

Accepted Manuscript

Synthesis of optically active 1,2,3-trisubstituted azetidines employing an organocatalytic approach with L-proline

Marcela Amongero, Teodoro S. Kaufman

PII: S0040-4039(13)00148-2
DOI: <http://dx.doi.org/10.1016/j.tetlet.2013.01.090>
Reference: TETL 42466

To appear in: *Tetrahedron Letters*

Received Date: 16 January 2013
Accepted Date: 18 January 2013



Please cite this article as: Amongero, M., Kaufman, T.S., Synthesis of optically active 1,2,3-trisubstituted azetidines employing an organocatalytic approach with L-proline, *Tetrahedron Letters* (2013), doi: <http://dx.doi.org/10.1016/j.tetlet.2013.01.090>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

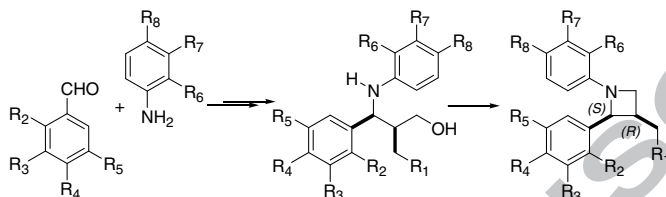
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis of optically active 1,2,3-trisubstituted azetidines employing an organocatalytic approach with L-proline

Leave this area blank for abstract info.

Marcela Amongero and Teodoro S. Kaufman





Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of optically active 1,2,3-trisubstituted azetidines employing an organocatalytic approach with L-proline

Marcela Amongero and Teodoro S. Kaufman*

Institute of Chemistry of Rosario (IQUIR, CONICET-UNR) and School of Biochemical and Pharmaceutical Sciences, National University of Rosario, Suipacha 531, S2002LRK Rosario, Argentine

ARTICLE INFO

Article history:

Received
Received in revised form
Accepted
Available online

Keywords:

Optically active azetidines
1,2,3-Trisubstituted azetidines
Organocatalysis
Synthesis of nitrogen heterocycles
Mannich reaction

ABSTRACT

A concise organocatalytic approach towards optically active 1,2,3-trisubstituted azetidines, including a study of the scope and limitations of the synthetic sequence, is reported. The synthesis comprises the one-pot L-proline promoted three-component reaction between substituted benzaldehydes, anilines and enolizable aldehydes, followed by the *in situ* reduction of the resulting β -aminoaldehydes to the corresponding γ -aminoalcohols and final intramolecular cyclization of the latter by way of the intermediate tosylates, formed *in situ*.

2013 Elsevier Ltd. All rights reserved.

Azetidines are four-membered nitrogen heterocycles. They are of great interest for fundamental research and useful for practical applications; for example, 2-azetidinone is the key feature of the β -lactam antibiotics.¹ Several natural products carry the azetidine motif; among them, the α -aminoacid azetidine-2-carboxylic acid, a powerful proline antagonist in plant tissue cultures,² and some of its functionalized derivatives, such as the phytosiderophores nicotianamine^{3a-c} and mugineic acid,^{3d-g} and the structurally related 2''-hydroxynicotianamine, an ACE-inhibitor (Figure 1).^{3h,i}

Other naturally-occurring azetidines include the vioprolides, antifungal and cytotoxic peptolides, exemplified by vioprolide A,^{4a} and the polyoxins A, F, H and K, peptide nucleosides with antifungal and antiparasitic activity, possibly involved in cell wall chitin biosynthesis.^{4b-e} Additional representatives of natural azetidines are the cytotoxic and antibacterial penaresidines⁵ and the related penazetidine A, an inhibitor of protein kinase C.⁶ Interestingly, natural products such as gelsemoxone,^{7a-c} the insecticidal alkaloid okaramine B^{7d,e} and calyphaphinone^{7f} also carry fused polysubstituted azetidine moieties.

Azetidines are also of interest because of their presence in synthetic intermediates and bioactive compounds,⁸ including the non-opioid analgesic ABT-594, the thrombin inhibitors exenta and melagatran,^{9a,b} and aggrecanase and β -amyloid cleaving

enzyme-1 inhibitors.^{9c,d} They are also found in certain NMDA receptor^{10a} and cholinergic channel modulators,^{10b} antivirals^{10c} and inducers of cytokine production.^{10d} Their suitability as natural aminoacid surrogates,^{11a} and tools in peptidomimetics^{11b} and nucleic acid chemistry,^{11c-e} is also remarkable.

Ligands featuring the azetidine moiety have been employed in various catalytic processes, including reductions,^{12a,b} asymmetric Et_2Zn ,^{12c-g} and Henry additions to aldehydes,^{12g} cycloadditions,^{13a} cyclopropanations^{13b} and other C-C bond forming reactions (Suzuki, Sonogashira, Michael)^{13b-e} with promising results. In addition, C_2 -symmetric bis(aziridines) have been used as bidentate ligands in transition metal catalyzed reactions.¹⁴

Synthetic approaches towards optically active polysubstituted azetidines have been recently reviewed.¹⁵ These have been comparatively less studied than the aziridines, pyrrolidines and piperidines, their lower and higher homologous small-ring saturated single-nitrogen heterocycles, and several authors have pointed out the paucity of short, general and efficient methods for the synthesis of enantiopure azetidines.¹⁶

Furthermore, the low number of publications on optically active polysubstituted azetidines also reflects the need of new enantioselective approaches towards these heterocycles.^{16b}

* Corresponding author. Tel.: +54-341-4370477, ext. 105; fax: +54-341-4370477, ext. 112; e-mail: kaufman@iquir-conicet.gov.ar

Marinetti *et al.*^{16c} conjectured that the reason for the lack of progress in the development of the chemistry of optically active azetidines could be related to synthetic difficulties associated to the formation of the four-membered ring from acyclic derivatives; this is a disfavored process compared to the analogous construction of slightly larger and even smaller rings.

Therefore, herein we report the development of the first enantioselective organocatalyzed approach to 1,2,3-trisubstituted azetidines employing a one-pot synthesis of γ -aminoalcohols followed by their microwave-assisted cyclization with TsCl-Et₃N. No protecting groups are employed. The γ -aminoalcohols result from a tri-component cross-Mannich synthesis of β -amino aldehydes,¹⁷ followed by their *in situ* reduction.

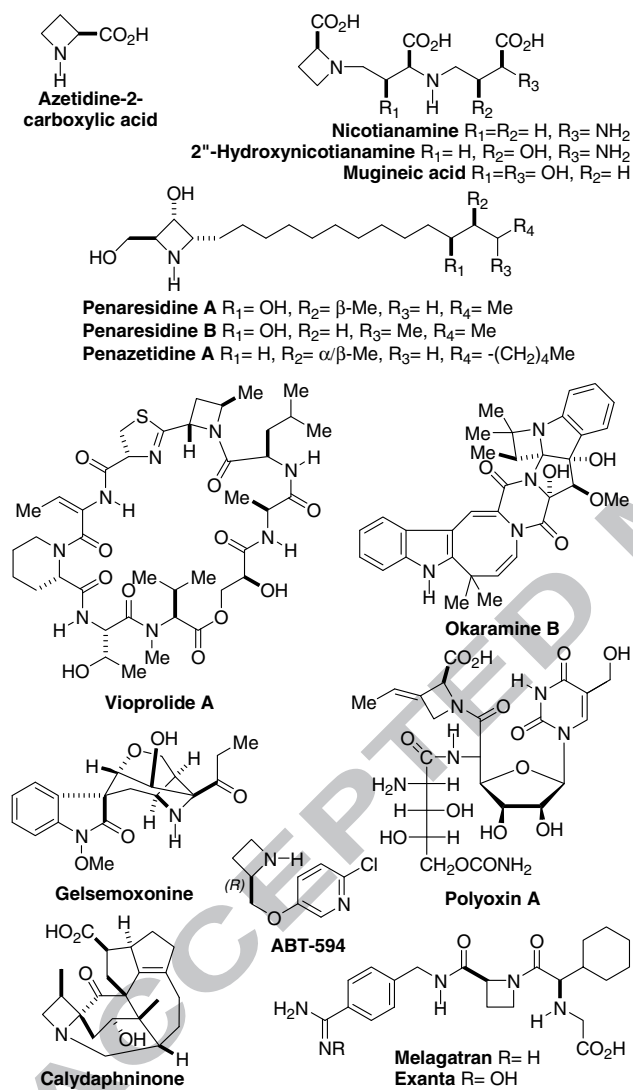
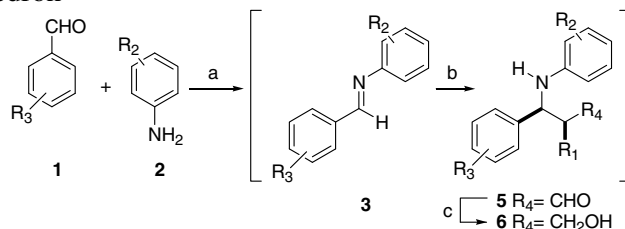


Figure 1. Some relevant azetidines-type natural and pharmaceutical products.

To that end, 4-nitrobenzaldehyde (**1**), propanal (**4**) and 3,4-dimethoxyaniline (**2**) were reacted with 20 mol% L-proline as chiral organocatalyst (Scheme 1).¹⁸ Under these conditions, the use of NMP at r.t. met with failure, while adding 4Å MS to a mixture of the benzaldehyde and the amine in order to promote pre-formation of the Schiff base (**3**), and reacting the latter at -20°C with propanal (**4**) provided only minor amounts of the expected intermediate **5**, which proved to be highly unstable to silica gel column chromatography.



Scheme 1. Reagents and conditions: a) L-proline (20 mol%), NMP, MW (70°C, 1 h); b) R₁CH₂CHO (**4**), NMP, -20°C, 24 h; c) NaBH₄, MeOH, Et₂O, 0°C, 1 h. **1:2:4**= 1.0:1.1:3.0. For the identity of R₁-R₃, see Table 2.

Therefore, the protocol was modified to include pre-formation of the Schiff base and to avoid isolation of the β -aminoaldehyde. Schiff base pre-formation in absence of molecular sieves proved to be more efficient under microwave irradiation (70°C, 1 h) than under conventional heating. Dropwise addition of **4** (3 equiv.) furnished the expected β -aminoaldehyde **5**, which was reduced *in situ* with NaBH₄ in MeOH, to the corresponding γ -aminoalcohol **6**, which was eventually purified (62% overall yield).¹⁹

It was also observed that the reaction solvent played a key role in the yield and outcome of the transformation. Anhydrous DMSO, gave 45% γ -aminoalcohol, while a 1:1 DMSO/CH₂Cl₂ mixture yielded no useful products and a 2:1 DMSO/CH₂Cl₂ solvent furnished mainly aldol condensation derivatives. Analogously, 50% yield of γ -aminoalcohol was realized in DMF, while a 1:1 mixture of DMF and CH₂Cl₂ gave mainly the imine. Therefore, the syntheses of γ -aminoalcohols **6** to explore the scope and limitations of the reaction were carried out in NMP.

The amination of alcohols has been performed employing various strategies, which involve converting the carbinol into a suitable leaving group (Mitsunobu, Appel-type halogenation, formation of sulfonates, carbonates and other esters), followed by base-assisted displacement of the latter with the cyclizing nitrogen moiety, as the final step.²⁰

Thus, suitable cyclization conditions were screened (Table 1). Initially, formation of the benzoate (PhCOCl-Et₃N) followed by intramolecular displacement of the latter was attempted;²¹ however, this resulted in an incomplete sequence, yielding a mixture of products which included the intermediate benzoate (runs 3 and 11). On the other hand, activation of the primary alcohol as the carbonate (ClCO₂Et, Et₃N) prior to intramolecular displacement gave several inseparable products and low yields of the expected products (runs 1 and 4). The report by Couty *et al.*, that chloroformates can cleave the azetidines ring, may explain the observed low yields.²²

Table 1. Selection of the cyclizing agent.

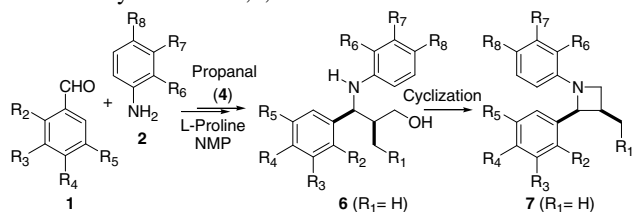
Run N°	Starting γ -Aminoalcohol	Activating agent	Azetidine % Yield	Azetidine ee (%) ^d
1	R= NO ₂ , R ₁ = H	ClCO ₂ Et	33	92
2		TsCl	94	92
3		BzCl	- ^a	
4	R= NO ₂ , R ₁ = OMe	ClCO ₂ Et	27	97
5		TsCl	95	97
6		ClCO ₂ Et	6 ^b	97
7		TsCl	51 ^c	
8	R= H, R ₁ = OMe	ClCO ₂ Et	16	91
9		TsCl	69	91

10	R= Cl, R ₁ =OMe	TsCl	90	96
11		BzCl	- ^a	
12		MsCl	55	96

^a Formation of the benzoate was observed; ^b Formation of the carbamate was observed (27%); ^c Under conventional heating; ^d Determined by chiral HPLC with a Chiralcel OD column, eluting with hexanes:IPA (10:1) at 1 mL/min.

Finally, reaction with TsCl and Et₃N under microwave irradiation resulted in smooth and clean cyclizations (entries 2, 5, 9 and 10), which successfully competed with the corresponding thermal conditions (entry 7) and with the related MsCl-Et₃N process (entry 12),²³ perhaps because in the latter case, the sulfene intermediates generated under the reaction conditions may undergo side reactions lowering product yields or demanding great excess of the reagent.²⁴

Table 2. Synthesis of 1,2,3-trisubstituted azetidines.



N ^o	Aldehyde (1)	Aniline (2)	6, % Yield	7, % Yield (ee, %) ^a	7, [α] _D (CHCl ₃)
1	R ₂ =R ₃ =R ₄ =R ₅ =H	R ₆ =H, R ₇ =R ₈ =OMe	41	69 (91)	-191.5 (c= 0.5)
2	R ₂ =R ₃ =R ₅ =H, R ₄ =Br	R ₆ =H, R ₇ =R ₈ =OMe	66	15 (93)	-156.3 (c= 0.2)
3	R ₂ =R ₃ =R ₅ =H, R ₄ =Me	R ₆ =H, R ₇ =R ₈ =OMe	52	67 (95)	-161.9 (c= 0.5)
4	R ₂ =R ₃ =R ₅ =H, R ₄ =NO ₂	R ₆ =H, R ₇ =R ₈ =OMe	62	57 (97)	-207.4 (c= 1.0)
5	R ₂ =R ₃ =OMe, R ₄ =R ₅ =H	R ₆ =H, R ₇ =R ₈ =OMe	67	70 (99)	-219.8 (c= 0.5)
6	R ₂ =R ₄ =R ₅ =H, R ₃ =OBn	R ₆ =H, R ₇ =R ₈ =OMe	50	45 (81)	-192.9 (c= 0.32)
7	R ₂ =R ₃ =R ₅ =H, R ₄ =Cl	R ₆ =H, R ₇ =R ₈ =OMe	67	90 (96)	-218.9 (c= 1.1)
8	R ₂ =Br, R ₃ =H, R ₄ =R ₅ =OMe	R ₆ =H, R ₇ =R ₈ =OMe	7	36 (86)	-129.5 (c= 0.12)
9	R ₂ =Cl, R ₃ =R ₄ =R ₅ =H	R ₆ =H, R ₇ =R ₈ =OMe	Imine	-	-
10	R ₂ =H, R ₃ =R ₄ =R ₅ =OMe	R ₆ =H, R ₇ =R ₈ =OMe	33	62 (88)	-143.7 (c= 0.2)
11	R ₂ =CF ₃ , R ₃ =R ₄ =R ₅ =H	R ₆ =H, R ₇ =R ₈ =OMe	Imine	-	-
12	R ₂ =CF ₃ , R ₃ =R ₄ =R ₅ =H	R ₆ =R ₇ =H, R ₈ =OMe	Imine	-	-
13	R ₂ =R ₃ =R ₅ =H, R ₄ =Cl	R ₆ =R ₇ =H, R ₈ =OMe	35	69 (92)	-168.7 (c= 1.2)
14	R ₂ =R ₃ =R ₅ =H, R ₄ =NO ₂	R ₆ =Ph, R ₇ =R ₈ =H	No Reaction	-	-
15	R ₂ =R ₃ =R ₅ =H, R ₄ =NO ₂	α-Naphthylamine	Imine	-	-
16	R ₂ =R ₃ =R ₅ =H, R ₄ =OMe	R ₇ =R ₈ =H, R ₆ =OMe	Imine	-	-
17	R ₂ =R ₃ =R ₅ =H, R ₄ =OMe	R ₆ =Ph, R ₇ =R ₈ =H	No Reaction	-	-
18	R ₂ =R ₃ =R ₅ =H, R ₄ =OMe	R ₆ =R ₇ =H, R ₈ =CO ₂ Et	21	34 (83)	-174.3 (c= 0.3)
19	R ₂ =R ₃ =R ₅ =H, R ₄ =NO ₂	R ₆ =R ₇ =H, R ₈ =OMe	62	94 (93)	-223.4 (c= 1.1)
20	R ₂ =R ₃ =R ₅ =H, R ₄ =NO ₂	R ₆ =R ₇ =H, R ₈ =OMe	56 ^b	36 (97)	-196.7 (c= 0.4)

^a by chiral HPLC with a Chiralcel OD column, eluting with hexanes:IPA

(10:1) at 1 mL/min; ^b Reaction with 3-phenylpropanal (R₁= Ph in 6 and 7).

With suitable cyclizing conditions, the scope and limitations of the protocol were studied with different benzaldehydes and anilines.²⁵ It was observed that steric hindrance exerted a major effect on the outcome. On the benzaldehyde side, the reaction accepted compounds carrying electron withdrawing and electron releasing substituents, but the presence substituents *ortho* to the formyl moiety resulted in intermediate imines (3), which failed to undergo the Mannich reaction (entries 9, 11 and 12), except with the more activated aldehydes (entries 5 and 8), albeit at the expense of reduced yield (entry 8); *meta*-substituted aldehydes reacted uneventfully (entries 6 and 10).

On the other hand, the results of steric effects were more evident on the aniline side. The bulky 2-phenylaniline failed to react (entries 14 and 17), while reaction with α-naphthylamine and 2-methoxyaniline (entries 15 and 16) furnished the corresponding Schiff bases, which failed to further undergo the Mannich reaction with propanal. Finally, it was observed that the synthetic sequence accepts enolizable aldehydes other than propanal, such as 3-phenylpropanal (entry 20).

The configuration of the azetidines was inferred from that of the precursor γ-aminoalcohols¹⁸ and NOE experiments confirmed their relative configuration. The C₂ - C₃ coupling constants of the heterocycles were in the range 7.2-8.5 Hz in their ¹H NMR spectra and only one diastereomer was always obtained.

Chemical yields ranged from moderate to good for both main stages (total= five steps), the synthesis of the γ-aminoalcohol and its cyclization, while enantiomeric excesses (*ees*) of the resulting products were mostly above 90%. A tendency to lower enantiomeric excess values was observed when electron releasing substituents were present in the benzaldehyde derived moiety (entries 8 and 10) of the γ-aminoalcohol and/or the starting aniline carried electron withdrawing substituents (entry 18).

In conclusion, a two-stage organocatalytic enantioselective approach to the synthesis of 1,2,3-trisubstituted azetidines, which does not require protective groups, was developed; its scope and limitations were studied. Overall chemical and optical yields were highly satisfactory; however, the one-pot synthesis of the intermediate γ-aminoalcohols was influenced by steric and electronic factors, sometimes resulting in unsuccessful transformations. Due to its simplicity and effectiveness, the sequence may find use in synthetic organic chemistry.

Acknowledgments

The authors are thankful to Agencia Nacional de Promoción Científica y Tecnológica, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Fundación Josefina Prats and Secretaría de Ciencia y Tecnología-UNR for financial support.

References and notes

- 1 a) Kamath, A.; Ojima, I. *Tetrahedron* **2012**, *68*, 10640; b) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631; c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.
- 2 a) Couty, F.; Evano, G. *Org. Prep. Proc. Int.* **2006**, *38*, 427; b) Rubenstein, E.; Zhou, H.; Krasinska, K. M.; Chien, A.; Becker, C. H. *Phytochemistry* **2006**, *67*, 898; c) Couty, F.; Evano, G.; Vargas-Sanchez, M.; Bouzas, G. *J. Org. Chem.* **2005**, *70*, 9028; d) Fouden, L. *Biochem. J.* **1956**, *64*, 323.
- 3 a) Budeshinsky, M.; Prochazka, Zh.; Budzikiewicz, H.; Roemer, A.; Ripperger, H. *Tetrahedron* **1981**, *37*, 191; b) Ripperger, H.; Faust, J.; Scholz, G. *Phytochemistry* **1982**, *21*, 1785; c) Miyakoshi, K.; Oshita, J.; Kitahara, T. *Tetrahedron* **2001**, *57*, 3355; d) Scholz, G.; Faust, J.; Ripperger, H.; Schreiber, K. *Phytochemistry* **1988**,

- 27, 2749; e) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 265; f) Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1986**, *51*, 5489; g) Singh, S.; Crossley, G.; Ghosal, S.; Lefievre, Y.; Pennington, M. W. *Tetrahedron Lett.* **2005**, *46*, 1419; h) Aoyagi, Y. *Phytochemistry* **2006**, *67*, 618; i) Yoshikawa, K.; Watanabe, H.; Aoyagi, Y.; Kitahara, T. *Heterocycles* **2010**, *81*, 1435.
- 4 a) Schummer, D.; Forche, E.; Wray, V.; Domke, T.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1996**, 971; b) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490; c) Isono, K. *J. Antibiotics* **1988**, *41*, 1711; d) Sobottka L.; Bartscht, K.; Schäfer, P.; Weitzel, T.; Schottelius, J.; Kock, N.; Laufs, R. *Parasitol. Res.* **2002**, *88*, 451; e) Cesario, C.; Miller, M. J. *J. Org. Chem.* **2009**, *74*, 5730.
- 5 a) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135; b) Kobayashi, J.; Ishibashi, M. *Heterocycles* **1996**, *42*, 943; c) Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **1995**, *36*, 4841; d) Liu, D.-G.; Lin, G.-Q. *Tetrahedron Lett.* **1999**, *40*, 337; e) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 977; f) Ohshita, K.; Ishiyama, H.; Takahashi, Y.; Ito, J.; Mikami, Y.; Kobayashi, J. *Bioorg. Med. Chem.* **2007**, *15*, 4910; g) Knapp, S.; Dong, Y. *Tetrahedron Lett.* **1997**, *38*, 3813; h) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283; i) Takikawa, H.; Maeda, T.; Mori, K. *Tetrahedron Lett.* **1995**, *36*, 7689.
- 6 a) Alvi, K. A.; Jaspars, M.; Crews, P. *Bioorg. Med. Chem.* **1994**, *4*, 2447; b) Yajima, A.; Takikawa, H.; Mori, K. *Liebigs Ann. Chem.* **1996**, 1083; c) Li, Z. M.; Wang, B.; Tao, F. G.; Lin, G. Q. **2004**, *15*, 138.
- 7 a) Kitajima, M.; Kogure, N.; Yamaguchi, K.; Takayama, H.; Aimi, N. *Org. Lett.* **2003**, *5*, 2075; b) Lin, L.-Z.; Cordell, G. A.; Ni, C.-Z.; Clardy, J. *Phytochemistry* **1991**, *30*, 1311; c) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 17634; d) Hayashi H.; Takiuchi, K.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1988**, *52*, 2131; e) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1519; f) Di, Y.-T.; He, H.-P.; Wang, Y.-S.; Li, L.-B.; Lu, Y.; Gong, J.-B.; Fang, X.; Kong, N.-C.; Li, S.-L.; Zhu, H.-J.; Hao, X.-J. *Org. Lett.* **2007**, *9*, 1355.
- 8 a) De Kimpe, N. in *Comprehensive Heterocyclic Chemistry II*. Padwa, A. (Ed.), Elsevier, **1996**, Vol. 1B, Chapter 1.18, pp. 507–589; b) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2002**, 3099.
- 9 a) Ericksson, B. I.; Carlsson, S.; Halvarsson, M.; Risberg, B.; Mattson, C. *Thromb. Haemostasis* **1997**, *78*, 1404; b) Astra Zeneca; PCT Int. Appl. WO 00/41716, 2000; *Chem. Abstr.* **2000**, *133*, 99559; c) Cherney, R. J.; Mo, R.; Meyer, D. T.; Wang, L.; Yao, W.; Wasserman, Z. R.; Liu, R. Q.; Covington, M. B.; Tortorella, M. D.; Arner, E. C.; Qian, M.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Magolda, R. L.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1297; d) Iserloh, U.; Wu, Y.; Cumming, J. N.; Pan, J.; Wang, L. Y.; Stamford, A. W.; Kennedy, M. E.; Kuvelkar, R.; Chen, X.; Parker, E. M.; Strickland, C.; Voigt, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 414.
- 10 a) Kozikowski, A. P.; Tueckmantel, W.; Reynolds, I. J.; Wroblewski, J. T. *J. Med. Chem.* **1990**, *33*, 1561; b) Abreo, M. A.; Lin, N.; Garvey, D. S.; Gunn, D. E.; Hettlinger, A.-M.; Wasicak, J. T.; Pavlik, P. A.; Martin, Y. C.; Donnelly-Roberts, D. L.; Anderson, D. J.; Sullivan, J. P.; Williams, M.; Arneric, S. P.; Holladay, M. W. *J. Med. Chem.* **1996**, *39*, 817; c) Hosono, F.; Nishiyama, S.; Yamamura, S.; Izawa, T.; Kato, K.; Terada, Y. *Tetrahedron* **1994**, *50*, 13335; d) Fuhshuku, K.-I.; Hongo, N.; Tashiro, T.; Masuda, Y.; Nakagawa, R.; Seino, K.-I.; Taniguchi, M.; Mori, K. *Bioorg. Med. Chem.* **2008**, *16*, 950.
- 11 a) Bräuner-Osborne, H.; Bunch, L.; Chopin, N.; Couty, F.; Evano, G.; Jensen, A. A.; Kusk, M.; Nielsen, B.; Rabasso, N. *Org. Biomol. Chem.* **2005**, *3*, 3926; b) Drouillard, B.; Wright, K.; Marrot, J.; Couty, F. *Tetrahedron: Asymmetry* **2012**, *23*, 690; c) Honcharenko, D.; Zhou, C.; Chattopadhyaya, J. *J. Org. Chem.* **2008**, *73*, 2829; d) Plashkevych, O.; Chatterjee, S.; Honcharenko, D.; Pathmasiri, W.; Chattopadhyaya, J. *J. Org. Chem.* **2007**, *72*, 4716; e) Honcharenko, D.; Varghese, O. P.; Plashkevych, O.; Barman, J.; Chattopadhyaya, J. *J. Org. Chem.* **2006**, *71*, 299.
- 12 a) Rama Rao, A. V.; Gurjar, M. K.; Kaiwar, V. *Tetrahedron: Asymmetry* **1992**, *3*, 859; b) Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **2001**, *12*, 605; c) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 1673; d) Zhang, Z.; Li, M.; Zi, G. *Chirality* **2007**, *19*, 802; e) Hermsen, P. J.; Cremers, J. G. O.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **2001**, *42*, 4243; f) Couty, F.; Prim, D. *Tetrahedron: Asymmetry* **2002**, *13*, 2619; g) Zhang, Z.; Bai, X.; Liu, R.; Zi, G. *Inorg. Chim. Acta* **2009**, *362*, 1687.
- 13 a) Starmans, W. A. J.; Walgers, R. W. A.; Thijs, L.; de Gelder, R.; Smits, J. M. M.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 4991; b) Starmans, W. A. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 629; c) Lee, D.-H.; Lee, Y. H.; Kim, D. I.; Kim, Y.; Lim, W. T.; Harrowfield, J. M.; Thuéry, P.; Jin, M.-J.; Park, Y.-C.; Lee, I.-M. *Tetrahedron* **2008**, *64*, 7178; d) Menguy, L.; Couty, F. *Tetrahedron: Asymmetry* **2010**, *21*, 2385; e) Lee, D.-H.; Lee, Y. H.; Harrowfield, J. M.; Lee, I.-M.; Lee, H. I.; Lim, W. T.; Kim, Y.; Jin, M.-J. *Tetrahedron* **2009**, *65*, 1630.
- 14 a) Tanner, D.; Andersson, P. G.; Harden, A.; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 4631; b) Andersson, P. G.; Harden, A.; Tanner, D.; Norrby, P.-O. *Chem. Eur. J.* **1995**, *1*, 12; c) Andersson, P. G.; Johansson, F.; Tanner, D. *Tetrahedron* **1998**, *54*, 11549; d) Tanner, D.; Marinetti, A.; Hubert, P.; Genêt, J.-P.; Johansson, F.; Harden, A.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 15731; e) Wilken, J.; Erny, S.; Wassmann, S.; Martens, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2143.
- 15 a) Royer, J. (Ed.). *Asymmetric Synthesis of Nitrogen Heterocycles*. Wiley, Weinheim, 2009; b) Bott, T. M.; West, F. G. *Heterocycles* **2012**, *84*, 223; c) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988; d) Couty, F.; Evano, G. *Synlett* **2009**, 3053.
- 16 a) Denis, J. B.; Masson, G.; Retailleau, P.; Zhu, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 5356; b) Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem.* **2004**, *1*, 133; c) Marinetti, A.; Hubert, P.; Genêt, J.-P. *Eur. J. Org. Chem.* **2000**, 1815; d) Enders, D.; Gries, J.; Kim, Z.-S. *Eur. J. Org. Chem.* **2004**, 4471.
- 17 a) Ibrahim, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem. Eur. J.* **2005**, *11*, 7024; b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797; c) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.
- 18 Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3677.
- 19 **Typical experimental procedure for the synthesis of the β -amino alcohols (6):** A solution of the benzaldehyde (1.0 equiv.), the aniline (1.1 equiv.) and L-proline (0.2 equiv.) in NMP (2 mL) was submitted to microwave irradiation at 70°C for 1 h; then, the mixture was cooled to -20°C and treated dropwise with a solution of propanal (3.0 equiv.) in NMP (1.5 mL). Stirring continued for 20 h at this temperature, when a 1:1 mixture of MeOH and Et₂O (4 mL) was added, the mixture was placed at 0°C, and treated with NaBH₄ (3.0 equiv.). After 60 min., the reaction was diluted with phosphate buffer pH= 7.0 (10 mL) and the organic materials were extracted with EtOAc (4 × 20 mL). The combined organic phases were dried (Na₂SO₄), the volatiles were removed in vacuum and the remaining oily residue was chromatographed.
- 20 a) Bianchi, D. A.; Kaufman, T. S. *Can. J. Chem.* **2000**, *78*, 1165; b) Bianchi, D. A.; Cipulli, M. A.; Kaufman, T. S. *Eur. J. Org. Chem.* **2003**, 4731; c) Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *J. Org. Chem.* **2006**, *71*, 4147; d) Itoh, T.; Miyazaki, M.; Nagata, K.; Yokoya, M.; Nakamura, S.; Oshawa, A. *Heterocycles* **2002**, *58*, 115; e) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400.
- 21 a) Rambaud, L.; Compain, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 1807; b) Liotta, L. J.; Ganem, B. *Synlett* **1990**, 503.
- 22 Vargas-Sánchez, M.; Lakhdar, S.; Couty, F.; Evano, G. *Org. Lett.* **2006**, *8*, 5501.
- 23 Fenoglio, I.; Nano, G. M.; Vander Velde, D. G.; Appendine, G. *Tetrahedron Lett.* **1996**, *37*, 3203.
- 24 Barluenga, J.; Fernández-Mari, F.; Viado, A. L.; Aguilar, E.; Olano, B. *J. Org. Chem.* **1996**, *61*, 5659.
- 25 **Typical experimental procedure for the synthesis of the azetidines (7):** DMAP (cat.), Et₃N (4 equiv.) and TsCl (2.5 equiv.) were successively added to a solution of the γ -aminoalcohol (1 equiv.) in CHCl₃ (2 mL) and the mixture was subjected to microwave irradiation at 70°C for 1 h. Then, brine (10 mL) was added and the organic materials were extracted with EtOAc (4 × 20 mL). The organic phases were combined, dried (Na₂SO₄), concentrated in vacuum, and the residue was submitted to chromatography. *Data of selected azetidines: (2S,3R)-1-(3,4-Dimethoxyphenyl)-3-methyl-2-(4-nitrophenyl)azetidine:* IR (film, ν): 2957, 2850, 1598, 1465, 1452, 1343, 1239, 1121, 1140, 1027, 849, 823 and 745 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ : 0.89 (d, *J* = 7.3, 3H), 2.95 (ddd, *J* = 3.0, 7.3 and 8.3, 1H), 3.61 (dd, *J* = 3.0 and 6.4, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.92 (dd *J* = 6.4 and 7.3, 1H), 5.07 (d, *J* = 8.3, 1H), 5.86 (dd, *J* = 2.6 and 8.6, 1H), 6.03 (d, *J* = 2.6, 1H), 6.71 (d, *J* = 8.6, 1H), 7.52 (d, *J* = 8.7, 2H) and 8.23 (d, *J* = 8.7, 2H); ¹³C NMR δ : 16.2, 29.9, 55.8, 56.7, 57.0, 68.6, 97.7, 103.5,

112.9, 123.6 (2C), 127.5 (2C), 142.2, 146.2, 147.2, 147.5 and 149.9. HRMS obsd.: m/z 329.1490; $C_{18}H_{21}N_2O_4$ requires m/z 329.1496. **(2*S*,3*R*)-2-(3,4,5-Trimethoxyphenyl)-1-(3,4-dimethoxyphenyl)-3-methylazetidone**: IR (film, ν): 2955, 2849, 1680, 1588, 1501, 1140, 1349, 1209, 1033 and 795 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ : 0.95 (d, $J=7.0$, 3H), 2.81 (ddt, $J=2.9$, 7.0 and 8.2, 1H), 3.54 (dd, $J=2.9$ and 6.6, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.84 (s, 6H), 3.85 (dd, $J=6.6$ and 7.0), 3.87 (s, 3H), 4.89 (d, $J=8.2$, 1H), 5.96 (dd, $J=2.6$ and 8.7, 1H), 6.08 (d, $J=2.6$, 1H), 6.57 (s, 2H), 6.72 (d, $J=8.7$, 1H); ^{13}C NMR δ : 15.9, 30.1, 55.8, 56.2 (2C), 56.7, 56.9, 60.9, 70.0, 98.0, 103.5 (2C), 103.8, 112.9, 135.5, 136.7, 141.9, 147.3, 149.7 and 153.2 (2C). HRMS obsd.: m/z 396.1781; $C_{21}H_{27}NNaO_5$ requires m/z 396.1781.

ACCEPTED MANUSCRIPT