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Stereocontrolled Access to Enantiopure 7-Substituted *cis*- and *trans*-Octahydroindoles

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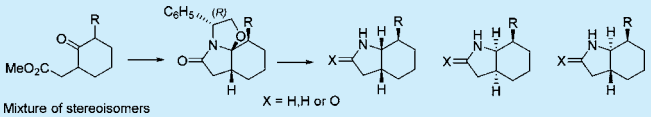
Supporting Information

ABSTRACT: Cyclocondensation of (*R*)-phenylglycinol with stereoisomeric mixtures (racemates, *cis*/*trans*) of 3-substituted 2-oxocyclohexaneacetates stereoselectively afforded tricyclic oxazoloindolone lactams, from which straightforward procedures for the stereocontrolled formation of enantiopure 7-substituted octahydroindoles with a variety of stereochemical patterns have been developed. The methodology has been successfully applied to the synthesis of (+)-α-lycorane.



Phenylglycinol- and other aminoalcohol-derived oxazolopiperidone and oxazoloquinolone lactams have proven to be versatile building blocks for the enantioselective synthesis of a wide variety of diversely substituted piperidine-containing heterocycles, including complex alkaloids belonging to different skeletal types.[1] The usefulness of these lactams lies in their easy preparation, by stereoselective cyclocondensation of the chiral nonracemic aminoalcohol with an appropriate δ-oxo acid derivative, and in their functionalization and conformational rigidity, which allow the stereocontrolled formation of C−C bonds at the different positions of the nitrogen heterocycle.

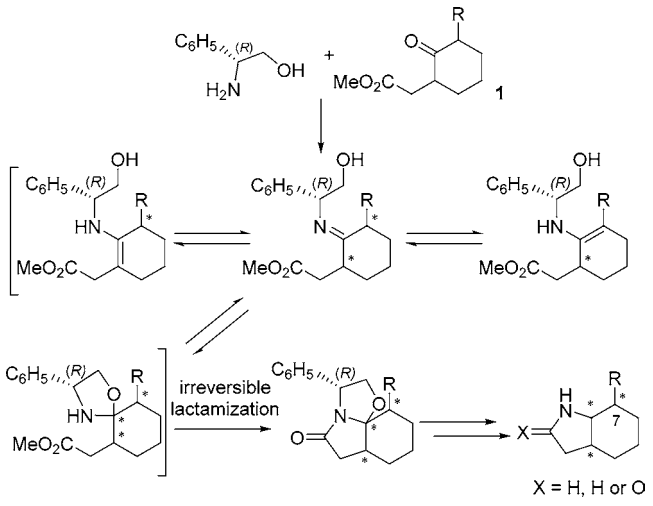
Starting from 2-oxocyclohexanepropionate-based δ-keto esters, the cyclocondensation stereoselectively affords tricyclic oxazoloquinolone lactams, which can be easily converted to enantiopure *cis*-decahydroquinoline alkaloids.[2] Depending on the structural characteristics of the substrate, the cyclocondensation involves a dynamic kinetic resolution and/or differentiation of enantiotopic or diastereotopic ester groups.

Bearing in mind that the octahydroindole nucleus is present in numerous natural bioactive compounds, for instance Amaryllidaceae alkaloids, we considered expanding the scope of the above stereoconvergent cyclocondensation reactions toward the generation of tricyclic oxazoloindolone lactams as precursors of this nucleus. This would require starting from appropriately substituted 2-oxocyclohexaneacetate derivatives (γ- instead of δ-keto esters).

In this letter, we report a general straightforward procedure for the stereocontrolled access to enantiopure 7-substituted *cis*- and *trans*-octahydroindoles. The few precedents of the enantioselective synthesis of 7-substituted octahydroindoles all deal with 7-aryl *cis*-derivatives,[3] used as intermediates in the synthesis of lycorane-like structures.

The preparation of the target enantiopure octahydroindoles was envisaged as outlined in Scheme 1. Starting from a

Scheme 1. Envisaged Access to Enantiopure 7-Substituted Octahydroindoles



stereoisomeric mixture of 3-substituted 2-oxocyclohexaneacetates **1** (two racemates when R = alkyl or aryl; one racemate and a *meso* form when R = CH_2CO_2Et), cyclocondensation with (*R*)-phenylglycinol would afford four stereoisomeric imines, which would be in equilibrium through the corresponding enamines with eight stereoisomeric

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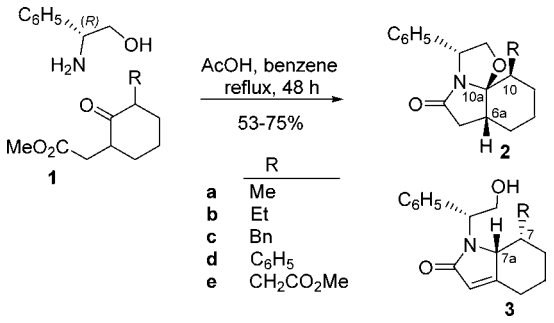
oxazolidines. A final irreversible lactamization would afford the target enantiopure tricyclic lactams. The stereoselectivity of the process would depend upon the kinetically controlled lactamization step.

Accordingly, cyclocondensation of γ-keto ester **1a** (mixture of two racemates) with (*R*)-phenylglycinol in the presence of AcOH in refluxing benzene afforded a single 10-substituted tricyclic lactam **2a** in 75% yield. Minor amounts (8%) of unsaturated bicyclic lactam **3a** were also formed (Scheme 2).

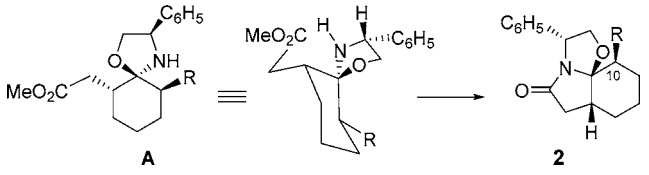
Scheme 2. Stereoconvergent Cyclocondensation Reactions



Similar stereoconvergent cyclocondensation reactions occurred starting from γ-keto esters **1b–d** (two racemates) or **1e** (mixture of one racemate and a *meso* form), leading to the respective tricyclic lactams **2b–e**, also accompanied by the corresponding unsaturated lactams **3** in series **b**, **c**, and **e** (but not **d**, when R = C_6H_5) as byproducts (8–13% yield). The absolute configuration of **2a**, **2d**, and **3a** was unambiguously established by X-ray crystallographic analysis.[4]

The stereoselective formation of **2a–e** can be rationalized by considering that steric constraints prevent the formation of *trans*-fused tricyclic lactams[5] and that irreversible lactamization from the equilibrating mixture of oxazolidines occurs faster from oxazolidine **A**, in which the substituent R on the cyclohexane ring is equatorial and the carboxylate approaches the nitrogen atom from the less hindered face, opposite to the phenyl, thus defining the configuration of the 6a and 10a stereocenters (Scheme 3). Indeed, our calculations indicate

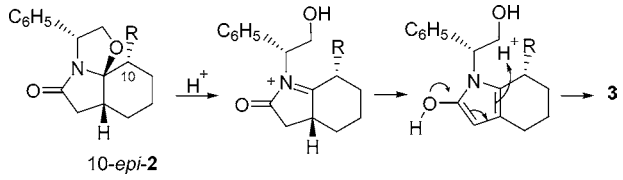
Scheme 3. Irreversible Lactamization Step



that the cyclization reactions involving intermediate **A** (R = Me or Ph) are kinetically ($\Delta\Delta G^{\ddagger} \approx 5$ kcal/mol) and also thermodynamically ($\Delta\Delta G_R \approx -5.5$ kcal/mol) favored over those processes where the R substituent is axial (see Figure S1 in the Supporting Information).[4]

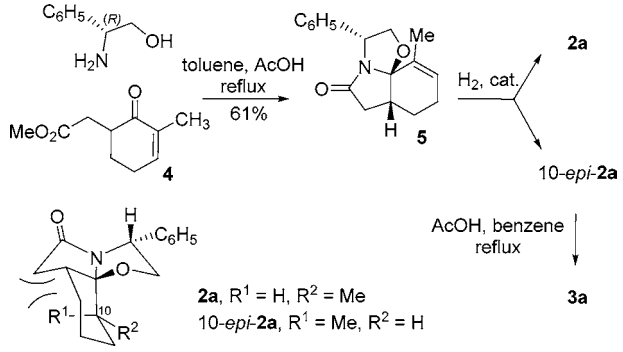
In turn, unsaturated lactams **3** would result from tricyclic lactams 10-*epi*-**2**, transiently formed during the cyclocondensation reaction. The opening of the oxazolidine ring of 10-*epi*-**2** under the acidic reaction conditions would be followed by isomerization of the double bond in the resulting *N*-acyl iminium species, with a final protonation from the less hindered face to give the 7-H/7a-H *cis* isomers **3**, as outlined in Scheme 4.

Scheme 4. Formation of Unsaturated Lactams 3



This hypothesis was confirmed when a mixture of lactams **2a** and 10-*epi*-**2a**, prepared by catalytic hydrogenation of unsaturated tricyclic lactam **5**, was converted into a mixture of recovered lactam **2a** and unsaturated lactam **3a** after heating (C_6H_6, reflux, AcOH) (Scheme 5). The required lactam **5** was

Scheme 5. Oxazolidine Ring Opening from Tricyclic Lactam 10-*epi*-2a



prepared by cyclocondensation of (*R*)-phenylglycinol with cyclohexenone-based γ-keto ester **4**. The lower stability of tricyclic lactams 10-*epi*-**2** compared with their C-10 epimers **2** can be explained by the occurrence of destabilizing 1,3-axial interactions caused by the axial C-10 substituent in 10-*epi*-**2**.

The fact that phenyl-substituted bicyclic lactam **3d** was not observed as a byproduct in the cyclocondensation reaction indicates that tricyclic lactam 10-*epi*-**2d** was not formed in the process. Again, this is supported by theoretical calculations, which suggest that equilibration of oxazolidine **A** (Scheme 3) to the corresponding epimer bearing an axial R substituent is energetically disfavored when R is phenyl (see Supporting Information).

We then explored the synthetic potential of lactams **2** in the synthesis of enantiopure octahydroindole derivatives. Alane reduction of **2a–e** brought about both the reduction of the lactam carbonyl and the reductive cleavage of the oxazolidine ring, with retention of configuration (see **B** in Scheme 6), to give *cis*-fused octahydroindoles **6a–e** and, after catalytic debenzylation, **7a–e** (3a-H/7a-H/7-H *cis,trans* series). The same stereochemical pattern resulted from the chemoselective reduction of **2a–e** with Et_3SiH (or Ph_3SiH)/$TiCl_4$ (see **C** in Scheme 6), affording *cis*-octahydroindolones **8a–e**[6] and, after Na/liq. NH_3-promoted debenzylation, **9a–e**[7] (Scheme 6).

Alternatively, treatment (rt, 18 h) of tricyclic lactams **2a–e** with $TiCl_4$ provided either unsaturated bicyclic lactams **10** (series **a–c**, **e**) or, somewhat surprisingly, the 7a-epimer **13** in the phenyl series (Scheme 7). Catalytic hydrogenation of **10a–c,e** followed by Na/liq. NH_3-promoted debenzylation gave *cis*-octahydroindolones **11** (3a-H/7a-H/7-H *cis,cis* series), whereas direct treatment of **10** with Na/liq. NH_3 caused debenzylation and simultaneous reduction of the C–C double

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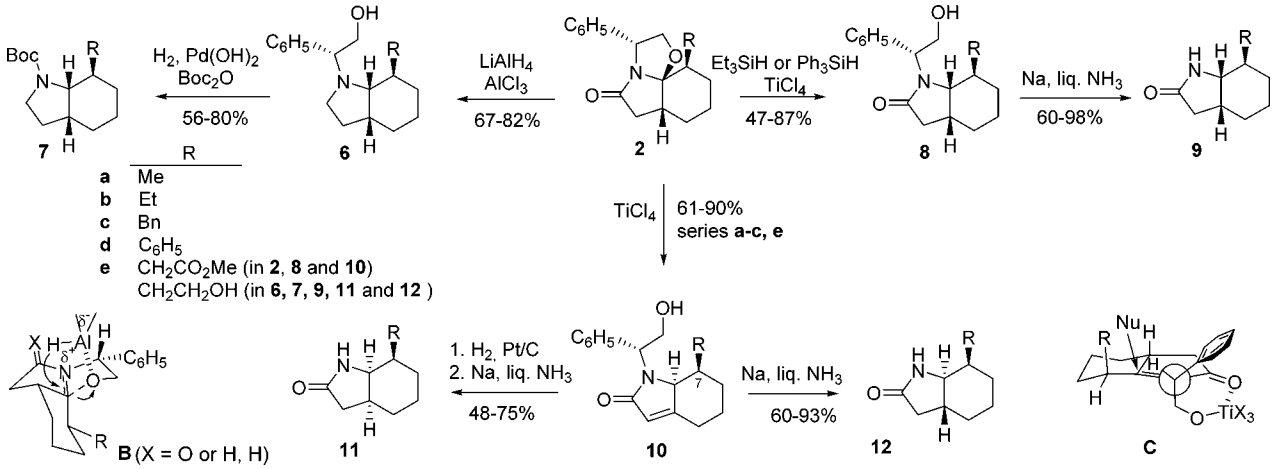
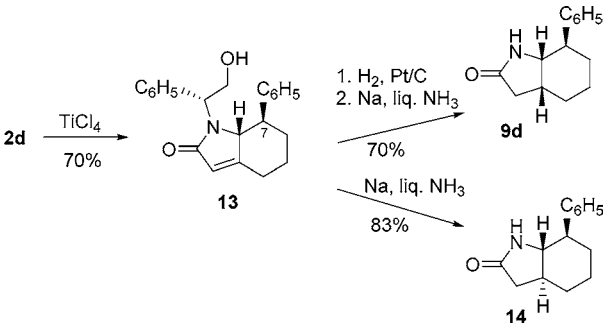
Scheme 6. Diastereodivergent Access to Enantiopure 7-Substituted Octahydroindoles



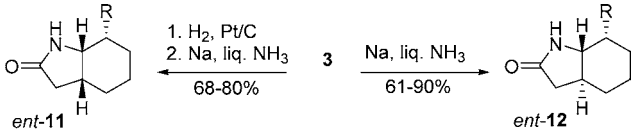
Scheme 7. Access to Enantiopure *cis*- and *trans*-7-Aryloctahydroindoles



bond, providing *trans*-octahydroindolones **12** (*trans,cis* series). Similar transformations from the phenyl-substituted unsaturated lactam **13** led to *cis*- and *trans*-octahydroindolones **9d** (*cis,trans* series) and **14** (*trans,trans* series), respectively (Scheme 7).[7]

The relative stereochemistry of **11** and **12** was confirmed by the conversion of the minor unsaturated lactams **3a−c**, **3e** to *ent*-**11** and *ent*-**12**, as outlined in Scheme 8.

Scheme 8. Confirmation of the Stereochemistry



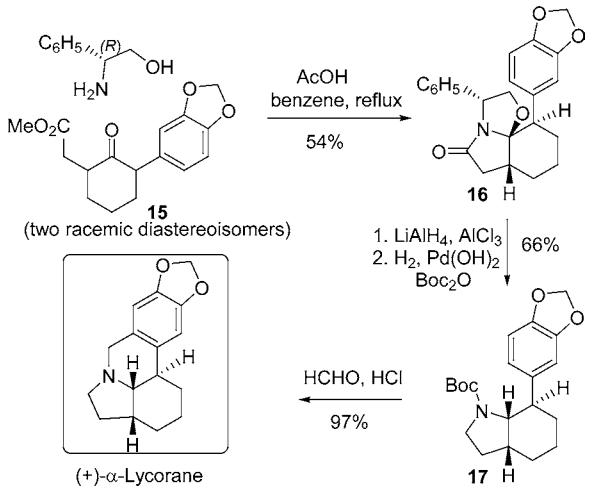
a, R = Me; **b**, R = Et; **c**, R = Bn; **e**, R = CH_2CO_2Me (in **3**) or CH_2CH_2OH (in *ent*-**11** and *ent*-**12**)

An explanation for the different stereochemical outcome of the $TiCl_4$-promoted opening of the oxazolidine ring observed in the phenyl series is that, in all cases (series **a−e**), the initially formed *N*-acyl iminium species are in equilibrium with the corresponding enamides and 2-hydroxypyrroles (dienols), which undergo a kinetic protonation on the less hindered face to give the 7-H/7a-H *cis*-unsaturated lactams **10**. A subsequent *in situ* equilibration takes place in the phenyl series, leading to the most stable *trans* isomer **13** (equatorial C-7 phenyl substituent),[8] which is stabilized by intramolecular $\pi-\pi$ interactions (see Figure S2 in the Supporting Information).

To further illustrate the usefulness of the methodology herein developed, we applied it to the synthesis of (+)-α-lycorane, which can be envisaged as a 7-aryl substituted *cis*-octahydroindole bearing an additional methylene bridge that connects the nitrogen atom with the aromatic ring.

The required starting γ-keto ester **15** (two racemic diastereoisomers),[9] which incorporates a (methylenedioxy)-phenyl substituent, reacted with (*R*)-phenylglycinol under the usual cyclocondensation reaction conditions to stereoselectively afford a single tricyclic lactam, **16**, with generation of three stereogenic centers of a well-defined configuration. A subsequent alane reduction followed by debenzylation stereoselectively afforded *cis*-7-aryloctahydroindole **17**, which was converted to the target (+)-α-lycorane by a final reaction with formaldehyde (Scheme 9).[10]

Scheme 9. Stereoconvergent Synthesis of (+)-α-Lycorane



In conclusion, cyclocondensation of (*R*)-phenylglycinol with stereoisomeric mixtures (racemates, *cis*/*trans*) of 3-substituted 2-oxocyclohexaneacetates stereoselectively provides tricyclic oxazoloindolone lactams in a stereoconvergent process involving a dynamic kinetic resolution of the racemic substrates. Further stereocontrolled transformations open straightforward routes to enantiopure 7-substituted octahydroindole derivatives bearing a variety of stereochemical patterns.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02861.

Complete experimental procedures and copies of ^{1}H and ^{13}C spectra of all new compounds; crystallographic data for compounds **2a**, **2d**, and **3a**; Figures S1 and S2, computational details, Cartesian coordinates (Å), and free energies of all the stationary points discussed in the text (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(4) CCDC 1504443, 1504444, and 1504442 contain the supplementary crystallographic data for compounds **2a**, **2d**, and **3a**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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