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Enantio- and Diastereoconvergent Cyclocondensation Reactions. Synthesis of Enantiopure *cis*-Decahydroquinolines

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Abstract: Up to four stereocenters with a well-defined configuration are generated in a single synthetic step by cyclocondensation of (*R*)-phenylglycinol or (1*S*,2*R*)-1-amino-2-indanol with stereoisomeric mixtures (racemates, meso forms, diastereoisomers) of cyclohexanone-based δ-keto acid and δ-keto diacid derivatives in enantio- and diastereoconvergent processes that involve dynamic kinetic resolution and/or desymmetrization of enantiotopic groups. A detailed analysis of the stereochemical outcome of the process is presented. The methodology provides easy access to enantiopure 8- and 6,8-substituted *cis*-decahydroquinolines, including alkaloids of the myrioxazine group.

Keywords: alkaloids • asymmetric synthesis • diastereoselectivity • lactams • nitrogen heterocycles

Introduction

The development of practical synthetic methods for the generation of multiple stereogenic centers with high diastereo- and enantioselectivity in a single synthetic step continues to be a challenging goal in synthetic organic chemistry. Such methods generally rely on the concerted or sequential generation of the stereocenters by stereocontrolled formation of two or more carbon–carbon bonds in the key step. An alternative approach in which all the stereogenic or prostereogenic centers are already present in a starting material consisting of a mixture of enantiomers and/or diastereoisomers has been less explored. The desired stereoselectivity in these enantio- and diastereoconvergent processes is ensured by dynamic kinetic resolution of the racemic substrate[1] and /or by differentiation of diastereotopic or enantiotopic ligands.[2]

In this context, some years ago we reported[3] enantioselective dynamic kinetic resolution and desymmetrization processes by cyclocondensation of chiral aminoalcohols with racemic and prochiral δ-oxoacid derivatives, ultimately leading to enantiopure polysubstituted piperidines.[4]

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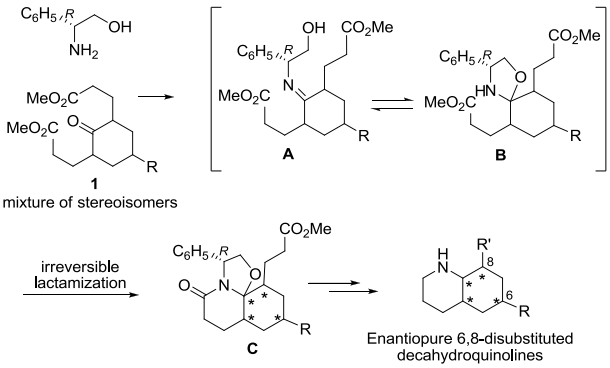
With the aim of exploring the synthetic potential of this methodology in the assembly of more complex enantiopure heterocyclic scaffolds, we planned to study cyclocondensation reactions of (*R*)-phenylglycinol with cyclohexanone-based δ-keto diesters **1**. Starting from a mixture of stereoisomeric δ-keto diesters **1** (*dl*, meso), the initially formed imines **A** would give rise to mixtures of four (R = H) or eight (R = substituent) stereoisomeric oxazolidines **B**, which would presumably be in equilibrium via the corresponding enamines. We hoped that the final, kinetically controlled, irreversible lactamization would selectively furnish one of the eight (R = H) or sixteen (R = substituent) possible diastereoisomeric tricyclic lactams **C**, in a process involving the generation of up to four stereocenters with a well-defined configuration in a single synthetic step (Scheme 1). This highly stereoconvergent process could open a straightforward route to enantiopure decahydroquinolines bearing substituents at the carbocyclic ring (6 and 8 positions).



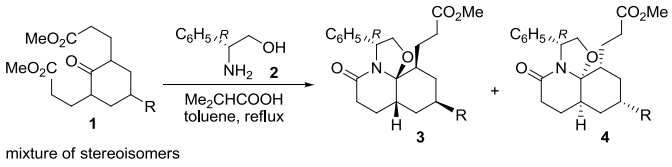
Scheme 1. Synthetic strategy.

Results and Discussion

In the event, refluxing a toluene solution of keto diester **1a**[5] (approximately 4:1 mixture of *cis*/*trans* isomers) with (*R*)-

phenylglycinol (**2**) in the presence of isobutyric acid gave a 3:1 mixture of tricyclic lactams **3a** and **4a**, respectively, in 86 % yield (Table 1).[6] A desymmetrization with differentiation of two enantiotopic propionate chains occurred from the *cis* (meso) isomer, whereas a dynamic kinetic resolution, with epimerization of the configurationally labile stereocenters in the substrate, took place from the *trans* isomers (an enantiomeric pair).

Table 1. Cyclocondensation reactions of δ-keto diesters **1** with (*R*)-phenylglycinol.

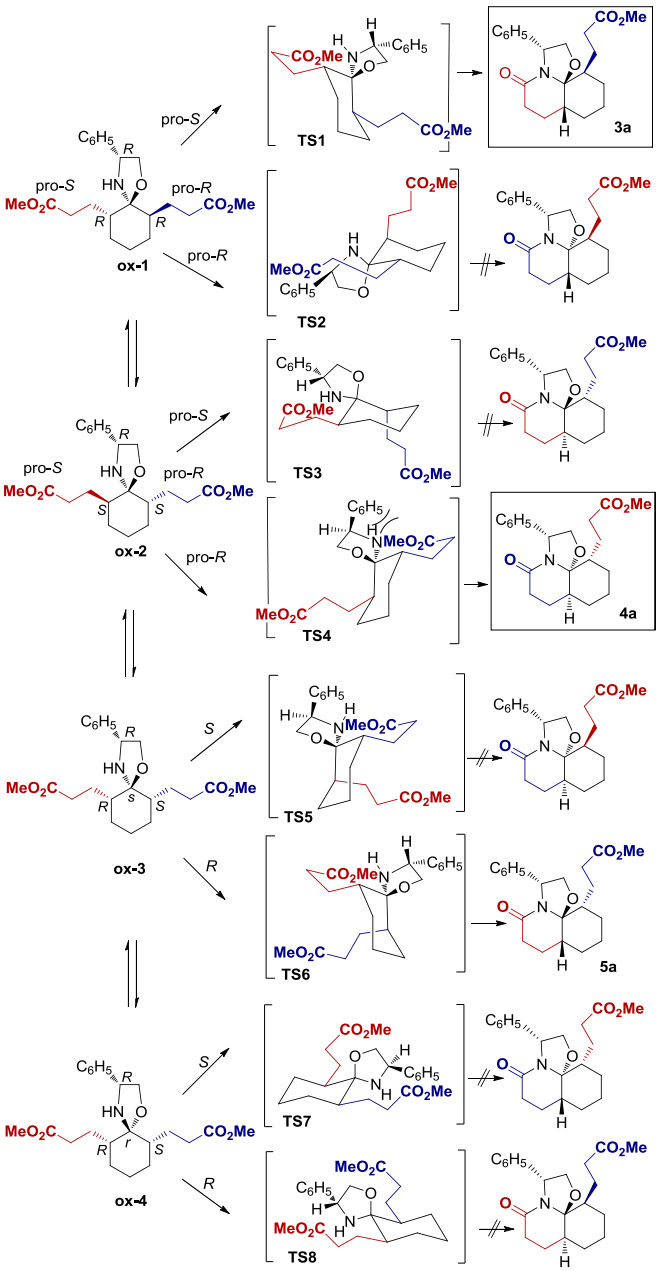


Entry	Substrate	R	Yield [%]	**3:4** Ratio
1	**1a**	H	86	3:1
2	**1b**	Me	75	7:3
3	**1c**	C_6H_5	82	4:1
4	**1d**	CH_2OPMB	83	7:3

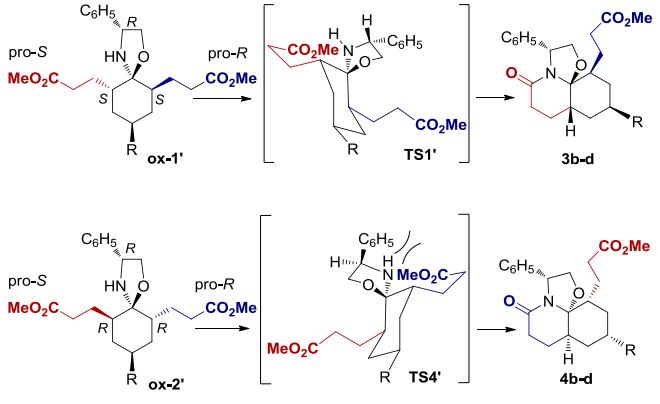
Scheme 2 outlines the four intermediate equilibrating oxazolidines resulting from the three stereoisomeric keto diesters **1a** and, in each case, the two possible lactamization pathways, which depend on the enantiotopic or diastereotopic propionate chain involved, and the corresponding chair-like transition states **TS1**-**TS8**, all of them with an equatorial exocyclic C–C bond at the 5-position of the incipient six-membered lactam. Lactamization eventually occurred to give *cis*-fused perhydroquinolones **3a** and **4a** as the major products, via oxazolidines **ox-1** and **ox-2** and transition states **TS1** and **TS4**, in which the propionate chain that does not undergo cyclization is equatorial with respect to the cyclohexane ring. The predominance of lactam **3a** is a consequence of the final irreversible lactamization being faster via **TS1**, which allows a less hindered approach of the ester group to the oxazolidine nitrogen, *anti* with respect to the phenyl substituent. Due to steric constraints no *trans*-fused lactams are formed.

The above results encouraged us to perform similar cyclocondensation reactions from keto diesters **1b-d** (mixtures of two meso forms and one enantiomeric pair),[7] which incorporate an additional substituent at the 4-position of the cyclohexanone ring. Gratifyingly, although sixteen different stereoisomeric tricyclic lactams could *a priori* be formed from the eight possible intermediate equilibrating oxazolidines, the process was highly stereoconvergent, leading to the *cis*-fused tricyclic lactams **3b-d**[8] and **4b-d**[9] in good yield and stereoselectivity (see Table 1).

The stereoselective formation of these lactams can be rationalized as in the above unsubstituted **a** series. The major lactams **3b-d** proceed from the irreversible lactamization of the pro-*S* propionate chain in oxazolidine **ox-1'**, via a transition state **TS1'** in which both the exocyclic C–C bond at the 5-position of the incipient piperidone ring and the R and propionate substituents at the cyclohexane ring are equatorial (Scheme 3). Similar all-*cis* transition states **TS4'**, arising from oxazolidine **ox-2'** but suffering from the repulsive interaction with the phenyl substituent, would account for the generation of lactams **4b-d** as minor products. Remarkably, an additional enantioselective desymmetrization occurred in these series as the 4-substituted carbon of the starting stereoisomeric mixtures of cyclohexanones **1b-d** becomes a stereogenic center with a well-defined configuration at the 6-position of the perhydroquinolone ring.



Scheme 2. Detailed analysis of the lactamization step.



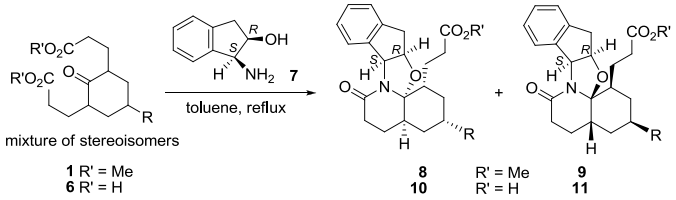
b R = Me; **c** R = C_6H_5; **d** R = CH_2OPMB

Scheme 3. Lactamization step in the cyclocondensation of **1b-d** with (*R*)-phenylglycinol (**2**).

The use of (1*S*,2*R*)-*cis*-1-amino-2-indanol (**7**),[10] a conformationally rigid analog of phenylglycinol, in the above

cyclocondensations slightly improved the stereoselectivity (Table 2), although the separation of the resulting diastereoisomers was quite problematic and had to be performed in a subsequent synthetic step. As the absolute configuration of the benzylic stereocenter in the starting amino alcohol is *S*, the decahydroquinoline stereocenters in the major diastereoisomers **8** and **10** have an opposite configuration to that of the major isomers **3** obtained from *R*-phenylglycinol.

Table 2. Cyclocondensation reactions of δ-keto acid derivatives **1** and **6** with (1*S*,2*R*)-*cis*-1-amino-2-indanol (**7**).

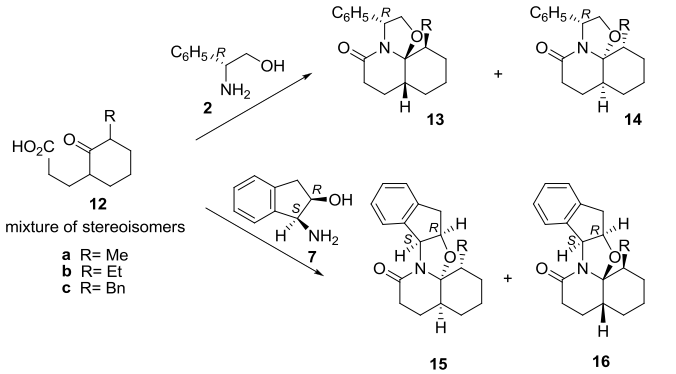


Entry	Substrate	R	R'	Yield [%]	Products[a],[b]	Ratio[c]
1	**1a**[d]	H	Me	82	**8a**+**9a**	3:1
2	**1b**[d]	Me	Me	67	**8b**+**9b**	3:1
3	**6c**	C_6H_5	H	[e]	**10c**+**11c**	6:1

[a] Diastereoisomers were not separated at this stage. [b] See reference 9. [c] Calculated by NMR from the crude reaction mixture. [d] In the presence of $Me_2CHCOOH$. [e] Not purified.

To expand the scope of the methodology, we explored related cyclocondensation reactions from cyclohexanone-based δ-keto acids **12a-c** (mixtures of two enantiomeric pairs)[11] bearing an additional substituent at the α'-position of the ketone carbonyl. The reactions led in all cases to a major lactam (**13**[8] or **15**) through a process that involves dynamic kinetic resolution with epimerization of the two configurationally labile stereocenters of the starting mixture of keto acids. As illustrated in Table 3, in this series aminoindanol **7** gave

Table 3. Cyclocondensation reactions of δ-keto acids **12** with amino alcohols **2** and **7**.

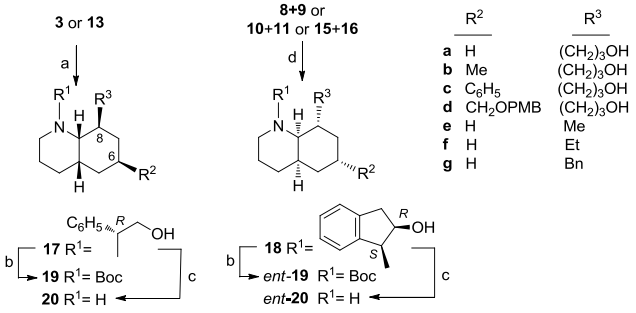


Entry	Reagents[a]	R	Yield [%]	Products[b]	Ratio
1	**2** + **12a**	Me	76	**13a** + **14a**	3:1
2	**2** + **12b**	Et	70	**13b** + **14b**	3:1
3	**2** + **12c**	Bn	72	**13c** + **14c**	7:3
4	**7** + **12a**	Me	78	**15a** + **16a**[c]	9:1[d]
5	**7** + **12b**	Et	78	**15b** + **16b**[c]	4:1[d]
6	**7** + **12c**	Bn	95	**15c** + **16c**[c]	5:1[d]

[a] Conditions: toluene, reflux. [b] See reference 9. [c] Diastereoisomers were not separated at this stage. [d] Calculated by NMR from the crude reaction mixture.

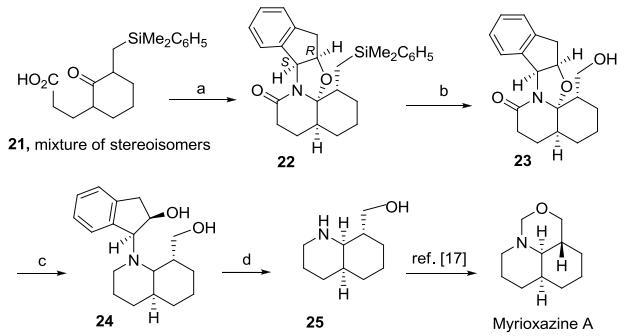
better results in terms of chemical yield and stereoselectivity than phenylglycinol **2**. Lactamization to the minor isomers **16** was further hampered by the presence of the indan nucleus *cis*-fused to the oxazolidine ring. The stereochemical outcome of these cyclocondensations can be rationalized on the basis of an analysis similar to that outlined in Scheme 2.

The chiral auxiliaries were easily removed taking advantage of the benzylic character of the exocyclic carbon-nitrogen bond in the above phenylglycinol- and aminoindanol-derived lactams. Thus, after only two additional steps, stereoselective alane reduction and catalytic hydrogenation with or without the presence of Boc_2O, tricyclic lactams **3** and **13** were converted to *cis*-decahydroquinolines **19** and **20**,[12] bearing substituents at the 6- and/or 8-positions of the carbocyclic ring (Scheme 4).[13] A similar two-step sequence from diastereoisomeric mixtures of pentacyclic aminoindanol-derived lactams **8**+**9**, **10**+**11** or **15**+**16** led to decahydroquinolines *ent*-**19** and *ent*-**20**. In this series, the major diastereoisomers **18** were satisfactorily isolated after the alane reduction.



Scheme 4. Synthesis of enantiopure substituted *cis*-decahydroquinolines. Reagents and conditions: a) $LiAlH_4$, $AlCl_3$, 60-90 %; b) H_2, $Pd(OH)_2$, MeOH, Boc_2O, 70-97 %; c) H_2, $Pd(OH)_2$, MeOH, 70-95 %; d) $LiAlH_4$, $AlCl_3$, then separation of diastereoisomers, 63-84 %.

To illustrate the usefulness of the methodology in the enantioselective synthesis of natural products, we applied it to the synthesis of myrioxazine A, a tricyclic alkaloid isolated from *Myrioneuron nutans*[14] that embodies an 8-substituted *cis*-decahydroquinoline moiety. Due to the difficulties encountered in preparing a δ-keto acid **12** bearing the *O*-protected hydroxymethyl substituent required to assemble the perhydro-1,3-oxazine ring, as the starting material for the synthesis we selected the silyl derivative **21** (mixture of two racemates)[11] since the $SiMe_2C_6H_5$ group can be envisaged as a masked hydroxy group (Scheme 5).[15]



Scheme 5. Enantioselective synthesis of myrioxazine A. Reagents and conditions: a) **7**, toluene, reflux; 74 %; b) $HBF_4{\cdot}Et_2O$, CH_2Cl_2, then *m*-CPBA, anh. KF, DMF, 60 %, then separation of diastereoisomers; c) $LiAlH_4$, $AlCl_3$, 75 %; d) H_2, $Pd(OH)_2$, MeOH, 66 %.

In this series, cyclocondensation with aminoindanol **7** also took place in good yield (74 %) and excellent stereoselectivity to give a major lactam **22** (d.r. 6:1). After oxidation of the silyl derivative **22** using Fleming's conditions,[16] removal of the chiral auxiliary by the usual two-step process gave aminoalcohol **25**, a known synthetic precursor of myrioxazine A.[17] The synthesis of **25** also represents a formal synthesis of the alkaloids (–)-myrionine,[18] (–)-myrionidine,[12b] (–)-schoberine,[12b] and (+)-*N*-formylmyrionine.[19]

Conclusion

In conclusion, the developed methodology allows the straightforward (only three synthetic steps) enantioselective generation of substituted *cis*-decahydroquinoline scaffolds from easily accessible stereoisomeric mixtures (racemates, meso forms, diastereoisomers) of δ-keto acid derivatives that already incorporate all the quinolone carbons and substitutents. The key step is an enantio- and diastereoconvergent cyclocondensation with a chiral non-racemic amino alcohol, which acts as a chiral latent source of ammonia. The equilibration of the intermediate oxazolidines, via the corresponding imines/enamines, ensures the stereoselective formation of the kinetic lactams regardless of the stereochemistry of the starting keto acid derivatives, in a process that involves dynamic kinetic resolution and/or desymmetrization of enantiotopic groups, with generation of up to four stereocenters of predictable absolute configuration in a single synthetic step.

Experimental Section

General Procedure for Cyclocondensation Reactions

From keto esters: *(R)*-Phenylglycinol (**2**, 1.3 equiv) or (1*S*,2*R*)-*cis*-1-amino-2-indanol (**7**, 1.3 equiv) and isobutyric acid (2.8 equiv) were added to a 0.06 M solution of keto diester **1** (1 equiv) in toluene. The mixture was heated at reflux for 19 h, with azeotropic elimination of water by a Dean-Stark system. Additional 1.3 equiv of aminoalcohol were added, and the stirring was continued for 5 h. After cooling, the mixture was concentrated under reduced pressure, and the resulting residue was dissolved in EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried, filtered, and concentrated. Flash chromatography of the residue under silica afforded lactams **3** and **4** (from **2**) or **8** and **9** (from **7**).

From keto acids: (*R*)-Phenylglycinol (**2**, 1.5 equiv) or (1*S*,2*R*)-*cis*-1-amino-2-indanol (**7**, 1-1.5 equiv) was added to a 0.1 M solution of keto acid **6**, **12** or **21** in toluene, and the mixture was heated at reflux for 24 h in the presence of anhydrous $MgSO_4$ (2 equiv). The suspension was filtered, and the filtrate was concentrated. Flash chromatography of the residue under silica afforded lactams **13** and **14** (from **2** and **12**), **15** and **16** (from **7** and **12**) or **22** (from **7** and **21**). The crude mixture of lactams **10** and **11** (from **6** and **7**) was used without further purification in the next reaction.

General Procedure for Alane Reductions

$LiAlH_4$ (6.6 equiv) was slowly added to a suspension of $AlCl_3$ (2.2 equiv) in THF at 0 ºC. The mixture was stirred at 25 ºC for 30 min and cooled to – 78 ºC. Then, a 0.08 M THF solution of pure lactam **3**, **13** or **23**, or a mixture of lactams **8**+**9**, **10**+**11** or **15**+**16**, (1 equiv) was added dropwise. After being stirred at – 78 ºC for 1-2 h, the mixture was allowed to reach room temperature and stirred for a 2-18 h period. Water was added, the resulting mixture was filtered through Celite®, the filtrate was concentrated, and the residue was taken up with EtOAc or CH_2Cl_2. The organic solution was washed with brine, dried, filtered, and concentrated. The resulting residue was purified by flash chromatography to give *cis*-decahydroquinolines **17** (from **3** or **13**), **18** (from the mixtures **8**+**9**, **10**+**11** or **15**+**16**) or **24** (from **23**).

General Procedure for Hydrogenation Reactions

Method A: A 0.04 M solution of *cis*-decahydroquinoline **17** or **18** (1 equiv) and di-*tert*-butyl dicarbonate (3 equiv) in EtOAc or MeOH was hydrogenated at rt for 8 h at atmospheric pressure in the presence of $Pd(OH)_2$ or Pd-C. The catalyst was removed by filtration, and the solvent was evaporated. The resulting oil was chromatographed to afford decahydroquinolines **19** (from **17**) or *ent*-**19** (from **18**).

Method B: The reaction was carried out as in the above method A but without adding di-*tert*-butyl dicarbonate. The resulting crude oil was chromathographed (compounds **20a-d**) or purified as follows: a solution of the oil in EtOAC was extracted with 1% aqueous HCl, the aqueous layer was basified with 10% aqueous KOH and extracted with ether. The combined organic extracts were dried, filtered and evaporated.

(1*R*,4a*S*,8a*S*,13a*R*,14a*R*)-1-[(Dimethylphenylsilyl)methyl]-7-oxo-3-phenyl-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydroindeno[1',2':4,5]oxazolo[2,3-*j*]quinoline (22): Following the general procedure for cyclocondensation reactions, from keto acid **21** (359 mg, 1.13 mmol) and (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol (**7**, 252 mg, 1.70 mmol) in anhydrous toluene (12 mL) containing anhydrous $MgSO_4$ (272 mg), a 6:1 (calculated by ^{1}H NMR) mixture of lactam **22** and its **(1*S*,4a*R*,8a*S*,13a*R*,14a*S*)** isomer (360 mg, 74%), and trace amounts of pure **22** were obtained after flash chromatography (SiO_2, from 1:1 to 0:1 hexane–CH_2Cl_2). Data for **22**: $[\alpha]^{23}_D$ +148.6 (*c* 0.33, MeOH); IR (NaCl): 1658, 1392 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY-HSQC, 25 °C) δ: -0.20 (dd, *J* = 14.8, 10.8 Hz, 1H, CH_2Si), -0.034 (d, *J* = 15.6 Hz, 1H), -0.09 (s, 3H, CH_3), 0.04 (s, 3H, CH_3), 0.32 (d, *J* = 13.6 Hz, 1H); 1.21-1.14 (m, 1H), 1.32-1.47 (m, 4H), 1.64-1.71 (m, 2H), 1.83-1.90 (m, 2H), 1.99-2.09 (m, 1H), 2.31-2.41 (m, 1H), 3.19 (d, *J* = 2.8 Hz, 2H, H-13), 4.75-4.78 (m, 1H, H-13a), 5.87 (d, *J* = 5.6 Hz, 1H, H-8a), 7.19-7.32 (m, 8H, ArH), 7.54 (d, *J* = 5.6 Hz, H-11); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ: -2.6 (CH_3), -2.2 (CH_3), 14.2 (C-1'), 18.8 (C-5), 19.8 (C-3), 26.6 (C-4), 28.2 (C-2), 30.7 (C-6), 36.1 (C-4a), 38.1 (C-13), 38.5 (C-1), 66.0 (C-8a), 77.7 (C-13a), 99.3 (C-14a), 124.9 (ArC), 126.4 (ArC), 127.4 (ArC), 127.6 (ArC), 128.3 (ArC), 128.7 (ArC), 133.4 (ArC), 139.1 (C-*i*), 141.0 (C-*i*), 141.7 (C-*i*), 171.3 (CO); HMRS calculated for $[C_{27}H_{33}NO_2Si+H]^+$: 432.2353; found: 432.2365.

(1*R*,4a*S*,8a*S*,13a*R*,14a*R*)-1-(Hydroxymethyl)-7-oxo-3-phenyl-1,2,3,4,4a,5,6,7,8a,13,13a,14a-dodecahydroindeno[1',2':4,5]oxazolo[2,3-*j*]quinoline (23): A solution of the above 6:1 mixture of lactams **22** and its isomer (110 mg, 0.26 mmol) and tetrafluoroboric acid-diethyl ether complex (1 mL, 0.51 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 1 h. The mixture was concentrated, and the residue was taken up with DMF (1 mL). Anhydrous potassium fluoride (61.4 mg, 1.05 mmol) and *m*-chloroperbenzoic acid (217 mg, 0.88 mmol) were added, and the pale yellow suspension was stirred for 16 h. The resulting mixture was filtered and the filtrate was concentrated. Flash chromatography (amine functionalized silica, 1:1 hexane–AcOEt) afforded lactam **23** (49 mg, 60 %) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HSQC, 25 ºC) : 1.40-1.45 (m, 2H, H-3, H-4), 1.50-1.55 (m, 2H, H-2, H-3), 1.62-1.70 (m, 2H, H-1, H-4), 1.80-1.93 (m, 4H, H-2, H-4a, H-5), 2.52-2.56 (m, 1H, H-6), 2.79 (dd, *J* = 11.6, 4.8 Hz, 1H, H-1'), 2.89 (dd, *J* = 11.6, 4.8 Hz, 1H, H-1'), 3.18 (d, *J* = 2.8 Hz, 1H, H-13), 4.74 (q, *J* = 2.8 Hz, 1H, H-13a), 5.88 (d, *J* = 5.2 Hz, 1H, H-8a), 7.26-7.30 (m, 3H, H-9, H-10, H-12), 7.52 (d, *J* = 6.8 Hz, 1H, H-11); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC) : 18.7 (C-5), 19.1 (C-3), 25.7 (C-4), 26.5 (C-2), 28.3 (C-6), 37.4 (C-13), 38.2 (C-4a), 42.3 (C-1),62.5 (C-1'), 65.9 (C-8a), 77.8 (C-13), 98.2 (C-14a), 125.4 (ArH), 126.0 (ArH), 127.8 (ArH), 128.8 (ArH), 140.2 (C-*i*), 140.8 (C-*i*), 171.8 (CO).

(4a*S*,8*R*,8a*S*)-1-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]-8-(hydroxymethyl)decahydroquinoline (24): Following the general procedure for alane reductions (reaction conditions: 1 h at – 78 ºC and 18 h at room temperature), from $LiAlH_4$ (30 mg, 0.80 mmol) and $AlCl_3$ (33 mg, 0.24 mmol) in THF (3 mL) and a solution of lactam **23** (38 mg, 0.12 mmol) in THF (1 mL), decahydroquinoline **24** (27 mg, 75%) was obtained as an oil after flash chromatography (SiO_2, from 1:0 to 95:5 CH_2Cl_2–MeOH): $[\alpha]^{22}_D$ – 4.8 (*c* 0.9, MeOH); IR (NaCl) 3301 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ: 0.99-1.73 (m, 11H), 2.13-2.23 (m, 3H), 2.70-2.80 (m, 2H), 2.83-2.89 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.00-3.07 (m, 2H), 3.58-3.60 (m, 1H), 3.70 (dd, *J* = 10.8, 4.4 Hz, 1H), 4.27-4.34 (m, 2H), 7.10-7.20 (m, 3H, ArH), 7.37 (d, *J* = 6.8 Hz, 1H, ArH); Several of the signals in the ^{13}C NMR spectrum of **24** at 25 ºC were broad and ill-defined, even not observed, thus indicating the existence of a slow conformational equilibrium. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC) δ: 20.2 (CH_2), 23.0 (CH_2), 29.7 (CH_2), 31.2 (CH), 39.6 (CH_2), 67.9 (CH_2), 125.4 (ArC), 126.3 (ArC), 127.3 (ArC), 128.4 (ArC), 140.2 (C-*i*), 142.5 (C-*i*); HMRS calculated for $[C_{19}H_{27}NO_2 + H]^+$: 302.2115; found: 302.2121.

(4a*S*,8*S*,8a*R*)-8-(Hydroxymethyl)decahydroquinoline (25): A solution of **24** hydrochloride (41 mg, 0.11 mmol) in MeOH (3 mL) containing 40% $Pd(OH)_2$ (16 mg) was hydrogenated at rt for 24 h at atmospheric pressure. The catalyst was removed by filtration, and the solvent was evaporated. The residue was taken-up with ether, washed with 10% aqueous NaOH solution, dried, filtered, and concentrated to afford **25** (10 mg, 66%), as an oil. Data for **25**: $[\alpha]^{22}_D$ – 2.0, (*c*. 0.15, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ: 0.74-0.90 (m, 1H), 1.34-1.48 (m, 6H), 1.54-1.57 (m, 1H), 1.70-1.77 (m, 3H),

2.10-2.20 (m, 1H), 2.54-2.70 (br s, 2H), 2.76-2.84 (m, 3H), 3.50 (t, J = 10.0 Hz, 1H, CH_2OH), 3.61 (dd, J = 10.8, 3.6 Hz, 1H, CH_2OH); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ: 19.9 (C-6), 25.1 (C-4), 27.8 (C-3), 28.4 (C-7), 31.4 (C-5), 33.4 (C-8), 37.5 (C-4a), 40.0 (C-2), 61.0 (C-8a), 70.7 (C-1').

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[6] Trace amounts of another stereoisomer, **5a** (see Scheme 2), were also isolated in some runs.

[7] Keto diesters **1b-d** (mixtures of stereoisomers) were prepared in 70-90% yield from the corresponding 4-substittuted cyclohexanones, by dialkylation of their pyrrolidine enamines with methyl acrylate in refluxing ethanol.

[8] The absolute configuration of lactams **3c, 13a,** and **14a** was unambiguously determined from the X-ray crystallographic analysis. CCDC 947819 (**3c**), 947820 (**13a**), and 947821 (**14a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] In some cases, trace amounts of other stereoisomers were detected by NMR in the crude reaction mixtures or isolated after chromatographic purification (see Supporting Information).

[10] a) 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; b) For cyclocondensation reactions of *cis*-1-amino-2-indanol with unbranched δ-keto acids, see: N. Yamazaki, T. Ito, C. Kibayashi, *Tetrahedron Lett*. **1999**, *40*, 739–742. See also ref. [3].

[11] Keto acids **12** and **21** (mixtures of stereoisomers) were prepared in excellent overall yields from the corresponding α-substituted cyclohexanones: 1. i) LDA, ClTMS, THF; ii) $CH_2{=}N^+Me_2Cl^-$, CH_2Cl_2; iii) 2N HCl. 2. i) $CH_2(CO_2Et)_2$, NaOH, toluene; ii) AcOH, HCl, reflux.

[12] The ^1H and ^{13}C NMR spectra of **20a** at 25 ºC indicated the presence of two conformations (see Supporting Information). For NMR conformational studies of *cis*-decahydroquinolines, including 6- and 8-substituted derivatives, see: a) F. W. Vierhapper, E. L. Eliel, *J. Org. Chem*. **1977**, *42*, 51–62; b) V. C. Pham, A. Jossang, A. Chiaroni, T. Sévenet, V. H. Nguyen, B. Bodo, *Org. Lett*. **2007**, *9*, 3531–3534.

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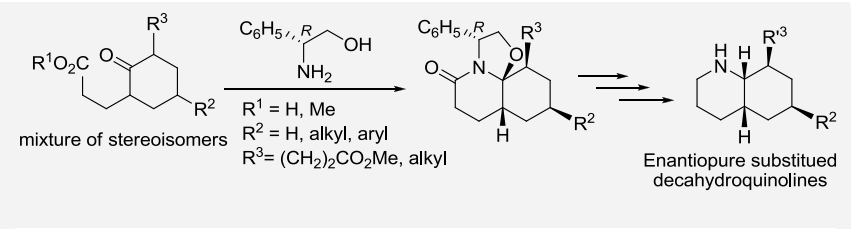
Enantio- and Diastereoconvergent Cyclocondensation Reactions. Synthesis of Enantiopure *cis*-Decahydroquinolines



Up to four stereocenters are generated by reaction of (*R*)-phenylglycinol or (1*S*,2*R*)-1-amino-2-indanol with stereoisomeric mixtures of δ-keto acid derivatives in stereoconvergent processes that involve dynamic kinetic resolution and/or desymmetrization of enantiotopic groups. The methodology provides easy access to *cis*-decahydroquinoline alkaloids of the myrioxazine group.