An Enantioselective Entry to *cis*-Perhydroisoquinolines

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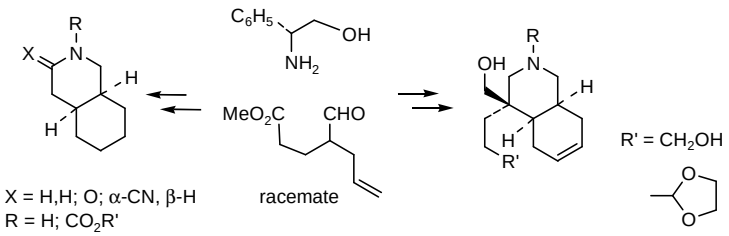
Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



An enantioselective route to *cis*-perhydroisoquinolines, involving a cyclocondensation reaction of (*R*)-phenylglycinol with a racemic oxoester, a stereoselective conjugate addition to an unsaturated bicyclic lactam, and the closure of the carbocyclic ring by a ring-closing metathesis as the key steps is reported. This route allows the preparation of 3-cyano derivatives as well as *cis*-octahydroisoquinolines bearing a quaternary center at the C4-position.

The totally (or partially) reduced *cis*-isoquinoline ring system is present in a large number of bioactive natural and synthetic products. Among them, of particular interest are the indole alkaloids of the yohimbine-reserpine type,[1] the marine sponge alkaloids of the manzamine[2] and madangamine groups,[3] all of them displaying a variety of notable pharmacological activities, and the HIV protease inhibitors nelfinavir and saquinavir,[4] which are characterized by the presence of a carboxamide function at the C3-position of the isoquinoline ring[5] (Figure 1). This widespread occurrence has

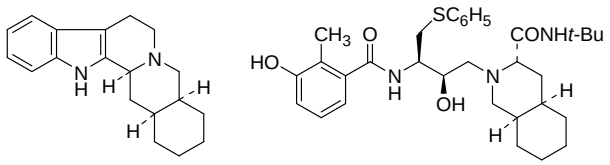


Figure 1. Compounds Bearing a *cis*-Perhydroisoquinoline Moiety.

(1) (a) Szántay, C.; Honty, K. In *Monoterpenoid Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Supplement to Vol. 25, Part 4, pp 161–216. (b) Creasey, W. A. In *Monoterpenoid Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Supplement to Vol. 25, Part 4, pp 715–754.

(2) (a) For reviews, see: Andersen, R. J.; Van Soest, R. W. M.; Kong, F. In *Alkaloids: Chemical and Biogical Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol.10, pp 301–355. (b) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765–794. (c) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201–6258. (d) Nakagawa, M. J. *Heterocyclic Chem*. **2000**, *37*, 567–581.

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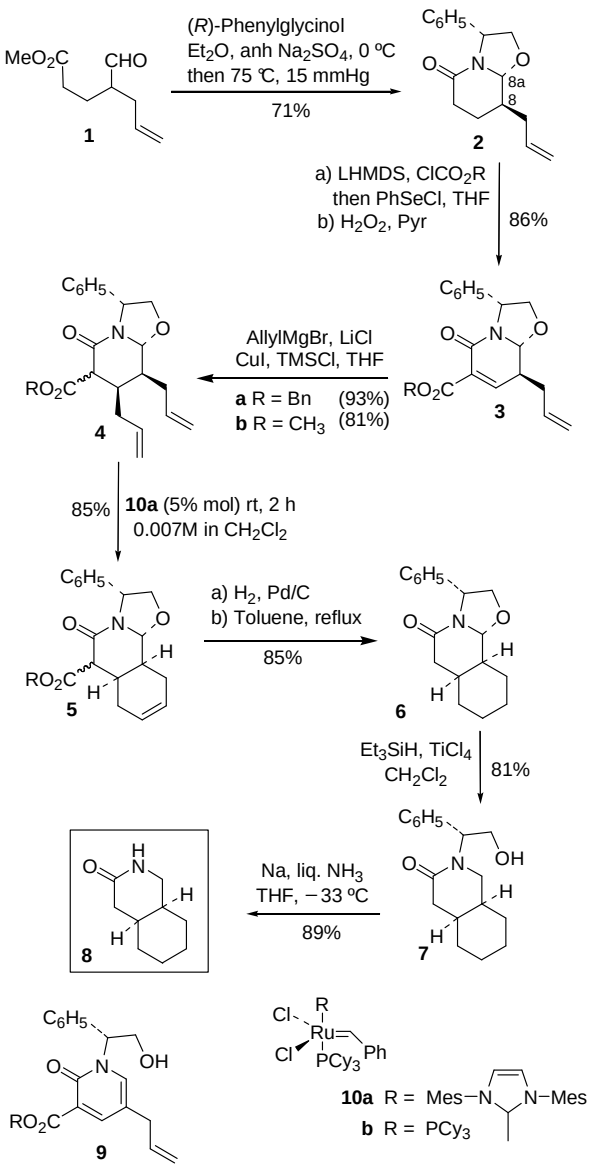
stimulated the development of general methodologies and strategies for the enantioselective synthesis of *cis*-perhydroisoquinoline derivatives.[6] In this context, we have recently reported[7] an enantiodivergent synthesis of *cis*-hydroisoquinolines, in which the key step was a diastereoselective Diels-Alder reaction of a phenylglycinol-derived unsaturated δ-lactam.

Scheme 1. Enantioselective Synthesis of *cis*-Perhydroisoquinolin-3-one



We present here an efficient enantioselective route to *cis*-perhydroisoquinolines. The key steps are i) the generation of the first enantiopure intermediate, the bicyclic lactam **2**, by cyclocondensation of (*R*)-phenylglycinol with racemic γ-substituted δ-oxoester **1**, in a process that involves a dynamic kinetic resolution; ii) a highly stereoselective conjugate addition to unsaturated lactam **3**; iii) the closure of the carbocyclic ring by a ring-closing olefin metathesis (RCM).

The starting racemic oxoester **1** was conveniently prepared in 64% yield by reaction of the piperidine enamine of 4-pentenal with methyl acrylate.[8] Cyclocondensation of **1** with (*R*)-phenylglycinol at 0 ºC in the presence of anhydrous Na_2SO_4, followed by heating at 75-80 ºC under vacuum (10-15 mmHg) stereoselectively afforded the enantiopure bicyclic lactam **2** in 71% yield (Scheme 1). Minor amounts (10%) of the (8*S*,8a*S*)-diastereoisomer were also isolated. The above result clearly indicated that a dynamic kinetic resolution,[9] with epimerization of the configurationally labile stereocenter α to the carbonyl group, had occurred during the cyclocondensation reaction.

Lactam **2** was then converted to the unsaturated lactams **3** by sequential treatment with LHMDS (2.2 equiv), methyl or benzyl chloroformate, and PhSeCl, followed by oxidation of the resulting mixtures of selenides with H_2O_2 in the presence of pyridine. Lactams **3** proved to be sensitive to both mild acid and basic conditions, affording the corresponding pyridones **9**. For this reason, they were prepared immediately before the next reaction and used without further purification.

The conjugate addition of an allyl group was accomplished in excellent chemical yield and complete *exo* facial diastereoselectivity[10] by reacting lactams **3a**

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(6) (a) Houpis, I. N.; Molina, A.; Reamer, R. A.; Lynch, J. E.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1993**, *34*, 2593–2596. (b) Aubé, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009–9018. (c) Kwak, B. S.; Kim, T. J.; Lee, S. I. *Catal. Lett.* **2002**, *83*, 93–96. (d) Hattori, K.; Grossman, R. B. *J. Org. Chem.* **2003**, *68*, 1409–1417. (e) Vila, X.; Quirante, J.; Paloma, L.; Bonjoch, J. *Tetrahedron Lett.* **2004**, *45*, 4661–4664.

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(8) (a) Costello, G.; Saxton, J. E. *Tetrahedron* **1986**, *42*, 6047–6069. (b) Lawton, G. Saxton, J. E.; Smith, A. J. *Tetrahedron* **1977**, *33*, 1641–1653.

(9) (a) For related examples, see: (a) Amat, M.; Cantó, M.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343–5351. (b) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681–8693. (c) For a recent review, see: Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327.

(10) For the stereochemical outcome of the conjugate addition of organocuprates to phenylglycinol-derived lactams, see: (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074–3084. (b) Amat, M.; Pérez, M.; Llor, N.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611–614.

and **3b** with allylmagnesium bromide in presence of CuI, LiCl, and TMSCl. The observed stereoselectivity can be explained by considering that the attack of the nucleophile takes place, under stereoelectronic control, axial to the electrophilic carbon of the conjugated double bond of the conformationally rigid lactams **3**, and consequently *cis* with respect to the allyl substituent, as depicted in Figure 2.

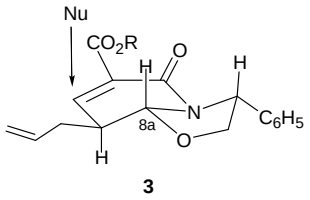


Figure 2. Stereoelectronic Control in the Conjugate Addition.

The resulting *cis*-diallyl lactams **4a** and **4b** were isolated as mixtures of epimers at the isomerizable stereocenter adjacent to the ester and lactam carbonyl groups (approximate ratio of CO_2R α:β isomers, 4:1 for **4a** and 3:1 for **4b**), which could be separated by column chromatography.

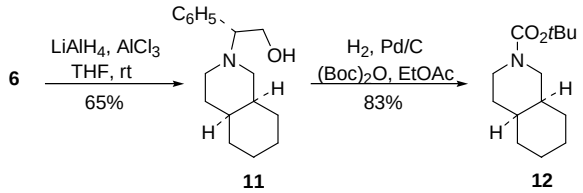
The RCM[11] of lactams **4a** and **4b** catalyzed by the second generation Grubbs catalyst **10a** resulted in the closure of the carbocyclic ring to give the respective hydroisoquinolones **5a** and **5b** in excellent yield. When the RCM from **4a** was carried out using the first generation Grubbs catalyst **10b** (7.5% mol), cyclization was slower and hydroisoquinolone **5a** was isolated in only 66% yield after 20 h.

Catalytic hydrogenation of **5a** using Pd/C as the catalyst brought about both the reduction of the carbon-carbon double bond and the debenzylation of the benzyloxycarbonyl group to give a β-keto acid, which was then decarboxylated by heating in refluxing toluene, leading to a single perhydroisoquinolone **6** in 85% overall yield.

Removal of the chiral auxiliary was performed in two steps, by reduction with triethylsilane in the presence of $TiCl_4$, followed by debenzylation of the resulting 2-piperidone **7** with Na in liquid NH_3. The enantiopure *cis*-perhydroisoquinolin-3-one **8** [$[\alpha]^{22}_D$ – 29.2 (*c* 0.8, MeOH); lit[12a] $[\alpha]^{22}_D$ –30.9 (*c* 1.02, MeOH)] was obtained in excellent overall yield. Bicyclic lactam **8** has previously been used as an advanced intermediate in the synthesis of (–)-alloyohimbane.[6b,12]

Alternatively, alane reduction of **6**, followed by debenzylation of the resulting tertiary amine **11** by hydrogenation in the presence of $Pd(OH)_2$ and $(Boc)_2O$ gave the enantiopure *N*-protected *cis*-perhydroisoquinoline **12**[13] (Scheme 2).

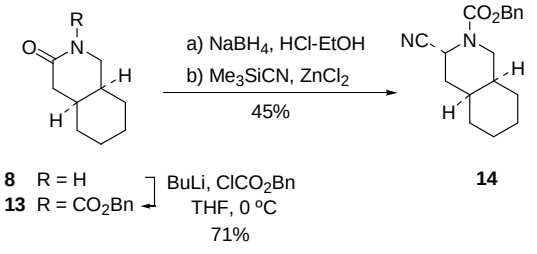
Scheme 2. Synthesis of Enantiopure *N*-Protected *cis*-Perhydroisoquinoline



On the other hand, perhydroisoquinolone **8** provides easy access to derivatives bearing a cyano substituent at the C3-position. Thus, after protection of the nitrogen atom as an *N*-benzyloxycarbonyl carbamate, the carbonyl group of **13** was reduced under Speckamp conditions[14] and the resulting ethoxy derivative was treated with Me_3SiCN in the presence of $ZnCl_2$ to give perhydroisoquinoline-3-carbonitrile **14** in good overall yield (Scheme 3).

The alkoxycarbonyl group present in **5b** not only enhances the reactivity of the conjugated system, thus allowing the subsequent conjugate addition of an organocuprate, but also can later be manipulated to ultimately lead to octahydroisoquinolines bearing a quaternary center at the C4-position.

Scheme 3. Enantioselective Access to *cis*-3-Cyanoperhydroisoquinolines



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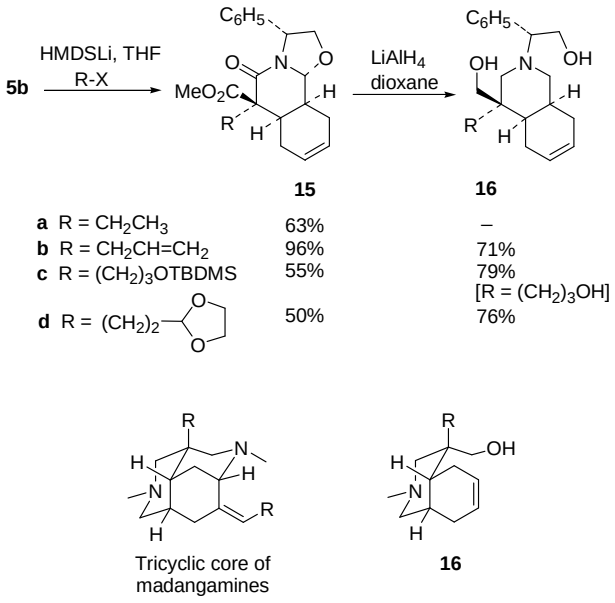
Thus, keto ester **5b** underwent stereoselective alkylation on the most accessible face with complete facial selectivity by treatment with LHMDS and ethyl iodide, allyl bromide, 3-(*tert*-butyldimethylsilyloxy) propyl iodide, or 2-(2-iodoethyl)-1,3-dioxolane (Scheme 4). $LiAlH_4$ reduction of the alkylated compounds **15b-15d** caused the cleavage of the C-O bond of the oxazolidine ring and the simultaneous reduction of the ester and amide carbonyl groups to give the respective alcohols **16b-16d** in good yields. Functionalized *cis*-octahydroisoquinolines **16**, bearing the crucial quaternary center of madangamines, may allow an enantioselective entry to the tricyclic core of these alkaloids.[15]

Scheme 4. Towards the First Enantioselective Entry to the Tricyclic Core of Madangamine Alkaloids



The results reported in this letter further illustrate that chiral non-racemic lactams generated by cyclocondensation reactions of 1,2-amino alcohols and δ-oxoesters are versatile building blocks for the enantioselective synthesis of piperidine-containing derivatives.[16]

Acknowledgment. Financial support from the Ministry of Science and Technology (Spain)-FEDER through project BQU2003-00505 and the DURSI, Generalitat de Catalunya (grant 2001SGR-0084) is gratefully acknowledged.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of compounds **2-8**, **11-16**. This material is available free of change via the Internet at http://pubs.acs.org.

(15) (a) For the racemic synthesis of a closely related bicyclic intermediate and its conversion to the tricyclic core of madangamines, see: Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 1920–1921. For more recent synthetic studies in the madangamine field, also in the racemic series, see: (b) Yamazaki, N.; Kusanagi, T.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 6509–6512. (c) Tong, H. M.; Martin, M.-T.; Chiaroni, A.; Bénéchie, M.; Marazano, C. *Org. Lett.* **2005**, *7*, 2437–2440.

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