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Diastereoselective Access to *trans*-2-Substituted Cyclopentylamines

Antoine Joosten, Émilie Lambert, Jean-Luc Vasse,* and Jan Szymoniak*

Institut de Chimie Moléculaire de Reims, CNRS (UMR 6229) and Université de Reims, 51687 Reims Cedex 2, France

jean-luc.vasse@univ-reims.fr; jan.szymoniak@univ-reims.fr

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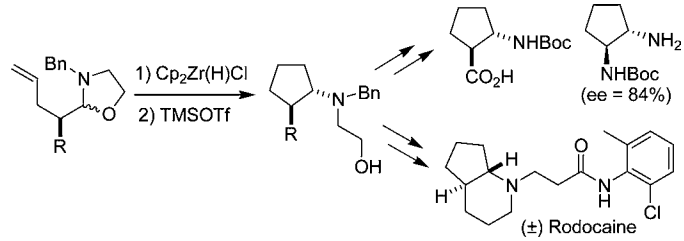
ABSTRACT



A highly diastereoselective synthesis of *trans*-2-substituted cyclopentylamines via a tandem hydrozirconation/Lewis acid-mediated cyclization sequence applied to butenyl oxazolidines is described. The method allows an easy preparation of diversely substituted cyclopentylamines which appear to be useful synthetic intermediates. This was further illustrated by the syntheses of (±)-Rodocaine, (±)-*trans*-pentacin, and enantiomerically enriched *trans*-cyclopentane-1,2-diamine.

The cyclopentylamine moiety is frequently encountered in naturally occurring molecules, especially alkaloids, and it constitutes a valuable building block for the preparation of biologically active molecules. Among them, 2-aminocyclopentanecarboxylic acids display various biological applications.[1] For example, cispentacin **A** (Figure 1), isolated from *Bacillus cereus*, is an antifungal agent.[2] In addition to their intrinsic biological properties, 2-aminocyclopentanecarboxylic acids can be incorporated into peptides instead of proteinogenic α-amino acids for modifying the original activity.[1] Also, *trans*-cyclopentanediamine **B** is intensively used as a valuable tool for SAR studies. For example, its incorporation into peptide nucleic acids results in a conformation constraint, improving bindings to DNA and RNA.[3]

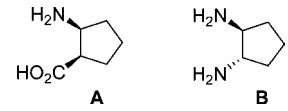


Figure 1. Cyclopentylamines **A** and **B**.

Furthermore, ligands based on the *trans*-cyclopentane-1,2-diamine scaffold offer interesting perspectives in asymmetric catalysis.[4]

Whereas access to both isomers of 2-aminocyclopentanecarboxylic acids[5] and to *trans*-cyclopentane-1,2-diamine derivatives[6] is well documented in the literature, no general synthetic method is available for the preparation of diversely

(1) (a) Gademann, K.; Hinterman, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905–925. (b) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983–1004. (c) Scarborough, R. M. *Curr. Med. Chem.* **1999**, *6*, 971. (d) Fulop, F. *Chem. Rev.* **2001**, *101*, 2181–2204.

(2) (a) Iwamoto, T.; Tsujii, E.; Ezaki, M.; Fujie, A.; Hashimoto, S.; Okuhara, M.; Kohsaka, M.; Imanaka, H.; Inamoto, Y.; Sakane, K. J. *Antibiotics* **1990**, *43*, 1–7. (b) Kawabata, K.; Inamoto, Y.; Sakane, K.; Iwamoto, T.; Hashimoto, S. *J. Antibiot.* **1990**, *43*, 513–518.

(3) (a) Myers, M. C.; Witschi, M. A.; Lariona, N. V.; Franck, J. M.; Haynes, R. D.; Hara, T.; Grajkowski, A.; Appella, D. H. *Org. Lett.* **2003**, *5*, 2695–2698. (b) Pokorski, J. K.; Witschi, M. A.; Purnell, B. L.; Appella, D. H. *J. Am. Chem. Soc.* **2004**, *126*, 15067–15073. (c) Zhang, N.; Appella, D. H. *J. Am. Chem. Soc.* **2007**, *129*, 8424–8425.

(4) (a) Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6*, 123–152. (b) Dominguez, B.; Hodnett, N. S.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 4289–4291. (c) Daly, A. M.; Gilheavy, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 127–137.

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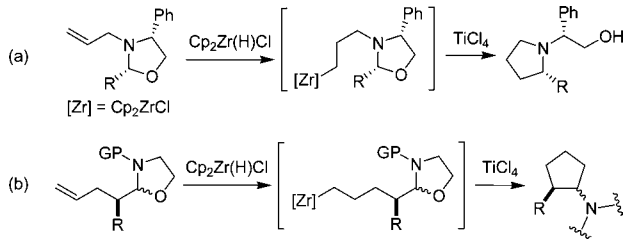
substituted cyclopentylamines. In fact, most of the reported procedures imply the ring opening of aziridines,[7] which is not suitable to all classes of nucleophilic agents.

Recently, we described an efficient stereoselective approach to 2-substituted pyrrolidines, based on a tandem hydrozirconation/Lewis acid-mediated cyclization starting from *N*-allyloxazolidines (Scheme 1, path a).[8] We thought

Scheme 1. Access to 2-Substituted Pyrrolidines and Extension of the Method to Cyclopentylamines



that the reaction could be extended toward the exo mode cyclization to afford cyclopentylamines (path b). An analogous radical cyclization of unsaturated oximes and hydrazones has been reported.[9]

To check this approach, the oxazolidine **1a** derived from 2-benzylaminoethanol was first obtained as a 1.3:1 mixture of diastereomers and subjected to the hydrozirconation/cyclization sequence (Table 1). By using several Lewis acids (entries 3−6), the expected cyclopentylamine **2a** was obtained in excellent to moderate yields and remarkably as the sole *trans* isomer.[10] It is noteworthy that when using an

(5) For asymmetric synthesis of cispentacin, see: (a) Aggarwal, V. K.; Roseblade, S. J.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227–1229. (b) Aggarwal, V. K.; Roseblade, S.; Alexander, R. *Org. Biomol. Chem.* **2003**, *1*, 684–691. For asymmetric synthesis of *trans*-pentacin, see: (c) Chippendale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253–3265.

(6) For the preparation of *trans*-diaminocyclopentane by resolution, see: (a) González-Sabín, J.; Gotor, V.; Rebolledo, F. *J. Org. Chem.* **2007**, *72*, 1309–1314. (b) Pena, C.; González-Sabín, J.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **2008**, *19*, 751–755. (c) Xu, Q.; Appella, D. H. *J. Org. Chem.* **2006**, *71*, 8655–8657.

(7) Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2–5. (b) Page, M. F. Z.; Jalisatgi, S. S.; Maderna, A.; Hawthorne, M. F. *Synthesis* **2008**, 555–563. (c) Blyumin, E. V.; Gallon, H. J.; Yudin, A. K. *Org. Lett.* **2007**, *9*, 4677–4680. (d) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16438–16439. (e) Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509–3512.

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

(9) (a) Godineau, E.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2008**, *73*, 6983–6993. (b) Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459–4479. (c) Bartell, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633–1634.

(10) The *trans* relative configuration in **1a** was deduced from NOESY experiment.

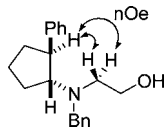
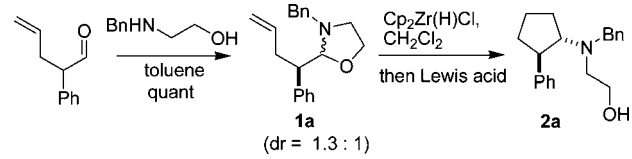


Table 1. Effect of the Lewis Acids and HCl on the Ring-Closure Step



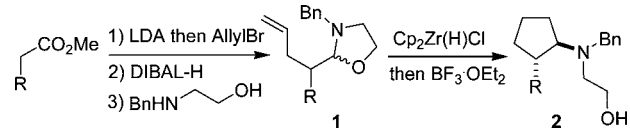
entry	acid	dr	yield (%)
1	HCl (1 M)	>95:5	84
2	HCl (4 M)	>95:5	64
3	$AlCl_3$	>95:5	83
4	$TiCl_4$	>95:5	49
5	$BF_3{\cdot}OEt_2$	>95:5	89
6	TMSOTf	>95:5	92

aqueous solution of HCl instead of the Lewis acid (entries 1 and 2) similar results were obtained, whereas hydrolysis products would have been expected.

To extend the scope of the reaction, a range of diversely substituted oxazolidines **1b**−**l** (for experimental procedures, see Supporting Information) were synthesized and submitted to the same reaction conditions.

The reaction appears as quite general and proceeds smoothly irrespective of the substituent, giving access to diversely substituted cyclopentylamines. Thus, cyclopentylamines substituted at the 2-position with aromatic (Table 2, entries 1−3), heteroaromatic (entry 4), and aliphatic

Table 2. Synthesis of Cyclopentylamines **2**



entry	R	dr	yield (%)
1	Ph	>95:5	89 (**2a**)
2	2-Br-C_6H_4	>95:5	88 (**2b**)
3	4-MeO-C_6H_4	>95:5	78 (**2c**)
4[a]	*N*-Boc-indolyl	>95:5	79 (**2d**)
5	*n*-C_6H_{11}	>95:5	89 (**2e**)
6	*i*-Pr	>95:5	92 (**2f**)
7	NBn_2	>95:5	98 (**2g**)
8	$(CH_2)_3$−OBn	96:4	91 (**2h**)
9	OBn	52:48	77 (**2i**)
10	OTr	>95:5	74 (**2j**)
11	CH_2OTr	>95:5	81 (**2k**)
12	Ph−CH=CH−CH_2	>95:5	78 (**2l**)

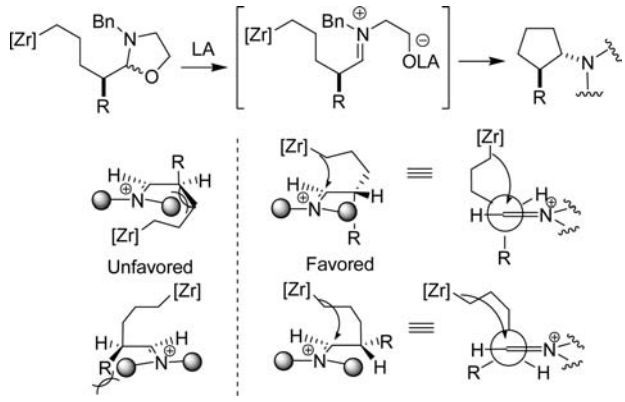
[a] The reaction was carried out without isolating the oxazolidine which appears to be unstable.

(entries 5 and 6) chains bearing N- (entry 7) or O-protected functions (entries 8, 10, and 11) were prepared in good yields as the sole *trans* diastereomer except in the case of the R = OBn group, for which no stereoselectivity was observed

(entry 9). In this case, the absence of selectivity might originate from a detrimental OBn chelation on zirconium. In fact, when switching the benzyl to a bulky trityl, less prone to metal chelation, a complete stereoselectivity was obtained (entry 10). Cyclopentylamine bearing an unsaturated chain could also be obtained owing to the chemoselective hydrozirconation in this case (entry 12).

To account for the observed high *trans* stereoselectivity, we assume that the Lewis (or protic) acid activation preferentially generates an iminium with a perpendicular orientation of one of the larger substituents of the adjascent stereocenter (the R group or the zirconium-containing chain) (Scheme 2). Accordingly, each of the two favored transition

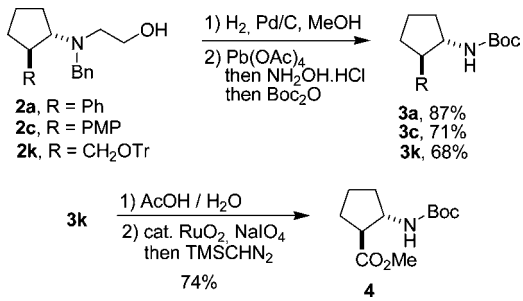
Scheme 2. Plausible Origin of the *trans* Selectivity



states leads to the major *trans* isomer, whereas the two unfavored transition states correspond to the minor *cis* isomer.

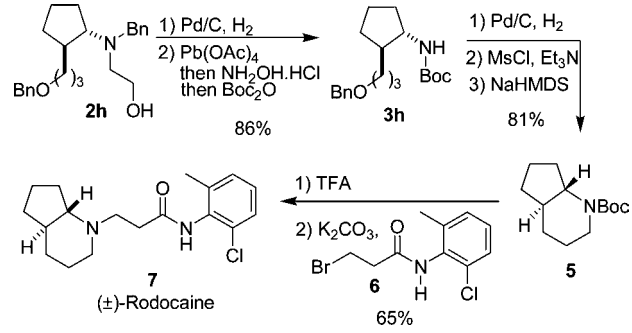
The synthetic interest of such a method is related to the possibility of obtaining the free amine. For that purpose, a two-step sequence was developed by hydrogenolysis and $Pb(OAc)_4$ oxidative cleavage of the hydroxyethyl fragment, the product being isolated in the *N*-Boc protected form (Scheme 3). Applied to **2k**, this sequence gave **3k**, a *trans*-pentacin precursor. Further alcohol deprotection and oxidation afforded the amino acid, isolated as its methyl ester **4**[11] after $TMSCHN_2$ treatment.

Scheme 3. Access to the Boc-Protected *trans*-2-Aminocyclopentanoate **4**



To further illustrate the synthetic potential of the method, the preparation of (±)-Rodocaine **7**,[12] an ophthalmic anesthesia, was undertaken (Scheme 4). The synthesis began by

Scheme 4. Synthesis of (±)-Rodocaine



applying the deprotection/N-Boc protection sequence to **2h** to give **3h**. Subsequent hydrogenolysis and condensation with mesyl chloride provided the bicyclic precursor. The cyclization step was promoted by adding NaHMDS to give the annulated heterocycle **5**. Boc removal and coupling with bromo amide **6**[13] afforded the target molecule **7** in 45% overall yield starting from **2h**.

The asymmetric version of this methodology was initiated by exploring the synthesis of *N*-Boc-protected *trans*-cyclopentane-1,2-diamine, starting from commercially available (*S*)-*N*-Boc-2-allylglycine. The required aldehyde was prepared after BOP coupling with a Weinreb amine, followed by LAH reduction.[14]

With optically pure aldehyde in hand, condensation with *N*-benzylaminoethanol provided the cyclopentylamine precursor **1m** (Scheme 5). The sequential hydrozirconation/cylization sequence was next applied to afford **2m**. Additional debenzylation and the oxidative hydroxyethyl chain removal gave the monoprotected diamine **3m** in 84% ee [($[\alpha]_{20}^{D} = +13.4$, *c* 1, EtOH); lit., ($[\alpha]_{20}^{D} = +16.0$)].[15] The observed partial racemization is assumed to occur at the iminium formation stage.[16]

In summary, we described a highly diastereoselective method for the preparation of *trans*-2-substituted cyclopentylamines. High substituent flexibility of the method allows a simple access to valuable building blocks as illustrated by

(11) (a) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571. (b) Gardiner, J.; Anderson, K. H.; Downard, A.; Abell, A. D. *J. Org. Chem.* **2004**, *69*, 3375–3382.

(12) Henshall, T.; Parnell, E. W. *J. Chem. Soc* **1962**, 661. Hermans, H.; Hubert, K. F.; Knaeps, G. A.; Willems, J. J. M. U.S. Patent No. 3,679,686, 1972.

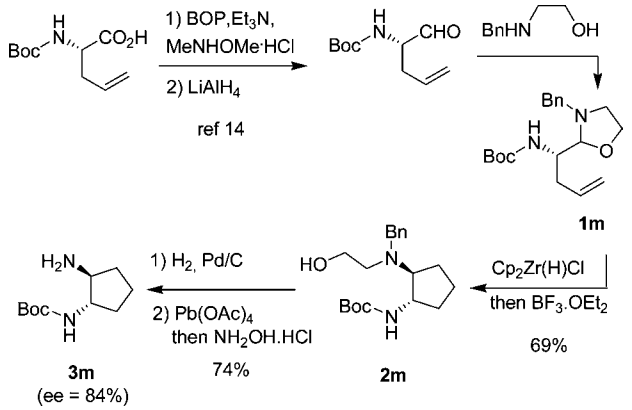
(13) **6** was prepared in 83% yield from the corresponding acyl chloride and aniline derivative according to: Tenthorey, P. A.; DiRubio, R. L.; Feldman, H. S.; Takman, B. H. *J. Med. Chem.* **1979**, *22*, 1182–1186.

(14) Rishel, M. J.; Hecht, S. M. *Org. Lett.* **2001**, *3*, 2867–2869.

(15) The enantiomeric excess was confirmed by chiral HPLC after derivatization. See ref 6a.

(16) In this case, $BF_3{\cdot}OEt_2$ was added at −10°C, and addition at higher temperature increases the racemization.

Scheme 5. Synthesis of (*S*,*S*)-Cyclopentane-1,2-diamine (**3m**)



the synthesis of (±)-Rodocaine. Moreover, the asymmetric version could be envisioned as demonstrated by the synthesis of enantiomerically enriched *trans*-cyclopentane-1,2-diamine. More interestingly, access to optically pure 2-substituted pent-4-enal derivatives is well-established,[17] allowing a nonracemic extension of such a method.

Acknowledgment. Financial support of this work by CNRS, ANR, and the Ministère de l'Enseignement Supérieur et de la Recherche is gratefully acknowledged.

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

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(17) For the synthesis of optically pure 2-substituted pent-4-enal derivatives via the diastereoselective allylation of pseudoephedrine-derived amides followed by reduction, see: (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1995**, *117*, 8488–8489. (c) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656–673. (d) Myers, A. G.; Schnider, P.; Yoon, T.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322–3327.