and **39b).** Operating as in the general procedure, from dimethyl 3-(1-ethyl-2-oxopropyl)pentadionate[7] (**1q;** 500 mg, 2.05 mmol) and aminoindanol **21** (336 mg, 2.25 mmol) in toluene (7 mL) for 24 h, lactams **39a** (190 mg, 27%) and **39b** (203 mg, 29%) were obtained after flash chromatography (8:1 hexane–EtOAc to EtOAc). **39a**: $[\alpha]^{22}_D$ +131.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.95 (t, *J* = 7.6 Hz, 3H, CH_3), 1.16–1.22 (m, 1H, H-1), 1.33–1.45 (m, 1H, CH_2), 1.40 (s, 3H, CH_3), 1.50–1.63 (m, 1H, CH_2), 2.10–2.20 (m, 2H, CH_2), 2.24 (dd, *J* = 17.6, 4.0 Hz, 1H, CH_2), 2.40–2.47 (m, 1H, CH_2), 2.68 (dd, *J* = 17.6, 8.4 Hz, 1H, CH_2), 3.12 (d, *J* = 17.6 Hz, 1H, H-9), 3.21 (dd, *J* = 17.6, 5.6 Hz, 1H, H-9), 3.65 (s, 3H, CH_3), 5.01 (dd, *J* = 5.6, 5.2 Hz, 1H, H-9a), 5.56 (d, *J* = 5.6 Hz, 1H, H-4b), 7.18–7.28 (m, 3H, ArH), 7.97 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 13.2 (CH_3), 19.5 (CH_3), 23.6 (CH_2), 32.7 (CH), 36.5 (CH_2), 37.0 (CH_2), 40.3 (CH_2), 50.1

(CH), 51.7 (CH_3), 64.2 (CH), 78.9 (CH), 95.8 (C), 124.8 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 140.5 (C), 141.6 (C), 167.4 (C), 172.5 (C); IR (film): ν = 1656, 1736 cm^{-1}; HMRS calcd for $C_{20}H_{25}NO_4$ 343.1784, found 343.1782. **39b**: m.p. 66–68 °C (hexane–acetone); $[\alpha]^{22}_D$ +247.4 (*c* 0.14, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.93 (s, 3H, CH_3), 1.04 (t, *J* = 7.2 Hz, 3H, CH_3), 1.34–1.45 (m, 2H, CH_2, H-1), 1.55–1.64 (m, 1H, CH_2), 2.08–2.17 (m, 1H, H-2), 2.20–2.28 (m, 2H, H-3, CH_2), 2.60 (dd, *J* = 15.2, 3.6 Hz, 1H), 2.72 (dd, *J* = 17.6, 7.6 Hz, 1H, CH_2), 3.16 (d, *J* = 17.6 Hz, 1H, H-9), 3.26 (dd, *J* = 17.6, 6.0 Hz, 1H, H-9), 3.70 (s, 3H, CH_3), 4.86 (td, *J* = 6.0, 1.6 Hz, 1H, H-9a), 5.92 (d, *J* = 6.0 Hz, 1H, H-4b), 7.21–7.27 (m, 3H, ArH), 7.53 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 13.9 (CH_3), 22.5 (CH_2), 22.6 (CH_3), 31.8 (CH), 36.7 (CH_2), 39.1 (CH_2), 39.4 (CH_2), 50.1 (CH), 51.7 (CH_3), 64.0 (CH), 79.0 (CH), 96.3 (C), 125.0 (CH), 126.0 (CH), 127.5 (CH), 128.5 (CH), 140.6 (C), 141.8 (C), 166.8 (C), 172.4 (C); IR (film): ν = 1654, 1736 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08; found: C, 69.82; H, 7.62; N, 4.15.

(2*R*,3*R*,8*R*,8a*S*)- and **(2*R*,3*R*,8*S*,8a*R*)-2-[(Benzhydryloxy) methyl]-8-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (40a** and **40b)**. Operating as in the general procedure, from methyl 4-formylhexanoate[1] (**1d**; 68.5

mg, 0.43 mmol) and (1*R*,2*R*)-1-amino-1-phenyl-3-(benzhydryloxy)-2-propanol[13] (**22**; 146.7 mg, 0.44 mmol) in toluene (1 mL) for 24 h, lactams **40a** (21 mg, 8%) and **40b** (128 mg, 70%) were obtained after flash chromatography (SiO_2 previously washed with hexane–Et_3N; gradient hexane to 95:5 hexane–EtOAc). **40a**: $[\alpha]^{22}_D$ –37.9 (*c* 1.06, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.04 (t, *J* = 7.5 Hz, 3H), 1.25–1.50 (m, 3H), 1.86 (m, 1H), 1.96 (m, 1H), 2.38 (ddd, *J* = 18.0, 11.1, 7.2 Hz, 1H), 2.54 (ddd, *J* = 18.0, 6.5, 1.8 Hz, 1H), 3.11 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.31 (dd, *J* = 10.2, 6.3 Hz, 1H), 4.60 (ddd, *J* = 7.5, 6.3, 5.4 Hz, 1H), 4.91 (d, *J* = 7.8 Hz, 1H), 5.02 (s, 1H), 5.52 (d, *J* = 7.5 Hz, 1H), 7.10–7.30 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.0 (CH_3), 22.4 (CH_2), 24.5 (CH_2), 31.1 (CH_2), 41.6 (CH), 60.1 (CH), 67.7 (CH_2), 77.8 (CH), 84.0 (CH), 91.6 (CH), 126.7 (CH), 127.1 (CH), 127.3 (CH), 127.5 (CH), 128.2 (CH), 128.2 (CH), 128.3 (CH), 136.5 (C), 141.7 (C), 168.2 (C); IR (film): ν = 1651 cm^{-1}; HMRS calcd for $C_{29}H_{31}NO_3$ 441.2304, found 441.2304. **40b**: $[\alpha]^{22}_D$ +29.9 (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.06 (t, *J* = 7.5 Hz, 3H, CH_3), 1.23–1.50 (m, 2H, CH_2, H-7), 1.73–1.94 (m, 2H, CH_2, H-8), 2.02 (m, 1H, H-7), 2.27 (ddd, *J* = 18.0, 11.1, 5.1 Hz, 1H, H-6), 2.40 (ddd, *J* = 18.0, 6.9, 2.1 Hz, 1H, H-6), 3.06 (dd, *J* = 10.2, 6.3 Hz, 1H, CH_2), 3.23 (dd, *J* = 10.2, 6.3 Hz, 1H, CH_2), 4.38 (q, *J* = 6.3 Hz, 1H, H-2), 4.58 (d, *J* = 9.0 Hz, 1H, H-8a), 5.00 (d, *J* = 6.3 Hz, 1H, H-

3), 5.04 (s, 1H, CH), 7.10–7.25 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 11.0 (CH_3), 23.6 (CH_2), 24.2 (CH_2), 31.3 (CH_2), 40.6 (CH), 61.1 (CH), 67.3 (CH_2), 79.9 (CH), 84.0 (CH), 92.0 (CH), 126.7 (CH), 127.3 (CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 137.0 (C), 141.4 (C), 141.5 (C), 167.0 (C); IR (film): ν = 1651 cm^{-1}; HMRS calcd for $C_{29}H_{31}NO_3$ 441.2304, found 441.2304.

Methyl (2*R*,3*R*,7*R*,8a*S*)- and **(2*R*,3*R*,7*S*,8a*R*)-2-[(Benzhydryloxy)methyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (41a** and **41b).** Operating as in the general procedure, from dimethyl 3-(2-oxoethyl)pentadionate[7] (**1m**; 120 mg, 0.59 mmol) and aminoalcohol **22**[13] (220 mg, 0.66 mmol) in toluene (4 mL) for 9 h, lactams **41a** (17.8 mg, 6%) and **41b** (231 mg, 80%) were obtained after flash chromatography (gradient 1:1 to 1:3 hexane–EtOAc). **41a**: $[\alpha]^{22}_D$ –49.4 (*c* 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 1.28 (ddd, *J* = 12.5, 12.5, 9.6 Hz, 1H, H-8), 2.00 (dd, *J* = 18.0, 10.8 Hz, 1H, H-6), 2.29–2.40 (m, 4H, CH_2, H-7, H-8), 2.60 (dd, *J* = 17.4, 3.0 Hz, 1H, H-6), 3.05 (dd, *J* = 10.8, 4.8 Hz, 1H, CH_2), 3.22 (dd, *J* = 10.8, 6.6 Hz, 1H, CH_2), 3.63 (s, 3H, CH_3), 4.55 (ddd, *J* = 7.8, 6.0, 4.8 Hz, 1H, H-2), 4.91 (s, 1H, CH), 5.26 (dd, *J* = 9.6, 4.2 Hz, 1H, H-8a), 5.44 (d, *J* = 7.8 Hz, 1H, H-3), 7.04–7.21 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 26.7

(CH), 35.2 (CH_2), 37.3 (CH_2), 39.8 (CH_2), 51.8 (CH_3), 59.9 (CH), 67.8 (CH_2), 78.2 (CH), 84.2 (CH), 87.1 (CH), 126.7 (CH), 126.8 (CH), 127.0 (CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 136.3 (C), 141.6 (C), 167.2 (C), 171.8 (C); IR (film): ν = 1658, 1732 cm^{-1}; HMRS calcd for $C_{30}H_{31}NO_5$ 485.2202, found 485.2202; elemental analysis calcd (%) for $C_{30}H_{31}NO_5 \cdot 1/2\ H_2O$: C, 72.86; H, 6.52; N, 2.83; found: C, 72.82; H, 6.53; N, 2.80. **41b**: $[\alpha]^{22}_D$ +13.9 (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 1.60 (q, *J* = 12.0 Hz, 1H, H-8), 1.95 (dd, *J* = 18.0, 10.8 Hz, 1H, H-6), 2.40–2.48 (m, 4H, CH_2, H-7, H-8), 2.53 (ddd, *J* = 18.0, 5.4, 1.8 Hz, 1H, H-6), 3.04 (dd, *J* = 10.8, 5.4 Hz, 1H, CH_2), 3.18 (dd, *J* = 10.8, 6.6 Hz, 1H, CH_2), 3.67 (s, 3H, CH_3), 4.43 (ddd, *J* = 6.6, 6.6, 5.4 Hz, 1H, H-2), 4.97 (d, *J* = 6.6 Hz, 1H, H-3), 4.98 (dd, *J* = 10.2, 3.0 Hz, 1H, H-8a), 5.03 (s, 1H, CH), 7.11–7.21 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 27.3 (CH), 34.0 (CH_2), 37.6 (CH_2), 40.0 (CH_2), 51.7 (CH_3), 60.9 (CH), 67.4 (CH_2), 80.3 (CH), 84.1 (CH), 87.8 (CH), 126.8 (CH), 126.8 (CH), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 136.7 (C), 141.4 (C), 141.5 (C), 165.7 (C), 171.7 (C); IR (film): ν = 1658, 1732 cm^{-1}; HMRS calcd for $C_{30}H_{31}NO_5$ 485.2202, found 485.2202; elemental analysis calcd (%) for $C_{30}H_{31}NO_5 \cdot 1/2\ H_2O$: C, 72.86; H, 6.52; N, 2.83; found: C, 72.78; H, 6.33; N, 2.87.

Methyl (2*R*,3*R*,8*R*,8a*S*)- and **(2*R*,3*R*,8*S*,8a*R*)-2-[(Benzhydryloxy)methyl]-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-8-propionate (42a** and **42b).** Operating as in the general procedure, from dimethyl 4-formylpimelate[4] (**1r**; 76.1 mg, 0.35 mmol) and aminoalcohol **22**[13] (128.9 mg, 0.39 mmol) in toluene (3 mL) for 9 h, lactams **42a** (6.6 mg, 4%) and **42b** (133.4 mg, 76%) were obtained after flash chromatography (SiO_2 previously washed with hexane–Et_3N; gradient 1:1 to 1:3 hexane–EtOAc). **42a**: $[\alpha]^{22}_D$ –52.0 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.58 (m, 2H, H-7, H-8), 1.74 (m, 1H, H-1′), 1.92 (m, 1H, H-7), 2.03 (m, 1H, H-1′), 2.40 and 2.55 (m, 4H, H-6, H-2′), 3.12 (dd, *J* = 10.2, 5.4 Hz, 1H, CH_2), 3.31 (dd, *J* = 10.2, 6.0 Hz, 1H, CH_2), 3.69 (s, 3H, CH_3), 4.58 (ddd, *J* = 7.2, 6.0, 5.4 Hz, 1H, H-2), 4.93 (d, *J* = 8.1 Hz, 1H, H-8a), 5.00 (s, 1H, CH), 5.50 (d, *J* = 7.2 Hz, 1H, H-3), 7.20 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.3 (CH_2), 27.4 (CH_2), 30.9 (CH_2), 31.5 (CH_2), 39.5 (CH), 51.6 (CH_3), 60.1 (CH), 67.7 (CH_2), 77.9 (CH), 84.1 (CH), 91.9 (CH), 126.7 (CH), 126.8 (CH), 127.2 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 136.5 (C), 141.6 (C), 141.7 (C), 167.9 (C), 173.7 (C); IR (film): ν = 1661, 1735 cm^{-1}; HMRS calcd for $C_{31}H_{35}NO_5$ (M^+ +H) *m/z* 499.2359, found 500.2433. **42b**: $[\alpha]^{22}_D$ +36.2 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): δ = 1.54 (m, 1H, H-7), 1.79 (m, 1H, H-1′), 1.99 (m, 3H, H-7,

H-8, H-1′), 2.35 (m, 2H, H-6, H-2′), 2.37 (dd, *J* = 18.6, 6.0 Hz, 1H, H-6), 2.45 (dd, *J* = 16.2, 2.4 Hz, 1H, CH_2), 2.59 (m, 2H, H-6, H-2′), 3.07 (dd, *J* = 13.2, 7.6 Hz, 1H, CH_2), 3.22 (dd, *J* = 13.2, 8.4 Hz, 1H, CH_2), 3.69 (s, 3H, CH_3), 4.39 (ddd, *J* = 8.4, 8.4, 7.6 Hz, 1H, H-2), 4.61 (d, *J* = 11.6 Hz, 1H, H-8a), 4.99 (d, *J* = 8.4 Hz, 1H, H-3), 5.03 (s, 1H, CH), 7.20 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 24.6 (CH_2), 27.1 (CH_2), 31.2 (CH_2), 31.5 (CH_2), 38.7 (CH), 51.6 (CH_3), 61.0 (CH), 67.4 (CH_2), 80.1 (CH), 84.0 (CH), 92.2 (CH), 126.8 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 137.0 (C), 141.4 (C), 141.5 (C), 166.8 (C), 173.7 (C); IR (film): ν = 1661, 1735 cm^{-1}; HMRS calcd for $C_{31}H_{35}NO_5$ (M^+ +H) *m/z* 499.2359, found 500.2433.

Methyl (2*R*,3*R*,7*R*,8*R*,8a*S*)- and **(2*R*,3*R*,7*S*,8*S*,8a*R*)-2-[(Benzhydryloxy)methyl]-8-ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (43a** and **43b).** Operating as in the general procedure, from dimethyl 3-(1-formylpropyl)glutarate[7] (**1v**; 80.4 mg, 0.35 mmol) and aminoalcohol **22**[13] (128 mg, 0.38 mmol) in toluene (3 mL) for 9 h, lactams **43a** (11 mg, 6%) and **43b** (122 mg, 66%) and minor amounts of C_8 epimer of **43b** were obtained after flash chromatography (gradient 2:1 to 1:1 hexane–EtOAc). **43a**: $[\alpha]^{22}_D$ −42.3 (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 0.94 (t, *J* = 7.2 Hz, 3H, CH_3), 1.43 (m, 1H, H-8), 1.57

(m, 1H, CH_2), 1.71 (m, 1H, CH_2), 2.11 (dd, *J* = 17.4, 9.0 Hz, 1H, H-6), 2.15 (dd, *J* = 15.0, 9.0 Hz, 1H, CH_2), 2.53 (dd, *J* = 15.0, 3.6 Hz, 1H, CH_2), 2.61 (dd, *J* = 17.4, 6.0 Hz, 1H, H-6), 3.07 (dd, *J* = 10.8, 6.6 Hz, 1H, CH_2), 3.24 (dd, *J* = 10.8, 5.4 Hz, 1H, CH_2), 3.62 (s, 3H, CH_3), 4.52 (ddd, *J* = 7.2, 6.6, 6.0 Hz, 1H, H-2), 4.92 (s, 1H, CH), 5.04 (d, *J* = 8.4 Hz, 1H, H-8a), 5.43 (d, *J* = 7.2 Hz, 1H, H-3), 7.13 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.8 (CH_3), 21.3 (CH_2), 29.7 (CH), 37.3 (CH_2), 37.4 (CH_2), 44.3 (CH), 51.8 (CH_3), 60.1 (CH), 67.6 (CH_2), 78.0 (CH), 84.2 (CH), 89.9 (CH), 126.7 (CH), 126.8 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 136.5 (C), 141.6 (C), 141.7 (C), 167.2 (C), 172.2 (C); IR (film). ν = 1651, 1738 cm^{-1}; HMRS calcd for $C_{32}H_{35}NO_5$ (M^+ +H) *m/z* 513.2515, found 514.2593. **43b**: $[\alpha]^{22}_D$ +17.6 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 0.98 (t, *J* = 7.8 Hz, 3H, CH_3), 1.63 (m, 1H, CH_2), 1.71 (m, 2H, CH_2, H-8), 2.06 (dd, *J* = 17.4, 8.4 Hz, 1H, CH_2), 2.16 (dd, *J* = 15.0, 9.0 Hz, 1H, CH_2), 2.47 (dd, *J* = 17.4, 6.0 Hz, 1H, CH_2), 2.50 (dd, *J* = 15.0, 4.8 Hz, 1H, CH_2), 3.01 (dd, *J* = 10.2, 6.0 Hz, 1H, CH_2), 3.19 (dd, *J* = 10.2, 6.6 Hz, 1H, CH_2), 3.60 (s, 3H, CH_3), 4.37 (ddd, *J* = 6.6, 6.6, 6.0 Hz, 1H, H-2), 4.68 (d, *J* = 9.0 Hz, 1H, H-8a), 4.94 (d, *J* = 6.6 Hz, 1H, H-3), 5.00 (s, 1H, CH), 7.01–7.21 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 10.0 (CH_3), 21.9 (CH_2), 31.2 (CH), 37.4 (CH_2), 38.1 (CH_2), 44.1 (CH), 51.7

(CH_3), 60.9 (CH), 67.4 (CH_2), 80.9 (CH), 84.1 (CH), 90.4 (CH), 126.8 (CH), 126.9 (CH), 127.3 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 137.0 (C), 141.5 (C), 141.6 (C), 166.1 (C), 172.1 (C); IR (film): ν = 1651, 1738 cm^{-1}; HMRS calcd for $C_{32}H_{35}NO_5$ (M^+ +H) *m/z* 513.2515, found 514.2616. 8-*epi*-**43b**: $[\alpha]^{22}_D$ +33.7 (*c* 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz, COSY, HETCOR): δ = 1.01 (t, *J* = 7.8 Hz, 3H, CH_3), 1.35 (m, 1H, CH_2), 1.82 (m, 1H, CH_2), 2.12 (dd, *J* = 16.2, 12.4 Hz, 1H, CH_2), 2.29 (dd, *J* = 18.6, 1.8 Hz, 1H, H-6), 2.37 (dd, *J* = 18.6, 6.0 Hz, 1H, H-6), 2.45 (dd, *J* = 16.2, 2.4 Hz, 1H, CH_2), 2.64 (m, 1H, H-7), 2.99 (dd, *J* = 10.8, 6.0 Hz, 1H, CH_2), 3.14 (dd, *J* = 10.8, 6.6 Hz, 1H, CH_2), 3.63 (s, 3H, CH_3), 4.39 (ddd, *J* = 6.6, 6.6, 6.0 Hz, 1H, H-2), 4.54 (d, *J* = 9.0 Hz, 1H, H-8a), 4.91 (d, *J* = 6.6 Hz, 1H, H-3), 4.96 (s, 1H, CH), 7.04–7.21 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 11.3 (CH_3), 21.0 (CH_2), 29.5 (CH), 33.1 (CH_2), 37.8 (CH_2), 43.2 (CH), 51.9 (CH_3), 61.5 (CH), 67.4 (CH_2), 80.2 (CH), 84.1 (CH), 89.5 (CH), 126.8 (CH), 126.9 (CH), 127.4 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 136.7 (C), 141.5 (C), 141.6 (C), 166.2 (C), 172.6 (C); IR (film): ν = 1667, 1738 cm-1; HMRS calcd for $C_{32}H_{35}NO_5$ (M^+ +H) *m/z* 513.2515, found 514.2573.

(2*R*,3*R*,8*R*,8a*S*) and **(2*R*,3*R*,8*S*,8a*R*)-2-[(Benzhydryloxy) methyl]-8-ethyl-8a-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-**

hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (44a and **44b)**. Operating as in the general procedure, from 4-ethyl-5-oxohexanoic acid[4] (**1h**; 35 mg, 0.22 mmol) and aminoalcohol **22**[13] (81 mg, 0.24 mmol) in toluene (5 mL) for 22 h, lactams **44a** (49 mg, 49%) and **44b** (32 mg, 32%) were obtained after flash chromatography (gradient hexane to 1:2 hexane–EtOAc). **44a**: $[\alpha]^{22}_{D}$ –38.9 (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.99 (t, *J* = 7.6 Hz, 3H, CH_3), 1.15–1.22 (m, 1H, CH_2), 1.33–1.41 (m, 1H, H-7), 1.47 (s, 3H, CH_3), 1.61–1.70 (m, 1H, H-8), 1.78–1.87 (m, 1H, CH_2), 2.02–2.11 (m, 1H, H-7), 2.47 (t, *J* = 7.6 Hz, 2H, H-6), 3.30 (dd, *J* = 10.0, 6.8 Hz, 1H, CH_2), 3.47 (dd, *J* = 10.0, 6.0 Hz, 1H, CH_2), 4.52 (ddd, *J* = 6.8, 6.8, 6.0 Hz, 1H, H-2), 5.09 (s, 1H, CH), 5.47 (d, *J* = 6.8 Hz, 1H, H-3), 7.09–7.36 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 12.1 (CH_3), 20.8 (CH_3), 21.4 (CH_2), 24.0 (CH_2), 29.1 (CH_2), 44.4 (CH), 61.9 (CH), 67.9 (CH_2), 76.9 (CH), 84.1 (CH), 96.1 (C), 126.7 (CH), 126.8 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.2 (CH), 128.3 (CH), 137.0 (C), 141.6 (C), 141.8 (C), 169.8 (C); IR (film): ν = 1645 cm^{-1}; HMRS calcd for $C_{30}H_{33}NO_3$ 455.2460, found 455.2443. **44b**: $[\alpha]^{22}_{D}$ +16.6 (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.05 (t, *J* = 7.2 Hz, 3H, CH_3), 1.18–1.28 (m, 1H, CH_2), 1.36 (s, 3H, CH_3), 1.41–1.48 (m, 1H, H-7), 1.79–1.93 (m, 2H, H-8, CH_2), 2.03–2.12 (m, 1H, H-7), 2.29 (dd, *J* = 18.4, 8.8 Hz, 1H, H-6), 2.41 (ddd, *J* = 18.4, 9.2, 2.8 Hz, 1H, H-6),

3.01 (dd, *J* = 10.0, 6.4 Hz, 1H, CH_2), 3.26 (dd, *J* = 10.0, 5.6 Hz, 1H, CH_2), 4.74 (q, *J* = 6.4 Hz, 1H, H-2), 5.09 (d, *J* = 7.2 Hz, 1H, H-3), 7.06–7.08 (m, 2H, ArH), 7.18–7.28 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 11.9 (CH_3), 18.7 (CH_3), 22.8 (CH_2), 23.6 (CH_2), 30.1 (CH_2), 45.6 (CH), 61.7 (CH), 68.0 (CH_2), 76.6 (CH), 84.1 (CH), 94.7 (C), 126.7 (CH), 126.8 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 137.1 (C), 141.6 (C), 141.7 (C), 167.1 (C); IR (film): ν = 1655 cm^{-1}.

Methyl (2*R*,3*R*,7*R*,8*R*,8a*S*)- and **(2*R*,3*R*,7*S*,8*S*,8a*R*)-2-[(Benzhydryloxy)methyl]-8-ethyl-8a-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (45a** and **45b).** Operating as in the general procedure, aminoalcohol **22**[13] (115 mg, 0.34 mmol) was added to a solution of dimethyl 3-(1-ethyl-2-oxopropyl)pentadionate[7] (**1q**; 75.6 mg, 0.31 mmol) and AcOH (9 mg, 0.15 mmol) in toluene (4 mL), and the mixture was stirred at reflux for 31 h. The solvent was eliminated under reduced pressure, and the residue was dissolved in EtOAc and washed with 5% aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried, and evaporated. Flash chromatography (1:1 hexane–EtOAc to EtOAc) afforded lactams **45a** (29 mg, 18%), **45b** (9 mg, 6%), minor amounts of a third diastereomer, and starting material (**1q**; 45 mg). **45a**: $[\alpha]^{22}_D$ –1.6 (*c* 2.74, $CHCl_3$); ^1H NMR ($CDCl_3$, 400

MHz, COSY, HETCOR): δ = 1.10 (t, *J* = 7.6 Hz, 3H, CH_3), 1.46–1.52 (m, 2H, CH_2, H-8), 1.58 (s, 3H, CH_3), 1.66–1.73 (m, 1H, CH_2), 2.15–2.19 (m, 1H, H-7), 2.20 (dd, *J* = 16.4, 1.6 Hz, 1H, CH_2), 2.35 (dd, *J* = 16.0, 10.0 Hz, 1H, CH_2), 2.54 (dd, *J* = 16.0, 3.2 Hz, 1H, CH_2), 2.67 (dd, *J* = 16.4, 9.6 Hz, 1H, CH_2), 3.27 (dd, *J* = 10.0, 6.4 Hz, 1H, CH_2), 3.44 (dd, *J* = 10.0, 6.0 Hz, 1H, CH_2), 3.69 (s, 3H, CH_3), 4.50 (ddd, *J* = 6.4, 6.4, 6.0 Hz, 1H, H-2), 5.09 (s, 1H, CH), 5.38 (d, *J* = 6.4 Hz, 1H, H-3), 7.07–7.09 (dd, *J* = 8.0, 2.0 Hz, 2H, ArH), 7.18–7.35 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 13.7 (CH_3), 21.4 (CH_3), 24.3 (CH_2), 31.7 (CH), 36.0 (CH_2), 40.0 (CH_2), 48.7 (CH), 51.7 (CH_3), 61.7 (CH), 67.4 (CH_2), 76.8 (CH), 84.0 (CH), 96.3 (C), 126.6 (CH), 126.7 (CH), 126.8 (CH), 127.4 (CH), 127.6 (CH), 127.6 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 137.0 (C), 141.6 (C), 141.8 (C), 168.7 (C), 172.4 (C); IR (film): ν = 1665, 1733 cm^{-1}. **45b**: $[\alpha]^{22}_D$ –10.3 (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.13 (t, *J* = 7.6 Hz, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.53-1.78 (m, 3H, CH_2, H-8), 2.11 (dd, *J* = 18.0, 4.8 Hz, 1H, CH_2), 2.17-2.31 (m, 2H, CH_2), 2.57-2.65 (m, 2H, H-6), 3.05 (dd, *J* = 10.0, 6.0 Hz, 1H, CH_2), 3.25 (dd, *J* = 10.0, 6.0 Hz, 1H, CH_2), 3.63 (s, 3H, CH_3), 4.74 (ddd, *J* = 6.8, 6.0, 6.0 Hz, 1H, H-2), 4.98 (s, 1H, CH), 5.06 (d, *J* = 6.8 Hz, 1H, H-3), 7.06 (dd, *J* = 8.0, 2.0 Hz, 2H, ArH), 7.15–7.32 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 13.5 (CH_3), 19.3 (CH_3), 23.7 (CH_2), 32.8

(CH_2), 36.6 (CH_2), 40.1 (CH_2), 50.6 (CH), 51.7 (CH_3), 61.3 (CH), 68.0 (CH_2), 76.8 (CH), 84.1 (CH), 95.0 (C), 126.8 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 137.0 (C), 141.6 (C), 141.7 (C), 166.1 (C), 172.3 (C); IR (film): ν = 1665, 1735 cm^{-1}.

Methyl (2*R*,3*S*,7*R*,8*R*,8a*S*)- and **(2*R*,3*S*,7*S*,8*S*,8a*R*)-8-Ethyl-3-(methoxymethyl)-5-oxo-2-phenyl 2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine-7-acetate (46a** and **46b).** Operating as in the general procedure, from dimethyl 3-(1-formylpropyl)glutarate[7] (**1v**; 250 mg, 1.09 mmol) and (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol[14] (**23**; 235 mg, 1.19 mmol) in toluene (5 mL) for 22 h, lactams **46a** (214 mg, 47%) and **46b** (73 mg, 17%) and a mixture of other stereoisomers (71 mg, 15%) were obtained after flash chromatography (SiO_2 previously washed with hexane–Et_3N; gradient hexane–EtOAc as eluent). **46a**: $[\alpha]^{22}_D$ –81.4 (*c* 2.57, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz, COSY, HETCOR): δ = 1.01 (t, *J* = 7.5 Hz, 3H, CH_3), 1.55 (m, 1H, H-8), 1.67 (m, 2H, CH_2), 2.22 (m, 3H, H-6, H-7, CH_2), 2.45 (dd, *J* = 19.0, 8.0 Hz, 1H, CH_2), 2.52 (dd, *J* = 15.0, 4.0 Hz, 1H, CH_2), 3.43 (s, 3H, CH_3), 3.54 (t, *J* = 8.5 Hz, 1H, CH_2), 3.68 (s, 3H, CH_3), 3.97 (dd, *J* = 8.5, 3.0 Hz, 1H, CH_2), 4.37 (m, 1H, H-3), 4.71 (d, *J* = 8.5 Hz, 1H, H-8a), 5.35 (bs, 1H, H-2), 7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR):

δ = 10.2 (CH_3), 22.7 (CH_2), 31.4 (CH), 37.2 (CH_2), 38.8 (CH_2), 45.1 (CH), 51.7 (CH_3), 60.5 (CH), 70.2 (CH_2), 80.9 (CH), 88.9 (CH), 125.7 (CH), 127.9 (CH), 128.7 (CH), 139.2 (C), 167.1 (C), 172.2 (C); IR (film): ν = 1651, 1732 cm^{-1}; HMRS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1889. **46b**: $[\alpha]^{22}_D$ +9.4 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.99 (t, *J* = 7.2 Hz, 3H, CH_3), 1.62 (m, 2H, CH_2, H-8), 1.80 (m, 1H, CH_2), 2.17 (dd, *J* = 17.6, 11.2 Hz, 1H, H-6), 2.19 (dd, *J* = 15.6, 4.0 Hz, 1H, CH_2), 2.31 (m, 1H, H-7), 2.64 (dd, *J* = 15.6, 4.0 Hz, 1H, CH_2), 2.70 (dd, *J* = 17.6, 4.8 Hz, 1H, H-6), 3.38 (s, 3H, CH_3), 3.55 (dd, *J* = 10.0, 2.8 Hz, 1H, CH_2), 3.70 (s, 3H, CH_3), 3.83 (dd, *J* = 10.0, 2.8 Hz, 1H, CH_2), 4.12 (ddd, *J* = 7.2, 4.4, 2.8 Hz, 1H, H-3), 4.84 (d, *J* = 8.0 Hz, 1H, H-8a), 5.07 (d, *J* = 7.2 Hz, 1H, H-2), 7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 9.6 (CH_3), 20.6 (CH_2), 29.8 (CH), 36.7 (CH_2), 37.6 (CH_2), 43.6 (CH), 51.7 (CH_3), 59.2 (CH_3), 62.0 (CH), 70.3 (CH_2), 79.9 (CH), 90.2 (CH), 126.4 (CH), 128.2 (CH), 128.5 (CH), 138.9 (C), 167.2 (C), 172.1 (C); IR (film): ν = 1654, 1735 cm^{-1}; HMRS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1889.

Reduction Reactions

(2*S*,3*R*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-phenylpiperidine (*cis*-11a). Operating as in the Method B, from lactam **8g** (500 mg, 1.7 mmol) and Red-Al (0.1M in THF, 44.3 mL, 4.4 mmol) in THF (3 mL) for 8 h, piperidine *cis*-**11a** (270 mg, 56%) was obtained after flash chromatography (hexane): $[\alpha]^{22}_{D}$ –75.2 (*c* 1.09, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): δ = 0.64 (t, *J* =7.2 Hz, 3H, CH_3), 1.23–1.38 (m, 2H, H-4, CH_2), 1.44–1.59 (m, 3H, H-3, H-5, CH_2), 1.67–1.88 (m, 2H, H-4, H-5), 1.95 (td, *J* = 11.4, 3.0 Hz, 1H, H-6), 3.09 (dm, *J* = 11.4 Hz, 1H, H-6), 3.50 (dd, *J* = 10.5, 5.4 Hz, 1H, H-2′), 3.58 (d, *J* = 2.4 Hz, 1H, H-2), 4.09 (t, *J* = 10.5 Hz, 1H, H-2′), 4.30 (dd, *J* = 10.5, 5.4 Hz, 1H, H-1′), 6.87–6.90 (m, 2H, ArH), 7.24–7.39 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.8 (CH_3), 18.3 (CH_2), 20.4 (CH_2), 26.6 (CH_2), 42.0 (CH), 45.6 (CH_2), 59.4 (CH_2), 61.0 (CH), 68.7 (CH), 127.5 (CH), 129.1 (CH), 126.4 (CH), 127.4 (CH), 127.8 (CH), 129.3 (CH), 134.2 (C), 140.8 (C); IR (film) ν = 3523 cm^{-1}; HMRS calcd for $C_{21}H_{27}NO$ 309.4501, found 309.4512. *cis*-**11a** hydrochloride: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.68 (t, *J* = 7.2 Hz, 3H), 1.70 (dm, *J* = 14.1 Hz, 1H), 2.01 (dm, *J* = 13.5 Hz, 1H), 2.22 (m, 1H), 2.50 (m, 1H), 2.61 (m, 1H), 3.68 (bs, 1H), 3.87 (bs, 1H), 4.03 (m, 1H), 4.18 (m, 1H), 4.64 (m, 1H), 10.32 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 12.0 (CH_3), 17.8 (CH_2), 18.1 (CH_2),

24.8 (CH_2), 41.8 (CH), 50.7 (CH_2), 59.4 (CH_2), 60.2 (CH_2), 69.8 (CH), 71.1 (CH), 128.4 (CH), 129.6 (CH), 128.5 (CH), 130.2 (CH), 129.1 (CH), 130.4 (CH), 129.4 (C), 133.7 (C).

(2*R*,3*R*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-phenylpiperidine (*trans*-**11a**). Operating as in the Method A, from lactam **8g** (100 mg, 0.31 mmol) and 9-BBN (0.5M in THF, 6.22 mL, 3.11 mmol) in THF (5 mL) for 8 h, piperidine *trans*-**11a** (83 mg, 86%) was obtained after flash chromatography (hexane to hexane–EtOAc 1:9): $[\alpha]^{22}_D$ –51.6 (*c* 1.06, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.68 (t, *J* =7.5 Hz, 3H), 0.84 (m, 1H), 1.03 (m, 2H), 1.40–1.70 (m, 4H), 1.97 (m, 1H), 2.41 (td, *J* = 11.1, 3.0 Hz, 1H), 2.89 (bd, *J* = 11.1 Hz, 1H), 3.44 (d, *J* = 9.3 Hz, 1H), 3.68 (t, *J* = 6.3 Hz, 1H), 4.08 (d, *J* = 6.3 Hz, 2H), 7.25–7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.1 (CH_3), 25.8 (CH_2), 26.1 (CH_2), 30.0 (CH_2), 45.4 (CH), 47.3 (CH_2), 59.3 (CH_2), 62.2 (CH), 71.4 (CH), 126.5 (CH), 127.1 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.6 (CH), 140.6 (C), 143.0 (C); IR (film): ν = 3523 cm^{-1}; HMRS calcd for $C_{21}H_{27}NO$ 309.4501, found 309.4513.

(4a*R*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]perhydroquinoline (13a). Operating as in the Method C, from lactam **8i** (300 mg, 1.1 mmol), $AlCl_3$ (558 mg, 4.4 mmol), and $LiAlH_4$ (546 mg, 14.5 mmol) in THF (44 mL), perhydroquinoline **13a** (200 mg, 70%) was obtained after flash chromatography (Et_2O): $[\alpha]^{22}_D$ –29.2 (*c*

1.59, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, 55 °C) δ = 1.24–1.91 (m, 12H), 2.07 (bt, *J* = 8.7 Hz, 1H), 2.23 (m, 1H), 2.55 (m, 1H), 2.85 (m, 1H), 3.17 (bs, 1H), 3.66 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.93 (dd, *J* = 10.5, 8.7 Hz, 1H), 4.10 (dd, *J* = 8.7, 5.1 Hz, 1H), 7.20-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz, 55 °C): δ = 21.9 (CH_2), 23.3 (CH_2), 24.8 (CH_2), 25.9 (CH_2), 28.3 (CH_2), 28.7 (CH_2), 37.3 (CH), 45.3 (CH_2), 57.2 (CH), 61.1 (CH_2), 64.0 (CH), 127.3 (CH), 128.0 (CH), 128.6 (CH), 137.4 (C). **13a** hydrochloride: m.p. 225–227 °C (THF-EtOH); $[\alpha]^{22}_{D}$ –32.2 (*c* 0.8, MeOH); ^{1}H NMR ($CDCl_3$–CD_3OD, 300 MHz): δ 0.75 (m, 1H), 1.31–1.94 (m, 10H), 2.50 (m, 1H), 2.56 (m, 2H), 3.05 (m, 2H), 3.96 (dd, *J* = 13.0, 3.0 Hz, 1H), 4.20 (dd, *J* = 7.0, 3.0 Hz, 1H), 4.24 (dd, *J* = 13.0, 3.0 Hz, 1H), 4.59 (dd, *J* = 13.0, 7.0 Hz, 1H), 7.42–7.70 (m, 5H), 10.5 (bs, 1H); ^{13}C NMR ($CDCl_3$–CD_3OD, 75.4 MHz): δ = 17.8 (CH_2), 19.4 (CH_2), 21.2 (CH_2), 22.3 (CH_2), 24.4 (CH_2), 30.2 (CH_2), 37.3 (CH), 47.4 (CH_2), 60.8 (CH), 63.1 (CH_2), 70.1 (CH), 128.6 (CH), 129.3 (CH), 129.5 (CH), 132.3 (C); IR (KBr): ν = 3253 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{26}ClNO$: C, 69.02; H, 8.86; N, 4.73; found: C, 69.15; H, 9.00; N, 4.59.

Methyl (3*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]piperidine-3-propionate (16a). Operating as in the Method D, from lactam **9r** (500 mg, 1.65 mmol) and BH_3 (1M in THF, 4.95 mL, 4.95 mmol) in THF (8.2 mL), piperidine **16a** was obtained (293 mg,

61%) after flash chromatography (EtOAc): $[\alpha]^{22}_D$ –11.8 (*c* 0.7, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): δ = 0.79 (m, 1H, H-4), 1.44–1.73 (m, 7H, H-6, H-5, H-4, H-3, 2H-1′), 1.98 (t, *J* = 9.3 Hz, 1H, H-2), 2.32 (t, *J* = 7.5 Hz, 2H, H-2′), 2.74–2.81 (m, 2H, H-6, H-2), 3.61 (dd, *J* = 10.0, 5.1 Hz, 1H, CH_2), 3.67 (s, 3H, CH_3), 3.70 (dd, *J* = 10.0, 5.1 Hz, 1H, CH_2), 3.98 (t, *J* = 10.0 Hz, 1H, CH), 7.14–7.37 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 25.4 (CH_2), 29.2 (CH_2), 30.5 (CH_2), 31.6 (CH_2), 36.3 (CH), 46.8 (CH_2), 51.6 (CH_3), 58.5 (CH_2), 59.9 (CH_2), 70.2 (CH), 127.8 (CH), 128.0 (CH), 128.8 (CH), 135.2 (C), 174.0 (C); IR (film): ν = 1786, 3440 cm^{-1}; HMRS calcd for $C_{17}H_{25}NO_3$ 291.3902, found 291.3910.

Ethyl (2*R*,4*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-methylpiperidine-4-acetate (17a). Operating as in the Method D (reaction conditions: – 78 °C for 2 h, 0 °C for 2 h, and 25 °C for 2 h), from lactam **10n** (1.1 g, 3.6 mmol) and BH_3 (1M in THF, 10.8 mL, 10.8 mmol) in THF (18 mL), piperidines **17a** (608 mg, 55%) and 2-*epi*-**17a** (209 mg, 19%) were obtained after flash chromatography (Et_2O). **17a**: $[\alpha]^{22}_D$ –35.4 (*c* 0.64, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (d, *J* = 6.6 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.38 (m, 1H), 1.48 (m, 2H), 1.74 (m, 1H), 2.17 (m, 3H), 2.44 (ddd, *J* = 11.5, 7.2, 3.6 Hz, 1H), 2.67 (ddd, *J* = 11.5, 7.2, 3.6 Hz, 1H), 2.82 (m, 1H), 3.71 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.82 (dd, *J* = 10.5, 7.0 Hz, 1H),

3.91 (dd, *J* = 7.0, 5.5 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 7.25–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.1 (CH_3), 15.2 (CH_3), 27.4 (CH), 31.3 (CH_2), 38.9 (CH_2), 39.2 (CH_2), 41.2 (CH_2), 48.4 (CH), 60.1 (CH_2), 61.4 (CH_2), 64.0 (CH), 127.5 (CH), 128.2 (CH), 128.4 (CH), 138.2 (C), 172.7 (C); IR (film): ν = 1733, 3410 cm^{-1}; HMRS calcd for $C_{18}H_{27}NO_3$ 305.4215, found 305.4213. 2-*epi*-**17a**: $[\alpha]^{22}_D$ +32.1 (*c*, 1.16, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.03 (q, *J* = 12.5 Hz, 1H), 1.06 (qd, *J* = 12.0, 3.5 Hz, 1H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H), 1.59 (dm, *J* = 12.0 Hz, 1H), 1.65 (ddd, *J* = 12.5, 6.5, 2.5 Hz, 1H), 1.82 (m, 1H), 2.16 (d, *J* = 7.0 Hz, 2H), 2.20 (bs, 1H), 2.54 (td, *J* = 12.0, 2.0 Hz, 1H), 2.70 (m, 1H), 2.86 (dt, *J* = 12.0, 3.5 Hz, 1H), 4.02 (dd, *J* = 10.5, 7.5 Hz, 1H), 4.07 (dd, *J* = 10.5, 7.5 Hz, 1H), 4.11 (q, *J* = 7.5 Hz, 2H), 4.18 (t, *J* = 7.5 Hz, 1H), 7.26 (tm, *J* = 7.5 Hz, 1H), 7.34 (tm, *J* = 7.5 Hz, 2H), 7.39 (dm, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.3 (CH_3), 21.3 (CH_3), 32.8 (CH_2), 33.4 (CH), 41.4 (CH_2), 42.2 (CH_2), 49.6 (CH_2), 54.0 (CH), 60.1 (CH_2), 60.2 (CH_2), 63.6 (CH), 127.1 (CH), 128.3 (CH), 128.4 (CH), 139.5 (C), 172.7 (C); IR (film): ν = 1733, 3645 cm^{-1}; 2-*epi*-**17a** hydrochloride: m.p. 155–157 °C (acetone–Et_2O); elemental analysis calcd (%) for $C_{18}H_{27}NO_3 \cdot 1/4\ H_2O$: C, 63.24; H, 8.25; N, 4.10; found: C, 63.42; H, 8.22; N, 4.04.

Ethyl (2*S*,4*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-methylpiperidine-4-acetate (1'-*epi*-*ent*-**17a).** Operating as in the Method D (reaction conditions: – 78 °C for 2 h, 0 °C for 2 h, and 25 °C for 2 h), from lactam **9n** (556 mg, 1.75 mmol) and BH_3 (1M in THF, 5.26 mL, 5.26 mmol) in THF (9 mL), piperidine 1'-*epi*-*ent*-**17a** (280 mg, 53%) was obtained after flash chromatography (Et_2O): $[\alpha]^{22}_D$ –10.8 (*c* 0.85, MeOH); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.98 (d, *J*= 6.6 Hz, 3H), 1.16 (qd, *J*= 12.5, 4.2 Hz, 1H), 1.23 (t, *J*= 7.2 Hz, 3H), 1.50–1.57 (m, 2H), 1.63 (dm, *J*= 12.5 Hz, 1H), 2.05 (m, 1H), 2.15 (m, 2H), 2.45 (td, *J*= 12.5, 2.5 Hz, 1H), 2.61 (ddd, *J*= 12.5, 4.0, 3.0 Hz, 1H), 3.35 (m, 1H), 3.60–3.80 (m, 3H), 4.08 (m, 2H), 7.21–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.8 (CH_3), 14.2 (CH_3), 27.5 (CH), 32.5 (CH_2), 38.7 (CH_2), 41.1 (CH_2), 41.6 (CH_2), 52.1 (CH), 60.1 (CH_2), 62.3 (CH_2), 68.1 (CH), 127.5 (CH), 128.3 (CH), 128.6 (CH), 140.2 (C), 172.6 (C); IR (film): ν = 1732, 3402 cm^{-1}; HMRS calcd for $C_{18}H_{27}NO_3$, 305.4212 found 305.4207.

Methyl (2*R*,3*R*,4*R*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-methylpiperidine-4-acetate (18a). Operating as described in the Method D (reaction conditions: – 78 °C for 20 min and 25 °C for 2 h), from lactam **10q** (504 g, 1.51 mmol) and BH_3 (1M in THF, 4.6 mL, 4.6 mmol) in THF (10 mL), piperidine **18a** (322 mg, 66%) was obtained after flash chromatography (gradient

4:1 to 1:1 hexane–EtOAc): $[\alpha]^{22}_D$ +16.4 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.71 (t, *J* = 7.6 Hz, 3H, CH_3), 0.84 (d, *J* = 6.4 Hz, 3H, CH_3), 1.01–1.13 (m, 1H, CH_2), 1.24–1.38 (m, 2H, H-5, H-3), 1.39–1.50 (m, 1H, CH_2), 1.71–1.77 (m, 1H, H-5), 1.92–2.01 (m, 1H, H-4), 2.06 (dd, *J* = 14.8, 8.4 Hz, 1H, CH_2), 2.46 (dd, *J* = 14.8, 5.2 Hz, 1H, CH_2), 2.62–2.70 (m, 2H, H-6), 2.93–2.98 (m, 1H, H-2), 3.65 (s, 3H, CH_3), 3.75–3.81 (m, 3H, CH_2, CH), 7.27–7.33 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 8.7 (CH_3), 11.5 (CH_3), 21.3 (CH_2), 31.4 (CH_2), 32.0 (CH), 38.3 (CH_2), 42.1 (CH_2), 46.5 (CH), 50.5 (CH), 51.4 (CH_3), 62.4 (CH_2), 64.5 (CH), 127.6 (CH), 128.3 (CH), 139.5 (C), 173.7 (C); IR (film): ν = 1736, 3000–3500 cm^{-1}.

(1*S*,2*R*)-1-[(2*S*,3*S*)-(2-Methyl-3-phenyl)-1-piperidyl)]-2-indanol (47). Operating as described in the Method D (reaction conditions: – 78 °C for 20 min and 25 °C for 8 h), from lactam **37b** (2 g, 6.26 mmol) and BH_3 (1M in THF, 19 mL, 19 mmol) in THF (30 mL), piperidine **47** (1.63 g, 89%) was obtained after flash chromatography (95:5 EtOAc–Et_3N): $[\alpha]^{22}_D$ –57.1 (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 1.55–1.66 (m, 1H, H-5), 1.71–1.81 (m, 2H, H-4, H-5), 1.92–2.02 (m, 1H, H-4), 2.54–2.59 (m, 1H, H-6), 2.91 (dd, *J* = 16.0, 6.8 Hz, 1H, CH_2), 2.97 (ddd, *J* = 12.4, 11.2, 2.8 Hz, 1H, H-6), 3.15 (dd, *J* = 16.0, 7.2 Hz, 1H, CH_2), 3.16 (ddd, *J*

= 11.2, 7.4, 4.4 Hz, 1H, H-3), 3.34–3.40 (m, 1H, H-2), 4.25 (d, *J* = 6.4 Hz, 1H, H-1'), 4.45 (ddd, *J* = 7.2, 6.8, 6.4 Hz, 1H, CH), 7.15–7.31 (m, 8H, ArH), 7.39 (d, *J* = 7.2 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 10.7 (CH_3), 23.7 (CH_2), 25.3 (CH_2), 40.5 (CH_2), 44.9 (CH_2), 46.1 (CH), 57.9 (CH), 69.7 (CH), 70.7 (CH), 125.5 (CH), 125.9 (CH), 126.2 (CH), 127.0 (CH), 127.8 (CH), 128.0 (CH), 128.9 (CH), 139.7 (C), 141.7 (C), 143.4 (C); IR (film): ν = 3000–3500 cm^{-1}.

(3*S*,4*S*)-1-[(1*R*,2*R*)-3-(Benzhydryloxy)-2-hydroxy-1-phenylpropyl]-3-ethyl-4-(2-hydroxyethyl)piperidine (49). Operating as described in the Method D (reaction conditions: – 78 °C for 20 min and 25 °C for 2 h) from lactam **43b** (270 mg, 0.53 mmol) and BH_3 (1M in THF, 1.6 mL, 1.6 mmol) in THF (4 mL), piperidine **49** (203 mg, 78%) was obtained after flash chromatography (EtOAc): $[\alpha]^{22}_D$ –10.3 (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.85 (t, *J* = 7.2 Hz, 3H, CH_3), 0.99–1.31 (m, 5H, CH_2, H-5, H-3, CH_2, H-4), 1.48–1.63 (m, 2H, H-5, CH_2), 1.73–1.85 (m, 3H, CH_2, H-6, H-2), 2.59–2.62 (m, 1H, H-6), 2.97–3.00 (m, 1H, H-2), 3.40–3.48 (m, 3H, CH_2, H-1'), 3.53–3.69 (m, 2H, CH_2), 4.43–4.48 (m, 1H, CH), 5.30 (s, 1H, CH), 7.28–7.31 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 11.1 (CH_3), 23.7 (CH_2), 31.2 (CH_2), 35.7 (CH_2), 36.4 (CH), 42.3 (CH), 49.7 (CH_2), 56.7 (CH_2), 60.7 (CH_2), 68.8 (CH), 71.4 (CH_2 and CH), 84.1 (CH), 126.9 (CH), 127.4 (CH),

127.9 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 129.5 (C), 136.1 (C), 142.0 (C), 142.1 (C); IR (film): ν = 3000–3500 cm^{-1}.

Hydrogenolysis Reactions

(*R*)-2-Phenylpiperidine (*ent*-6b). Operating as described in the general procedure, piperidine ***ent*-6b** (48 mg, 56 %) was obtained from **5b** (150 mg, 0.53 mmol) and Pd-C (10%, 37.5 mg) after flash chromatography (CH_2Cl_2): $[\alpha]^{22}_D$ +25.2 (*c* 0.4, MeOH), (lit[15] $[\alpha]^{24}_D$ +27.6 (*c* 1.0, MeOH)); HMRS calcd for $C_{11}H_{15}N$ 161.1199, found 161.1202.

(2*S*,3*R*)-3-Ethyl-2-phenylpiperidine (*cis*-11b). Following the general procedure, from piperidine ***cis*-11a** (400 mg, 1.3 mmol) and 10 % $Pd(OH)_2$-C (100 mg) in MeOH (26 mL) was obtained piperidine ***cis*-11b** (140 mg, 70%) after flash chromatography (EtOAc): $[\alpha]^{22}_D$ –24.3 (*c* 1.48, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): δ = 0.66 (t, *J* =7.5 Hz, 3H, CH_3), 1.02 (m, 1H, CH_2), 1.39–1.51 (m, 2H, H-5, CH_2), 1.61–1.72 (m, 3H, H-3, H-4, H-5), 1.96 (m, 1H, H-4), 2.78 (td, *J* =11.4, 3.0 Hz, 1H, H-6), 3.22 (dd, *J* =11.4, 3.0 Hz, 1H, H-6), 3.93 (d, *J* = 2.7 Hz, 1H, H-2), 7.17–7.33 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 12.3 (CH_3), 17.2 (CH_2), 20.6 (CH_2), 27.7 (CH_2), 41.5 (CH), 48.0 (CH_2), 64.7 (CH), 126.2 (CH), 126.4 (CH), 127.9 (CH),

144.1 (C); IR (film): ν = 3321 cm^{-1}; HMRS calcd for $C_{13}H_{19}N$ 189.1517, found 189.1512.

(2*R*,3*R*)-3-Ethyl-2-phenylpiperidine (*trans*-11b). Following the general procedure, from compound *trans*-**11a** (400 mg, 1.3 mmol) and 10% Pd-C (100 mg) in MeOH (26 mL) was obtained piperidine *trans*-**11b** (110 mg, 60%) after flash chromatography (EtOAc): $[\alpha]^{22}_D$ −23.1 (*c* 0.67, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.71 (t, *J* =7.5 Hz, 3H), 0.87 (m, 1H), 1.09 (m, 1H), 1.48 (m, 1H), 1.60−1.72 (m, 2H), 1.72 (bs, 1H), 1.86 (m, 1H), 2.04 (m, 1H), 2.74 (td, *J* = 11.7, 2.7 Hz, 1H), 3.14 (dm, *J* = 11.7 Hz, 1H), 3.22 (d, *J* = 9.9 Hz, 1H), 7.26−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 10.9 (CH_3), 25.3 (CH_2), 26.4 (CH_2), 30.2 (CH_2), 43.5 (CH), 47.6 (CH_2), 68.3 (CH), 127.2 (CH), 127.9 (CH), 128.2 (CH), 143.6 (C); IR (film): ν = 3327 cm^{-1}; HMRS calcd for $C_{13}H_{19}N$ 189.1512, found 189.1518.

(2*R*,3*R*)-1-(*tert*-Butoxycarbonyl)-3-ethyl-2-methylpiperidine (12c). Following the general procedure, from piperidine **12a** (160 mg, 0.64 mmol), 20% $Pd(OH)_2$-C (64 mg), and di-*tert*-butyl dicarbonate (282 mg, 1.29 mmol) in EtOAc (22 mL) was obtained carbamate **12c** (121 mg, 82%) after flash chromatography (hexane): $[\alpha]^{22}_D$ −41.3 (*c* 0.75, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, broad signals): δ 0.90 (t,□= *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 2.77 (bs, 1H), 3.80 (bs, 2H), 4.20

and 4.38 (2 bs, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 10.3 (CH_3), 11.5 (CH_3), 24.7 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 29.4 (CH_3), 39.0 (CH_2), 41.2 (CH), 48.9 (CH), 78.9 (C), 146.6 (C); IR (film): ν = 1811 cm^{-1}; HMRS calcd for $C_{13}H_{25}NO_2$ 227.2080, found 227.2083.

(4a*R*,8a*R*)-Decahydroquinoline (13b). *Method A*. Following the above general procedure, from **13a** hydrochloride (350 mg, 1.35 mmol) and 10% Pd-C (35 mg) in MeOH (17 mL) was obtained decahydroquinoline **13b** hydrochloride (200 mg, 85%): m.p. 246–248 °C (EtOH–Et_2O); $[\alpha]^{22}_D$ +7.4 (*c* 1.62, MeOH), [lit[16] $[\alpha]^{20}_D$ +6.2 (*c*, 2.0, EtOH)]; ^1H NMR ($CDCl_3$, 300 MHz, 55°C): δ = 1.31–2.01 (m, 13H), 2.98 (m, 1H), 3.25 (m, 1H), 3.39 (m, 1H), 9.15 (bs, 1H), 9.70 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 19.7 (CH_2), 21.8 (CH_2), 22.9 (CH_2), 25.7 (CH_2), 26.0 (CH_2), 27.2 (CH_2), 33.2 (CH), 42.1 (CH_2), 54.8 (CH); IR (KBr): ν = 3415 cm^{-1}; elemental analysis calcd (%) for $C_9H_{18}ClN$: C, 61.52; H, 10.33; N, 7.97; found: C, 61.49; H, 10.39; N, 7.80.

Method B. Following the general procedure, from decahydroquinoline **13a** (425 mg, 1.64 mmol), di-*tert*-butyl dicarbonate (715 mg, 3.28 mmol), and 20% $Pd(OH)_2$-C (170 mg) in EtOAc (55 mL) was obtained **(4a*R*,8a*R*)-1-(*tert*-Butoxycarbonyl)decahydroquinoline** (**13c**; 203 mg, 65%) after flash chromatography (98:2 CH_2Cl_2–Et_2O): $[\alpha]^{22}_D$ –17.9 (*c* 0.73,

MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.88 (m, 1H), 1.25–1.90 (m, 12H), 1.45 (s, 9H), 2.75 (td, *J* = 12.6, 3.0 Hz, 1H), 3.93 (dm, *J* = 12.0 Hz, 1H), 4.06 (dt, *J* = 12.6, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 54.3 MHz): δ = 20.4 (CH_2), 23.9 (CH_2), 24.0 (CH_2), 25.8 (CH_2), 26.0 (CH_2), 28.5 (CH_3), 31.5 (CH_2), 35.0 (CH), 38.9 (CH_2), 53.0 (CH), 79.0 (C), 155.0 (C). TFA (0.927 mL, 12.1 mmol) was added to a solution of **13c** (38.6 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (1 mL). The resulting solution was stirred at 25 °C for 15 min. The crude mixture was cooled to 0 °C and brought to basic pH by careful addition to Ca_2CO_3. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried and concentrated. Flash chromatography (80:15:5 CH_2Cl_2–Et_2O–Et_2NH) gave decahydroquinoline **13b** (19 mg, 85%): $[\alpha]^{22}_{D}$ –8.7 (*c* 0.37, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.70–1.90 (m, 12H), 2.03 (bs, 1H), 2.65 (td, *J* = 12.0, 3.6 Hz, 1H), 2.84 (dd, *J* = 7.2, 3.6 Hz, 1H), 3.04 (dt, *J* = 12.0, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 21.7 (CH_2), 22.6 (CH_2), 26.0 (CH_2), 26.3 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 35.6 (CH), 46.8 (CH_2), 54.9 (CH); IR (film): ν = 3323 cm^{-1}.

Ethyl (3*S*,4*S*)-3-Ethylpiperidine-4-acetate (14b). Following the general procedure, from piperidine **14a** (70 mg, 0.22 mmol) and 10% Pd-C (17.5 mg) in MeOH (50 mL) was obtained piperidine **14b** (30 mg, 70 %) after flash chromatography

(EtOAc to 95:5 EtOAc–Et_2NH): $[\alpha]^{22}_D$ –43.1 (*c* 0.7, MeOH); ^1H NMR ($CDCl_3$, 500 MHz, COSY, HETCOR): δ = 0.86 (t, *J* = 7.5 Hz, 3H, CH_3), 1.29 (t, *J* = 7.5 Hz, 3H, CH_3), 1.25 (s, 1H, CH_2), 1.59 (ddd, *J* = 14.5, 7.5, 3.5 Hz, 1H, CH_2), 1.71 (td, *J* = 13.0, 3.5 Hz, 1H, H-5), 1.75–1.81 (m, 2H, H-3, H-4), 1.95 (dd, *J* = 13.0, 3.0 Hz, 1H, H-5), 2.08 (dd, *J* = 16.0, 8.6 Hz, 1H, CH_2), 2.55 (t, *J* = 12.0 Hz, 1H, H-2), 2.56 (dd, *J* = 16.0, 3.5 Hz, 1H, CH_2), 2.81 (td, *J* = 13.0, 3.0 Hz, 1H, H-6), 3.40 (bd, *J* = 12.0 Hz, 1H, H-2), 3.42 (dd, *J* = 13.0, 3.5 Hz, 1H, H-6), 4.11 (q, *J* = 7.5 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 9.8 (CH_3), 14.2 (CH_3), 22.9 (CH_2), 28.2 (CH_2), 35.2 (CH), 37.5 (CH_2), 38.5 (CH), 43.8 (CH_2), 47.4 (CH_2), 60.7 (CH_2), 172.1 (C); IR (film) 3419, 1731 cm^{-1}; HMRS calcd for $C_{11}H_{21}NO_2$ 199.1572, found 199.1577.

Ethyl (4*S*,5*S*)-5-Ethyl-2-oxopiperidine-4-acetate (15b). Into a three-necked, 250 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice–acetone were condensed 15 mL of NH_3 at –78 °C, and calcium metal was added in small portions until the blue color persisted. Then, a solution of lactam **9o** (100 mg, 0.30 mmol) in THF (2 mL) was added, and the mixture was stirred at –78 °C for 3 h. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared, and the mixture was stirred at room temperature for 2 h. The resulting residue was digested with EtOAc, and the resulting suspension was filtered and

concentrated to give an oil (80 mg), which was used in the next reaction without further purification. Et_3SiH (100 μL, 0.06 mmol) and TFA (1.7 mL) were added to the above obtained oil (80 mg), and the resulting mixture was stirred at room temperature for 18 h and concentrated. The residue was dissolved in CH_2Cl_2, and the organic extract was washed with aqueous $NaHCO_3$, dried, filtered, and concentrated to give a yellow oil (50 mg). Flash chromatography (4:6 hexane–EtOAc to EtOAc) afforded piperidone **15b** (30 mg, 48%): $[\alpha]^{22}_D$ −70.9 (*c* 0.26, EtOH); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.93 (t, *J* = 7.5 Hz, 1H), 1.26 (t, *J* = 6.9 Hz, 3H), 1.30 (m, 1H, CH_2), 1.63 (m, 1H, CH_2), 1.83 (m, 1H), 2.17 (dd, *J* = 14.5, 4.0 Hz, 1H), 2.23 (dd, *J* = 14.5, 8.4 Hz, 1H), 2.51 (m, 2H), 3.03 (ddd, *J* = 12.0, 8.4, 1.6 Hz, 1H), 3.40 (ddd, *J* = 12.0, 4.6, 3.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 6.25 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 11.0 (CH_3), 14.2 (CH_3), 23.5 (CH_2), 33.5 (CH), 35.7 (CH_2), 38.1 (CH), 38.2 (CH_2), 44.9 (CH_2), 60.6 (CH_2), 171.5 (C), 171.8 (C); IR (film): ν = 1728, 1660 cm^{-1}; HMRS calcd for $C_{11}H_{19}NO_3$ 231.1364, found 213.1367.

Methyl (3*R*)-3-Piperidine-3-propionate (16b). Following the general procedure, from piperidine **16a** (140 mg, 0.48 mmol) and 20% $Pd(OH)_2$-C (35 mg) in EtOAc (12 mL) was obtained piperidine **16b** (90 mg, 91%) after flash chromatography (95:5 EtOAc–Et_2NH): $[\alpha]^{22}_D$ +6.1 (*c* 0.75, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300

MHz): δ = 1.05 (qd, *J* = 13.0, 4.2 Hz, 1H), 1.43 (m, 2H), 1.54 (t, *J* = 7.8 Hz, 2H), 1.65 (dm, *J* = 13.0 Hz, 1H), 1.84 (dm, *J* = 13.0 Hz, 1H), 2.19 (m, 1H), 2.32 (t, *J* = 7.8 Hz, 2H), 2.52 (td, *J* = 13.0, 2.4 Hz, 1H), 3.01 (m, 2H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 26.4 (CH_2), 29.5 (CH_2), 31.2 (CH_2), 31.4 (CH_2), 36.6 (CH), 46.8 (CH_2), 51.5 (CH_3), 52.5 (CH_2), 174.1 (C); IR (film): ν = 1734, 3326 cm^{-1}; HMRS calcd for $C_9H_{17}NO_2$ 171.1259, found 171.1258.

Ethyl (2*R*,4*S*)-2-Methylpiperidine-4-acetate (17b). Following the general procedure, from piperidine **17a** hydrochloride (151 mg, 0.5 mmol) and 10% Pd-C (15 mg) in MeOH (6 mL) was obtained piperidine **17b** hydrochloride (102 mg, 93%): m.p. 165–167 °C (acetone–Et_2O); $[\alpha]^{22}_D$ +5.4 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (t,□= *J*= 6.9 Hz, 3H), 1.47 (d, *J*= 6.9 Hz, 3H), 1.68 (m, 1H), 1.81 (m, 2H), 2.02 (m, 1H), 2.34 (m, 3H), 3.15 (bs, 2H), 3.58 (bs, 1H), 4.14 (q, *J*= 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.1 (CH_3), 16.6 (CH_3), 26.2 (CH), 27.2 (CH_2), 33.9 (CH_2), 38.3 (CH_2), 38.5 (CH_2), 47.8 (CH), 60.6 (CH_2), 171.7 (C); IR (film): ν = 1724, 3501 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_{20}ClNO_2$: C, 54.17; H, 9.09; N, 6.32; found: C, 53.99; H, 9.07; N, 6.11. **17b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (d, *J* = 6.6 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.39 (m, 3H), 1.67 (ddd, *J* = 17.7, 9.0, 4.5

Hz, 1H), 1.81 (bs, 1H), 2.31 (m, 1H), 2.33 (dd, *J* = 11.7, 4.0 Hz, 1H), 2.34 (t, *J* = 4.0 Hz, 1H), 2.84 (m, 2H), 2.94 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.2 (CH_3), 21.4 (CH_3), 28.5 (CH), 30.8 (CH_2), 38.2 (CH_2), 38.3 (CH_2), 40.9 (CH_2), 46.5 (CH), 60.1 (CH_2), 172.9 (C).

Ethyl (2*S*,4*R*)-2-Methylpiperidine-4-acetate (*ent*-17b). Following the general procedure, from piperidine 1′-*epi*-*ent*-**17a** was obtained *ent*-**17b** hydrochloride: 87% yield; $[\alpha]^{22}_D$ –5.4 (*c* 1.0, MeOH).

Ethyl (2*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-2-methyl-4-piperidineacetate (17c). Following the general procedure, from piperidine **17a** (285 mg, 0.98 mmol), 20% $Pd(OH)_2$-C (120 mg), and di-*tert*-butyl dicarbonate (428 mg, 1.96 mmol) in EtOAc (30 mL) was obtained carbamate **17c** (250 mg, 94%) after flash chromatography (2:8 hexane–Et_2O): $[\alpha]^{22}_D$ –36.2 (*c* 0.48, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.08 (qd, *J* = 13.2, 4.5 Hz), 1.13 (d, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.5 Hz, 3H), 1.35 (td, *J* = 12.3, 5.7 Hz, 1H), 1.45 (s, 9H), 1.55 (dm, *J* = 12.3 Hz, 1H), 1.60 (dm, *J* = 13.2 Hz, 1H), 2.12 (m, 1H), 2.18 (m, 2H), 2.86 (bt, *J* = 13.2 Hz, 1H), 3.95 (bs, 1H), 4.11 (m, 2H), 4.42 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 14.2 (CH_3), 16.1 (CH_3), 27.5 (CH), 28.4 (CH_3), 31.9 (CH_2), 36.6 (CH_2), 38.2

(CH_2), 41.4 (CH_2), 46.4 (CH), 60.2 (CH_2), 79.2 (C), 155.0 (C), 172.4 (C); IR (film): ν = 1690, 1736 cm^{-1}.

Ethyl (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-2-methyl-4-piperidineacetate (*ent*-17c). Following the above procedure, from 1′-*epi*-*ent*-**17a** was obtained *ent*-**17c**: 92% yield; $[\alpha]^{22}_D$ +36.0 (*c* 1.51, MeOH).

Methyl (2*R*,3*R*,4*R*)-3-Ethyl-2-methylpiperidine-4-acetate (18b). Following the general procedure, from piperidine **18a** (290 mg, 0.91 mmol) and 20% $Pd(OH)_2$-C (140 mg) in MeOH (18 mL) was obtained piperidine **18b** (153 mg, 84%) after flash chromatography (7:2:1 EtOAc–MeOH–Et_3N to 95:5 EtOAc–Et_2NH): $[\alpha]^{22}_D$ +19.4 (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.91 (d, *J* = 6.8 Hz, CH_3), 1.19 (d, *J* = 6.8 Hz, 3H, CH_3), 1.20–1.28 (m, 1H, CH_2), 1.39–1.58 (m, 2H, CH_2), 1.78–1.84 (m, 1H, H-5), 2.06–2.14 (m, 1H, H-4), 2.21 (dd, *J* = 15.2, 8.8 Hz, 1H, CH_2), 2.54 (dd, *J* = 15.2, 5.6 Hz, 1H, CH_2), 2.94–2.98 (m, 2H, H-6), 3.38–3.44 (m, 1H, H-2), 3.68 (s, 3H, CH_3), 5.96 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 11.3 (CH_3), 12.7 (CH_3), 20.5 (CH_2), 28.5 (CH_2), 31.0 (CH), 37.6 (CH_2), 38.7 (CH_2), 43.5 (CH), 48.7 (CH), 51.4 (CH_3), 173.0 (C); IR (film): ν = 1736 cm^{-1}; HMRS calcd for $C_{12}H_{17}N$ 199.1572, found 199.1574.

(2*S*,3*S*)-*cis*-2-Methyl-3-phenylpiperidine (48). Following the general procedure, from piperidine **47** (250 mg, 0.81 mmol) and 20% $Pd(OH)_2$-C (100 mg) in MeOH (16 mL) was obtained piperidine **48** (121 mg, 68%) after flash chromatography (4:1:1 EtOAc–MeOH–Et_3N): $[\alpha]^{22}_D$ –2.9 (*c* 0.97, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR): δ = 0.90 (d, *J* = 6.8 Hz, CH_3), 1.54–1.62 (m, 1H, H-5), 1.76–1.86 (m, 2H, H-5, H-4), 1.91–2.00 (m, 1H, H-4), 2.81–2.86 (m, 1H, H-6), 2.93 (bs, 1H, NH), 2.96–3.02 (m, 2H, H-6, H-3), 3.30–3.37 (m, 1H, H-2), 7.16–7.22 (m, 1H, ArH), 7.28 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz, HETCOR): δ = 14.2 (CH_3), 25.1 (CH_2), 25.5 (CH_2), 41.1 (CH_2), 45.6 (CH), 53.5 (CH), 125.9 (CH), 128.0 (CH), 128.1 (CH), 143.8 (C); IR (film): ν = 3059 cm^{-1}; HMRS calcd for $C_{12}H_{17}N$ 175.1361, found 175.1367.

(3*S*,4*S*)-3-Ethyl-4-hydroxyethylpiperidine (50). Following the general procedure, from piperidine **49** (51 mg, 0.16 mmol) and 20% $Pd(OH)_2$-C (20 mg) in MeOH (5 mL) was obtained piperidine **50** (12 mg, 48%) after flash chromatography (10:2:1 EtOAc–MeOH–Et_3N): ^1H NMR ($CDCl_3$. 500 MHz, COSY, HETCOR): δ = 0.83 (t, *J* = 8.0 Hz, 3H, CH_3), 1.11 (m, 1H, CH_2), 1.16 (m, 1H, H-4), 1.21 (m, 1H, H-5), 1.28 (m, 1H, H-3), 1.31 (m, 1H, CH_2), 1.57 (m, 1H, CH_2), 1.74 (dq, *J* = 13.0, 3.0 Hz, 1H, H-5), 1.83 (m, 1H, CH_2), 2.25 (dd, *J* = 12.0, 10.5, 1H, H-2), 2.54 (td, *J* = 12.0, 3.0 Hz, 1H, H-6), 3.03 (dt, *J* = 12.0, 2.5 Hz,

1H, H-6), 3.08 (ddd, *J* = 12.0, 4.0, 1.0 Hz, 1H, H-2), 3.64 (m, 1H, CH_2), 3.68 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): δ = 10.9 (CH_3), 23.5 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 36.8 (CH), 42.5 (CH), 46.4 (CH_2), 50.7 (CH_2), 60.2 (CH_2); IR (film): ν = 3000–3500 cm^{-1}.

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