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A Direct Stereoselective Approach to *trans*-2,3-Disubstituted Piperidines: Application in the Synthesis of 2-Epi-CP-99,994 and (+)-Epilupinine

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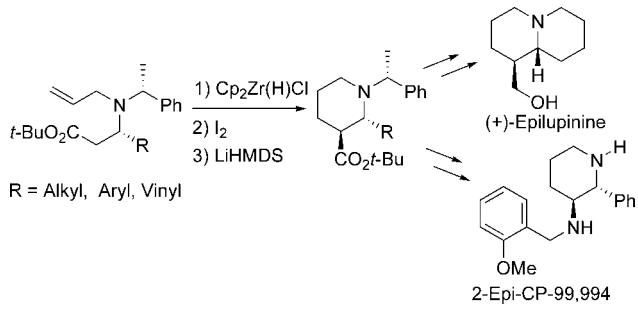
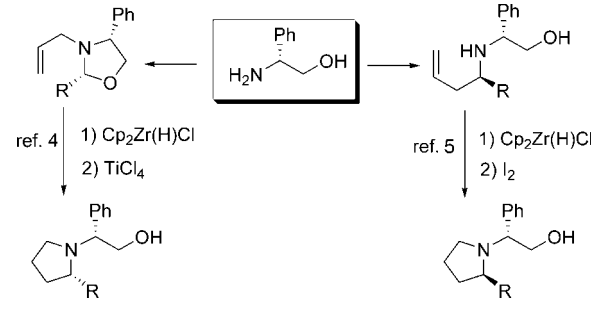
ABSTRACT



A simple synthesis of enantiomerically pure piperidine esters is described, offering a straightforward access to the trans-2,3-disubstituted piperidine skeleton which is present in a broad range of biologically active compounds.

The piperidine skeleton is common to a number of natural products and medicinal drugs and constitutes an important class of building blocks for the synthesis of a broad range of alcaloids.[1] Although many asymmetric syntheses of piperidine derivatives have been reported,[2] the development of new synthetic strategies opening the way to optically pure piperidines is still important. In this paper we present a hydrozirconation strategy that allows an easy access to optically pure piperidines having a *trans*-2,3-disubstituted skeleton.[3] It was inspired by our diastereoselective syntheses of both enantiomeric 2-substituted pyrrolidines from *N*-allyloxazolidines and homoallylic amines (Scheme 1).[4,5] These reactions involve (i) hydrozirconation−Lewis acid mediated cyclization and (ii) hydrozirconation−iodination and subsequent intramolecular N-

Scheme 1. Access to Enantiomerically Pure 2-Substituted Pyrrolidines



(1) (a) Daly, J. W.; Garraffo, H. M.; Spande T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1999; Vol. 13, pp 1−161. (b) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681. (c) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400–4405. (d) Vazzana, I.; Budriesi, R.; Terranova, E.; Ioan, P.; Ugenti, M. P.; Tasso, B.; Chiarini, A.; Sparatore, F. *J. Med. Chem.* **2007**, *50*, 334–343.

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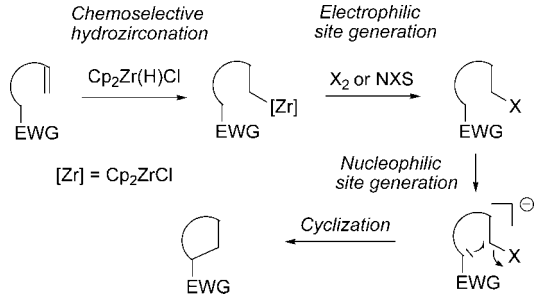
alkylation. In the second pathway, C=C double bond hydrozirconation is performed in the presence of a secondary amine.

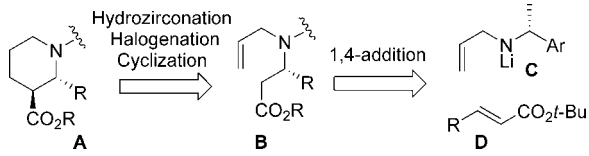
The synthetic strategy presented herein takes advantage of both the remarkable chemoselectivity of hydrozirconation[6] and the sequential generation of an electrophilic site (via halogenation), followed by that of a nucleophilic site to promote the cyclization step (Scheme 2).

Scheme 2. Synthetic Strategy



The flexibility of such an approach is illustrated here by a three step synthesis of piperidine esters **A** which can be obtained from **B** by applying the hydrozirconation/halogenation/base-mediated cyclization sequence (Scheme 3).[7] The

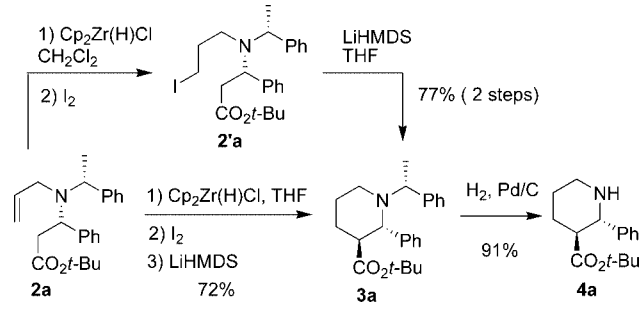
Scheme 3. Disconnective Approach to Piperidine Esters (**A**)



configuration of the α carbon in compound **B** is controlled through diastereoselective Davies 1,4-addition of the chiral amide **C** to the α,β-unsaturated *tert*-butyl ester **D**.[8] According to this strategy, the allylic fragment is not used as a protecting group (as it is in the Davies approach), but as an electrophilic site precursor, and thus is included in the core structure of the target molecule.

N-Allyl β-amino ester **2a** was first prepared in a totally diastereoselective manner.[8] The hydrozirconation reaction was next performed in CH_2Cl_2, by using 1 equiv of the Schwartz reagent, followed by the addition of iodine (1 equiv). The expected iodo ester **2′a** was obtained quantitatively. Subsequent treatment with LiHMDS in THF at −78 °C afforded **3a** in 77% yield as a unique stereoisomer (≥95% de). Generation of the second stereocenter in a totally diastereoselective manner, during ring closure, demonstrates the synthetic utility of this method. Subsequent catalytic hydrogenolysis afforded the piperidine ester **4a** in good yield (Scheme 4). A one-pot procedure was also tested by simply

Scheme 4. Synthesis of Piperidine Ester **4a**



carrying out the hydrozirconation/iodination in THF, followed by the addition of the base at −78 °C. Comparable yields are obtained without altering the diastereoselectivity.

This methodology was further extended to diversely substituted piperidine esters. First, β-amino esters **2b**−**h** were prepared. These reactions proceeded with total diastereoselectivity, except for **2h** (84% de) where the major diastereomer was easily purified by flash chromatography. The hydrozirconation/iodination sequence followed by LiHMDS-mediated ring closure was next applied to **2**, leading to the *trans*-piperidine esters **3** (Table 1).[9]

Piperidine esters bearing phenyl or substituted phenyl groups (entries 1 and 2), heteroaromatic groups (entries 3−5),

(2) (a) Cossy, J.; Vogel, P. In *Studies in Natural Products Chemistry, Part H*; Atta-ur-Raman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, pp 275−363. (b) Angle, S. R.; Breittenbucher, J. G. In *Studies in Natural Products Chemistry, Part J*; Atta-ur-Raman, Ed;. Elsevier: Amsterdam, 1995; Vol. 16, pp 453−502. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, *178*, 1–1813. (d) Guilloteau-Bertin, B.; Compère, D.; Gil, L.; Marazano, C.; Das, B. C. *Eur. J. Org. Chem.* **2000**, *139*, 1–1399. (e) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (f) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (g) Agami, C.; Dechoux, L.; Hebbe, S. *J. Org. Chem.* **2002**, *67*, 7573–7576. (h) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855–3857. (i) Davis, F. A.; Zhang, J.; Li, Y.; Xu, H.; DeBrosse, C. *J. Org. Chem.* **2005**, *70*, 5413–5419. (j) Amat, M.; Escolano, C.; Lozano, O.; Gomez-Esqué, A.; Griera, R.; Molins, E.; Bosch, J. *J. Org. Chem.* **2006**, *71*, 3804–3815. (k) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Lett.* **2007**, *9*, 2473–2476. (l) Noël, R.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Eur. J. Org. Chem.* **2007**, 476–486.

(3) For recent syntheses of 2,3-disubstituted piperidines, see: (a) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2004**, *68*, 6197–6201. (b) Suga, S.; Nishida, T.; Nagaki, A.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2004**, *126*, 14338–14339. (c) Pedersen, C. M.; Bols, M. *Tetrahedon* **2005**, *61*, 115–122. (d) Takahashi, M.; Macalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 7514–7516.

(4) Vasse, J.-L.; Joosten, A.; Denhez, C.; Szymoniak, J. *Org. Lett.* **2005**, *7*, 4887–4889.

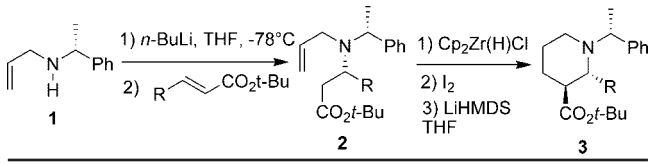
(5) Ahari, M.; Joosten, A.; Vasse, J.-L.; Szymoniak, J. *Synthesis* **2008**, 61–68.

(6) Reviews: (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853–12910. (b) Lipshutz, B. H.; Pfeiffer, S. S.; Noson, K.; Tomioka, T. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 110. (c) Wipf, P.; Kendall, C. In *Topics in Organometallic Chemistry*; Takahashi, T., Ed.; Springer-Verlag: New York, 2005; Vol. 8, p 1.

(7) The hydrozirconation compatibility with *tert*-butyl esters is known; see ref 6a.

(8) High level of asymmetric induction was reported with *tert*-butyl esters, see: (a) Davies, S. G.; Fenwick, D. R. *J. Chem Soc., Perkin Trans. 1* **1995**, *110*, 9–1110. (b) Davies, S. G.; Smyth, G. D.; Chippindale, A. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3089–3104.

Table 1. Synthesis of Piperidine Esters **3**



1 2 3

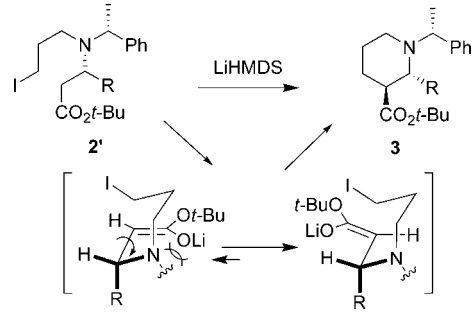
entry	R	**2** (yield, %)[a]	**3** (yield, %)[a]
1	Ph	**2a**(87)	**3a**(77)
2	4F-C_6H_4	**2b**(82)	**3b**(72)
3	2-thienyl	**2c**(90)	**3c**(79)
4[b]	2-thienyl	**2c**(90)	**3c**(65)
5	3-pyridyl	**2d**(76)	**3d**(51)
6	Me	**2e**(84)	**3e**(55)
7[c]	^{i}Pr	**2f** (81)	**3f** (64)
8	Bn	**2g**(68)	**3g**(58)
9	cinnamyl	**2h**(75)	**3h**(69)

[a] Isolated yields. [b] Obtained according to the one-pot procedure. [c] LDA was used as base.

as well as alkyl or alkenyl groups (entries 6−9) on the C2 atom, were obtained in good to moderate yields. Interestingly, compound **3h** was selectively obtained from the β-amino ester **2h** with two alkene chains having a different degree of substitution (entry 9). In all cases, the unique stereochemistry obtained was due to the highly diastereoselective 1,4-addition and cyclization steps.

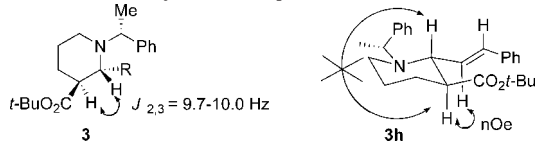
The high level of stereoselectivity observed during the ring-closure step is postulated to result from a chairlike transition state involving a nonchelated *E*-enolate (Scheme 5). The control in enolate conformation could be a result of

Scheme 5. Stereochemical Pathway Explaining the Formation of **3**



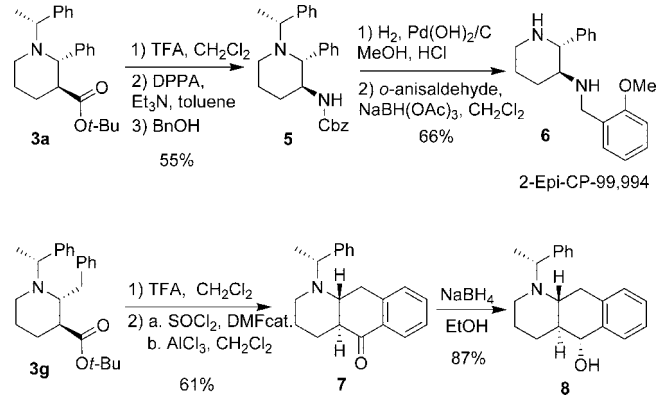
(i) the R group's almost perpendicular orientation with respect to the enolate plan and (ii) an efficient discrimination in favor of the less sterically hindered rotameric form of the enolate.

(9) The *trans* configuration in **3** was deduced from the J_{2-3} coupling constants and NOE study of the compond **3h**.



Piperidine esters **3** are versatile building blocks, offering an easy access to the 2,3-disubstituted piperidine skeleton, which is present in numerous biologically active compounds.[1,2] Among them, 3-amino 2-substituted piperidines are key structural features of natural products and pharmaceutical drugs.[10] Whereas the synthesis of *cis*-3-amino 2-substituted piperidines has widely been established,[11] only a few examples of *trans* analogues have been reported.[12] The described method offers a rapid access to such compounds, as exemplified with a simple synthesis of the *trans* (2*R*,3*S*) analogue (**6**) of CP-99,994, a highly potent substance P antagonist.[10a–d] This was acomplished in a straightforward manner from the piperidine ester **3a** through a Curtius type rearrangement, deprotection and reductive amination (Scheme 6). Furthermore, an easy access to *trans*-fused polycyclic

Scheme 6. Synthesis of 2-*epi*-CP-99,994 (**6**) and Octahydrobenzoquinoline **8**



piperidines is possible and is exemplified by the synthesis of the octahydrobenzoquinoline derivative **8**.[13] Compound **7** was first obtained in two steps starting from **3g** via TFA-mediated hydrolysis followed by Friedel−Crafts annulation. Starting from **7**, diastereoselective reduction of the oxo group

(10) (a) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, M. *J. Med. Chem.* **1992**, *35*, 4911–4913. (b) Rosen, T.; Seeger, T. F.; McLean, S.; Desai, M. C.; Guarino, K. J.; Bryce, D.; Pratt, K.; Heym, J.; Chalabi, P. M.; Windels, J. H.; Roth, R. W. *J. Med. Chem.* **1993**, *36*, 3197–3201. (c) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *4*, 3517–3520. (d) Davis, F. A.; Zhang, Y.; Li, D. *Tetrahedron Lett.* **2007**, *48*, 7838–7840. (e) Ward, P.; Armour, D. R.; Bays, D. E.; Evans, B.; Giblin, G. M. P.; Heron, N.; Hubbard, T.; Liang, K.; Middlemiss, D.; Mordaunt, J.; Naylor, A.; Pegg, N. A.; Vinader, V.; Watson, S. P.; Bountra, C.; Evans, D. C. *J. Med. Chem.* **1995**, *38*, 4985–4992.

(11) (a) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F. *Tetrahedron Lett.* **1993**, *34*, 5831–5834. (b) Diez, A.; Voldoine, A.; Lopez, I.; Rubralta, M.; Segarra, V.; Pages, L.; Palacios, J. M. *Tetrahedron* **1995**, *51*, 5143–5156. (c) Laschat, S.; Fox, T. *Synthesis* **1997**, 475–479. (d) Oshitari, T.; Mandai, T. *Synlett* **2006**, 3395–3398. (e) Kokotos, C. G.; Aggarwal, V. K. *Chem Commun.* **2006**, 2156–2158.

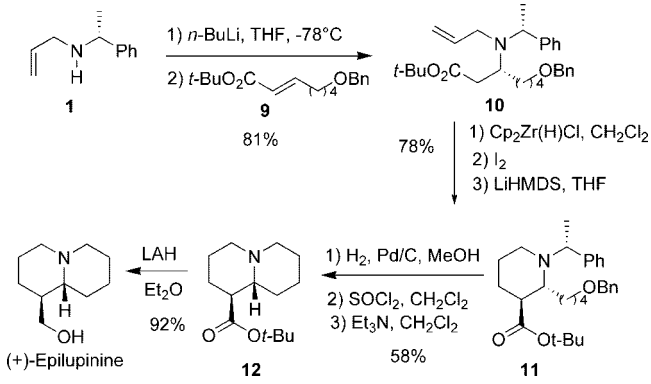
(12) (a) Liu, L.-X.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2006**, *17*, 3265–3272. (b) Kokotos, C.; Aggarwal, V. K. *Org. Lett.* **2007**, *9*, 2099–2102.

(13) Trans- and cis-fused octahydrobenzoquinolines are known to exhibit various biological properties; see: (a) Cannon, J. G.; Amoo, V. E. D.; Long, J. P.; Bhatnagar, R. K.; Flynn, J. R. *J. Med. Chem.* **1986**, *29*, 2529–2534. (b) Smissman, E. E.; El-Antabbly, S.; Hedrich, L. W.; Walaszek, E. J.; Tseng, L.-F. *J. Med. Chem.* **1973**, *16*, 109–113. (c) Thermos, K.; Froudakis, G. E.; Tagmatarchis, N.; Katerinopoulos, H. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 883–886.

afforded **8** in which three contiguous stereogenic centers are controlled.

The described methodology can also be applied to the preparation of quinolizidine alkaloids as illustrated by the asymmetric synthesis of naturally occurring (+)-epilupinine (Scheme 7).[14] The reaction of α,β-unsaturated ester **9**[15] with

Scheme 7. Asymmetric Synthesis of (+)-Epilupinine



the amide derived from **1** provided the β-amino ester **10** in good yield with total diastereoselectivity. Compound **10** was next submitted to the hydrozirconation/iodination/LiHMDS-mediated ring-closure sequence to afford the expected piperidine **11**. Subsequent hydrogenolysis and alcohol conversion to chloride,[16] followed by Et_3N treatment, gave the bicyclic compound **12**. Finally, $LiAlH_4$ reduction of the ester function afforded (+)-epilupinine ($[\alpha]_D$ +30.7 (*c* 1.4, EtOH), optical purity 95% based on literature data: $[\alpha]_D$ +32 (*c* 1.49, EtOH).[17]

In summary, we have described an efficient diastereoselective approach to enantiomerically pure piperidine esters based on a simple three step hydrozirconation/iodination and base-mediated ring-closure sequence. This methodology opens a wide access to the *trans*-2,3-disubstituted piperidine skeleton and has potential for the synthesis of biologically active piperidine derivatives.

Acknowledgment. We thank the CNRS and the Ministère de l'Education Nationale et de la Recherche for their financial support.

Supporting Information Available: Experimetal procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For the synthesis of optically active epilupinine, see: (a) Nagao, Y.; Wei, M.; Mashahito, T.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289–290. (b) Hua, D. H.; Miao, S. W.; Bravo, A. A. *Synthesis* **1991**, 970–974. (c) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420–8421. (d) Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349–10362. (e) Ledoux, S.; Marchalant, E.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **2001**, *42*, 5397–5399. (f) Huang, H.-L.; Sung, W.-H.; Liu, R.-S. *J. Org. Chem.* **2001**, *66*, 6193–6296. (g) Michael, J. P.; de Koning, C. B.; San Fat, C.; Natrass, G. L. *Arkinov* **2002**, 62–77. (h) Agami, C.; Dechoux, L.; Hebbe, S.; Menard, C. *Tetrahedron* **2004**, *60*, 5433–5438. (i) Ma, S.; Ni, B. *Chem. Eur. J.* **2004**, *10*, 3286–3300.

(15) Chang, M.-Y.; Chen, C.-Y.; Chen, S.-T.; Chang, N.-C. *Tetrahedron* **2003**, *59*, 7547–7553.

(16) Agami, C.; Couty, F.; Evano, G.; Darro, F.; Kiss, R. *Eur. J. Org. Chem.* **2003**, 2062–2070.

(17) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289–291.