Published in final edited form as:

Org Lett. 2011 August 5; 13(15): 4108–4111. doi:10.1021/ol201626h.

Enantioselective Total Synthesis of (–)-Zampanolide, a Potent Microtubule-Stabilizing Agent

Arun K. Ghosh* and Xu Cheng

Departments of Chemistry and Medicinal Chemistry, Purdue University, 560 Oval drive, West Lafayette, IN 47907

Abstract

An enantioselective total synthesis of zampanolide has been accomplished using a novel DDQ/Brønsted acid catalyzed cyclization as the key reaction. The synthesis features cross-metathesis to construct the tri-substituted olefin and a ring-closing metathesis to form the macrolactone. The final *N*-acyl amination was stereoselectively accomplished by an organocatalytic reaction.

The isolation of taxol in the 1970's and subsequent decade-long studies led to the approval of paclitaxel as an important anticancer drug.¹ Paclitaxel inhibits cell division by stabilizing microtubule assembly.² Since the discovery of this unique mechanism of action, the search for new agents has become the subject of immense interest. In recent years, epothilones and discodermolide-based antitumor therapeutics have received significant attention.³ Also, laulimalide and pelorusides were identified as the exciting new generation of microtubule-stabilizing agents.⁴ Both laulimalide and pelorusides have exhibited intriguing synergistic effects with taxol, maintained potent activity against taxol-resistant cell lines and are not substrates for P-glycoprotein-mediated drug efflux pump.^{5,6} More recently, Northcote, Miller and co-workers reported that (–)-zampanolide **1** (Figure 1), a 20-membered macrolide also possesses potent microtubule-stabilizing properties.⁷

Zampanolide (**1**) was originally isolated by Tanaka and Higa from the marine sponge *Fasciospongia rimosa* in Okinawa in 1996.⁸ More recently, (–)-zampanolide **1** was isolated from a Tongan marine sponge, *Cacospongia mycofijiensis*, and reported to block cell division in the G2/M of the cell cycle.⁷ Uenishi and co-workers reported potent cytotoxic activity of (–)-zampanolide against SKM-1 and U937 cell lines with IC₅₀ values of 1.1 and 2.9 nM respectively.⁹ Furthermore, it is potent against HL-60, 1A9 cells and especially against A2780AD which is quite resistant to paclitaxel.⁷ Zampanolide's natural abundance is very scarce which has resulted in only limited biological studies. Zampanolide possesses a

akghosh@purdue.edu .

Supporting Information Available: Experimental procedures and ¹H- and ¹³C-NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

unique unsaturated macrocyclic structural feature containing only three stereogenic centers and a chiral *N*-acyl aminal side chain.

The chemistry and biology of zampanolide has attracted much synthetic attention. Smith and co-workers achieved the first total synthesis of (+)-zampanolide, the unnatural antipode, in 2001.¹⁰ Subsequently, both Hoyer et al. in 2003¹¹ and Uenishi et al.⁹ in 2009, reported the total synthesis of natural (–)-zampanolide. These syntheses established that the natural (–)-zampanolide core is the opposite enantiomer of the related natural product (+)-dactylolide (**2**). Dactylolide displayed only modest cytotoxicity. Since its discovery by Riccio and co-workers in 2001¹², a number of total syntheses^{13,14,15,16,17,18,19} and a synthetic approach to (+)-dactylolide have been reported.²⁰ It appears that the *N*-acyl aminal side chain of (–)-zampanolide is important for its potent cytotoxic properties. The key *N*-acylation reaction typically⁹ provided only 12% yield of zampanolide along with its epimer and *bis*-acylated product, suggesting that an improvement is necessary for the synthesis of structural variants. Herein, we report an enantioselective synthesis of (–)-zampanolide that can be amenable to the synthesis of *N*-acyl aminal derivatives.

Our synthetic strategy for (–)-zampanolide (**1**) is shown in Figure 2. We planned to synthesize the macrocyclic core in a convergent manner in order to prepare a variety of structural analogs. Our strategic bond disconnection of the sensitive *N*-acyl aminal side chain at C20 provides macrolactone **3**, which can be formed from alcohol **4** and acid **5** by esterification followed by a ring-closing metathesis. A similar RCM strategy was first employed by Hoyer and Hu.¹¹ The tri-substituted olefin in **4** would be installed by a cross metathesis of **6**. The tetrahydropyran ring **6** would be constructed by an oxidative cyclization reaction of a cinnamyl ether derived from β-hydroxy ester **7**. The polyene carboxylic acid **5** would be assembled by a Reformatsky reaction with γ-bromo unsaturated ester **8** followed by Wittig olefination of the corresponding aldehyde.

As shown in Scheme 1, the synthesis commenced with known ester **7**, which was readily prepared with excellent enantioselectivity using Noyori hydrogenation as the key step.²¹ Selective protection of the primary alcohol as a TBDPS ether provided **9**. Etherification of the secondary alcohol with *t*-butyl cinnamyl carbonate in the presence of a catalytic amount of Pd(PPh₃)₄ afforded cinnamyl ether **10** in 73% yield. The ethyl ester **10** was converted to allylsilane **11** by employing a modified procedure of Narayanan and Bunnelle to provide **11** in 81% yield.²² Our subsequent plan was to carry out an oxidative Sakurai type cyclization to construct the 4-methylenetetrahydro-2H-pyran ring stereoselectively. For this transformation, we initially explored an oxidative cyclization reaction with DDQ as benzylic/allylic ethers have been converted to carbocation intermediates using DDQ with or without Lewis acids by Mukaiyama and Hayashi,²³ She et al.,²⁴ and Floreancig and co-workers.²⁵ The reaction with DDQ at –40 °C for 3 days resulted in only 30–35% desired product **6** along with unidentified side products possibly due to the presence of the allylsilane functionality. The same reaction in the presence of a variety of Lewis acids also provided similar results. However, oxidative cyclization with DDQ in the presence of a mild Brønsted acid such as PPTS provided the best results. Reaction of **11** with 1.5 equiv of DDQ and 1.5 equiv of PPTS at –38 °C in acetonitrile for 3 h afforded **6** in 81% yield as a single diastereomer (by ¹H-NMR analysis). The NOESY data fully corroborated the depicted *cis*-stereochemistry of **6**. Presumably, the cyclization proceeded through a Zimmerman-Traxler transition state where all substituents are equatorially oriented.²⁶

Our synthetic strategy then called for the elaboration of the *E*-trisubstituted olefin in **4** by a cross-metathesis reaction. The corresponding olefin substrate **12** was obtained in optically active form by opening of PMB-protected glycidyl derivative with isopropenylmagnesium bromide followed by protection of the resulting alcohol as TES-ether. Our attempted cross-

metathesis of **6** with **12** under a variety of conditions did not provide any cross-metathesis product. Assuming the lack of reactivity of the styrene chain, we planned to convert the styrene chain into a methylene chain. This was achieved by selective dihydroxylation of the styrene chain with ADMix- α followed by diol cleavage with NaIO₄ to provide the corresponding aldehyde as described by Smith and Dong.²⁷ Wittig olefination of the resulting aldehyde with methylene phosphorane afforded **13** in 78% yield (3 steps). Cross-metathesis²⁸ of **13** with **12** using Grubbs' second generation catalyst (10 mol %) in CH₂Cl₂ at reflux for 9 h provided *E/Z* olefin mixture (1.7:1) in 57% yield. The mixture was treated with HF·py to remove all silyl groups. The resulting alcohols were separated by silica gel chromatography. Photochemical isomerization of the *Z*-isomer **15** provided a 51% yield (68% brsm) of tri-substituted olefin **14**.

The synthesis of polyene carboxylic acid **5** is shown in Scheme 2. Allyl bromide **8** was prepared as an *E/Z* mixture (1.3:1) using the procedure of Fallis and Lei.²⁹ Reformatsky reaction of the mixture of bromides **8** with acrolein resulted in allylic alcohol **16** (47% yield) and unsaturated δ -lactone **17** (36% yield) after separation by silica gel chromatography. DIBAL-H reduction followed by Wittig reaction with (carbethoxymethylene)triphenylphosphorane afforded allylic alcohol **18**. Protection of the resulting alcohol as a PMB-ether followed by saponification of the ester provided acid **5** in 62% yield (2 steps).

The synthesis of macrolactone **3** is shown in Scheme 3. The primary alcohol in **14** was selectively oxidized with TEMPO in the presence of PhI(OAc)₂. The resulting aldehyde was subjected to Wittig olefination with methylenetriphenylphosphorane to provide **19** in 60% yield (2 steps). Esterification of acid **5** with alcohol **19** under Yamaguchi conditions using 2,4,6-trichlorobenzoyl chloride and DMAP furnished ester **20** in 91% yield. Ring-closing metathesis using Grubbs' second generation catalyst (12 mol %) in benzene at 60 °C for 20 h afforded **3** as a mixture (1:1) of diastereomers at the C7 chiral center. Removal of both PMB-ethers by treatment with DDQ provided the corresponding diol. Dess-Martin oxidation of the diol furnished (–)-**2**, the unnatural antipode of dactylolide (52% for the 3 steps).

The conversion of (–)-**2** to (–)-zampanolide **1** required the addition of a carboxamide to the aldehyde to form a *N*-acyl aminal. Such direct addition in one previous synthesis⁹ afforded only 12% yield of (–)-zampanolide, 12% yield of epimeric product **23** and 16% yield of *bis*-amide **24**. In an effort to improve this reaction, we investigated Brønsted acid-catalyzed *N*-acyl aminal formation under a variety of reaction conditions. In one of our initial successful attempts, reaction of (–)-**2** with carboxamide **21** in the presence of diphenylphosphoric acid clearly provided a mixture of all three products, (–)-zampanolide, *epi*-zampanolide, and *bis*-amide **24**, although analysis of the mixture showed that (–)-zampanolide formation was favored slightly. Encouraged by this result, we then investigated *N*-acyl aminal formation between aldehyde (–)-**2** and amide **21** in the presence of matched chiral phosphoric acid (*S*)-TRIP^{30,31} (**22**, 20 mol %) at 23 °C for 12 h. These reaction conditions provided excellent chemoselectivity towards mono addition and the formation of *bis*-amide **24** was not observed. The reaction furnished (–)-zampanolide in 51% yield and *epi*-zampanolide **23** in 18% yield after separation/purification by HPLC. We have also investigated the corresponding mismatched reaction with (*R*)-TRIP, however, this reaction afforded a 1:1 mixture of (–)-**1** and *epi*-**1**. Again, the formation of *bis*-amide **24** was not observed. The spectral data (¹H NMR and ¹³C NMR) of synthetic **1** ([α]_D²² - 94, *c* 0.08, CH₂Cl₂) is in agreement with that of natural zampanolide (Lit.⁸ [α]_D²² - 101, *c* 0.12, CH₂Cl₂).

In summary, we have accomplished an enantioselective synthesis of (–)-zampanolide. The synthesis features a novel intramolecular oxidative cyclization reaction, a cross-metathesis reaction to construct a tri-substituted olefin, a ring-closing metathesis to form a highly

functionalized macrolactone, and a chiral phosphoric acid catalyzed stereoselective *N*-acyl aminal formation that stereoselectively furnished (–)-zampanolide and no bis-amide byproduct. The present synthesis is amenable to the synthesis of structural variants of (–)-zampanolide and further investigations of important analogs are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research is supported in part by the National Institutes of Health.

References

- (1). Pazdur R, Kudelka AP, Kavanagh JJ, Cohen PR, Raber MN. *Cancer Treat. Rev.* 1993; 19:351–386. [PubMed: 8106152]
- (2). Schiff PB, Fant J, Horwitz SB. *Nature.* 1979; 277:665–667. [PubMed: 423966]
- (3). Mani S, Macapinlac MJ, Goel S, Verdier-Pinard D, Fojo T, Rothenberg M, Colevas D. *Anti-cancer Drugs.* 2004; 15:553–558. [PubMed: 15205596]
- (4). Hamel E, Day BW, Miller JH, Jung MK, Northcote PT, Ghosh AK, Curan DP, Cushman M, Nicolaou KC, Paterson I, Sorenson EJ. *J. Mol. Pharmacology.* 2006; 70:1555–1564.
- (5). Gapud EJ, Bai R, Ghosh AK, Hamel E. *Mol. Pharmacology.* 2004; 66:113–121.
- (6). Hood KA, West LM, Rouwe B, Northcote PT, Berridge MV, Wakefield SJ, Miller JH. *Cancer Res.* 2002; 62:3356–3360. [PubMed: 12067973]
- (7). Field JJ, Singh AJ, Kanakkanthara A, Halafihi T, Northcote PT, Miller JH. *J. Med. Chem.* 2009; 52:7328–7332. [PubMed: 19877653]
- (8). Tanaka J, Higa T. *Tetrahedron Lett.* 1996; 37:5535–5538.
- (9). Uenishi J, Iwamoto T, Tanaka J. *Org. Lett.* 2009; 11:3262–3265. [PubMed: 19586001]
- (10). Smith AB III, Safonov IG, Corbett RM. *J. Am. Chem. Soc.* 2001; 123:12426–12427. [PubMed: 11734051]
- (11). Hoyer TR, Hu M. *J. Am. Chem. Soc.* 2003; 125:9576–9577. [PubMed: 12904009]
- (12). Cutignano A, Bruno I, Bifulco G, Casapullo A, Debitus C, Gomez-Paloma L, Riccio R. *Eur. J. Org. Chem.* 2001:775–778.
- (13). Smith AB III, Safonov IG, Corbett RM. *J. Am. Chem. Soc.* 2002; 124:11102–11113. [PubMed: 12224958]
- (14). Ding F, Jennings MP. *Org. Lett.* 2005; 7:2321–2324. [PubMed: 15932188]
- (15). Aubele DL, Wan S, Floreancig PE. *Angew. Chem.* 2005; 117:3551–3554. *Angew. Chem. Int. Ed.* 2005; 44:3485–3488.
- (16). Sanchez CC, Keck GE. *Org. Lett.* 2005; 7:3053–3056. [PubMed: 15987203]
- (17). Louis I, Hungerford NL, Humphries EJ, McLeod MD. *Org. Lett.* 2006; 8:1117–1120. [PubMed: 16524282]
- (18). Zurwerra D, Gertsch J, Altmann K-H. *Org. Lett.* 2010; 12:2302–2305. [PubMed: 20415434]
- (19). Yun SY, Hansen EC, Volchkov I, Cho EJ, Lo WY, Lee D. *Angew. Chem.* 2010; 122:4357–4359. *Angew. Chem. Int. Ed.* 2010; 49:4261–4263.
- (20). Troast DM, Yuan J, Porco JA Jr. *Adv. Synth. Catal.* 2008; 350:1701–1711.
- (21). Kitamura M, Ohkuma T, Inoue S, Sayo N, Kumobayashi H, Akutagawa S, Ohta T, Takaya H, Noyori R. *J. Am. Chem. Soc.* 1988; 110:629–631.
- (22). Narayanan BA, Bunnelle WH. *Tetrahedron Lett.* 1987; 28:6261–6264.
- (23). Hayashi Y, Mukaiyama T. *Chem. Lett.* 1987:1811–1814.
- (24). Yu B, Jiang T, Li J, Su Y, Pan X, She X. *Org. Lett.* 2009; 11:3442–3445. [PubMed: 19603799]

- (25). Tu W, Liu L, Floreancig PE. *Angew. Chem.* 2008; 120:4252–4255. *Angew. Chem. Int. Ed.* 2008; 47:4184–4187.
- (26). Zimmerman HE, Traxler MD. *J. Am. Chem. Soc.* 1957; 79:1920–1923.
- (27). Smith AB III, Dong S. *Org. Lett.* 2009; 11:1099–1102. [PubMed: 19182995]
- (28). Chatterjee AK, Choi T-L, Sanders DP, Grubbs RH. *J. Am. Chem. Soc.* 2003; 125:11360–11370. [PubMed: 16220959]
- (29). Lei B, Fallis AG. *Can. J. Chem.* 1991; 69:1450–1456.
- (30). Hoffmann S, Seayad AM, List B. *Angew. Chem.* 2005; 117:7590–7593. *Angew. Chem. Int. Ed.* 2005; 44:7424–7427.
- (31). Akiyama T. *Chem. Rev.* 2007; 107:5744–5758. [PubMed: 17983247]

Figure 1.
(-)-Zampanolide **1** (natural form) and (+)-dactylolide **2** (enantiomer of natural form)

Figure 2.
Synthetic plan for (-)-Zampanolide 1

Scheme 1.
Synthesis of tetrahydropyran **14**

Scheme 2.
Synthesis of polyene carboxylic acid **5**

Scheme 3.
The synthesis of (-)-2

Scheme 4.
The synthesis of (-)-Zampanolide