ARTICLE

Cyclocondensation reactions of racemic diastereomers of dimethyl-2-oxocyclohexanepropionic acids with (*R*)-phenylglycinol: access to both enantiomers of dimethyl *cis*-decahydroquinolines†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Arnau Calbó, Rosa Griera, Joan Bosch and Mercedes Amat *

Starting from racemic diastereomeric mixtures of dimethyl-2-oxocyclohexanepropionic acids (**4**-**6**) the synthesis of enantiopure 7,8-, 6,8-, and 5,8-dimethyl-substituted *cis*-decahydroquinolines (**11**, **13**, and **15**) and their enantiomers (*ent*-**11**, *ent*-**13**, and *ent*-**15**) is reported. The procedure involves a dynamic kinetic asymmetric transformation in the cyclocondensation of keto-acids **4**-**6** with (*R*)-phenylglycinol to give in each case two major oxazoloquinolone lactams (**7a**/**7b**, **8a**/**8b**, **9a**/**9b**), which differ in the absolute configuration of all the stereogenic centers except that of the chiral inductor. A subsequent two-step stereoselective removal of the phenylglycinol moiety with simultaneous reduction of the lactam carbonyl affords the enantiopure *cis*-decahydroquinolines in both enantiomeric series.

Introduction

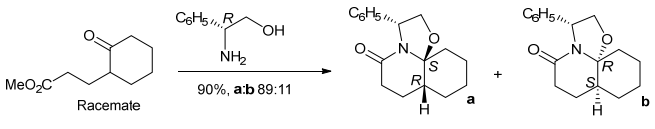
The search for new and efficient methodologies for the preparation of optically pure compounds continues to be an important issue in synthetic organic chemistry, particularly in the context of the synthesis of drugs and bioactive products.[1] In this respect, the development of practical synthetic methods for the generation of multiple stereocenters with high diastereo- and enantioselectivity in a single synthetic step has long constituted a challenging goal for organic chemists.

The preparation of a single enantiomer from a racemate may be achieved by conventional resolution procedures or by exploiting the differences in reactivity, as in the enzymatic[2] and nonenzymatic[3] kinetic resolutions. The main drawback of these widely used de-racemization processes is that the maximum yield of the isolated enantiomer is always limited to 50%. A more efficient approach for the transformation of enantiomeric or diastereomeric mixtures into a single stereoisomeric product is the dynamic kinetic resolution (DKR) of racemates,[4] 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 or epimerization during the reaction. The resolution of racemates via diastereomeric intermediates as well as the de-epimerization of diastereomeric mixtures are dynamic kinetic asymmetric transformations (DYKATs),[5] which have been extensively used to access enantiomerically pure compounds.

In previous work we have explored the synthetic utility of aminoalcohol-derived tricyclic oxazoloquinolone lactams as chiral scaffolds for the enantioselective total synthesis of decahydroquinoline alkaloids.[6] The decahydroquinoline core is found as a prime structural motif in a wide variety of biologically relevant natural products, ranging from diversely substituted simple decahydroquinolines to more complex polycyclic systems.

The simplest oxazoloquinolone lactam, lacking substituents on the decahydroquinoline core, was easily available in a single step by cyclocondensation of (*R*)-phenylglycinol and racemic methyl 2-oxocyclohexanepropionate. The reaction was highly stereoselective, leading to an 89:11 diastereomeric mixture of lactams **a** and **b** in excellent yield,[6i] in a process involving the de-racemization of the epimerizable stereocenter at the ketone α-position and the generation of a second stereocenter from the prochiral carbonyl (Scheme 1).

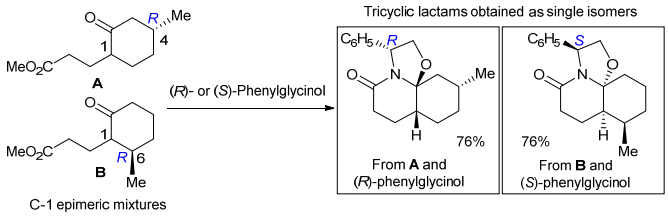
Subsequent studies using 4- and 6-methyl substituted cyclohexanones revealed the dramatic influence of the absolute configuration of the non-isomerizable C-4 and C-6 stereocenters on the stereochemical course of the reactions with (*R*)- or (*S*)-phenylglycinol.[6g] Thereby, treatment of keto-esters **A** with (*R*)-phenylglycinol or **B** with (*S*)-phenylglycinol provided single isomers of the corresponding tricyclic lactams (Scheme 2), whereas mixtures of isomers in modest or very low



Scheme 1 Access to simple oxazoloquinolone lactam.

Laboratory of Organic Chemistry, Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine (IBUB), University of Barcelona, 08028-Barcelona, Spain. E-mail: amat@ub.edu

†Electronic Supplementary Information available. See DOI:



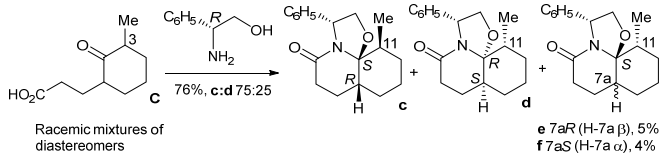
Scheme 2 Cyclocondensation reactions using 4- and 6-methyl substituted cyclohexanones.

selectivity were observed from the pairs **A** and (*S*)-phenylglycinol or **B** and (*R*)-phenylglycinol.

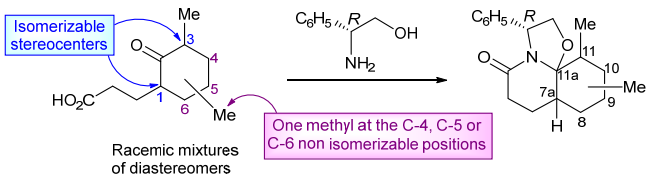
On the other hand, the cyclocondensation of (*R*)-phenylglycinol with a mixture of racemic cyclohexanone-propionic acid diastereomers **C,** which incorporate a methyl substituent at the isomerizable 3-position, afforded the 11-methyl substituted tricyclic lactams **c** and **d** in a 75:25 ratio. This dynamic kinetic asymmetric transformation involves the epimerization of the two configurationally labile stereocenters of the starting mixture of keto-esters. Only small amounts of other diastereomers (**e** and **f**) were isolated (Scheme 3).[6c]

With these precedents in mind, we decided to analyze the stereoselectivity in the generation of tricyclic lactams from racemic diastereomeric mixtures of 2-oxocyclohexanepropionic acids bearing two methyl groups on the carbocyclic ring, one at the isomerizable C-3 position and the other at the C-4, C-5 or C-6 position. Their cyclocondensation with (*R*)- or (*S*)-phenylglycinol would lead to enantiopure 10,11-, 9,11- or 8,11-disubstituted tricyclic lactams (Scheme 4).

Since the C-4, C-5 or C-6 stereocenters in the above cyclohexanones cannot isomerize, in each case the reaction can provide two series of lactams differing at least in the configuration of these non-isomerizable stereocenters: a C-7a, C-11, and C-11a diastereomeric mixture of tricyclic lactams with an *S* configuration (*S* series) at the non-epimerizable stereocenter (C-10, C-9 or C-8) and an analogous mixture with an *R* configuration (*R* series) at this stereocenter. Obviously, the highest possible yield for each series is 50%. Therefore, the main goal of this work was to analyze the stereoselectivity in the formation of tricyclic oxazoloquinolone lactams in both *R* and *S* series (configuration of the non-isomerizable stereocenter), with the final purpose of establishing a procedure for the stereoselective preparation of enantiopure disubstituted decahydroquinolines from racemic mixtures of diastereomeric keto-acids.



Scheme 3 Cyclocondensation reaction using a mixture of racemic isomerizable diastereomers.



Scheme 4 Cyclocondensation reactions studied in this work.

Results and discussion

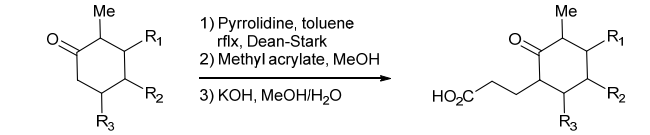
The required keto-acids **4**-**6** were easily available by Michael addition of the pyrrolidine-enamines of cyclohexanones **1**-**3** to methyl acrylate, followed by saponification of the resulting methyl esters (Scheme 5). The starting dimethyl cyclohexanones **1**-**3** were prepared following reported procedures.[7]

Heating a mixture of keto-acid **4** and (*R*)-phenylglycinol in refluxing benzene for 24 h stereoselectively afforded two major tricyclic lactams, **7a** (10*R* series; 28%) and **7b** (10*S* series; 30%), showing an opposite configuration at the four stereocenters on the carbocyclic ring. Two minor diastereomeric lactams, **7c** and **7d**, differing in the configuration at the C-7a position were also isolated in the 10*R* series. Lactam **7b** was isolated as the only isomer in the 10*S* series (Scheme 6A).

Similarly, cyclocondensation of keto-acid **5** with (*R*)-phenylglycinol stereoselectively afforded lactams **8a** (9*R* series) and **8b** (9*S* series) in 31% and 34% yield, respectively. Only trace amounts of other two diastereomers in the 9*R* series, **8c** and **8d**, differing in the configuration at the C-7a stereocenter were isolated from the reaction mixture (Scheme 6B).

Finally, tricyclic lactams **9a** (8*S* series) and **9b** (8*R* series) were obtained in 30% and 29% yield, respectively, by cyclocondensation of keto-acid **6** with (*R*)-phenylglycinol. Again, only very minor amounts of other two diastereomers, **9c** and **9d**, differing in the configuration at the C-7a stereocenter were observed in the 8*S* series (Scheme 6C).

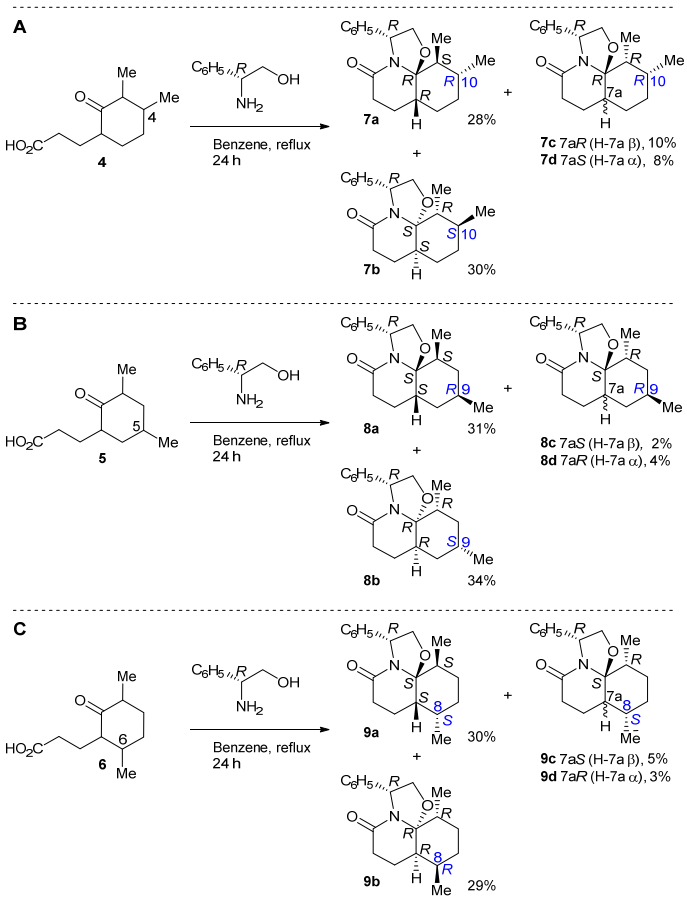
The above results indicate that the simultaneous presence of two methyl substituents in the starting keto-acid, one at a non-isomerizable position of the cyclohexanone ring and the other at the isomerizable C-3 position, induces a high degree of stereoselectivity in the studied cyclocondensation reactions. This results in the formation of two major tricyclic lactams (**7a**/**7b**, **8a**/**8b** and **9a**/**9b**; about 30% yield each one) that differ in the absolute configuration of the four stereogenic centers on the carbocyclic ring. Only minor amounts of two other diastereomers were isolated. Starting from a mixture of a



1 R_1 = Me, R_2 = R_3 = H
2 R_1 = H, R_2 = Me, R_3 = H
3 R_1 = R_2 = H, R_3 = Me

4 R_1 = Me, R_2 = R_3 = H (87%)
5 R_1 = H, R_2 = Me, R_3 = H (43%)
6 R_1 = R_2 = H, R_3 = Me (84%)

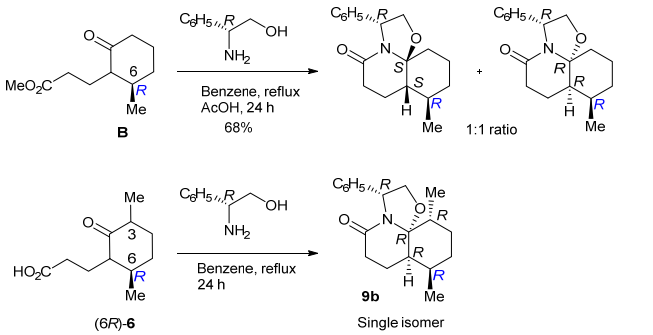
Scheme 5 Synthesis of the starting keto-acids.



Scheme 6 Cyclocondensation reaction of keto-acids **4-6**.

mixture of eight stereoisomers (four racemates), a remarkable dynamic kinetic asymmetric transformation occurred, in which three stereogenic centers with a well-defined configuration were generated by de-epimerization of the isomerizable C-1 and C-3 positions of the starting carbocyclic ring and the spiro chiral carbon of the intermediate spiro-oxazolidine.

For comparison purposes, Scheme 7 summarizes the stereochemical outcome of the cyclocondensation reactions of (*R*)-phenylglycinol with keto-ester **B**, with a defined *R* configuration at C-6 (see Scheme 2), and with the 6*R* stereoisomers of keto-acid **6** (6*R* series). As can be observed, keto-ester **B** afforded an equimolecular mixture of tricyclic lactams that differ in the configuration of the ring fusion carbons C-7a and C-11a.[6g] In contrast, the presence of a methyl substituent at the isomerizable C-3 position of the analogous keto-acid (6*R*)-**6** provokes the generation of a single isomer (**9b**). However, in a similar cyclocondensation with a mixture of racemic diastereomers **C**, lacking the C-6 methyl substituent, the lactam with the same configuration at C-7a and C-11a as **9b** was a minor isomer (**d** in Scheme 3).[6c] Therefore, both C-3 and C-6 methyl substituents cooperatively contribute to increase or even invert the stereoselectivity of the reaction.



Scheme 7 The effect of the 3-methyl substituent in the 6*R* series.

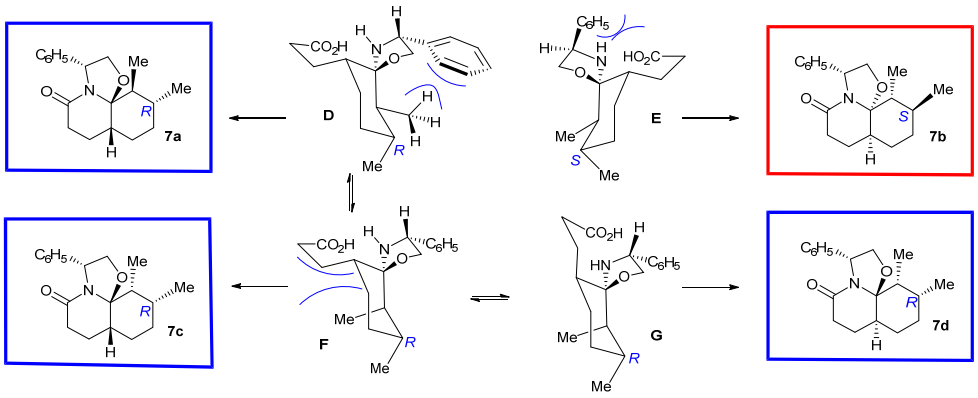
The high stereoselectivity observed in the formation of tricyclic lactams **7a**/**7b**, **8a**/**8b** and **9a**/**9b** can be rationalized by considering that the reaction of (*R*)-phenylglycinol with the keto-acids **4**, **5** and **6**, respectively, affords a mixture of 16 diastereomeric spiro-oxazolidines. Eight of them (*R* configuration at the non-isomerizable stereocenter) are in equilibrium through the corresponding imine-enamines, as are the other eight in the *S* series. In both series, the final irreversible lactamization step takes place faster from the spiro-oxazolidines in which the two methyl substituents on the cyclohexane ring are equatorial.

For instance, in the reaction of keto-ester **4** with (*R*)-phenylglycinol, the intermediate spiro-oxazolidines **D** (10*R* series) and **E** (10*S* series) display both methyl substituents in equatorial disposition, leading to the major isomers **7a** and **7b**, respectively (Scheme 8).

The formation of two minor isomers, **7c** and **7d**, in the 10*R* series can be attributed to the severe steric interactions in **D** between the phenyl group and the isomerizable methyl substituent, which induce a configurational change of this stereocenter via the equilibrium oxazolidine-imine-enamine.

However, in oxazolidine **F**, which is the precursor of lactam **7c**, the isomerizable methyl substituent shows a 1,3-diaxial interaction with the propionate chain. This strain is released in oxazolidine **G**, generated by an inversion in the configuration of the stereocenter next to this chain, again via the equilibrium oxazolidine-imine-enamine. Oxazolidine **G** is the precursor of the highly strained lactam **7d**, with a *trans* fusion of the two six-membered rings. It is worth mentioning that the formation of two minor diastereomers (**e** and **f**; Scheme 3) with the same relative configuration at the C-7a, C-11 and C-11a positions as lactams **7c** and **7d** was already observed[6c] in the cyclocondensation of keto-ester **C** (the C-4 demethyl analog of **4**) with (*R*)-phenylglycinol.

The C_6H_5/CH_3 interactions do not exist in the spiro-oxazolidine **E** (10*S* series), since the phenyl substituent is on the opposite face of the oxazolidine ring, so a single lactam **7b** was formed in this series. The lower yield (30%) in the cyclocondensation leading to **7b** in comparison with the overall yield for the lactams in the 10*R* series (**7a** + **7c** + **7d**; 46%) could be accounted for by considering that in **7b** the carboxylate approaches the nitrogen from the more hindered face of the oxazolidine, next to the phenyl substituent.



Scheme 8 Stereochemical outcome of the cyclocondensation reaction from keto-acid **4**.

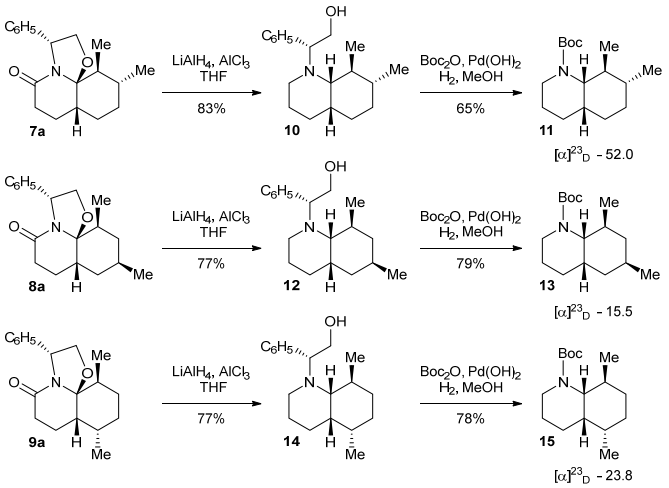
A similar analysis of the results observed in the cyclocondensation of keto-acid **5**, leading to tricyclic lactams **8a-d**, and keto-acid **6**, providing lactams **9a-d**, allows the course of these reactions to be rationalized (see Schemes S1 and S2 in the ESI).

The configurational assignment of all new tricyclic lactams was unequivocally determined by X-ray analysis, except for compounds **7d** and **8d**. On the other hand, the ^{1}H- and ^{13}C-NMR spectra show characteristic signals for protons and carbons at the C-2 and C-3 positions on the oxazolidine ring, which are of diagnostic value (see the ESI).

Attempts to improve the stereoselectivity of the above cyclocondensations by using the conformationally more rigid (1*S*,2*R*)-aminoindanol, instead of (*R*)-phenylglycinol, resulted in mixtures of lactams. As they could not be separated by chromatographic methods, and the ratio of isomers could not be determined by GC-MS, no further studies were performed using this chiral inductor.

To demonstrate the synthetic utility of the above tricyclic lactams, the two major isomers of each series were converted into the corresponding enantiomeric pairs of dimethyl *cis*-decahydroquinolines. Thus, treatment of lactams **7a**, **8a**, and **9a** with $LiAlH_4$ and $AlCl_3$ brought about the reduction of the lactam carbonyl and the stereoselective reductive cleavage of the oxazolidine ring to give *cis*-decahydroquinolines **10**, **12**, and **14**, respectively, in good yields. Finally, removal of the 2-phenylethanol moiety of the chiral inductor was achieved by debenzylation using Pearlman's catalyst in the presence of Boc_2O to provide the target enantiopure 7,8-dimethyl-, 6,8-dimethyl-, and 5,8-dimethyl-cis-decahydroquinolines **11**, **13**, and **15** (Scheme 9).

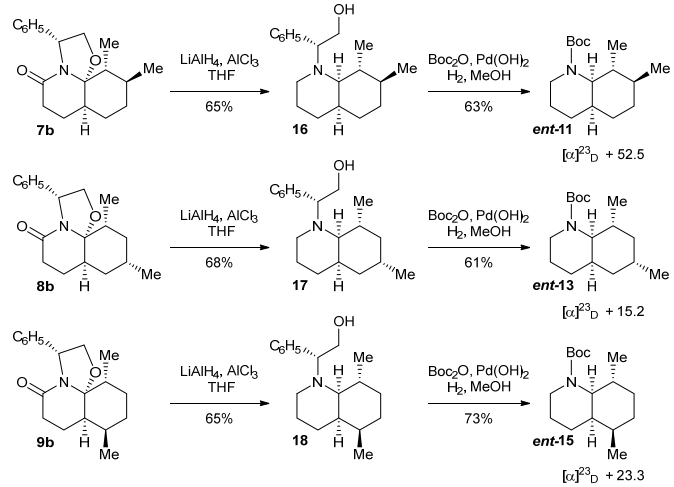
Similarly, starting from the diastereomeric tricyclic lactams **7b**, **8b**, and **9b**, the enantiomers of the corresponding *cis*-decahydroquinolines, *ent*-**11**, *ent*-**13**, and *ent*-**15**, respectively, were obtained in good yields (Scheme 10).



Scheme 9 Synthesis of enantiopure dimethyl-*cis*-decahydroquinolines.

Conclusions

A dynamic kinetic asymmetric transformation occurs in the cyclocondensation reaction of (*R*)-phenylglycinol with diastereomeric mixtures of 2-oxocyclohexanepropionic acid racemates (**4**-**6**) bearing two methyl groups on the carbocyclic ring, one at the isomerizable C-3 position and the other at the C-4, C-5 or C-6 position. In all cases, two major oxazoloquinolone lactams (**7a**/**7b**, **8a**/**8b**, **9a**/**9b**) that differ in the absolute configuration of all the stereogenic centers, except that of the chiral inductor, were obtained. After the stereoselective removal of the phenylethanol moiety of the chiral inductor, the procedure provides access to enantiopure



Scheme 10 Synthesis of enantiopure dimethyl-*cis*-decahydroquinolines in the opposite enantiomeric series.

7,8-, 6,8-, and 5,8-dimethyl-substituted *cis*-decahydroquinolines (**11**, **13**, and **15**, respectively) and their enantiomers (*ent*-**11**, *ent*-**13**, and *ent*-**15**). This methodology can be of interest in the field of drug discovery for the easy and efficient generation of disubstituted *cis*-decahydroquinolines in both enantiomeric series, with the final aim of evaluating the differences in their biological activities.

Data availability

Complete experimental procedures, spectroscopic data, supplementary schemes, tables and figures, copies of ^{1}H and ^{13}C NMR spectra of all new compounds (PDF), and X-ray crystallographic data of **7a, 7b, 7d, 8a, 8b, 8d, 9a, 9b, 9c, and 9d**. CCDC 2217474, 2217475, 2217480, 2217478, 2217476, 2217477, 2217473, 2217479, 2217472, 2217481, contain the supplementary crystallographic data for compounds **7a,7b, 7d, 8a, 8b, 8d, 9a, 9b, 9c, and 9d**, respectively. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/.....

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the MINECO/FEDER (project RTI2018-093974-B-I00) is gratefully acknowledged. Thanks are also due to the MIU, Spain (grant FPU19/04160) for a fellowship to A.C.; R.G. is a Serra Húnter Fellow.

Notes and references

1 a) A. Calcaterra and I. D'Acquarica, The market of chiral drugs: Chiral switches versus de novo enantiomerically pure compounds, *J. Pharm. Biomed. Anal.,* 2018, **147**, 323–340; b) T. J. Hagen and T. R. Helgren, "Chirality and Drug Discovery". In Burger's Medicinal Chemistry, Drug Discovery and Development, Eighth Edition. D. J. Abraham and M. Myers, Eds.; John Wiley & Sons Inc.: Hoboken, NJ, USA, 2021; pp. 1–45.

2 For reviews, see: a) H. B. Kagan and J. C. Fiaud, In Topics in Stereochemistry; E. L. Eliel, S. H. Wilen, Eds; John Wiley & Sons, Inc., 1988, Vol. 18, pp 249-330; b) M. Ohno and M. Otsuka, Chiral Synthons by Ester Hydrolysis Catalyzed by Pig Liver Esterase, *Org. React*., 1989, **37**, 1–55.

3 a) J. M. Keith, J. F. Larrow and E. N. Jacobsen, Practical Considerations in Kinetic Resolution Reactions, *Adv. Synth. Catal.,* 2001, **343**, 5–26; b) E. Vedejs and M. Jure, Efficiency in Nonenzymatic Kinetic Resolution, *Angew. Chem. Int. Ed.,* 2005, **44**, 3974–4001.

4 For reviews, see: a) R. Noyori, M. Tokunaga and M. Kitamura, Stereoselective Organic Synthesis via Dynamic Kinetic Resolution, *Bull. Chem. Soc. Jpn.,* 1995, **68**, 36–56; b) R. S. Ward, Dynamic kinetic resolution, *Tetrahedron: Asymmetry,* 1995, **6**, 1475–1490; c) S. Caddick and K. Jenkins, Dynamic resolutions in asymmetric synthesis, *Chem. Soc. Rev*., 1996, **25**, 447–456; d) H. Stecher and K. Faber, Biocatalytic Deracemization Techniques: Dynamic Resolutions and Stereoinversions, *Synthesis,* 1997, 1–16; e) U. T. Strauss, U. Felfer and K. Faber, Biocatalytic transformation of racemates into chiral building blocks in 100% chemical yield and 100% enantiomeric excess, *Tetrahedron: Asymmetry*, 1999, **10**, 107–117; f) F. F. Huerta, A. B. E. Minidis and J.-E. Bäckvall, Racemisation in asymmetric synthesis. Dynamic kinetic resolution and related processes in enzyme and metal catalysis, *Chem. Soc. Rev.*, 2001, **30**, 321–331; g) K. Faber, Non-Sequential Processes for the Transformation of a Racemate into a Single Stereoisomeric Product: Proposal for Stereochemical Classification, *Chem. Eur. J.*, 2001, **7**, 5005–5010; h) H. Pellissier, Dynamic kinetic resolution, *Tetrahedron*, 2003, **59**, 8291–8327, and references therein.

5 J. Steinreiber, K. Faber and H. Griengl, De-racemization of Enantiomers versus De-epimerization of Diastereomers—Classification of Dynamic Kinetic Asymmetric Transformations (DYKAT), *Chem. Eur. J*., 2008, **14**, 8060– 8072.

6 a) M. Amat, R. Griera, R. Fabregat, E. Molins and J. Bosch, A Biomimetic Enantioselective Approach to the Decahydroquinoline Class of Dendrobatid Alkaloids, *Angew. Chem., Int. Ed.,* 2008, **47**, 3348−3351; b) M. Amat, R. Fabregat, R. Griera, P. Florindo, E. Molins and J. Bosch, Biomimetic Construction of the Hydroquinoline Ring System. Diastereodivergent Enantioselective Synthesis of 2,5-Disubstituted *cis*-Decahydroquinolines, *J. Org. Chem*., 2010, **75**, 3797–3805; c) M. Amat, E. Ghirardi, L. Navio, R. Griera, N. Llor, E. Molins and J. Bosch, Enantio- and Diastereoconvergent Cyclocondensation Reactions: Synthesis of Enantiopure *cis*-Decahydroquinolines, *Chem. Eur. J*., 2013, **19**, 16044−16049; d) M. Amat, A. Pinto, R. Griera and J. Bosch, Stereoselective Synthesis of (−)-Lepadins A-C. *Chem. Commun*., 2013, **49**, 11032−11034; e) M. Amat, A. Pinto, R. Griera and J. Bosch, Enantioselective Synthesis of Lepadins A-D from a Phenylglycinol-Derived Hydroquinolone Lactam, *Chem._Eur. J.,* 2015, **21**, 12804−12808; f) M. Piccichè, A. Pinto, R. Griera, J. Bosch and M. Amat, Enantioselective Total Synthesis of (+)-Gephyrotoxin 287C, *Org. Lett*., 2017, **19**, 6654−6657; g) A. Pinto, R. Griera, E. Molins, I. Fernandez, J. Bosch and M. Amat, Access to Enantiopure 5-, 7-, and 5,7-Substituted *cis*-Decahydroquinolines: Enantioselective Synthesis of (−)-Cermizine B, *Org. Lett*., 2017, **19**, 1714−1717; h) A. Pinto, M. Piccichè, R. Griera, E. Molins, J. Bosch and M. Amat, Studies on the Synthesis of Phlegmarine-Type Lycopodium Alkaloids: Enantioselective Synthesis of (−)-Cermizine B, (+)-Serratezomine E, and (+)-Luciduline, *J. Org. Chem*., 2018, **83**, 8364−8375; i) M. Piccichè, A. Pinto, R. Griera, J. Bosch and M. Amat, Total Synthesis of (−)-Cylindricine H, *Org. Lett*., 2022, **24**, 5356−5360.

7 Compounds **1**-**4** were prepared as *cis/trans* diastereomeric mixtures following reported procedures: a) for compound **1**, see: H. Abe, Y. Ogura, T. Kobayashi and H. Ito, Total Synthesis of Paralemnolide A, *Org. Lett*., 2017, **19**, 5996−5999; b) for compound **2**, see: T. Oritani, H. Kondo and K. Yamashita, Preparation of Chiral *trans*-2,4-Dimethyl-1-cyclohexanones, the Key Intermediates in Cycloheximide Synthesis, Using Microbial Resolution *Agric. Biol. Chem*., 1987, **51**, 263−264; c) for compound **3**, see: J. E. Baldwin and R. C. Burrell, Quantitative Analyses of the Seven Isomeric 3,4- and 3,6-Dimethylcyclohexenes by Gas Chromatography, *J. Org. Chem.,* 2000, **65**, 7145-7150.