

# Studies toward the Synthesis of an Oxazole-Based Analog of (–)-Zampanolide

Christian P. Bold, Cindy Klaus, Bernhard Pfeiffer, Jasmine Schürmann, Rafael Lombardi, Daniel Lucena-Agell, J. Fernando Díaz, and Karl-Heinz Altmann\*



bond of the macrocycle was prone to migration into conjugation with the oxazole ring, which may generally limit the usefulness of zampanolide analogs with aromatic moieties as tetrahydropyran replacements.

(-)-Zampanolide (1) (Figure 1) is a marine macrolide with potent *in vitro* antitumor activity that was first isolated in 1996



Figure 1. Structure of (-)-zampanolide (1) and oxazole-based zampanolide analog 2.

from the marine sponge *Fasciospongia rimosa* by Tanaka and Higa.<sup>1</sup> In 2009, **1** was reisolated from *Cacospongia mycofijensis* by Northcote and co-workers, who also established that the compound was a microtubule-stabilizing agent (MSA).<sup>2</sup> The inhibition of cancer cell proliferation by (–)-zampanolide (**1**) is thus based on the same mechanism of action as for the anticancer drugs paclitaxel, taxotere, cabazitaxel, and ixabepilone.<sup>3</sup> However, **1** is the only MSA that interacts with tubulin by covalent bond formation, which entails 1,4-addition of His229 in the  $\beta$ -tubulin subunit to the enone moiety in the macrocycle.<sup>4</sup>

The structure of (-)-zampanolide (1) is composed of a macrobicyclic core comprising a 20-membered macrolactone ring and an embedded 2,6-syn-disubstituted tetrahydropyran (THP) moiety, as well as a (Z,E)-sorbamide-derived side chain that is connected to C(19) of the macrolactone ring via a hemiaminal group.

Several total syntheses of (-)-zampanolide (1) have been reported<sup>5-9</sup> since the pioneering work of Smith and coworkers on (+)-zampanolide,<sup>10,11</sup> which had established the absolute configuration of natural zampanolide as 11*S*, 15*S*, 19*S*, 20*S*. Part of the chemistry developed in the context of these total syntheses has also served as a basis for the preparation of analogs for SAR studies.<sup>12–18</sup> While these studies have shown that mono(macro)cyclic analogs lacking the C<sub>3</sub> bridge between C(11) and C(15) can retain sub- $\mu$ M antiproliferative activity, they are still substantially less potent than the natural product.<sup>9,13–15</sup> At the same time, recent work from our own group has demonstrated that the removal of the C(13) methylene group<sup>17</sup> (see also ref 16) or the complete replacement of the tetrahydropyran ring by a suitably substituted morpholine moiety<sup>18</sup> is well tolerated, with the corresponding analogs still exhibiting nanomolar IC<sub>50</sub> values for the inhibition of cancer cell growth *in vitro*.

When inspecting the tubulin-bound structure of (-)-zampanolide (1)<sup>4</sup>, it is immediately obvious that C(10), C(11), O(11'), C(15), and C(16) are all in the same plane (as for all 2,6-syn-disubstituted tetrahydropyran-based systems with the 2 and 6 substituents in an equatorial orientation). This situation is recapitulated in meta-substituted 5- or 6-membered aromatic rings, except that bond angles are slightly different from those in THP-based systems, which leads to not exactly superimposable positions of the atoms attached to the ring. We were nevertheless intrigued by the question if aromatic heterocycles could serve as THP bioisosteres in zampanolide and perhaps also in other bioactive natural products incorporating a 2,6-syndisubstituted THP motif as part of a bicyclic scaffold.<sup>19,20</sup> In a proof-of-concept study we thus embarked on the synthesis of oxazole-based zampanolide analog 2 (Figure 1), where the oxygen in the aromatic ring mimics the natural THP oxygen.

Received: February 1, 2021 Published: February 26, 2021





Preliminary modeling studies have indicated that the replacement of the THP ring in 1 by the oxazole ring in 2 can be accommodated in the structure of the tubulin–zampanolide (1) complex without major distortions in the conformation of the macrolactone ring; in addition, no unfavorable steric interactions of the oxazole ring with the protein are obvious (Figure 2).



Figure 2. (A) Superimposition of energy-minimized structures of 1 (green) and 2 (magenta) starting from the structure of 1 bound to tubulin (PDB ID code: 4I4T). (B) Superimposition of 2 (magenta) on 1 (green) in the X-ray structure of the 1-tubulin complex.

The overall strategy for the synthesis of **2** was conceived in analogy to our approach toward the synthesis of  $1^9$  and different zampanolide analogs (Scheme 1).<sup>9,17,18</sup> Thus, macro-

#### Scheme 1. Retrosynthesis of Oxazole-Zampanolide Analog 2



cyclization was to rely on an intramolecular Horner–Wadsworth–Emmons (HWE) reaction, while the elaboration of the (Z,E)-sorbamide-derived side chain was to be based on an aza-aldol reaction, for which we have recently also developed a stereoselective variant.<sup>17</sup>

The precursor for the HWE macrocyclization would be obtained by the esterification of acid  $4^9$  and alcohol 5. The latter was envisioned to be accessible from vinyl iodide 7 via iodine/lithium exchange and subsequent epoxide opening in PMB-protected *R*-glycidol (6). Oxazole 7 was planned to be assembled from aldehyde 9 and *p*-toluenesulfonylmethyl isocyanide (TosMIC, 8) in a van Leusen oxazole synthesis,<sup>21</sup> followed by formylation and elaboration of the ensuing aldehyde into vinyl iodide 7 by Corey–Fuchs alkynylation<sup>22</sup> and stannylcupration/iodination.

As depicted in Scheme 2, the synthesis of vinyl iodide 7 departed from 1,3-propanediol (10), which was converted into aldehyde 9 by mono-TBDPS protection and subsequent Swern oxidation in 85% yield. Employing a modified, two-step van Leusen procedure that involves treatment of the 4-methoxy-

### Scheme 2. Synthesis of Vinyl Iodide 7



oxazoline formed in the initial reaction between 9 and 8 with a strong base,<sup>23</sup> oxazole 11 could be obtained in 48% overall yield from 9. Formylation of 11 (*n*-BuLi, DMF)<sup>24</sup> followed by a Corey–Fuchs reaction<sup>22</sup> furnished alkyne 13 in 40% yield over 3 steps; the latter was then converted into vinyl iodide 7 by stannylcupration/iodination with Bu<sub>3</sub>Sn(Bu)CuCNLi<sub>2</sub><sup>25,26</sup> and *N*-iodosuccinimide (82%).

In accordance with our original synthetic plan, initial attempts toward the elaboration of vinyl iodide 7 into alcohol 5 involved iodine—lithium exchange on 7, followed by reaction of the ensuing vinyllithium species with PMB-protected *R*-glycidol (6) in the presence of BF<sub>3</sub>·Et<sub>2</sub>O. Unfortunately, none of the desired alcohol 5 was obtained when using either *n*-BuLi or *t*-BuLi to effect iodine/lithium exchange. With *n*-BuLi, only the product of protodehalogenation could be isolated (29% yield), while *t*-BuLi gave the product of protodehalogenation together with the elimination product 13. This stands in marked contrast to the successful opening of the epoxide ring in 6 with a variety of vinyllithiums generated from vinyl iodides related to 7 in the synthesis of 1<sup>9</sup> or of zampanolide analogs.<sup>12,17,18</sup>

Ghosh et al., as part of their total synthesis of 1, have described the construction of the C(16)-C(17) double bond by cross-metathesis.<sup>7,8</sup> Thus, 5 was attempted to be accessed from olefins 14 (obtained from 12 by Wittig reaction (Scheme 3); see the Supporting Information (SI)) and 15<sup>7</sup> or 16<sup>7</sup>,

Scheme 3. Unsuccessful Attempt towards 5 by Cross-Metathesis



respectively, by Grubbs II mediated cross-metathesis in  $CH_2Cl_2$  or toluene. Unfortunately, again none of the desired product **5** or **17**, respectively, could be obtained; instead both starting olefins were reisolated.

Hoarau and co-workers have reported the palladiumcatalyzed C(2)-selective coupling of an unfunctionalized oxazole with a vinyl iodide  $(Pd(OAc)_2, CyJohnPhos, Cs_2CO_3, 1,4-dioxane, 110 °C)$ .<sup>27</sup> Applying Hoarau's conditions to 11 and vinyl iodide  $18^{28,29}$  (see Scheme 4 for the structure of 18) or the corresponding TBS-ether, however, solely led to decomposition of the latter and reisolation of oxazole 11. pubs.acs.org/OrgLett



## Scheme 4. Building Block Assembly and Macrocyclization

Gratifyingly, the coupling of **11** and **18** could be achieved by Negishi cross-coupling,<sup>30</sup> which furnished the desired homoallylic alcohol **5** in 80% yield (Scheme 4).

Subsequent Yamaguchi esterification<sup>31</sup> of 5 with acid 4 followed by global desilylation afforded diol 19 in 55% yield over 2 steps. Oxidation of 19 with DMP<sup>32</sup> gave a keto aldehyde that underwent smooth  $Ba(OH)_2$ -mediated HWE olefination, to furnish the macrolactone 20 as a crude product. While <sup>1</sup>H NMR analysis indicated a yield of approximately 84%, all attempts to purify the material were unsuccessful. Upon standard silica gel chromatography, partial migration of the C(8)-C(9) double bond into conjugation with the oxazole ring occurred. Addition of triethylamine to the eluent only aggravated the problem and resulted in complete conversion of 20 into this undesired regioisomer. Therefore, the crude macrolactone was directly submitted to oxidative PMBcleavage with DDQ. After extensive screening of different purification methods, the free alcohol 21 could be purified by flash column chromatography with acidic silica gel (SiO<sub>2</sub>. HCl)<sup>33</sup> and was finally obtained in 36% yield over 3 steps from 19. DMP oxidation<sup>32</sup> of alcohol 21 gave the crude aldehyde 22, which is an analog of the non-natural enantiomer of the marine macrolide (+)-dactylolide.<sup>34</sup> Given the susceptibility of the macrocycle to double bond migration upon exposure to silica gel and an anticipated lability of the C(19) stereocenter under acidic conditions (SiO<sub>2</sub>·HCl), crude 22 was directly used in the following aza-aldol reaction. However, none of the desired hemiaminal 2 could be isolated upon mixing 22 with a solution of (Z,E)-sorbamide (3) that had been pretreated with DIBAL-H for 50 min, conditions that had been successfully employed in the total synthesis of 1.5,9 While the mass of 2 could be detected in the HRMS spectrum of the crude material obtained after extractive workup, the <sup>1</sup>H NMR spectrum was completely uninformative. The only interpretable signals were those of 3 (of which a 10-fold excess was used) and a signal at 9.2 ppm, corresponding to unreacted aldehyde 22 (ca. 27%).

In order to gain some preliminary understanding of the biological consequences of the replacement of the 2,6-syndisubstituted tetrahydropyran moiety in the zampanolide macrocycle by a planar aromatic ring, the antiproliferative activity of alcohol **21** was assessed against A549 human lung carcinoma cells. The IC<sub>50</sub> of **21** was 12.4  $\mu$ M, compared to 127 nM for the corresponding analog incorporating the natural 4-methylene THP moiety.<sup>9</sup> While this seems to indicate that the oxazole moiety is not a suitable bioisostere for the THP ring in zampanolide-derived structures, the results have to be interpreted with some care. It is well conceivable that isomerization of the C(8)–C(9) double bond occurs under the conditions of the cellular experiments, thus destroying the enone system that is critical for the covalent interaction of 1 with tubulin.<sup>4</sup>

In summary, we have established an efficient route for the synthesis of an oxazole-derived analog of the non-natural enantiomer of the (-)-dactylolide alcohol **21**, but the desired conversion into the corresponding analog of (-)-zampanolide (1) could not be accomplished. We have found the modified zampanolide macrocycle to be highly susceptible to the migration of the C(8)–C(9) double bond, which makes it doubtful if the replacement of the THP ring in 1 by any aromatic moiety would yield useful analogs. Analogs of other THP-containing natural products will have to be investigated to assess the potential of such an approach for the optimization of natural product leads in drug discovery.<sup>19</sup>

# ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00378.

Experimental procedures, full analytical data for all new compounds, including <sup>1</sup>H and <sup>13</sup>C NMR spectra, and details of the modeling studies leading to the minimized structures shown in Figure 2 (PDF)

# AUTHOR INFORMATION

## **Corresponding Author**

Karl-Heinz Altmann – ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, 8093 Zürich, Switzerland;
orcid.org/0000-0002-0747-9734; Email: karlheinz.altmann@pharma.ethz.ch

# Authors

- Christian P. Bold ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, 8093 Zürich, Switzerland
- Cindy Klaus ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, 8093 Zürich, Switzerland; © orcid.org/0000-0001-5977-1158
- **Bernhard Pfeiffer** ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, 8093 Zürich, Switzerland
- Jasmine Schürmann ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, 8093 Zürich, Switzerland
- **Rafael Lombardi** ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, 8093 Zürich, Switzerland
- Daniel Lucena-Agell Centro de Investigaciones Biológicas Margarita Salas, Consejo Superior de Investigaciones Científicas, 28040 Madrid, Spain

J. Fernando Díaz – Centro de Investigaciones Biológicas Margarita Salas, Consejo Superior de Investigaciones Científicas, 28040 Madrid, Spain; o orcid.org/0000-0003-2743-3319

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00378

#### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We gratefully acknowledge financial support by the Swiss National Science Foundation (Projects 200021\_149253 and 200020\_175744 (K.H.A.)). Funding was also obtained from Ministerio de Ciencia e Innovaci\_n PID2019-104545RB-I00 and Fondo de Investigaciones Sanitarias COV20/01007 (J.F.D.) and H2020-MSCA-ITN-2019 860070 TUBINTRAIN (J.F.D.). We are indebted to Dr. Bernhard Pfeiffer and Philipp Waser (ETHZ) for NMR support, to Kurt Hauenstein (ETHZ) for technical advice, and to Oswald Greter, Louis Bertschi, Michael Meier, and Daniel Wirz (ETHZ) for HRMS spectra acquisition.

#### REFERENCES

(1) Tanaka, J.; Higa, T. Zampanolide, a New Cytotoxic Macrolide from a Marine Sponge. *Tetrahedron Lett.* **1996**, *37*, 5535–5538.

(2) Field, J. J.; Singh, A. J.; Kanakkanthara, A.; Halafihi, T.; Northcote, P. T.; Miller, J. H. Microtubule-Stabilizing Activity of Zampanolide, a Potent Macrolide Isolated from the Tongan Marine Sponge *Cacospongia Mycofijiensis*. J. Med. Chem. **2009**, 52, 7328–7332.

(3) Cao, Y. N.; Zheng, L. L.; Wang, D.; Liang, X. X.; Gao, F.; Zhou, X. L. Recent Advances in Microtubule-Stabilizing Agents. *Eur. J. Med. Chem.* **2018**, *143*, 806–828.

(4) Prota, A. E.; Bargsten, K.; Zurwerra, D.; Field, J. J.; Díaz, J. F.; Altmann, K.-H.; Steinmetz, M. O. Molecular Mechanism of Action of Microtubule-Stabilizing Anticancer Agents. *Science* **2013**, 339, 587– 590.

(5) Hoye, T. R.; Hu, M. Macrolactonization via Ti(IV)-Mediated Epoxy-Acid Coupling: A Total Synthesis of (–)-Dactylolide [and Zampanolide]. J. Am. Chem. Soc. 2003, 125, 9576–9577.

(6) Uenishi, J.; Iwamoto, T.; Tanaka, J. Total Synthesis of (-)-Zampanolide and Questionable Existence of (-)-Dactylolide as the Elusive Biosynthetic Precursor of (-)-Zampanolide in an Okinawan Sponge. Org. Lett. **2009**, 11, 3262–3265.

(7) Ghosh, A. K.; Cheng, X. Enantioselective Total Synthesis of (-)-Zampanolide, a Potent Microtubule-Stabilizing Agent. *Org. Lett.* **2011**, *13*, 4108–4111.

(8) Ghosh, A. K.; Cheng, X.; Bai, R.; Hamel, E. Total Synthesis of Potent Antitumor Macrolide (–)-Zampanolide: An Oxidative Intramolecular Cyclization-Based Strategy. *Eur. J. Org. Chem.* **2012**, 2012, 4130–4139.

(9) Zurwerra, D.; Glaus, F.; Betschart, L.; Schuster, J.; Gertsch, J.; Ganci, W.; Altmann, K.-H. Total Synthesis of (–)-Zampanolide and Structure-Activity Relationship Studies on (–)-Dactylolide Derivatives. *Chem. Eur. J.* **2012**, *18*, 16868–16883.

(10) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. Total Synthesis of (+)-Zampanolide. J. Am. Chem. Soc. 2001, 123, 12426-12427.

(11) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. Total Synthesis of (+)-Zampanolide and (+)-Dactylolide Exploiting a Unified Strategy. J. Am. Chem. Soc. 2002, 124, 11102–11113.

(12) Zurwerra, D.; Gertsch, J.; Altmann, K.-H. Synthesis of (-)-Dactylolide and 13-Desmethylene-(-)-Dactylolide and Their Effects on Tubulin. *Org. Lett.* **2010**, *12*, 2302–2305.

(13) Chen, G.; Wang, R.; Vue, B.; Patanapongpibul, M.; Zhang, Q.; Zheng, S.; Wang, G.; White, J. D.; Chen, Q.-H. Optimized synthesis and antiproliferative activity of desTHPdactylolides. *Bioorg. Med. Chem.* 2018, 26, 3514–3520.

(14) Chen, G.; Patanapongpibul, M.; Jiang, Z.; Zhang, Q.; Zheng, S.; Wang, G.; White, J. D.; Chen, Q.-H. Synthesis and Antiproliferative Evaluation of New Zampanolide Mimics. *Org. Biomol. Chem.* **2019**, *17*, 3830–3844.

(15) Chen, G.; Jiang, Z.; Zhang, Q.; Wang, G.; Chen, Q.-H. New Zampanolide Mimics: Design, Synthesis, and Antiproliferative Evaluation. *Molecules* **2020**, *25*, 362.

(16) Henry, J. L.; Wilson, M. R.; Mulligan, M. P.; Quinn, T. R.; Sackett, D. L.; Taylor, R. E. Synthesis, Conformational Preferences, and Biological Activity of Conformational Analogues of the Microtubule-Stabilizing Agents, (-)-Zampanolide and (-)-Dactylolide. *MedChemComm* **2019**, *10*, 800–805.

(17) Brütsch, T. M.; Berardozzi, S.; Rothe, M. L.; Horcajo, M. R.; Díaz, J. F.; Altmann, K.-H. A Method for the Stereoselective Construction of the Hemiaminal Center in Zampanolides. *Org. Lett.* **2020**, *22*, 8345–8348.

(18) Bold, C. P.; Gut, M.; Schürmann, J.; Lucena-Agell, D.; Gertsch, J.; Díaz, J. F.; Altmann, K.-H. Synthesis of Morpholine-Based Analogs of (–)-Zampanolide and Their Biological Activity. *Chem. Eur. J.* **2020**, DOI: 10.1002/chem.202003996.

(19) We are aware of only one other example, where a metasubstituted aromatic moiety has been explored as a THP surrogate in natural product, namely a phenyl analog of peloruside A (pelofen): Van der Eycken, J.; Smans, G.; Cornelus, J.; Van den Bossche, D.; Jacobs, N. Preparation of peloruside analogs as antiproliferative agents. *PCT Int. Appl.* (2015), WO 2015079009 A1 20150604.

(20) The replacement of 2,5-syn-disubstituted tetrahydrofuran rings has been investigated more frequently. See, e.g.: (a) Neves, A. R.; Trefzger, O. S.; Barbosa, N. V.; Honorato, A. M.; Carvalho, D. B.; Moslaves, I. S.; Kadri, M. C. T.; Yoshida, N. C.; Kato, M. J.; Arruda, C. C. P.; Baroni, A. C. M. Effect of isoxazole derivatives of tetrahydrofuran neolignans on intracellular amastigotes of *Leishmania* (*Leishmania*) amazonensis: A structure-activity relationship comparative study with triazole-neolignan-based compounds. *Chem. Biol. Drug Des.* 2019, 94, 2004–2012. (b) Florence, G. J.; Fraser, A. L.; Gould, E. R.; King, E. F.; Menzies, S. K.; Morris, J. C.; Thomson, M. I.; Tulloch, L. B.; Zacharova, M. K.; Smith, T. K. Development of Simplified Heterocyclic Acetogenin Analogues as Potent and Selective *Trypanosoma brucei* Inhibitors. *ChemMedChem* 2016, 11, 1503–1506. (21) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. A Novel and Efficient Synthesis of Oxazoles from Tosylmethylisocyanide and

Carbonyl Compounds. *Tetrahedron Lett.* **1972**, *13*, 2369–2372. (22) Corey, E. J.; Fuchs, P. L. A. Synthetic Method for Formyl→

ethynyl Conversion (RCHO $\rightarrow$ RCCH or RCCR'). *Tetrahedron Lett.* **1972**, 13, 3769–3772.

(23) van Leusen, D.; van Leusen, A. M. Synthetic Uses of Tosylmethyl Isocyanide (TosMIC). In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2001; Vol. 13, pp 417–666. (24) Ŝindler-Kulyk, M.; Vojnović, D.; Defterdarović, N.; Marinić, Ž.; Srzić, D. Formylation of 2,5-Unsubstituted Oxazole: Preparation and Characterization of 2- and 5-Formyl-4-Methyloxazoles. *Heterocycles* **1994**, 38, 1791–1796.

(25) Betzer, J.-F.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. An efficient Method in Stannylcupration of a Methyl Substituted Enyne or Alkyne by Kinetic Control Using Methanol. *Tetrahedron Lett.* **1997**, *38*, 2279–2282.

(26) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. Radical Hydrostannylation, Pd(0)-Catalyzed Hydrostannylation, Stannylcupration of Propargyl Alcohols and Enynols: Regio- and Stereoselectivities. J. Org. Chem. **1997**, *62*, 7768–7780.

(27) Verrier, C.; Hoarau, C.; Marsais, F. Direct Palladium-Catalyzed Alkenylation, Benzylation and Alkylation of Ethyl Oxazole-4-Carboxylate with Alkenyl-, Benzyl- and Alkyl Halides. *Org. Biomol. Chem.* **2009**, *7*, 647–650.

(28) Carpenter, J.; Northrup, A. B.; Chung, D.; Wiener, J. J. M.; Kim, S.-G.; MacMillan, D. W. C. Total Synthesis and Structural Revision of Callipeltoside C. Angew. Chem. Int. Ed. 2008, 47, 3568–3572.

(29) White, J. D.; Jana, S. Studies of the Synthesis of Providencin: Construction and Assembly of Two Major Subunits. *J. Org. Chem.* **2014**, *79*, 700–710.

(30) Crowe, E.; Hossner, F.; Hughes, M. J. 2-Metallated Oxazoles; pKa Dependent Deuterations, NMR Studies and Palladium Catalysed Couplings. *Tetrahedron* **1995**, *51*, 8889–8900.

(31) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(32) Dess, D. B.; Martin, J. C. Readily Accessible 12-I-5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(33) Vorndam, P. E. Efficient, Trimethylsilyl Triflate Mediated Conversion of Diels-Alder Adducts of 1-Methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's Diene) to Cyclohexenones. J. Org. Chem. 1990, 55, 3693–3695.

(34) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. Dactylolide, a New Cytotoxic Macrolide from the Vanuatu Sponge *Dactylospongia* sp. *Eur. J. Org. Chem.* **2001**, 2001, 775–778.