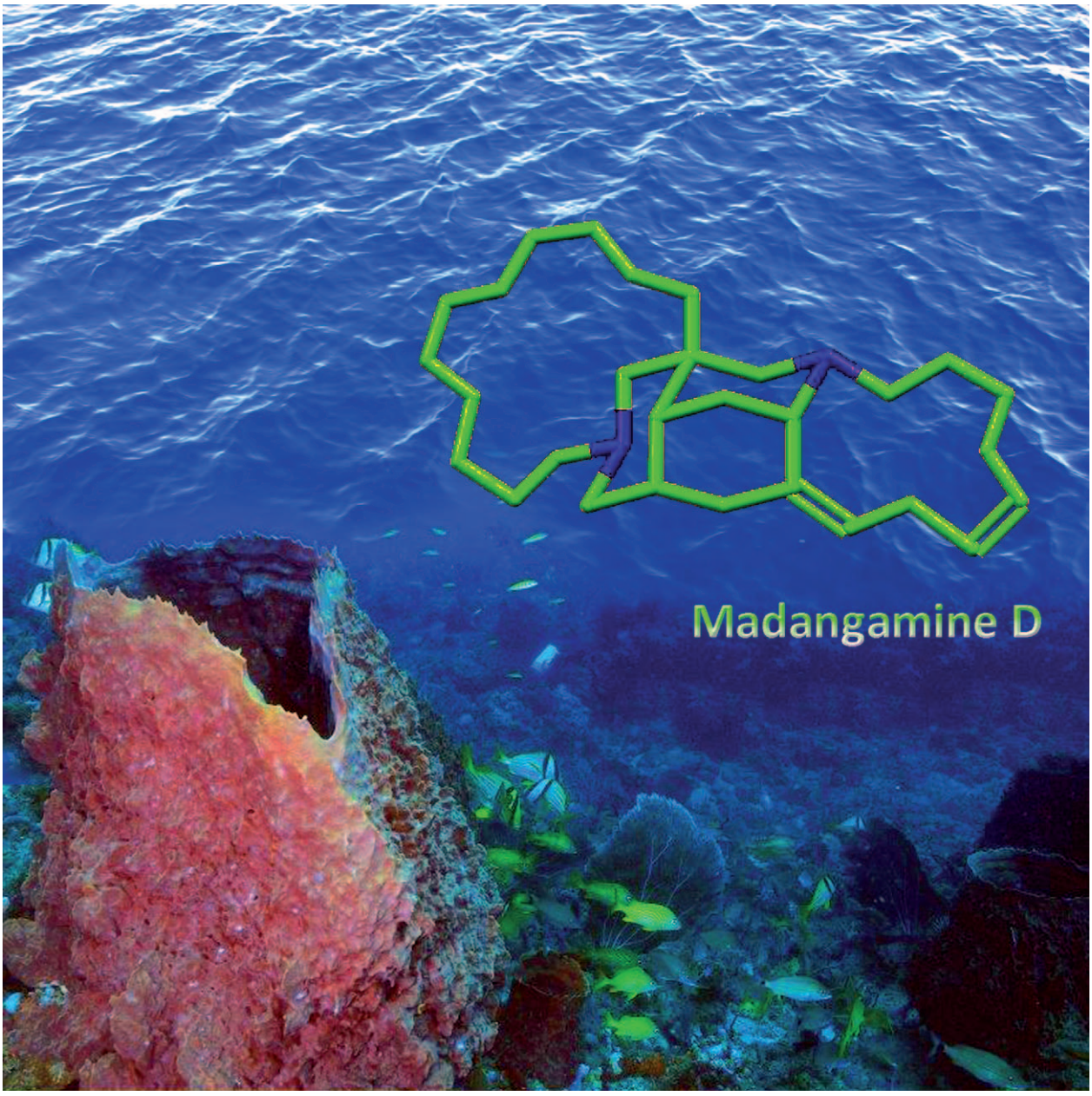
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000421

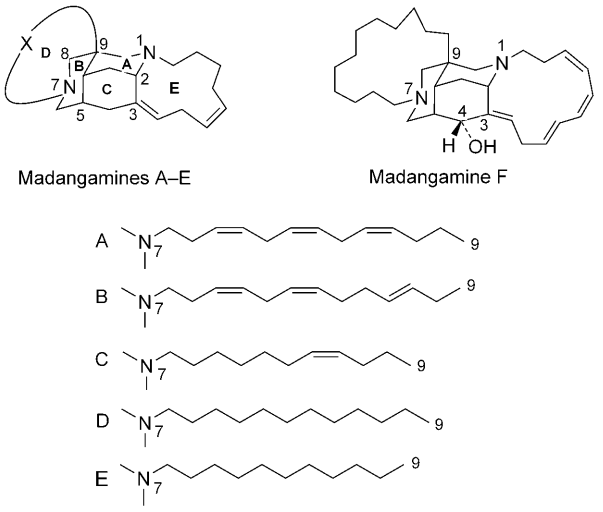
3rd EuCheMS Chemistry Congress

# First Enantioselective Synthesis of the Diazatricyclic Core of Madangamine Alkaloids

**Mercedes Amat,* Maria Pérez, Stefano Proto, Teresa Gatti, and Joan Bosch*[a]**



Madangamines are a small group of complex pentacyclic alkaloids isolated from marine sponges of the order Haplosclerida, biogenetically derived from partially reduced bis-3-alkylpyridine macrocycles.[1] Madangamine A, isolated from *Xestospongia ingens* by Andersen and co-workers in 1994,[2] was the first example of this new class of pentacyclic alkaloids and showed significant in vitro cytotoxicity against a number of cancer cell lines (Scheme 1). Soon afterwards,



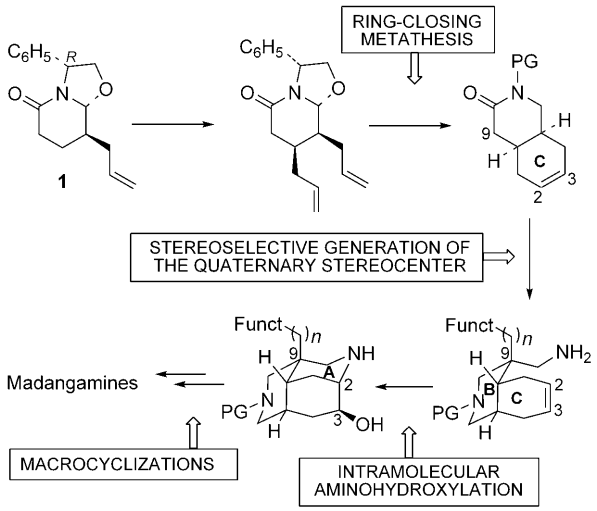

Scheme 1. Madangamine alkaloids.

four new members of this group, madangamines B–E, were isolated from the same sponge,[3] and more recently madangamine F, also showing cytotoxic activity, has been isolated from the marine sponge *Pachychalina alcaloidifera*.[4]

Structurally, madangamines possess an unprecedented diazatricyclic core (ABC rings) and two linear bridges connecting N-7 to C-9 (D ring) and N-1 to C-3 (E ring), the former varying in each madangamine both in carbon length and in the position and degree of unsaturation, whereas the latter is identical in madangamines A–E (an 11-membered E ring), but different in madangamine F (a 13-membered E ring). In addition, madangamine F incorporates a hydroxy group at C-4. The absolute configuration of the madangamines remains unknown.

No total syntheses of the madangamine alkaloids have been reported so far. Only four synthetic approaches to the diazatricyclic ABC core of madangamines[5] and the synthesis of a tricyclic substructure embodying the 11-membered E macrocycle of madangamines A–E[6] have been reported to date, all of them in the racemic series.[7]

We present herein, the enantioselective construction of the bridged diazatricyclic ABC ring system of madangamines, containing the appropriate substitution and functionality for the synthesis of these alkaloids. The synthesis starts from the known[8] enantiopure oxazolopiperidone lactam **1**, which is easily accessible by a cyclocondensation reaction of (*R*)-phenylglycinol[9] with racemic methyl 4-formyl-6-heptenoate, in a process that involves a dynamic kinetic resolution[10] (Scheme 2; madangamine numbering). The key steps




Scheme 2. Synthetic strategy; PG = protecting group.

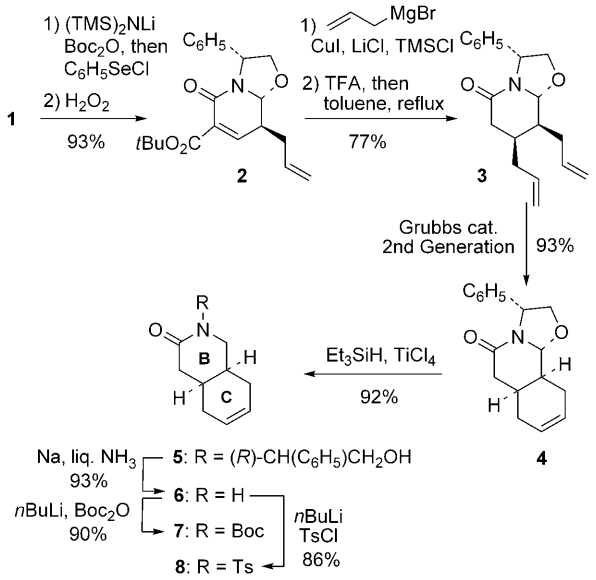
of the synthesis are: 1) a stereoselective conjugate addition of an allyl group to an activated unsaturated lactam derived from **1**; 2) the closure of the carbocyclic C ring by a ring-closing olefin metathesis reaction; 3) the stereoselective generation of the C-9 quaternary stereocenter, after reductive removal of the chiral inductor; and 4) the closure of the piperidine A ring by an intramolecular aminohydroxylation reaction by taking advantage of the carbon–carbon double bond of the cyclohexene moiety.

Scheme 3 outlines the initial steps of the synthesis. The starting lactam **1** was converted in excellent yield to the unsaturated lactam **2** by sequential treatment with $(TMS)_2NLi$ (TMS = trimethylsilyl), di-*tert*-butyl dicarbonate ($Boc_2O$), and PhSeCl, followed by oxidation of the resulting mixture of selenides. We selected the easily removable electron-withdrawing *tert*-butoxycarbonyl (Boc) group as the activating group for the subsequent conjugate addition,[11] since it can be easily removed under nonreductive conditions, without affecting the carbon–carbon double bonds. The conjugate addition of an allyl group to **2** was satisfactorily accomplished with allylmagnesium bromide in the presence of CuI, LiCl, and TMSCl.[12] The reaction was stereoselective as a consequence of the stereoelectronic control,[13] which was made evident by the isolation (77% overall yield) of a *cis*-diallyl derivative **3** after the removal of the Boc group.

[a] Prof. M. Amat, Dr. M. Pérez, S. Proto, T. Gatti, Prof. J. Bosch
Laboratory of Organic Chemistry, Faculty of Pharmacy
and Institute of Biomedicine (IBUB), University of Barcelona
Av. Joan XXIII s/n, 08028 Barcelona (Spain)
Fax: (+34) 934024539
E-mail: amat@ub.edu
joanbosch@ub.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000421.




Scheme 3. Enantioselective construction of the *cis*-hexahydroisoquinolone moiety; TFA = trifluoroacetic acid, Ts = tosyl.

Ring-closing metathesis[14] of **3**, followed by reductive removal of the phenylethanol moiety from the resulting tricyclic lactam **4** by treatment with $Et_3SiH/TiCl_4$ and then Na/liq. $NH_3$, led to *cis*-hexahydroisoquinolone (**6**), which was then protected as either an *N*-Boc **7** or *N*-tosyl **8** derivative.

The crucial quaternary stereocenter at C-9 was installed by taking advantage of the acidity of the methylene protons α to the lactam carbonyl. Thus, introduction of a methoxycarbonyl group from **7**, followed by stereoselective alkylation of the resulting 1,3-dicarbonyl derivative with a functionalized alkyl iodide, afforded **9** (Scheme 4). The methoxycarbonyl group not only acts as an element of stereocontrol, allowing the subsequent alkylation to occur at the most accessible face, but is also the precursor of the aminomethyl chain required for the closure of the A ring. Indeed, after removal of the *N*-Boc protecting group, $LiAlH_4$ treatment of **10** brought about the reduction of the lactam and ester carbonyl groups leading to alcohol **11**, which was protected as an *N*-sulfonyl derivative **12** and then converted into the amino derivative **13** via an azide.

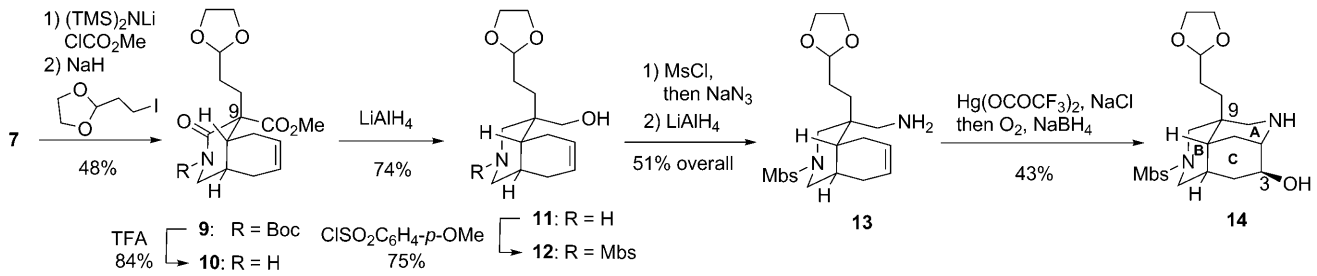
Finally, closure of the piperidine A ring was accomplished following the Weinreb procedure,[5a] by an aminomercuriation reaction by using mercuric trifluoroacetate, with subsequent treatment of the organomercury intermediate with oxygen and $NaBH_4$. The resulting enantiopure diazatricyclic alcohol **14** possesses suitable functionality both at C-3 and the C-9 chain to allow the building of the macrocyclic D and E rings of madangamines. The synthesis of **14** constitutes the first enantioselective construction of the diazatricyclic core of these alkaloids.

With minor modifications, the above strategy was adapted for the synthesis of other enantiopure ABC substructures of madangamine alkaloids en route to these natural products. Thus, Scheme 5 outlines the synthesis of the diazatricyclic derivative **23**, which has an 11-carbon chain at C-9 functionalized at the terminal position as required for the construction of the 14-membered D ring of madangamine D. This chain was incorporated in a straightforward manner, either from the *N*-Boc-protected hexahydroisoquinolone **7** or, in higher overall yield, from the *N*-tosyl derivative **8**, by using 11-(benzyloxy)undecyl iodide in the alkylation step. The synthetic sequence parallels that previously developed, although in this series a Boc group was used as the protecting group of the hydroisoquinoline nitrogen, and the Staudinger procedure ($Ph_3P/H_2O$) was employed for the reduction of the intermediate azide **19**.

The closure of the piperidine A ring was initially accomplished by the aminomercuriation procedure, which led to the tricyclic amino alcohol **21** in only moderate overall yield. A subsequent protection of the piperidine nitrogen with *p*-methoxybenzenesulfonyl chloride led to the orthogonally protected diazatricyclic derivative **22** (72% yield), which was then oxidized to ketone **23** (78% yield).

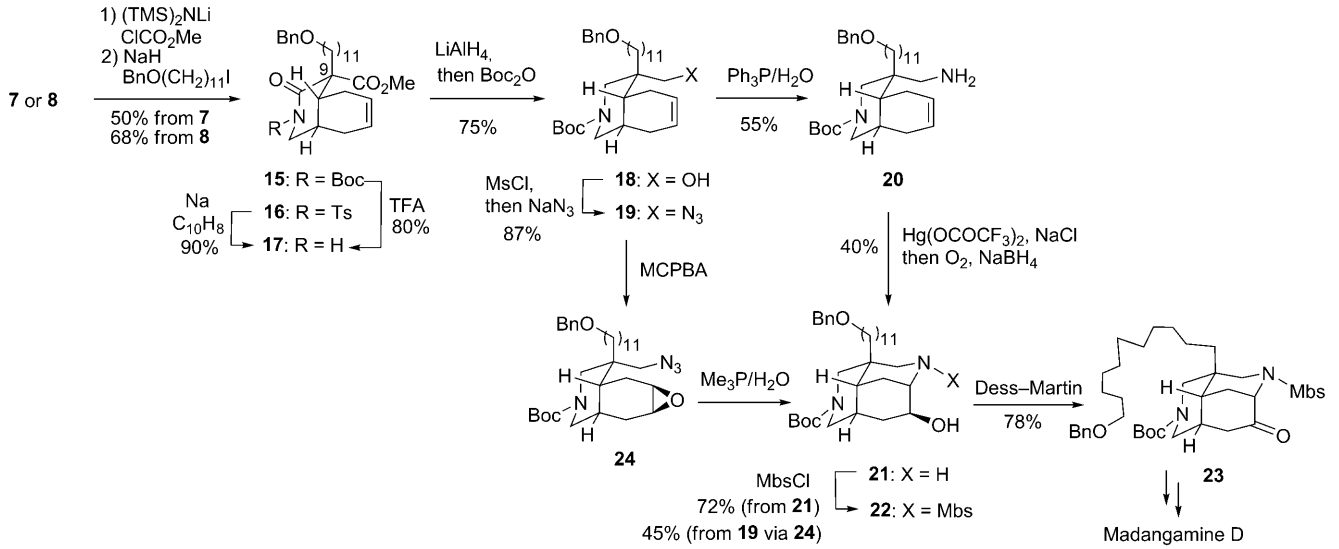
The intramolecular aminohydroxylation step was substantially improved by using a different methodology involving the *meta*-chloroperbenzoic acid (*m*CPBA) oxidation of the cyclohexene double bond of the intermediate azide **19** and reduction of the resulting azido epoxide **24** with $Me_3P/H_2O$. Under these conditions, the initially formed amino epoxide undergoes a smooth in situ cyclization, leading directly to the tricyclic amino alcohol **21**, which was immediately converted to sulfonamide **22**. The overall yield of these four transformations from azide **19** was 45%.

In summary, the diazatricyclic core common to all madangamines has been enantioselectively assembled for the first time, which represents a significant breakthrough in the total synthesis of these complex natural products. Further




Scheme 4. First enantioselective assembling of the diazatricyclic core of madangamines; Ms = methanesulfonyl, Mbs = *para*-methoxybenzenesulfonyl.




Scheme 5. Towards the enantioselective synthesis of madangamine D; Bn = benzyl.

elaboration of the advanced synthetic intermediate **23** into madangamine D is currently in progress in our laboratory.

## Acknowledgements

Financial support from the MICINN, Spain (project CTQ2009-07021/BQU), and the AGAUR, Generalitat de Catalunya (grant 2009-SGR-111) is gratefully acknowledged. Thanks are also due to the Leonardo da Vinci programme (Unipharma Graduates-4) for a mobility grant to T.G.

**Keywords:** alkaloids · aminohydroxylation · lactams · madangamines · natural products

[1] a) R. J. Andersen, R. W. M. van Soest, F. Kong in *Alkaloids: Chemical and Biological Perspectives, Vol. 10* (Ed.: S. W. Pelletier), Pergamon, New York, **1996**, pp. 301–355; b) N. Matzanke, R. J. Gregg, S. M. Weinreb, *Org. Prep. Proced.* **1998**, *30*, 1–51; c) R. G. S. Berlinck, *Top. Heterocycl. Chem.* **2007**, *10*, 211–238.

[2] F. Kong, R. J. Andersen, T. M. Allen, *J. Am. Chem. Soc.* **1994**, *116*, 6007–6008.

[3] F. Kong, E. I. Graziani, R. J. Andersen, *J. Nat. Prod.* **1998**, *61*, 267–271.

[4] J. H. H. L. De Oliveira, A. M. Nascimento, M. H. Kossuga, B. C. Cavalcanti, C. O. Pessoa, M. O. Moraes, M. L. Macedo, A. G. Ferreira, E. Hajdu, U. S. Pinheiro, R. G. S. Berlinck, *J. Nat. Prod.* **2007**, *70*, 538–543.

[5] a) N. Matzanke, R. J. Gregg, S. M. Weinreb, M. Parvez, *J. Org. Chem.* **1997**, *62*, 1920–1921; b) N. Yamazaki, T. Kusanagi, C. Kibayashi, *Tetrahedron Lett.* **2004**, *45*, 6509–6512; c) H. M. Tong, M.-T. Martin, A. Chiaroni, M. Bénéchie, C. Marazano, *Org. Lett.* **2005**, *7*, 2437–2440; d) J. Quirante, L. Paloma, F. Diaba, X. Vila, J. Bonjoch, *J. Org. Chem.* **2008**, *73*, 768–771; e) Y. Yoshimura, T. Kusanagi, C. Kibayashi, N. Yamazaki, S. Aoyagi, *Heterocycles* **2008**, *75*, 1329–1354.

[6] Y. Yoshimura, J. Inoue, N. Yamazaki, S. Aoyagi, C. Kibayashi, *Tetrahedron Lett.* **2006**, *47*, 3489–3492.

[7] For a review, see: A. Nishida, T. Nagata, M. Nakagawa, *Top. Heterocycl. Chem.* **2006**, *5*, 255–280.

[8] a) M. Amat, M. Pérez, A. T. Minaglia, N. Casamitjana, J. Bosch, *Org. Lett.* **2005**, *7*, 3653–3656; b) M. Amat, M. Pérez, A. T. Minaglia, B. Peretto, J. Bosch, *Tetrahedron* **2007**, *63*, 5839–5848.

[9] For reviews on the use of aminoalcohol-derived oxazolopiperidone lactams as chiral building blocks for the enantioselective synthesis of complex piperidine-containing alkaloids, see: a) M. D. Groaning, A. I. Meyers, *Tetrahedron* **2000**, *56*, 9843–9873; b) C. Escolano, M. Amat, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 8198–8207; for more recent work, see: c) M. Amat, O. Lozano, C. Escolano, E. Molins, J. Bosch, *J. Org. Chem.* **2007**, *72*, 4431–4439; d) M. Amat, M. M. M. Santos, O. Bassas, N. Llor, C. Escolano, A. Gómez-Esqué, E. Molins, S. M. Allin, V. McKee, J. Bosch, *J. Org. Chem.* **2007**, *72*, 5193–5201; e) M. Amat, R. Griera, R. Fabregat, J. Bosch, *Angew. Chem.* **2008**, *120*, 3396–3399; *Angew. Chem. Int. Ed.* **2008**, *47*, 3348–3351; f) M. Amat, A. Gómez-Esqué, C. Escolano, M. M. M. Santos, E. Molins, J. Bosch, *J. Org. Chem.* **2009**, *74*, 1205–1211; g) M. Amat, N. Llor, B. Checa, E. Molins, J. Bosch, *J. Org. Chem.* **2010**, *75*, 178–189.

[10] For reviews, see: a) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; b) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490; c) S. Caddick, K. Jenkins, *Chem. Soc. Rev.* **1996**, *25*, 447–456; d) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321–331; e) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327; f) C. Wolf, *Dynamic Stereochemistry of Chiral Compounds*, RSC, Cambridge, **2008**, Chapter 7.

[11] a) L. E. Overman, A. J. Robichaud, *J. Am. Chem. Soc.* **1989**, *111*, 300–308; b) J. Cossy, O. Mirguet, D. Gomez Pardo, J.-R. Desmurs, *New J. Chem.* **2003**, *27*, 475–482; c) A. Deiters, M. Pettersson, S. F. Martin, *J. Org. Chem.* **2006**, *71*, 6547–6561, and references therein.

[12] a) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6019–6022; b) A. Alexakis, J. Berlan, Y. Besace, *Tetrahedron Lett.* **1986**, *27*, 1047–1050; c) E. Nakamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 4029–4032.

[13] a) P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, **1983**, p. 221; b) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1992**, p. 25.

[14] a) *Handbook of Metathesis, Vols. 1–3* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**; b) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712; c) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199–2238.

Received: February 17, 2010
Published online: April 8, 2010