ChemPubSoc Europe

DOI: 10.1002/open.201500122

Open Access ChemistryOPEN Communications

Turning Spiroketals Inside Out: A Rearrangement Triggered by an Enol Ether Epoxidation

Chris Lorenc,[a] Josep Saurí,[b] Arvin Moser,[c] Alexei V. Buevich,[b] Antony J. Williams,[d] R. Thomas Williamson,[b] Gary E. Martin,[b] and Mark W. Peczuh*[a]

Spiroketals organize small molecule structures into well-defined, three-dimensional configurations that make them good ligands of proteins. We recently discovered a tandem cycloisomerization–dimerization reaction of alkynyl hemiketals that delivered polycyclic, enol-ether-containing spiroketals. Here we describe rearrangements of those compounds, triggered by epoxidation of their enol ethers that completely remodel their structures, essentially turning them "inside out". Due to the high level of substitution on the carbon skeletons of the substrates and products, characterization resorted to X-ray crystallography and advanced computation and NMR techniques to solve the structures of representative compounds. In particular, a new proton-detected ADEQUATE NMR experiment (1,1-HD-ADEQUATE) enabled the unequivocal assignment of the carbon skeleton of one of the new compounds. Solution of the structures of the representative compounds allowed for the assignment of product structures for the other compounds in two separate series. Both the rearrangement and the methods used for structural determination of the products are valuable tools for the preparation of characterization of new small molecule compounds.

Spiroketals organize the subunits of small molecule structures so that their rings and attached functionality are juxtaposed in well-defined orientations. This feature makes them a prevalent substructure in numerous natural products and small molecule libraries. Several spiroketal-containing natural products exert their biological activity by acting as ionophores.[1] Others are ligands of proteins that can mimic β-turns and other peptide motifs to disrupt protein–ligand and protein–protein interactions.[2,3] Binding in these cases results in antiproliferative activity and cytotoxicity. The unique structural features of spiroketals linked to their biological activity served as motivation for the development of methods for their synthesis.

There are several synthetic strategies to make spiroketals. Examples include acid-catalyzed spiroketalization of keto-diols, oxidative cyclization of hydroxy-alkyl substituted dihydropyrans, and hetero-Diels–Alder reactions.[2,4,5] In another method, a tandem sequence of enol ether epoxidation followed by epoxide ring opening is used as a practical strategy for synthesizing various spirocycles from simple starting materials in a diastereocontrolled manner.[6,7] Libraries of compounds that result from these syntheses can be structurally diverse and illustrate how spiroketals can be an integral functionality in Diversity-Orientated Synthesis (DOS) campaigns.[3,8,9] Here we report on a similar epoxide-opening spirocyclization reaction demonstrated on a novel multicyclic spiroketal starting material. By virtue of their functionality and structure, the spiroketal starting materials undergo total rearrangement of their skeletons, essentially turning them "inside out". Based on the intricacies of these structures, characterization of the products relied on X-ray crystallography and the capability of 1,1-ADEQUATE NMR experiments to identify directly adjacent carbon resonances that cannot be achieved using HMBC data.[10–12] Characterization of these structures subsequently enabled a mechanistic rationalization of their origin.

We recently reported the discovery of a phosphine-mediated cycloisomerization of alkynyl hemiketals (e.g., **1** to **2** in Figure 1). For terminal alkynes, enone intermediate **2** rapidly

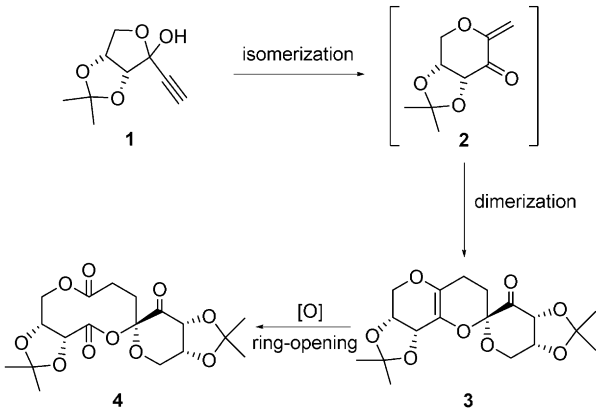


Figure 1. Synthesis of macrocycle **4** via tandem cycloisomerization–dimerization followed by ozonolysis.

[a] C. Lorenc, Prof. Dr. M. W. Peczuh
Department of Chemistry, University of Connecticut
55 N. Eagleville Road, U3060, Storrs, CT 06269 (USA)
E-mail: mark.peczuh@uconn.edu

[b] Dr. J. Saurí, Dr. A. V. Buevich, Dr. R. T. Williamson, Dr. G. E. Martin
Process & Analytical Chemistry, NMR Structure Elucidation
Merck Research Laboratories, Rahway, NJ 07065 (USA)

[c] A. Moser
Advanced Chemistry Development, Inc.
8 King Street E. Suite 107, Toronto, ON M5C 1B5 (Canada)

[d] Dr. A. J. Williams
ChemConector, Inc., 904 Tamaras Circle, Wake Forest, NC 27587 (USA)

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/open.201500122.

dimerized to give a spiroketal product, **3**.[13] The reaction led to relatively complex spiroketals from starting materials that were readily accessible. With DOS in mind,[14] we took the opportunity to further diversify these small molecules through subsequent reactions. One obvious choice was to cleave the carbon–carbon double bond through oxidation to produce new macrocycles.[15] Conversion of spiroketal **3** to macrocycle **4** under various oxidation conditions (O_3, $NaIO_4$) proceeded in modest (23–44%) yields.[16] With an eye toward a step-wise oxidative cleavage of the bond, epoxidation of **2** with *m*-chloro peroxybenzoic acid (*m*CPBA) was conducted. To our surprise, the physical data for the isolated material (76%, Table 1) was inconsistent with a product of simple epoxidation or even epoxidation–hydrolysis to give **4**.

Data from a series of NMR spectra (^1H, ^{13}C, COSY, HSQC, HMBC) provided clues about the structure of the new compound. For example, the presence of signals corresponding to six ketal/hemi-ketal carbons and the absence of a ketone carbonyl carbon revealed that the ketone in the starting material was pyramidalized at some point during the reaction. This, together with signals corresponding to the *m*-chlorobenzoyl group, suggested that *m*-chlorobenzoic acid had added into an oxocarbenium ion en route to the product. HMBC correlations suggested a skeletal structure containing fused and spirocyclic rings but assembling the fragments of data into an overall structure was problematic. For example, the exact locations of the hemi-ketal and the acylated ketal were uncertain. A sample of the compound ultimately yielded crystals suitable for X-ray diffraction experiments and its structure, **7**, is shown in Figure 2 and Table 1. The product spiroketal consisted of a highly congested, polycyclic core onto which the *m*-chlorobenzoyl unit was attached. The core itself contained six contiguously fused rings, one that contains two spiroketal carbons

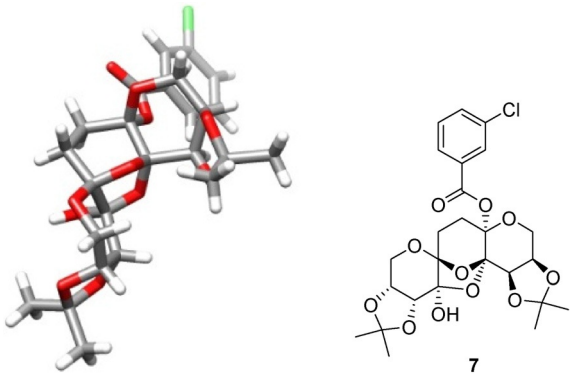
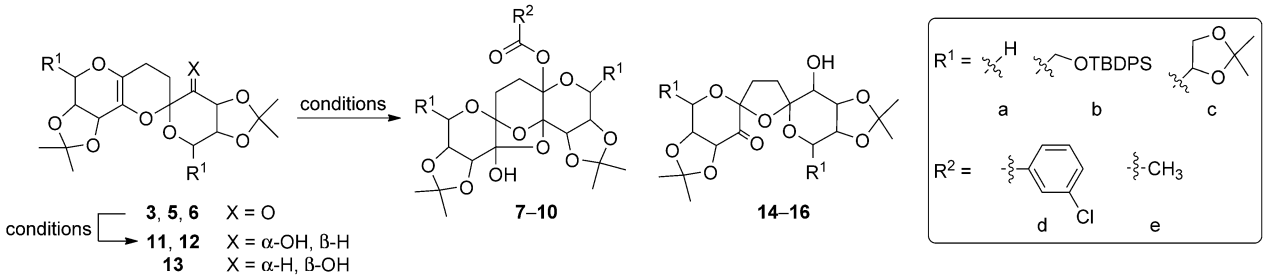


Figure 2. Crystal structure of rearranged spiroketal **7**.

and another that has one ketal and one hemi-ketal carbon. The structure, when compared to that of the starting material, showed that a total rearrangement of the spiroketal had occurred. The spiroketal in **3**[13] was of the variety where both linkages contained anomeric relationships.[2] Product **7**, in contrast, contained two spiroketals, each with one anomeric and one nonanomeric relationship. The contributions of these stereoelectronic effects, while substantial to the stability of a compound, must be balanced with other factors such as steric effects. The new spiroketals balanced these interactions and stabilized the congested molecules while at the same time minimizing steric interactions. Having gained insight on the structure of the product, we examined the scope of the reaction using other reagents (peracetic acid) and substrates (**5** and **6**) to explore its generality (Table 1). Product structures **8**–**10** were assigned from the similarity of their NMR spectra in comparison to **7**.

Table 1. Inside-out rearrangements of spiroketals.[a]



Entry	Reactant	R^1	R^2	Reaction conditions	Product	Yield
1	**3**	a	d	*m*CPBA, CH_2Cl_2, rt, 5 h	**7**	76%
2	**3**	a	e	CH_3CO_2OH, CH_2Cl_2, rt, 5 h	**8**	42%
3	**5**	b	d	*m*CPBA, CH_2Cl_2, rt, 5 h	**9**	70%
4	**6**	c	d	*m*CPBA, CH_2Cl_2, rt, 5 h	**10**	58%
5	**3**	a	–	$NaBH_4$, THF, 0 °C to rt, 4 h	**11**	75%
6	**5**	b	–	$NaBH_4$, THF, 0 °C to rt, 4 h	**12**	67%
7	**6**	c	–	$NaBH_4$, THF, 0 °C to rt, 4 h	**13**	80%
8	**11**	a	–	*m*CPBA, CH_2Cl_2, rt, 5 h	**14**	52%
9	**12**	b	–	*m*CPBA, CH_2Cl_2, rt, 5 h	**15**	24%
10	**13**	c	–	*m*CPBA, CH_2Cl_2, rt, 5 h	**16**	37%

[a] All reactions were stereoselective, and only one product stereoisomer is isolated in each case. Absolute stereochemistry for all starting materials and products is shown in the Supporting Information.

In an effort to extend the diversity of structures that could be obtained by this new reaction, we reduced the ketone unit of spiroketals **3**, **5**, and **6** to create another set of starting materials, **11**–**13** (Table 1). The reductions were efficient and stereoselective, providing only one product in each case. Epoxidation of **11**–**13** under the conditions previously established provided a single product in each case. Because the products were not solids, we were reliant on methods other than X-ray crystallography to determine their structures. Compound **14** was chosen for the structural investigation. The initial challenge to the structure elucidation was with the potential ambiguity associated with the standard array of NMR spectra (^{1}H, ^{13}C, COSY, HSQC, and HMBC). Hence, alternative approaches to the interpretation of the spectral data were utilized.

Computer-assisted structure elucidation (CASE) is a computational approach to analyze the analytical data and suggest hypothetical structures consistent with it.[17] The capabilities and performance of the ACD/Structure Elucidator software suite[18] have been reported previously.[19,20] The process can be summarized as utilizing the available NMR chemical shift and correlation data together with the molecular formula to assemble molecular structures consistent with that data. While many tens of thousands of structures may be assembled from the data, rank-ordering of the structures using NMR prediction algorithms[21] compares experimental chemical shifts to predicted shifts to identify the most likely candidate(s). The ACD/Structure Elucidator software (version 14.02) was utilized to analyze the initially available NMR data, and the top ranked candidates are summarized in the Supporting Information in Figure S14. Generally, although not always, the correct structure appears first in the output list of the Structure Elucidator program. The acquisition of additional NMR data as described below confirmed the structure as that listed first in the output list providing further substantiation regarding the power of the CASE approach for the analysis of analytical data.

The compact nature of the product structure and the indeterminate nature of correlations in the HMBC spectrum can be circumvented by utilizing 1,1-ADEQUATE spectra to unequivocally define the carbon skeleton of these molecules. To facilitate the acquisition of the ADEQUATE data, we utilized a newly developed, partially homodecoupled 1,1-ADEQUATE (1,1-HD-ADEQUATE) experiment optimized for $^{1}J_{CC}$ = 40 Hz (comparison of conventional versus 1,1-HD-ADEQUATE data is presented in the Supporting Information).[22] Utilizing these data and beginning from the hydroxyl-bearing methine (C1, see Figure 3), the constitution of rings B (C1–C2–C6–C7), C (C20–C21), and D (C13–C17–C18) suggested in the Structure Elucidator calculation were confirmed. Correlations from C1 and C21 to the C9 spiroketal carbon linked rings B and C. A correlation from C20 to the C11 spiroketal carbon and an unexpected $^{2}J_{CC}$ correlation from C13 to C11 established the link between rings C and D. Density functional theory (DFT) calculations revealed an unusually large $^{2}J_{CC}$ coupling (12.8 Hz calculated; 11.3 Hz measured using a *J*-modulated ADEQUATE spectrum) between C13 and C11 that was visualized in the 40 Hz optimized 1,1-HD-ADEQUATE spectrum (see Supporting Information). The ADEQUATE $^{1}J_{CC}$ correlations linked the 22- and 23-methyl groups to C4 and the 24- and 25-methyl groups to C15. Additionally, $^{4}J_{CH}$ correlations in a 2 Hz optimized LR-HSQMBC[23] experiment linked the two dimethylspiroketal moieties to rings B and D, respectively completing the confirmation of the structure (see Supporting Information).

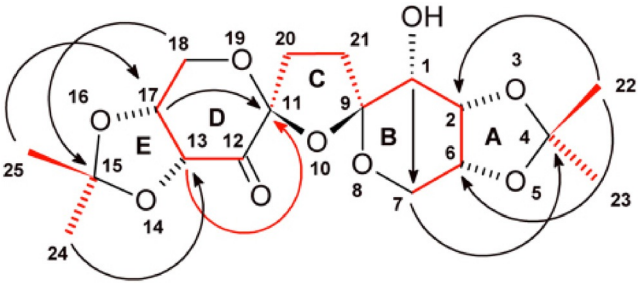


Figure 3. Numbering scheme for compound **14**. Bonds shown in bold red were determined from the 40 Hz optimized 1,1-HD-ADEQUATE data. The correlation from C13 to the C12 carbonyl was intentionally folded to afford better F_1 digitization and to minimize data acquisition times. The red arrow denotes the $^{2}J_{CC}$ = 11.3 Hz correlation observed in the 1,1-HD-ADEQUATE spectrum. The black arrows denote correlations in the 2 Hz optimized LR-HSQMBC spectrum that linked the two dimethyl sprioketals to rings B and D, in addition to providing some additional cross-ring correlations, for example H7ax–C1 and H17–C11.

Consideration of the mechanisms for conversion of **3** to **7** and **11** to **14** accounted for the novel rearrangements (Figure 4). They were triggered by the instability of the highly oxygenated epoxide intermediates that initially form (i.e., **I** and **V**),[3,24] especially in light of the acidity of the medium.[25,26] The epoxidation, which follows a "majority rules" model,[27] appears to have been highly diastereoselective because we were only able to detect and isolate one product from each reaction. Following epoxidation, a cascade of steps including oxocarbenium ion formation and attack by nucleophiles occurred en route to both **7** and **14**. Whereas **V** opened to oxocarbenium ion **VI** and was trapped by the hydroxyl group of the erstwhile hemiketal, the pathway followed by epoxide **I** was more complex. Oxocarbenium **II** is regioisomerically different than **VI** and likely reflected the influence of the ketone unit in the reaction trajectory. The ketone acted as the initial nucleophile followed by formation of a second oxocarbenium (**IV**) and trapped with *m*-chlorobenzoic acid to give **7**.

In conclusion, a new oxidative rearrangement of spiroketal-olefins was described. This "inside-out" rearrangement provided structural diversity and complexity allowing for the synthesis of natural product-like molecules. The described rearrangements emulated reaction conditions that could be used as a strategy for library design as the spiroketal motif was found in an array of biologically active molecules. Utilization of a newly developed partially homodecoupled 1,1-HD-ADEQUATE experiment provided the means of unequivocally establishing the carbon skeleton of **14**, which may have been problematic and prone to the potential misassignment of the structures relying solely on HMBC data. The ADEQUATE data were acquired using a relatively modest (~2.5 mg) sample in a 1.7 mm cryoprobe at 600 MHz.[12] In summary these structure elucidation efforts underscored the capability of substrates

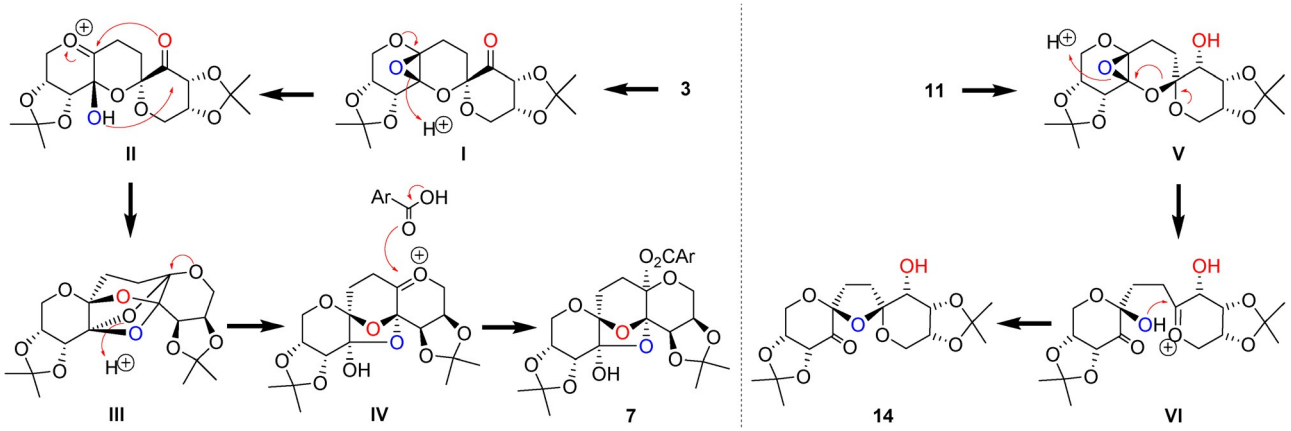


Figure 4. Mechanisms depicting the conversion of **3** to **7** and **11** to **14** via epoxidation, ring opening and oxocarbenium ion formation, and trapping by nucleophiles.

such as **3**, **5**—**6**, and **11**–**13** to deliver multiple natural-product-like compounds in an additional synthetic step.

Abbreviations used. 1,1-ADEQUATE: Adequate DoublE QUAntum Transfer Experiment; HMBC: heteronuclear multiple-bond correlation spectroscopy; CASE: computer-assisted structure elucidation; COSY: correlation spectroscopy; HSQC: heteronuclear single-quantum coherence spectroscopy; LR-HSQMBC: long-range heteronuclear single-quantum multiple-bond correlation spectroscopy.

Acknowledgements

*Martha Morton (University of Nebraska) is acknowledged for her assistance on the interpretation of NMR data for compound **7**. Brandon Q. Mercado (Yale University) collected the X-ray data on compound **7**. The US National Science Foundation (NSF) supported this work through a grant to M. W. P. (CHE-0957626). 400 MHz/100 MHz NMR spectra were collected on an instrument that was upgraded by an NSF-Chemistry Research Instrumentation and Facilities Program (NSF-CRIF) grant (CHE-0947019). Dr. Mikhail Reibarkh (Merck Research Laboratories) is also acknowledged for providing the amplitude transfer curves for the $^2J_{CC}$ correlation between C13–C11 shown in Figure S8 in the Supporting Information. Thanks to Lea Gerber and Samuel Coendet of Atelier Volvox (www.ateliervolvox.ch) for allowing the use of their "inside-out" image in the table of contents graphic.*

Keywords: cheminformatics · computer-assisted structure elucidation · NMR spectroscopy · rearrangement · spiro compounds · spiroketals

[1] F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617.
[2] J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406.
[3] B. A. Kulkarni, G. P. Roth, E. Lobkovsky, J. A. Porco, Jr., *J. Comb. Chem.* **2002**, *4*, 56.
[4] E. M. Carreira, T. C. Fessard, *Chem. Rev.* **2014**, *114*, 8257.
[5] L. F. Tietze, C. Schneider, *J. Org. Chem.* **1991**, *56*, 2476.
[6] B. Thirupathi, P. Reddy, D. K. Mohapatra, *J. Org. Chem.* **2011**, *76*, 9835.
[7] J. M. Wurst, G. Liu, D. S. Tan, *J. Am. Chem. Soc.* **2011**, *133*, 7916.
[8] S. B. Moilanen, J. S. Potuzak, D. S. Tan, *J. Am. Chem. Soc.* **2006**, *128*, 1792.
[9] G. Liu, J. Wurst, D. S. Tan, *Org. Lett.* **2009**, *11*, 3670.
[10] G. E. Martin, *Ann. Rep. NMR Spectrosc., Vol. 74* (Ed.: G. A. Webb), Elsevier, London, **2011**, pp. 215 – 291.
[11] G. E. Martin, M. Reibarkh, A. V. Buevich, K. A. Blinov, R. T. Williamson, *eMagRes* **2014**, *3*, 215.
[12] A. V. Buevich, R. T. Williamson, G. E. Martin, *J. Nat. Prod.* **2014**, *77*, 1942.
[13] J. Saha, C. Lorenc, V. Surana, M. W. Peczuh, *J. Org. Chem.* **2012**, *77*, 3846.
[14] a) C. J. O'Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 4444; b) S. L. Schreiber, *Science* **2000**, *287*, 1964.
[15] a) F. Kopp, C. F. Stratton, L. B. Akella, D. S. Tan, *Nat. Chem. Biol.* **2012**, *8*, 358; b) R. D. Rapp, I. J. Borowitz, *J. Chem. Soc. D* **1969**, 1202.
[16] Procedures and characterization data for all new compounds can be found in the Supporting Information.
[17] M. E. Elyashberg, A. J. Williams, G. E. Martin, *Prog. Nucl. Magn. Reson. Spectrosc.* **2008**, *53*, 1 – 104.
[18] ACD/Structure Elucidator, version 14.02, Advanced Chemistry Development, Inc. Toronto, Ont., Canada www.acdlabs.com, **2015**.
[19] A. Moser, M. E. Elyashberg, A. J. Williams, K. A. Blinov, J. C. DiMartino, *J. Cheminf.* **2012**, *4*, 5.
[20] M. E. Elyashberg, K. A. Blinov, S. Molodtsov, Y. Smurnyy, A. J. Williams, T. Churanova, *J. Cheminf.* **2009**, *1*, 3.
[21] K. A. Blinov, M. E. Elyashberg, A. J. Williams, *Contemporary Computer Assisted Approaches to Molecular Structure Elucidation*, Royal Society of Chemistry, London, **2011**.
[22] J. Saurí, W. Bermel, A. V. Buevich, E. C. Sherer, L. A. Joyce, M. H. M. Sharaf, P. L.Schiff, Jr., T. Parella, R. T. Williamson, G. E. Martin, *Angew. Chem. Int. Ed.* **2015**, *in press*; DOI: 10.1002/anie.201502540.
[23] R. T. Williamson, A. V. Buevich, G. E. Martin, T. Parella, *J. Org. Chem.* **2014**, *79*, 3887.
[24] R. Cong, Y. Zhang, W. Tian, *Tetrahedron Lett.* **2010**, *51*, 3890.
[25] A. Yamamoto, A. Ueda, P. Bremond, P. S. Tiseni, Y. Kishi, *J. Am. Chem. Soc.* **2012**, *134*, 893.
[26] L. Wang, Y. Su, X. Xu, W. Zhang, *Eur. J. Org. Chem.* **2012**, 6606.
[27] a) S. D. Markad, S. Xia, N. L. Snyder, B. Surana, M. D. Morton, C. M. Hadad, M. W. Peczuh, *J. Org. Chem.* **2008**, *73*, 6341; b) G. Cheng, F. P. Boulineau, S. T. Liew, Q. Shi, P. G. Wenthold, A. Wei, *Org. Lett.* **2006**, *8*, 4545; c) I. Marín, J. Castilla, M. I. Matheu, Y. Díaz, S. Castillón, *J. Org. Chem.* **2011**, *76*, 9622; d) R. L. Halcomb, S. J. Danishefsky, *J. Am. Chem. Soc.* **1989**, *111*, 6661; e) L. Alberch, G. Cheng, S. Seo, X. Li, F. P. Boulineau, A. Wei, *J. Org. Chem.* **2011**, *76*, 2532.

Received: May 7, 2015
Published online on June 17, 2015

