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Letter

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

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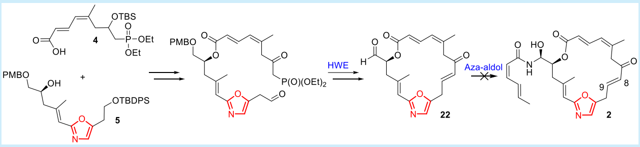
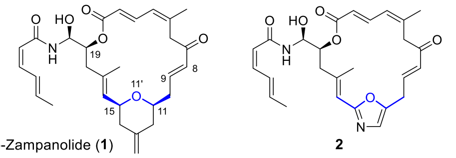
ABSTRACT: Studies are described toward the synthesis of an oxazole-based analog of (−)-zampanolide (**2**). Construction of (−)-dactylolide analog **22** was achieved via alcohol **5** and acid **4** through esterification and Horner−Wadsworth−Emmons (HWE)-based macrocyclization; however, attempts to attach (*Z*,*E*)-sorbamide to **22** proved unsuccessful. The C(8)−C(9) double 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 from the marine sponge *Fasciospongia rimosa* by Tanaka and Higa.[1] 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).[2] 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.[3] However, **1** is the only MSA that interacts with tubulin by covalent bond formation, which entails 1,4-addition of His229 in the *β*-tubulin subunit to the enone moiety in the macrocycle.[4]



(-)-Zampanolide (**1**) **2**

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

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[5−9] since the pioneering work of Smith and co-workers on (+)-zampanolide,[10,11] 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.[12−18] While these studies have shown that mono(macro)cyclic analogs lacking the C_3 bridge between C(11) and C(15) can retain sub-μM antiproliferative activity, they are still substantially less potent than the natural product.[9,13−15] At the same time, recent work from our own group has demonstrated that the removal of the C(13) methylene group[17] (see also ref 16) or the complete replacement of the tetrahydropyran ring by a suitably substituted morpholine moiety[18] is well tolerated, with the corresponding analogs still exhibiting nanomolar IC_{50} values for the inhibition of cancer cell growth *in vitro*.

When inspecting the tubulin-bound structure of (−)-zampanolide (**1**),[4] 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-*syn*-disubstituted THP motif as part of a bicyclic scaffold.[19,20] 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.

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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).

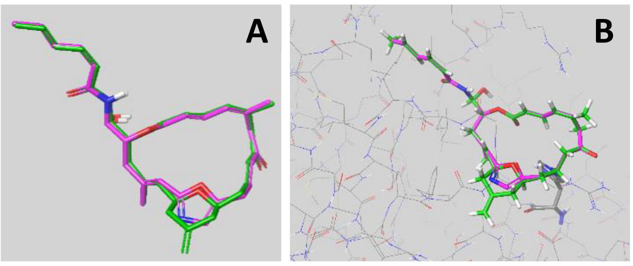
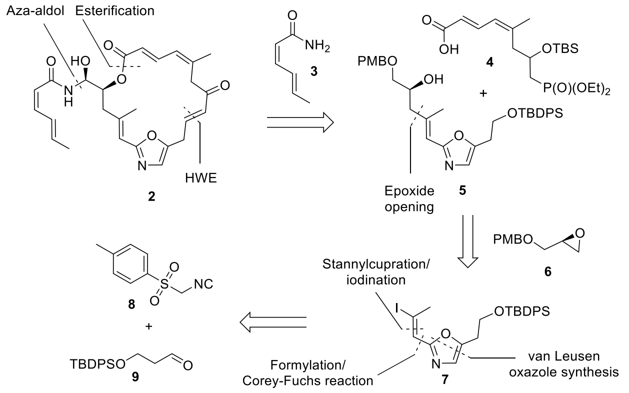


Figure 2. (A) Superimposition of energy-minimized structures of **1** (green) and **2** (magenta) starting from the structure of **1** bound to tubulin (PDB ID code: 4I4T). (B) Superimposition of **2** (magenta) on **1** (green) in the X-ray structure of the **1**·tubulin complex.

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).[9,17,18] Thus, macrocyclization 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.[17]

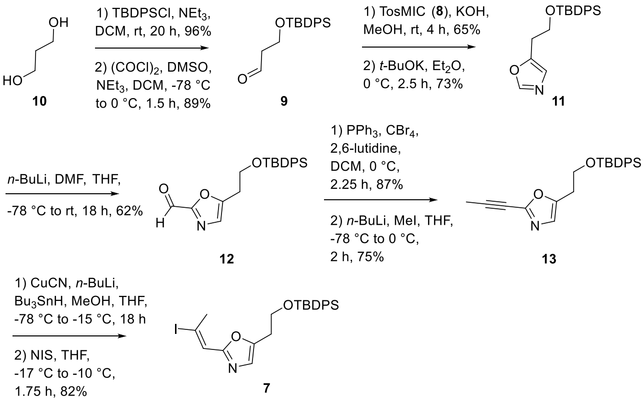
Scheme 1. Retrosynthesis of Oxazole-Zampanolide Analog 2



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,[21] followed by formylation and elaboration of the ensuing aldehyde into vinyl iodide **7** by Corey–Fuchs alkynylation[22] 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-methoxyoxazoline formed in the initial reaction between **9** and **8** with a strong base,[23] oxazole **11** could be obtained in 48% overall yield from **9**. Formylation of **11** (*n*-BuLi, DMF)[24] followed by a Corey–Fuchs reaction[22] furnished alkyne **13** in 40% yield over 3 steps; the latter was then converted into vinyl iodide **7** by stannylcupration/iodination with $Bu_3Sn(Bu)CuCNLi_2$[25,26] and *N*-iodosuccinimide (82%).

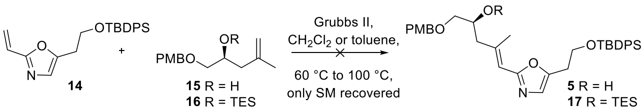
Scheme 2. Synthesis of Vinyl Iodide 7



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 $BF_3{\cdot}Et_2O$. 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**[9] or of zampanolide analogs.[12,17,18]

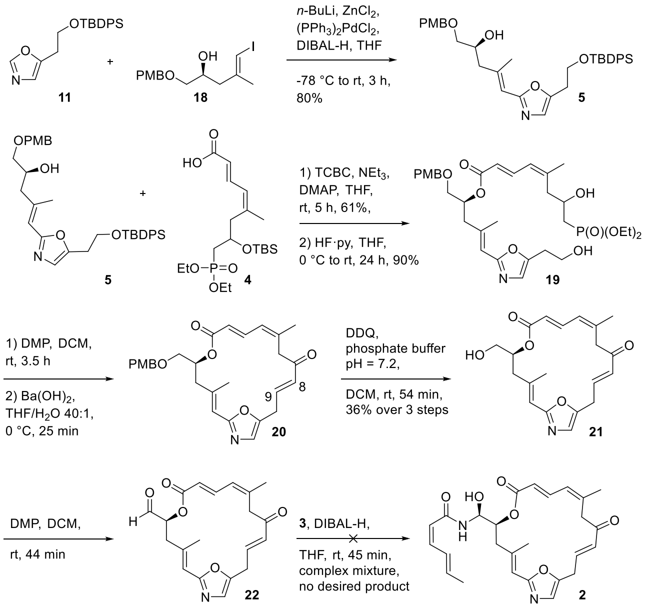
Ghosh et al., as part of their total synthesis of **1**, have described the construction of the C(16)–C(17) double bond by cross-metathesis.[7,8] Thus, **5** was attempted to be accessed from olefins **14** (obtained from **12** by Wittig reaction (Scheme 3); see the Supporting Information (SI)) and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

Scheme 3. Unsuccessful Attempt towards 5 by Cross-Metathesis



Hoarau and co-workers have reported the palladium-catalyzed C(2)-selective coupling of an unfunctionalized oxazole with a vinyl iodide ($Pd(OAc)_2$, CyJohnPhos, Cs_2CO_3, 1,4-dioxane, 110 °C).[27] 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**.

Scheme 4. Building Block Assembly and Macrocyclization



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

Subsequent Yamaguchi esterification[31] of **5** with acid **4** followed by global desilylation afforded diol **19** in 55% yield over 2 steps. Oxidation of **19** with DMP[32] gave a keto aldehyde that underwent smooth $Ba(OH)_2$-mediated HWE olefination,[9] to furnish the macrolactone **20** as a crude product. While ^1H 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 PMB-cleavage with DDQ. After extensive screening of different purification methods, the free alcohol **21** could be purified by flash column chromatography with acidic silica gel ($SiO_2 \cdot HCl$)[33] and was finally obtained in 36% yield over 3 steps from **19**. DMP oxidation[32] of alcohol **21** gave the crude aldehyde **22**, which is an analog of the non-natural enantiomer of the marine macrolide (+)-dactylolide.[34] 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 ($SiO_2 \cdot HCl$), 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 ^1H 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-*syn*-disubstituted 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_{50} of **21** was 12.4 μM, compared to 127 nM for the corresponding analog incorporating the natural 4-methylene THP moiety.[9] 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.[4]

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.[19]

■ 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 ^1H and ^{13}C NMR spectra, and details of the modeling studies leading to the minimized structures shown in Figure 2 (PDF)

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Notes

The authors declare no competing financial interest.

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