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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]

Abstract: A straightforward procedure for the synthesis of enantiopure polysubstituted piperidines is reported. It involves 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 amino alcohols 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.

Keywords: asymmetric synthesis · chiral auxiliaries · cyclocondensation · dynamic kinetic resolution · enantioselectivity · piperidines

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 by conventional resolution or by exploiting 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 rarely been used in synthetic sequences as a result of 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 to the synthesis of enantiopure compounds and have become powerful synthetic tools,[4] the chemical, nonenzymatic differentiation of two enantiotopic functional groups is still little developed in spite of the impressive advances in this field in recent 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-oxo acid derivatives with chiral non-racemic amino alcohols have received considerable attention[7] since the resulting oxazolopiperidone lactams have

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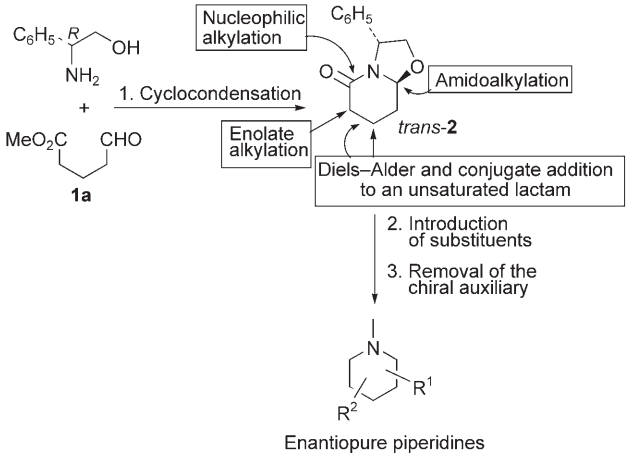
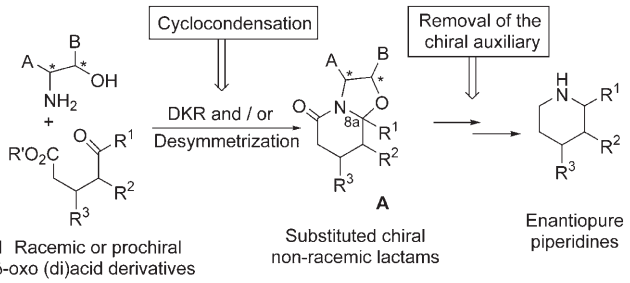
Supporting information for this article (experimental details and characterization data for all compounds) is available on the WWW under http://www.chemeurj.org/ or from the author.

proven to be versatile building blocks for the enantioselective synthesis of piperidine-containing derivatives.[8] In particular, in previous work we have demonstrated that the simple phenylglycinol-derived bicyclic lactams *trans*-**2**, *cis*-**2**, and their enantiomers allow the stereocontrolled formation of C–C bonds at different positions of the nitrogen heterocycle.[7d,f–h,j] Our approach involves three phases: 1) a cyclocondensation reaction of (*R*)- or (*S*)-phenylglycinol with methyl 5-oxopentanoate (**1a**) to generate the required bicyclic lactam, 2) successive stereoselective introduction of ring substituents taking advantage of the functionalization and conformational rigidity of the bicyclic lactam system, and 3) 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. Synthetic strategy: First generation oxazolopiperidone lactams.

Herein we report a more straightforward procedure for the synthesis of enantiopure polysubstituted piperidines. It involves the direct generation of chiral non-racemic 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 the cyclocondensation reaction of (*R*)-phenylglycinol or other amino alcohols with racemic or prochiral δ-oxo (di)acid derivatives in processes involving dynamic kinetic resolution (DKR) and/or the desymmetrization of enantiotopic or diastereotopic ester groups.

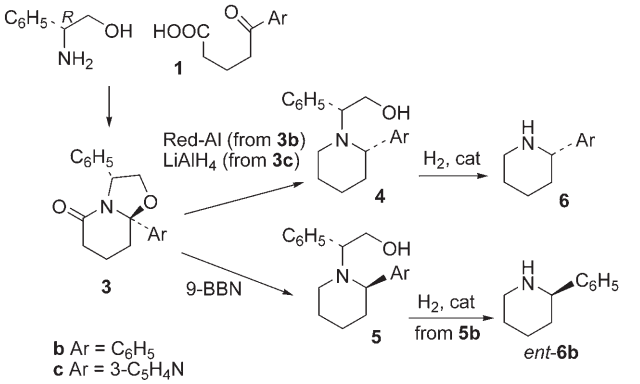


Scheme 2. Synthetic strategy: Second generation oxazolopiperidone lactams.

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 using 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).

Interestingly, treatment of lactam **3b** with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) gave 2-phenylpiperidine **4b** (54%) as the only stereoisomer detectable by spectroscopic methods. In contrast, reduction of **3b** with 9-borabicyclo[3.3.1]nonane (9-BBN) stereoselectively provided 2-phenylpiperidine **5b** (75%) by 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

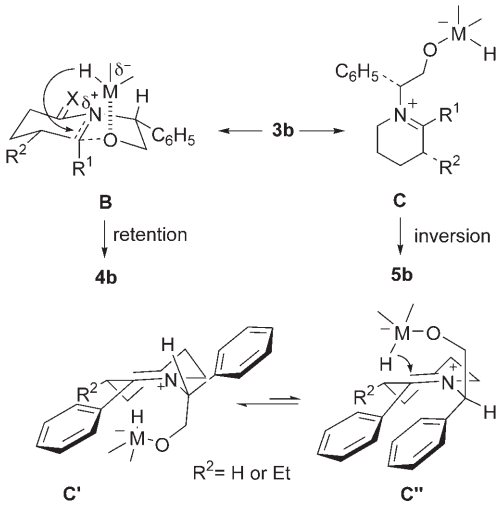


Scheme 3. Enantiodivergent synthesis of 2-arylpiperidines. Enantioselective synthesis of (−)-anabasine.

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 amino alcoholes quirales, con derivados de δ-oxo ácidos racémicos o proquirales, en procesos altamente estereoselectivos que implican una resolución cinética dinámica y/o la desimetrización de grupos diastereotópicos o enantiotópicos.*

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 offers a short enantiodivergent route to 2-arylpiperidines from readily available achiral δ-oxo acids.

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 atom 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**. Owing 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 cleavage than in related 8a-alkyl-substituted lactams.



Scheme 4. Stereoselective reduction of 8a-substituted lactams.

To further illustrate the potential of the cyclodehydration/stereocontrolled reduction sequence developed here, we synthesized 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 the 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 lower 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 the pure isomer **4c** over Pearlman's catalyst afforded (−)-anabasine (**6c**).

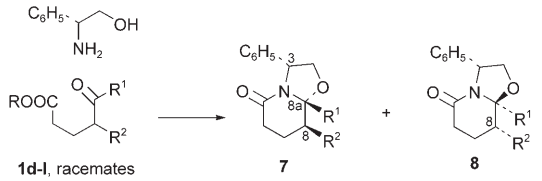
We then examined the stereochemical outcome of the cyclocondensation reactions of (*R*)-phenylglycinol with racemic γ-alkyl-δ-oxo acid derivatives, both aldehydes and ketones, which incorporate a chirally labile stereogenic center capable of undergoing in situ racemization or epimerization during reaction.[12] Cyclocondensation reactions of aldehyde esters **1d–f**, 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–f**, 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 cyclodehydration reactions occurred with α-alkyl-substituted ketones **1g–i**, including both dialkyl (noncyclic and cyclic) and alkyl aryl ketones, although in all these cases the corresponding 3-H/8a-R^1 *trans* lactams **8g–i** were the major products (approximate **7**/**8** ratio, 1:4).[15]

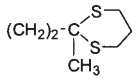
These results can be accounted for by considering that the two diastereoisomeric imines initially formed in the reaction of (*R*)-phenylglycinol with racemic oxo esters **1d–i** are in equilibrium via an enamine and, consequently, that a mixture of four equilibrating oxazolidines is formed.[16,17] Subsequent irreversible lactamization occurs faster for 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).

In contrast, cyclocondensation of δ-oxo acid derivatives (**1j–l**) bearing a protected hydroxy 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]

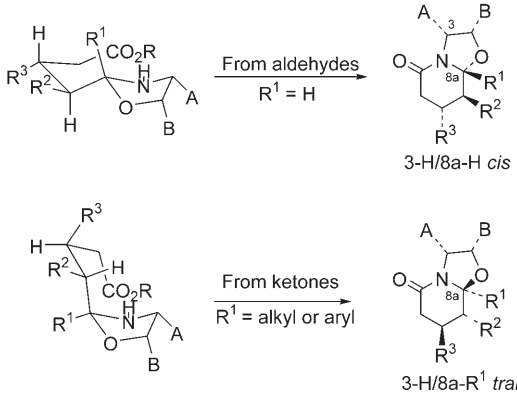
To study enantioselective desymmetrizations of prochiral δ-oxo diesters with (*R*)-phenylglycinol, we selected the glutaric and pimelic acid derivatives **1m,n** and **1r**, respectively. Interestingly, cyclocondensation of aldehyde diester **1m** and keto diester **1n** with (*R*)-phenylglycinol stereoselectively afforded the lactams **9m** (3-H/8a-H *cis*) and **10n** (3-H/8a-R^1 *trans*), respectively, as the major products, together with

Table 1. Cyclocondensation reactions of racemic γ-substituted δ-oxo acid 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] Lactam **8l**, its C-8 epimer (3:2 ratio), and minor amounts of **7l**. TBDMS = *tert*-butylmethylsilyl, MEM = methoxyethoxymethoxy.



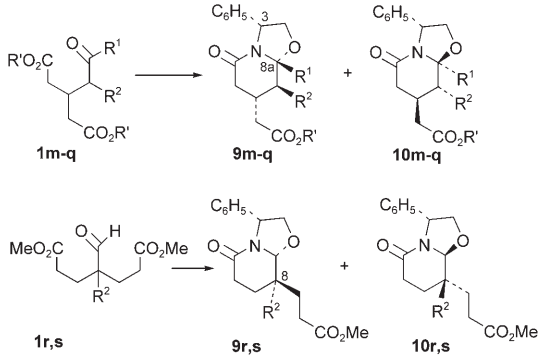
Scheme 5. Lactamization step during the cyclocondensation of δ-oxo acid derivatives with 1,2-amino alcohols.

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*) with very high stereoselectivity (ratio **9r**/**10r**, 9:1). Note again that cyclocondensation reactions involving aldehydes lead to lactams with a *cis* 3-H/8a-H relationship whereas in the case of ketones the preferential formation of 3-H/8a-R^1 *trans* isomeric lactams is observed.

The above results can be rationalized by taking into account that, after the formation of the corresponding oxazolidines, lactamization occurs faster through a chair-like 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 along with equimolecular amounts of the corresponding 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-oxo diesters **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 chair-like six-membered lactam are equatorial (Scheme 5).

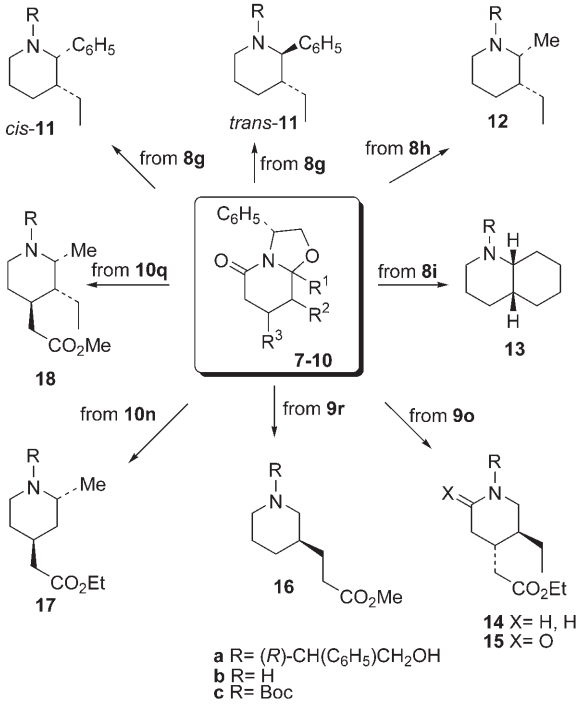
Table 2. Cyclocondensation reactions of (*R*)-phenylglycinol with prochiral or racemic δ-oxo diesters.



	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 catalyst. [b] The relative stereochemistry of **10n** was confirmed by X-ray crystallography. [c] Using glacial AcOH as catalyst. [d] Isomers **9s** and **10s** were isolated along with their respective C-8 epimers (**9s**′ and **10s**′; 1:1 mixtures).

The substituted chiral lactams **7**–**10** are immediate precursors of a variety of diversely substituted enantiopure piperidine derivatives, including piperidine-4-acetates. 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).



Scheme 6. Synthesis of a diverse range of substituted enantiopure piperidines.

Reduction of **8g** with AlH_3 and BH_3 showed the same level of stereoselectivity as 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%). In this way, starting from readily available racemic γ-substituted δ-oxo acids, the above three-step sequence provides a stereodivergent entry to enantiopure *cis*- and *trans*-3-alkyl-2-arylpiperidines.

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 an 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% yields, 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 yield to the enantiopure *cis*-perhydroquinoline **13b**, either directly or via the *N*-Boc derivative **13c**.

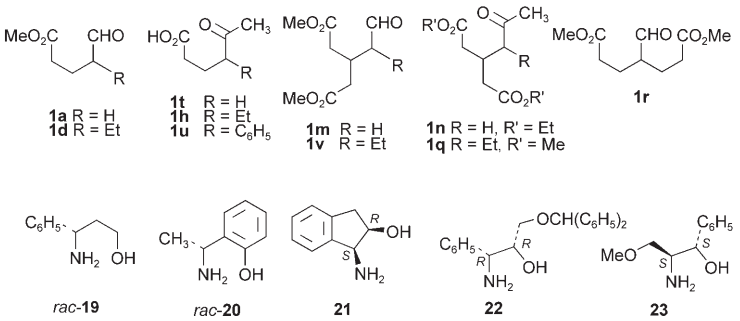
The reductive opening of the oxazolidine ring in the lactams bearing an ester function was chemoselectively accomplished with borane. Thus, lactams **9o** and **9r** were efficiently converted into *trans*-3-ethylpiperidine-4-acetate **14b** (70%) and piperidine-3-propionate **16b** (91%), respectively, 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 calcium 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 yields. A similar two-step sequence starting from the minor lactam **9n** led to *ent*-**17b** and *ent*-**17c**.

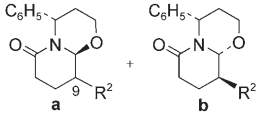
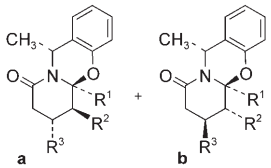
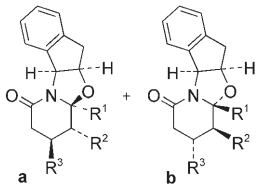
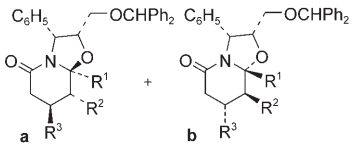
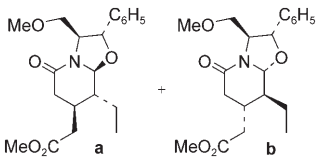
The above results make evident that substituted phenylglycinol-derived lactams **7**–**10**, readily accessible by cyclocondensation reaction of (*R*)-phenylglycinol with racemic or prochiral δ-oxo acid derivatives, are useful chiral synthons that allow the straightforward preparation of a variety of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

Other amino alcohol derived lactams: With the aim of improving the diastereoselectivity of the above phenylglycinol-induced cyclocondensation reactions, we undertook a study of the behavior of other amino alcohols 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-amino alcohols[21] (**19**–**23**) and a variety of δ-oxo acid derivatives, including unbranched aldehydes (**1a**) and ketones (**1t**), simple racemic aldehydes (**1d**) and ketones (**1h** and **1u**), prochiral aldehydo- (**1m** and **1r**) and keto diesters (**1n**) bearing enantiotopic ester groups, and racemic aldehydo- (**1v**) and keto diesters (**1q**) bearing diastereotopic ester groups. The results are summarized in Table 3.[22]

We initially explored the use of 1,3-amino alcohols **19** and **20**.[23] Although amino alcohol *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**.

Table 3. Cyclocondensation reactions of amino alcohols with racemic or prochiral δ-oxo acid 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
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	$(CH_2)_2CO_2Me$	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 did not undergo lactamization, was isolated in ~10% yield. [b] A 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] The **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 with racemic aldehyde **1d** or prochiral ketone **1n**, reaction with racemic ketones **1h** and **1u** gave the respective tricyclic lactams *rac*-**29** and *rac*-**30** with good stereoselectivity (**a/b** diastereomeric ratios 9:1) but only moderate chemical yields.[24] The isolation of considerable amounts of 2-vinylphenol accounts for the low yield of the above reactions.

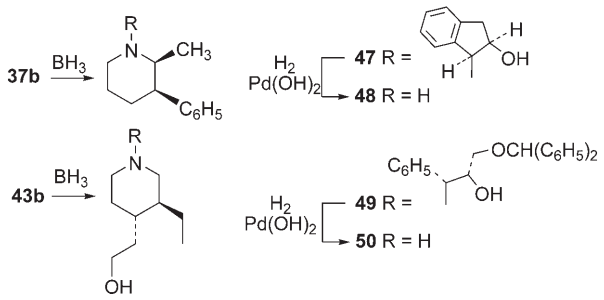
More successful results were obtained when using *cis*-1-amino-2-indanol (**21**),[25] a conformationally rigid analog of phenylglycinol.[24] Thus, although no DKR was observed with racemic aldehyde **1d**, enantioselective desymmetrization of two enantiotopic ester groups occurred in the cyclo-

condensation 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 with excellent chemical yields and even better stereoselectivity than when using phenylglycinol. Enantiopure tetracyclic lactams **36b** and **37b** were isolated in 61 and 77% yields, 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 cyclocondensation reactions involving desymmetrization of the acetate chains of keto diesters **1n** and **1q**. The higher stereoselectivities observed with racemic ketones **1h** and **1u** as compared with racemic aldehyde **1d** in the above cyclocondensation reactions with amino alcohols *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 amino alcohol **22**.[26] Thus, **22** reacted with racemic aldehyde **1d** to give a 9:1 stereoisomeric mixture of lactams **40** in 78% yield, which clearly indicates that DKR had again occurred. Similarly, prochiral aldehyde 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 yields. The major isomers **b** were isolated in 80 and 76% yields, respectively. Finally, racemic oxo diester **1v**, on reaction with amino alcohol **22**, stereoselectively provided enantiopure lactam **43b**, which was isolated in 66% yield, in a highly stereoselective process that involves the tandem DKR/desymmetrization of two diastereotopic acetate chains with the generation of three stereogenic centers in a single synthetic step. In contrast with the above satisfactory results, similar cyclocondensation reactions with racemic ketones **1h** and **1q** occurred with low stereoselectivity.

The higher stereoselectivities observed in the cyclocondensation reactions promoted by amino alcohols **21** (with ketones) and **22** (with aldehydes) as compared with phenylglycinol can be rationalized by considering that the substituents at the 4- and 5-positions of the ring 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 with *erythro* amino alcohol **22**, cyclocondensation of *threo* amino alcohol **23**[27] with racemic diester **1v** took place with low stereoselectivity to give a 2:1 diastereomeric mixture of lactams **46a** and **46b**, along with other stereoisomers.

Finally, to fully illustrate the synthetic usefulness of amino alcohols **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 of the resulting *N*-substituted piperidines **47** and **49**, respectively (Scheme 7).



Scheme 7. Removal of the chiral auxiliary.

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 amino alcohol provides easy access to enantiopure piperidines in both enantiomeric series. On the other hand, although aminoindanol **21** and protected aminopropanediol **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 cyclocondensation reactions with racemic ketones involving DKR, the less accessible alcohol **22** reacts with exceptionally high stereoselectivities (diastereoisomeric ratios 9–20:1) in cyclocondensation reactions with aldehydes involving either DKR or the 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 a diverse range of substituted piperidine derivatives.

Experimental Section

General procedure for the cyclocondensation reactions: A solution of amino alcohol (1.2 equiv) and the 1,5-dicarbonyl compound (1 equiv) in anhydrous toluene containing molecular sieves (4 Å) was refluxed for 12–66 h with azeotropic removal of water using 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 purified by chromatography to afford the desired lactams. The epimeric ratios were determined by using HPLC and/or ^{1}H NMR spectroscopy.

(3*R*,8a*R*)-5-Oxo-3,8a-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (3b): Following 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); $[\alpha]_D^{22}=+9.2$ ($c=1.0$ in MeOH), $[\alpha]_D^{22}=+20.4$ ($c=0.63$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): $\delta=1.60$ (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 ppm (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta=$ 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 ppm (C); IR (film): $\tilde{\nu}=1650\ cm^{-1}$; 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): Following 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); $[\alpha]_D^{22}=+$ 4.3 ($c=1.0$ in EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz, HETCOR): $\delta=1.58$ (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 ppm (dd, $J=2.4$, 0.9 Hz, 1H, H-2pyr); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta=15.2$ (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 ppm (C); IR (KBr): $\tilde{\nu}=1653\ cm^{-1}$; elemental analysis calcd (%) for $C_{18}H_{18}N_20_2$: C 73.45, H 6.16, N 9.52; found: C 73.51, H 6.25, N 9.64.

General procedure for the reduction reactions: *Method A*: A mixture of 9-BBN (0.5 M in THF, 1–10 equiv) and the lactam (1 equiv) was refluxed for 5–8 h. Then the crude mixture was cooled to 0 °C, a 1:1 solution of aqueous 2 N 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 purified by chromatography.

Method B: Red-Al (0.1 M in THF, 2.5–5 equiv) was added to a solution of the lactam (1 equiv) in anhydrous THF and the mixture was refluxed 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 purified by chromatography.

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 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 purified by chromatography.

Method D: BH_3 (1 M THF, 3 equiv) was added to a solution of the 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 0.2 N NaOH, and extracted with EtOAc. The combined organic extracts were dried and concentrated and the residue was purified by chromatography.

(2*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-phenylpiperidine (4b): Following the procedure described in the above Method B, from lactam **3b** (100 mg, 0.34 mmol) and Red-Al (0.1 M 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]; $[\alpha]_D^{22}=-165.1$ ($c=0.95$ in $CHCl_3$) [lit:[29] $[\alpha]_D^{20}=-165.9$ ($c=1.0$ in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): $\delta=1.12$–1.26 (m, 1H, H-4), 1.53–1.76 (m, 5H, 2×H-3, H-4, 2×H-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 (br s, 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 ppm (m, 8H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta=24.9$ (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 ppm (C); IR (film): $\tilde{\nu}=3441\ cm^{-1}$; 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): Following the procedure described in the above Method A, from lactam **3b** (1 g, 3.4 mmol) and 9-BBN (0.5 M in THF, 68.2 mL, 34 mmol) in THF (40 mL) for 8 h, piperidine **5b** (720 mg, 75%) was obtained after flash chromatography (gradient hexane to 7:3 hexane/EtOAc): m.p. 77–78 °C (Et_2O/hexane), [lit.:[27] 78 °C]; $[\alpha]_D^{22}=-30.2$ ($c=1.1$ in $CHCl_3$) [lit:[29] $[\alpha]_D^{20}=-30.3$ ($c=1.08$ in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): $\delta=1.25$–1.80 (m, 7H, 2×H-3, 2H-4, 2×H-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, 2×H-2′), 7.20–7.42 ppm (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta=25.1$ (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 ppm (C); IR (film): $\tilde{\nu}=3405\ cm^{-1}$; 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-(3-pyridyl)piperidine (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: $[\alpha]_D^{22}=-120.0$ ($c=1.3$ in $CHCl_3$) [lit.:[30] $[\alpha]_D^{22}=-123.1$ ($c=1.3$ in $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=1.18$–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 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta=24.7$ (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 ppm (CH); IR (film): $\tilde{\nu}=3408\ cm^{-1}$.

5c: $[\alpha]_D^{22}=-22.7$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=$ 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 ppm (d, $J=$ 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta=24.9$ (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 ppm (CH); IR (film): $\tilde{\nu}=3355\ cm^{-1}$.

(2*R*,3*R*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-methylpiperidine (12a): Following the procedure described 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):

$[\alpha]_D^{22} = -15.2$ ($c = 1.36$ in MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY): $\delta = 0.79$ (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, 2×H-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 ppm (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta = 9.9$ (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 ppm (C); IR (film): $\nu = 3414$ 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): Following the procedure described in the above Method D, from lactam **9o** (175 mg, 0.52 mmol) and BH_3 (1 M in THF, 1.58 mL, 1.58 mmol) in THF (8 mL), piperidine **14a** was obtained (103 mg, 61%) after flash chromatography (gradient 8:2 EtOAc/hexane to EtOAc): $[\alpha]_D^{22} = -53.0$ ($c = 0.5$ in MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR): $\delta = 0.88$ (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 ppm (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR): $\delta = 11.1$ (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 ppm (C); IR (film): $\nu = 3440$, 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 the 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 the disappearance of the 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), piperidine **6b** (50 mg, 58%) was obtained as a transparent oil after flash chromatography (CH_2Cl_2): $[\alpha]_D^{22} = -26.9$ ($c = 1.0$ in MeOH), $[\alpha]_D^{22} = -63.8$ ($c = 0.5$ in $CHCl_3$) [lit.:[29] $[\alpha]_D^{20} = -27.0$ ($c = 0.43$ in MeOH)]; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.43$–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 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) $\delta =$ 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 ppm (C); IR (film): $\nu = 3420$ 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) pure anabasine (**6c**, 70 mg, 81%) was obtained as a transparent oil after flash chromatography (95:5 EtOAc/EtOH): $[\alpha]_D^{22} = -74.7$ ($c = 0.1$ in $CHCl_3$) [lit.:[30] $[\alpha]_D^{22} = -75.5$ ($c =$ 0.1 in $CHCl_3$)], $[\alpha]_D^{22} = -77.04$ ($c = 0.5$ in MeOH) [lit.:[31] $[\alpha]_D^{24} = -79.2$ ($c =$ 0.5 in MeOH)]; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.50$–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 ppm (d, $J = 1.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta = 25.2$ (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 ppm (CH).

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[1] For reviews, see: a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249–330; b) M. Ohno, M. Otsuka, *Org. React.* **1989**, *37*, 1–55.

[2] For a review on the controlled racemization of optically active compounds, see: E. J. Ebbers, G. J. A. Ariaans, J. P. M. Houbiers, A. Bruggink, B. Zwanenburg, *Tetrahedron* **1997**, *53*, 9417–9476.

[3] For reviews, see: a) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; b) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490; c) S. Caddick, K. Jenkins, *Chem. Soc. Rev.* **1996**, *25*, 447–456; d) H. Stecher, K. Faber, *Synthesis* **1997**, 1–16; e) U. T. Strauss, U. Felfer, K. Faber, *Tetrahedron: Asymmetry* **1999**, *10*, 107–117; f) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321–331; g) K. Faber, *Chem. Eur. J.* **2001**, *7*, 5005–5010; h) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327, and references therein.

[4] For reviews, see: a) R. S. Ward, *Chem. Soc. Rev.* **1990**, *19*, 1–19; b) B. Danieli, G. Lesma, D. Passarella, S. Riva in *Advances in the Use of Synthons in Organic Chemistry, Vol. 1* (Ed.: A. Dondoni), JAI Press, London, **1993**, pp. 143–219; c) S. R. Magnuson *Tetrahedron* **1995**, *51*, 2167–2213; d) E. Schoffers, A. Golebiowski, C. R. Johnson, *Tetrahedron* **1996**, *52*, 3769–3826; e) M. C. Willis, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1765–1784; f) B. Danieli, G. Lesma, D. Passarella, A. Silvani, *Curr. Org. Chem.* **2000**, *4*, 231–261; g) E. García-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313–353; see also ref. [1b].

[5] a) G. M. Strunz, J. A. Findlay in *The Alkaloids, Vol. 26* (Ed.: A. Brossi), Academic Press, London, **1985**, pp. 89–183; b) H. Takahata, T. Momose in *The Alkaloids, Vol. 44* (Ed.: G. A. Cordell), Academic Press, San Diego, CA, **1993**, pp. 189–256; c) S. Ohmiya, K. Saito, I. Murakoshi in *The Alkaloids, Vol. 47* (Ed.: G. A. Cordell), Academic Press, San Diego, CA, **1995**, pp. 1–114; d) M. J. Schneider in *Alkaloids: Chemical and Biological Perpectives, Vol. 10* (Ed.: S. W. Pelletier), Pergamon Press, Oxford, **1996**, pp. 155–299; e) R. J. Andersen, R. W. M. Van Soest, F. Kong in *Alkaloids: Chemical and Biological Perpectives, Vol. 10* (Ed.: S. W. Pelletier), Pergamon Press, Oxford, **1996**, pp. 301–355; f) J. W. Daly, H. M. Garraffo, T. F. Spande in *Alkaloids: Chemical and Biological Perspectives, Vol. 13* (Ed.: S. W. Pelletier), Pergamon Press, New York, **1999**, pp. 1–161; g) P. S. Watson, B. Jiang, B. Scott, *Org. Lett.* **2000**, *2*, 3679; h) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 603–626, and previous reviews in this series.

[6] a) M. Rubiralta, E. Giralt, A. Díez, *Piperidine. Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*, Elsevier, Amsterdam, **1991**; b) C. Kibayashi in *Studies in Natural Products Chemistry. Stereoselective Synthesis (Part G), Vol. 11* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1992**, pp. 229–275; c) J. Cossy, P. Vogel in *Studies in Natural Products Chemistry. Stereoselective Synthesis (Part H), Vol. 12* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1993**, pp. 275–363; d) S. R. Angle, J. G. Breitenbucher in *Studies in Natural Products Chemistry, Part J; Vol. 16* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1995**, pp. 453–502; e) S. Leclerq, D. Daloze, J.-C. Braekman, *Org. Prep. Proced. Int.* **1996**, *28*, 501–543; f) P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.* **1998**, 633–640; g) H.-P. Husson, J. Royer, *Chem. Soc. Rev.* **1999**, *28*, 383–394; h) D. L. Comins, *J. Heterocycl. Chem.* **1999**, *36*, 1491–1500; i) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781–1813; j) B. Guilloteau-Bertin, D. Compère, L. Gil, C. Marazano, B. C. Das, *Eur. J. Org. Chem.* **2000**, 1391–1399; k) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953–2989; l) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701–1729.

[7] For reviews, see: a) A. I. Meyers, G. P. Brengel, *Chem. Commun.* **1997**, 1–9; b) M. D. Groaning, A. I. Meyers, *Tetrahedron* **2000**, *56*, 9843–9873; for recent work, see: c) J. Jiang, R. J. DeVita, G. A. Doss, M. T. Goulet, M. J. Wyvratt, *J. Am. Chem. Soc.* **1999**, *121*, 593–594; d) M. Amat, J. Bosch, J. Hidalgo, M. Cantó, M. Pérez, N.

Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque, *J. Org. Chem.* **2000**, *65*, 3074–3084; e) S. M. Allin, D. G. Vaidya, S. L. James, J. E. Allard, T. A. D. Smith, V. Mckee, W. P. Martin, *Tetrahedron Lett.* **2002**, *43*, 3661–3663; f) M. Amat, N. Llor, J. Hidalgo, C. Escolano, J. Bosch, *J. Org. Chem.* **2003**, *68*, 1919–1928; g) M. Amat, C. Escolano, N. Llor, M. Huguet, M. Pérez, J. Bosch, *Tetrahedron: Asymmetry* **2003**, *14*, 1679–1683; h) N. Casamitjana, M. Amat, N. Llor, M. Carreras, X. Pujol, M. M. Fernández, V. López, E. Molins, C. Miravitlles, J. Bosch, *Tetrahedron: Asymmetry* **2003**, *14*, 2033–2039; i) S. M. Allin, C. I. Thomas, K. Doyle, M. R. J. Elsegood, *J. Org. Chem.* **2005**, *70*, 357–359; j) M. Amat, C. Escolano, O. Lozano, A. Gómez-Esqué, R. Griera, E. Molins, J. Bosch, *J. Org. Chem.* **2006**, *71*, 3804–3815.

[8] For related work, see: a) H. Poerwono, K. Higashiyama, T. Yamauchi, H. Kubo, S. Ohmiya, H. Takahashi, *Tetrahedron* **1998**, *54*, 13955–13970; b) M. Amat, N. Llor, M. Huguet, E. Molins, E. Espinosa, J. Bosch, *Org. Lett.* **2001**, *3*, 3257–3260; c) M. Penhoat, V. Levacher, G. Dupas, *J. Org. Chem.* **2003**, *68*, 9517–9520; d) P. Tremmel, J. Brand, V. Knapp, A. Geyer, *Eur. J. Org. Chem.* **2003**, 878–884; e) L. F. Roa, D. Gnecco, A. Galindo, J. L. Terán, *Tetrahedron: Asymmetry* **2004**, *15*, 3393–3395; f) T. Tite, M.-C. Lallemand, E. Poupon, N. Kunesch, F. Tillequin, C. Gravier-Pelletier, Y. Le Merrer, H.-P. Husson, *Bioorg. Med. Chem.* **2004**, *12*, 5091–5097; g) C. Agami, L. Dechoux, S. Hebbe, C. Ménard, *Tetrahedron* **2004**, *60*, 5433–5438; h) X. Wang, Y. Dong, J. Sun, X. Xu, R. Li, Y. Hu, *J. Org. Chem.* **2005**, *70*, 1897–1900; i) S. Calvet-Vitale, C. Vanucci-Bacqué, M.-C. Fargeau-Bellassoued, G. Lhommet, *Tetrahedron* **2005**, *61*, 7774–7782.

[9] For a preliminary account of this part of the work, see: M. Amat, M. Cantó, N. Llor, J. Bosch, *Chem. Commun.* **2002**, 526–527.

[10] a) M. J. Munchhof, A. I. Meyers, *J. Org. Chem.* **1995**, *60*, 7084–7085; b) S. Fréville, J. P. Célérier, V. M. Thuy, G. Lhommet, *Tetrahedron: Asymmetry* **1995**, *6*, 2651–2654; c) A. I. Meyers, C. J. Andres, J. E. Resek, C. C. Woodall, M. A. McLaughlin, P. H. Lee, D. A. Price, *Tetrahedron* **1999**, *55*, 8931–8952; see also: d) L. Micouin, J. C. Quirion, H.-P. Husson, *Tetrahedron Lett.* **1996**, *37*, 849–852; e) S. Fréville, M. Bonin, J.-P. Célérier, H.-P. Husson, G. Lhommet, J.-C. Quirion, V. M. Thuy, *Tetrahedron* **1997**, *53*, 8447–8456.

[11] For previous asymmetric syntheses, see: a) W. Pfrengle, H. Kunz, *J. Org. Chem.* **1989**, *54*, 4261–4263; b) K. Hattori, H. Yamamoto, *Tetrahedron* **1993**, *49*, 1749–1760; c) J.-M. Andrés, I. Herráiz-Sierra, R. Pedrosa, A. Pérez-Encabo, *Eur. J. Org. Chem.* **2000**, 1719–1726; d) A. Barco, S. Benetti, C. De Risi, P. Marchetti, G. P. Pollini, V. Zanirato, *Eur. J. Org. Chem.* **2001**, 975–986; e) F.-X. Felpin, S. Girard, G. Vo-Thanh, R. J. Robins, J. Villiéras, J. Lebreton, *J. Org. Chem.* **2001**, *66*, 6305–6312.

[12] a) For a preliminary account of this part of the work, see: M. Amat, M. Cantó, N. Llor, V. Ponzo, M. Pérez, J. Bosch, *Angew. Chem.* **2002**, *114*, 345–348; *Angew. Chem. Int. Ed.* **2002**, *41*, 335–338; b) for cyclocondensation reactions of γ-aryl δ-oxo acid derivatives, see: M. Amat, M. Cantó, N. Llor, C. Escolano, E. Molins, E. Espinosa, J. Bosch, *J. Org. Chem.* **2002**, *67*, 5343–5351.

[13] For synthetic applications of **7d** and **7f** see: a) M. Amat, M. Pérez, N. Llor, J. Bosch, E. Lago, E. Molins, *Org. Lett.* **2001**, *3*, 611–614; b) M. Amat, M. Pérez, N. Llor, C. Escolano, F. J. Luque, E. Molins, J. Bosch, *J. Org. Chem.* **2004**, *69*, 8681–8693; c) M. Amat, M. Pérez, A. T. Minaglia, N. Casamitjana, J. Bosch, *Org. Lett.* **2005**, *7*, 3653–3656; see also ref. [7j].

[14] For related examples involving DKR which lead to tricyclic five-membered lactams, see: a) J. A. Ragan, M. C. Claffey, *Heterocycles* **1995**, *41*, 57–70; b) M. D. Ennis, R. L. Hoffman, N. B. Ghazal, D. W. Old, P. A. Mooney, *J. Org. Chem.* **1996**, *61*, 5813–5817; c) J. A. Nieman, M. D. Ennis, *Org. Lett.* **2000**, *2*, 1395–1397; d) S. M. Allin, S. L. James, M. R. J. Elsegood, W. P. Martin, *J. Org. Chem.* **2002**, *67*, 9464–9467.

[15] Starting from aryl ketone **1g**, the initially formed minor stereoisomer **7g** underwent epimerization at C-8a to a *trans*-8,8a relative configuration as a consequence of the benzylic character of the C-8a–O bond.

[16] a) S. Arséniyadis, P. Q. Huang, N. Morellet, J.-C. Beloeil, H.-P. Husson, *Heterocycles* **1990**, *31*, 1789–1799; b) H. Takahashi, T. Tsubuki, K. Higashiyama, *Heterocycles* **1992**, *33*, 281–290.

[17] For mechanistic considerations about the stereochemistry in related cyclocondensation reactions of unsubstituted keto acids, see: A. I. Meyers, S. V. Downing, M. J. Weiser, *J. Org. Chem.* **2001**, *66*, 1413–1419.

[18] M. Amat, M. Huguet, N. Llor, O. Bassas, A. M. Gómez, J. Bosch, J. Badia, L. Baldoma, J. Aguilar, *Tetrahedron Lett.* **2004**, *45*, 5355–5358.

[19] For a related example, see: J.-P. Alazard, C. Terrier, A. Mary, C. Thal, *Tetrahedron* **1994**, *50*, 6287–6298.

[20] For reviews, see: a) T. Fujii, M. Ohba, *Heterocycles* **1988**, *27*, 1009–1033; b) T. Fujii, M. Ohba, *Heterocycles* **1998**, *47*, 525–539.

[21] For a review on 1,2-amino alcohols as chiral auxiliaries, see: D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–875.

[22] For a preliminary account covering part of these results, see: M. Amat, O. Bassas, M. A. Pericàs, M. Pastó, J. Bosch, *Chem. Commun.* **2005**, 1327–1329.

[23] Although both alcohol **19** (see ref. [23a]) and phenol **20** (see ref. [23b]) have been prepared in enantiopure forms, we used them as racemates, which are more easily accessible: a) S. Liu, J. F. K. Müller, M. Neuburger, S. Schaffner, M. Zehnder, *Helv. Chim. Acta* **2000**, *83*, 1256–1267; b) N. Yamazaki, M. Atobe, C. Kibayashi, *Tetrahedron Lett.* **2001**, *42*, 5029–5032.

[24] For cyclocondensation reactions of **20** and *ent*-**21** with unbranched keto acids, see: N. Yamazaki, T. Ito, C. Kibayashi, *Tetrahedron Lett.* **1999**, *40*, 739–742.

[25] For a review on the use of *cis*-1-amino-2-indanol in asymmetric synthesis, see: A. K. Ghosh, S. Fidanze, C. H. Senanayake, *Synthesis* **1998**, 937–961.

[26] a) C. Puigjaner, A. Vidal-Ferran, A. Moyano, M. A. Pericàs, A. Riera, *J. Org. Chem.* **1999**, *64*, 7902–7911; b) M. Pastó, B. Rodríguez, A. Riera, M. A. Pericàs, *Tetrahedron Lett.* **2003**, *44*, 8369–8372.

[27] A. I. Meyers, G. Knaus, K. Kamata, M. E. Ford, *J. Am. Chem. Soc.* **1976**, *98*, 567–576.

[28] G. B. R. de Graaff, W. C. Melger, J. V. Bragt, S. Schukking, *Recl. Trav. Chim. Pays-Bas*, **1964**, *83*, 910–918.

[29] H. Poerwono, K. Hihashiyama, T. Yamauchi, H. Takahashi, *Heterocycles* **1997**, *46*, 385–400.

[30] J. M. Andrés, I. Herráiz-Sierra, R. Pedrosa, A. Pérez-Encabo, *Eur. J. Org. Chem.* **2000**, 1719–1726.

[31] K. Hattori, H. Yamamoto, *J. Org. Chem.* **1992**, *57*, 3264–3265.

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