Highly enantioselective dynamic kinetic resolution and desymmetrization processes by cyclocondensation of chiral aminoalcohols with racemic or prochiral δ-oxoacid derivatives†

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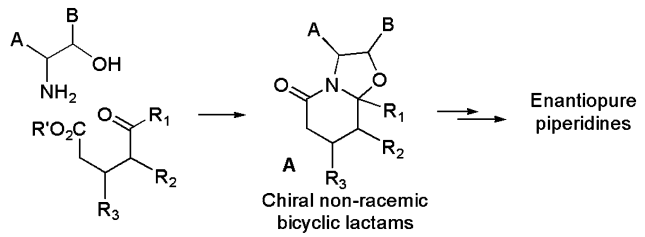
Cyclocondensation reactions of aminoalcohols 7 and 8 with racemic or prochiral δ-oxoacid derivatives provide polysubstituted lactams with high enantioselectivity in a process that involves dynamic kinetic resolution and/or desymmetrization of enantiotopic or diastereotopic ester groups.

The development of new and practical methodologies for the generation of 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. Since the piperidine ring is the central structure of many biologically active alkaloid natural products and therapeutic agents, with thousands of piperidine compounds mentioned as drug candidates in clinical and preclinical studies,[1] much effort has been devoted to the development of general methods for the synthesis of enantiopure piperidine derivatives.[2]

In this context, in previous work we have demonstrated that simple phenylglycinol-derived bicyclic lactams **A** ($R_1 = R_2 = R_3 = H$; Scheme 1) are versatile synthons that provide easy access to a variety of enantiopure substituted piperidines by successive introduction of the substituents on the lactam ring.[3] More recently, we envisaged a procedure for the direct generation of bicyclic lactams **A** that already incorporate the carbon substituents on the heterocyclic ring.[4] It involves the dynamic kinetic resolution (DKR)[5] of racemic δ-oxoacid derivatives or the desymmetrization[6] of prochiral δ-oxodiesters in cyclocondensation processes using (*R*)- or (*S*)-phenylglycinol. However, the moderate diastereoselectivity (4 : 1) of most of the above phenylglycinol-induced cyclocondensations was a synthetic drawback that had to be overcome.



Scheme 1

† Electronic supplementary information (ESI) available: Typical experimental procedure and ^1H and ^{13}C NMR spectra for all new compounds. See http://www.rsc.org/suppdata/cc/b4/b413937b/

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In this communication we report highly enantioselective cyclocondensation reactions involving DKR and/or differentiation of enantiotopic or diastereotopic ester groups using a variety of δ-oxoacid derivatives including simple racemic aldehydes (**1**) and ketones (**2**, **3**), prochiral aldehydo-diesters bearing enantiotopic ester groups (**4** and **6**), and racemic aldehydo-diesters bearing diastereotopic ester groups (**5**; Fig. 1).

Preliminary studies using 3-amino-3-phenyl-1-propanol or 2-(1-aminoethyl)phenol were disappointing because cyclocondensation reactions with aldehyde **1** and ketones **2** and **3** took place with low stereoselectivity and/or chemical yield.

More successful results, in particular with ketones, were obtained using *cis*-1-amino-2-indanol (**7**), a conformationally rigid analog of phenylglycinol (Table 1). Thus, although cyclocondensation with aldehyde **4** took place in good chemical yield with a stereoselectivity similar to that previously observed when using phenylglycinol[4] giving lactam **10a** as the major product, no DKR was observed from racemic aldehyde **1**. Interestingly, the generation of enantiopure lactam **10a** (isolated in 60% yield) involves the enantioselective desymmetrization of two enantiotopic ester groups. In contrast, cyclocondensation of **7** with racemic ketones **2** and **3** took place in excellent chemical yield and with better stereoselectivity than when using phenylglycinol. Enantiopure tetracyclic lactams **11b** and **12b** were isolated in 61% and 77% yield, respectively, thus making evident that DKR of the isomerizable stereocenter α to the ketone carbonyl had occurred to a considerable extent.

The best results in terms of chemical yield and stereoselectivity in cyclocondensation reactions with aldehydes were obtained when using aminoalcohol **8**.[7] Thus, **8** reacted with racemic aldehyde **1** to give a 9 : 1 stereoisomeric mixture of lactams **13** in 78% yield.[8] Similarly, prochiral aldehydo-diesters **4** and **6** underwent highly enantioselective desymmetrizations during cyclocondensation with **8** since 14 : 1 and 24 : 1 stereoisomeric mixtures of the respective lactam esters **14** and **16** were formed in excellent yield. The major

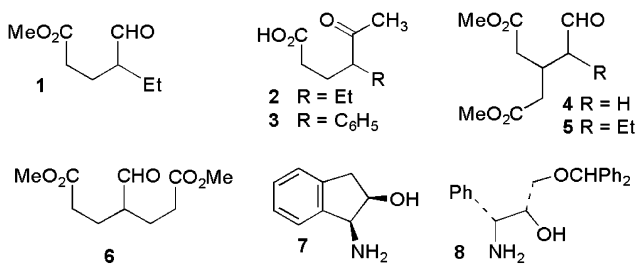
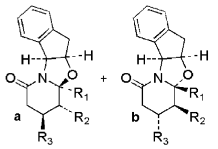
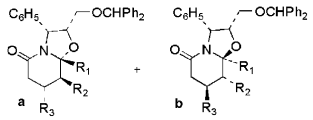


Fig. 1

Table 1 Cyclocondensation reactions of aminoalcohols with racemic or prochiral δ-oxoacid derivatives

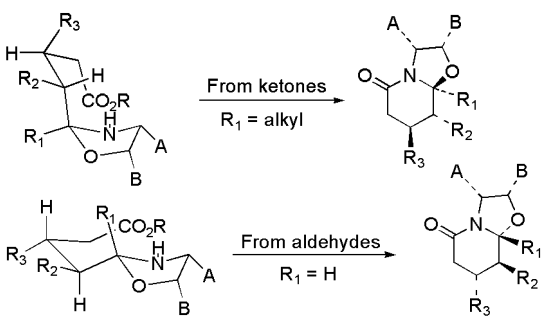
Starting materials	Products		R_1	R_2	R_3	Yield	**a** : **b** Ratio
1 + **7**		**9**	H	Et	H	87%	7 : 5: 3[a]
4 + **7**		**10**	H	H	CH_2CO_2Me	78%	4 : 1
2 + **7**		**11**	CH_3	Et	H	74%	1 : 8
3 + **7**		**12**	CH_3	C_6H_5	H	86%	1 : 13
1 + **8**		**13**	H	Et	H	78%	9 : 1
4 + **8**		**14**	H	H	CH_2CO_2Me	86%	14 : 1
5 + **8**		**15**	H	Et	CH_2CO_2Me	77%	15:1
6 + **8**		**16**	H	$(CH_2)_2CO_2Me$	H	77%	24 : 1
2 + **8**		**17**	CH_3	Et	H	81%	2 : 3

[a] **a** : **b**: **c** ratio (**c** is the epimer of **b** at the piperidine α-position).

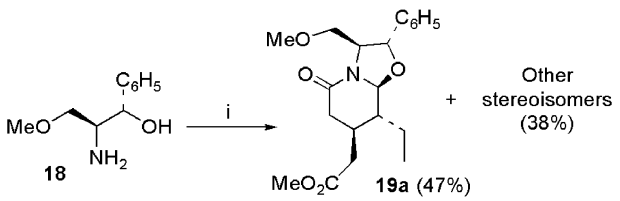
isomers **a** were isolated in 80% and 74% yield, respectively. As could be expected from the above results, racemic aldehydo-diester **5** on reaction with aminoalcohol **8** stereoselectively provided one of the eight possible stereoisomeric lactams, **15a**, which was isolated in 65% yield. Three stereogenic centers with a well-defined absolute configuration have been generated in a single synthetic step in a highly stereoselective process that involves DKR, with epimerization of the configurationally labile stereocenter in the substrate, and desymmetrization of two diastereotopic acetate chains.

The stereochemical outcome of the above reactions can be accounted for by considering that the diastereomeric imines formed after interaction of the aminoalcohol with the aldehyde or ketone carbonyl group are in equilibrium *via* an enamine and, consequently, that a mixture of equilibrating oxazolidines is formed. Subsequent irreversible lactamization takes place faster from the diastereomer that allows a less hindered approach of the ester group to the nitrogen atom, *via* a transition state in which all the substituents in the incipient chair-like six-membered lactam, including the diastereotopic ester chain that does not undergo cyclization, are equatorial (Scheme 2).

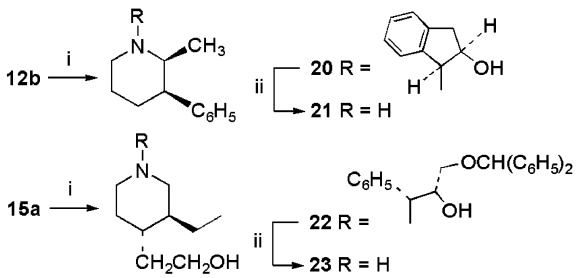
The higher stereoselectivities observed in cyclocondensations promoted by *erythro* aminoalcohols **7** (from ketones) and **8** (from aldehydes) as compared to phenylglycinol can be rationalized taking into account that the substituents A and B in the intermediate oxazolidine are on the same face of the ring, thus making the opposite face more easily accessible. In agreement with this interpretation, cyclocondensation of *threo* aminoalcohol **18**[9] with racemic diester **5** took place with low stereoselectivity to give a mixture of lactams **19** (Scheme 3).



Scheme 2



Scheme 3 *Reagents and conditions*: (i) **5**, toluene, reflux.



Scheme 4 *Reagents and conditions*: (i) BH_3·THF, 89% (**20**), 78% (**22**). (ii) H_2, $Pd(OH)_2$/C, MeOH, 68% (**21**), 72% (**23**).

To fully illustrate the synthetic usefulness of the above methodology, lactams **12b** and **15a** were converted into the corresponding enantiopure piperidines **21** and **23** by a two-step sequence involving borane reduction, followed by removal of the auxiliary by catalytic hydrogenation from the resulting *N*-substituted piperidines **20** and **22**, respectively (Scheme 4).

The highly enantioselective processes reported herein, leading to a variety of polysubstituted lactams in a single synthetic step, expand the potential of these chiral synthons for the enantioselective construction of diversely substituted piperidine derivatives.

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8 A similar cyclocondensation from racemic ketone **2** occurred (81% yield) with low stereoselectivity (3 : 2 ratio).

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