ORGANIC LETTERS

2011
Vol. 13, No. 9
2376–2379

Nitrenium Ion-Mediated Alkene Bis-Cyclofunctionalization: Total Synthesis of (−)-Swainsonine

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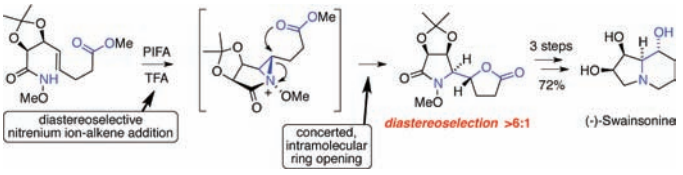
Received March 8, 2011

ABSTRACT



The total synthesis of (−)-swainsonine from 2,3-*O*-isopropylidene-D-erythrose in 12 steps and an overall yield of 28% is reported. The pivotal transformation in our route to this indolizidine alkaloid is the formation of the pyrrolidine ring and C-8a/8 stereodiad through the diastereoselective, bis-cyclofunctionalization of an γ,δ-unsaturated *O*-alkyl hydroxamate. This transformation is believed to proceed via the intramolecular capture of an *N*-acyl-*N*-alkoxyaziridinium ion generated by the diastereoselective addition of a singlet acylnitrenium ion to the pendant alkene.

(−)-Swainsonine (**1**), an alkaloid isolated first from the fungal plant pathogen *Rhizoctonia leguminicola*[1] and subsequently from a range of other sources,[2] has become one of the most keenly studied of all naturally occurring azasugars (Scheme 1). Interest in this indolizidine stems principally from its role as an inhibitor of Golgi α-mannosidase II (GMII)[3,4] and, to a lesser extent, lysosomal α-mannosidase (LM).[5] While the latter enzyme is involved in the catabolism of *N*-linked oligosaccharides, GMII plays a key role in the biosynthesis of glycoproteins, specifically in the formation of their trimannose core.[6] Since alterations in the normal glycosylation patterns of such proteins are often found on the surface of tumor cells and are associated with metathesis and disease progression, inhibition of GMII offers potential as a cancer treatment. In this context, swainsonine is notable as being the first glycoprotein processing inhibitor selected for clinical evaluation.[7] Most recently, **1** has also been found to be a strain-selective inhibitor of infectious mammalian prions,[8] which are associated with a variety of neurodegenerative disorders including Creutzfeldt−Jakob disease and kuru.[9] Although the mechanism of action in this case awaits clarification, swainsonine's activity does not appear to be associated its glycosidase inhibitory properties.

Since its isolation, swainsonine has proven a highly popular target of both total[10] and formal syntheses.[11,12] Furthermore, the search for more potent glycosidase

(1) (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055. (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29.

(2) (a) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* 1979, *32*, 2257 (*Swainsona canescens*). (b) Molyneux, R. J.; James, L. F. *Science* **1982**, *216*, 190 (*Astragalus lentiginosus*). (c) Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* 1985, *38*, 926 (*Metarhizium anisoplia*). (d) Molyneux, R. J.; McKenzie, R. A.; O'Sullivan, B. M.; Elbein, A. D. *J. Nat. Prod.* 1995, *58*, 878 (*Ipomoea calobra*). (e) Braun, K.; Romero, J.; Liddell, C.; Creamer, R. *Mycol. Res.* 2003, *107*, 980 (*Undifilum oxytropis*).

(3) (a) Elbein, A. D.; Solf, R.; Dorling, P. R.; Vosbeck, K. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 7393. (b) Tulsiani, D. R.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936.

(4) For a comprehensive review of the enzyme inhibitory activity of swainsonine, see ref 12c.

(5) Dorling, P. R.; Huxtable, C. R.; Colegate, S. M. *Biochem. J.* **1980**, *191*, 649.

(6) Hubbard, S. C.; Ivatt, R. J. *Annu. Rev. Biochem.* **1981**, *50*, 555.

(7) (a) Goss, P. E.; Baptista, J.; Fernandes, B.; Baker, M.; Dennis, J. W. *Cancer Res.* **1994**, *54*, 1450. (b) Baptista, J. A.; Goss, P. E.; Nghiem, M.; Krepinsky, J. J.; Baker, M.; Dennis, J. W. *Clin. Chem.* **1994**, *40*, 426. (c) Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer. Res.* **1997**, *3*, 1077.

(8) Li, J. L.; Browning, S.; Mahal, S.; Oelschlegel, A. M.; Weissmann, C. *Science* **2010**, *327*, 869.

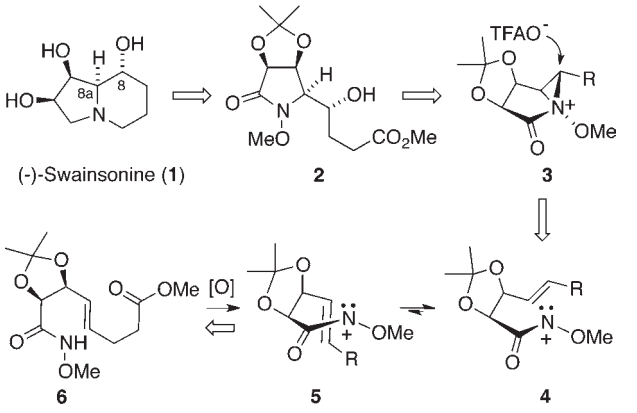
(9) Shorter, J. *Mol. Biosyst.* **2010**, *6*, 1115.

10.1021/ol2006117
Published on Web 04/12/2011

inhibitors, which display improved GMII vs LM selectivity, has spurred the preparation of a large number of analogues.[13] That swainsonine has recently been the subject of a process research study further underscores the continued relevance of this natural product as a synthetic target.[11n]

As part our ongoing study of the chemistry of nitrenium ions,[14] we recently reported a versatile method for the preparation of α-hydroxyalkyl lactams involving the intramolecular addition of acylnitrenium ions to alkenes.[15] Having successfully utilized this methodology in the stereocontrolled synthesis of the piperidine core of the azasugar castanospermine,[16] we were prompted to consider whether this chemistry might also be brought to bear on (−)-swainsonine. Herein we report the successful development of an efficient route to this indolizidine alkaloid in which the pyrrolidine ring and C-8a/8 *threo* stereodiad of the target are simultaneously established in a substrate-controlled nitrenium ion oxamidation reaction. Furthermore, we demonstrate that interception of the putative bicyclic aziridinium ion in this key transformation by a proximate carboxylate group offers a novel means of alkene bis-cyclofunctionalization.

Scheme 1. Retrosynthetic Analysis of (−)-Swainsonine (**1**)



From a retrosynthetic perspective, we initially envisioned that the indolizidine skeleton of **1** could be generated from α-hydroxyalkyl lactam **2** through a sequence of functional group reductions and *N*-alkylative ring closure (Scheme 1). In turn, this compound would be accessed through the intramolecular oxamidation of unsaturated hydroxamate **6**. On the basis of our previous studies,[17] we anticipated that this reaction would proceed via aziridinium ion **3**, which upon regioselective ion-pair collapse at the external (α) position[18] and hydrolysis of the resulting trifluoroacetate ester adduct would provide *δ*-lactam **2**, thereby establishing the C-8/8a stereodiad of the natural product. With regard to the diastereoselectivity of the addition process, we anticipated that cyclization of the singlet nitrenium ion generated from **6** would preferentially proceed via a transition state resembling pseudochair **4**, thereby avoiding the 1,3-allylic strain[19] present in boat-like conformer **5**.[20]

Our route to (−)-swainsonine (**1**) began from 2,3-*O*-isopropylidene-D-erythronolactone (**7**), which is readily available from the oxidative cleavage of sodium D-isoascorbate with hydrogen peroxide (Scheme 2).[21] Following a sequence of reactions developed by Pearson and Hembre during their synthesis of **1**,[10c] reduction of **7** with DIBAL-H yielded the corresponding D-erythrose derivative,[22]

(10) For selected total syntheses of (−)-swainsonine, see: (a) Bashyal, B. P.; Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083. (b) Bennett, R. B.; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580. (c) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217. (d) Mukai, C.; Sugimoto, Yi, Y.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281. (e) Buschmann, N.; Ruckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325. (f) Lindsay, K.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774. (g) Martin, R.; Murruzzu, C.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325. (h) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609. (i) Ceccon, J.; Greene, A.; Poisson, J. *Org. Lett.* **2006**, *8*, 4739. (j) Au, C. W.; Pyne, S. G. *J. Org. Chem.* **2006**, *71*, 7097. (k) Hakansson, A. E.; Van Ameijde, J.; Horne, G.; Nash, R. J.; Wormald, M. R.; Kato, A.; Besra, G. S.; Gurcha, S.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 179. (l) Guo, H.; O'Doherty, G. A. *Tetrahedron* **2008**, *64*, 304. (m) Ajish Kumar, K. S.; Chaudhari, V. D.; Dhavale, D. D. *Org. Biomol. Chem.* **2008**, *6*, 703. (n) Sharma, P. K.; Shah, R. N.; Carver, J. P. *Org. Process Res. Dev.* **2008**, *12*, 831. (o) Kwon, H.; Park, C.; Lee, S.; Youn, J.-H.; Kang, S. *Chem.—Eur. J.* **2008**, *14*, 1023. (p) Alam, M. A.; Kumar, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2008**, 4972. (q) Shi, G. F.; Li, J. Q.; Jiang, X. P.; Cheng, Y. *Tetrahedron* **2008**, *64*, 5005. (r) Tian, Y. S.; Joo, J. E.; Kong, B. S.; Pham, V. T.; Lee, K. Y.; Ham, W. H. *J. Org. Chem.* **2009**, *74*, 3962. (s) Li, X.; Zhu, Z.; Duan, K.; Chen, H.; Li, Z.; Li, Z.; Zhang, P. *Tetrahedron* **2009**, *65*, 2322. (t) Chooprayoon, S.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2011**, *9*, 531.

(11) For recent formal syntheses of (−)-swainsonine, see: (a) Déchamps, I.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082. (b) Kwon, H.; Park, C.; Lee, S.; Youn, J.-H.; Kang, S. *Chem.—Eur. J.* **2008**, *14*, 1023. (c) Bates, R. W.; Dewey, M. R. *Org. Lett.* **2009**, *11*, 3706. (d) Choi, H. G.; Kwon, J. H.; Kim, J. C.; Lee, W. K.; Eum, H.; Ha, H.-J. *Tetrahedron Lett.* **2010**, *51*, 3284. (e) Oxenford, S. J.; Moore, S. P.; Carbone, G.; Barker, G.; O'Brien, P.; Shipton, M. R.; Gilday, J.; Campos, K. R. *Tetrahedron: Asymmetry* **2010**, *21*, 1563.

(12) For reviews of recent total syntheses of (−)-swainsonine and related glycosidase inhibitors, see: (a) López, M.; Cobo, J.; Nogueras, M. *Curr. Org. Chem.* **2008**, *12*, 718. (b) Pyne, S. *Curr. Org. Synth.* **2005**, *2*, 39. (c) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579.

(13) For recent examples of swainsonine analogues, see: (a) Kuntz, D. A.; Nakayama, S.; Shea, K.; Hori, H.; Uto, Y.; Nagasawa, H.; Rose, D. R. *ChemBioChem* **2010**, *11*, 673. (b) Abrams, J. N.; Babu, R. S.; Guo, H.; Le, D.; Le, J.; Osbourn, J. M.; O'Doherty, G. A. *J. Org. Chem.* **2008**, *73*, 1935. (c) Bi, J.; Aggarwal, V. K. *Chem. Commun.* **2008**, 120. (d) Ajish Kumar, K. S.; Chaudhari, V. D.; Dhavale, D. D. *Org. Biomol. Chem.* **2008**, *6*, 703. (e) Murray, A. J.; Parsons, P. J.; Hitchcock, P. *Tetrahedron* **2007**, *63*, 6485.

(14) (a) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053. (b) Wardrop, D. J.; Zhang, W. M. *Org. Lett.* **2001**, *3*, 2353. (c) Wardrop, D. J.; Zhang, W. M.; Landrie, C. L. *Tetrahedron Lett.* **2004**, *45*, 4229. (d) Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230. (e) Wardrop, D. J.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271.

(15) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 1188.

(16) Bowen, E. G.; Wardrop, D. J. *Org. Lett.* **2010**, *12*, 5330.

(17) (a) Reference 15. (b) Rudchenko, V. F.; Ignatov, S. M.; Kostyanovsky, R. G. *Chem. Commun.* **1990**, 261. (c) Vedejs, E.; Sano, H. *Tetrahedron Lett.* **1992**, *33*, 3261. (d) Hoffman, R. V.; Christophe, N. B. *J. Org. Chem.* **1988**, *53*, 4769.

(18) For regioselective ring opening of a 1-azabicyclo[4.1.0]heptane-based aziridinium ion, see: D'hooghe, M. D.; Vanlangendonck, T.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 4678.

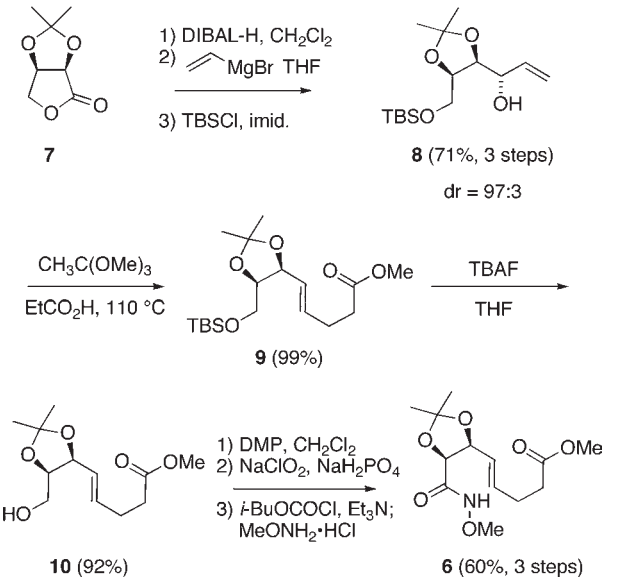
(19) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(20) For a related conformational made in reference to an intramolecular Huisgen diene−azide cycloaddition, see: (a) Hudlicky, T.; Seoane, G.; Lovelace, T. C. *J. Org. Chem.* **1988**, *53*, 2094. (b) Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683.

(21) (a) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. In *Organic Syntheses*; Wiley & Sons: New York, 1990; Vol. IV, pp 432−435. (b) Dunigan, J.; Weigel, L. O. *J. Org. Chem.* **1991**, *56*, 6225.

which through stereoselective addition of vinylmagnesium bromide[23] and selective *O*-silylation of the primary alcohol, was converted to allylic **8** alcohol is excellent overall yield. Upon heating with trimethyl orthoacetate in the presence of propionic acid, compound **8** underwent Johnson–Claisen rearrangement to provide β,γ-unsaturated ester **9** as the *E*-isomer.[24]

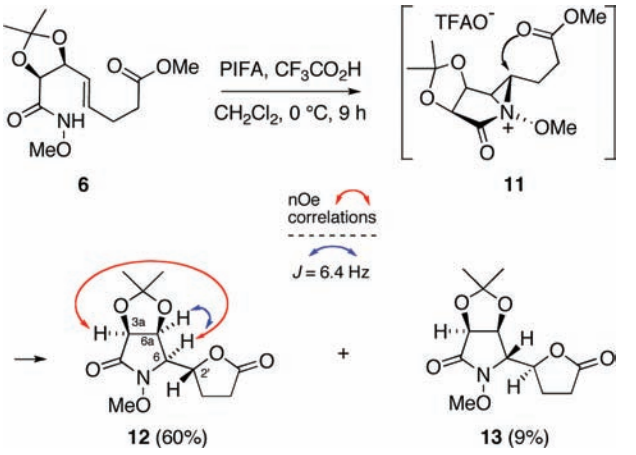
Scheme 2. Preparation of Oxamidation Substrate **6**



Removal of the TBS ether from **9** using TBAF provided primary alcohol **10**, which through a sequence of Dess–Martin and Pinnick oxidations was transformed to the corresponding carboxylic acid. Conversion of this material to methyl hydroxamate **6** was accomplished by treatment with isobutyl chloroformate to generate the corresponding mixed anhydride and coupling with methoxylamine.

Employing our previously reported oxamidation conditions,[15] cyclization of substrate **6** was now accomplished by treatment with phenyliodine(III) bis(trifluoroacetate) (PIFA, 1.2 equiv) and trifluoroacetic acid (1 equiv) in methylene chloride at 0 °C (Scheme 3). After 9 h, the reaction was simply concentrated to provide a 6:1 mixture of bis-cyclization products **12** and **13**. Notably, no products arising from alkene trifluoroacetoxyamidation were observed in this mixture suggesting that interception of aziridinium ion **11** (in the case of product **12**) by the proximate carboxylate group occurs significantly faster than ion pair collapse.[25] Fortuitously, separation of **12** from unwanted diastereomer **13** was readily accomplished by flash chromatography on silica gel.

Scheme 3. Bis(cyclofunctionalization) of Substrate **6**



The relative stereochemistry at the C6 position of the cyclization products was established by NOE analysis. In the case of compound **12**, the 2D NOESY spectrum displayed a strong correlation between H-6 and H-3a, which was conspicuously absent in the spectrum of **13** (Scheme 3). Further confirmation of the desired *cis-cis* stereochemistry of the lactam ring in **12** was gleaned from the vicinal coupling constant between H6 and H6a (6.4 Hz), which is diagnostic of the *cis* relationship between these protons.[26] At this point, assignment of the relative C2′ stereochemistry in **12** was made difficult by the conformational freedom of the C6–C2′ bond, although was assumed to be *R* in view of the stereospecificity of the oxamidation process with respect to alkene geometry.[15]

In order to progress toward swainsonine, we now sought to globally reduce **12** to gain compound **14** (Scheme 4). While treatment of **12** with excess $LiAlH_4$ in THF heated at reflux led to lactam and lactone reduction, cleavage of the N–O bond under these conditions proved to be rather sluggish.[27] Fortunately, reaction of **12** with $LiAlH_4$ at higher temperature, in 1,4-dioxane at reflux (bp 101 °C), proved to be more fruitful and lead to the reduction of all three functional groups and formation of 1-amino-2,5-diol **14** in excellent yield.

Formation of the indolizidine ring system was now accomplished through use of an Appel reaction.[28] Thus, selective bromination of the primary alcohol in **14** was accompanied by spontaneous cyclization to generate **15**. Finally, removal of the acetonide group, using 6 M HCl,[10c] provided (−)-swainsonine (**1**), after purification by ion-exchange chromatography. The ^1H and ^{13}C NMR spectral

(22) Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberger, M.; Liu, Y. Y.; Thom, E.; Liebman, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661.

(23) Mekki, B.; Singh, G.; Wightman, R. H. *Tetrahedron Lett.* **1991**, *32*, 5143.

(24) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

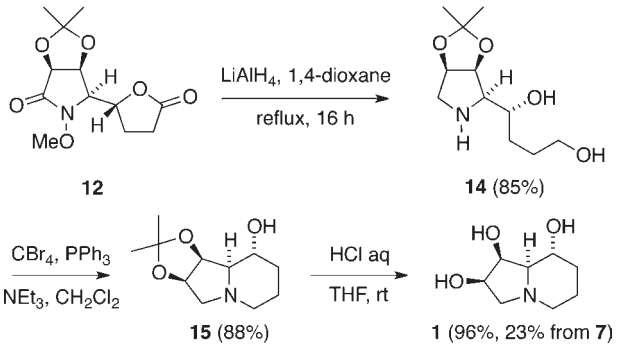
(25) For the formation of a related bis-cyclic lactone–lactam via intramolecular capture of a 1-azabicyclo[4.1.0]heptane-based aziridinium ion by a carboxylate group, see: Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721.

(26) Comin, M. J.; Parrish, D. A.; Deschamps, J. R.; Marquez, V. E. *Org. Lett.* **2006**, *8*, 705.

(27) For an example of the formation of a *N*-methoxylamine through the incomplete reduction of an *N*-methoxy-γ-lactam, see ref 14a.

(28) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801.

Scheme 4. Total Synthesis of (−)-Swainsonine (**1**)



data obtained from this material were identical to those reported for the natural product.[1b] In addition, the optical rotation of synthetic **1** ($[\alpha]^{24}_D$ −86.0; *c* 0.1, MeOH) closely matched that of the natural product ($[\alpha]^{25}_D$ −87.2; *c* 2.1, MeOH).[1b]

In conclusion, we have developed a 12-step, azide-free synthesis of (−)-swainsonine (**1**) in which the C-8/8a stereodiad and pyrrolidine ring of the target are simultaneously established through the diastereoselective bis-cyclization of an unsaturated *O*-alkyl hydroxamate. Although lost through reduction in our current synthesis, the bis-cyclic lactone−lactam framework accessible through this nitrenium ion cyclization is present in a number of alkaloids, most recognizably in the tuberostemospironine subgroup of the *Stemona* alkaloid family,[29] their biogenetic relatives, the pandamarilactonines,[30] and the *Securinega* alkaloid (−)-norsecurinine.[31] Extension of this type of transformation to the preparation of these alkaloids is now in progress.

Acknowledgment. We thank the National Institutes of Health (GM-67176) and the University of Illinois at Chicago for financial support of this work.

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

(29) (a) Pilli, R.; Rosso, G.; De Oliveira, M. *Nat. Prod. Rep* **2010**, *27*, 1908. (b) Alibes, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421.

(30) (a) Takayama, H.; Ichikawa, T.; Kuwajima, T.; Kitajima, M.; Seki, H.; Aimi, N.; Nonato, M. G. *J. Am. Chem. Soc.* **2000**, *122*, 8635. (b) Tan, M. A.; Kitajima, M.; Kogure, N.; Nonato, M. G.; Takayama, H. *Tetrahedron Lett.* **2010**, *51*, 4143.

(31) (a) Weinreb, S. M. *Nat. Prod. Rep* **2009**, *26*, 758. (b) Alibés, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421.