Pure Appl. Chem., Vol. 84, No. 7, pp. 1567–1574, 2012.
http://dx.doi.org/10.1351/PAC-CON-11-09-06

Spiroketals: Toward the synthesis of 39-oxobistramide K*

Malgorzata Commandeur, Claude Commandeur, and Janine Cossy‡

Laboratoire de Chimie Organique Associé au CNRS, ESPCI ParisTech, 10 rue Vauquelin, 75231 Paris Cedex 05, France

Abstract: An advanced spiroketal intermediate toward the synthesis of 39-oxobistramide K was prepared, fragment C14–C40. This fragment was obtained in 19 steps with an overall yield of 6.2 % using a $FeCl_3$-catalyzed spiroketalization as the key step.

Keywords: cyclizations; organic synthesis; spiroketalization.

INTRODUCTION

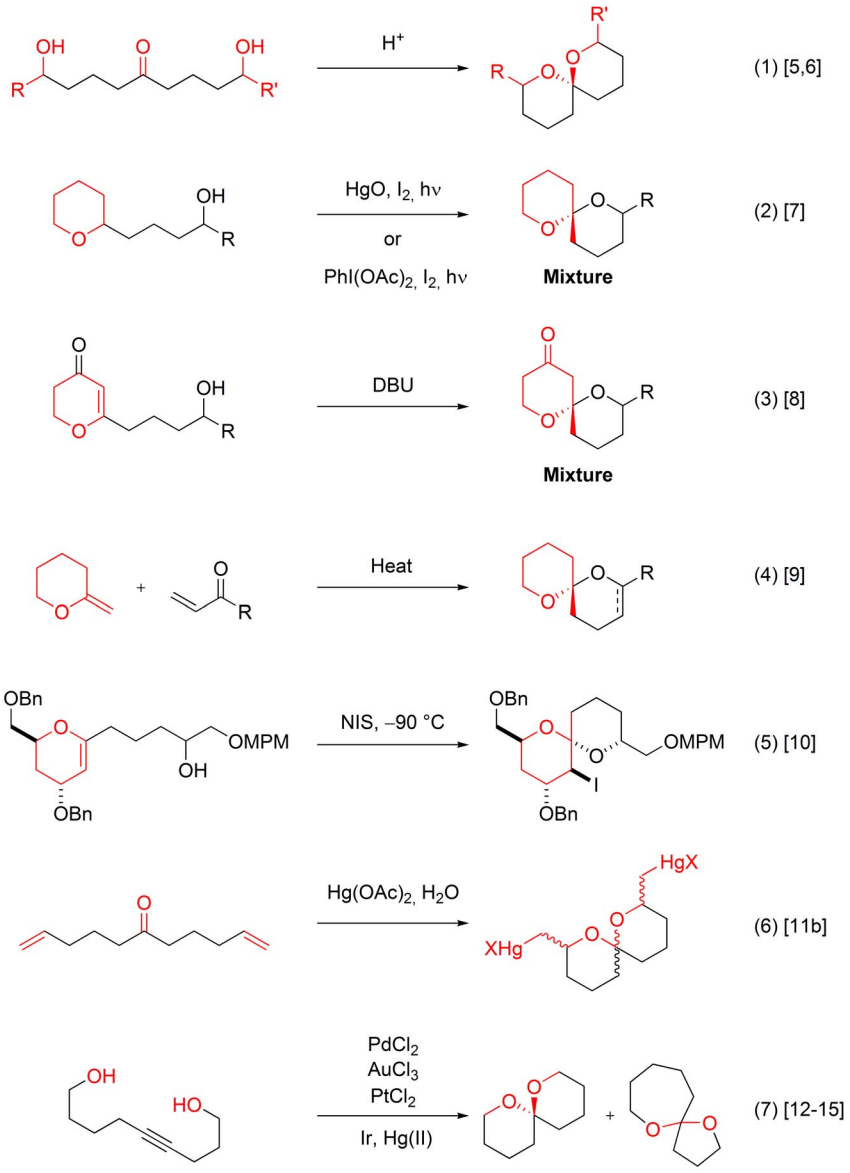
The use of inexpensive and eco-compatible catalysts such as $FeCl_3$ to synthesize complex molecules can be very attractive [1]. For our part, we were interested in the synthesis of spiroketals from unsaturated lactols by utilizing $FeCl_3$ and applying this method to the synthesis of 39-oxobistramide K, an antiproliferative agent [2].

SPIROKETALS

Spiroketal units can be found in a wide range of naturally occurring substances isolated from many sources such as microbes, insects, plants, fungi, and marine organisms [3]. The biological activity of compounds containing a spiroketal unit has triggered intense interest in both the synthesis and chemistry reactivity [4].

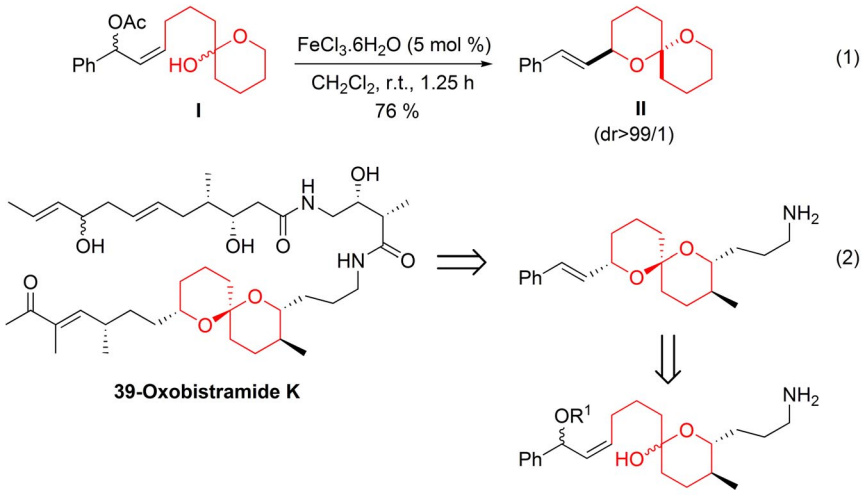
Traditionally, the synthesis of spiroketals has been realized under acid-catalyzed cyclization of dihydroxyketones [5] or hydroxydihydropyranes [6], and, in most cases, the thermodynamic products were formed, which corresponds to the maximum of anomeric effects and the minimum of steric interactions (Scheme 1, eq. 1). However, as the substrates can be sensitive to acidic conditions, other methods have been developed for synthesizing spiroketals such as oxidative radical cyclization of ω-hydroxypyrans (Scheme 1, eq. 2) [7], ring closure involving intramolecular conjugate addition (Scheme 1, eq. 3) [8], hetero-Diels–Alder cycloaddition (Scheme 1, eq. 4) [9], iodo-spiroketalization (Scheme 1, eq. 5) [10], hydroxymercuration (Scheme 1, eq. 6) [11], and, more recently, cyclization induced by metals such as $PdCl_2$ [12], $AuCl_3$ [12b,13], $PtCl_2$ [14], or Ir complexes [15] (Scheme 1, eq. 7). Except for some examples of acid-catalyzed cyclization of dihydroxyketones [16], the other processes are not highly diastereo- and/or regioselective [17]. Recently, we have shown that the treatment of an ω-unsaturated lactol of type **I** with $FeCl_3$ led to the corresponding spiroketal **II** (Scheme 2, eq. 1) [18]. As, under these conditions, the spiroketalization was high yielding and highly diastereo- and

Pure Appl. Chem. **84**, 1543–1667 (2012). A collection of invited papers based on presentations at the 23rd International Conference on Heterocyclic Chemistry (ICHC-23), Glasgow, UK, 31 July–4 August 2011.
‡Corresponding author: E-mail: janine.cossy@espci.fr



Scheme 1 Methods to access spiroketals.

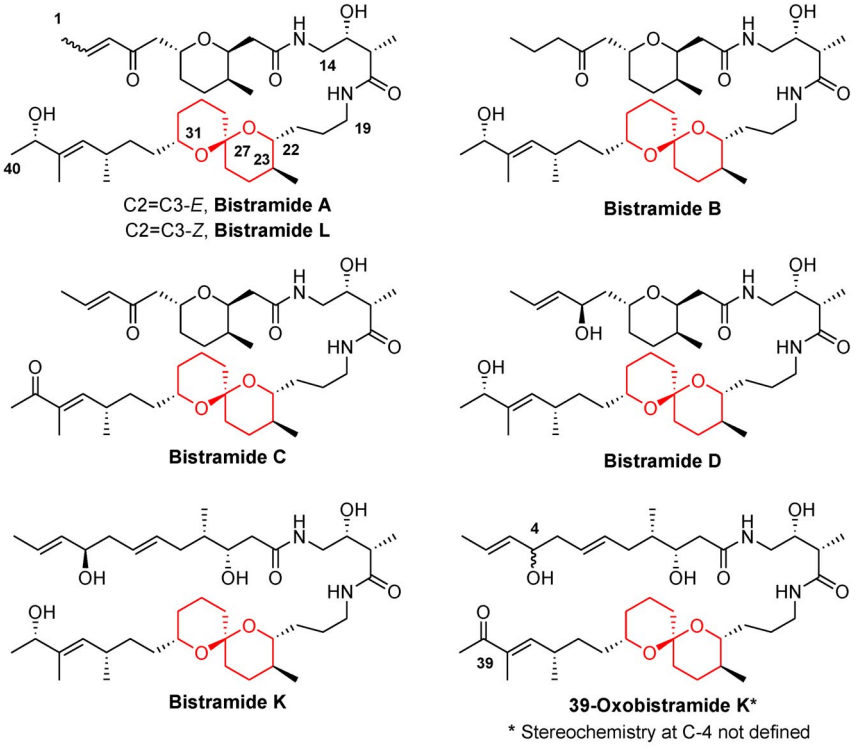
regioselective, its use to synthesize complex natural spiroketals, such as, for example, bistramides and more particularly 39-oxobistramide K, was planned (Scheme 2, eq. 2).



Scheme 2 Retrosynthetic analysis of 39-oxobistramide K.

39-OXOBISTRAMIDE K: STRUCTURE AND BIOLOGICAL PROPERTIES

39-Oxobistramide K was extracted from the tunicate *Trididemnum cyclops* Michaelsen in 1921 [2] in conjunction with two other bistramides, bistramides A and D, which were previously isolated in 1988 by Gouiffès et al. from the ascidian *Lissoclinum bistratum* [19] and belong to the Didemnidae family (Scheme 3) [20].

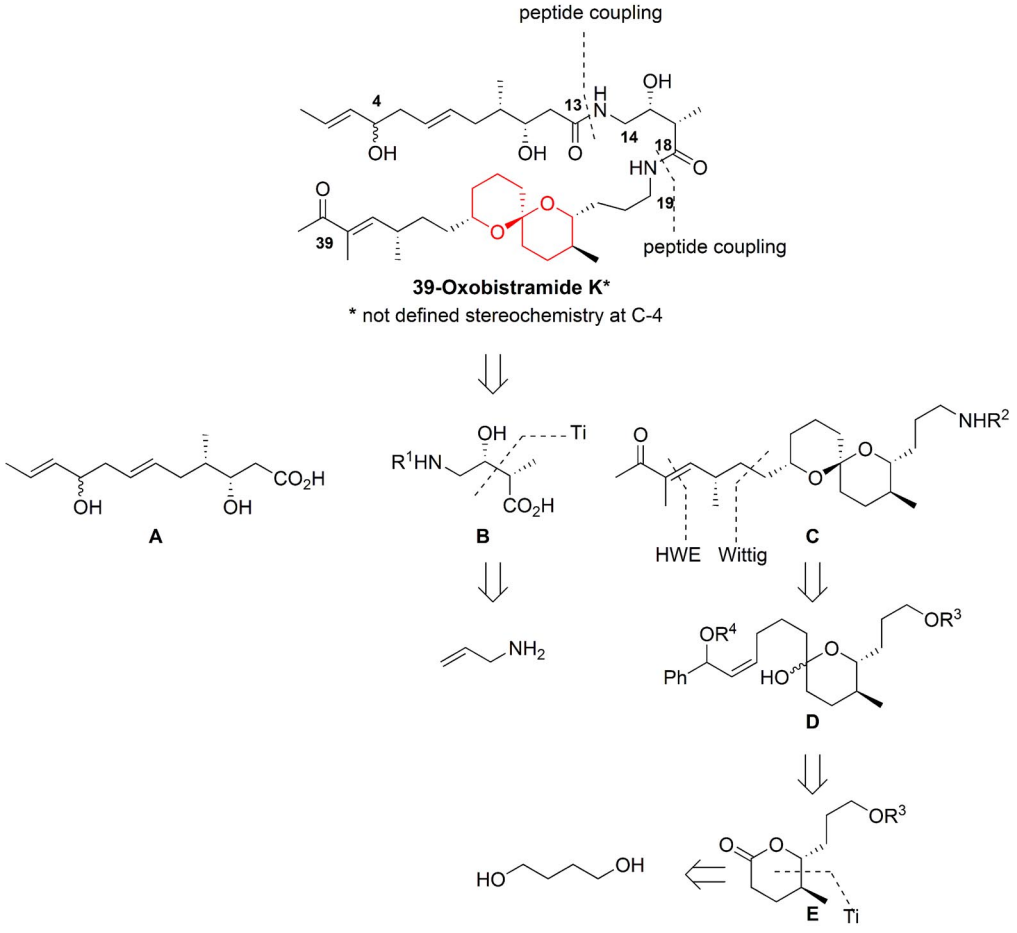


Scheme 3 Bistramides A–D, K, L, and 39-oxobistramide K.

39-Oxobistramide K is a new lipopeptide, and its structure elucidation was carried out by analysis of one- and two-dimensional NMR spectroscopy and high-resolution mass spectrometry (HRMS) data [2]. We have to point out that the stereogenic center at C4 was not elucidated. 39-Oxobistramide K has been reported to have antiproliferative activity against the A2780 cell line and exhibited an IC_{50} value of 0.34 μM [2]. Owing to its biological properties and its challenging molecular architecture, we decided to embark on the synthesis of 39-oxobistramide K according to a convergent approach and by utilizing the spiroketalization of an ω-unsaturated lactol induced by $FeCl_3$, as the key step (Scheme 2, eq. 2).

RETROSYNTHESIS OF 39-OXOBISTRAMIDE K

Two appropriate disconnections appeared to be the peptide bonds C13–C14 and C18–C19 which resulted in three fragments: dihydroxycarboxylic acid **A**, amino acid **B**, and spiroketal **C** (Scheme 4). As the synthesis of fragment **A** has already been achieved [21], we focused on the synthesis of fragments **B** [22] and **C**.

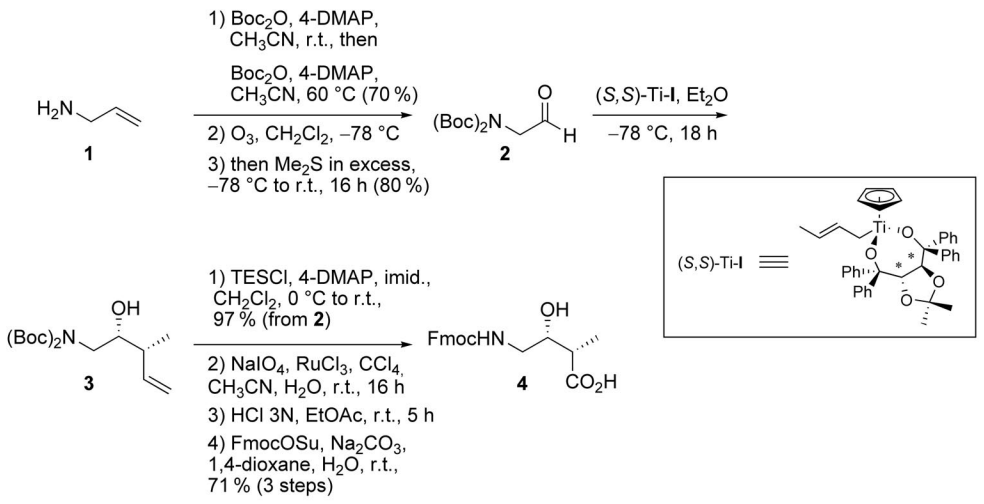


Scheme 4 Fragments **A**, **B**, and **C**; and retrosynthetic analysis of **B** and **C**.

The synthesis of amino acid **B** was envisaged from allylamine, and the control of the two stereogenic centers would be achieved by using an enantioselective crotyltitanation [23] applied to an aldehyde. Concerning spiroketal **C**, the C36–C37 bond would be constructed by using a Horner–Wadsworth–Emmons reaction, the C32–C33 bond by using a Wittig reaction, and the spiroketal would be obtained by treatment of lactol **D** with $FeCl_3$. This latter lactol would be synthesized from lactone **E** in which the two stereogenic centers would be controlled by utilizing an enantioselective crotyltitanation [23]. The access to **E** was planned from 1,4-butanediol (Scheme 4).

SYNTHESIS OF FRAGMENT B (FRAGMENT C14–C18)

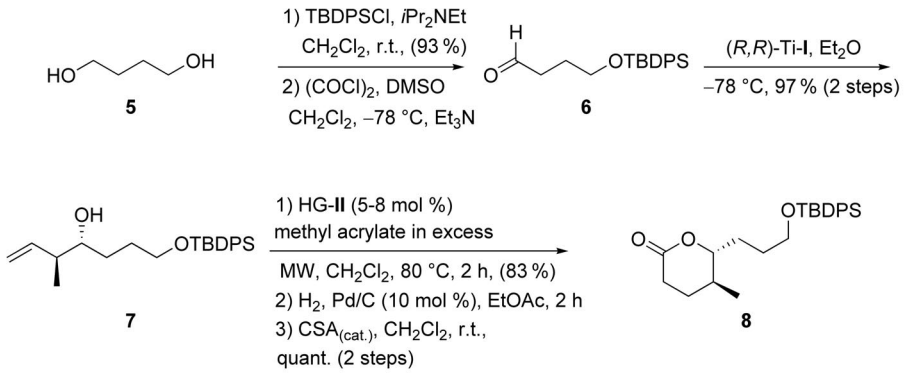
The synthesis of fragment **B** was realized in seven steps from allylamine **1**. This latter compound was transformed to the protected amino-aldehyde **2** in two steps [Boc_2O, 4-DMAP, r.t. then 60 °C (70 %), then O_3, CH_2Cl_2 −78 °C then Me_2S in excess, −78 °C to r.t. (80 %)] [24] and after addition of the highly face-selective crotyltitanium complex (*S*,*S*)-Ti-**I** (Et_2O, –78 °C, 18 h) [23], the homoallylic alcohol **3** was obtained with excellent diastereoselectivity and enantioselectivity (dr > 95:5; ee > 95 %). This alcohol was then transformed to the desired protected amino acid **4** via the following sequence: triethylsilyl-protection of the hydroxyl group, oxidative cleavage, deprotection, then Fmoc-protection of the amine (Scheme 5) [22]. Fragment **B** was achieved in seven steps with an overall yield of 34 % starting from allylamine **1**.



Scheme 5 Synthesis of amino acid **4**.

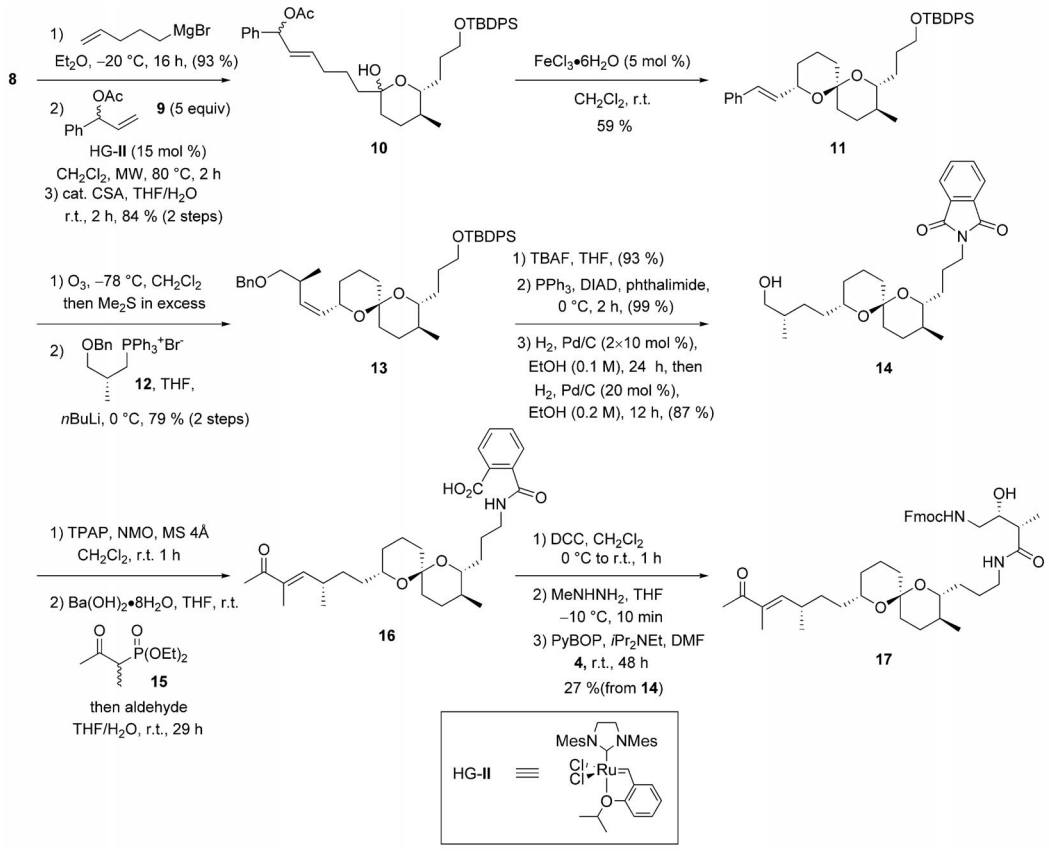
SYNTHESIS OF FRAGMENT C (FRAGMENT C19–C40)

The synthesis of spiroketal **C** was undertaken from the commercially available 1,4-butanediol **5**, which was transformed in two steps to the corresponding protected hydroxyaldehyde **6** (Scheme 6) [25]. After treatment of **6** with the crotyltitanium complex (*R*,*R*)-Ti-**I** [23], the stereogenic centers at C22 and C23 were controlled. The transformation of the obtained homoallylic alcohol **7** to the lactone of type **E**, compound **8**, was accomplished in three steps—sequential cross-metathesis with methyl acrylate, hydrogenation, and treatment under acidic conditions (Scheme 6).



Scheme 6 Synthesis of lactone **8**.

Lactone **8** was then transformed to the key spiroketal **11** via lactol **10**. After addition of 4-pentenylmagnesium bromide to lactone **8**, cross-metathesis with allyl acetate **9** [26] using the Hoveyda–Grubbs catalyst (HG-**II**) [27], and hydration of the obtained glycal, lactol **10** was isolated in 78 % yield over three steps (Scheme 7). Lactol **10** was then treated with $FeCl_3 \cdot 6H_2O$, and the resulting spiroketal **11** was transformed to **13** after an oxidative cleavage and a Wittig reaction with bromophosphonium **12** (79 % yield over the two steps) [28]. Subsequently, a desilylation followed by a



Scheme 7 Synthesis of spiroketal **17**.

Mitsunobu reaction using phthalimide and a hydrogenation/hydrogenolysis one-pot sequence provided alcohol **14** in 80 % overall yield. In order to obtain fragment **C**, compound **14** was oxidized and the resulting aldehyde was condensed with keto-phosphonate **15** [29] utilizing $Ba(OH)_2 \cdot 8H_2O$ as the base. Under these conditions, the unsaturated ketone was introduced, however, a secondary reaction was observed as the phthalimido group was transformed to an amino acid, leading to compound **16** in 75 % yield over two steps. This latter transformation was not dramatic as after treatment with *N*,*N*′-dicyclohexylcarbodiimide (DCC), followed by the addition of methylhydrazine [30], the amine at C19 was formed and directly involved in a coupling reaction with amino acid **4** to furnish the C14–C40 fragment of 39-oxobistramide K, compound **17**.

Compound **17**, which corresponds to the C14–C40 fragment of 39-oxobistramide K, was synthesized from 1,4-butanediol **5** in 19 steps with an overall yield of 6.2 % for the longer sequence of reactions. We have to point out that **17** is a useful fragment that would allow the access to 39-oxobistramide K as well as to bistramide C.

ACKNOWLEDGMENT

Dr. Serge Sablé (Sanofi-Aventis, Vitry-sur-Seine, France) is acknowledged for his contribution to structural determination.

REFERENCES

1. (a) C. Bolm, J. Legros, J. Le Paih, L. Zani. *Chem. Rev*. **104**, 6217 (2004); (b) C.-L. Sun, B.-J. Li, Z.-J. Shi. *Chem. Rev*. **111**, 1293 (2011).
2. B. T. Murphy, S. Cao, P. Brodie, J. Maharavo, H. Andriamanantoanina, P. Ravelonandro, D. G. Kingston. *J. Nat. Prod.* **72**, 1338 (2009).
3. (a) F. Perron, K. F. Albizati. *Chem. Rev.* **89**, 1617 (1989); (b) M. T. Fletcher, W. Kitching. *Chem. Rev*. **95**, 789 (1995); (c) M. F. Jacobs, W. Kitching. *Curr. Org. Chem.* **2**, 395 (1998); (d) S. Favre, P. Vogel, S. Gerber-Lemaire. *Molecules* **13**, 2570 (2008).
4. (a) A. F. Kluge. *Heterocycles* **24**, 1699 (1986); (b) V. Vaillancourt, N. E. Pratt, K. F. Albizati. *The Total Synthesis of Natural Products*, John Wiley, New York (1992); (c) K. T. Mead, B. N. Brewer. *Curr. Org. Chem.* **7**, 227 (2003); (d) M. A. Brimble, D. P. Furkert. *Curr. Org. Chem.* **7**, 1461 (2003); (e) J. E. Aho, P. M. Pihko, T. K. Rissa. *Chem. Rev.* **105**, 4406 (2005); (f) G. Zinzalla, L.-G. Milroy, S. V. Ley. *Org. Biomol. Chem.* **4**, 1977 (2006); (g) B. R. Raju, A. K. Saikia. *Molecules* **13**, 1942 (2008).
5. D. Bondar, J. Liu, T. Müller, L. A. Paquette. *Org. Lett.* **7**, 1813 (2005).
6. N. Pothier, S. Goldstein, P. Deslongchamps. *Helv. Chim. Acta* **75**, 604 (1992).
7. J. Sperry, Y.-C. Liu, M. A. Brimble. *Org. Biomol. Chem.* **8**, 29 (2010).
8. I. Paterson, D. J. Wallace, K. R. Gibson. *Tetrahedron Lett.* **38**, 8911 (1997).
9. R. E. Ireland, S. Thaisrivongs, P. H. Dussault. *J. Am. Chem. Soc.* **110**, 5768 (1988).
10. (a) H. Fuwa, M. Sasaki. *Org. Lett.* **10**, 2549 (2008); (b) E. B. Holson, W. R. Roush. *Org. Lett.* **4**, 3719 (2002).
11. (a) W. Kitching, J. A. Lewis, M. T. Fletcher, J. J. De Voss, R. A. I. Drew, C. J. Moore. *J. Chem. Soc., Chem. Commun.* 855 (1986); (b) W. Kitching, J. A. Lewis, M. V. Perkins, R. Drew, C. J. Moore, V. Schurig, W. A. König, W. Francke. *J. Org. Chem.* **54**, 3893 (1989).
12. (a) K. Utimoto. *Pure Appl. Chem*. **55**, 1845 (1983); (b) C. V. Ramana, S. B. Suryawanshi, R. G. Gonnade. *J. Org. Chem.* **74**, 2842 (2009).
13. (a) S. Antoniotti, E. Genin, V. Michelet, J.-P. Genêt. *J. Am. Chem. Soc.* **127**, 9976 (2005); (b) Y. Li, F. Zhou, C. J. Forsyth. *Angew. Chem., Int. Ed.* **46**, 279 (2007); (c) Y. Zhang, J. Xue, Z. Xin, Z. Xie, Y. Li. *Synlett* 940 (2008); (d) A. Aponick, C.-Y. Li, J. A. Palmes. *Org. Lett.* **11**, 121 (2009).

14. B. Liu, J. K. De Brabander. *Org. Lett*. **8**, 4907 (2006).
15. (a) X. Li, A. R. Chianese, T. Vogel, R. H. Crabtree. *Org. Lett.* **7**, 5437 (2005); (b) B. A. Messerle, K. Q. Vuong. *Pure Appl. Chem.* **78**, 385 (2006); (c) S. Selvaratnam, J. H. H. Ho, P. B. Huleatt, B. A. Messerle, C. L. L. Chai. *Tetrahedron Lett.* **50**, 1125 (2009).
16. B. Lastdrager, M. S. M. Timmer, G. A. van de Marel, H. S. Overkleeft. *Tetrahedron Lett.* **46**, 6195 (2005).
17. (a) T. Shimizu, T. Masuda, K. Hiramoto, T. Nakata. *Org. Lett* **2**, 2153 (2000); (b) P. M. Pihko, J. E. Aho. *Org. Lett*. **6**, 3849 (2004).
18. A. Guérinot, A. Serra-Muns, C. Gnamm, C. Bensoussan, S. Reymond, J. Cossy. *Org. Lett.* **12**, 1808 (2010).
19. (a) D. Gouiffès, M. Jugé, N. Grimaud, L. Welin, Y. Barbin, D. Laurent, C. Roussakis, J. P. Hénichart, J. F. Verbist. *Toxicon* **26**, 1129 (1988); for isolation of bistramide A, see: (b) D. Gouiffès, S. Moreau, N. Helbecque, J. L. Bernier, J. P. Hénichart, Y. Barbin, D. Laurent, J. F. Verbist. *Tetrahedron* **44**, 451 (1988) and cited refs.; for isolation of bistratenes, which were deduced to be identical with bistramides, see: (c) B. M. Degnan, C. J. Hawkins, M. F. Lavin, E. J. McCaffrey, D. L. Parry, D. J. Watters. *J. Med. Chem.* **32**, 1354 (1989).
20. For isolation of bistramides A–D and K, see: (a) J. F. Biard, C. Roussakis, J. M. Komprobst, D. Gouiffès-Barbin, J. F. Verbist, P. Cotelle, M. P. Foster, C. M. Ireland, C. Debitus. *J. Nat. Prod.* **57**, 1336 (1994); for isolation of bistramides D, K, and L, see: (b) J. F. Biard, D. Cortadellas, C. Debitus, D. Laurent, C. Roussakis, J. F. Verbist. WO 9420503 A1 (1994).
21. C. Bauder. *Eur. J. Org. Chem.* 6207 (2010).
22. (a) A. V. Statsuk, D. Liu, S. A. Kozmin. *J. Am. Chem. Soc.* **126**, 9546 (2004); (b) M. T. Crimmins, A. C. DeBaillie. *J. Am. Chem. Soc.* **128**, 4936 (2006).
23. (a) A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rhote-Streit, F. Schwarzenbach. *J. Am. Chem. Soc.* **114**, 2321 (1992); (b) J. Cossy, S. Bouzbouz, F. Pradaux, C. Willis, V. Bellosta. *Synlett* 1595 (2002).
24. M. D. Varney, W. H. Romines, C. L. Palmer. U.S. Patent 5,594,139 (20 pp.), Filed 28 July 1994, Issued 14 January 1997.
25. F. Freeman, D. S. H. L. Kim, E. Rodriguez. *J. Org. Chem.* **57**, 1722 (1992).
26. Allyl acetate **9** was prepared from benzaldehyde via a two-step sequence: a Grignard addition of vinylmagnesium bromide then the acetylation of the obtained alcohol. Procedure inspired by the literature: N. Marion, R. Gealageas, S. P. Nolan. *Org. Lett.* **9**, 2653 (2007).
27. (a) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs. *Org. Lett.* **1**, 953 (1999); (b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda. *J. Am. Chem. Soc.* **122**, 8168 (2000).
28. Compound **12** was prepared according to the following synthetic sequence: benzylation: (a) U. Widmer. *Synthesis* 568 (1987); ester reduction: (b) J. D. White, M. Kawasaki. *J. Org. Chem.* **57**, 5292 (1992); bromination: (c) G.-J. Boons, J. A. Clase, J. C. Lennon, S. V. Ley, J. Staunton. *Tetrahedron* **51**, 5417 (1995); preparation of phosphonium salt: (d) J. T. Lowe, I. E. Wrona, J. S. Panek. *Org. Lett.* **9**, 327 (2007).
29. Keto-phosphonate **15** was prepared according to the literature procedure: B. Corbel, L. Medinger, J.-P. Haelters, G. Sturtz. *Synthesis* 1048 (1985).
30. M. G. Stocksdale, S. Ramurthy, M. J. Miller. *J. Org. Chem.* **63**, 1221 (1998).

